(12) STANDARD PATENT (11) Application No. **AU 2007202350 B2**
(19) AUSTRALIAN PATENT OFFICE

(54) Title
Mono- and bicyclic azole derivatives that inhibit the interaction of ligands with RAGE

(51) International Patent Classification(s)

A61K 31/4184 (2006.01)	***A61P 35/00*** (2006.01)
A61K 9/12 (2006.01)	***A61P 43/00*** (2006.01)
A61K 31/4164 (2006.01)	***C07D 233/54*** (2006.01)
A61K 31/4178 (2006.01)	***C07D 233/64*** (2006.01)
A61K 31/42 (2006.01)	***C07D 235/08*** (2006.01)
A61K 31/4439 (2006.01)	***C07D 235/12*** (2006.01)
A61K 31/454 (2006.01)	***C07D 235/14*** (2006.01)
A61K 31/4725 (2006.01)	***C07D 235/18*** (2006.01)
A61K 31/496 (2006.01)	***C07D 235/30*** (2006.01)
A61K 45/00 (2006.01)	***C07D 401/04*** (2006.01)
A61P 3/10 (2006.01)	***C07D 401/06*** (2006.01)
A61P 9/10 (2006.01)	***C07D 401/12*** (2006.01)
A61P 11/00 (2006.01)	***C07D 401/14*** (2006.01)
A61P 11/06 (2006.01)	***C07D 403/12*** (2006.01)
A61P 13/12 (2006.01)	***C07D 403/14*** (2006.01)
A61P 15/10 (2006.01)	***C07D 405/04*** (2006.01)
A61P 25/28 (2006.01)	***C07D 405/12*** (2006.01)
A61P 27/02 (2006.01)	***C07D 413/12*** (2006.01)
A61P 29/00 (2006.01)	***C07D 453/02*** (2006.01)

(21) Application No: **2007202350** (22) Date of Filing: **2007.05.24**

(43) Publication Date: **2007.06.14**
(43) Publication Journal Date: **2007.06.14**
(44) Accepted Journal Date: **2009.07.30**

(62) Divisional of:
2003217943

(71) Applicant(s)
TransTech Pharma, Inc.

(72) Inventor(s)
Qabaja, Ghassan;Mjalli, Adnan M M;Jones, David R.;Andrews, Robert C;Avor, Kwasi;Guo, Xiao-Chuan;Hari, Anitha;Gopalaswamy, Ramesh;Gupta, Suparna;Chen, Xin

(74) Agent / Attorney
Pizzeys, Level 2, Woden Plaza Offices Woden Town Square, Woden, ACT, 2606

(56) Related Art
US5358960
EP586806

2007202350 24 May 2007

ABSTRACT

This invention provides certain compounds of formula I wherein A_1 is O, S or $-N(R^2)-$, 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.

2007202350 24 May 2007

Regulation 3.2

AUSTRALIA

Patents Act 1990

COMPLETE SPECIFICATION

STANDARD PATENT

APPLICANT: **TRANSTECH PHARMA, INC.**

Invention Title: **MONO- AND BICYCLIC AZOLE DERIVATIVES THAT INHIBIT THE INTERACTION OF LIGANDS WITH RAGE**

The following statement is a full description of this invention, including the best method of performing it known to me:

2007202350 24 May 2007

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 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 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 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 (*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 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 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-κB, and the activation of NF-κB regulated genes, such as the cytokines IL-1β, 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-κB. 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.

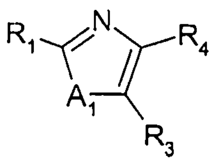
Summary of the Invention

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 heterocyclylaryl, -fused heterocyclylheteroaryl, -alkylene-fused cycloalkylaryl, -alkylene-fused cycloalkylheteroaryl, -alkylene-fused heterocyclylaryl, -alkylene-fused heterocyclylheteroaryl, 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)-, -O-C(O)-, -C(O)-O-, $-C(O)N(R_6)-$, $-N(R_6)C(O)-$, $-S(O_2)N(R_6)-$, $N(R_6)S(O_2)-$, -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 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 heterocyclylaryl, fused heterocyclylheteroaryl, -alkylene-fused cycloalkylaryl, -alkylene-fused cycloalkylheteroaryl, -alkylene-fused heterocyclylaryl, or -alkylene-fused heterocyclylheteroaryl;

A_1 comprises O, S, or $–N(R_2)-$;

wherein

R_2 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;

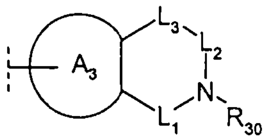
q) -alkylene-fused cycloalkylaryl,

r) -alkylene-fused cycloalkylheteroaryl,

s) -alkylene-fused heterocyclylaryl,

t) -alkylene-fused heterocyclylheteroaryl; or

u) a group of the formula

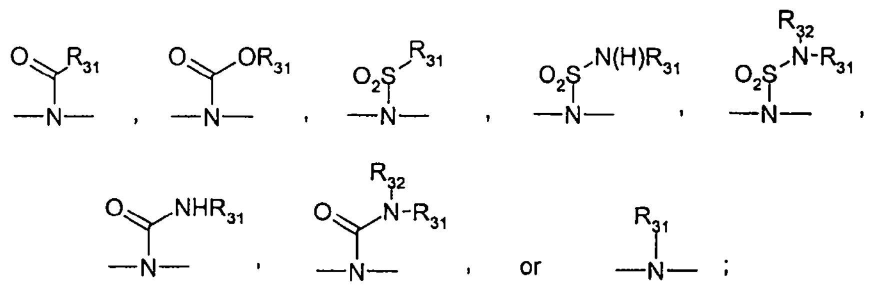


wherein

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-, -$S(O_2)$-, -C(O)-, -CON(H)-, -NHC(O)-, -NHCON(H)-, -$NHSO_2$-, -$SO_2N(H)$-, -C(O)-O-, -O-C(O)-, -$NHSO_2NH$-,



wherein R_{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,

d) -cyano,

e) -carbamoyl,

f) -carboxyl,

g) -aryl,

h) -heteroaryl,
i) -cycloalkyl,
j) -heterocyclyl,
k) -alkyl,
l) -alkenyl,
m) -alkynyl,
n) -alkylene-aryl,
o) -alkylene-heteroaryl,
p) -alkylene-heterocyclyl,
q) -alkylene-cycloalkyl,
r) -fused cycloalkylaryl,
s) -fused cycloalkylheteroaryl,
t) -fused heterocyclylaryl,
u) -fused heterocyclylheteroaryl,
v) -alkylene-fused cycloalkylaryl,
w) -alkylene-fused cycloalkylheteroaryl,
x) -alkylene-fused heterocyclylaryl,
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) -SO_2-alkyl;
ee) -SO_2-alkylene-aryl;
ff) -SO_2-aryl;
gg) -SO_2-NH-alkyl;
hh) -SO_2-NH- alkylene-aryl;
ii) -C(O)-alkyl;
jj) -C(O)-alkylene-aryl;
kk) -G_4-G_5-G_6-R_7;
ll) –Y_1-alkyl;
mm) –Y_1-aryl;
nn) –Y_1-heteroaryl;
oo) –Y_1-alkylene-aryl;
pp) –Y_1-alkylene-heteroaryl;
qq) –Y_1-alkylene-NR_9R_{10}; or
rr) –Y_1-alkylene-W_1-R_{11};

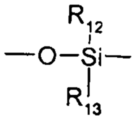
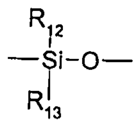
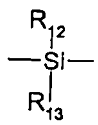
wherein

G_4 and G_6 independently comprise alkylene, alkenylene, alkynylene, cycloalkylene, heterocyclylene, arylene, heteroarylene, (aryl)alkylene, (heteroaryl)alkylene, (aryl)alkenylene, (heteroaryl)alkenylene, or a direct bond;

G_5 comprises -O-, -S-, -N(R_8)-, -S(O)-, -S(O)$_2$-, -C(O)-, -O-C(O)-, -C(O)-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 cycloalkylarylene, fused cycloalkylheteroarylene, fused heterocyclylarylene, fused heterocyclylheteroarylene, or a direct bond, wherein R_8 comprises -hydrogen, -aryl, -alkyl, -alkylene-aryl, or -alkylene-O-aryl;

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 -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$_2$N(H)-, -C(O)-O-, -NHSO$_2$NH-, -O-CO-,

 ,  or  ;

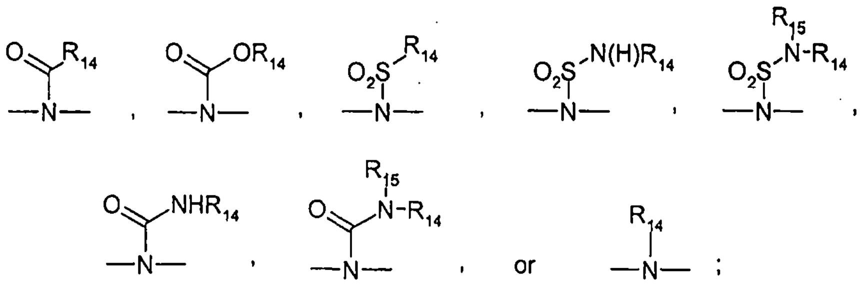
wherein R_{12} and R_{13} independently comprise aryl, alkyl,-alkylene-aryl, alkoxy, or -alkylene-O-aryl; and

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 -(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; and

X_1 comprises a direct bond, –CH$_2$-, -O-, -S-, -S(O_2)-, -C(O)-, -CON(H)-, -NHC(O)-, -NHCON(H)-, -NHSO$_2$-, -SO$_2$N(H)-, -C(O)-O-, -O-C(O)-, -NHSO$_2$NH-,



wherein R_{14} and R_{16} independently hydrogen, aryl, heteroaryl, alkyl, -alkylene-aryl, or -alkylene-heteroaryl;

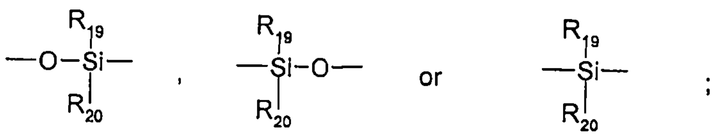
wherein

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:

a) -H,
b) -halogen,
c) -hydroxyl,
d) -cyano,
e) -carbamoyl,
f) -carboxyl,
g) -Y_2-alkyl;
h) -Y_2-aryl;
i) -Y_2-heteroaryl;
j) -Y_2- alkylene-heteroarylaryl;
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
p) –Y_3-Y_4 –Y_5-A_2,

wherein

Y_2 and W_2 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-$S(O)_2$-, -O-CO-,

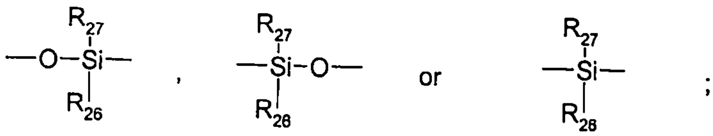


wherein;

R_{19} and R_{20} independently comprise hydrogen, aryl, alkyl, -alkylene-aryl, alkoxy, or –alkylene-O-aryl; and

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

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_{28} 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) $-S(O_2)-$; or

s) $-S(O)-$;

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

A_2 comprises

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

b) -imidazolyl, or

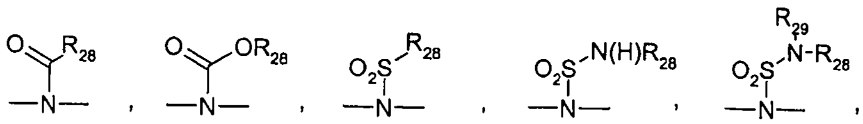
c) -pyridyl; and

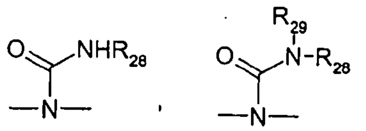
R_{23}, R_{24}, and R_{25} independently comprise hydrogen, aryl, heteroaryl, -alkylene-heteroaryl, alkyl, -alkylene-aryl, -alkylene-O-aryl, or -alkylene-O-heteroaryl; and R_{23} and R_{24} may be taken together to form a ring having the formula $-(CH_2)_s-X_3-(CH_2)_t-$ bonded to the nitrogen atom to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

wherein

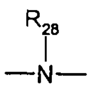
s and t are, independently, 1, 2, 3, or 4;

X_3 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)-, $-NHSO_2NH-$,





and

 ;

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

wherein

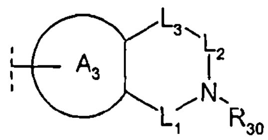
either

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

$C(=NR_{25})NR_{23}R_{24}$, or $-Y_3-Y_4-Y_5-A_2$, with the proviso that no more than one of R_{23}, R_{24}, and R_{25} may comprise aryl or heteroaryl;

or

R_2 is a group of the formula



and

wherein

one of R_3 and R_4, R_3 and R_2, or R_1 and R_2 may be taken together to constitute, together with the atoms to which they are bonded, an aryl, heteroaryl, fused arylcycloalkyl, fused arylheterocyclyl, fused heteroarylcycloalkyl, or fused heteroarylheterocyclyl ring system, wherein

said ring system or R_1, R_2, R_3, or R_4 is substituted with at least one group of the formula

a) $-Y_5-Y_6-NR_{33}R_{34}$;

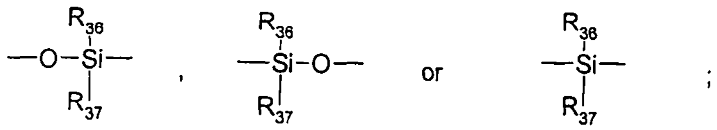
b) $-Y_5-Y_6-NH-C(=NR_{35})NR_{33}R_{34}$;

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-, $-NHSO_2NH-$, -O-CO-,



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;

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) $-S(O_2)-$; or

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

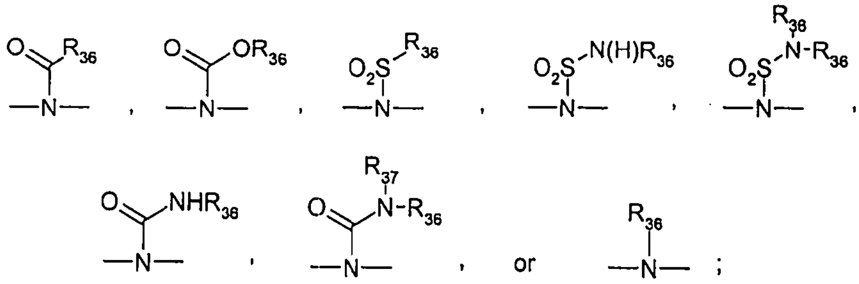
c) -pyridyl; and

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)-, $-NHSO_2NH-$,



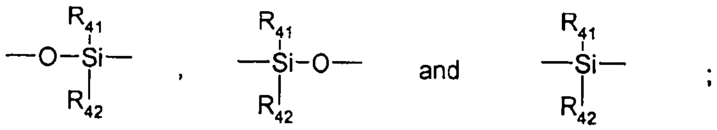
wherein R_{36} and R_{37} independently comprise hydrogen, aryl, heteroaryl, alkyl, -alkylene-aryl, or -alkylene-heteroaryl; and

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

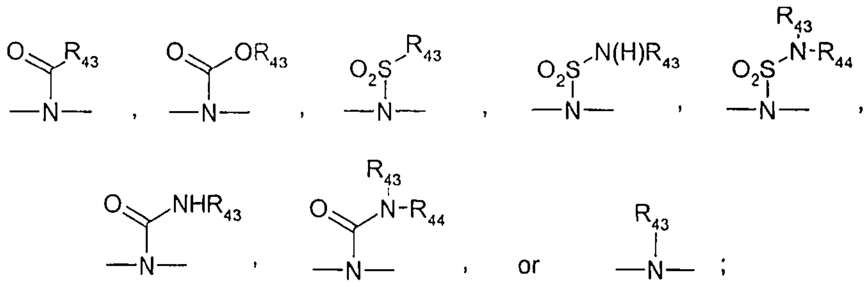
Y_8 and W_3 independently comprise $-CH_2-$, -O-, -N(H), -S-, SO_2-, -CON(H)-, -NHC(O)-, -NHCON(H)-, $-NHSO_2-$, $-SO_2N(H)-$, -C(O)-O-, $-NHSO_2NH-$, -O-CO-,



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 -alkyene-O-aryl; and R_{38} and R_{39} may be taken together to form a ring having the formula $-(CH_2)_w-X_7-(CH_2)_x-$ 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;

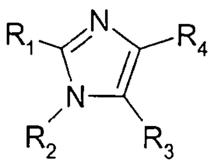
X_7 comprises a direct bond, $-CH_2$-, -O-, -S-, $-S(O_2)$-, -C(O)-, -CON(H)-, -NHC(O)-, -NHCON(H)-, $-NHSO_2$-, $-SO_2N(H)$-, -C(O)-O-, -O-C(O)-, $-NHSO_2NH$-,



wherein R_{43} and R_{44} 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)



(Ia)

wherein

R_1 comprises -hydrogen, -aryl, -heteroaryl, -cycloalkyl, -heterocyclyl, -alkyl, -alkylene-aryl, -alkylene-heteroaryl, -alkylene-heterocyclyl, -alkylene-cycloalkyl, or $-G_1-G_2-G_3-R_5$ wherein

G_1 and G_3 independently comprise alkylene or a direct bond;

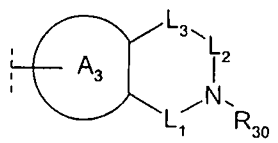
G_2 comprises -O-, $-CO_2$-, or a direct bond; and

R_5 comprises hydrogen, aryl, heteroaryl, cycloalkyl, heterocyclyl, alkyl, alkenyl, alkynyl, -alkylene-aryl, -alkylene-heteroaryl, -alkylene-heterocyclyl, or -alkylene-cycloalkyl.

R_2 comprises

a) -hydrogen,

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

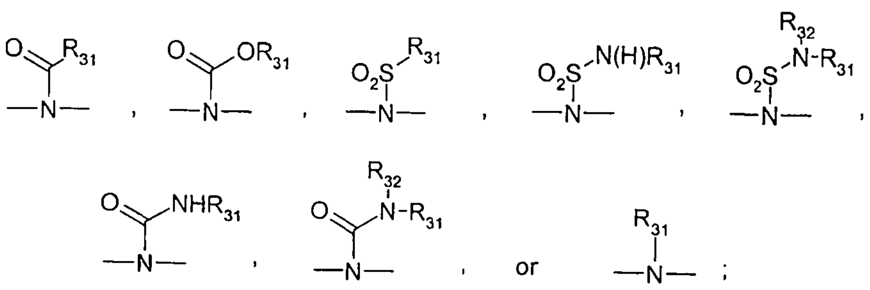


wherein

A_3 comprises an aryl or heteroaryl group;

L_1 and L_2 independently comprise alkylene or alkenylene;

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 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,
d) -cyano,
e) -carbamoyl,
f) -carboxyl;
g) -aryl,
h) -heteroaryl,
i) -cycloalkyl,
j) -heterocyclyl,
k) -alkyl,
l) -alkenyl,
m) -alkynyl,
n) -alkylene-aryl,
o) -alkylene-heteroaryl,
p) -alkylene-heterocyclyl,
q) -alkylene-cycloalkyl,
r) -fused cycloalkylaryl,
s) -fused cycloalkylheteroaryl,
t) -fused heterocyclylaryl,
u) -fused heterocyclylheteroaryl,
v) -alkylene-fused cycloalkylaryl,
w) -alkylene-fused cycloalkylheteroaryl,
x) -alkylene-fused heterocyclylaryl,
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) -SO_2-alkyl;
ee) -SO_2-alkylene-aryl;
ff) -SO_2-aryl;
gg) -SO_2-NH-alkyl;
hh) -SO_2-NH- alkylene-aryl
ii) -C(O)-alkyl;
jj) -C(O)-alkylene-aryl;
kk) -G_4-G_5-G_6-R_7

ll) $-Y_1$-alkyl;

mm) $-Y_1$-aryl;

nn) $-Y_1$-heteroaryl;

oo) $-Y_1$-alkylene-aryl;

pp) $-Y_1$-alkylene-heteroaryl;

qq) $-Y_1$-alkylene-NR_9R_{10}; and

rr) $-Y_1$-alkylene-W_1-R_{11};

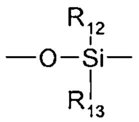
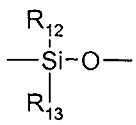
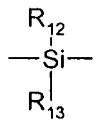
wherein

G_4 and G_6 independently comprise alkylene, alkenylene, alkynylene, cycloalkylene, heterocyclylene, arylene, heteroarylene, (arylalkylene, (heteroary) alkylene, (aryl)alkenylene, (heteroaryl)alkenylene, or a direct bond;

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;

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 -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-,

 ,  or  ;

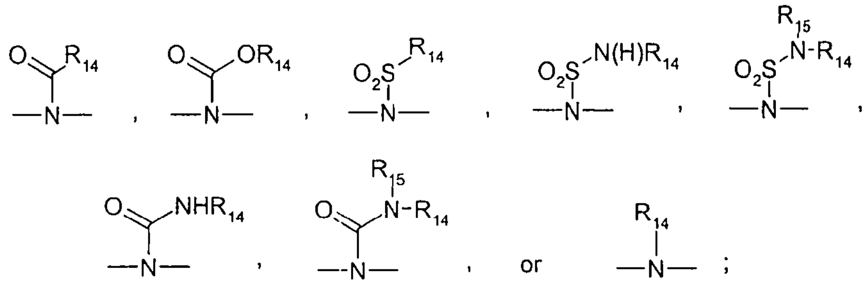
wherein R_{12} and R_{13} independently comprise aryl, alkyl,-alkylene-aryl, alkoxy, or -alkylene-O-aryl;

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;

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)-, $-NHSO_2NH-$,



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-(4-chlorophenoxy)-propyl, 2,4,4-trimethyl-pentyl, 1-ethyl-propyl, 1-propyl-butyl, benzyloxymethyl, 2-cyclopropy-ethyl, 2-phenyl-ethyl, 4-tert-butylphenoxymethyl, 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 1,2,3,4-tetrahydroisoquinoline group, wherein the phenyl group is substituted with at least one substitutent comprising

a) $-Y_2$-alkyl;
b) $-Y_2$-aryl;
c) $-Y_2$-heteroaryl;
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

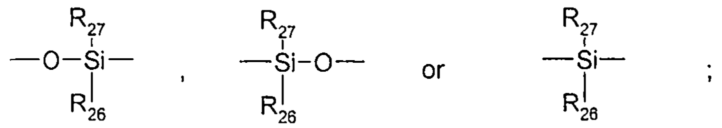
j) $-Y_3$-Y_4 $-Y_5$-A_2;

wherein

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;

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-, -$NHSO_2$NH-, -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;

t) -heterocyclylene-alkylene;

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 SO_2 atoms;

A_2 comprises

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

b) -imidazolyl, or

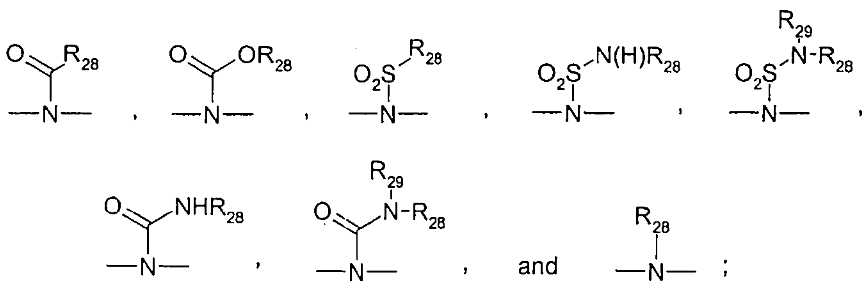
c) -pyridyl; and

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;

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)-, $-NHSO_2NH-$,



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

In another group of preferred embodiments of compounds of Formula (Ia), R_2 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, 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), R_3 comprises hydrogen; and R_4 comprises a phenyl group, wherein the phenyl group is substituted with at least one substituent comprising

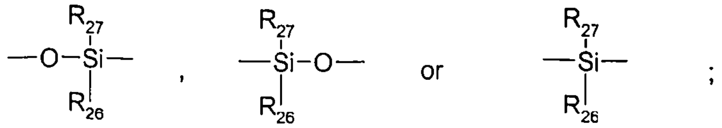
a) $-Y_2$-alkyl;
b) $-Y_2$-aryl;
c) $-Y_2$-heteroaryl;
d) $-Y_2$- alkylene-heteroarylaryl;
e) $-Y_2$-alkylene-aryl;
f) $-Y_2$-alkylene-W_2-R_{18};
g) $-Y_3$-Y_4 $-NR_{23}R_{24}$;
h) $-Y_3$-Y_4 $-NH-C(=NR_{25})NR_{23}R_{24}$;
i) $-Y_3$-Y_4 $-C(=NR_{25})NR_{23}R_{24}$; or
j) $-Y_3$-Y_4 $-Y_5$-A_2;

wherein

Y_2 and W_2 independently comprise $-CH_2-$ or -O-;

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

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

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) $-S(O_2)-$; or
s) -S(O)-;

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

A_2 comprises

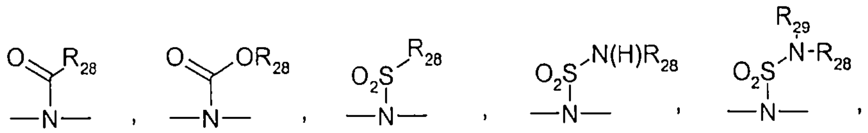
a) heterocyclyl, fused arylheterocyclyl, or fused heteroarylheterocyclyl, containing at least one basic nitrogen atom,
b) -imidazolyl, or
c) -pyridyl;

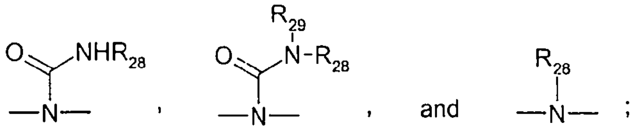
R_{23}, R_{24}, and R_{25} independently comprise hydrogen, aryl, heteroaryl, -alkylene-heteroaryl, alkyl, -alkylene-aryl, -alkylene-O-aryl, or -alkylene-O-heteroaryl; and R_{23} and R_{24} may be taken together to form a ring having the formula $-(CH_2)_s-X_3-(CH_2)_t-$ bonded to the nitrogen atom to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

wherein

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

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)-, $-NHSO_2NH-$,



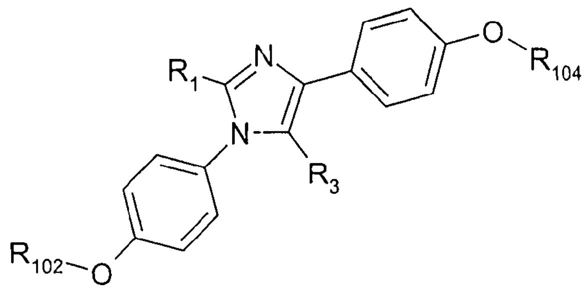


wherein R_{28} and R_{29} independently comprise hydrogen, aryl, heteroaryl, alkyl, -alkylene-aryl, or -alkylene-heteroaryl.

In a more preferred group of compounds of Formula (Ia), 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-ylmethyl-amino)-ethoxy]-phenyl, 4-[2-(guanidinyl)-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-ylmethyloxy)-phenyl, 4-(4-amino-3,5-dimethyl-pyrrolidin-2-ylmethyloxy)-phenyl, dibenzofuran-2-yl, 4-[3-(piperazin-1-yl)-propoxy]-phenyl, 4-(piperazin-4-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-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-ylmethyloxy]-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)-allyoxy]-phenyl, 4-(4-chlorophenoxy)-naphthalenyl, 4-[2-(biphenyl-4-yl)-acetamido]-phenyl, 4-(2-(9H-carbazole)-ethoxy]-phenyl, 4-[4-methoxyphenyoxy]-phenyl, 4-(4-tert-butyl-phenoxy)-phenyl, or 4-(naphthylen-2-ylmethoxy)-phenyl.

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



(Ib)

wherein

R_1 comprises -hydrogen, -aryl, -heteroaryl, -cycloalkyl, -heterocyclyl, -alkyl, -alkenyl, -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 $-G_1-G_2-G_3-R_5$

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)-, $-CO_2-$, $-C(O)N(R_6)-$, $N(R_6)C(O)-$, $-S(O_2)N(R_6)-$, $N(R_6)S(O_2)-$, -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_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 heterocyclylaryl, fused heterocyclylheteroaryl;-alkylene-fused cycloalkylaryl, -alkylene-fused cycloalkylheteroaryl, -alkylene-fused heterocyclylaryl, or -alkylene-fused heterocyclylheteroaryl;

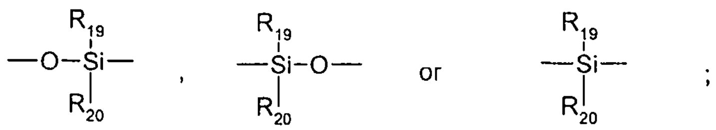
R_3 comprises hydrogen or an alkyl group; and

R_{102} and R_{104} independently comprise

a) -H;
b) -alkyl;
c) -aryl;
d) -heteroaryl;
e) -alkylene-heteroarylaryl;
f) -alkylene-aryl;
g) -alkylene-W_2-R_{18};
h) $-Y_4-NR_{23}R_{24}$;
i) $-Y_4-NH-C(=NR_{25})NR_{23}R_{24}$;
j) $-Y_4-C(=NR_{25})NR_{23}R_{24}$; or
k) $-Y_4-Y_5-A_2$;

wherein

W_2 comprises $-CH_2-$, -O-, -N(H), -S-, SO_2-, -CON(H)-, -NHC(O)-, -NHCON(H)-, $-NHSO_2-$, $-SO_2N(H)-$, -C(O)-O-, $-NHSO_2NH-$, $-O-S(O)_2-$, -O-CO-,

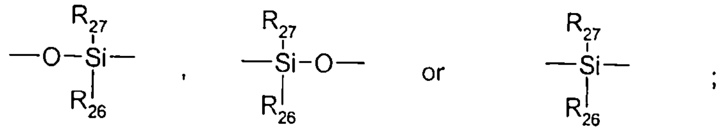


wherein R_{19} and R_{20} independently comprise hydrogen, aryl, alkyl, -alkylene-aryl, alkoxy, or –alkylene-O-aryl; and

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

Y_5 comprises 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-,

2007202350 24 May 2007



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(O_2)-; or
s) -S(O)-;

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

A_2 comprises

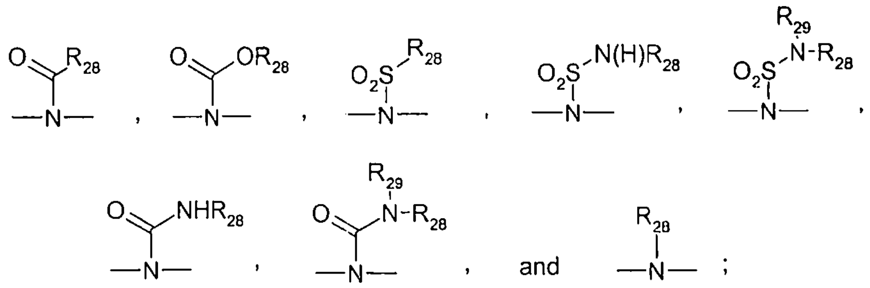
a) heterocyclyl, fused arylheterocyclyl, or fused heteroarylheterocyclyl, containing at least one basic nitrogen atom,
b) -imidazolyl, or
c) -pyridyl;

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;

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)-, $-NHSO_2NH-$,



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:

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

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-cyclopropy-ethyl, 2-phenyl-ethyl, 4-tert-butylphenoxymethyl, 4-tert-butylcyclohexyl, 4-ethylcyclohexyl, 4-butylcyclohexyl, 3-methoxycarbonyl-1-propyl, or 2-(pyridin-3-yl)-ethyl group, and R_3 comprises hydrogen.

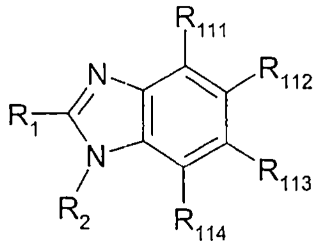
In another group of preferred embodiments of the compound of Formula (Ib), R_{102} and R_{104} independently comprise 2-(4-chlorophenyl)-ethyl, 3-(N,N'-diethylamino)-propyl, 2-amino-ethyl, 2-(N-methyl-N'-pyridin-4-yl-amino)-ethyl, 2-(N-ethyl-N'-pyridin-4-yl-amino)-ethyl, 2-(N-pyridin-4-yl-amino)-ethoxy, 4-(4-amino-pyridin-3-yl-oxy), 4-(pyridin-4-yl)-amino, 2-(N,N'-bis-pyridin-2-ylmethyl-amino)-ethyl, 2-(guanidinyl)-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 naphthylen-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 ary 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.

2007202350 24 May 2007

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



(Ic)

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

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)-, -CO$_2$-, -C(O)N(R_6)-, N(R_6)C(O)-, -S(O$_2$)N(R_6)-, N(R_6)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_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 heterocyclylaryl, fused heterocyclylheteroaryl;-alkylene-fused cycloalkylaryl, -alkylene-fused cycloalkylheteroaryl, -alkylene-fused heterocyclylaryl, or -alkylene-fused heterocyclylheteroaryl;

R_2 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,

R_{111}, R_{112}, R_{113} and R_{114} independently comprise

a) -hydrogen,
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-W_3-R_{40},
m) –Y_5-Y_6 –$NR_{33}R_{34}$,

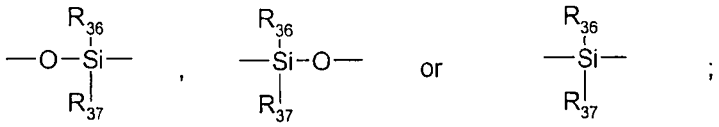
n) $-Y_5-Y_6-NH-C(=NR_{35})NR_{33}R_{34}$,

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

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

wherein

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-,



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;
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) $-S(O_2)-$; or
s) -S(O)-;

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

A_4 comprises

2007202350 24 May 2007

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

b) -imidazolyl, or

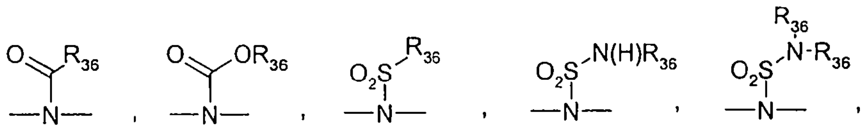
c) -pyridyl;

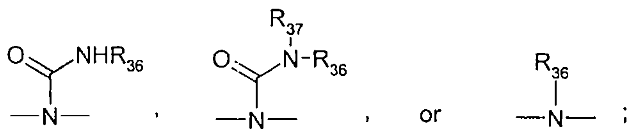
R_{33}, R_{34} and R_{35} independently comprise hydrogen, aryl, heteroaryl, alkyl, -alkylene-aryl, or -alkylene-O-aryl; and R_{33} and R_{34} may be taken together to form a ring having the formula $-(CH_2)_u-X_4-(CH_2)_v-$ bonded to the nitrogen atom to which R_{33} and R_{34} are attached,

wherein

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

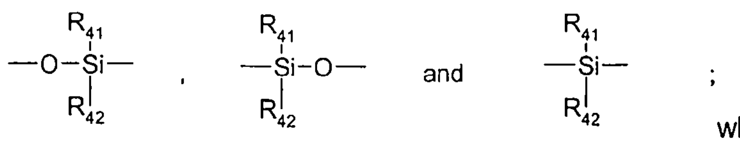
X_4 comprises a direct bond, $-CH_2-$, -O-, -S-, $-S(O_2)-$, -C(O)-, -CON(H)-, -NHC(O)-, -NHCON(H)-, $-NHSO_2-$, $-SO_2N(H)-$, -C(O)-O-, -O-C(O)-, $-NHSO_2NH-$,





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

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-,



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 -alkyene-O-aryl;

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), R_2 comprises hydrogen or alkyl.

In another group of preferred embodiments of the compound of Formula (Ic), R_1 comprises a phenyl group substituted by one or more substituents comprising

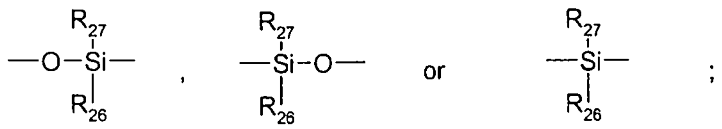
a) $-Y_2$-alkyl;
b) $-Y_2$-aryl;
c) $-Y_2$-heteroaryl;
d) $-Y_2$- alkylene-heteroarylaryl;
e) $-Y_2$-alkylene-aryl;
f) $-Y_2$-alkylene-W_2-R_{18};
g) $–Y_3-Y_4–NR_{23}R_{24}$
h) $–Y_3-Y_4$ –NH-C(=NR_{25})$NR_{23}R_{24}$
i) $–Y_3-Y_4$ –C(=NR_{25})$NR_{23}R_{24}$
j) $–Y_3-Y_4–Y_5-A_2$

wherein

Y_2 and W_2 independently comprise -CH_2-, -O-, and

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

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-, -$NHSO_2$NH-, -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) $-S(O_2)-$; or

s) -S(O)-;

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

A_2 comprises

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

b) -imidazolyl, or

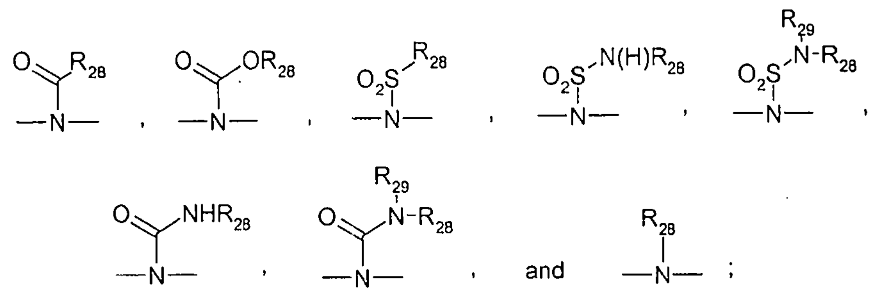
c) -pyridyl;

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;

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)-, $-NHSO_2NH-$,



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

In another group of preferred embodiments of the compound of Formula (Ic), R_1 comprises 2-methoxy-3,5-dimethyoxy-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), 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.

In another group of preferred embodiments of the compound of Formula (Ic), R_{111}, R_{112} and R_{114} comprise hygrogen; and R_{113} comprises $-Y_3$-Y_4 $-NR_{23}R_{24}$, or $-Y_3$-Y_4 $-Y_5$-A_2.

In another group of preferred embodiments of the compound of Formula (Ic), 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 hygrogen; and R_{111} and R_{113} comprise $-Y_3$-Y_4 $-NR_{23}R_{24}$, or $-Y_3$-Y_4 $-Y_5$-A_2.

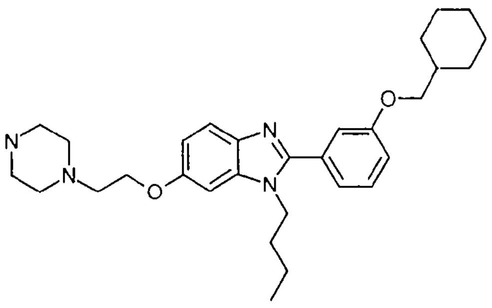
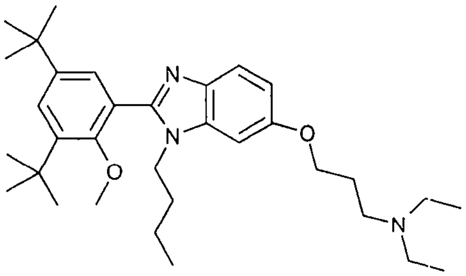
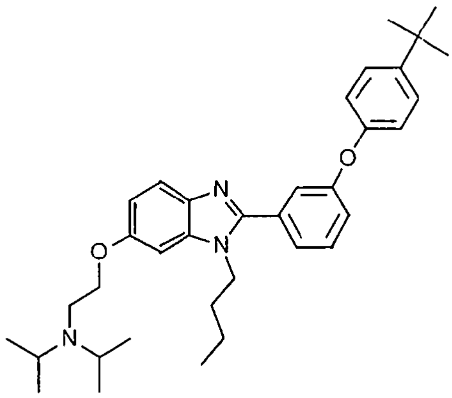
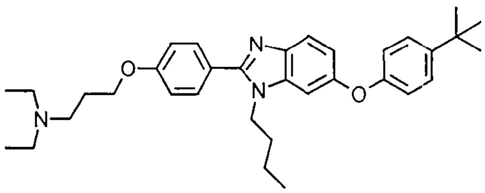
2007202350 24 May 2007

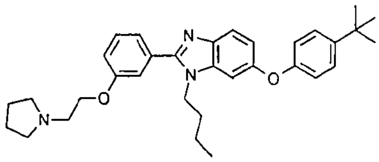
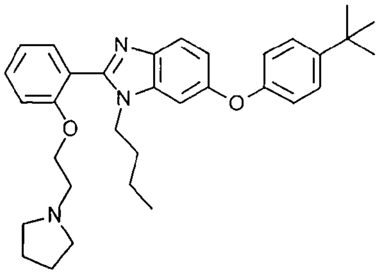
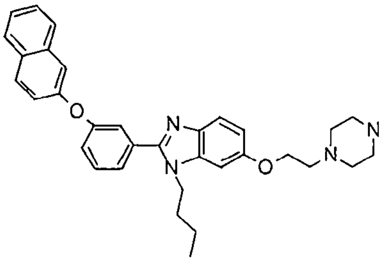
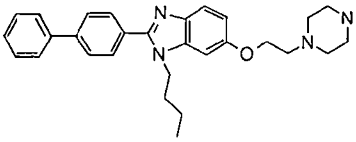
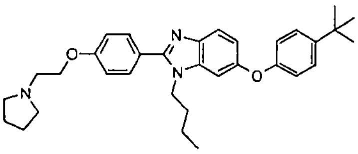
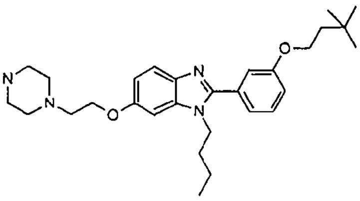
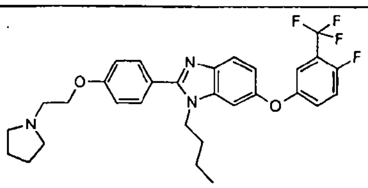
In the compounds of Formula (I), the various functional groups represented should be understood to have a point of attachment at the functional group having the hyphen. In other words, in the case of $-C_{1-6}$ alkylaryl, it should be understood that the point of attachment is the alkyl group; an example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

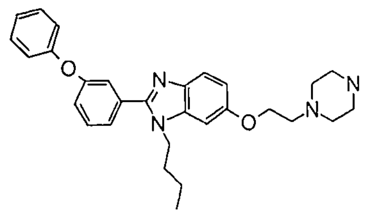
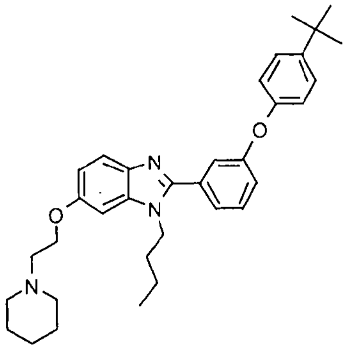
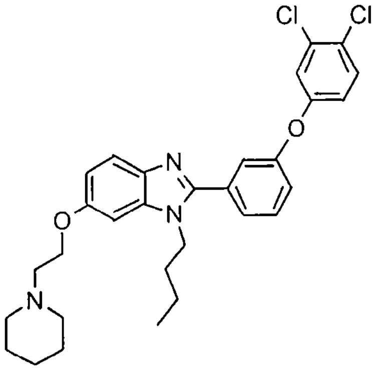
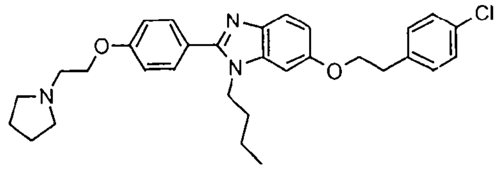
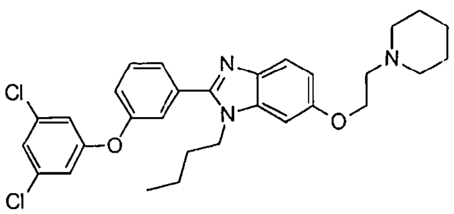
Also included within the scope of the invention are the individual enantiomers of the compounds represented by Formula (I) above as well as any wholly or partially racemic mixtures thereof. The present invention also covers the individual enantiomers of the compounds represented by the Formula above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

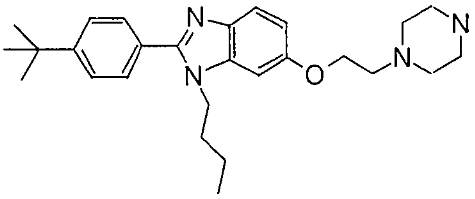
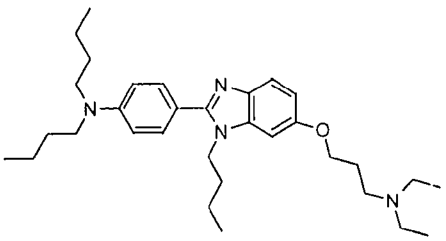
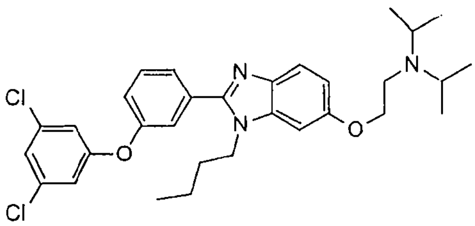
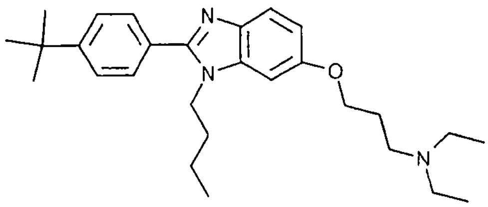
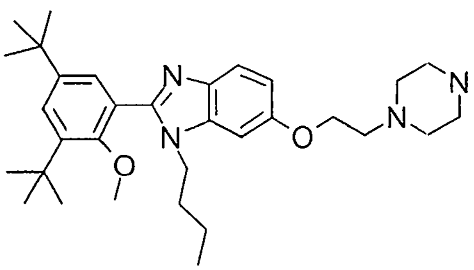
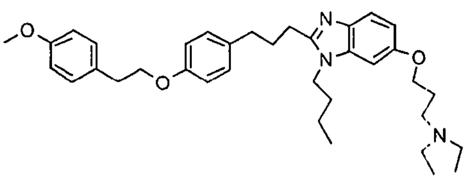
Compounds of the present invention preferred for their high biological activity are listed by name below in Table 1.

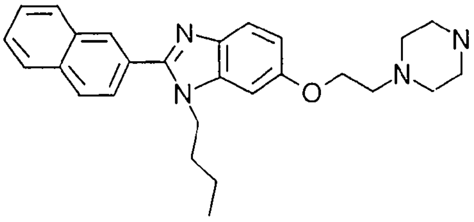
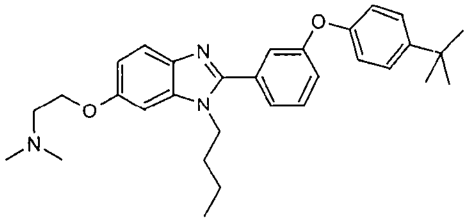
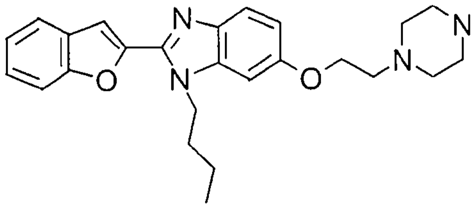
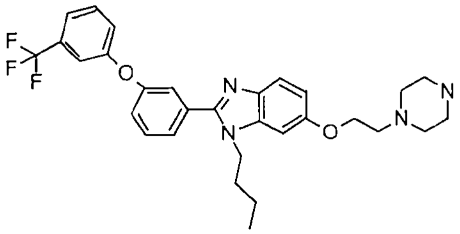
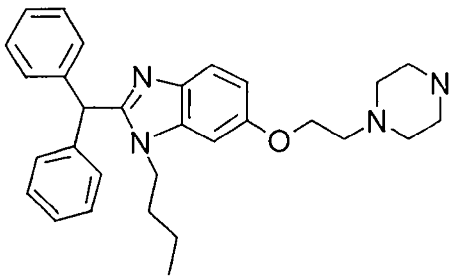
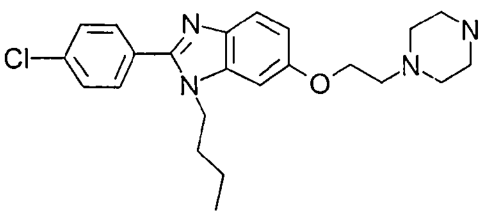
Table 1

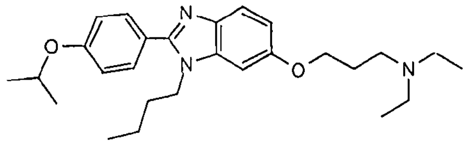
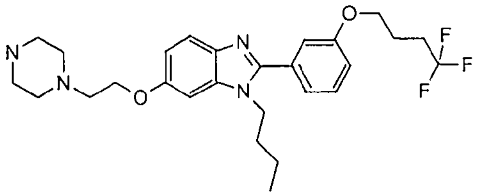
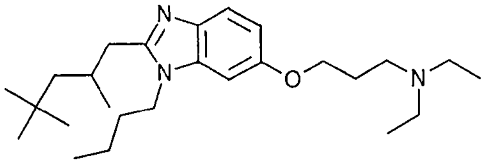
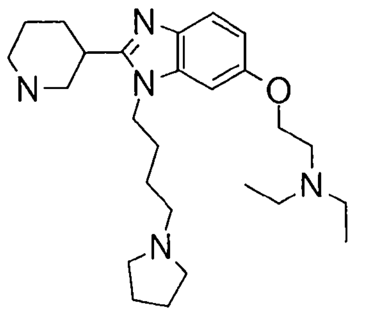
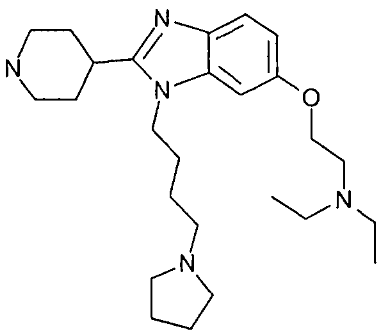
Ex.	Structure	Name
1		1-butyl-2-(3-cyclohexylmethoxy-phenyl)-6-(2-piperazin-1-yl-ethoxy)-1H-benzoimidazole
2		{3-[3-butyl-2-(3,5-di-tert-butyl-2-methoxy-phenyl)-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
3		(2-{3-butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-3H-benzoimidazol-5-yloxy}-ethyl)-diisopropyl-amine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

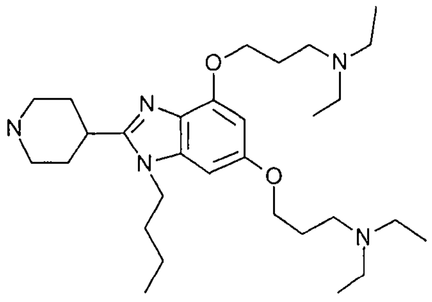
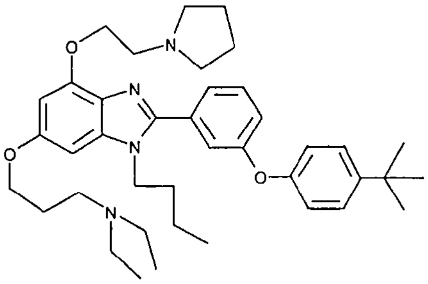
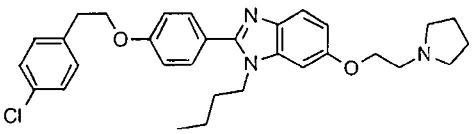
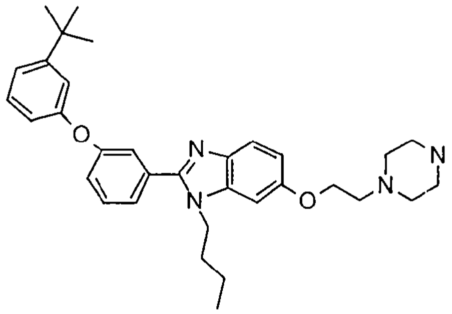
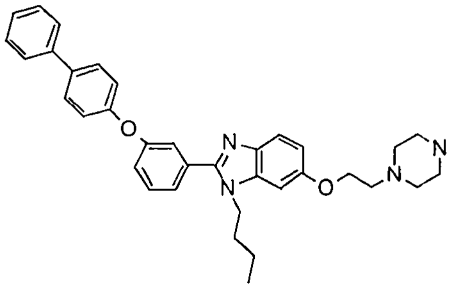
Ex.	Structure	Name
5		1-butyl-6-(4-tert-butyl-phenoxy)-2-[3-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1H-benzimidazole
6		1-butyl-6-(4-tert-butyl-phenoxy)-2-[2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1H-benzimidazole
7		1-butyl-2-[3-(naphthalen-2-yloxy)-phenyl]-6-(2-piperazin-1-yl-ethoxy)-1H-benzoimidazole
8		2-biphenyl-4-yl-1-butyl-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidaz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

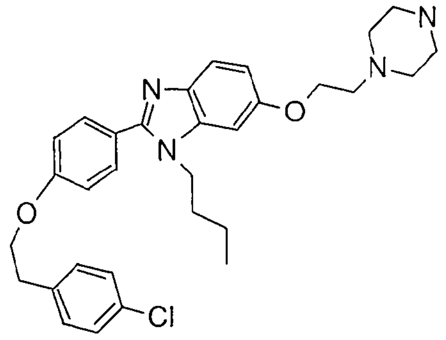
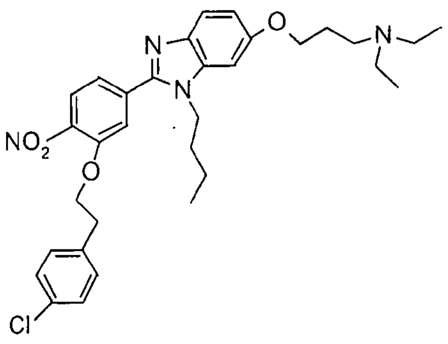
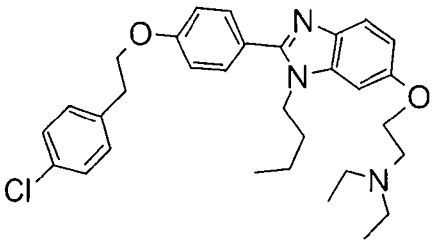
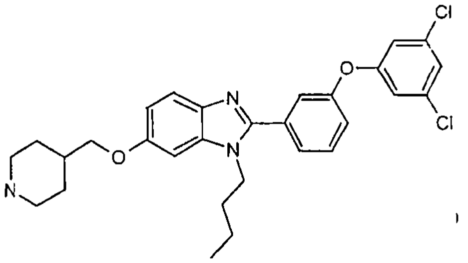
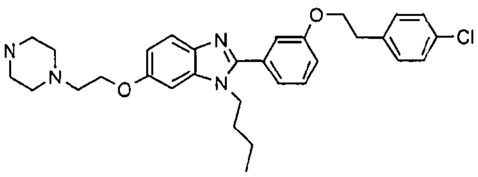
Ex.	Structure	Name
12		1-butyl-2-(3-phenoxy-phenyl)-6-(2-piperazin-1-yl-ethoxy)-1H-benzoimidazole
13		1-butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-6-(2-piperidin-1-yl-ethoxy)-1H-benzimidazole
14		1-butyl-2-[3-(3,4-dichloro-phenoxy)-phenyl]-6-(2-piperidin-1-yl-ethoxy)-1H-benzimidazole
15		1-butyl-6-[2-(4-chloro-phenyl)-ethoxy]-2-[4-(2-pyrrolidin-1-yl-ethoxy)-pheny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

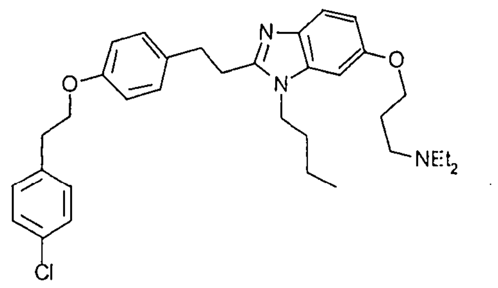
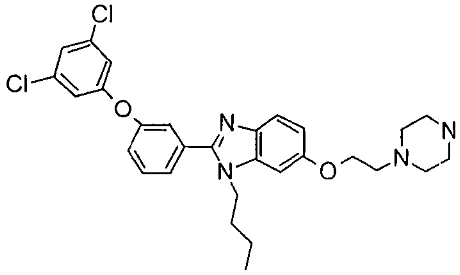
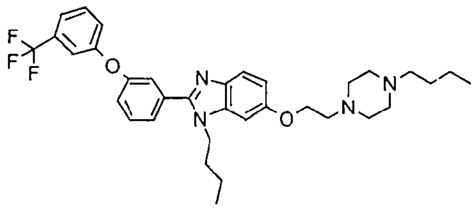
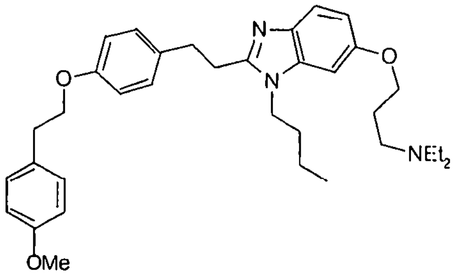
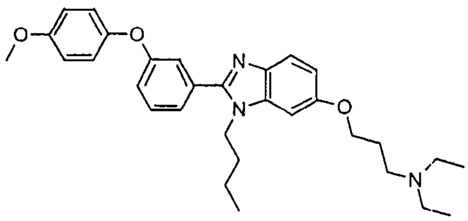
Ex.	Structure	Name
17		1-butyl-2-(4-tert-butyl-phenyl)-6-(2-piperazin-1-yl-ethoxy)-1H-benzoimidazole
18		dibutyl-{4-[1-butyl-6-(3-diethylamino-propoxy)-1H-benzimidazol-2-yl]-phenyl}-amine
19		(2-{3-butyl-2-[3-(3,5-dichloro-phenoxy)-phenyl]-3H-benzoimidazol-5-yloxy}-ethyl)-diisopropyl-amine
20		{3-[3-butyl-2-(4-tert-butyl-phenyl)-3H-benzimidazol-5-yloxy]-propyl}-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

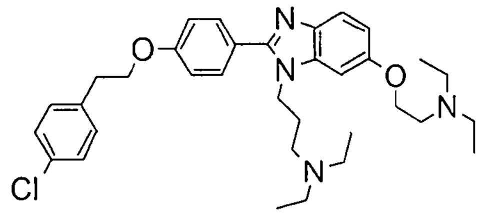
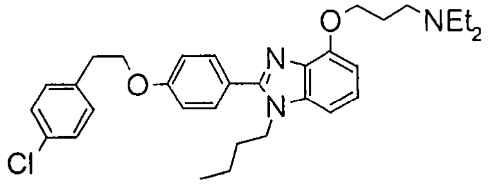
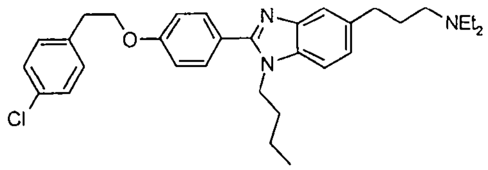
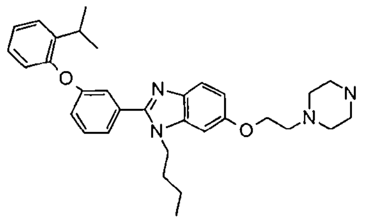
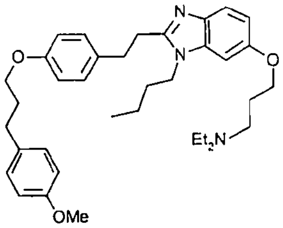
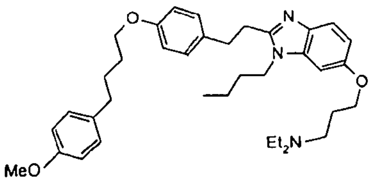
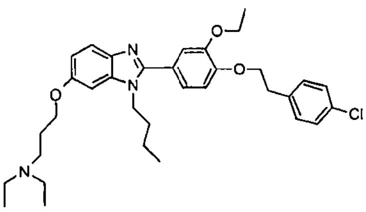
Ex.	Structure	Name
23		1-butyl-2-naphthalen-2-yl-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole
24		(2-{3-butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-3H-benzoimidazol-5-yloxy}-ethyl)-dimethyl-amine
25		2-benzofuran-2-yl-1-butyl-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole
26		1-butyl-6-(2-piperazin-1-yl-ethoxy)-2-[3-(3-trifluoromethyl-phenoxy)-phenyl]-1H-benzimidazo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

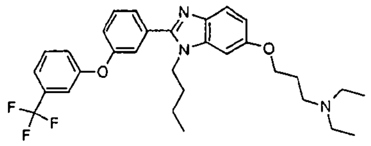
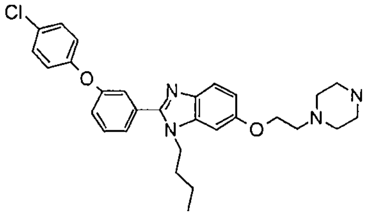
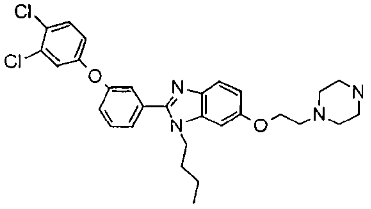
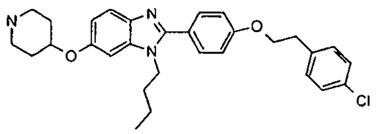
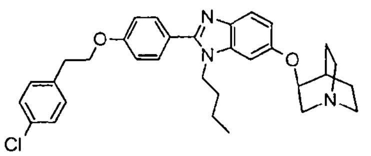
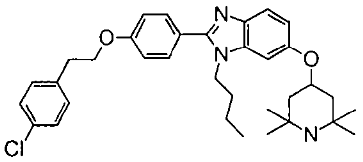
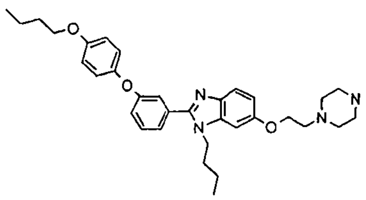
Ex.	Structure	Name
29		{3-[3-Butyl-2-(4-isopropoxy-phenyl)-3H-benzoimidazol-5-yloxy]-propyl}-diethyl-amine
30		1-Butyl-6-(2-piperazin-1-yl-ethoxy)-2-[3-(4,4,4-trifluoro-butoxy)-phenyl]-1H-benzoimidazole
31		{3-[3-Butyl-2-(2,4,4-trimethyl-pentyl)-3H-benzoimidazol-5-yloxy]-propyl}-diethyl-amine
32		Diethyl-{2-[2-piperidin-3-yl-3-(4-pyrrolidin-1-yl-butyl)-3H-benzoi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

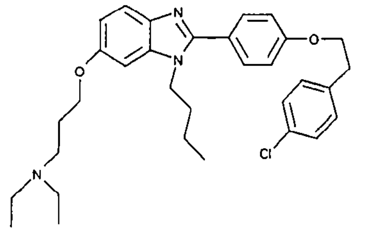
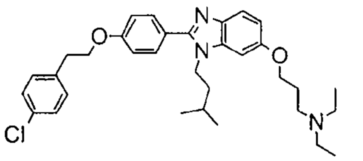
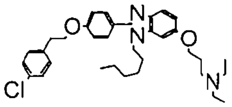
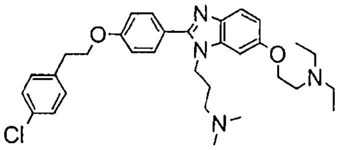
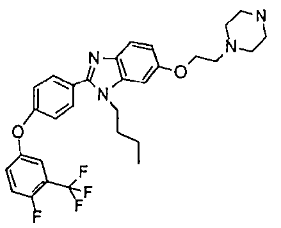
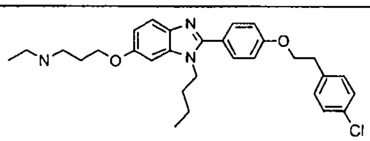
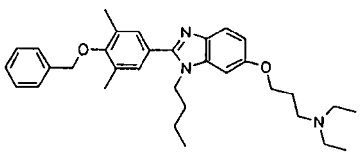
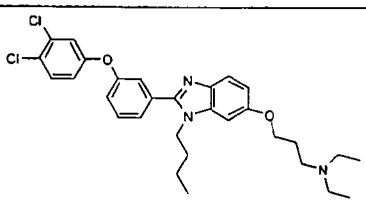
Ex.	Structure	Name
34		{3-[1-Butyl-6-(3-diethylamino-propoxy)-2-piperidin-4-yl-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine
35		{3-[3-butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-7-(2-pyrrolidin-1-yl-ethoxy)-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
36		1-Butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazole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

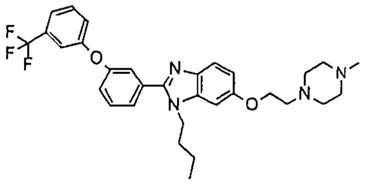
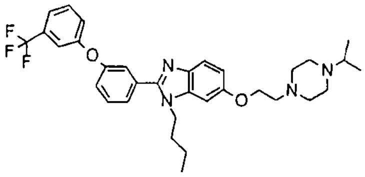
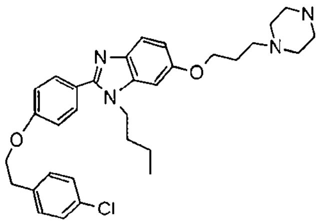
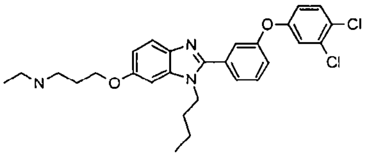
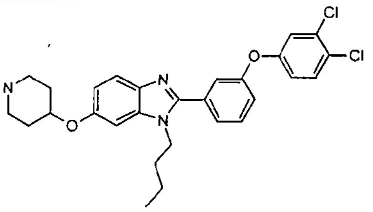
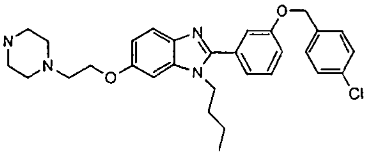
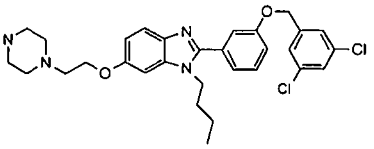
Ex.	Structure	Name
39		1-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole
40		[3-(3-butyl-2-{3-[2-(4-chloro-phenyl)-ethoxy]-4-nitro-phenyl}-3H-benzimidazol-5-yloxy)-propyl]-diethyl-amine
41		[2-(3-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-3H-benzimidazol-5-yloxy)-ethyl]-diethyl-amine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

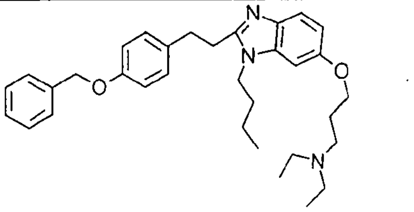
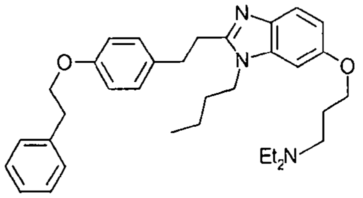
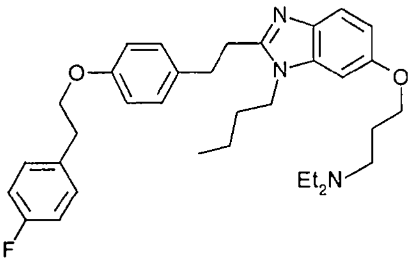
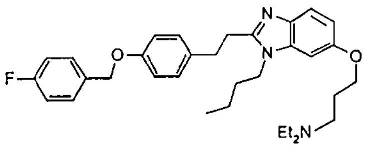
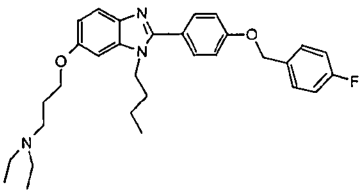
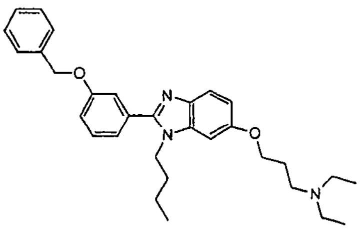
Ex.	Structure	Name
44		{3-[3-butyl-2-(2-{4-[2-(4-chlorophenyl)-ethoxy]-phenyl}-ethyl)-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
45		1-butyl-2-[3-(3,5-dichloro-phenoxy)-phenyl]-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole
46		1-butyl-6-[2-(4-butyl-piperazin-1-yl)-ethoxy]-2-[3-(3-trifluoromethyl-phenoxy)-phenyl]-1H-benzimidazole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

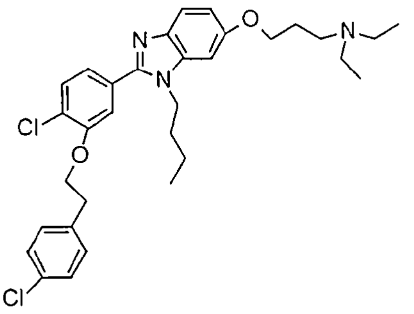
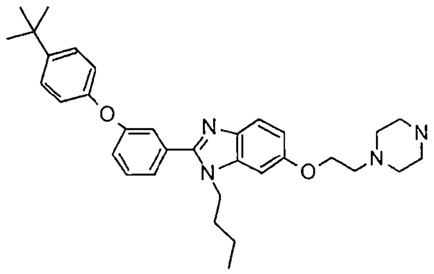
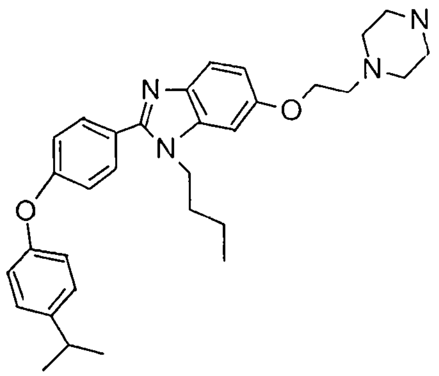
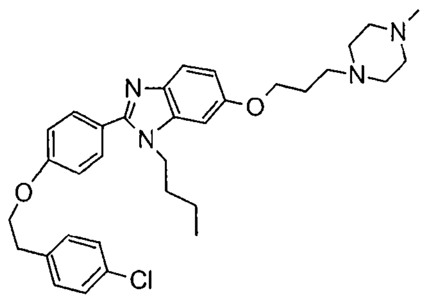
Ex.	Structure	Name
49		{3-[2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-(2-diethylamino-ethoxy)-benzimidazol-1-yl]-propyl}-diethyl-amine
50		[3-(1-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-1H-benzimidazol-4-yloxy)-propyl]-diethyl-amine
51		[3-(1-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-1H-benzimidazol-5-yl)-propyl]-diethyl-amine
52		1-butyl-2-[3-(2-isopropyl-phenoxy)-phenyl]-6-(2-piperazin-1-yl-ethoxy)-1H-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

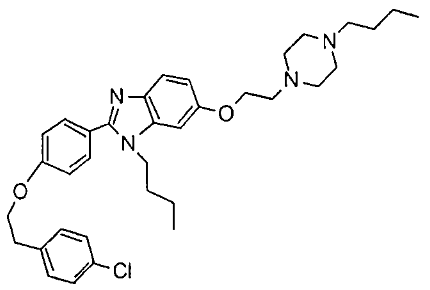
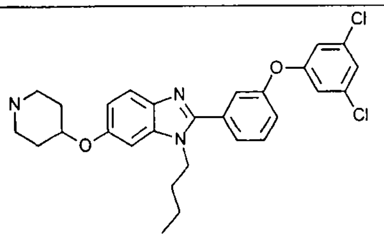
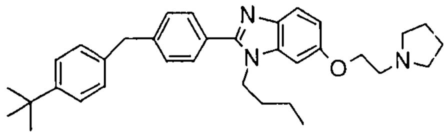
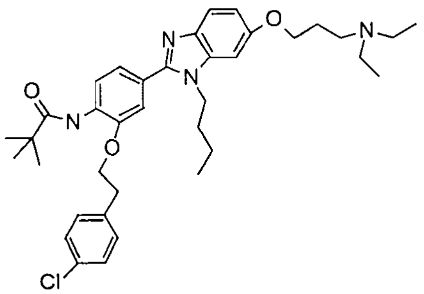
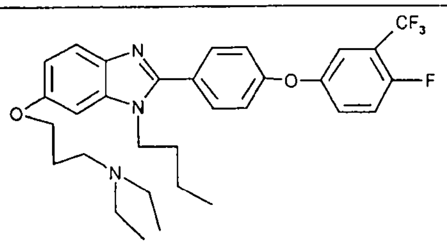
Ex.	Structure	Name
56		(3-{3-butyl-2-[3-(3-trifluoromethyl-phenoxy)-phenyl]-3H-benzimidazol-5-yloxy}-propyl)-diethyl-amine
57		1-butyl-2-[3-(4-chloro-phenoxy)-phenyl]-6-(2-piperazin-1-yl-ethoxy)-1H-benzoimidazole
58		1-butyl-2-[3-(3,4-dichloro-phenoxy)-phenyl]-6-(2-piperazin-1-yl-ethoxy)-1H-benzoimidazole
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

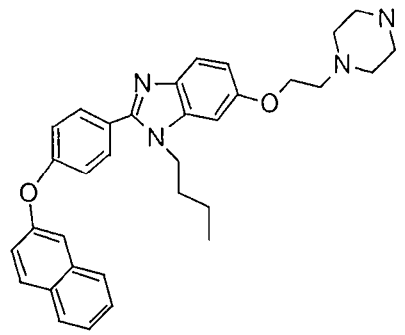
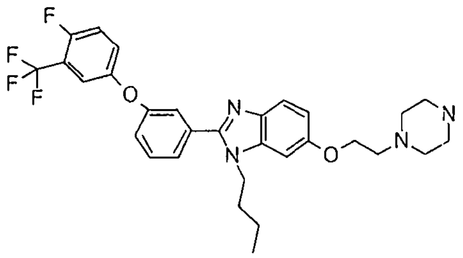
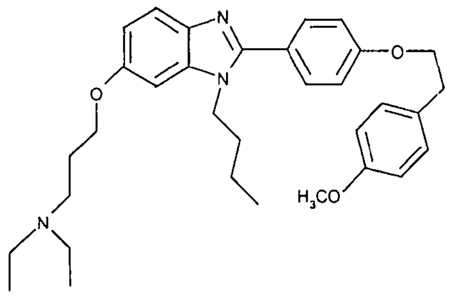
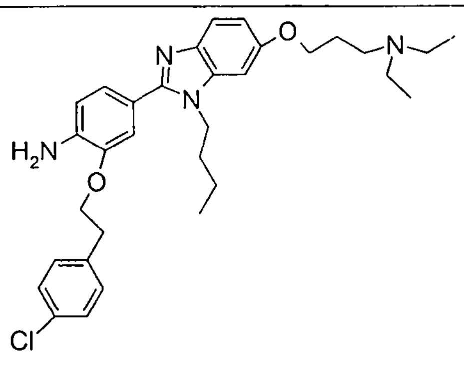
Ex.	Structure	Name
63		[3-(3-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-3H-benzimidazol-5-yloxy)-propyl]-diethyl-amine
64		{3-[2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-3-(3-methyl-butyl)-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
65		[3-(2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-3-hexyl-3H-benzimidazol-5-yloxy)-propyl]-diethyl-amine
66		{3-[2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-(2-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

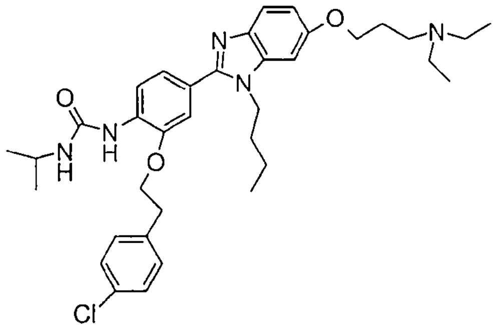
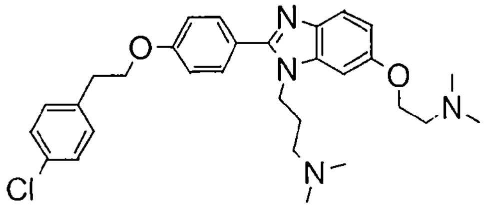
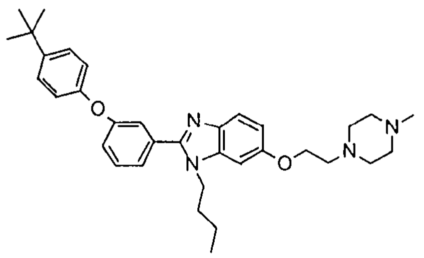
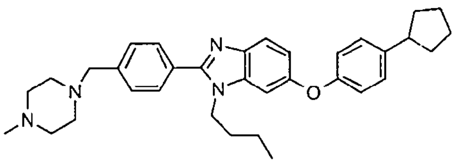
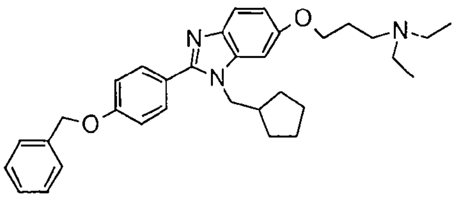
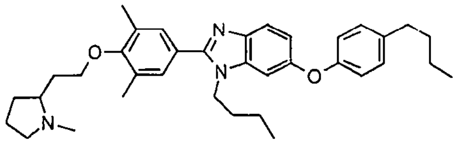
Ex.	Structure	Name
71		1-butyl-6-[2-(4-methyl-piperazin-1-yl)-ethoxy]-2-[3-(3-trifluoromethyl-phenoxy)-phenyl]-1H-benzimidazole
72		1-butyl-6-[2-(4-isopropyl-piperazin-1-yl)-ethoxy]-2-[3-(3-trifluoromethyl-phenoxy)-phenyl]-1H-benzoimidazole
73		1-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-(3-piperazin-1-yl-propoxy)-1H-benzoimidazole
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

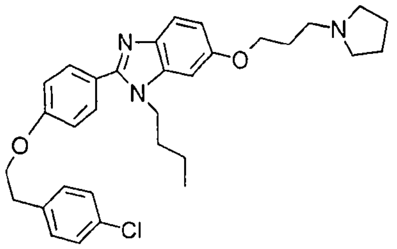
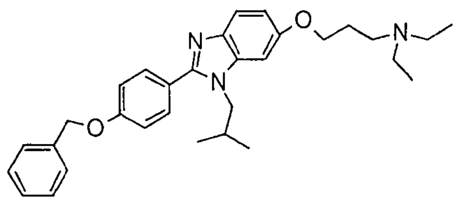
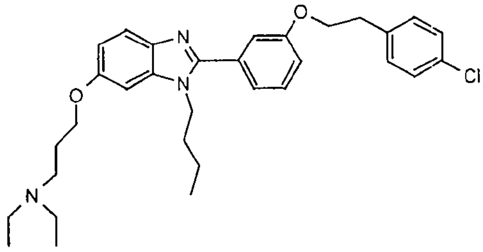
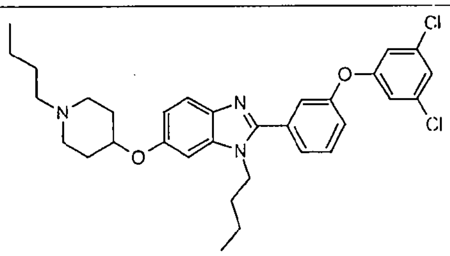
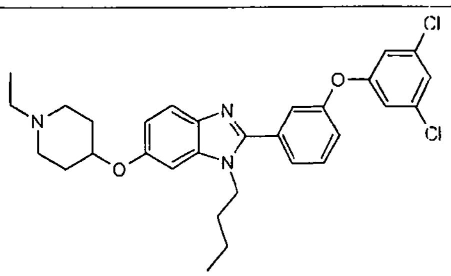
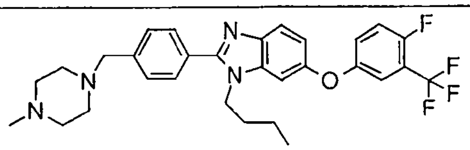
Ex.	Structure	Name
78		(3-{2-[2-(4-benzyloxy-phenyl)-ethyl]-3-butyl-3H-benzimidazol-5-yloxy}-propyl)-diethyl-amine
79		(3-{3-butyl-2-[2-(4-phenethyloxy-phenyl)-ethyl]-3H-benzimidazol-5-yloxy}-propyl)-diethyl-amine
80		{3-[3-butyl-2-(2-{4-[2-(4-fluoro-phenyl)-ethoxy]-phenyl}-ethyl)-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine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

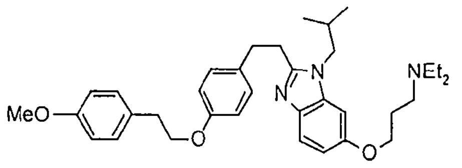
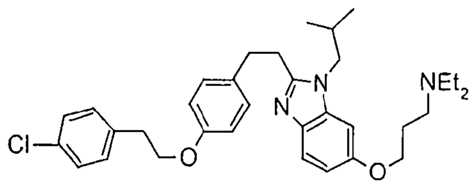
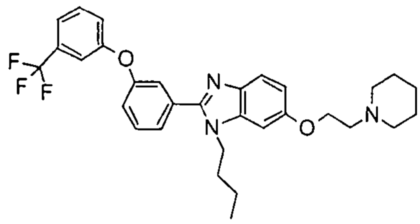
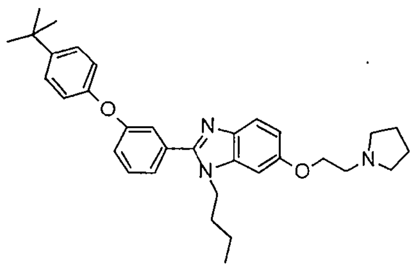
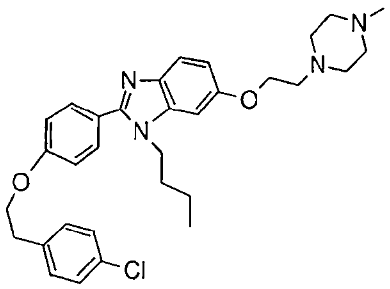
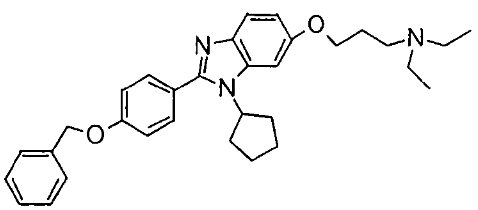
Ex.	Structure	Name
84		[3-(3-butyl-2-{4-chloro-3-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-3H-benzimidazol-5-yloxy)-propyl]-diethyl-amine
85		1-butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-6-(2-piperazin-1-yl-ethoxy)-1H-benzimidazole
86		1-butyl-2-[4-(4-isopropyl-phenoxy)-phenyl]-6-(2-piperazin-1-yl-ethoxy)-1H-benzoimidazole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

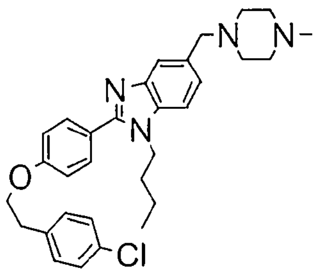
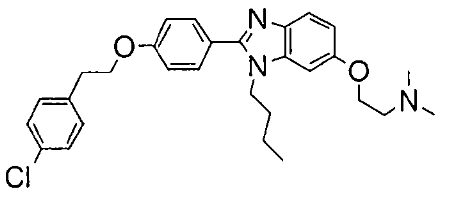
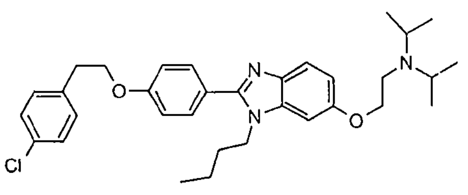
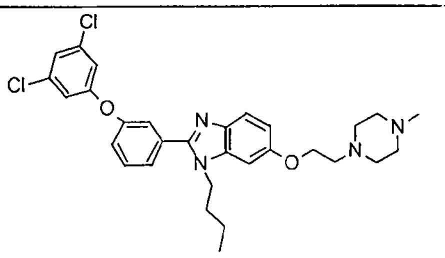
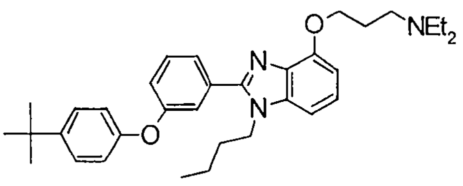
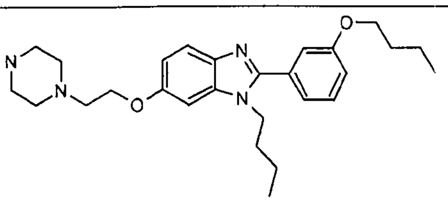
Ex.	Structure	Name
88		1-butyl-6-[2-(4-butyl-piperazin-1-yl)-ethoxy]-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-1H-benzoimidazole
89		1-butyl-2-[3-(3,4-dimethoxy-phenoxy)-phenyl]-6-(2-piperazin-1-yl-ethoxy)-1H-benzoimidazole
90		1-butyl-2-[4-(4-tert-butyl-benzyl)-phenyl]-6-(2-piperazin-1-yl-ethoxy)-1H-benzoimidazole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

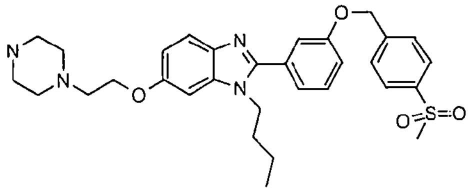
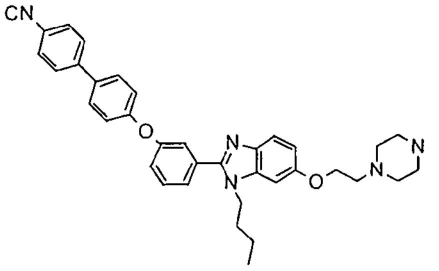
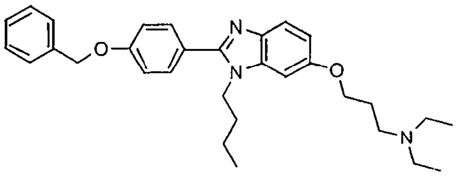
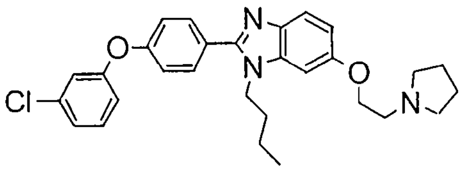
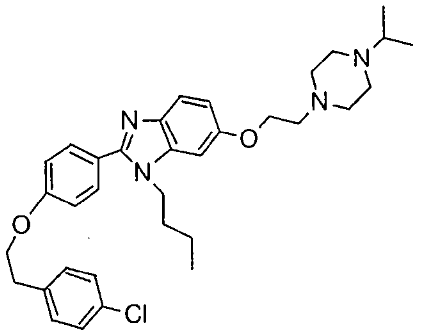
Ex.	Structure	Name
93		1-butyl-2-[4-(naphthalen-2-yloxy)-phenyl]-6-(2-piperazin-1-yl-ethoxy)-1H-benzoimidazole
94		1-butyl-2-[3-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-6-(2-piperazin-1-yl-ethoxy)-1H-benzoimidazole
95		[3-(3-butyl-2-{4-[2-(4-methoxy-phenyl)-ethoxy]-phenyl}-3H-benzimidazol-5-yloxy)-propyl]-diethyl-amine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

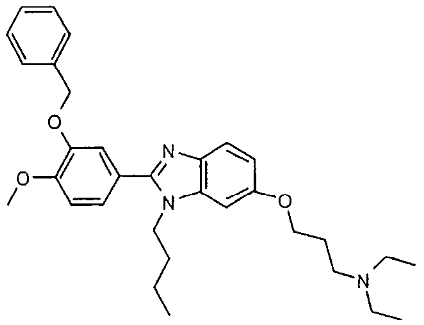
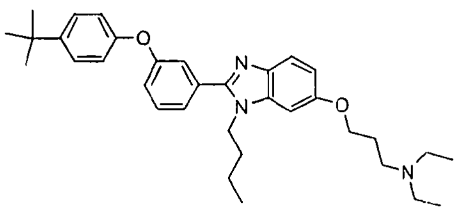
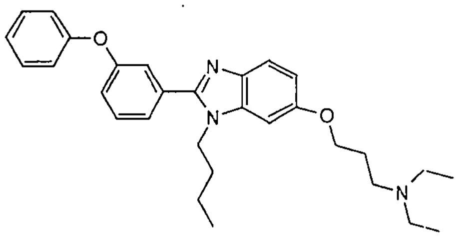
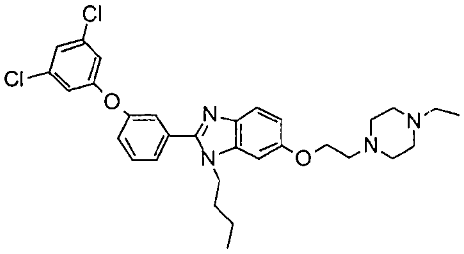
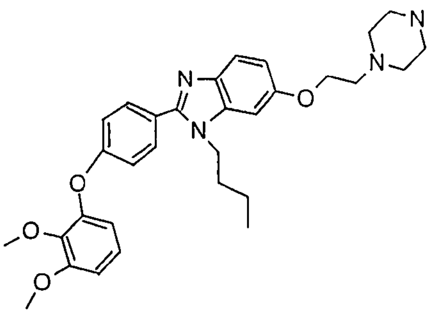
Ex.	Structure	Name
97		1-{4-[1-butyl-6-(3-diethylamino-propoxy)-1H-benzimidazol-2-yl]-2-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-3-isopropyl-urea
98		{3-[2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-(2-dimethylamino-ethoxy)-benzimidazol-1-yl]-propyl}-dimethyl-amine
99		1-butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-6-[2-(4-methyl-piperazin-1-yl)-ethoxy]-1H-benzimidazole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

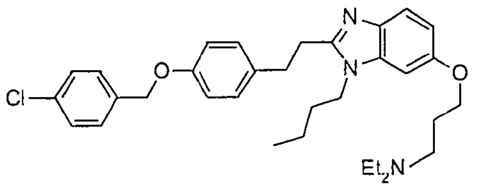
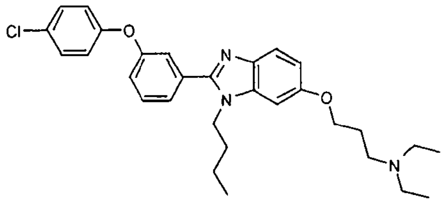
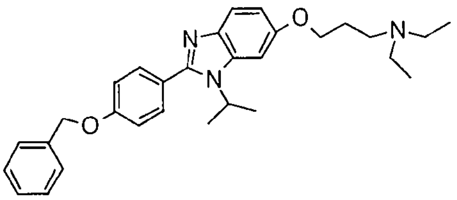
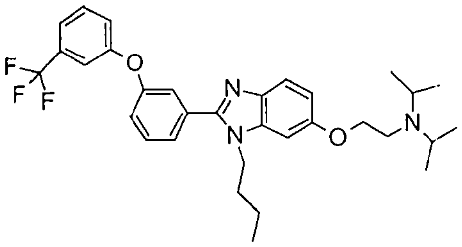
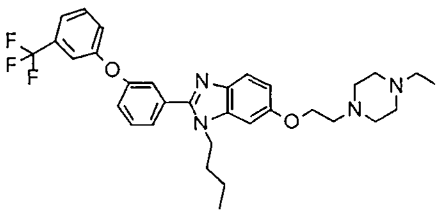
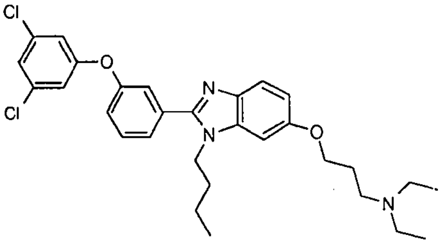
Ex.	Structure	Name
103		1-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-(3-pyrrolidin-1-yl-propoxy)-1H-benzoimidazole
104		{3-[2-(4-benzyloxy-phenyl)-3-isobutyl-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
105		[3-(3-butyl-2-{3-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-3H-benzimidazol-5-yloxy)-propyl]-diethyl-amine
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

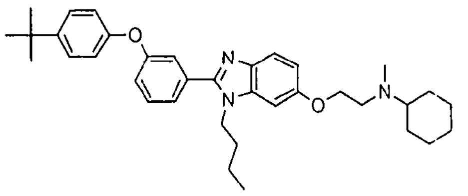
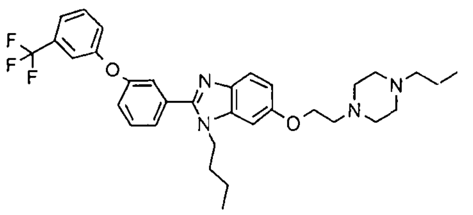
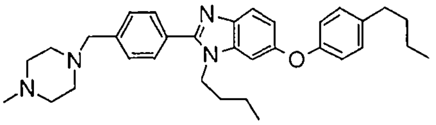
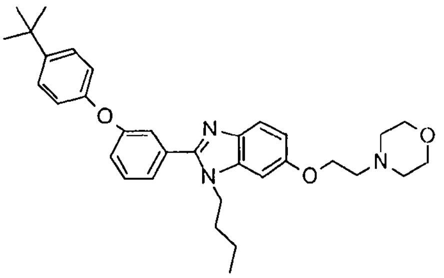
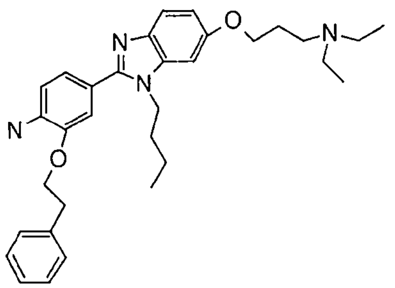
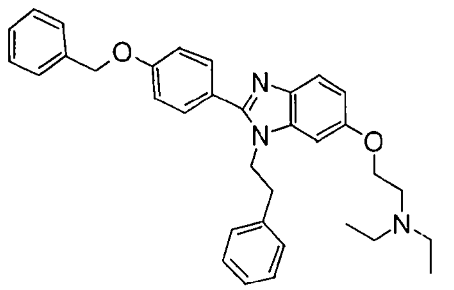
Ex.	Structure	Name
109		diethyl-{3-[3-isobutyl-2-(2-{4-[2-(4-methoxy-phenyl)-ethoxy]-phenyl}-ethyl)-3H-benzimidazol-5-yloxy]-propyl}-amine
110		{3-[2-(2-{4-[2-(4-chlorophenyl)-ethoxy]-phenyl}-ethyl)-3-isobutyl-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
111		1-butyl-6-(2-piperazin-1-yl-ethoxy)-2-[3-(3-trifluoromethyl-phenoxy)-phenyl]-1H-benzimidazole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

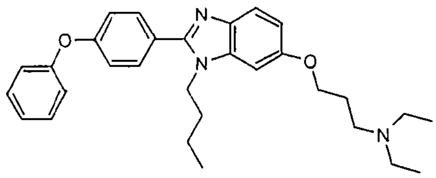
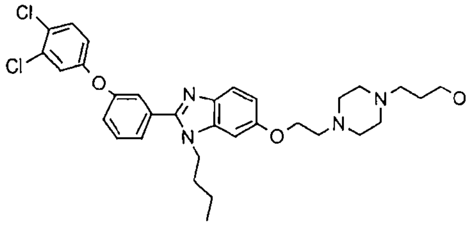
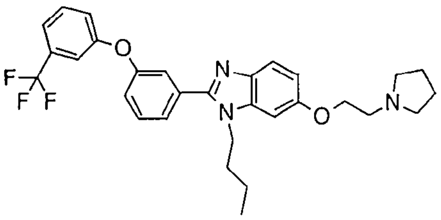
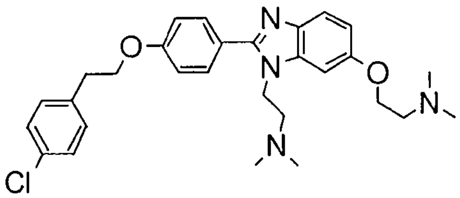
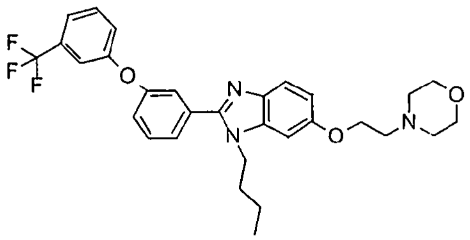
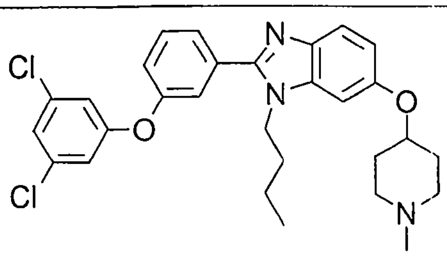
Ex.	Structure	Name
115		1-Butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-5-(4-methyl-piperazin-1-ylmethyl)-1H-benzoimidazole
116		[2-(3-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-3H-benzimidazol-5-yloxy)-ethyl]-dimethyl-amine
117		[2-(3-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-3H-benzimidazol-5-yloxy)-ethyl]-diisopropyl-amine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

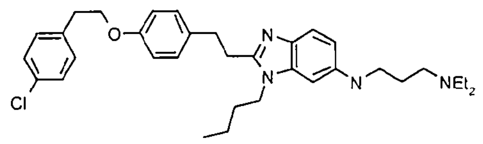
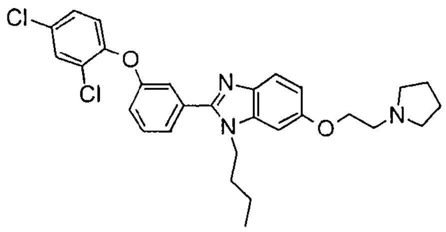
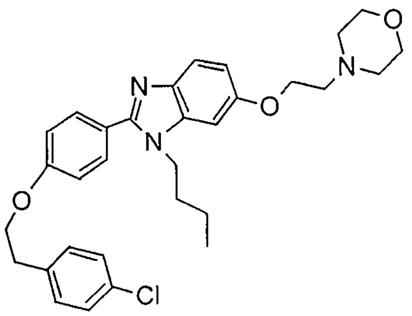
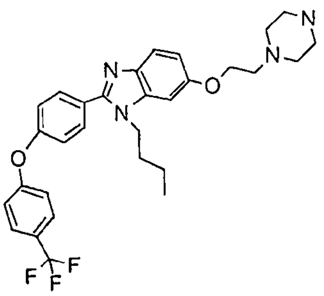
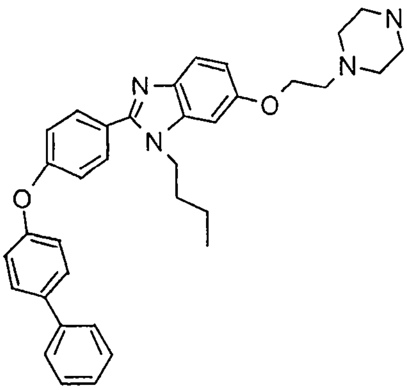
Ex.	Structure	Name
121		1-butyl-2-[3-(4-methanesulfonyl-benzyloxy)-phenyl]-6-(2-piperazin-1-yl-ethoxy)-1H-benzoimidazole
122		4'{3-[1-butyl-6-(2-piperazin-1-yl-ethoxy)-1H-benzoimidazol-2-yl]-phenoxy}-biphenyl-4-carbonitrile
123		{3-[2-(4-benzyloxy-phenyl)-3-butyl-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine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

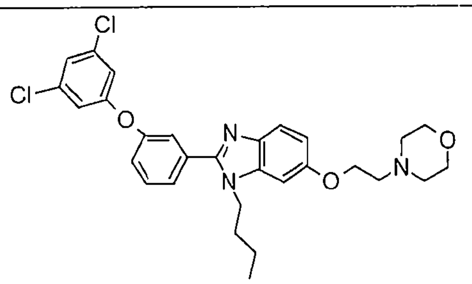
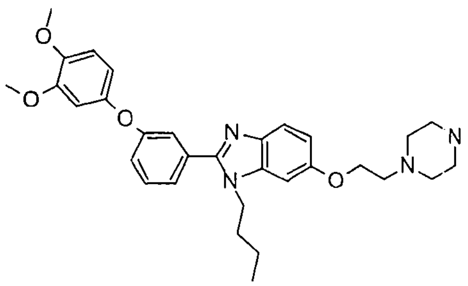
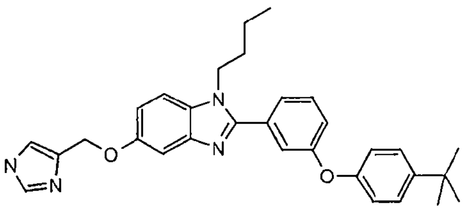
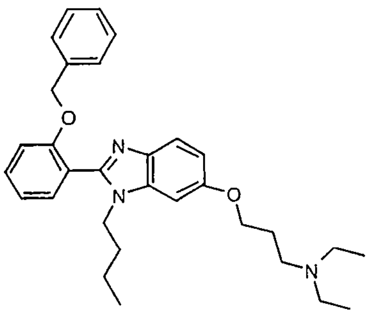
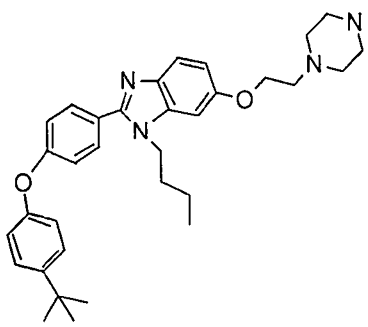
Ex.	Structure	Name
126		{3-[2-(3-benzyloxy-4-methoxy-phenyl)-3-butyl-3H-benzimidazol-5-yloxy)-propyl]-diethyl-amine
127		(3-{3-butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-3H-benzimidazol-5-yloxy}-propyl)-diethyl-amine
128		{3-[3-butyl-2-(3-phenoxy-phenyl)-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
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-benzoimidazole

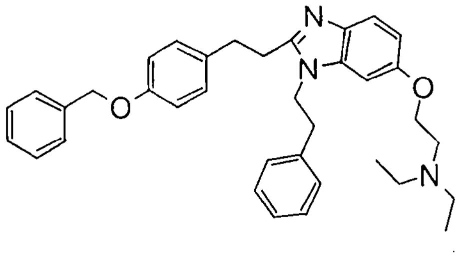
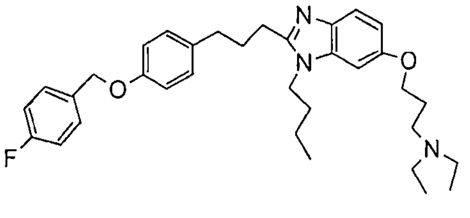
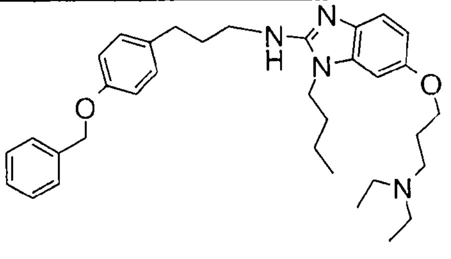
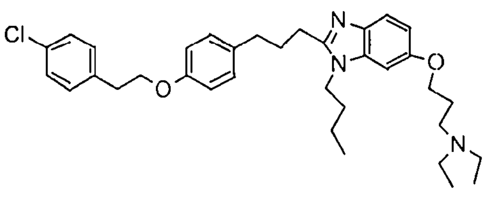
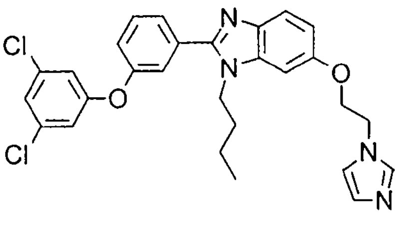
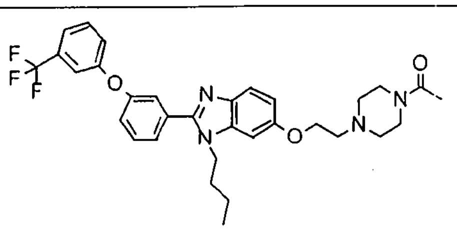
Ex.	Structure	Name
131		[3-(3-butyl-2-{2-[4-(4-chloro-benzyloxy)-phenyl]-ethyl}-3H-benzimidazol-5-yloxy)-propyl]-diethyl-amine
132		(3-{3-butyl-2-[3-(4-chloro-phenoxy)-phenyl]-3H-benzimidazol-5-yloxy}-propyl)-diethyl-amine
133		{3-[2-(4-benzyloxy-phenyl)-3-isopropyl-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
134		(2-{3-butyl-2-[3-(3-trifluoromethyl-phenoxy)-phenyl]-3H-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

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-benzoimidazole
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

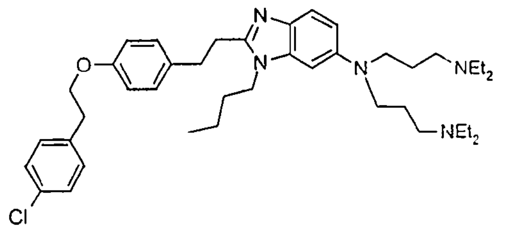
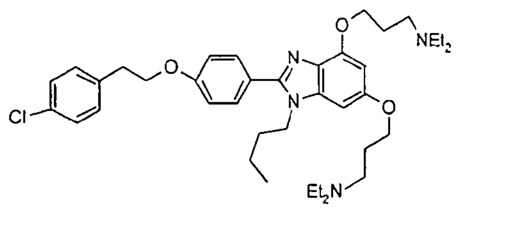
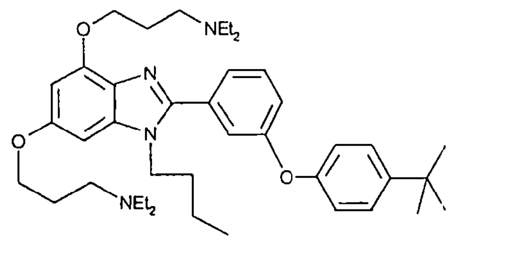
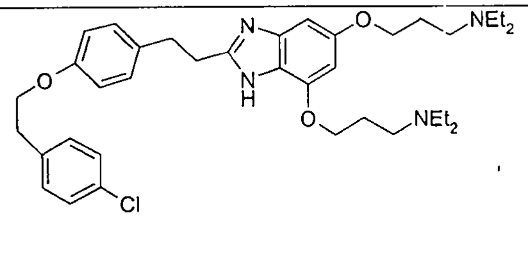
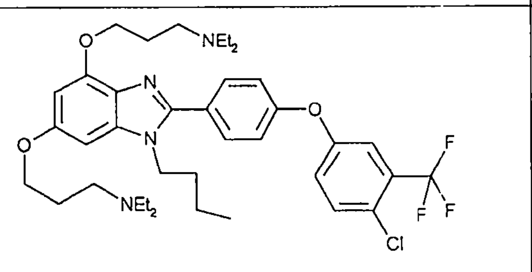
Ex.	Structure	Name
143		{3-[3-butyl-2-(4-phenoxy-phenyl)-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
144		3-[4-(2-{3-butyl-2-[3-(3,4-dichloro-phenoxy)-phenyl]-3H-benzimidazol-5-yloxy}-ethyl)-piperazin-1-yl]-propan-1-ol
145		1-butyl-6-(2-pyrrolidin-1-yl-ethoxy)-2-[3-(3-trifluoromethyl-phenoxy)-phenyl]-1H-benzimidazole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

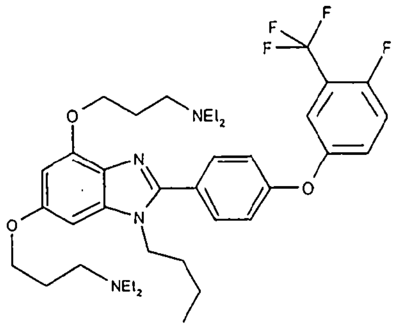
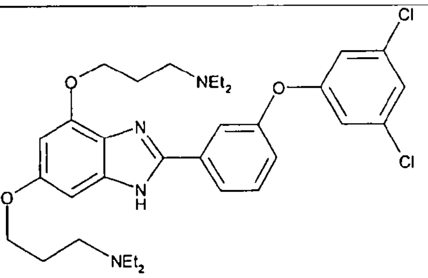
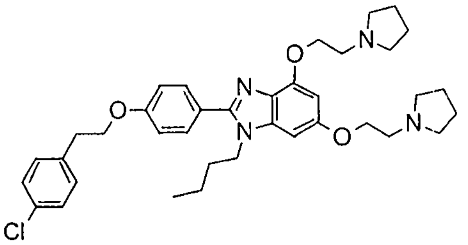
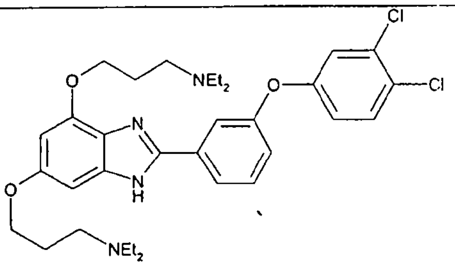
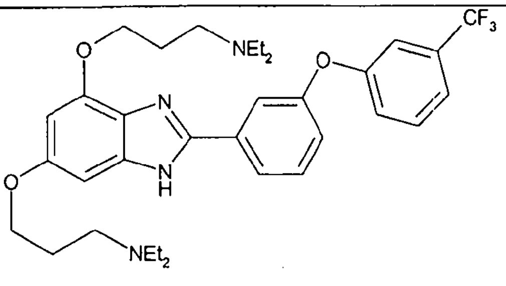
Ex.	Structure	Name
149		N'-[3-butyl-2-(2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-ethyl)-3H-benzimidazol-5-yl]-N,N-diethyl-propane-1,3-diamine
150		1-butyl-2-[3-(2,4-dichloro-phenoxy)-phenyl]-6-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazole
151		1-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-(2-morpholin-4-yl-ethoxy)-1H-benzimidazole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

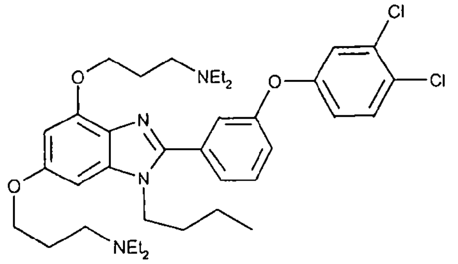
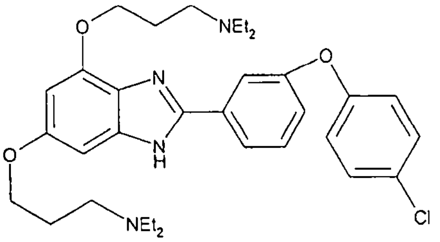
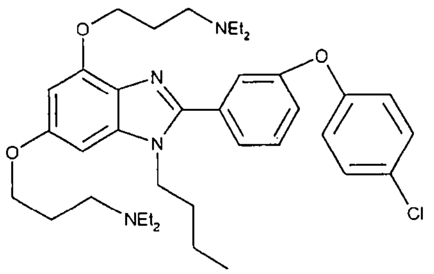
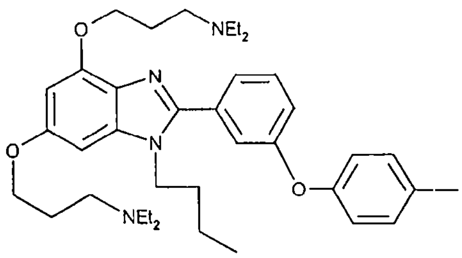
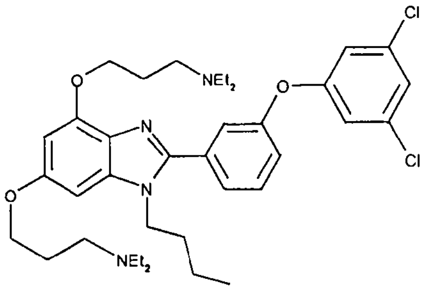
Ex.	Structure	Name
154		1-butyl-2-[3-(3,5-dichloro-phenoxy)-phenyl]-6-(2-morpholin-4-yl-ethoxy)-1H-benzimidazole
155		1-butyl-2-[3-(3,4-dimethoxy-phenoxy)-phenyl]-6-(2-piperazin-1-yl-ethoxy)-1H-benzoimidazole
156		1-butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-5-(1H-imidazol-4-ylmethoxy)-1H-benzoimidazole
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-benzoimidazol-4-yloxy]-propyl}-diethyl-amine

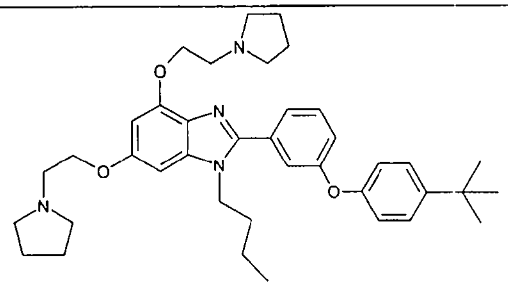
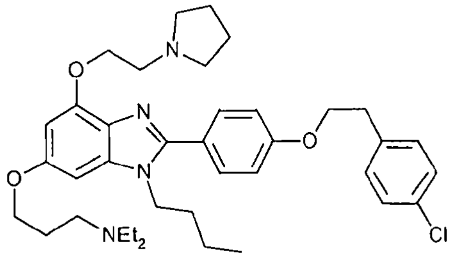
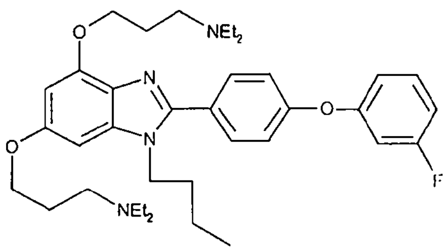
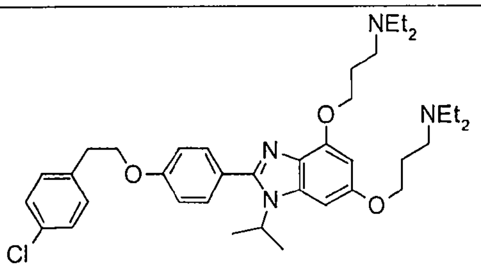
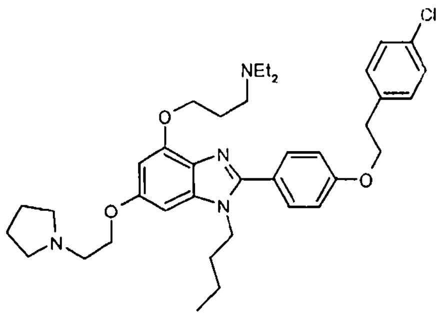
Ex.	Structure	Name
159		(2-{2-[2-(4-Benzyloxy-phenyl)-ethyl]-3-phenethyl-3H-benzoimidazol-5-yloxy}-ethyl)-diethyl-amine
160		[3-(3-Butyl-2-{3-[4-(4-fluoro-benzyloxy)-phenyl]-propyl}-3H-benzoimidazol-5-yloxy)-propyl]-diethyl-amine
161		[3-(4-Benzyloxy-phenyl)-propyl]-[1-butyl-6-(3-diethylamino-propoxy)-1H-benzoimidazol-2-yl]-amine
162		{3-[3-Butyl-2-(3-{4-[2-(4-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

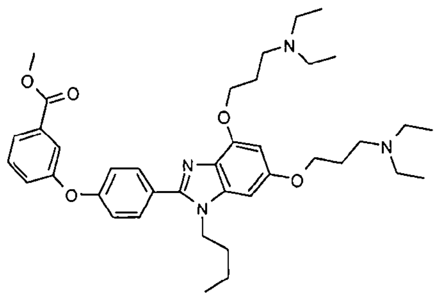
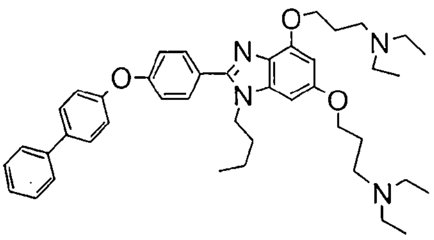
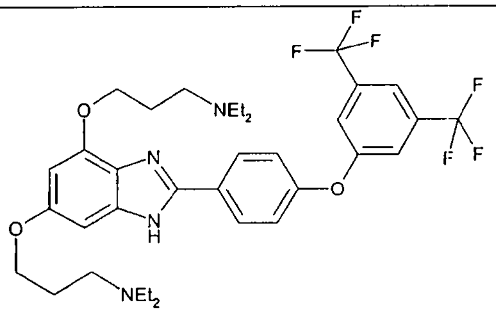
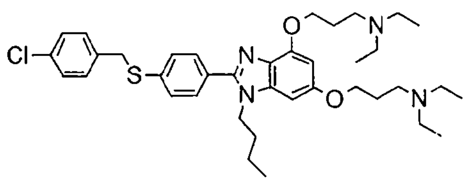
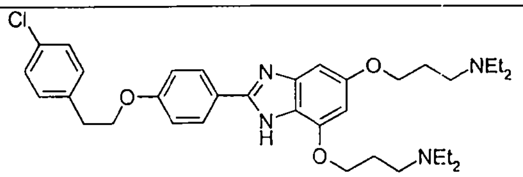
2007202350 24 May 2007

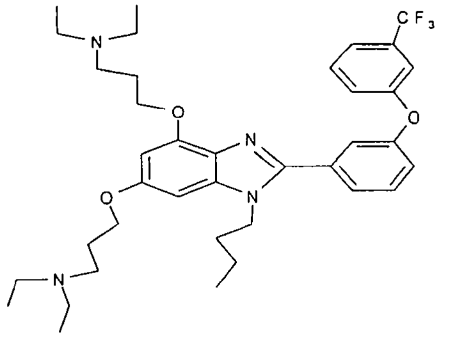
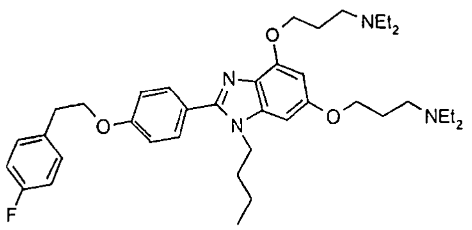
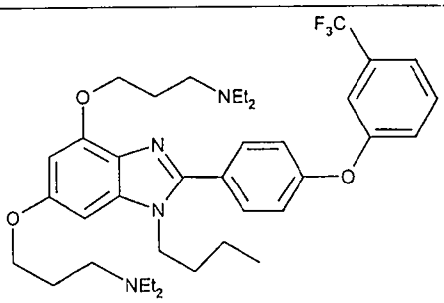
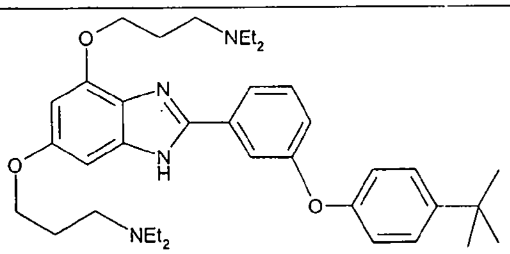
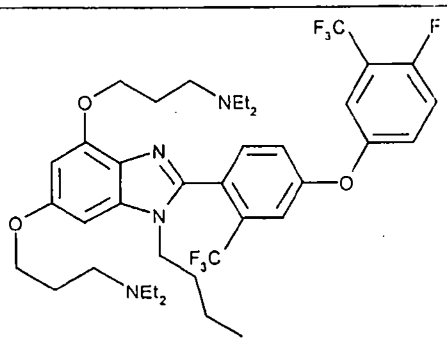
Ex.	Structure	Name
165		N-[3-Butyl-2-(2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-ethyl)-3H-benzoimidazol-5-yl]-N-(3-diethylamino-propyl)-N',N'-diethyl-propane-1,3-diamine
166		{3-[1-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yl]-propyl}-diethyl-amine
167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

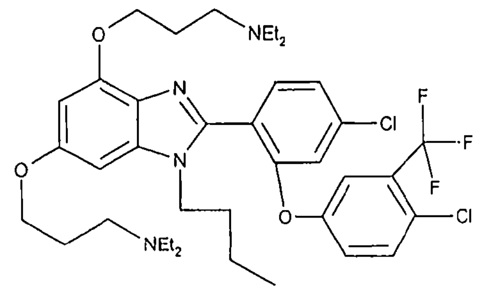
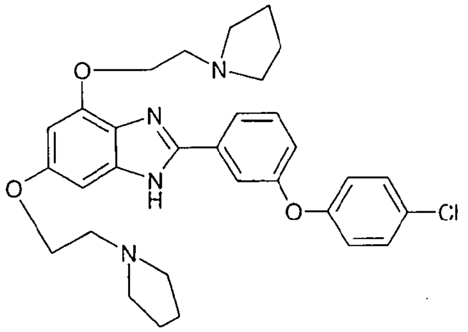
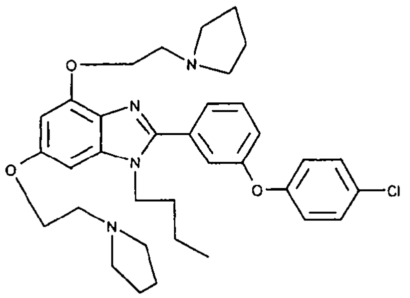
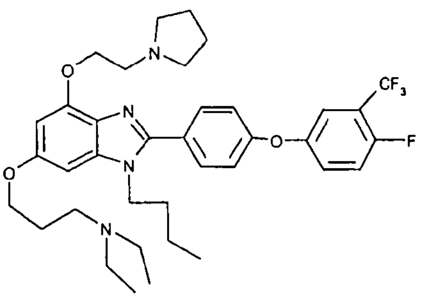
Ex.	Structure	Name
170		(3-{1-Butyl-6-(3-diethylamino-propoxy)-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-1H-benzoimidazol-4-yloxy}-propyl)-diethyl-amine
171		{3-[2-[3-(3,5-Dichloro-phenoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine
172		1-Butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-4,6-bis-(2-pyrrolidin-1-yl-e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

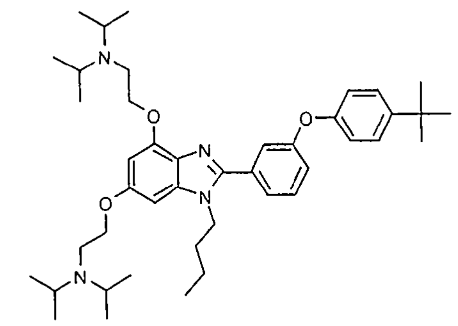
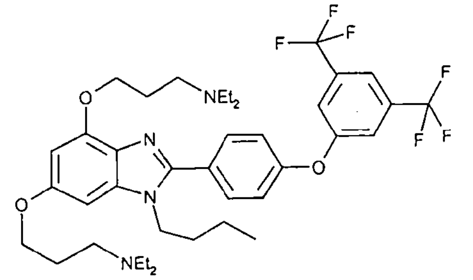
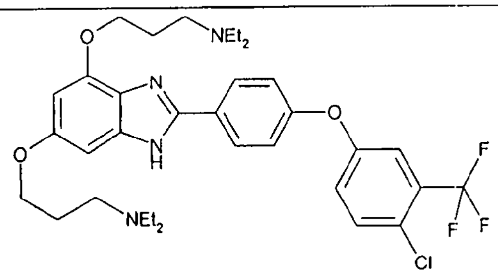
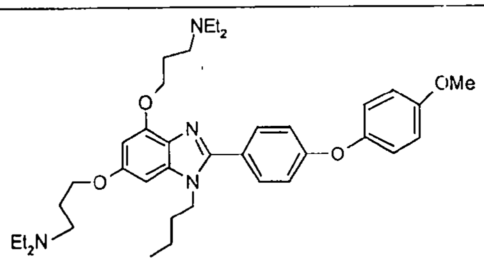
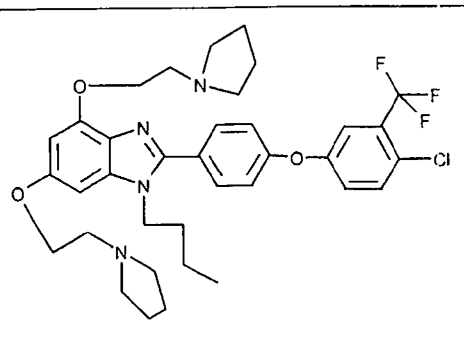
Ex.	Structure	Name
175		{3-[1-Butyl-2-[3-(3,4-dichloro-phenoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine
176		{3-[2-[3-(4-Chloro-phenoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine
177		{3-[1-Butyl-2-[3-(4-chloro-phenoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzoimidazol-4-yloxy]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

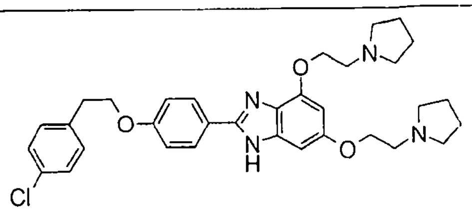
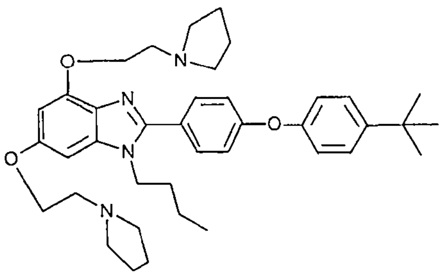
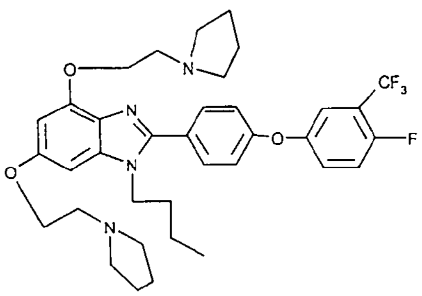
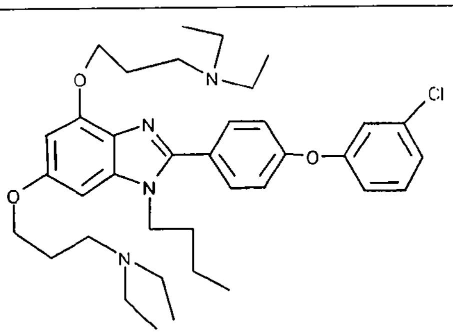
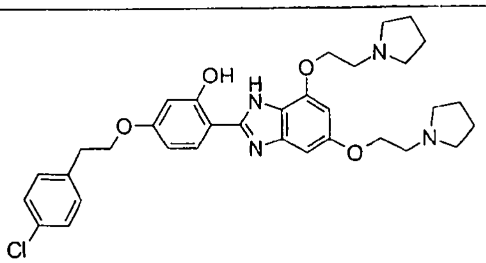
Ex.	Structure	Name
180		1-Butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazole
181		{3-[3-Butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-7-(2-pyrrolidin-1-yl-ethoxy)-3H-benzoimidazol-5-yloxy]-propyl}-diethyl-amine
182		(3-{1-butyl-6-(3-diethylamino-propoxy)-2-[4-(3-fluoro-phenoxy)-phenyl]-1H-benzimidazol-4-yloxy}-propyl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

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

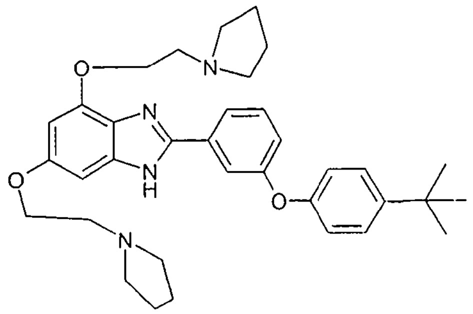
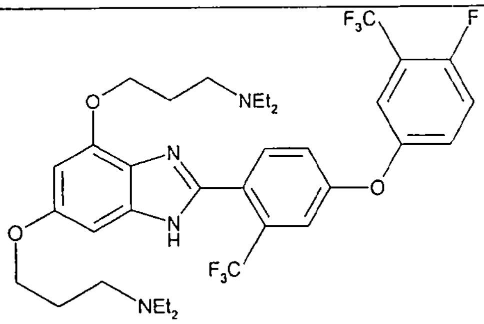
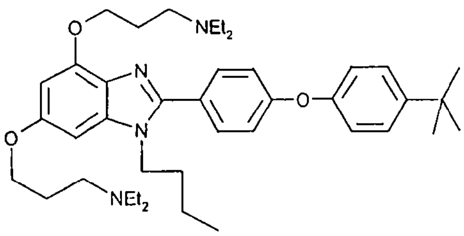
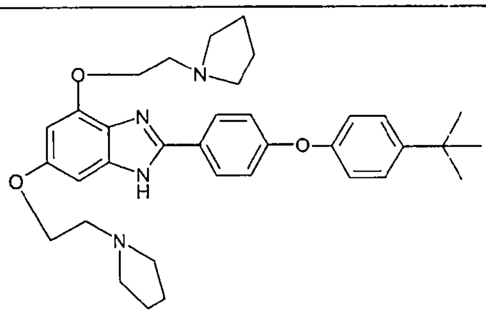
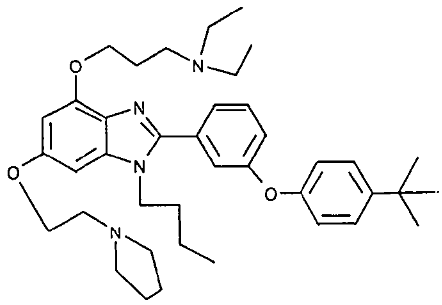
Ex.	Structure	Name
190		(3-{1-butyl-6-(3-diethylamino-propoxy)-2-[3-(3-trifluoromethyl-phenoxy)-phenyl]-1H-benzimidazol-4-yloxy}-propyl)-diethyl-amine
191		[3-(1-butyl-6-(3-diethylamino-propoxy)-2-{4-[2-(4-fluoro-phenyl)-ethoxy]-phenyl}-1H-benzimidazol-4-yloxy}-propyl)-diethyl-amine
192		(3-{1-butyl-6-(3-diethylamino-propoxy)-2-[4-(3-trifluoromethyl-phenoxy)-phe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

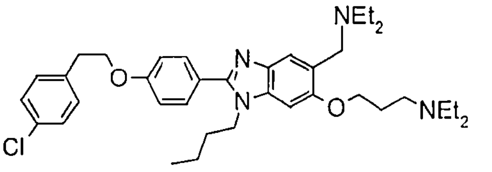
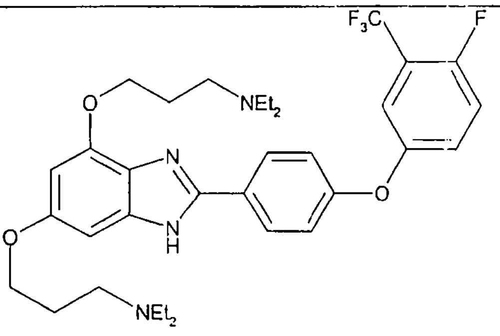
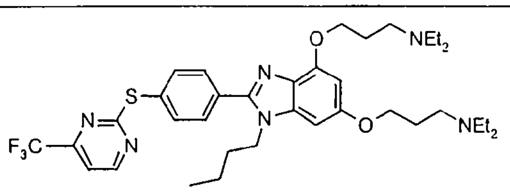
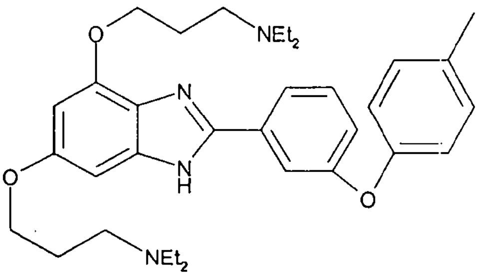
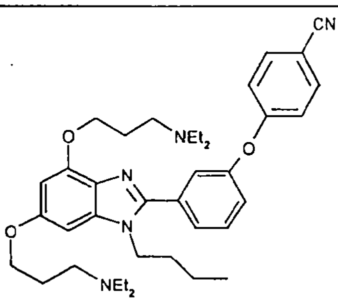
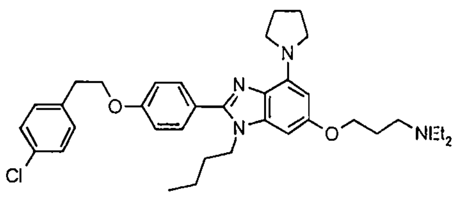
Ex.	Structure	Name
195		{3-[1-Butyl-2-[4-chloro-2-(4-chloro-3-trifluoromethyl-phenoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine
196		2-[3-(4-Chloro-phenoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazole
197		1-Butyl-2-[3-(4-chloro-phenoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazole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

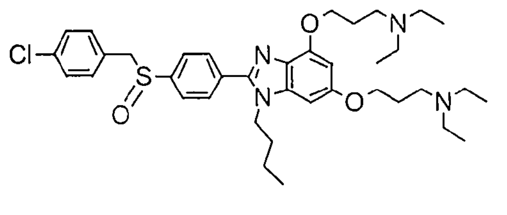
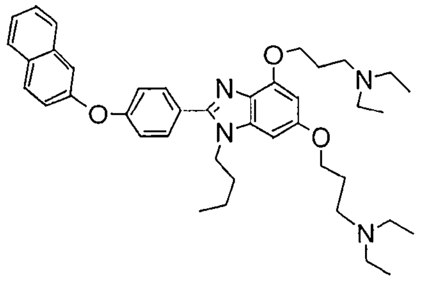
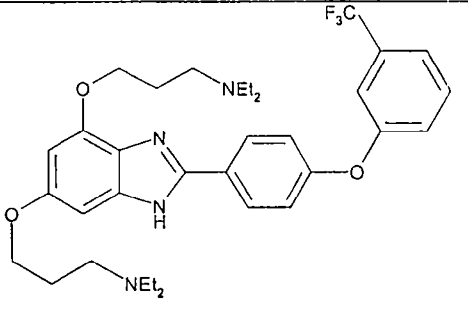
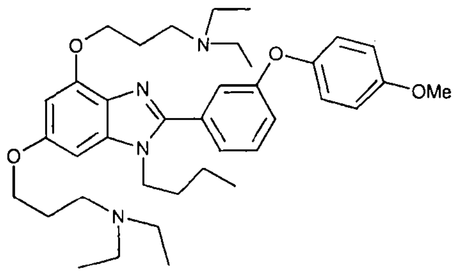
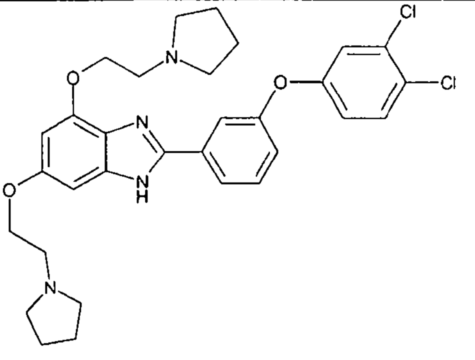
Ex.	Structure	Name
199		{2-[1-butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-6-(2-diisopropylamino-ethoxy)-1H-benzimidazol-4-yloxy]-ethyl}-diethyl-amine
200		{3-[2-[4-(3,5-Bis-trifluoromethyl-phenoxy)-phenyl]-1-butyl-6-(3-diethylamino-propoxy)-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine
201		{3-[2-[4-(3,5-Bis-trifluoromethyl-phenoxy)-phenyl]-1-butyl-6-(3-diethylamino-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

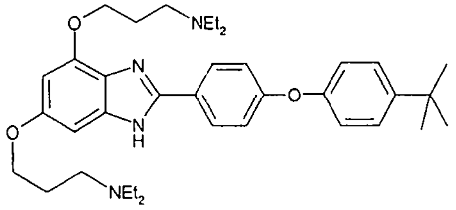
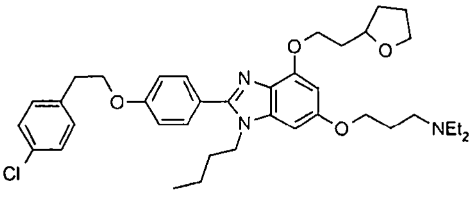
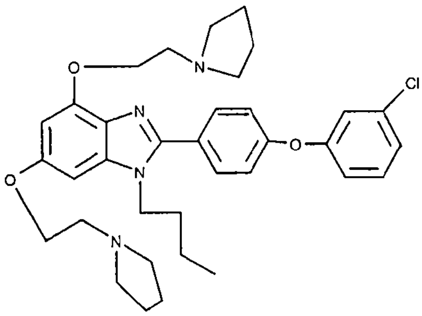
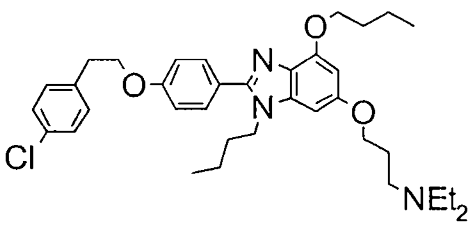
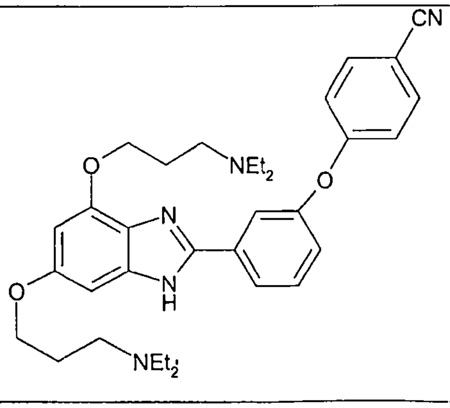
Ex.	Structure	Name
204		2-{4-[2-(4-Chloro-phenyl)-ethoxy]-phenyl}-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazole
205		1-Butyl-2-[4-(4-tert-butyl-phenoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazole
206		1-Butyl-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazole
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

2007202350 24 May 2007

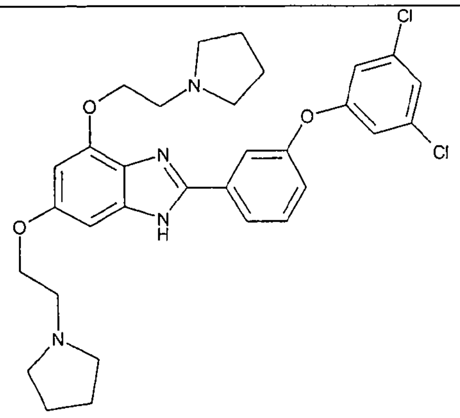
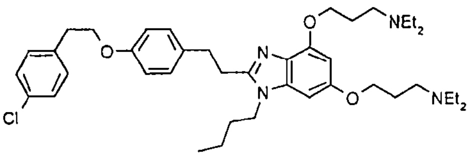
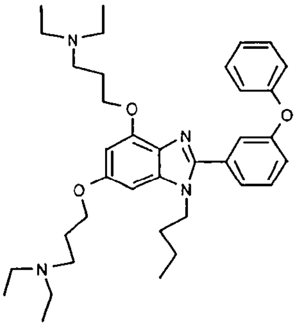
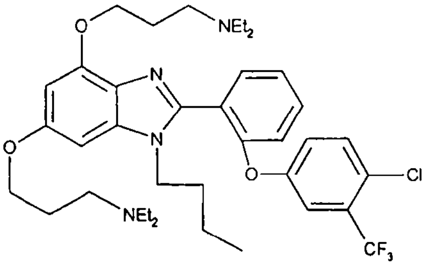
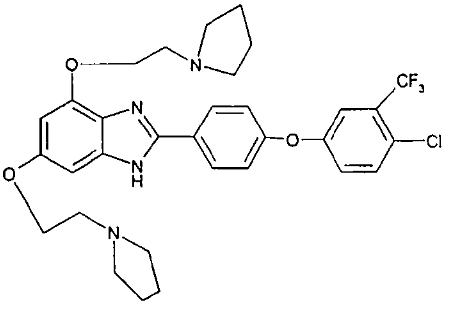
Ex.	Structure	Name
209		2-[3-(4-tert-butyl-phenoxy)-phenyl]-4,6-bis-(2-pyrrolodin-1-yl-ethoxy)-1H-benzimidazole
210		(3-{6-(3-Diethylamino-propoxy)-2-[2-(1,1-difluoro-ethyl)-4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-1H-benzoimidazol-4-yloxy}-propyl)-diethyl-amine
211		{3-[1-Butyl-2-[4-(4-tert-butyl-phenoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzoimidazo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

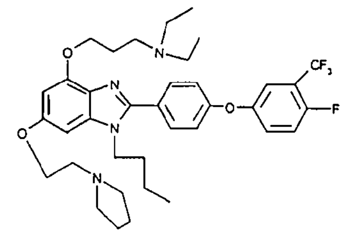
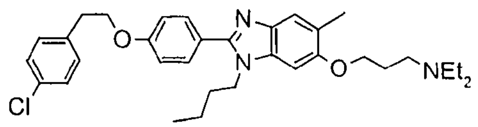
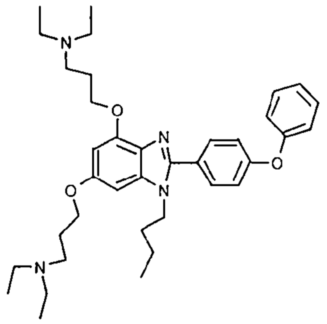
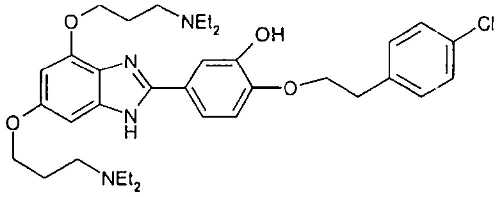
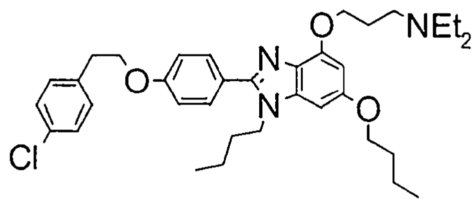
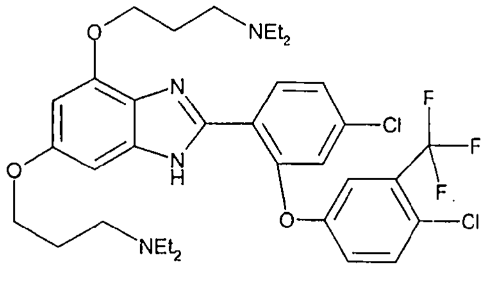
Ex.	Structure	Name
214		[3-(3-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-diethylaminomethyl-3H-benzimidazol-5-yloxy)-propyl]-diethyl-amine
215		(3-{6-(3-Diethylamino-propoxy)-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-1H-benzoimidazol-4-yloxy}-propyl)-diethyl-amine
216		(3-{1-butyl-6-(3-diethylamino-propoxy)-2-[4-(4-trifluoromethyl-pyrimidin-2-ylsulfanyl)-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

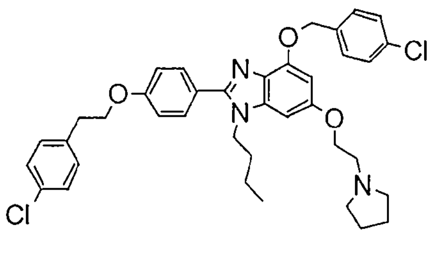
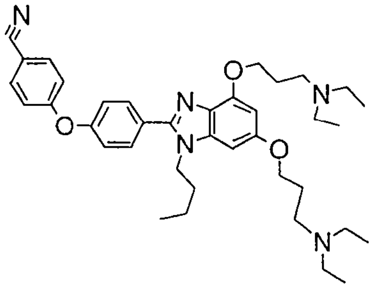
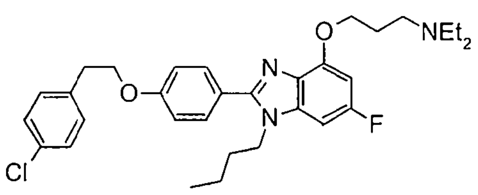
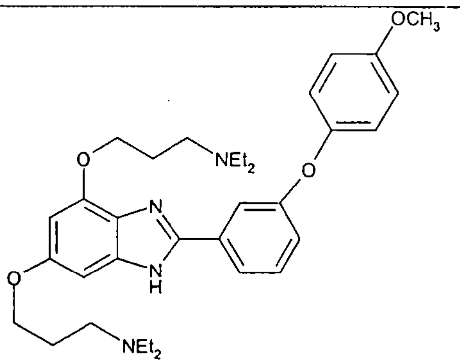
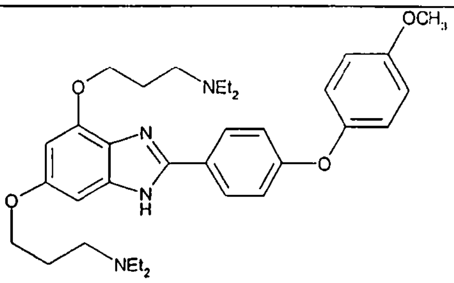
Ex.	Structure	Name
220		{3-[1-butyl-2-[4-(4-chloro-phenylmethanesulfinyl)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
221		(3-{1-butyl-6-(3-diethylamino-propoxy)-2-[4-(naphthalen-2-yloxy)-phenyl]-1H-benzoimidazole-4-yloxy}-propyl)-diethyl-amine
222		(3-{6-(3-diethylamino-propoxy)-2-[4-(3-trifluoromethyl-phenoxy)-phenyl]-1H-benzimidazol-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-benzoimidazole

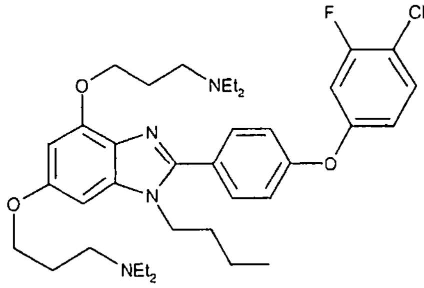
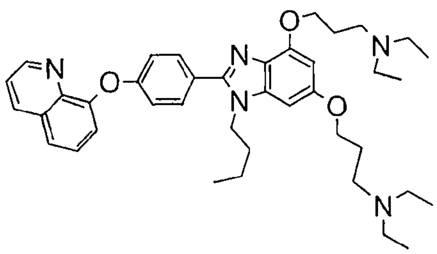
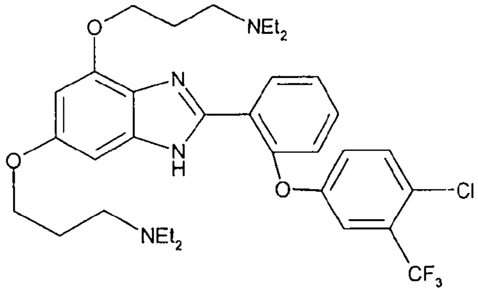
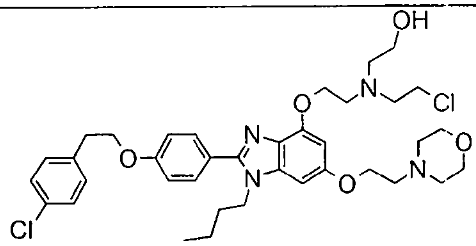
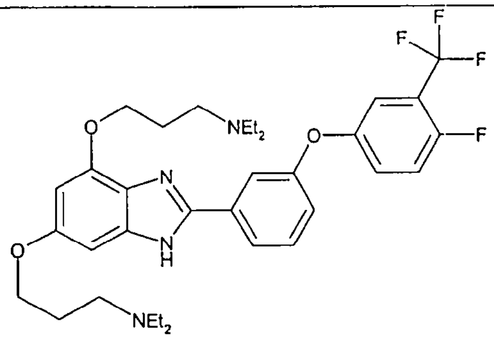
Ex.	Structure	Name
225		{3-[2-[4-(4-tert-Butyl-phenoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine
226		{3-[3-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-7-[2-(tetrahydro-furan-2-yl)-ethoxy]-3H-benzimidazol-5-yloxy}-propyl)-diethyl-amine
227		1-Butyl-2-[4-(3-chloro-phenoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H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

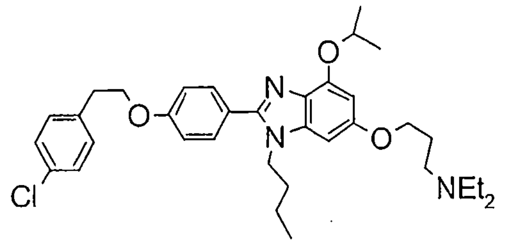
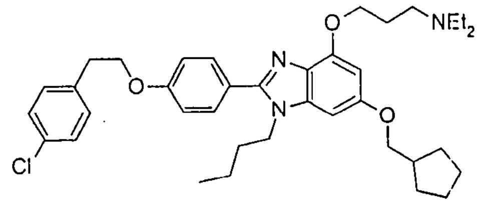
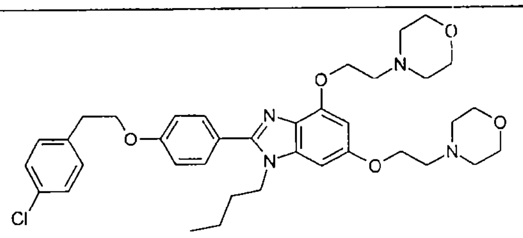
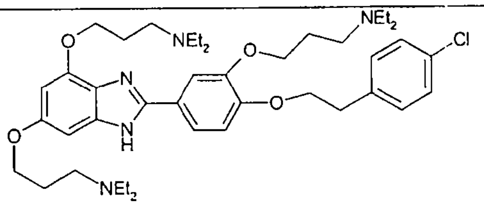
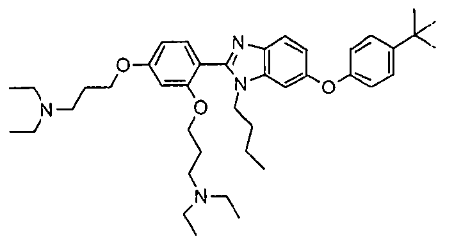
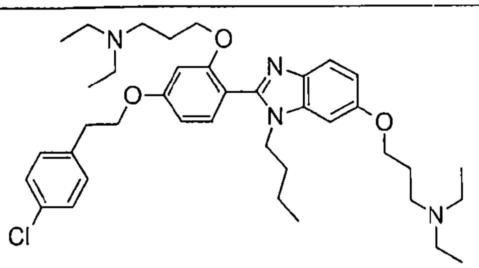
2007202350 24 May 2007

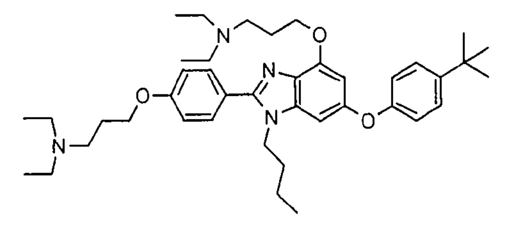
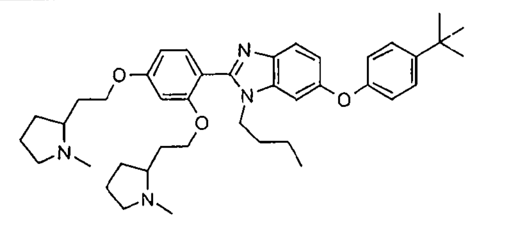
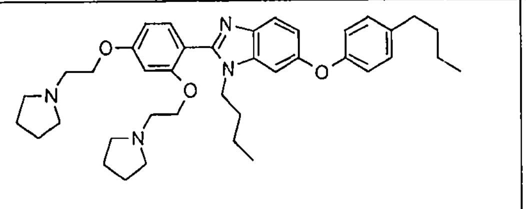
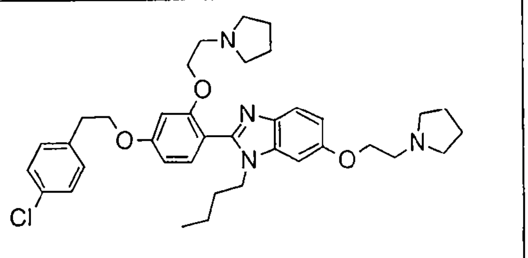
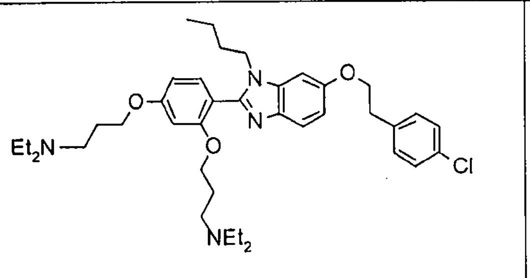
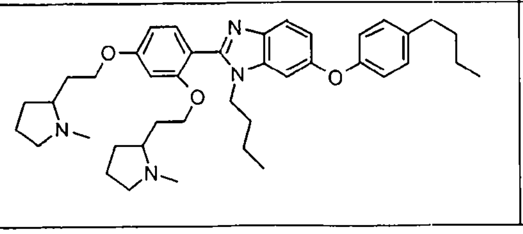
Ex.	Structure	Name
230		2-[3-(3,5-Dichloro-phenoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazole
231		{3-[1-butyl-2-(2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-ethyl)-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
232		{3-[1-butyl-6-(3-diethylamino-propoxy)-2-(3-phenoxy-phenyl)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-am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

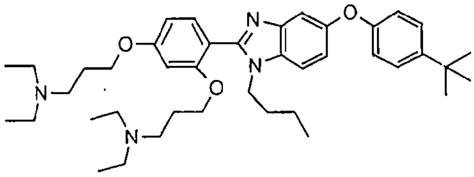
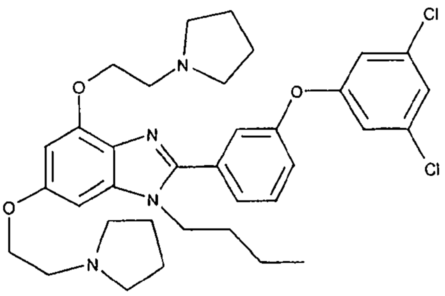
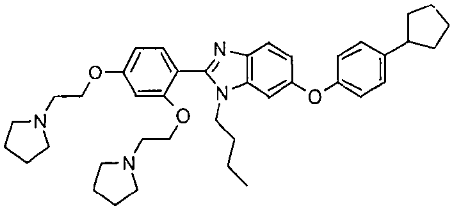
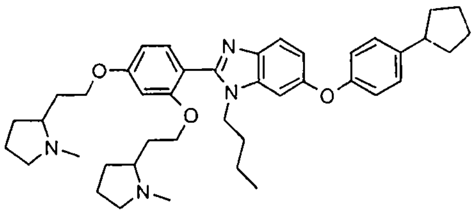
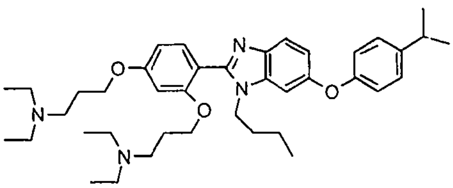
Ex.	Structure	Name
235		{3-[1-Butyl-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-6-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine
236		[3-(3-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-methyl-3H-benzimidazol-5-yloxy)-propyl]-diethyl-amine
237		{3-[1-butyl-6-(3-diethylamino-propoxy)-2-(4-phenoxy-phenyl)-1H-benzimidazol-4-ylo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

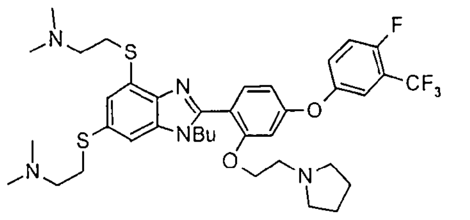
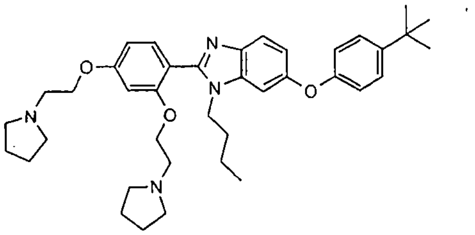
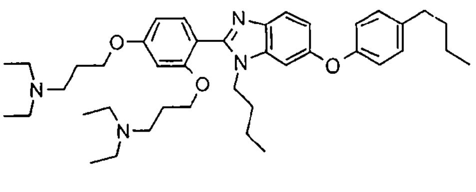
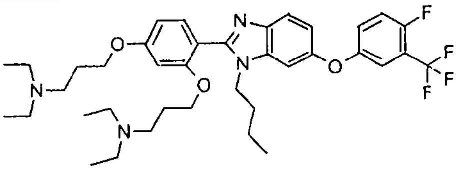
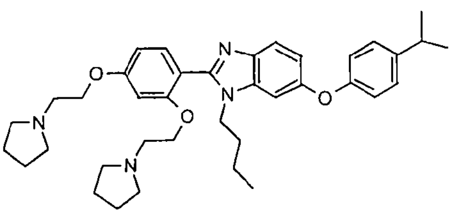
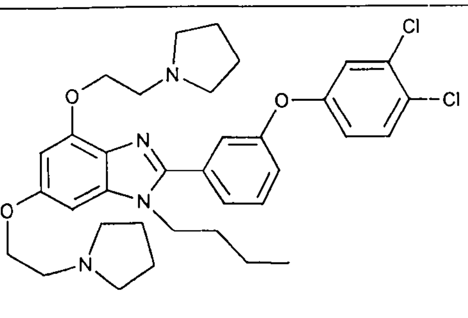
Ex.	Structure	Name
241		1-butyl-4-(4-chloro-benzyloxy)-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazole
242		4-{4-[1-butyl-4,6-bis-(3-diethylamino-propoxy)-1H-benzimidazol-2-yl]-phenoxy}-benzonitrile
243		[3-(1-Butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-fluoro-1H-benzoimidazol-4-yloxy)-propyl]-diethyl-amine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

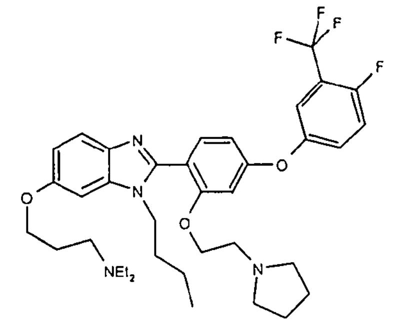
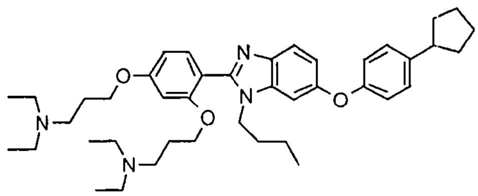
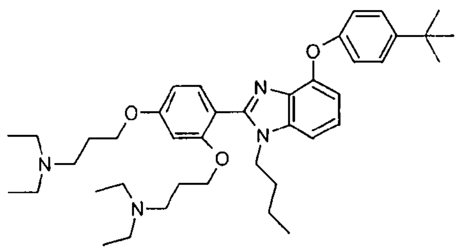
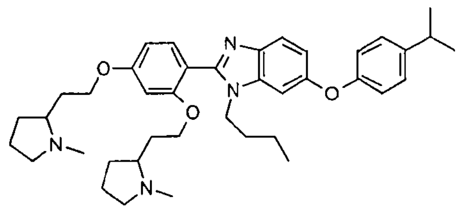
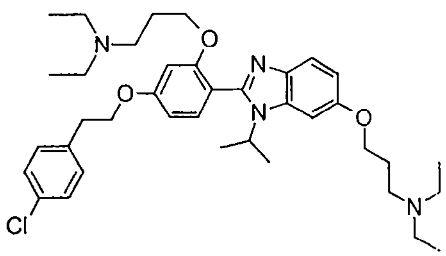
Ex.	Structure	Name
246		{3-[1-butyl-2-[4-(4-chloro-3-fluoro-phenoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yl]-propyl}-diethyl-amine
247		(3-{1-butyl-6-(3-diethylamino-propoxy)-2-[4-(quinolin-8-yloxy)-phenyl]-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
248		{3-[2-[2-(4-chloro-3-trifluoromethyl-phenoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzoimidazol-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

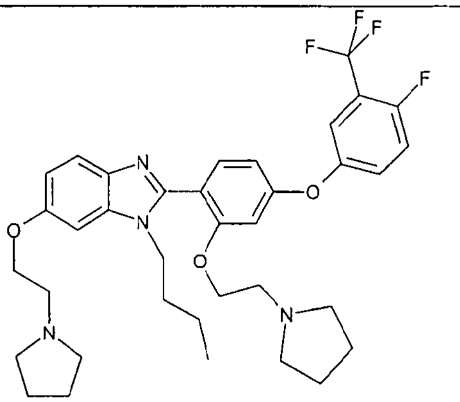
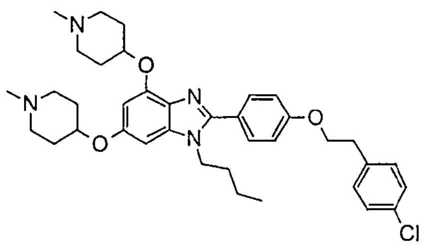
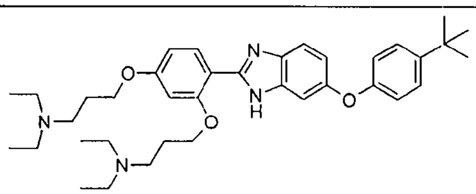
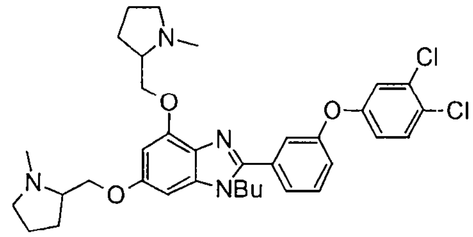
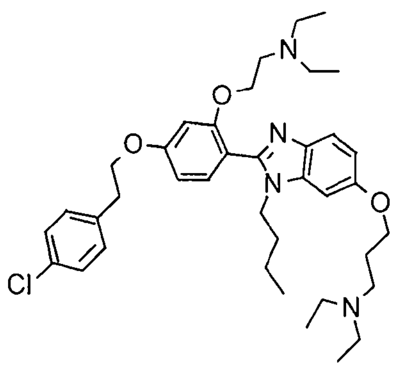
Ex.	Structure	Name
251		[3-(3-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-7-isopropoxy-3H-benzimidazol-5-yloxy)-propyl]-diethyl-amine
252		[3-(1-Butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-cyclopentylmethoxy-1H-benzoimidazol-4-yloxy)-propyl]-diethyl-amine
253		1-Butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-4,6-bis-(2-morpholin-4-yl-ethoxy)-1H-benzoimidazole
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
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

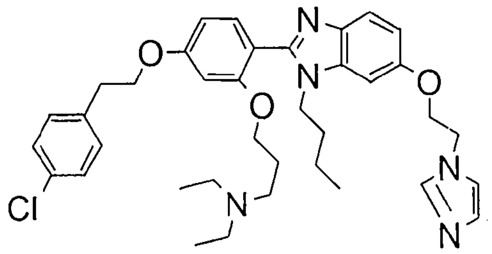
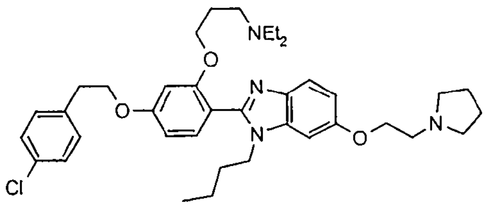
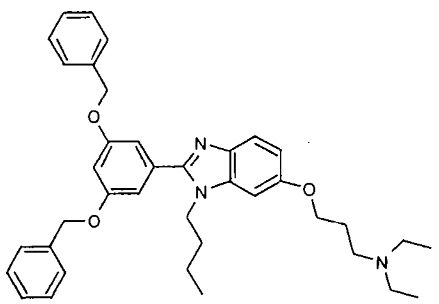
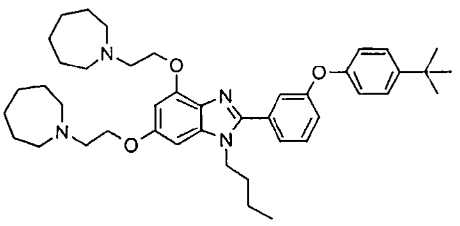
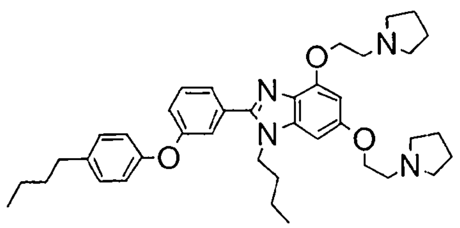
Ex.	Structure	Name
257		(3-{1-butyl-6-(4-tert-butyl-phenoxy)-2-[4-(3-diethylamino-propoxy)-phenyl]-1H-benzoimidazol-4-yloxy}-propyl)-diethyl-amine
258		2-{2,4-bis-[2-(1-methyl-pyrrolidin-2-yl)-ethoxy]-phenyl}-1-butyl-6-(4-tert-butyl-phenoxy)-1H-benzoimidazole
259		2-[2,4-bis-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1-butyl-6-(4-butyl-phenoxy)-1H-benzoimidazole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

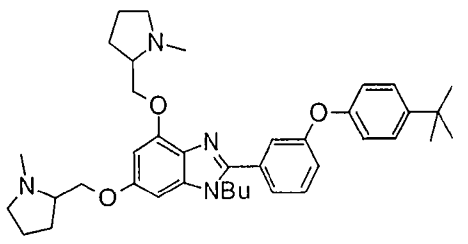
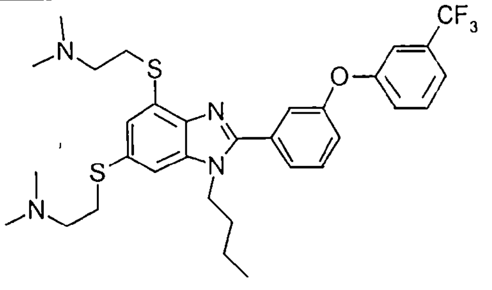
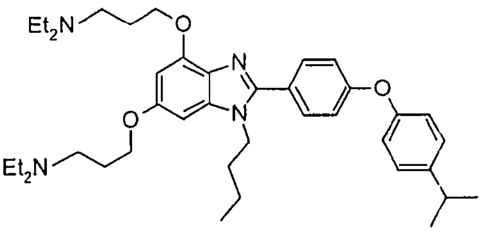
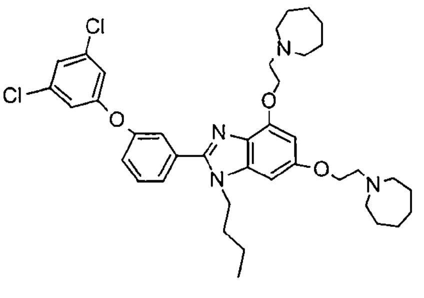
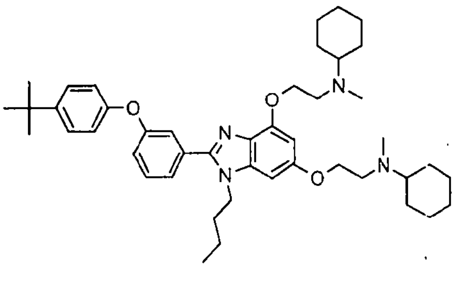
Ex.	Structure	Name
263		{3-[2-[1-butyl-5-(4-tert-butyl-phenoxy)-1H-benzimidazol-1-yl]-5-(3-diethylamino-propoxy)-phenoxy]-propyl}-diethyl-amine
264		1-Butyl-2-[3-(3,5-dichloro-phenoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazole
265		2-[2,4-bis-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1-butyl-6-(4-cyclopentyl-phenoxy)-1H-benzoimidazole
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

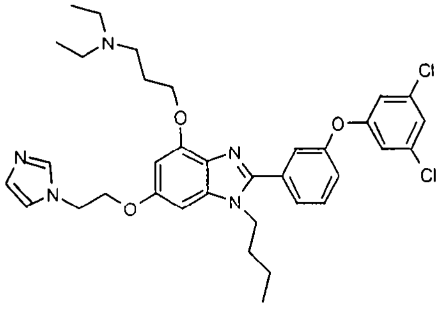
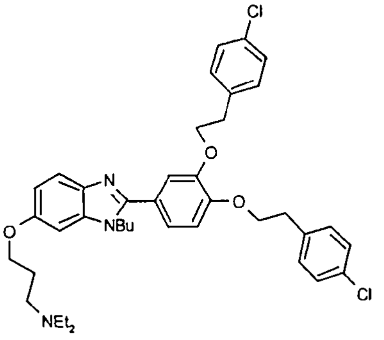
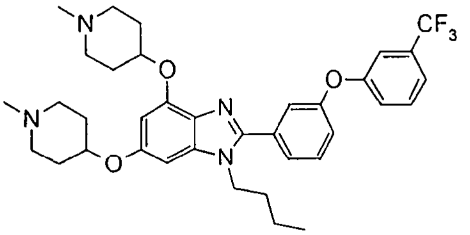
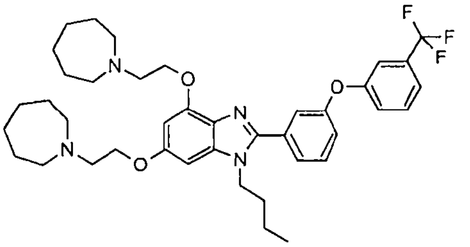
Ex.	Structure	Name
268		(2-{1-butyl-6-(2-dimethylamino-ethylsulfanyl)-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1H-benzoimidazol-4-ylsulfanyl}-ethyl)-dimethyl-amine
269		2-[2,4-bis-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1-butyl-6-(4-tert-butyl-phenoxy)-1H-benzimidazole
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

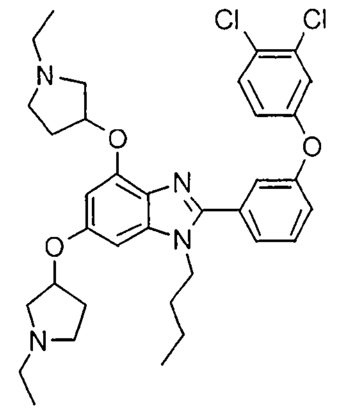
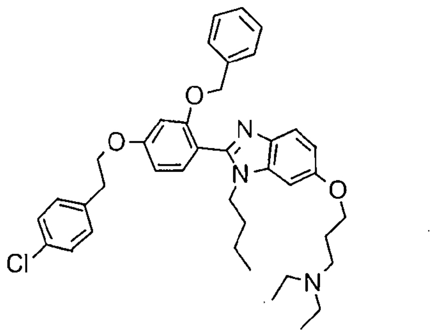
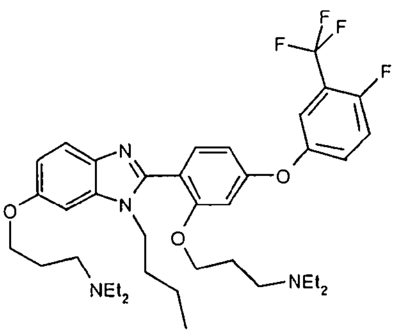
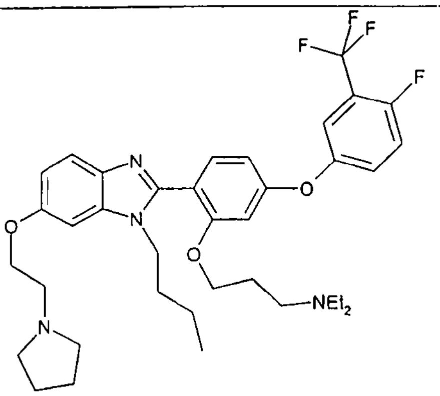
Ex.	Structure	Name
274		(3-{3-Butyl-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-3H-benzoimidazol-5-yloxy}-propyl)-diethyl-amine
275		{3-[2-[1-butyl-6-(4-cyclopentyl-phenoxy)-1H-benzimidazol-2-yl]-5-(3-diethylamino-propoxy)-phenoxy]-propyl}-diethyl-amine
276		{3-[2-[1-butyl-4-(4-tert-butyl-phenoxy)-1H-benzimidazol-2-yl]-5-(3-die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

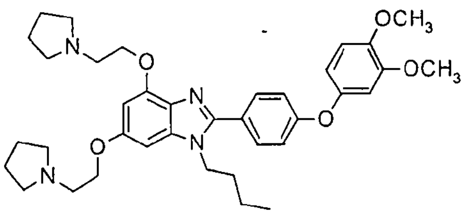
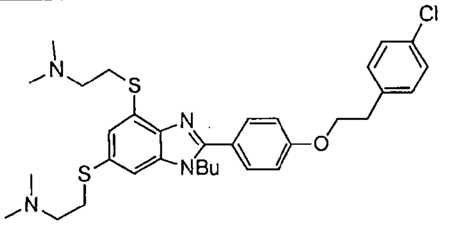
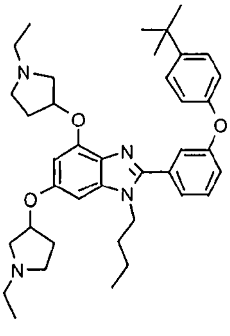
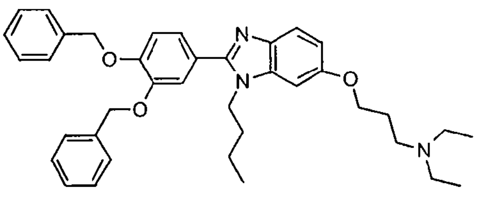
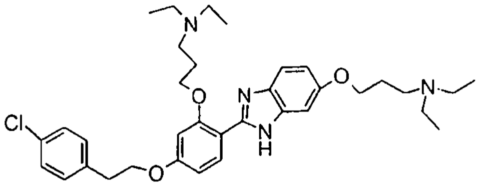
Ex.	Structure	Name
279		1-Butyl-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-6-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazole
280		1-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-4,6-bis-(1-methyl-piperidin-4-yloxy)-1H-benzimidazole
281		{3-[2-[6-(4-tert-butyl-phenoxy)-1H-benzimidazol-2-yl]-5-(3-diethylamino-propoxy)-phenoxy]-pr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

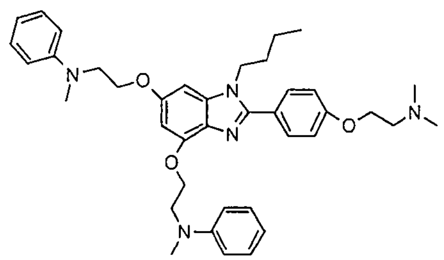
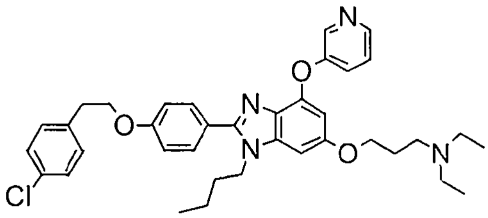
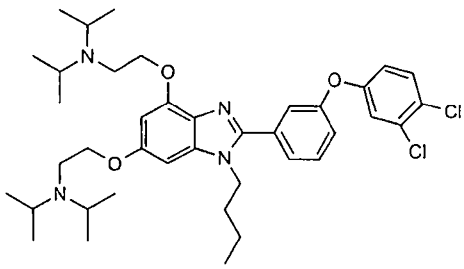
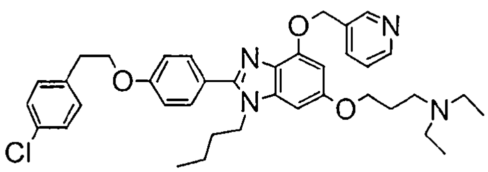
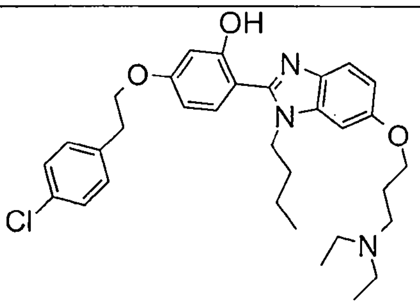
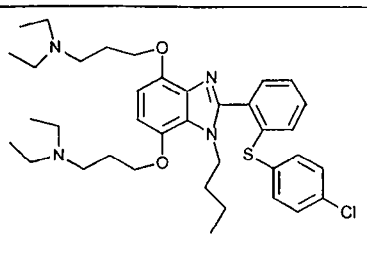
Ex.	Structure	Name
284		(3-{2-[1-Butyl-6-(2-imidazol-1-yl-ethoxy)-1H-benzoimidazol-2-yl]-5-[2-(4-chloro-phenyl)-ethoxy]-phenoxy}-propyl)-diethyl-amine
285		(3-{2-[1-Butyl-6-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazol-2-yl]-5-[2-(4-chloro-phenyl)-ethoxy]-phenoxy}-propyl)-diethyl-amine
286		{3-[2-(3,5-bis-benzyloxy-phenyl)-3-butyl-3H-benzimidazol-5-yloxy]-propyl}-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

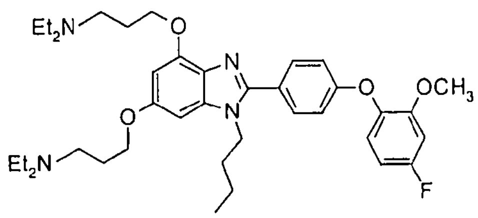
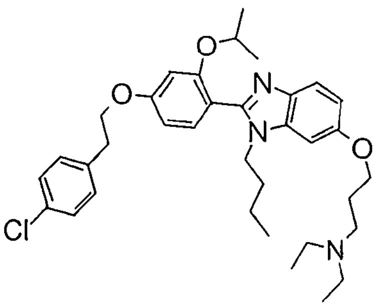
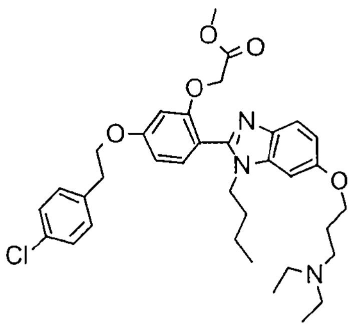
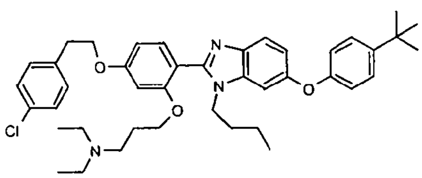
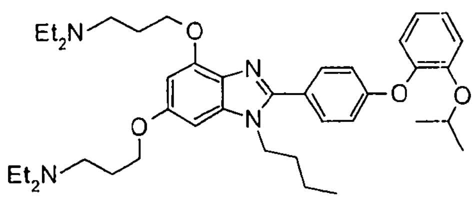
Ex.	Structure	Name
289		1-butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-4,6-bis-(1-methyl-pyrrolidin-2-ylmethoxy)-1H-benzoimidazole
290		(2-{1-butyl-6-(2-dimethylamino-ethylsulfanyl)-2-[3-(3-trifluoromethyl-phenoxy)-phenyl]-1H-benzoimidazole-4-ylsufanyl}-ethyl)-dimethyl-amine
291		(3-{1-butyl-6-(3-diethylamino-propoxy)-2-[4-(4-isopropyl-phenoxy)-phenyl]-1H-benzimidazol-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-benzoimidazole
297		4,6-bis-(2-azepan-1-yl-ethoxy)-1-butyl-2-[3-(3-trifluoromethyl-phenoxy)-phenyl]-1H-benzoimidazole

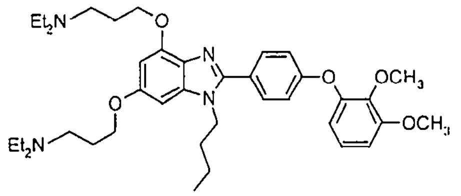
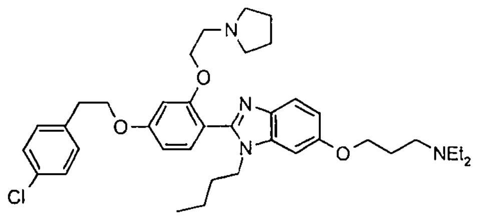
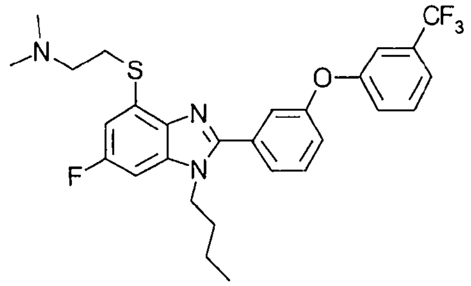
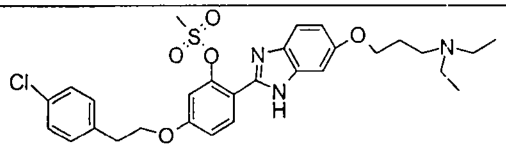
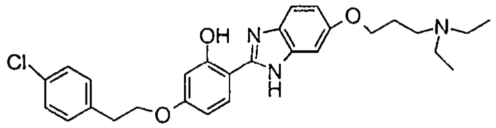
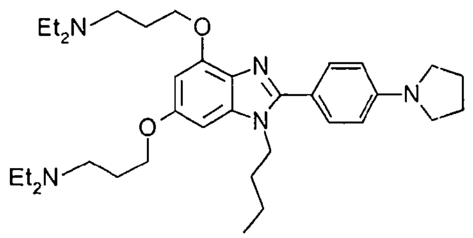
Ex.	Structure	Name
298		1-butyl-2-[3-(3,4-dichloro-phenoxy)-phenyl]-4,6-bis-(1-ethyl-pyrrolidin-2-ylmethoxy)-1H-benzoimidazole
299		[3-(2-{2-benzyloxy-4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-3-butyl-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
300		{3-[2-[1-Butyl-6-(3-diethylamino-propoxy)-1H-benzoimidazol-2-yl]-5-(4-fluoro-3-trifluoromethyl-phenoxy)-phenoxy]-p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

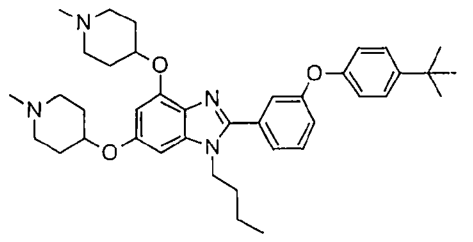
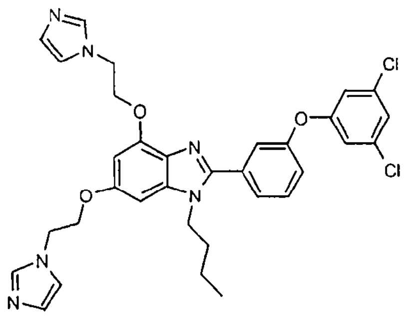
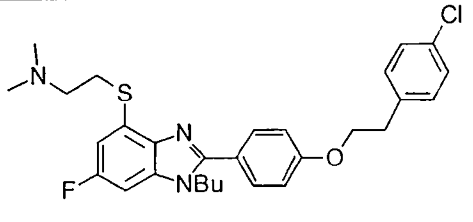
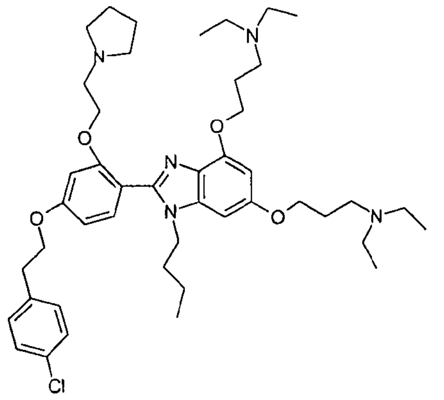
Ex.	Structure	Name
302		1-butyl-2-[3-(3,4-dimethoxy-phenoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazole
303		(2-{1-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-(2-dimethylamino-ethylsulfanyl)-1H-benzoimidazol-4-ylsulfanyl}-ethyl)-dimethyl-amine
304		1-butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-4,6-bis-(1-ethyl-pyrrolidin-3-yloxy)-1H-benzoimidazole
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

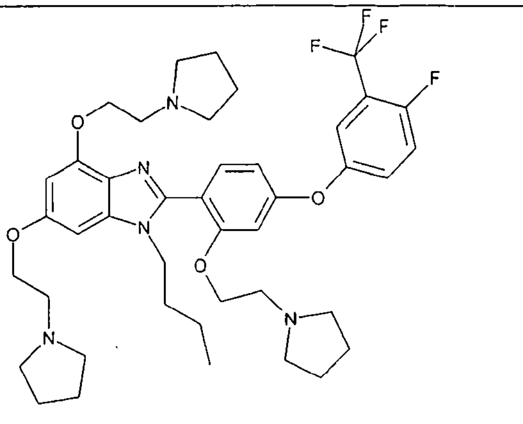
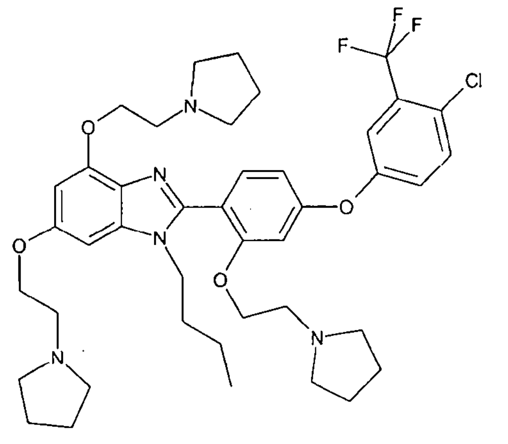
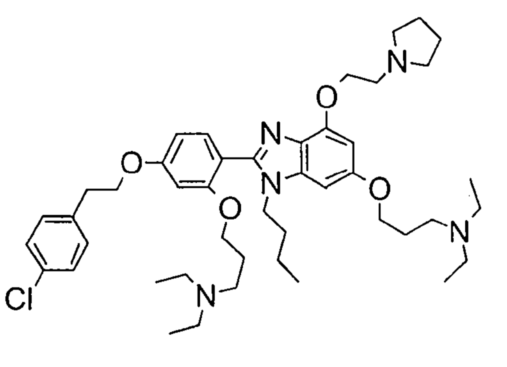
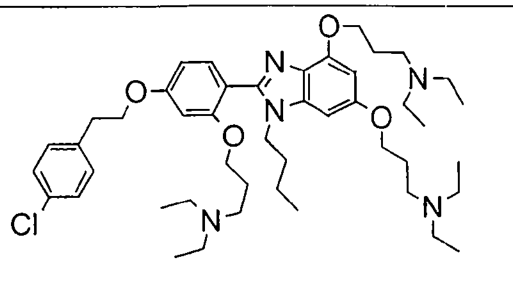
Ex.	Structure	Name
307		1-butyl-2-[4-(2-diethylamino-ethoxy)-phenyl]-4,6-bis-[2-(methyl-phenyl-amino)-ethoxy]-1H-benzimidazole
308		{3-[3-butyl-2-{4-[2-(4-chlorophenyl)-ethoxy]-phenyl}-7-(pyridin-3-yloxy)-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine
309		{2-[1-butyl-2-[3-(3,4-dichloro-phenoxy)-phenyl]-6-(2-diisopropylamino-ethoxy)-1H-benzimidazol-4-yloxy]-ethyl}-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-benzoimidazlo-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-benzoimidazlo-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

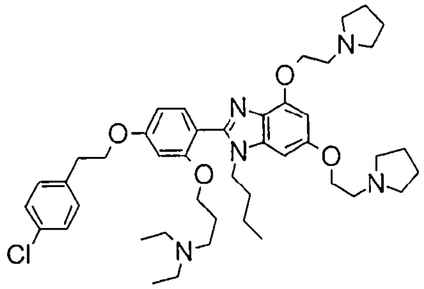
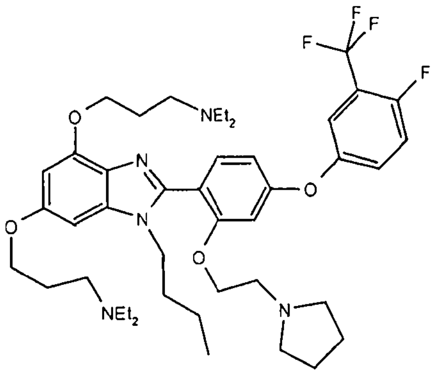
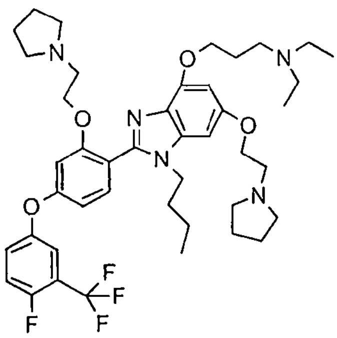
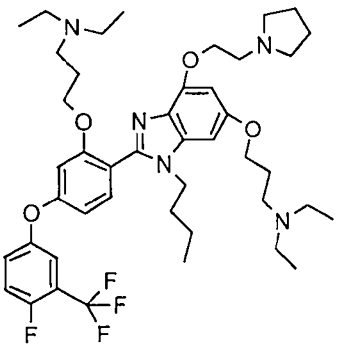
2007202350 24 May 2007

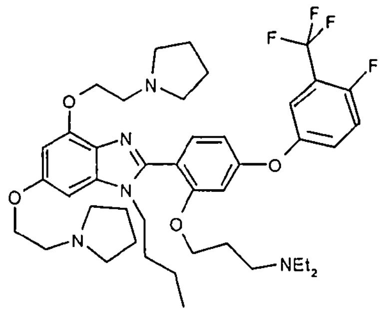
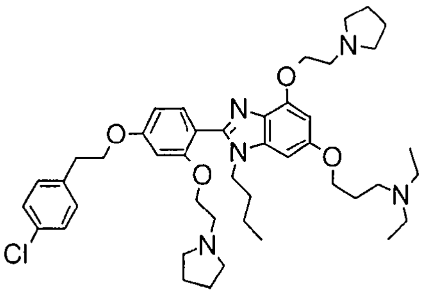
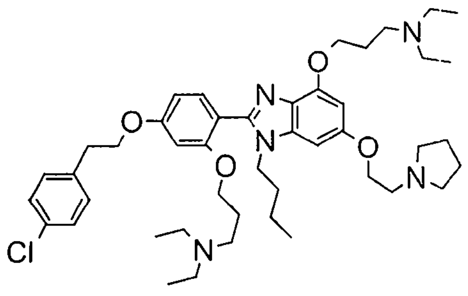
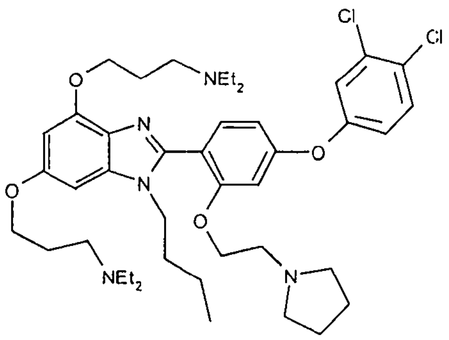
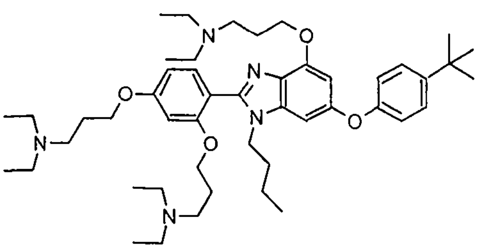
Ex.	Structure	Name
318		(3-{1-butyl-6-(3-diethylamino-propoxy)-2-[4-(2,3-dimethoxy-phenoxy)-phenyl]-1H-benzimidazol-4-yloxy}-propyl)-diethyl-amine
319		(3-{3-Butyl-2-[4-[2-(4-chloro-phenyl)-ethoxy]-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-3H-benzoimidazol-5-yloxy}-propyl)-diethyl-amine
320		(2-{1-butyl-6-fluoro-2-[3-(3-trifluoromethyl-phenoxy)-phenyl]-1H-benzoimidazole-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

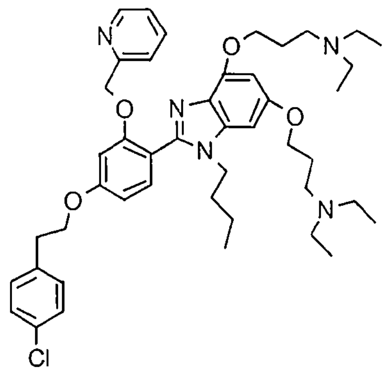
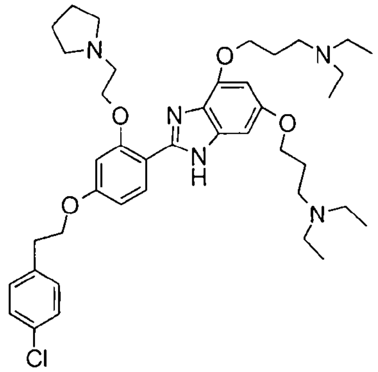
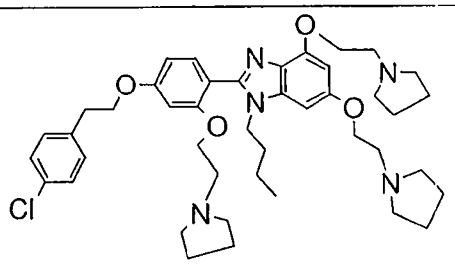
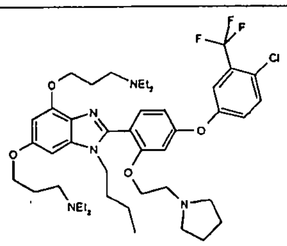
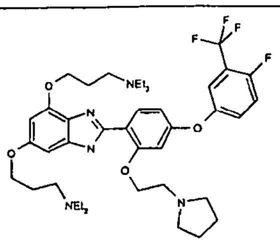
Ex.	Structure	Name
324		1-butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-4,6-bis-(1-methyl-piperidin-4-yloxy)-1H-benzimidazole
325		1-butyl-2-[3-(3,5-dichloro-phenoxy)-phenyl]-4,6-bis-(2-imidazol-1-yl-ethoxy)-1H-benzoimidazole
326		[2-(1-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-fluoro-1H-benzoimidazol-4-ylsulfanyl)-ethyl]-dimethyl-amine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

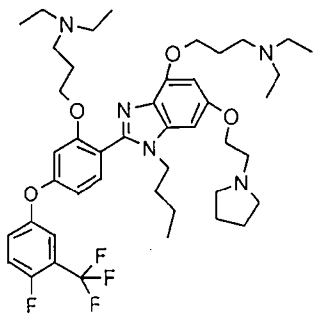
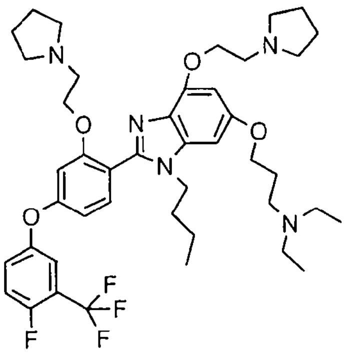
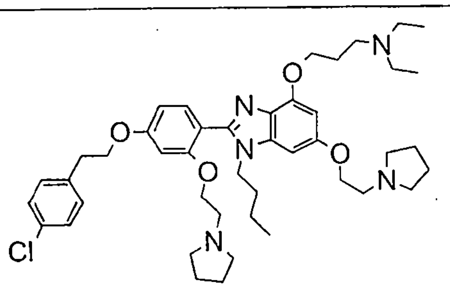
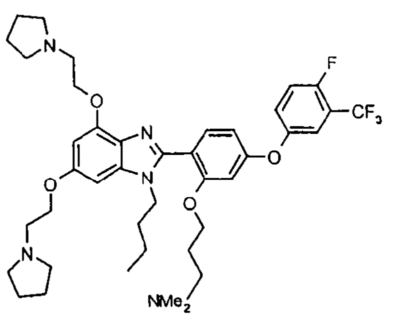
Ex.	Structure	Name
328		1-Butyl-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazole
329		1-Butyl-2-[4-(4-chloro-3-trifluoromethyl-phenoxy)-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazole
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

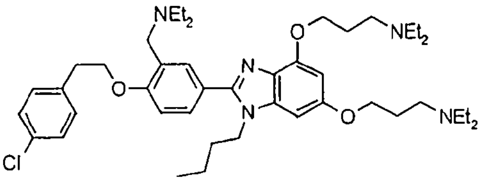
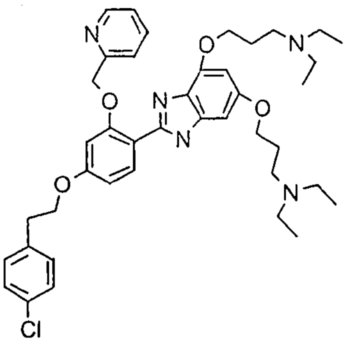
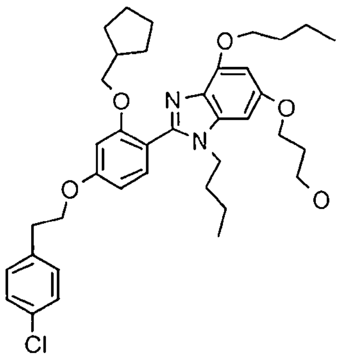
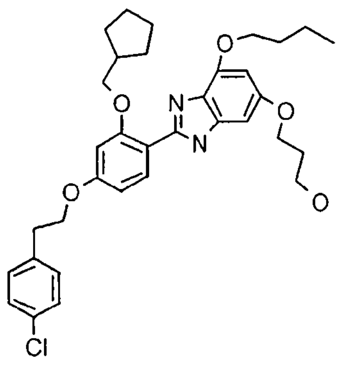
2007202350 24 May 2007

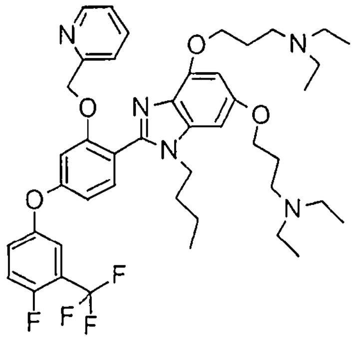
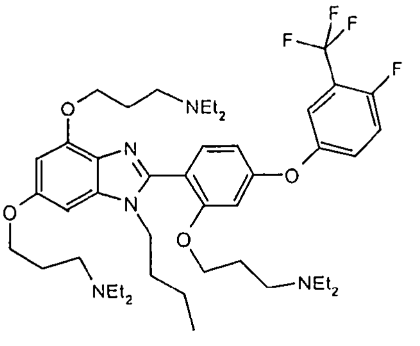
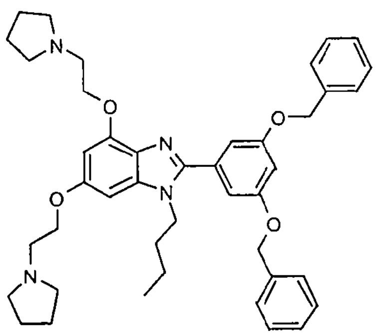
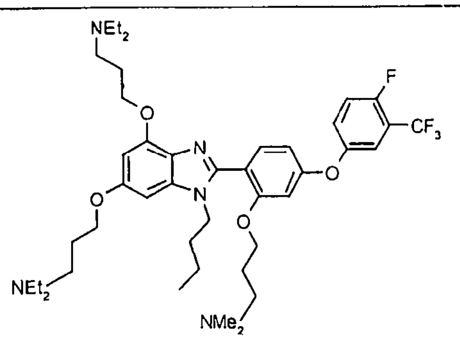
Ex.	Structure	Name
332		(3-{2-[1-Butyl-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazol-2-yl]-5-[2-(4-chloro-phenyl)-ethoxy]-phenoxy}-propyl)-diethyl-amine
333		(3-{1-Butyl-6-(3-diethylamino-propoxy)-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1H-benzoimidazol-4-yloxy}-propyl)-diethyl-amine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

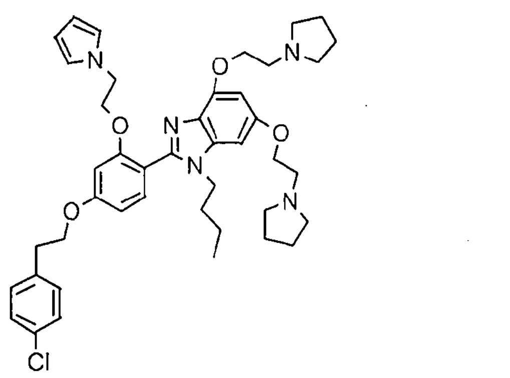
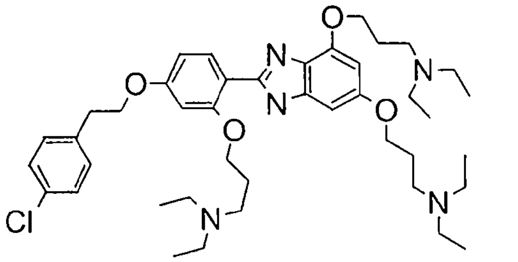
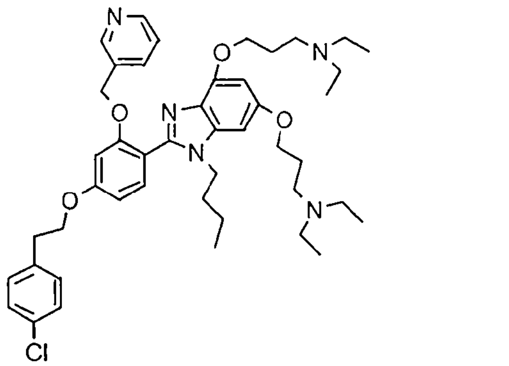
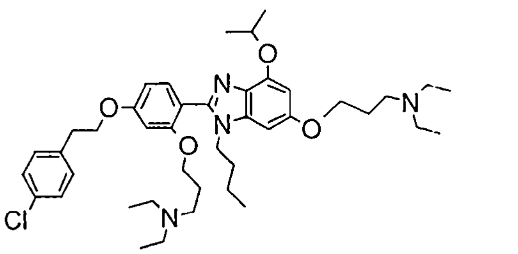
Ex.	Structure	Name
336		{3-[2-[1-Butyl-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazol-2-yl]-5-(4-fluoro-3-trifluoromethyl-phenoxy)-phenoxy]-propyl}-diethyl-amine
337		{3-[3-butyl-2-[4-[2-(4-chloro-phenyl)-ethoxy]-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-7-(2-pyrrolidin-1-yl-ethoxy)-3H-benzimidazol-5-yloxy]-propyl}-diethyl-amine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

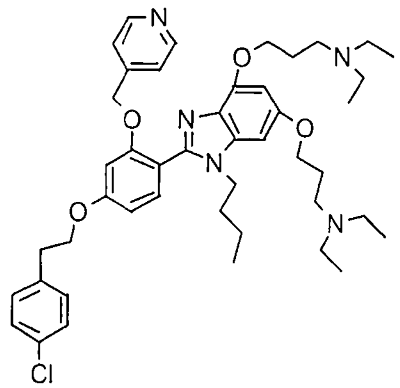
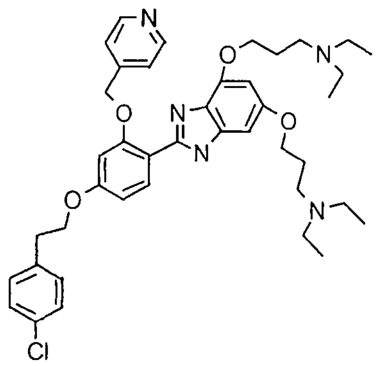
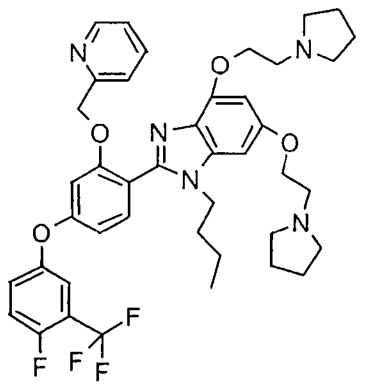
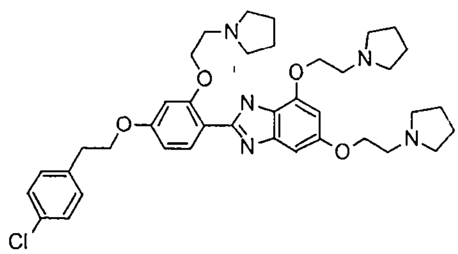
Ex.	Structure	Name
346		{3-[2-[1-Butyl-4-(3-diethylamino-propoxy)-6-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazol-2-yl]-5-(4-fluoro-3-trifluoromethyl-phenoxy)-phenoxy]-propyl}-diethyl-amine
347		{3-[3-Butyl-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-7-(2-pyrrolidin-1-yl-ethoxy)-3H-benzoimidazol-5-yloxy]-propyl}-diethyl-amine
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

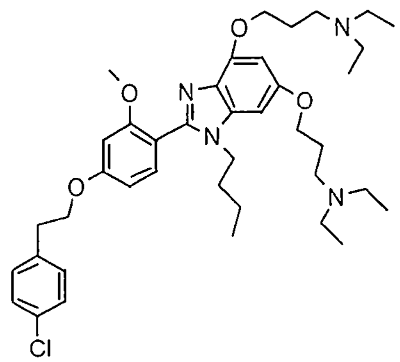
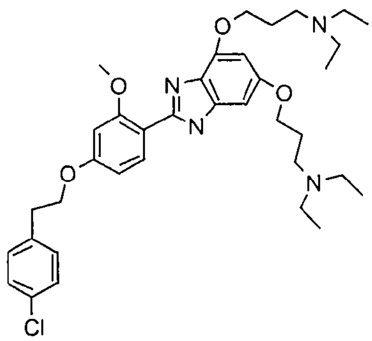
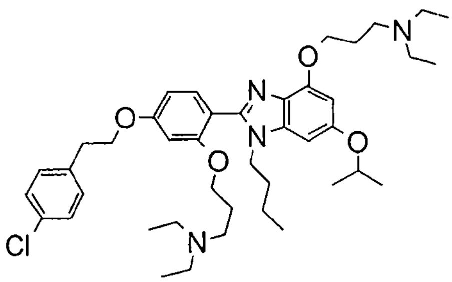
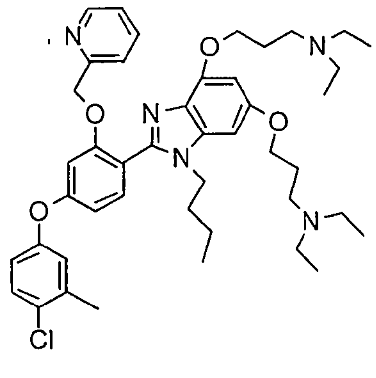
Ex.	Structure	Name
350		{3-[1-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-3-diethylaminomethyl-phenyl}-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
351		{3-[2-[4-[2-(4-chloro-phenyl)-ethoxy]-2-(pyridin-2-ylmethoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yl]-propyl}-diethyl-amine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

Ex.	Structure	Name
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

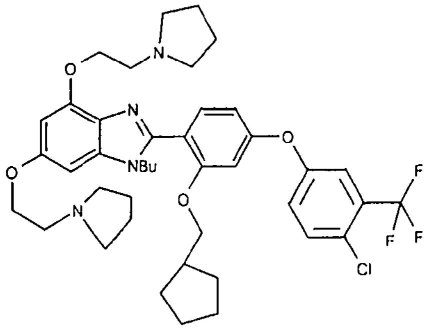
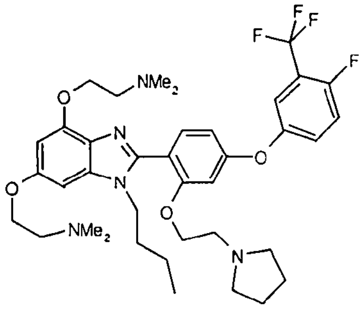
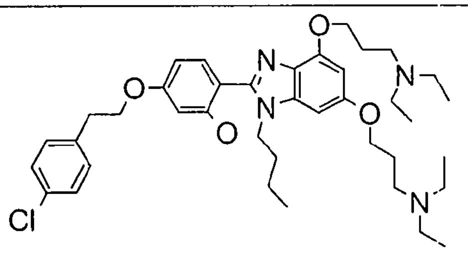
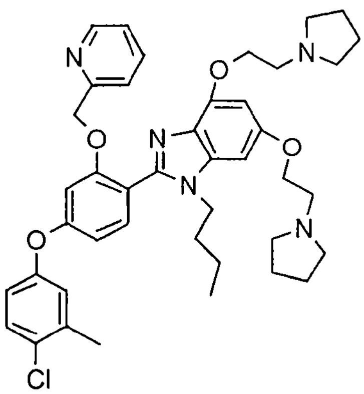
Ex.	Structure	Name
358		1-butyl-2-[4-[2-(4-chloro-phenyl)-ethoxy]-2-(2-pyrrol-1-yl-ethoxy)-phenyl]-4,6-bis-(2-pyrrolodin-1-yl-ethoxy)-1H-benzoimidazole
359		{3-[2-{4-[2-(4-chloro-phenyl)-ethoxy]-2-(3-diethylamino-propoxy)-phenyl}-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
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

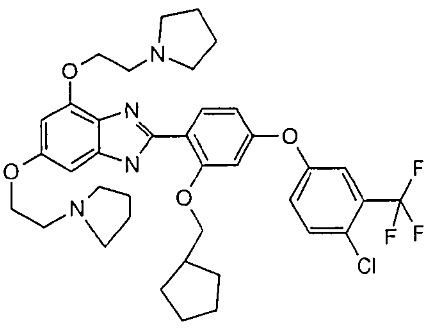
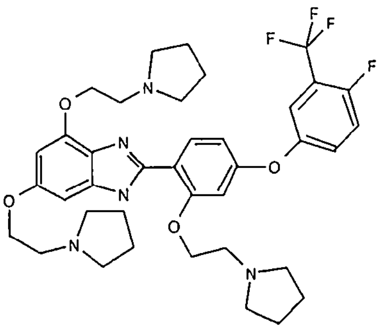
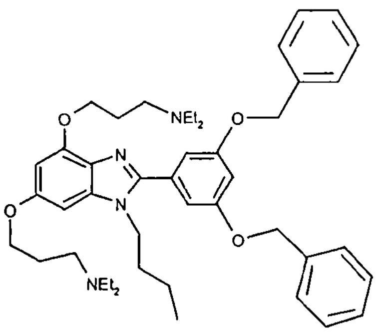
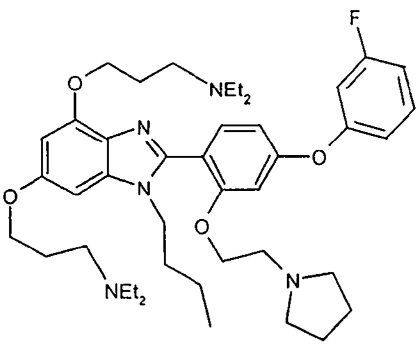
2007202350 24 May 2007

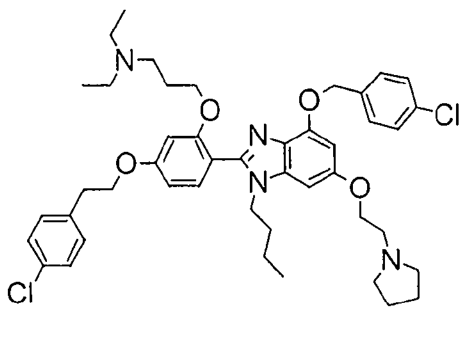
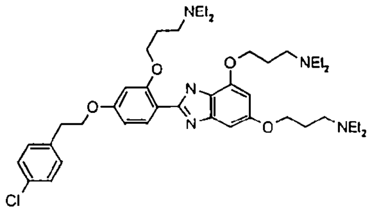
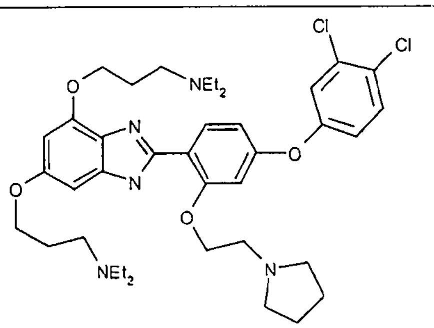
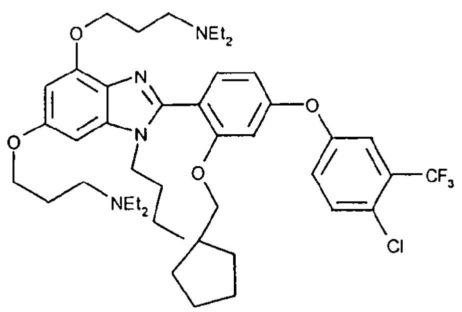
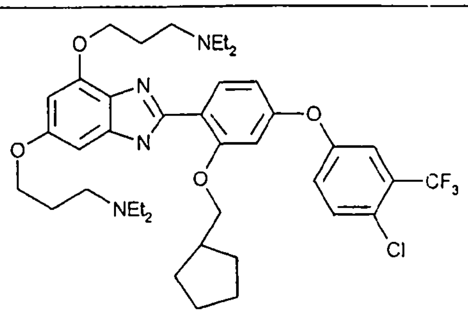
Ex.	Structure	Name
362		{3-[1-Butyl-2-[4-[2-(4-chloro-phenyl)-ethoxy]-2-(pyridin-4-ylmethoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine
363		{3-[2-[4-[2-(4-Chloro-phenyl)-ethoxy]-2-(pyridin-4-ylmethoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine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

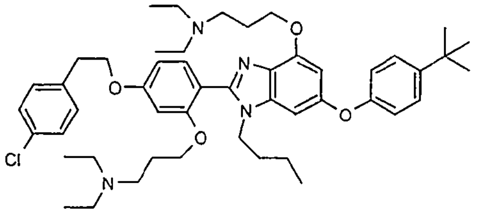
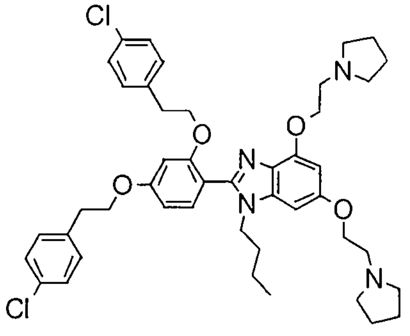
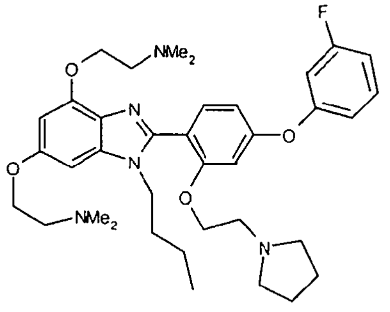
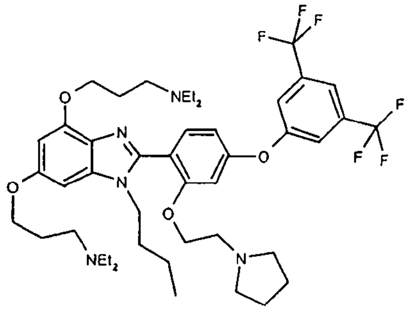
Ex.	Structure	Name
366		{3-[1-Butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-2-methoxy-phenyl}-6-(3-diethylamino-propoxy)-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine
367		{3-[2-{4-[2-(4-Chloro-phenyl)-ethoxy]-2-methoxy-phenyl}-6-(3-diethylamino-propoxy)-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine
368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

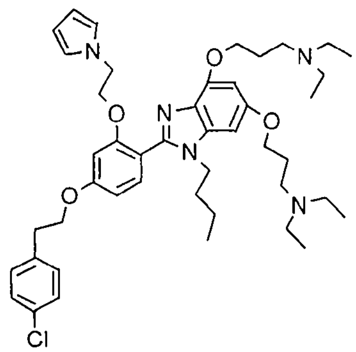
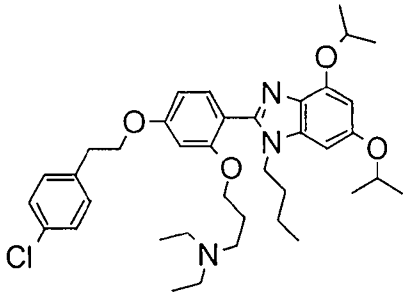
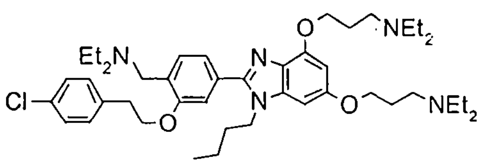
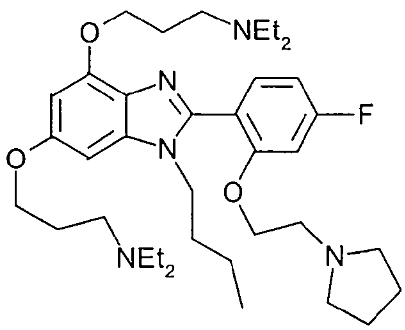
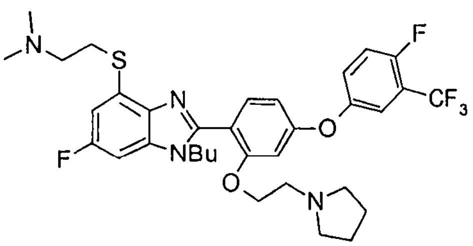
2007202350 24 May 2007

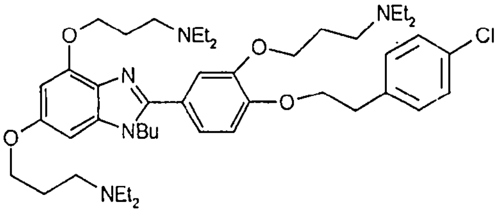
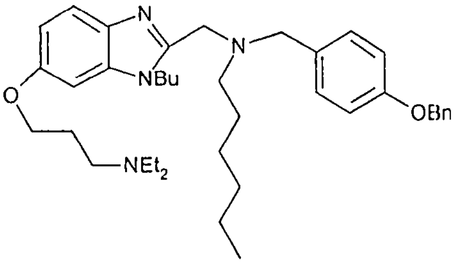
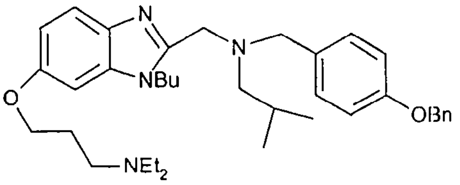
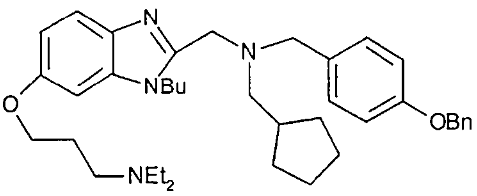
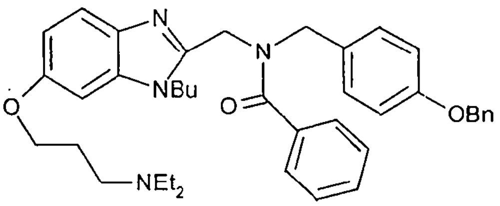
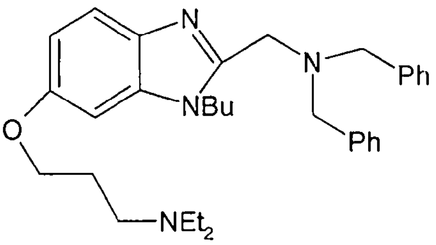
Ex.	Structure	Name
370		1-Butyl-2-[4-(4-chloro-3-trifluoromethyl-phenoxy)-2-cyclopentylmethoxy-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazole
371		(2-{1-butyl-6-(2-dimethylamino-ethoxy)-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1H-benzoimidazole-4-yloxy}-ethyl)-dimethyl-amine
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

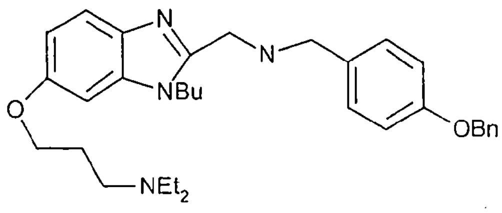
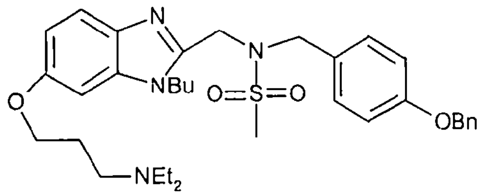
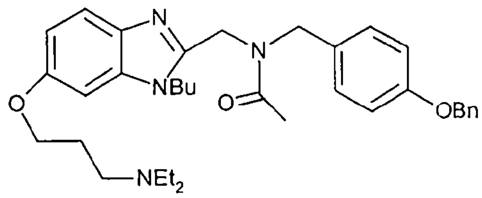
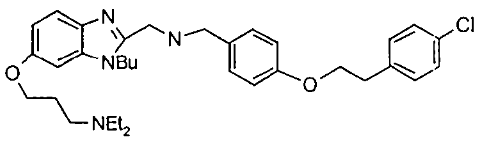
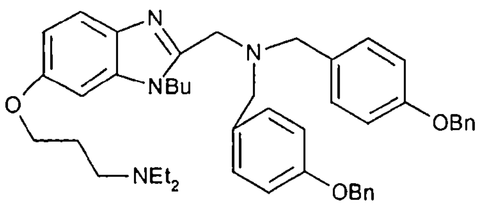
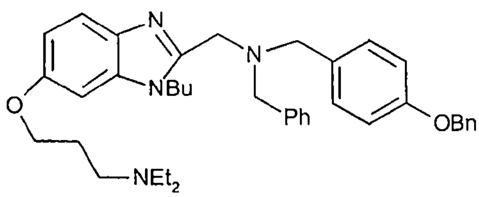
Ex.	Structure	Name
374		2-[4-(4-Chloro-3-trifluoromethyl-phenoxy)-2-cyclopentylmethoxy-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazole
375		2-[4-(4-Fluoro-3-trifluoromethyl-phenoxy)-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazole
376		{3-[2-(3,5-bis-benzyloxy-phenyl)-1-butyl-6-(3-diethylamino-propoxy)-1H-benzimidazol-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-benzoimidazole-4-yloxy}-propyl)-diethyl-amine

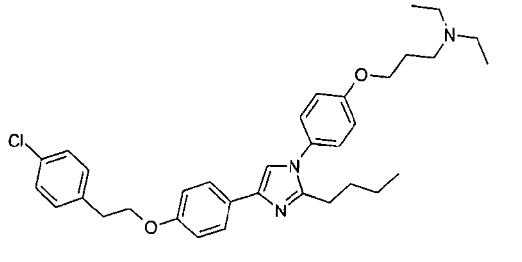
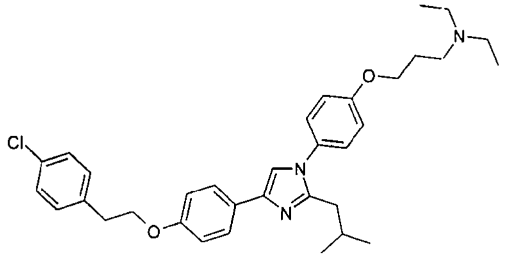
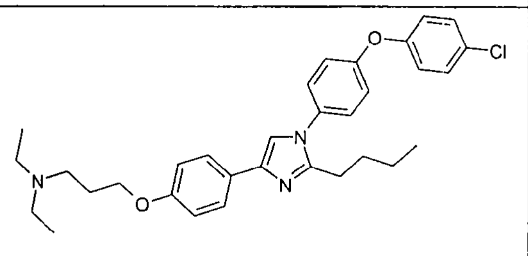
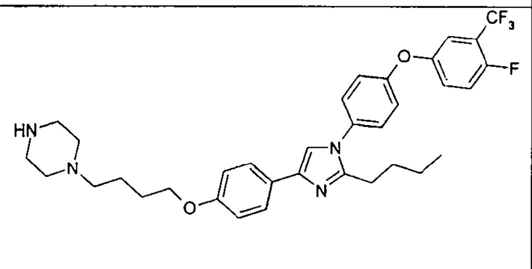
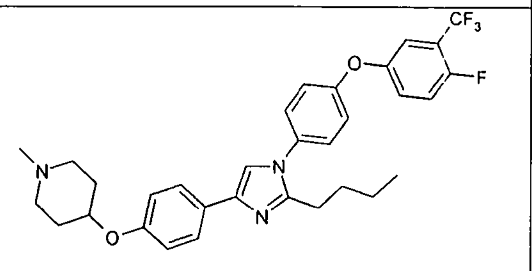
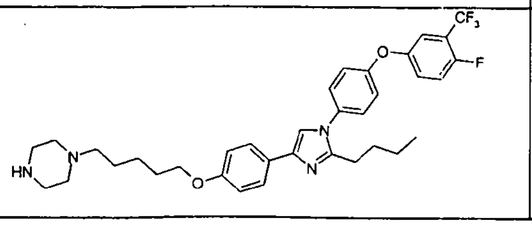
Ex.	Structure	Name
378		{3-[2-{1-butyl-4-(4-chloro-benzyloxy)-6-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazol-2-yl]-5-[2-(4-chloro-phenyl)-ethoxy]-phenoxy}-propyl)-diethyl-amine
379		{3-[2-{4-[2-(4-chloro-phenyl)-ethoxy]-2-(3-diethylamino-propoxy)-phenyl]-6-(3-diethylamino-propoxy)-3H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
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
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

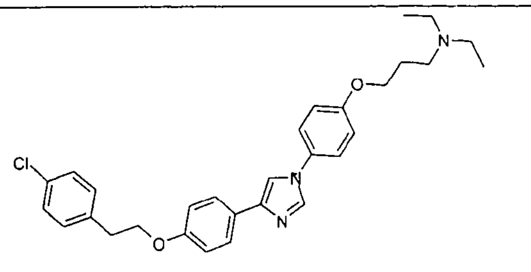
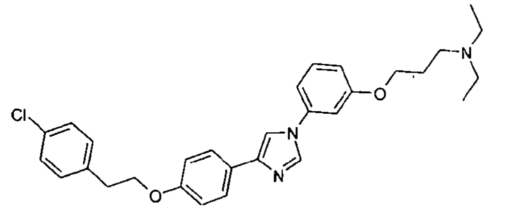
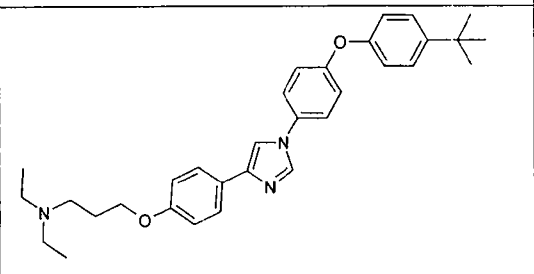
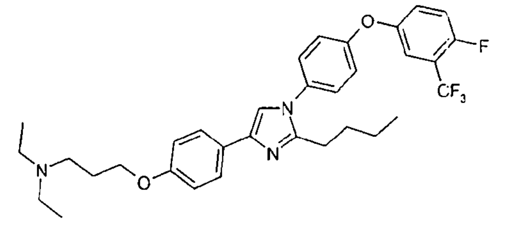
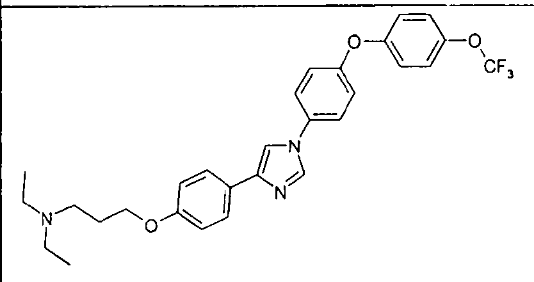
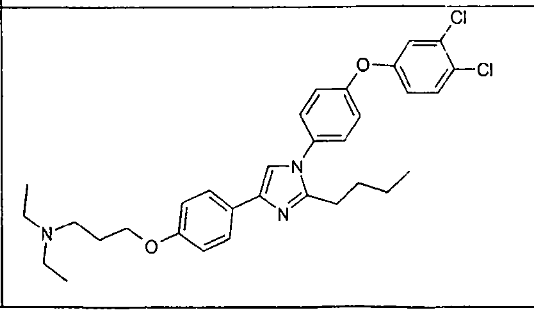
Ex.	Structure	Name
383		(3-{1-butyl-6-(4-tert-butyl-phenoxy)-2-[4-[2-(4-chloro-phenyl)-ethoxy]-2-(3-diethylamino-propoxy)-phenyl]-1H-benzimidazol-4-yloxy}-propyl)-diethyl-amine
384		2-{2,4-bis-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-1-butyl-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzimidazole
385		(2-{1-butyl-6-(2-dimethylamino-ethoxy)-2-[4-(3-fluoro-phenoxy)-2-(2-p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

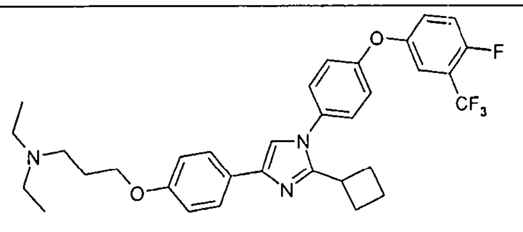
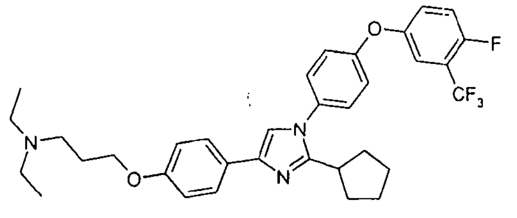
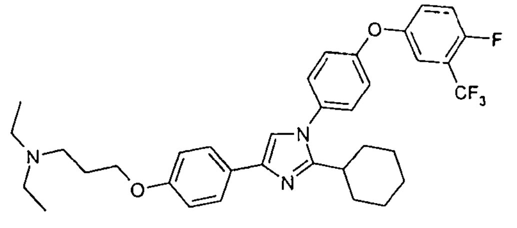
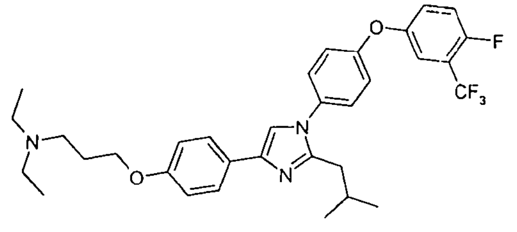
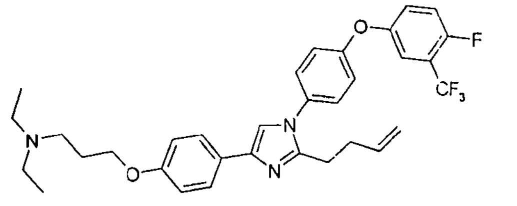
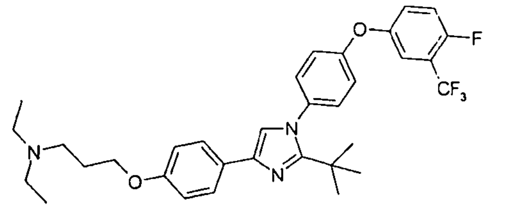
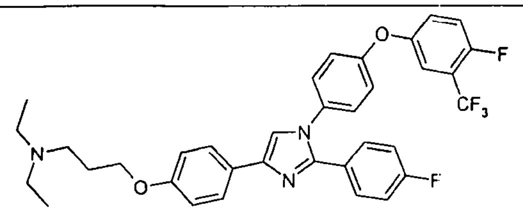
Ex.	Structure	Name
387		{3-[1-butyl-2-[4-[2-(4-chloro-phenyl)-ethoxy]-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzimidazol-4-yloxy]-propyl}-diethyl-amine
388		(3-{2-(1-Butyl-4,6-diisopropoxy-1H-benzoimidazol-2-yl)-5-[2-(4-chloro-phenyl)-ethoxy]-phenoxy}-propyl)-diethyl-amine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

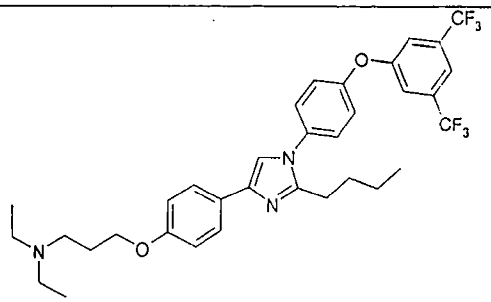
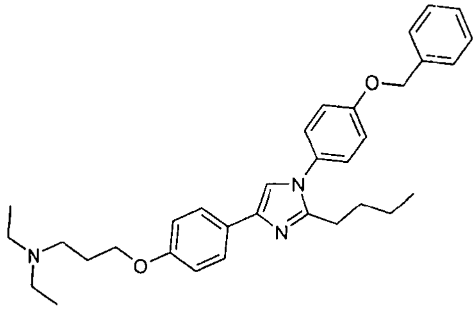
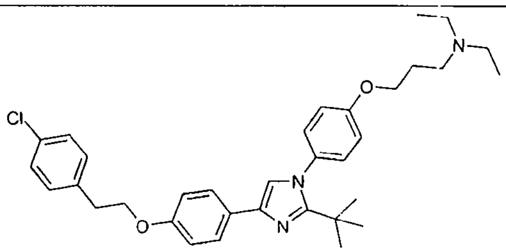
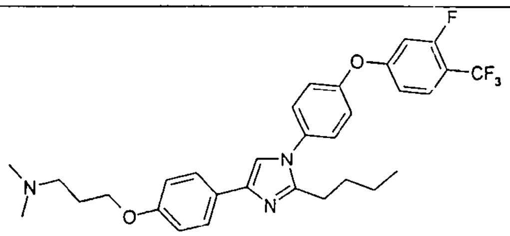
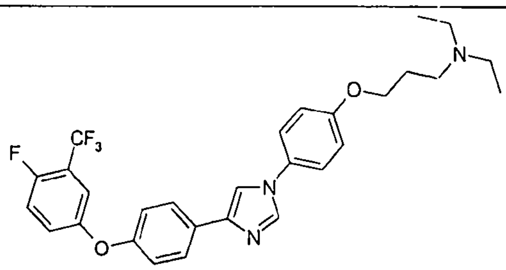
Ex.	Structure	Name
398		(3-{2-[(4-benzyloxy-benzylamino)-methyl]-3-butyl-3H-benzimidazol-5-yloxy}-propyl)-diethyl-amine
399		N-(4-benzyloxy-benzyl)-N-[1-butyl-6-(3-diethylamino-propoxy)-1H-benzimidazol-2-ylmethyl]-methanesulfonamide
400		N-(4-benzyloxy-benzyl)-N-[1-butyl-6-(3-diethylamino-propoxy)-1H-benzimidazol-2-ylmethyl]-acetamide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

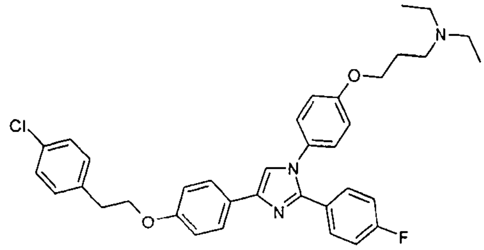
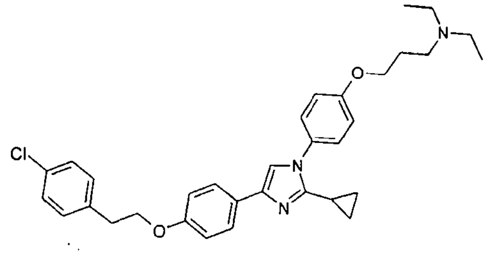
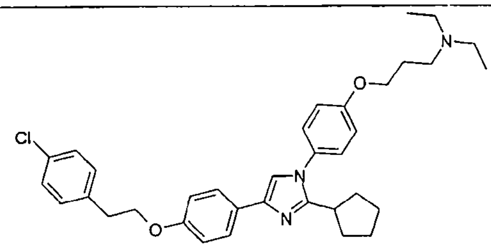
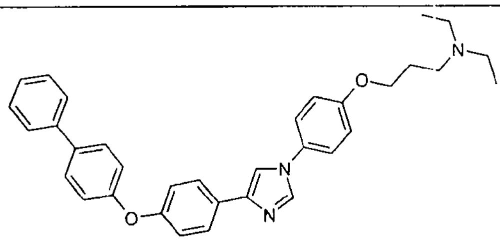
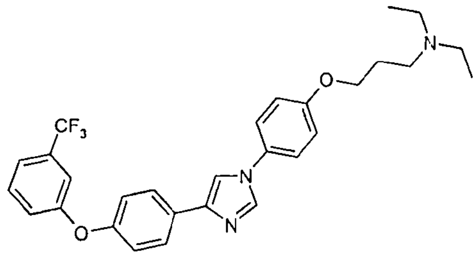
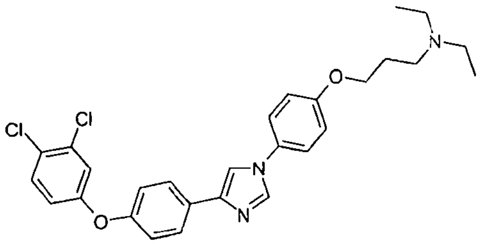
Ex.	Structure	Name
404		{3-[4-(2-butyl-4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-imidazol-1-yl)-phenoxy]-propyl}-diethyl-amine
405		{3-[4-(4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-isobutyl-imidazol-1-yl)-phenoxy]-propyl}-diethyl-amine
406		[3-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine
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

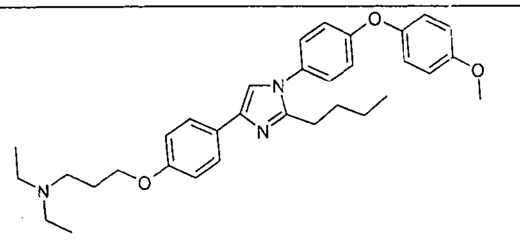
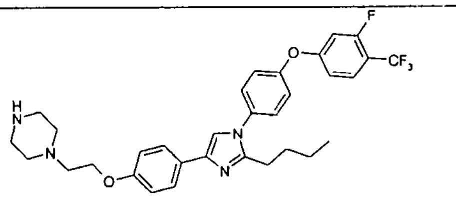
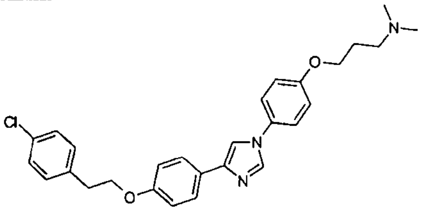
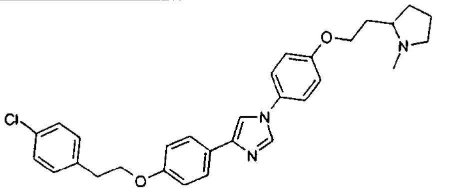
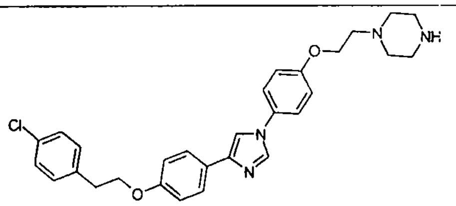
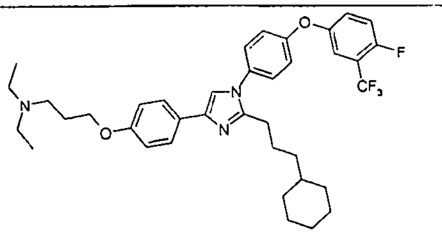
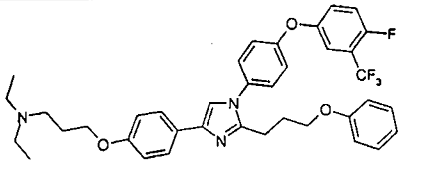
Ex.	Structure	Name
410		{3-[4-(4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-imidazol-1-yl)-phenoxy]-propyl}-diethyl-amine
411		{3-[3-(4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-imidazol-1-yl)-phenoxy]-propyl}-diethyl-amine
412		[3-(4-{1-[4-(4-tert-butyl-phenoxy)-phenyl]-1H-imidazol-4-yl)-phenoxy)-propyl]-diethyl-amine
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

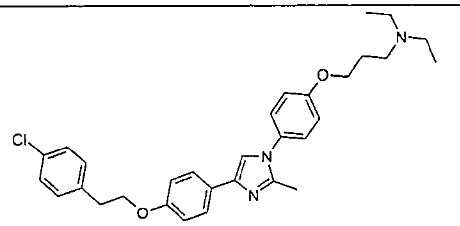
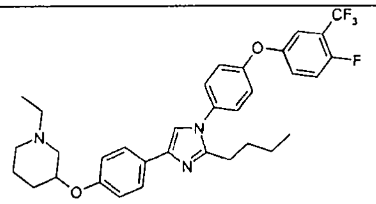
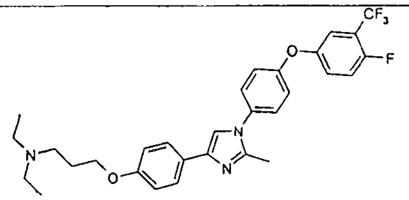
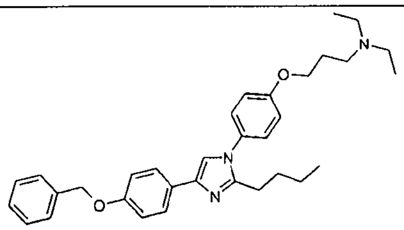
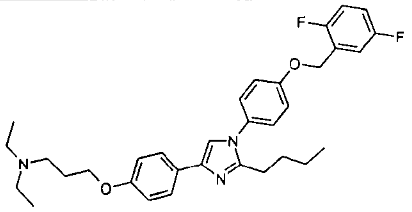
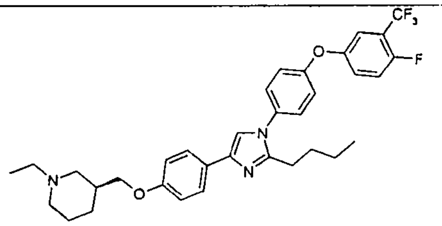
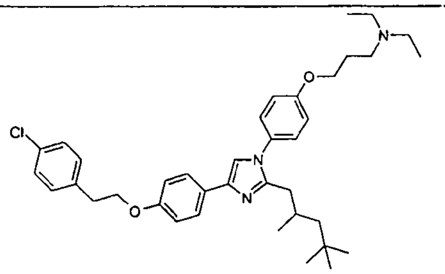
Ex.	Structure	Name
416		[3-(4-{2-cyclobutyl-1-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine
417		[3-(4-{2-cyclopentyl-1-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine
418		[3-(4-{2-cyclohexyl-1-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-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

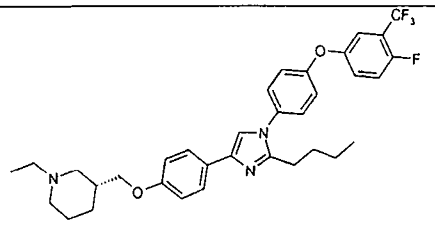
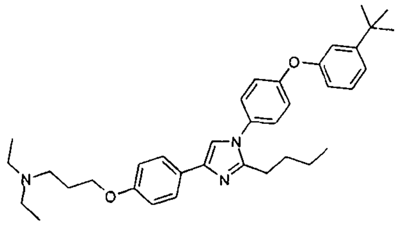
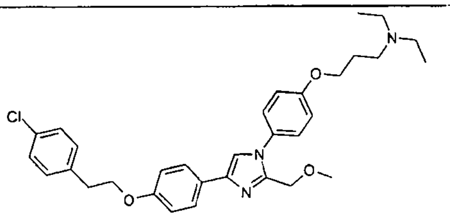
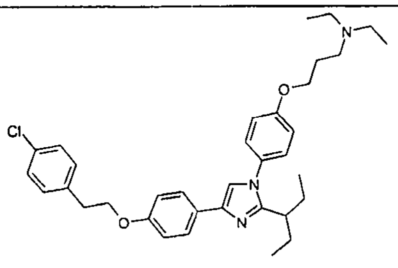
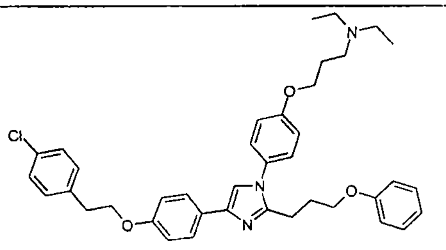
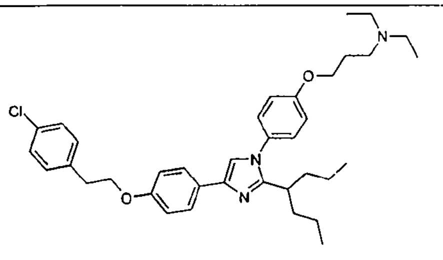
2007202350 24 May 2007

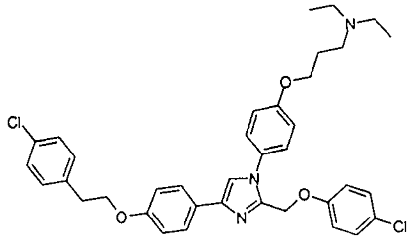
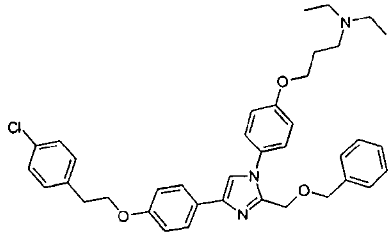
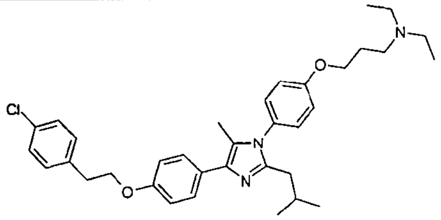
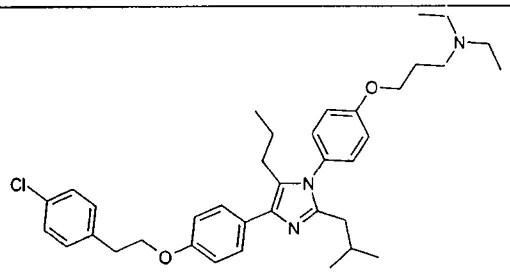
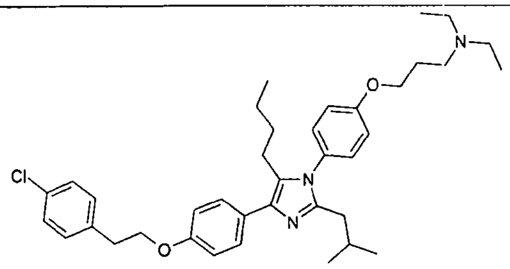
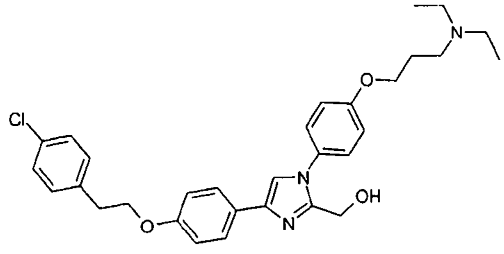
Ex.	Structure	Name
423		[3-(4-{1-[4-(3,5-bis-trifluoromethyl-phenoxy)-phenyl]-2-butyl-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine
424		(3-{4-[1-(4-benzyloxy-phenyl)-2-butyl-1H-imidazol-4-yl]-phenoxy}-propyl)-diethyl-amine
425		{3-[4-(2-tert-butyl-4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-imidazol-1-yl)-phenoxy]-propyl}-diethyl-amine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

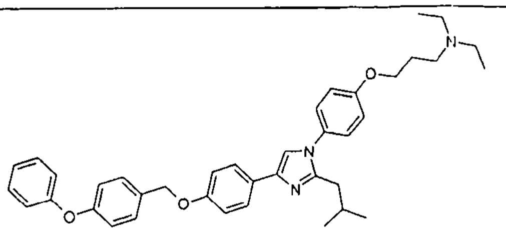
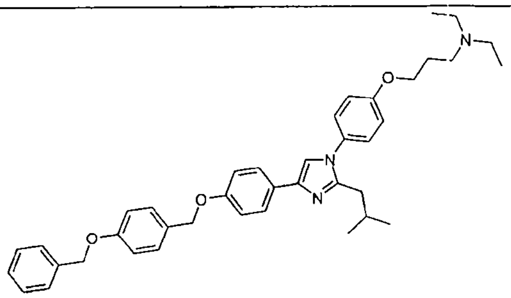
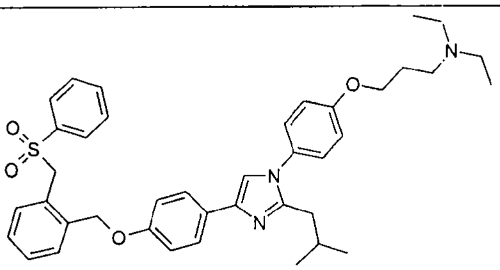
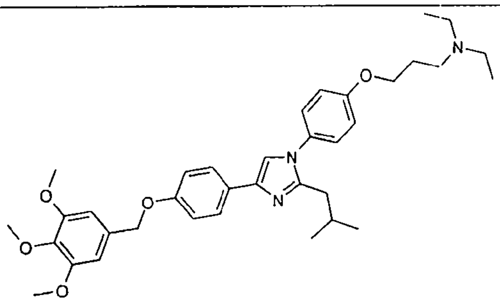
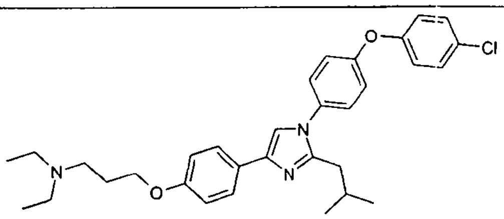
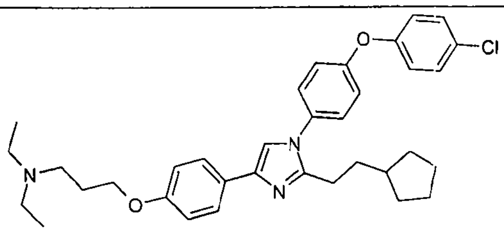
Ex.	Structure	Name
428		(3-{4-[4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-(4-fluoro-phenyl)-imidazol-1-yl]-phenoxy}-propyl)-diethyl-amine
429		{3-[4-(4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-cyclopropyl-imidazol-1-yl)-phenoxy]-propyl}-diethyl-amine
430		{3-[4-(4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-cyclopentyl-imidazol-1-yl)-phenoxy]-propyl}-diethyl-amine
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

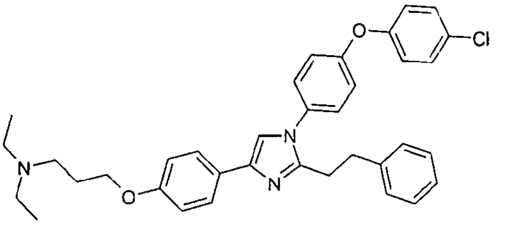
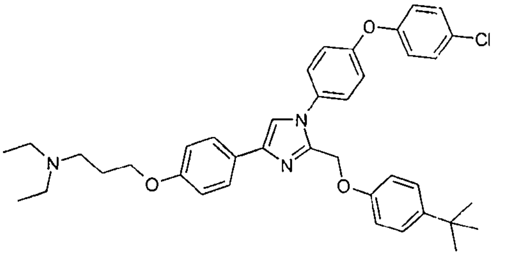
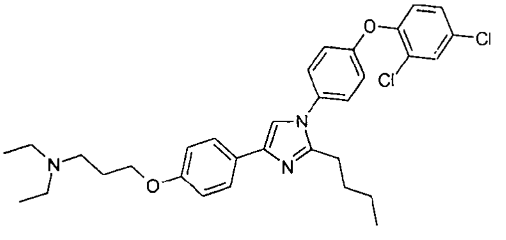
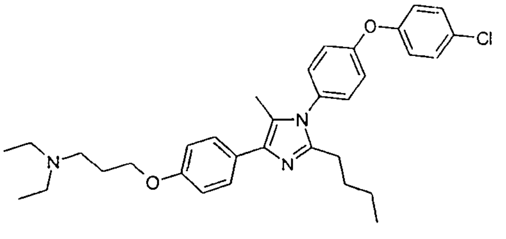
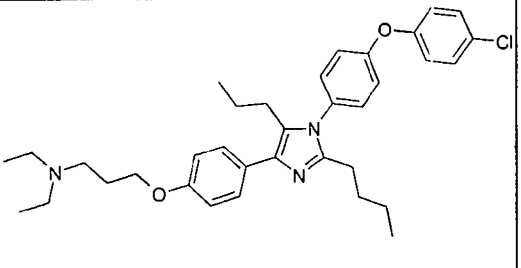
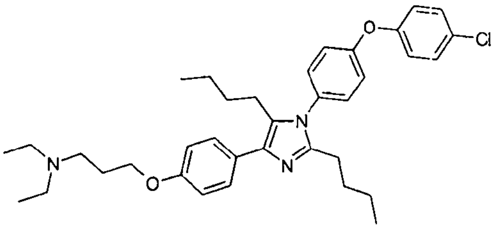
Ex.	Structure	Name
434		[3-(4-{2-butyl-1-[4-(4-methoxy-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine
435		1-[2-(4-{2-butyl-1-[4-(3-fluoro-4-trifluoromethyl-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-ethyl]-piperazine
436		{3-[4-(4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-imidazol-1-yl)-phenoxy]-propyl}-dimethyl-amine
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

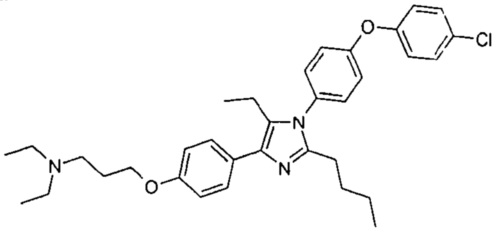
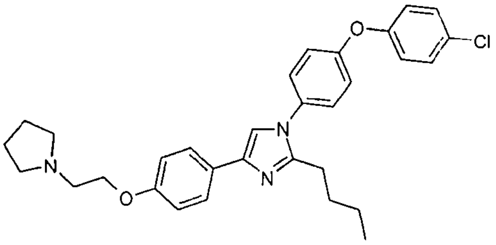
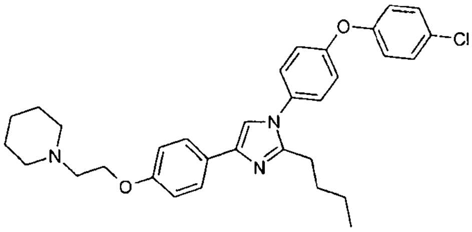
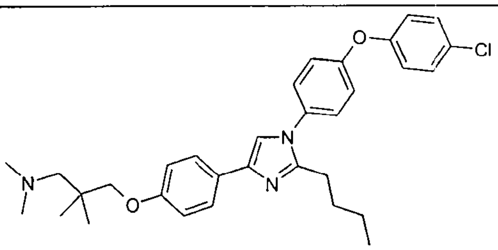
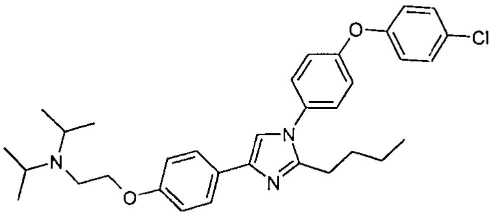
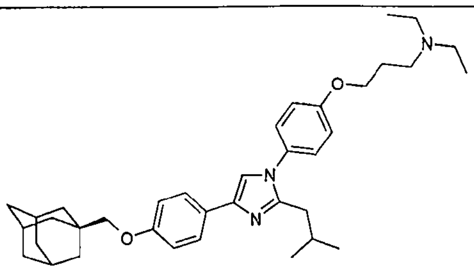
Ex.	Structure	Name
441		{3-[4-(4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-methyl-imidazol-1-yl)-phenoxy]-propyl}-diethyl-amine
442		3-(4-{2-butyl-1-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-1-ethyl-piperidine
443		diethyl-[3-(4-{1-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-2-methyl-1H-imidazol-4-yl}-phenoxy)-propyl]-amine
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-difluoro-benzyloxy)-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}-phenoxymethyl)-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}-phenoxymethyl)-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

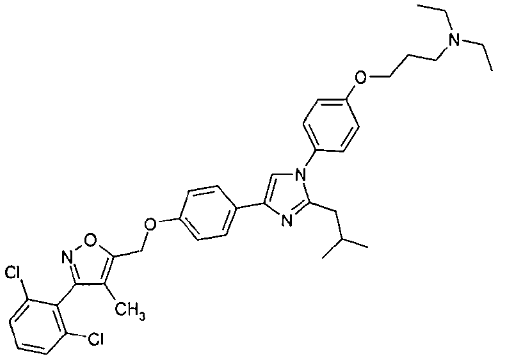
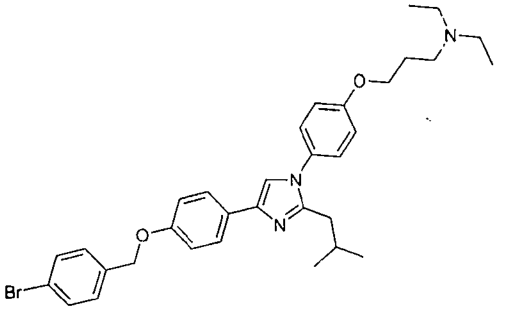
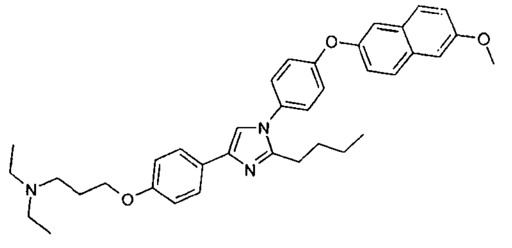
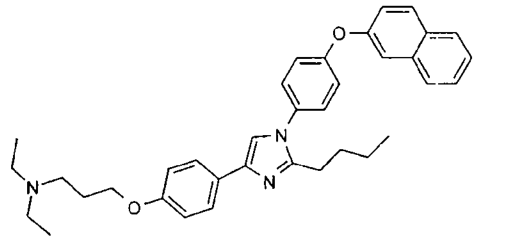
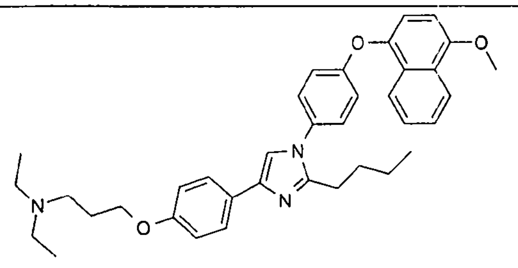
Ex.	Structure	Name
454		{3-[4-(2-(4-chloro-phenoxymethyl)-4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-imidazol-1-yl)-phenoxy]-propyl}-diethyl-amine
455		{3-[4-(2-benzyloxymethyl-4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-imidazol-1-yl)-phenoxy]-propyl}-diethyl-amine
456		{3-[4-(4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-isobutyl-5-methyl-imidazol-1-yl)-phenoxy]-propyl}-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

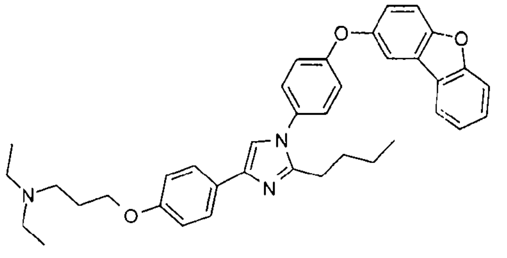
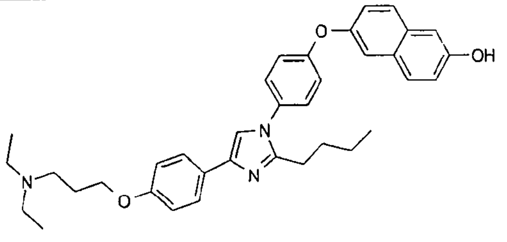
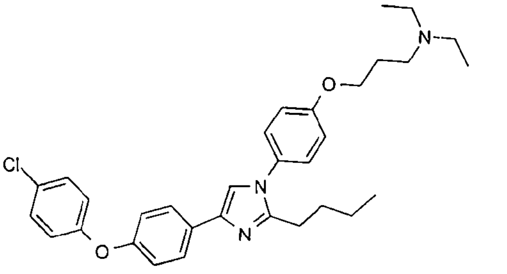
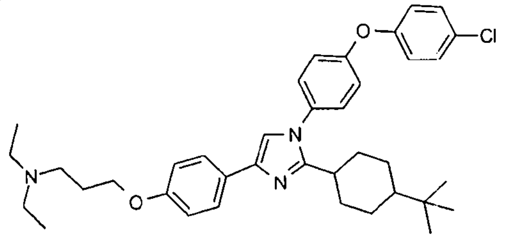
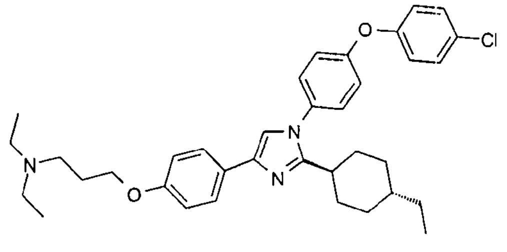
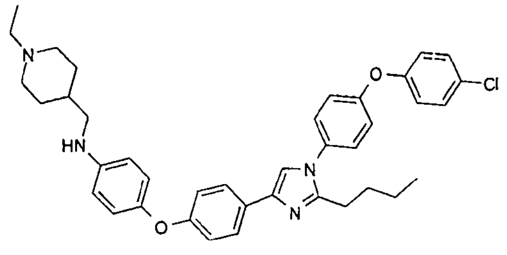
Ex.	Structure	Name
460		diethyl-[3-(4-{2-isobutyl-4-[4-(4-phenoxy-benzyloxy)-phenyl]-imidazol-1-yl}-phenoxy)-propyl]-amine
461		[3-(4-{4-[4-(4-benzyloxy-benzyloxy)-phenyl]-2-isobutyl-imidazol-1-yl}-phenoxy)-propyl]-diethyl-amine
462		[3-(4-{4-[4-(2-benzenesulfonylmethyl-benzyloxy)-phenyl]-2-isobutyl-imidazol-1-yl}-phenoxy)-propyl]-diethyl-amine
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

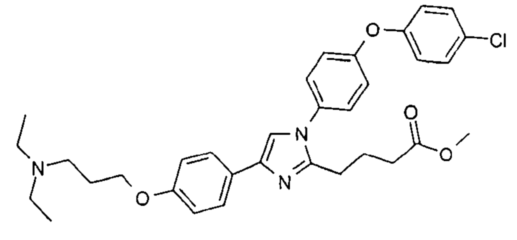
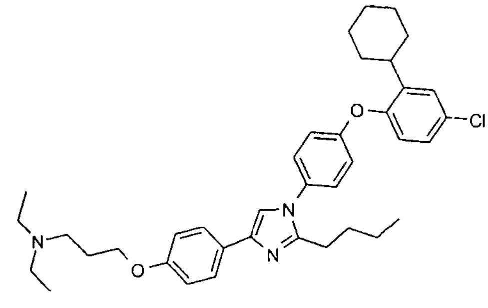
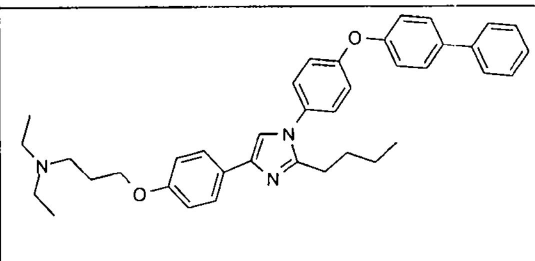
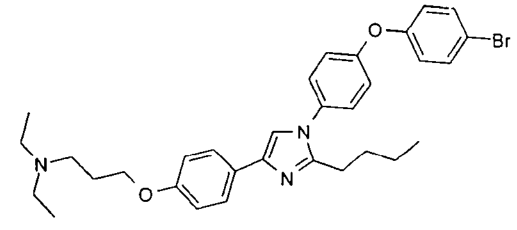
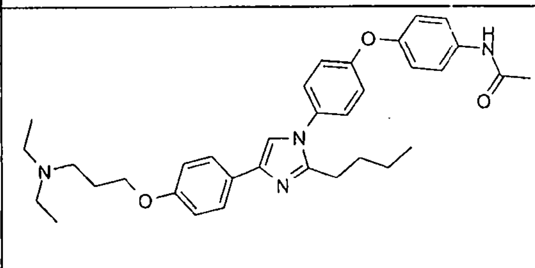
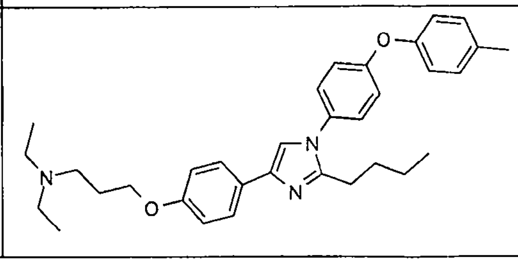
Ex.	Structure	Name
466		[3-(4-{1-[4-(4-chloro-phenoxy)-phenyl]-2-phenethyl-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine
467		[3-(4-{2-(4-tert-butyl-phenoxymethyl)-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine
468		[3-(4-{2-butyl-1-[4-(2,4-dichloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine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

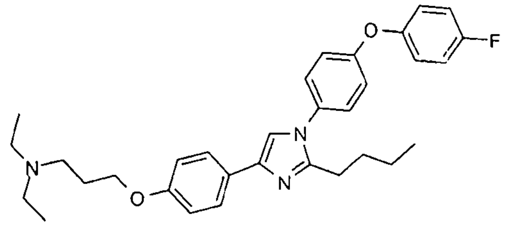
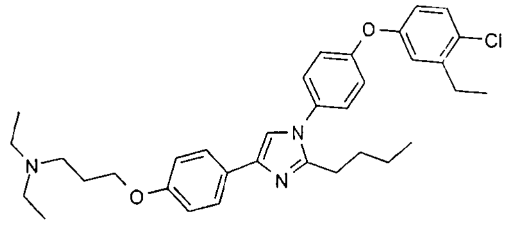
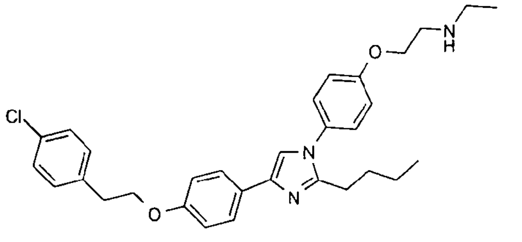
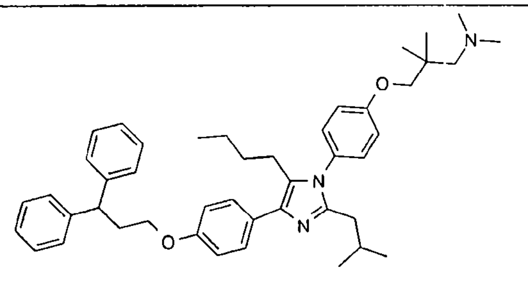
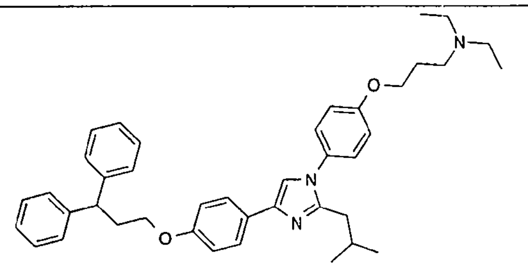
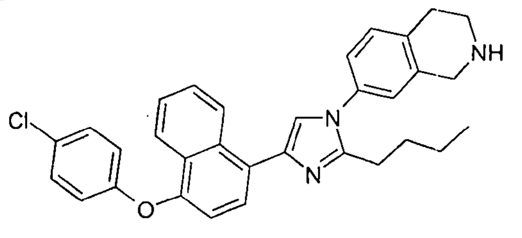
Ex.	Structure	Name
472		[3-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-5-ethyl-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine
473		2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-4-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1H-imidazole
474		1-[2-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-ethyl]-piperidine
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

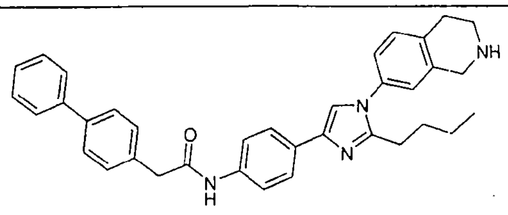
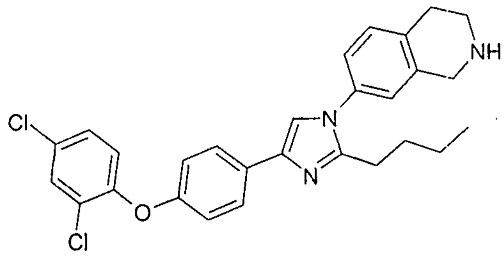
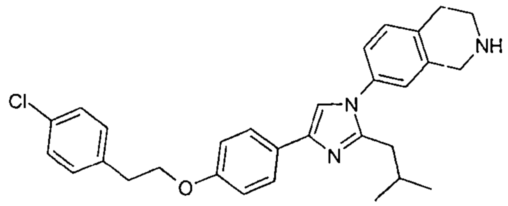
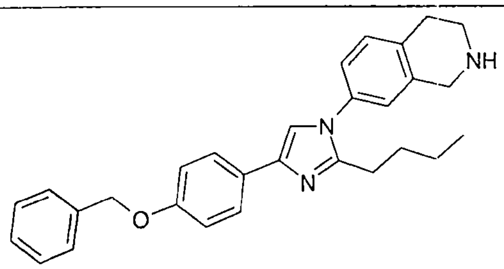
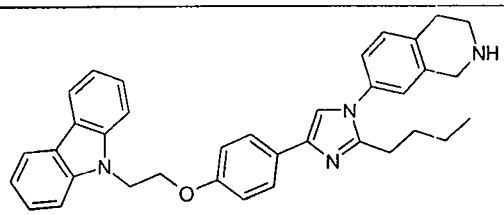
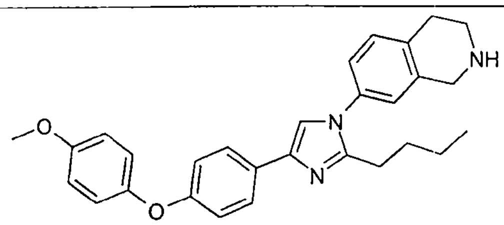
2007202350 24 May 2007

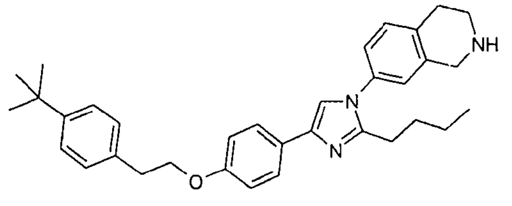
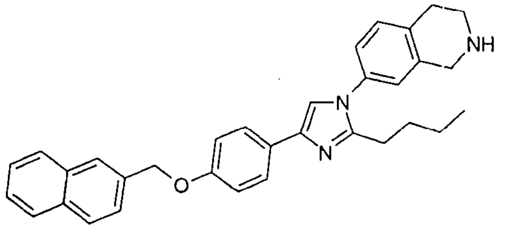
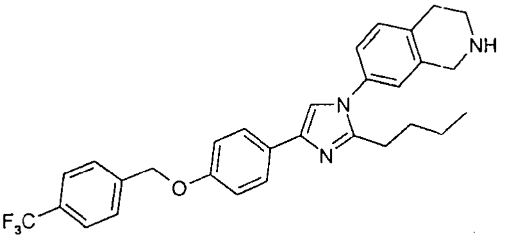
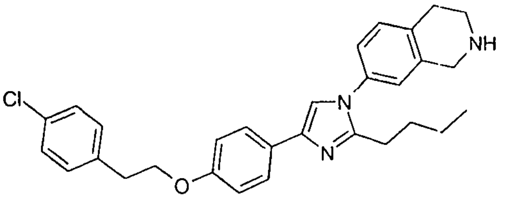
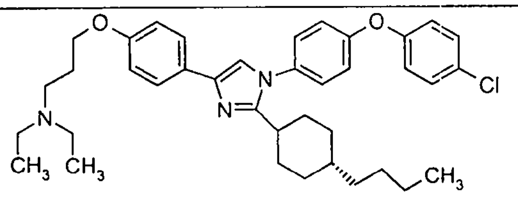
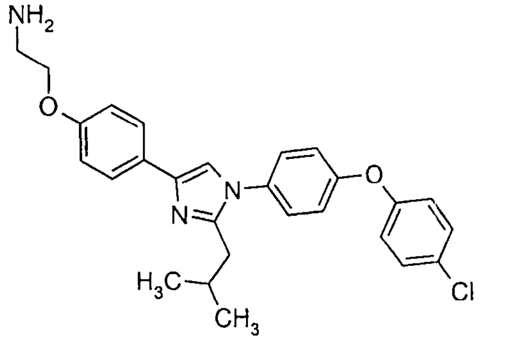
Ex.	Structure	Name
478		{3-[4-(4-{4-[3-(2,6-dichloro-phenyl)-4-methyl-isoxazol-5-ylmethyloxy]-phenyl}-2-isobutyl-imidazol-1-yl)-phenoxy]-propyl}-diethyl-amine
479		[3-(4-{4-[4-(4-bromo-benzyloxy)-phenyl]-2-isobutyl-imidazol-1-yl}-phenoxy)-propyl]-diethyl-amine
480		[3-(4-{2-butyl-1-[4-(6-methoxy-naphthalen-2-yloxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diet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

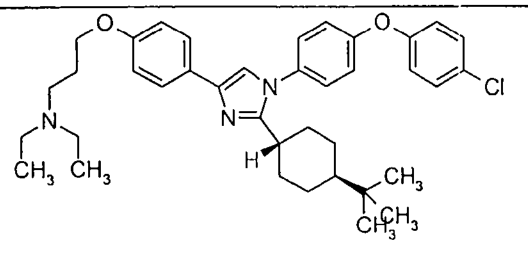
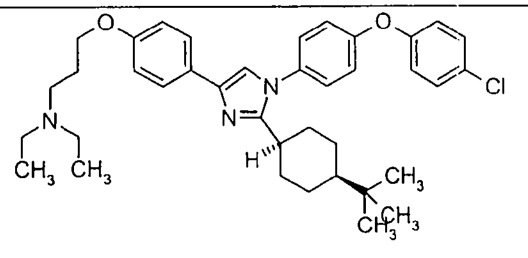
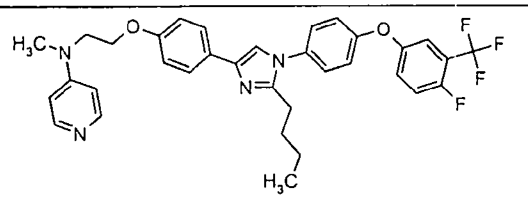
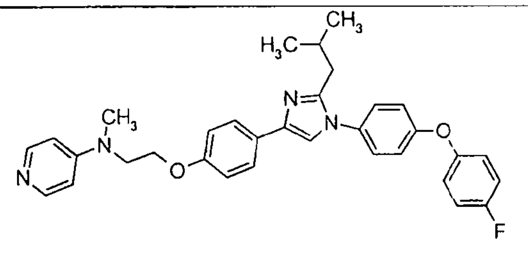
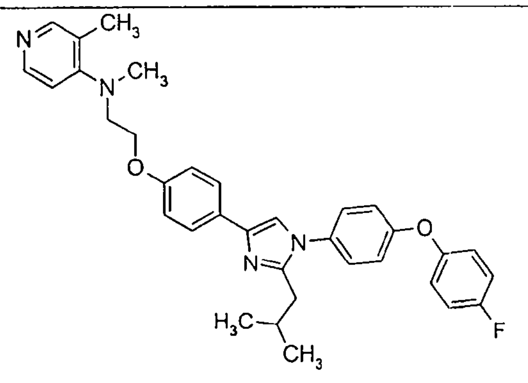
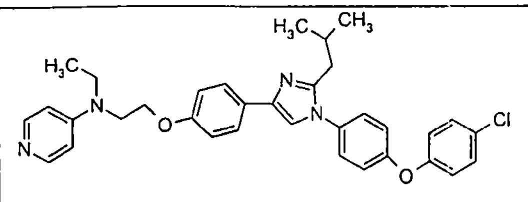
Ex.	Structure	Name
483		[3-(4-{2-butyl-1-[4-(dibenzofuran-2-yloxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine
484		6-(4-{2-butyl-4-[4-(3-diethylamino-propoxy)-phenyl]-imidazol-1-yl}-phenoxy)-naphthalen-2-ol
485		[3-(4-{2-butyl-4-[4-(4-chloro-phenoxy)-phenyl]-imidazol-1-yl}-phenoxy)-propyl]-diethyl-amine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

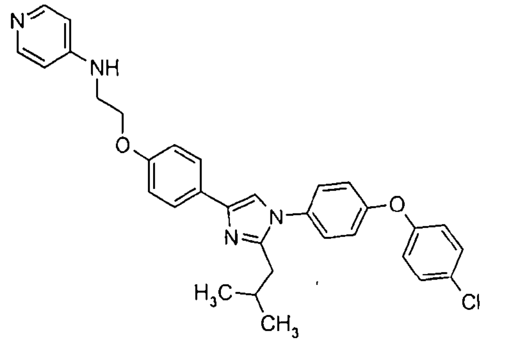
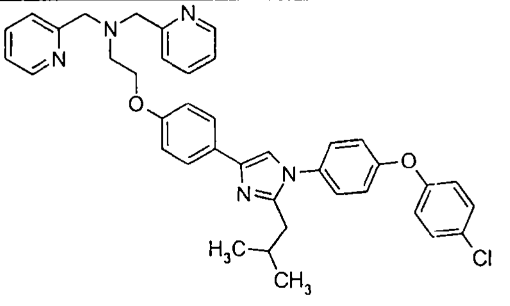
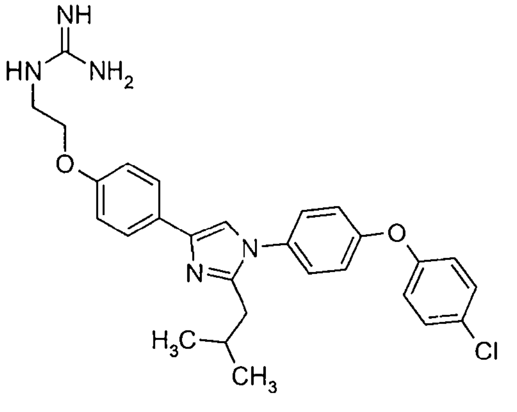
Ex.	Structure	Name
489		[4-{1-[4-(4-chloro-phenoxy)-phenyl]-4-[4-(3-diethylaminopropoxy)-phenyl]-1H-imidazol-2-yl}-butyric acid methyl ester
490		[3-(4-{2-butyl-1-[4-(4-chloro-2-cyclohexyl-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine
491		[3-(4-{1-[4-(biphenyl-4-yloxy)-phenyl]-2-butyl-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine
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-porpoxy)-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

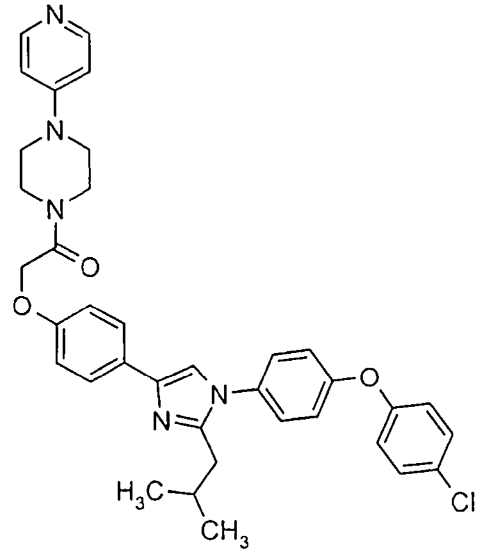
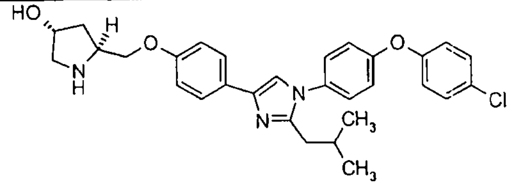
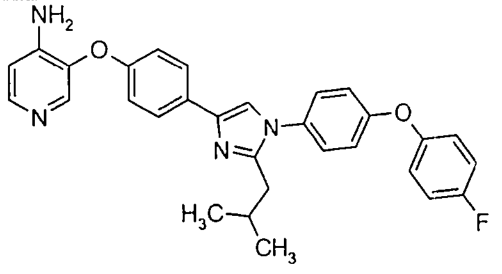
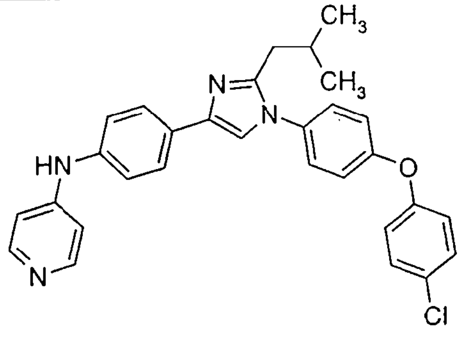
Ex.	Structure	Name
495		[3-(4-{2-butyl-1-[4-(4-fluoro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine
496		[3-(4-{2-butyl-1-[4-(4-chloro-3-ethyl-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine
497		{2-[4-(2-butyl-4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-imidazol-1-yl)-phenoxy]-ethyl}-ethyl-amine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

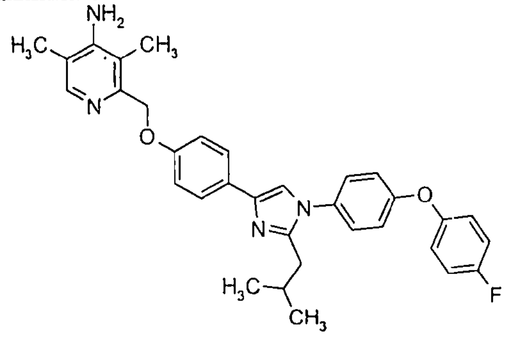
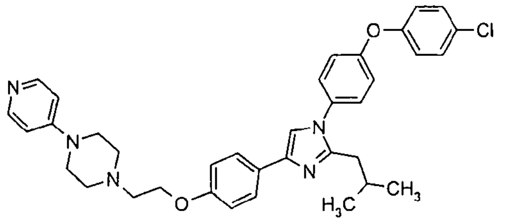
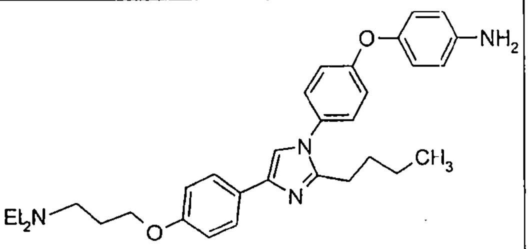
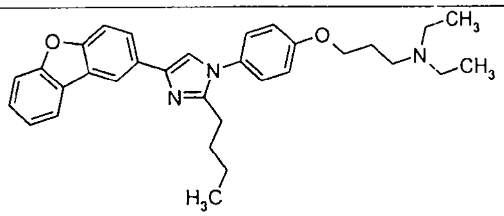
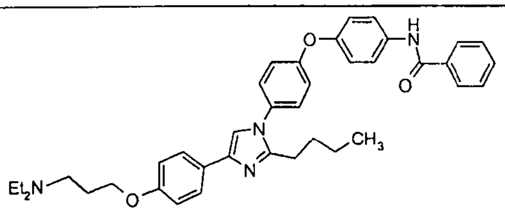
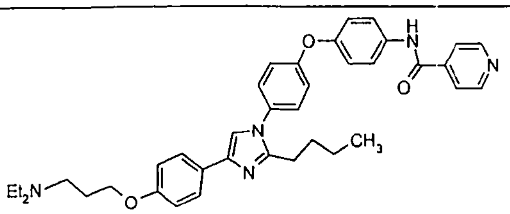
Ex.	Structure	Name
501		2-biphenyl-4-yl-N-{4-[2-butyl-1-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-1H-imidazol-4-yl]-phenyl}-acetamide
502		7-{2-butyl-4-[4-(2,4-dichloro-phenoxy)-phenyl]-imidazol-1-yl}-1,2,3,4-tetrahydro-isoquinoline
503		7-(2-butyl-4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-isobutyl-imidazol-1-yl)-1,2,3,4-tetrahydro-isoquinoline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

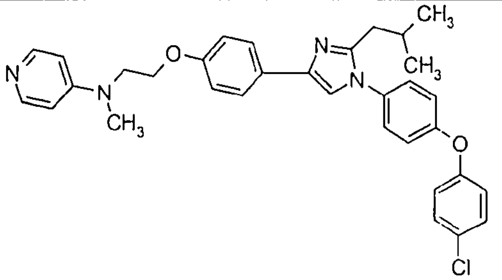
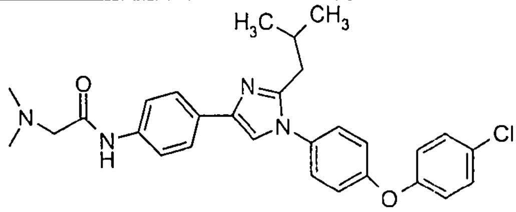
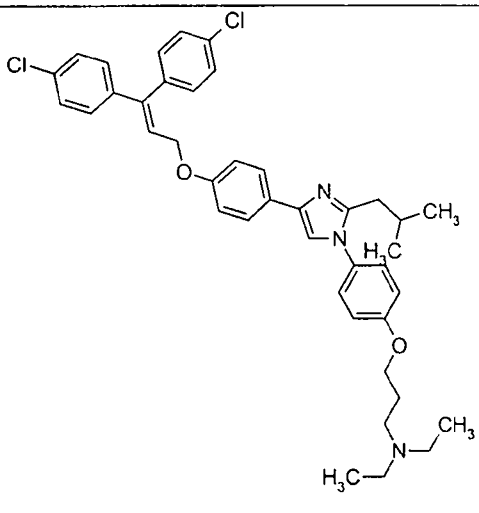
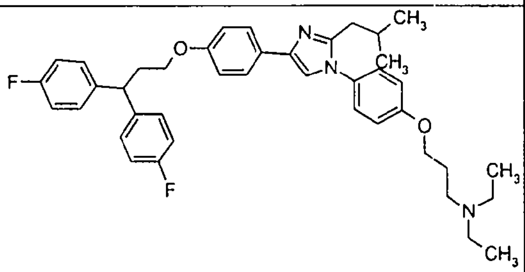
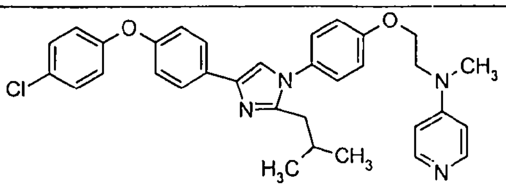
Ex.	Structure	Name
507		7-(2-butyl-4-{4-[2-(4-tert-butyl-phenyl)-ethoxy]-phenyl}-imidazol-1-yl)-1,2,3,4-tetrahydro-isoquinoline hydrochloride
508		7-{2-butyl-4-[4-(naphthalen-2-ylmethoxy)-phenyl]-imidazol-1-yl}-1,2,3,4-tetrahydro-isoquinoline hydrochloride
509		7-{2-butyl-4-[4-(4-trifluoromethyl-phenoxy)-phenyl]-imidazol-1-yl}-1,2,3,4-tetrahydro-isoquinoline 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

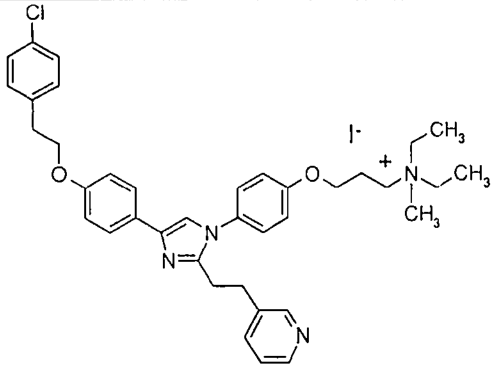
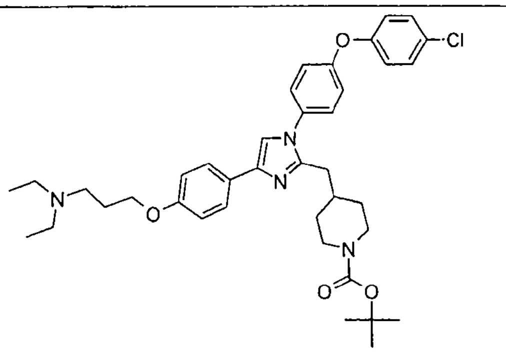
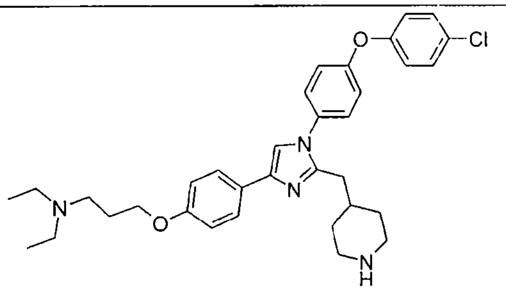
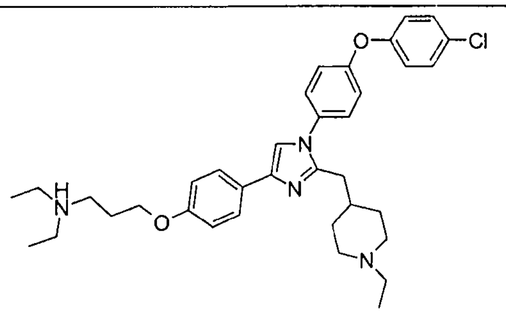
Ex.	Structure	Name
513		[3-(4-{2-(trans-4-tert-Butyl-cyclohexyl)-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine
514		[3-(4-{2-(cis-4-tert-Butyl-cyclohexyl)-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine
515		[2-(4-{2-Butyl-1-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-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

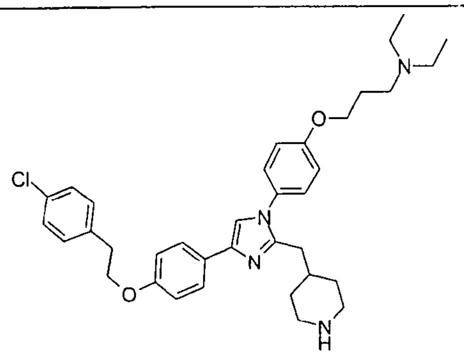
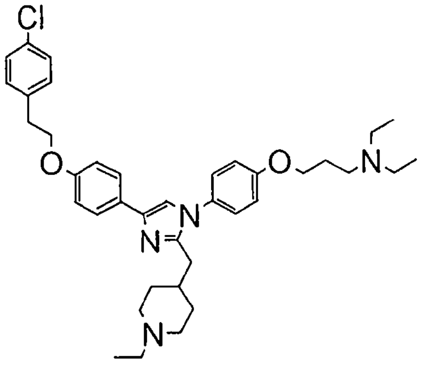
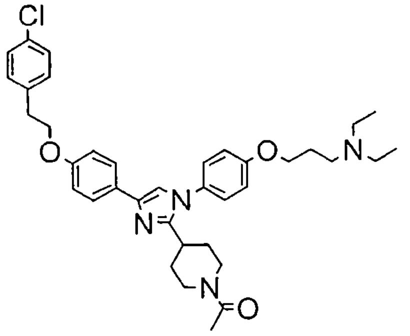
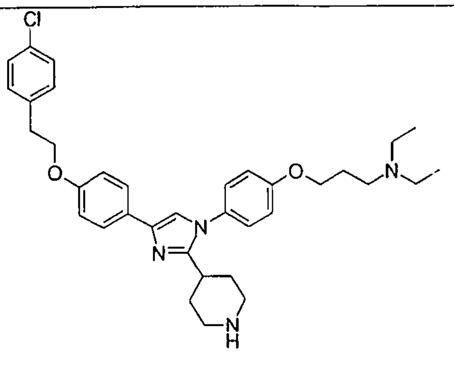
Ex.	Structure	Name
519		[2-(4-{1-[4-(4-Chloro-phenoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenoxy)-ethyl]-pyridin-4-yl-amine
520		[2-(4-{1-[4-(4-Chloro-phenoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenoxy)-ethyl]-bis-pyridin-2-ylmethyl-amine
521		N-[2-(4-{1-[4-(4-Chloro-phenoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenoxy)-ethyl]-guanidine

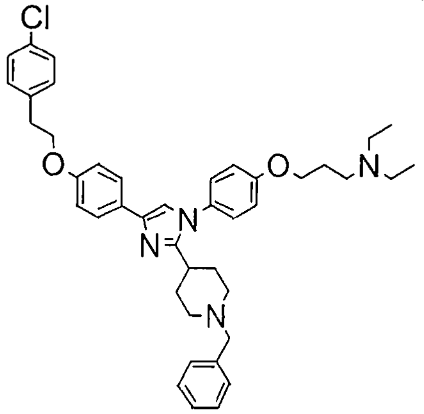
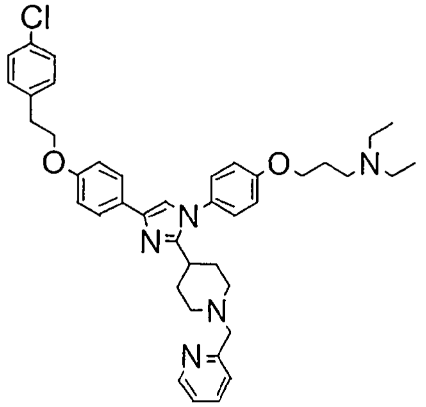
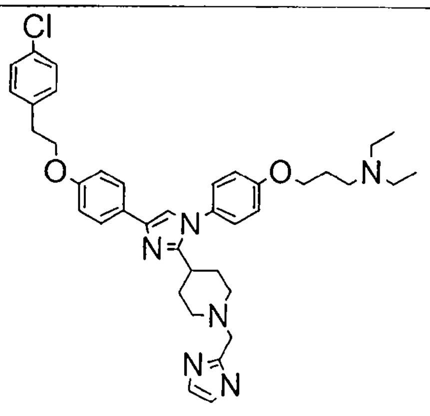
Ex.	Structure	Name
522		2-(4-{1-[4-(4-Chloro-phenoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenoxy)-1-(4-pyridin-4-yl-piperazin-1-yl)-ethanone
523		5-(4-{1-[4-(4-Chloro-phenoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenoxymethyl)-pyrrolidin-3-ol
524		3-(4-{1-[4-(4-Fluoro-phenoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenoxy)-pyridin-4-ylamine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

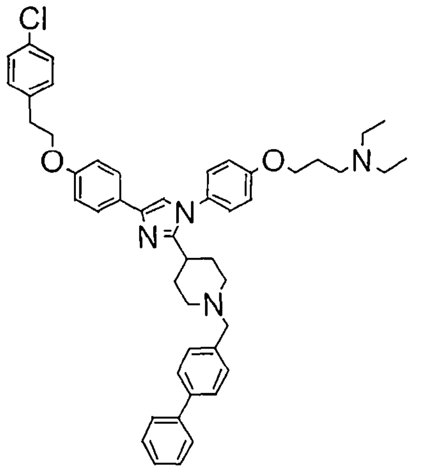
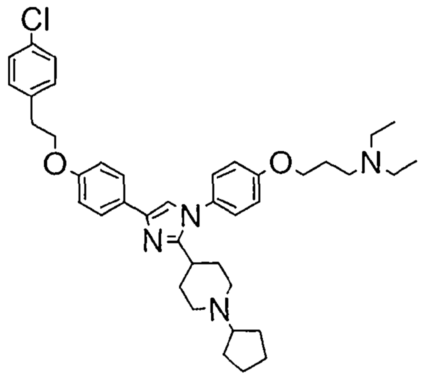
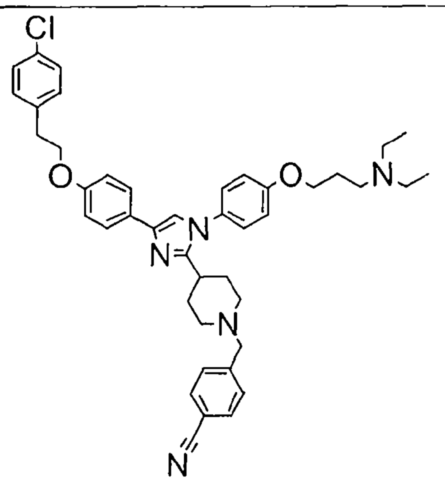
Ex.	Structure	Name
532		[2-(4-{1-[4-(4-Chloro-phenoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenoxy)-ethyl]-methyl-pyridin-4-yl-amine
533		N-(4-{1-[4-(4-Chloro-phenoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenyl)-2-dimethylamino-acetamide
534		{3-[4-(4-{4-[3,3-Bis-(4-chloro-phenyl)-allyloxy]-phenyl}-2-isobutyl-imidazol-1-yl)-phenoxy]-propyl}-diethyl-amine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

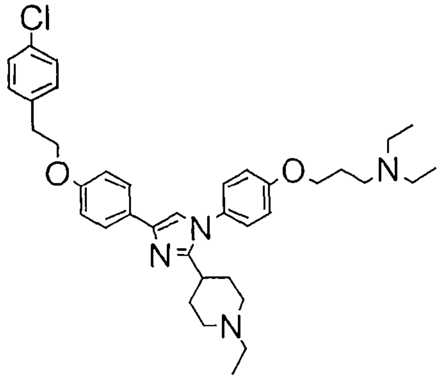
Ex.	Structure	Name
537		[3-(4-{4-{4-[2-(4-Chloro-phenyl)-ethoxy]-phenyl}-2-[2-(1-methyl-pyridin-3-yl)-ethyl]-imidazol-1-yl}-phenoxy)-propyl]-diethylmethyl ammonium iodide
538		[3-(4-{2-(N-BOC-piperidine-4-ylmethyl)-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine
539	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

2007202350 24 May 2007

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

Definitions of Terms

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

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.

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, 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.

As used herein, the term "alkyline" 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 "alkyline" as used herein include, but are not limited to, methine, 1,1,2-ethyline, and the like.

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.

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.

2007202350 24 May 2007

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.

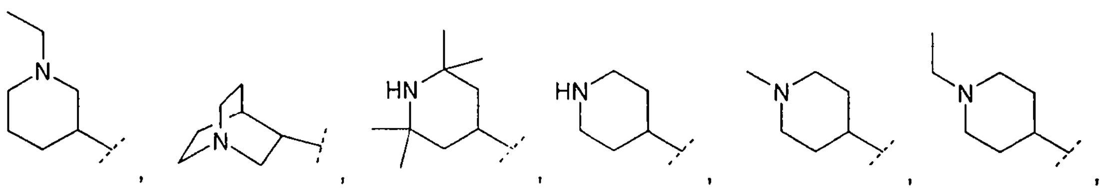
As used herein, "cycloalkyl" refers to an alicyclic hydrocarbon group optionally possessing one or more degrees of unsaturation, having from three to twelve carbon atoms, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower 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.

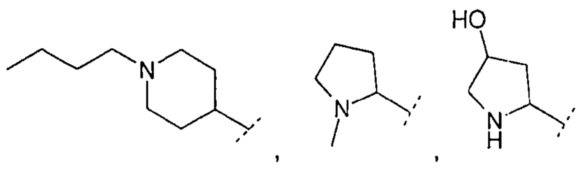
As used herein, the term "cycloalkylene" refers to an non-aromatic alicyclic divalent hydrocarbon radical having from three to twelve carbon atoms and optionally possessing one or more degrees of unsaturation, optionally substituted with substituents selected from the group consisting of lower alkyl, 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, SO_2, 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,





and the like.

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, SO_2, 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.

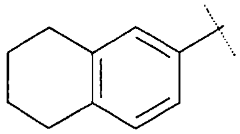
As used herein, the term "aryl" refers to a benzene ring or to an optionally substituted benzene ring system fused to one or more optionally substituted benzene rings, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower 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.

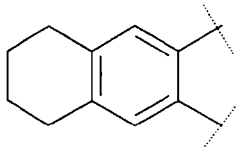
As used herein, the term "heteroarylene" refers to a five - to seven - membered aromatic ring diradical, or to a polycyclic heterocyclic aromatic ring diradical, containing one or more nitrogen, oxygen, or sulfur heteroatoms, where N-oxides and sulfur monoxides and sulfur dioxides are permissible heteroaromatic 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,



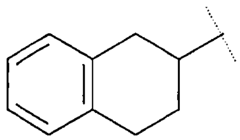
, and the like.

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



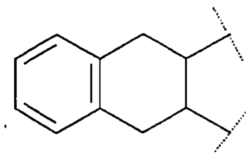
, and the like.

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),

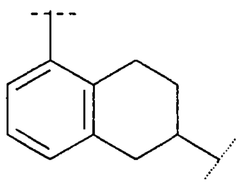


, and the like.

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

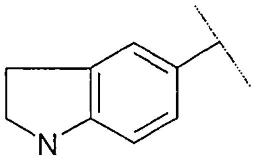


,



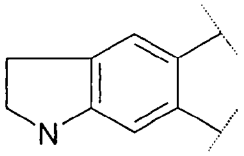
, and the like.

As used herein, the term "fused heterocyclylaryl" refers to one or more heterocyclyl groups fused to an aryl group, the aryl and heterocyclyl groups having two atoms in common, and wherein the aryl group is the point of substitution. Examples of "fused heterocyclylaryl" used herein include 3,4-methylenedioxy-1-phenyl,



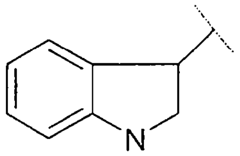
, and the like

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

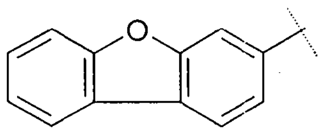


, and the like.

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



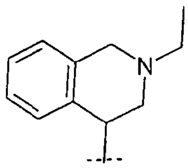
,



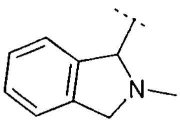
, and the like.

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

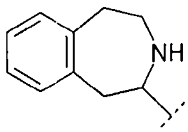
wherein said heterocyclyl group contains at least one nitrogen atom flanked by hydrogen, alkyl, alkylene, or alkylyne groups, wherein said alkyl and/or alkylene groups are not substituted by oxo. Examples of "fused arylheterocyclyl containing at least one basic nitrogen atom" include, but are not limited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



,

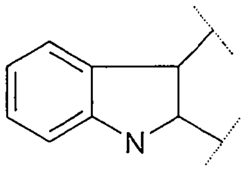


,

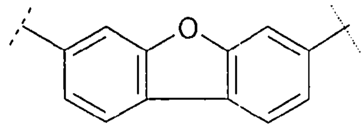


, and the like.

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

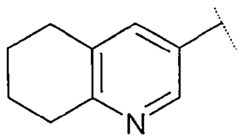


,



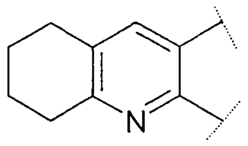
, and the like.

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,



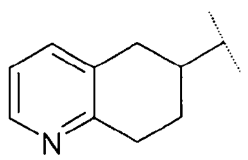
, and the like.

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



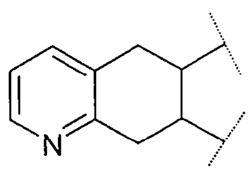
, and the like.

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,



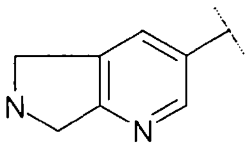
and the like.

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



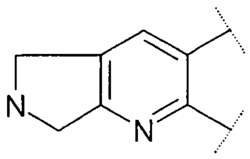
, and the like.

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,



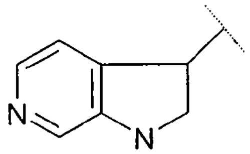
and the like.

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



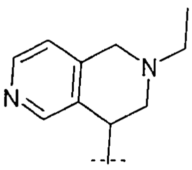
, and the like.

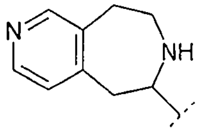
As used herein, the term "fused heteroarylheterocyclyl" refers to one or more heteroaryl groups fused to a heterocyclyl group, the heterocyclyl and heteroaryl groups having two atoms in common, and wherein the heterocyclyl group is the point of substitution. Examples of "fused heteroarylheterocyclyl"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



, and the like.

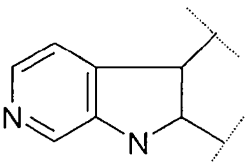
As used herein, the term "fused heteroarylheterocyclyl containing at least one basic nitrogen atom" refers to a "fused heteroarylheterocyclyl" group as defined above, wherein said heterocyclyl group contains at least one nitrogen atom flanked by hydrogen, alkyl, alkylene, or alkylyne groups, wherein 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,



, 

, and the like.

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



, and the like.

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.

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.

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.

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.

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.

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.

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.

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 "aroyloxy" refers to the group $R_aC(O)O$- , where R_a is aryl.

As used herein, the term "heteroaroyloxy" 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 $-SO_2NH_2$.

As used herein, the term “carbamoyl” shall refer to the substituent $-C(O)NH_2$.

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

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

As used herein, the term “sulfonyl” shall refer to the substituent $-S(O)_2-$.

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.

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.*, C_1-C_4), lower acyloxyalkyl esters, lower alkoxyacyloxyalkyl esters, alkoxyacyloxy esters, alkyl acylamino alkyl esters, and choline esters.

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

2007202350 24 May 2007

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 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 R_2 and an amine in R_4, 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-dihydropyridine, N-alkylcarbonyl-1,4-dihydropyridine, 1,4-cyclohexadiene, tert-butyl, and the like.

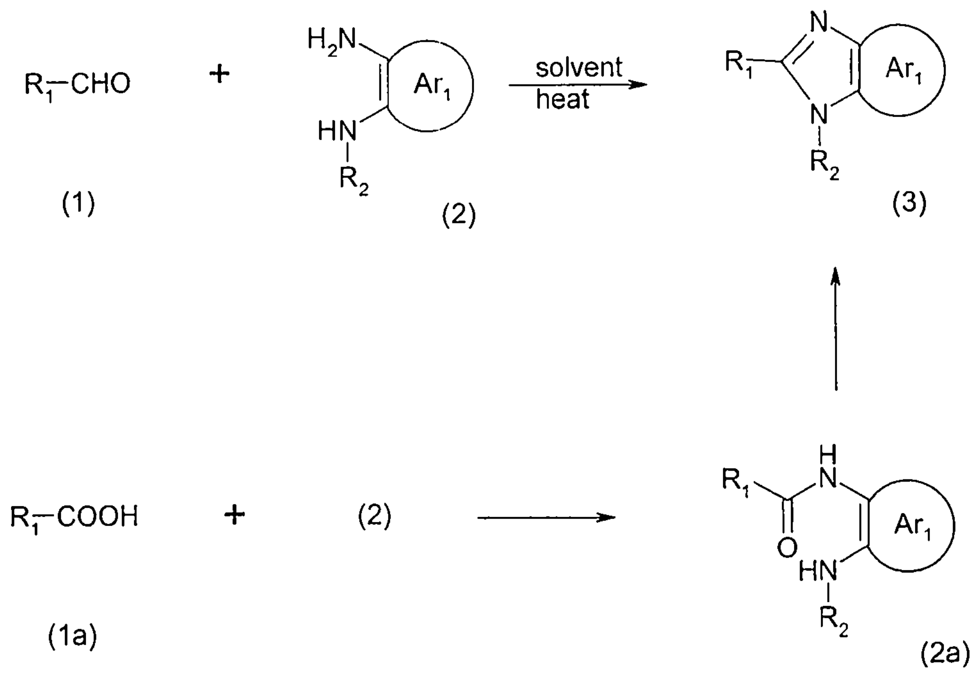
The term "pharmacologically effective amount" or shall mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, animal or human that is being sought by a researcher or clinician. This amount can be a therapeutically effective amount. The term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

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.

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).

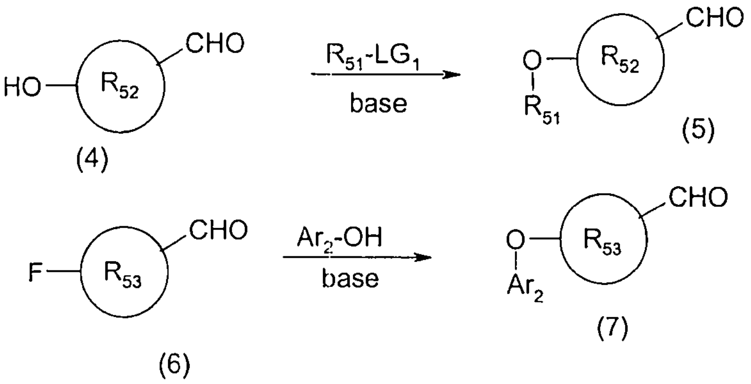
An aldehyde (1) (Scheme 1) may be condensed with a diamine compound (2) in a solvent such as ethanol at a temperature of from 25 to 100 degrees Celsuis, to obtain the product benzimidazole (3), where the intermediate adduct undergoes spontaneous oxidation. Alternately, the acid (1a) may be coupled with 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 Celsuis, to obtain the cyclized product (3). Ar_1 is a group such as but not limited to an optionally substituted aryl or heteroaryl ring system.

Scheme 1



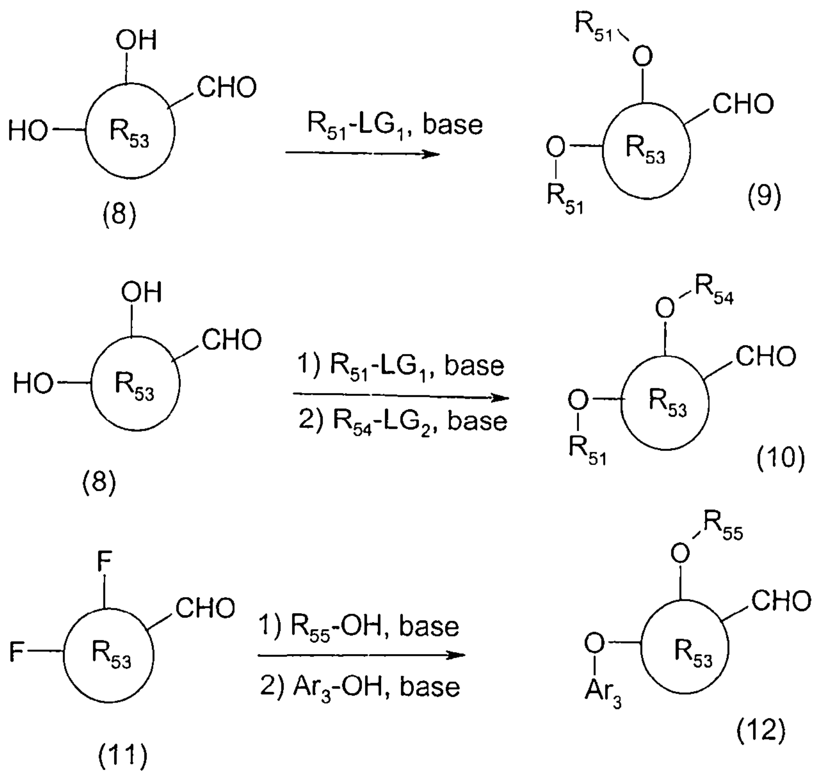
Where R_{52} is aryl, heteroaryl, or contains an aryl or heteroaryl group possessing a phenolic substituent, or where R_{52} possesses a free hydroxyl group, an aldehyde of formula (4) (Scheme 2) may be treated with an optionally substituted alkyl halide R_{51}-LG_1 and a base such as potassium carbonate, in a solvent such as DMF, at a temperature of from 0 to 120 °C, to afford (5). LG_1 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



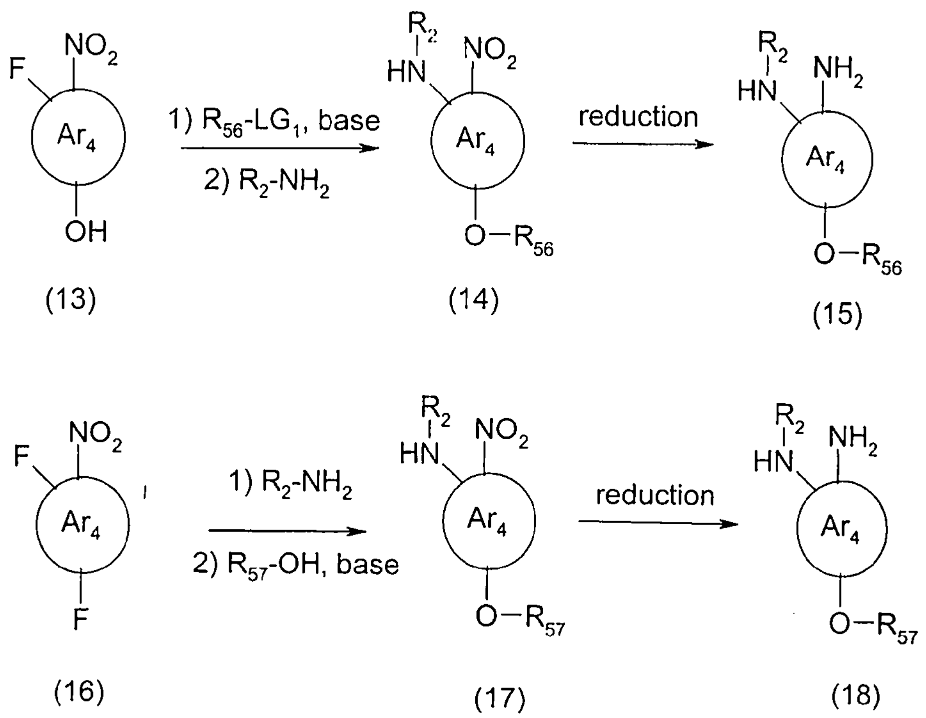
In Scheme 3, an aldehyde (8) posessing two free hydroxyl groups , two free phenolic groups, of a combination of phenolic and hydroxyl groups may be treated with two equivalents of an alkylating agent R_{51}-LG_1, in the presence of a suitable base such as potassium carbonate or DIEA, in a solvent such as DMF, to afford (9). Alternately, where R_{53} is an aryl ring posessing ortho and para hydroxyl groups relative to the aldehyde group, treatment of (8) with one equivalent of base and an alkylating agent R_{51}-LG_1 in the presence of a suitable base such as DIEA of potassium carbonate, followed by treatment with a second alkylating agent R_{54}-LG_2 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, folllowed 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


OH
CHO
HO
R53
(8)
R51-LG1, base
R51
O
CHO
O
R53
R51
(9)
OH
CHO
HO
R53
(8)
1) R51-LG1, base
2) R54-LG2, base
R54
O
CHO
O
R53
R51
(10)
F
CHO
F
R53
(11)
1) R55-OH, base
2) Ar3-OH, base
R55
O
CHO
O
R53
Ar3
(12)

Scheme 4 describes the synthesis of substituted arylenediamines.

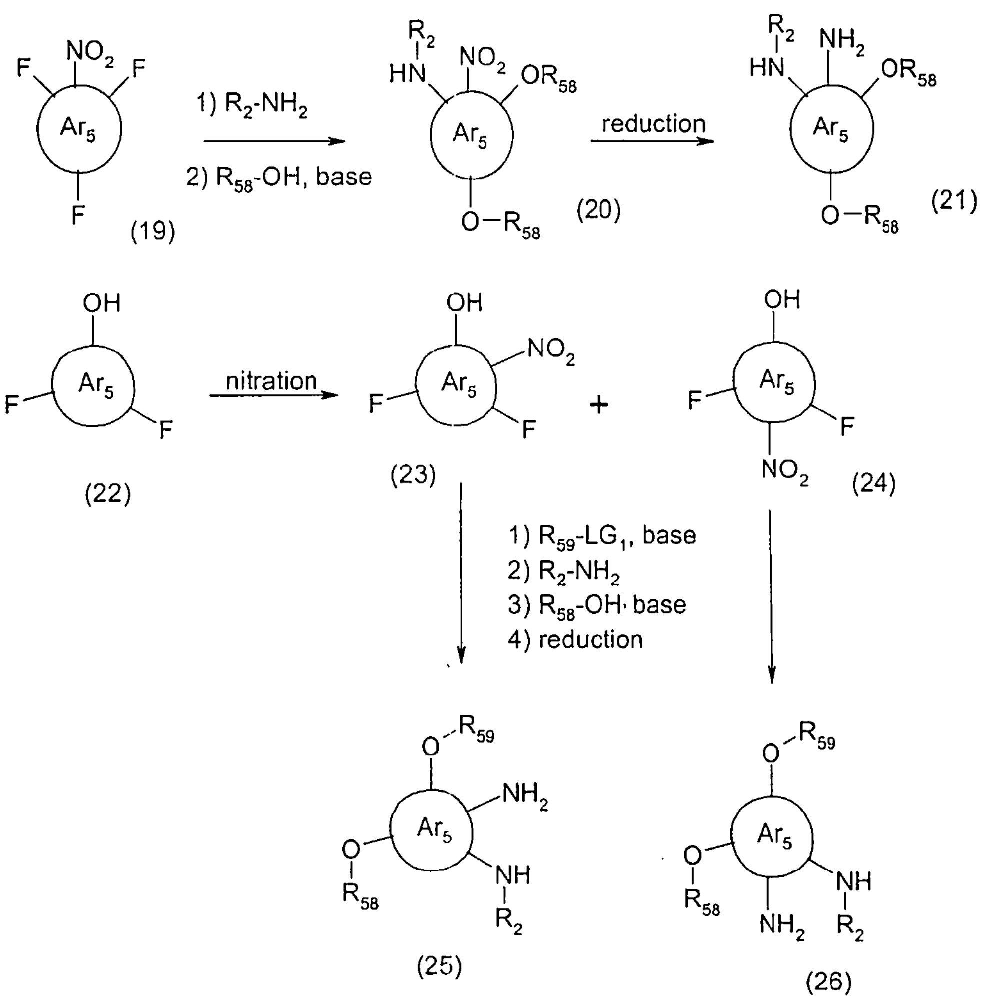
Scheme 4



In Scheme 4, an ortho-fluoro nitrophenol such as (13) may be alkylated with an alkyl halide or other alkylating agent R_{56}-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-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-NH_2 gives preferential substitution of the ortho fluorine. The second fluorine in the intermediate may be substituted by an alcohol R_{57}-OH to afford (17). In this instance, R_{57} may also be aryl. Reduction of the nitro group in (17) as before with stannous chloride provides (18). Ar_4 represents a group such as but not limited to aryl or heteroaryl.

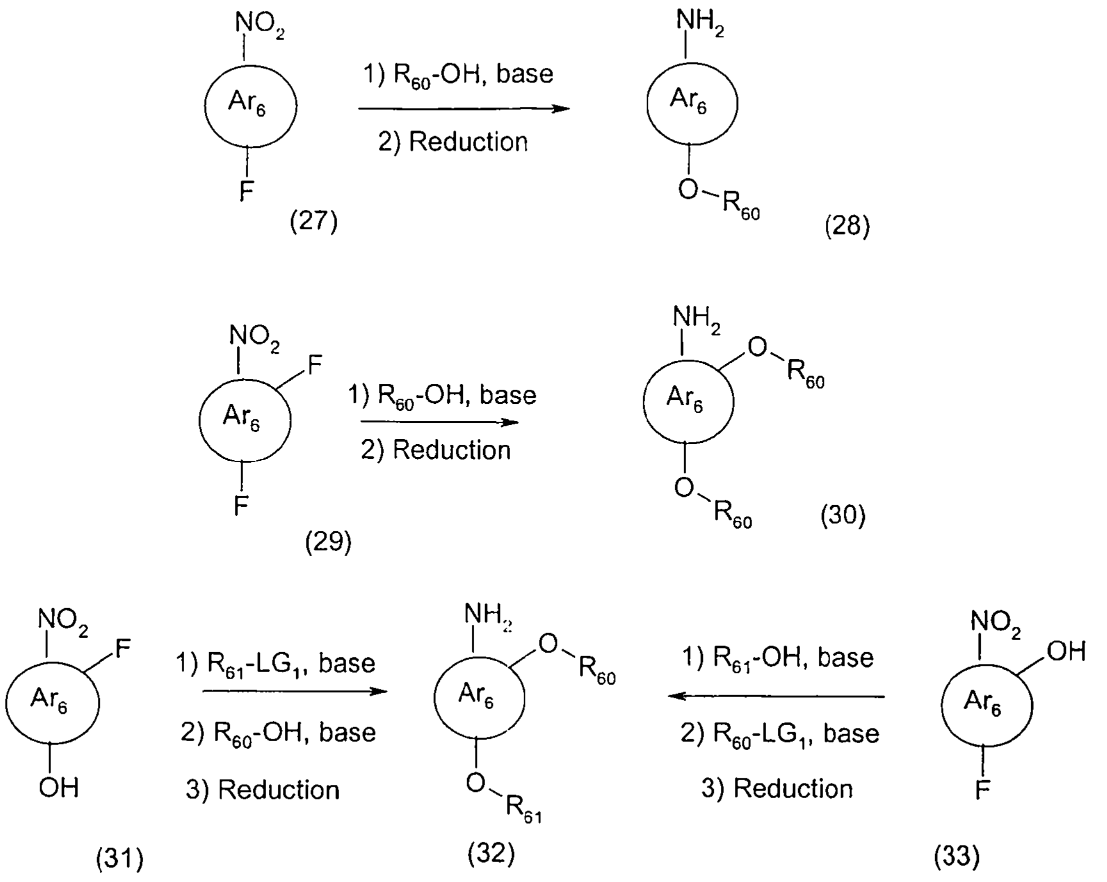
Scheme 5 describes synthesis of aryl diamines. The 2,4,6-trifluoronitroaromatic compound (19) may be treated with one equivalent of an amine R_2-NH2 to afford the product of substitution at one ortho fluoro; excess R_{58}-OH may then be employed in the presence of a base such as potassium tert-butoxide 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 R_2-NH_2, and para or ortho fluorodisplacement by R_{58}-OH, to afford (25) and (26) after reduction, following chemistries in the predceding general procedures. Ar_5 represents a group such as but not limited to aryl or heteroaryl.

Scheme 5



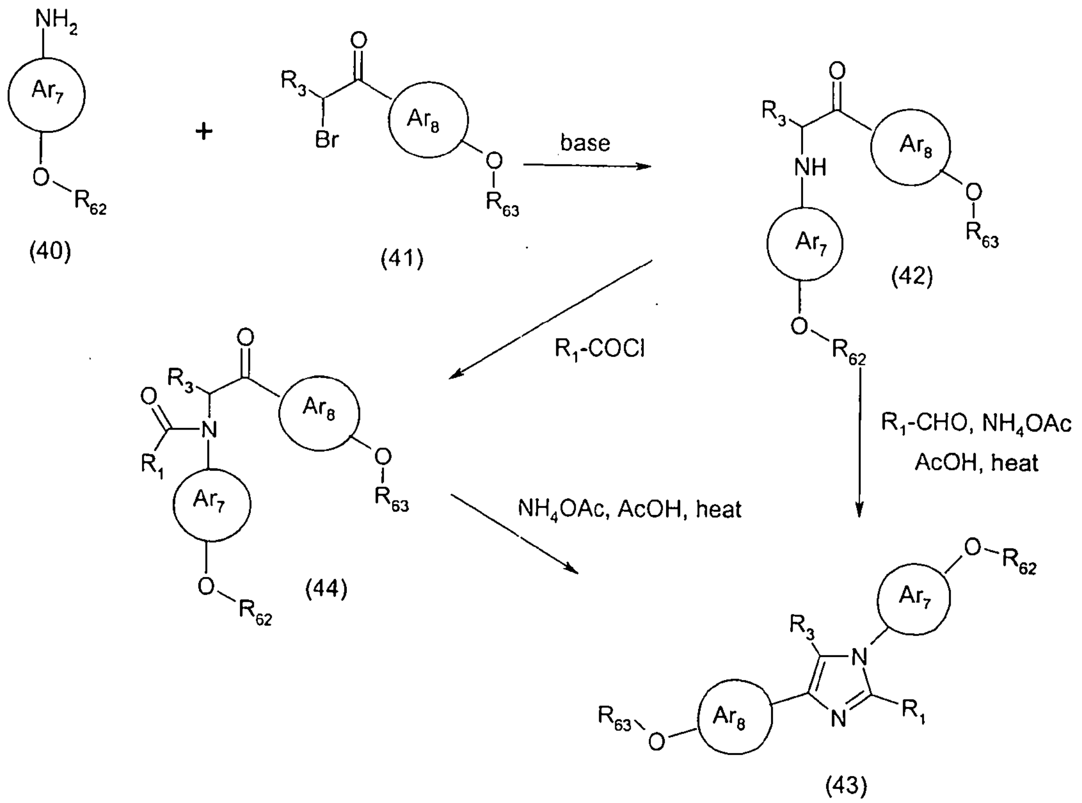
Scheme 6 describes the synthesis of mono and di alkoxy – substituted aminoaryl and aminoheteroaryl compounds. A fluoronitroaromatic (27), where F is preferably ortho or para to the nitro, may be treated with an alcohol or phenol R_{60}-OH and a base such as potassium tert-butoxide or sodium hydride, 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 R_{60}-OH followed by reduction as before give (30). The nitro compound (31) may be treated with a base and R_{61}-LG_1 to afford the alkylation product, then treated with R_{60}-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.

Scheme 6


NO2
Ar6
F
(27)
1) R60-OH, base
2) Reduction
NH2
Ar6
O-R60
(28)
NO2
F
Ar6
F
(29)
1) R60-OH, base
2) Reduction
NH2
O-R60
Ar6
O-R60
(30)
NO2
F
Ar6
OH
(31)
1) R61-LG1, base
2) R60-OH, base
3) Reduction
NH2
O-R60
Ar6
O-R61
(32)
1) R61-OH, base
2) R60-LG1, base
3) Reduction
NO2
OH
Ar6
F
(33)

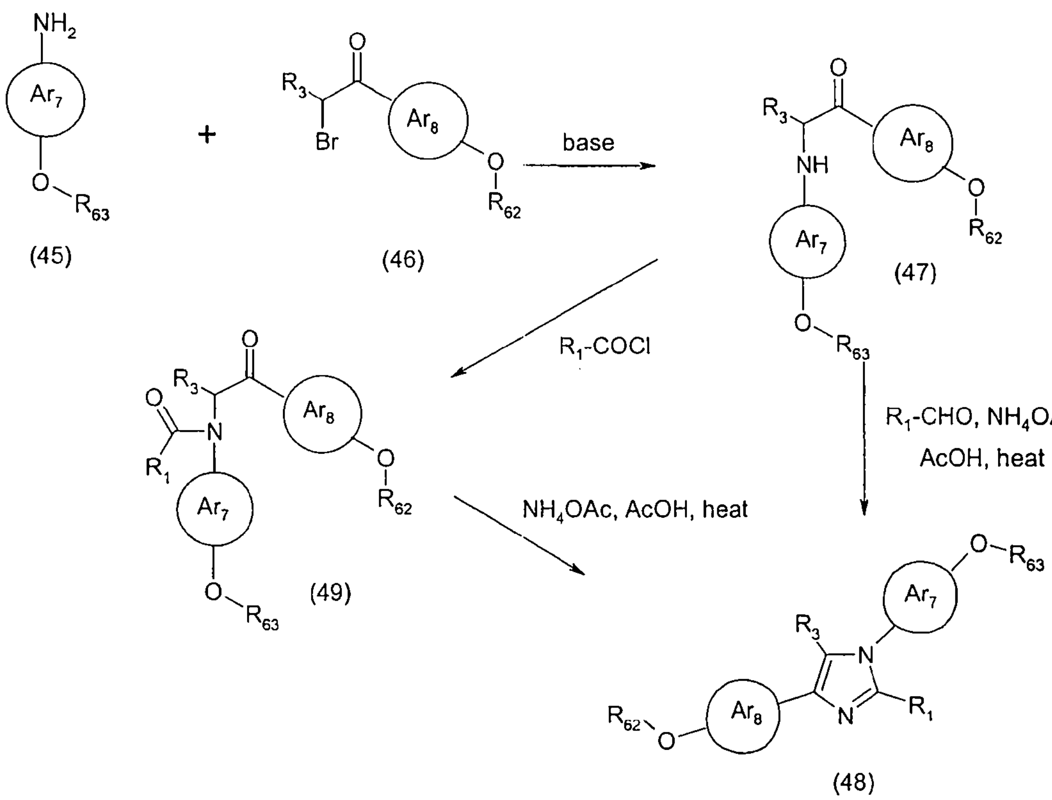
Scheme 7 describes a general synthesis of imidazoles. An aniline containing a basic side chain (–O-R_{62}) (40) may be coupled with a bromoketone containing a non-basic side chain(–O-R_{63}) (41) to give the aminoketone (42), which may then be treated with acetic acid, heat, an aldehyde R_1-CHO, and ammonium acetate to afford (43). Alternately, (42) may be treated with an acid chloride R_1-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



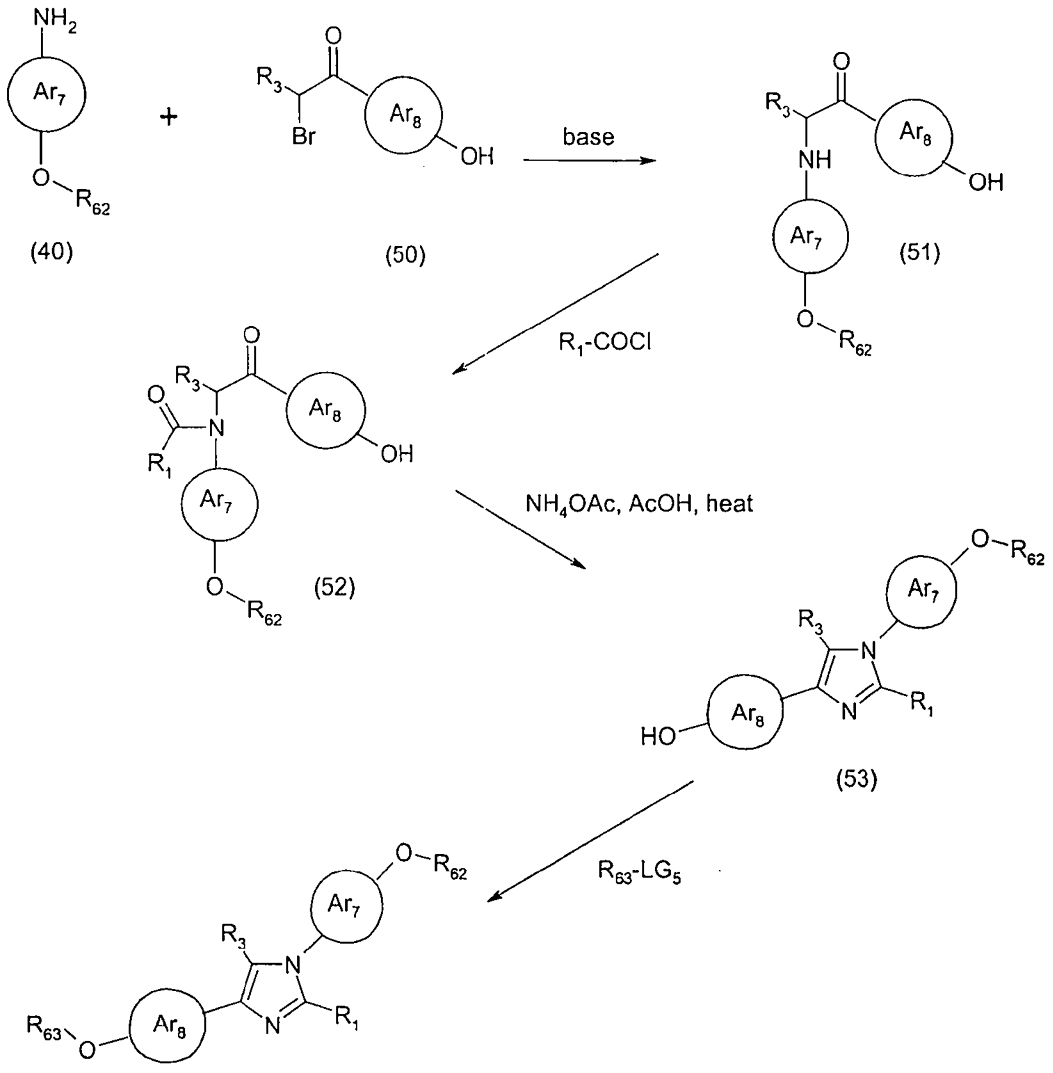
Scheme 8 describes another general synthesis of imidazoles. An aniline containing a non-basic side chain (45) may be coupled with a bromoketone containing a basic side chain (46) to give the aminoketone (47), which may then be treated with acetic acid, heat, an aldehyde R_1-CHO, and ammonium acetate to afford (48). Alternately, (42) 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 (43). 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-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 a alkylating agent R_{63}-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.

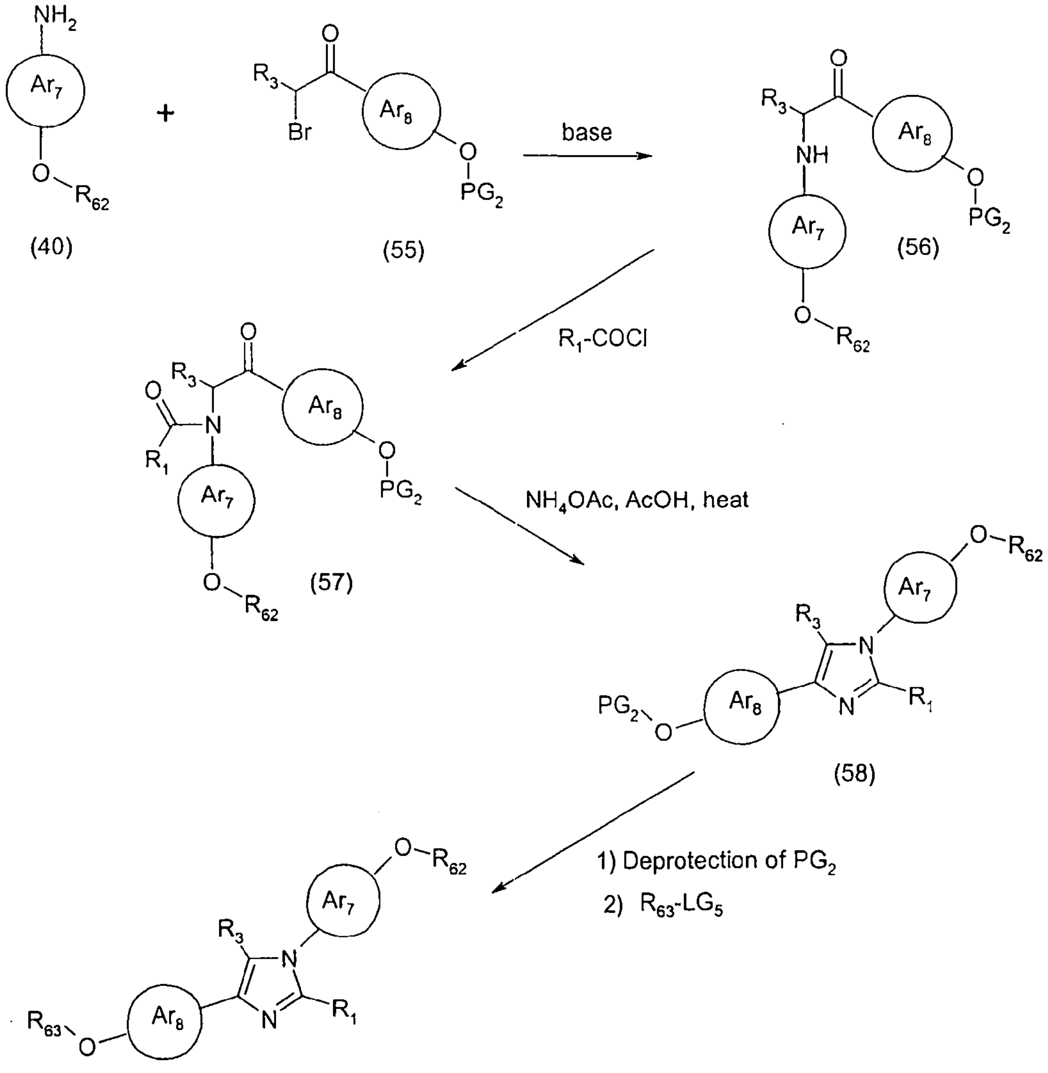
Scheme 9



(54)

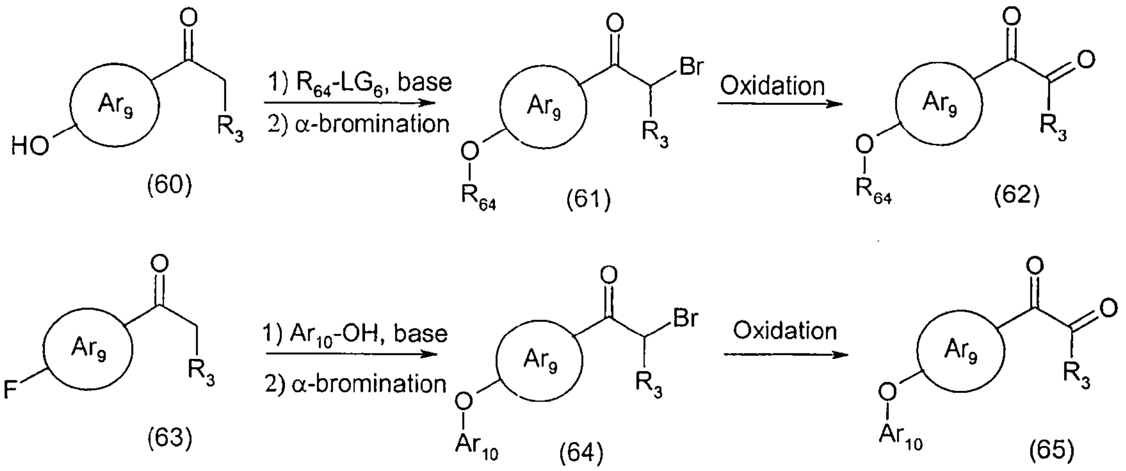
Scheme 10 describes another general synthesis of imidazoles. An aniline containing a hydrophobic side chain (40) may be coupled with a bromoketone (55) to give the aminoketone (56), which may then be treated with an acid chloride R_1-COCl to afford (57), which may subsequently be treated with ammonium acetate, acetic acid and heat to afford (58). The phenol is then deprotected; PG_1 may be a group sych 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}-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.

Scheme 10



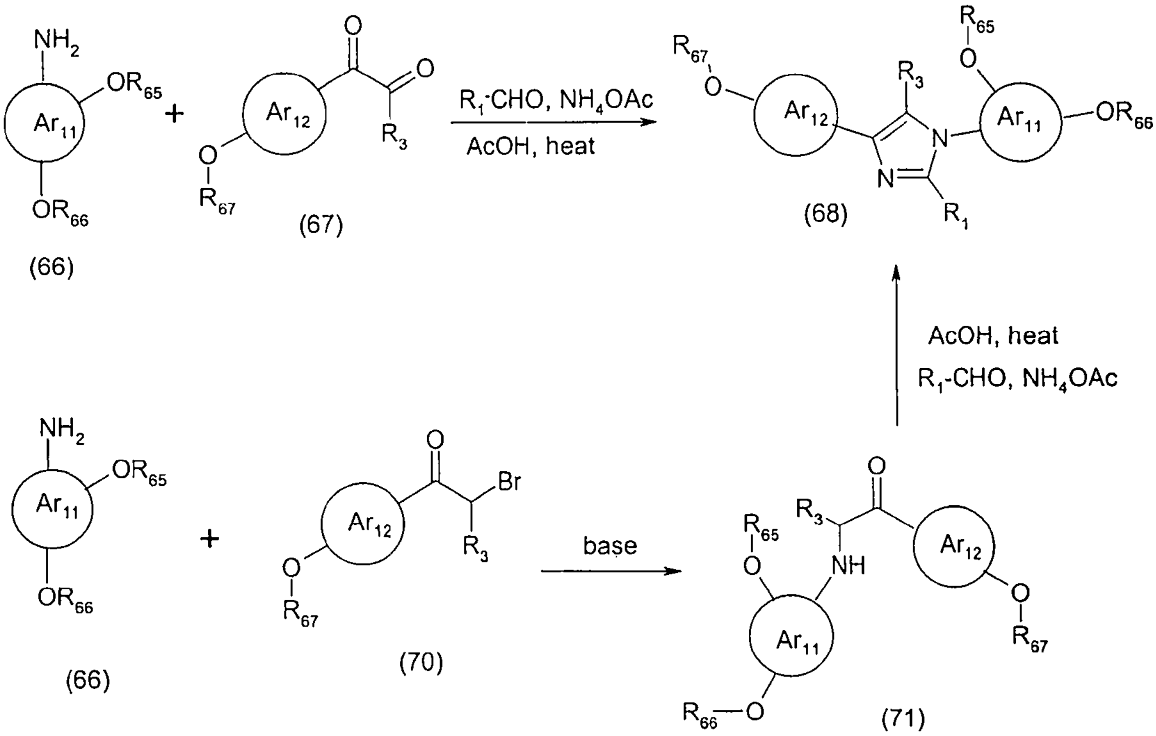
Scheme 11 describes the symnthesis of diones or bromoketones. A aryl ketone (60) may be treated with base and an alkylating agent R_{64}-LG_6 to generate the phenyl ether. R_{64} is a group such as but not limited to substituted alkyl, and LG_6 is a leaving group such as iodide or methanesulfonate. The 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 Ar_{10}-OH and base, followed by bromination, to afford (64). Oxidation as before gives the dione (65). Ar_9 is a group such as but not limited to aryl or heteroaryl.

Scheme 11



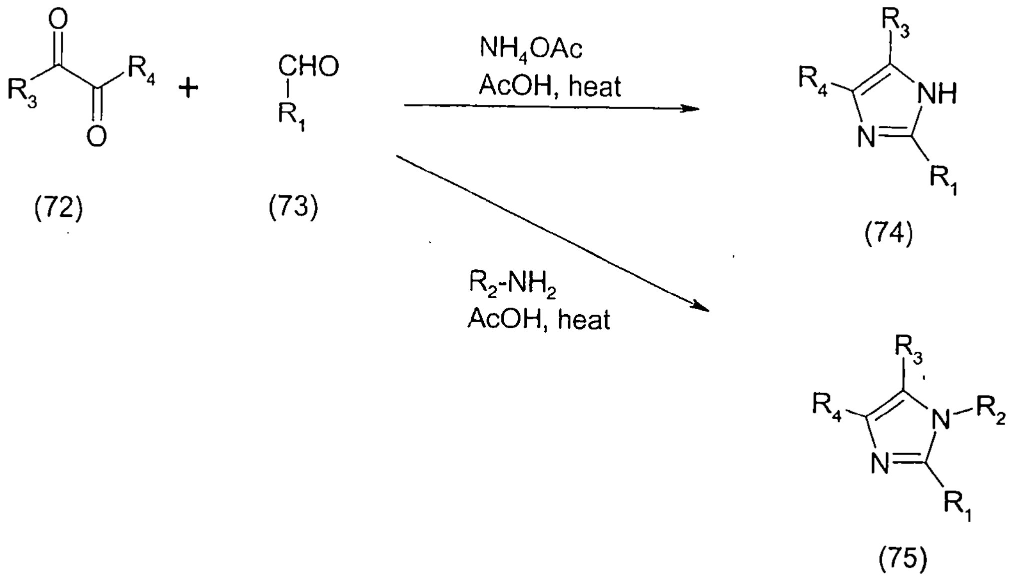
Scheme 12 describes the synthesis of imidazoles. (66) may be treated with (67) and an aldehyde R_1-CHO to afford (68). Alternately, (66) may be coupled with the bromoketone (70) to give the aminoketome (71), which may be treated with acetic acid, heat, an aldehyde R_1-CHO, and ammonium acetate to afford (68). Ar_{11} and Ar_{12} are groups such as but not limited to aryl or heteroaryl.

Scheme 12



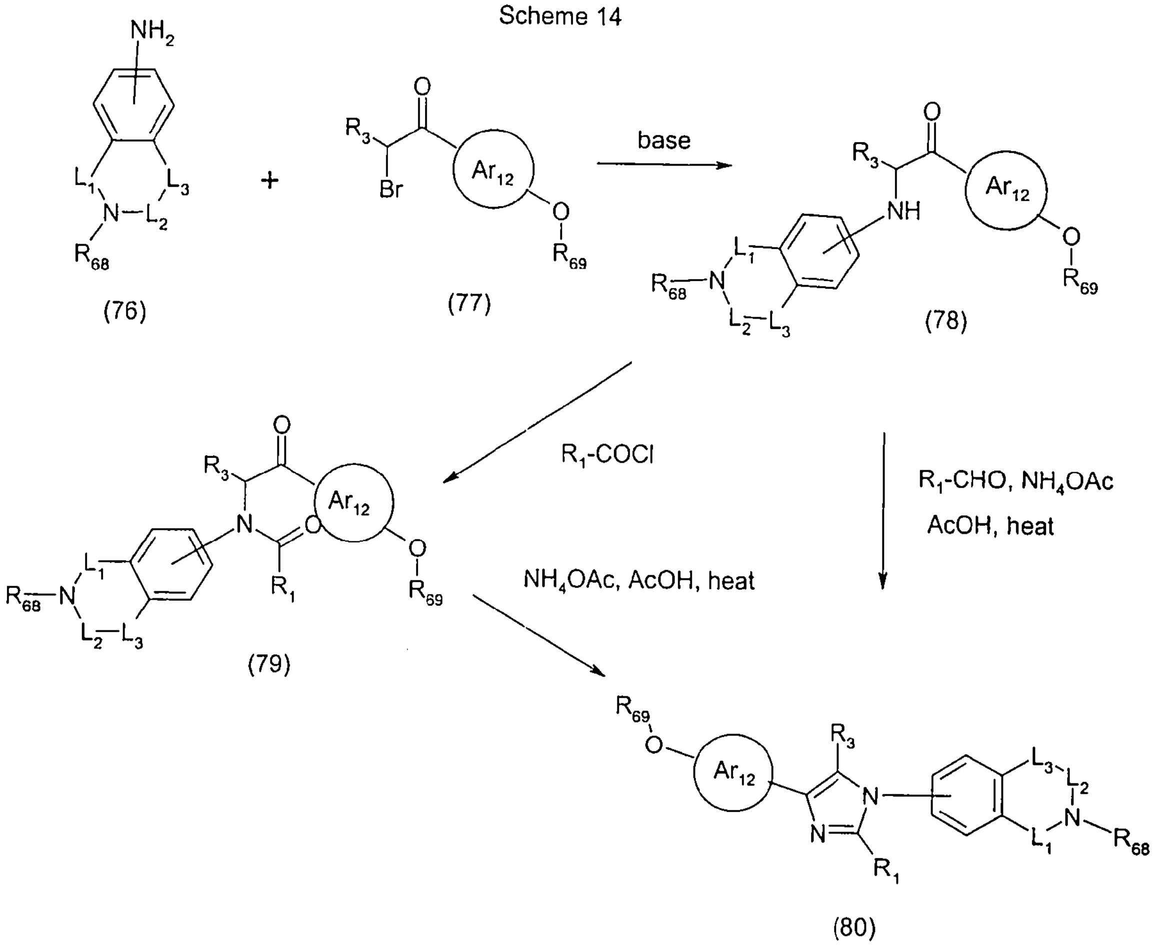
Scheme 13 describes the synthesis of imidazoles. A dione (72) may be treated with R_1-CHO and ammonium acetate – acetic acid to afford (74). Alternately, an amine R_2-NH_2 may be used in place of ammonium acetate to give (75).

Scheme 13



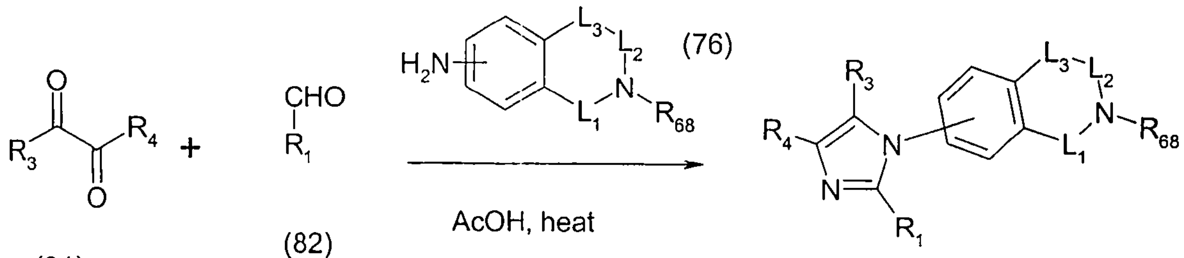
Scheme 14 describes another synthesis of imidazoles. (76) may be coupled with the bromoketone (77) to give the aminoketone (78), which may be treated with acetic acid, heat, an aldehyde R_1-CHO, and ammonium acetate to afford (80). Alternately, (78) may be treated with an acid chloride R_1-COCl to afford (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 treament of (80) 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


NH2
R68
L1
L2
L3
(76)
+
R3
Br
O
Ar12
R69
(77)
base
NH
(78)
R1-COCl
R1-CHO, NH4OAc
AcOH, heat
N
R1
(79)
NH4OAc, AcOH, heat
(80)

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.

Scheme 15



(81) (82) (83)

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-toluyl)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-

2007202350 24 May 2007

(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, triiospropylsilyl and thexyldimethylsilyl. The choice of 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,

2007202350 24 May 2007

phenyldimethylsilyl, triiospropylsilyl and thexyldimethylsilyl. 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. 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.

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

2007202350 24 May 2007

Methods

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 data is obtained in the positive mode unless otherwise noted. ^{1}H NMR and ^{13}C NMR data is obtained on a Varian 400 MHz spectrometer.

Abbreviations used in the Examples are as follows:

APCI = atmospheric pressure chemical ionization
BOC = tert-butoxycarbonyl
BOP= (1-benzotriazolyloxy)tris(dimethylamino)phosphonium hexafluorophosphate
d = day
DIAD = diisopropyl azodicarboxylate
DCC = dicyclohexylcarbodiimide
DCM = dichloromethane
DIC = diisopropylcarbodiimide
DIEA = diisopropylethylamine
DMA = N, N-dimethylacetamide
DMAP = dimethylaminopyridine
DME = 1,2 dimethoxyethane
DMF = N, N-dimethylformamide
DMPU = 1,3-dimethypropylene urea
DMSO = dimethylsulfoxide
Et = ethyl
iPr = isopropyl
Bn = benzyl
Me = methyl
tBu = tert-butyl
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
ether = diethyl ether
EtOAc = ethyl acetate
FBS = fetal bovine serum
g = gram
h = hour
HBTU = O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate
HMPA= hexamethylphosphoric triamide
HOBt =1-hydroxybenzotriazole
Hz = hertz
i.v. = intravenous
kD = kiloDalton
L = liter
LAH = lithium aluminum hydride
LDA = lithium diisopropylamide
LPS = lipopolysaccharide
M = molar
m/z = mass to charge ratio
mbar = millibar
MeOH = methanol
mg = milligram
min = minute
mL = milliliter
mM = millimolar
mmol = millimole
mol = mole
mp = melting point
MS = mass spectrometry
N = normal
NMM = N-methylmorpholine, 4-methylmorpholine
NMR = nuclear magnetic resonance spectroscopy
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
rt = room temperature
s.c. = subcutaneous
SPA = scintillation proximity assay
TEA = triethylamine
TFA = trifluoroacetic acid
THF = tetrahydrofuran
THP = tetrahydropyranyl
TLC = thin layer chromatography
TMSBr= bromotrimethylsilane, trimethylsilylbromide
T_r = retention time

General synthesis of monoalkoxybenzaldehydes:

General Procedure A

To a stirred solution of a 2-, 3-, or 4-hydroxybenzaldehyde (2 mmol) in DMF (6 mL) at rt solid K_2CO_3 (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 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:

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 K_2CO_3 (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 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

2007202350 24 May 2007

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:

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.

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.

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.

General synthesis of 2-alkoxy-4-aryloxybenzaldehydes:

General Procedure E

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 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 monoalkoxy ortho-phenylenediamines:

Method A

General Procedure F1

To a stirred solution of 3-fluoro-4-nitrophenol (4 mmol) in DMF (6 mL) at rt solid K_2CO_3 (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 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 H_2O (10 mL), and extracted with EtOAc (2x15 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 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

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 H_2O (10 mL), and extracted with EtOAc (2x15 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 2-alkylamino-4-fluoronitrobenzene. The crude product may be used for further transformation without any purification or after purifying using silica gel column chromatography.

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 N_2 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 H_2O (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.

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.

General Procedure I

To a stirred solution of afforded 2-alkylamino-4-alkoxynitrobenzene intermediate [as obtained in (b)](2 mmol) in EtOH (20 mL), $SnCl_2.2H_2O$ (8 mmol) is added and the mixture is

2007202350 24 May 2007

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 $NaHCO_3$ 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 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 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 H_2O (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-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) 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 N_2 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 H_2O (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 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 compounbd 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, conc. HNO_3 (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 H_2O (30 mL) is added to the reaction flask and stirred. The contents are then 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

To a stirred solution of 3,5-difluoro-4-nitrophenol (4 mmol) in DMF (6 mL) at rt solid K_2CO_3 (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

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 H_2O (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

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 N_2 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 H_2O (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 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 N_2 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 H_2O (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 vacuuo* 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 H_2O (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 vacuuo* 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 N_2 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 H_2O (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 vacuuo* 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 N_2 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 H_2O (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 vacuuo* afforded the desired hetero-substituted dilkoxynitrobenzene. 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 N_2 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 H_2O (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 vacuuo* afforded the hetero-substituted dilkoxynitrobenzene. 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 vacuuo* 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 vacuuo* and treating the residue with saturated sodium bicarbonate. The aqueous layer is poured into EtOAc (20ml) and washed with H_2O (2X10 ml) and brine (15 ml). The organic layer is dried over magnesium sulfate, and the solvent is removed *in vacuuo* 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 H_2O (2X10 ml) and brine (15 ml). The organic layer is dried over magnesium sulfate, and the solvent is removed *in vacuuo* 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 vacuuo* 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 H_2O and the product is isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuuo* 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 vacuuo*, 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 H_2O (2x15 mL) and brine, and dried over sodium sulfate. Evaporation of the solvent *in vacuuo* 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 H_2O (10 mL). The organic layer is washed with H_2O (2x15 mL) and brine, and dried over sodium sulfate. Evaporation of the solvent *in vacuuo* 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 NH_4OAc (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 H_2O (2x15 mL) and brine, and dried over sodium sulfate. Evaporation of the solvent *in vacuuo* afforded the

2007202350 24 May 2007

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

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.

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.

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, K_2CO_3 as base). The reaction is quenched by adding sat. $NaHCO_3$ .The resulting mixture is extracted with EtOAc washed with brine and dried. The crude product is purified by silica gel column chromatography if desired.

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 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 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 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 $(M+H)^+$

Example 2

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

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 N^2-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)-diiethyl-amine (45.0 mg).

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

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 Cs_2CO_3 (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 H_2O (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 Na_2SO_4). 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% Et_3N, 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 Et_3N (0.5 to 1%), affording the desired benzimidazole (120 mg).
MS m/z 528 $(M+H)^+$
^{1}H NMR (400 MHz, $CDCl_3$):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 Cs_2CO_3 (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 H_2O (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 Na_2SO_4). The solvent was removed *in vacuo* to afford crude 3-(2-pyrrolidin-1-yl-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 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 Et_3N (0.5 to 1%), to afford the desired benzimidazole (100 mg).

MS m/z 512 $(M+H)^+$

^{1}H NMR (400 MHz, $CDCl_3$):δ0.83 (t, 3H), 1.22 (m, 2H), 1.29 (s, 9H), 1.74 (m, 2H), 1.87 (m, 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 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)-

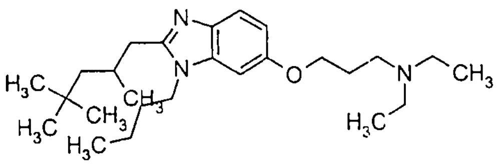
2007202350 24 May 2007

Example	Name
	phenyl]-1H-benzimidazole
10	1-butyl-2-[3-(3,3-dimethyl-butoxy)-phenyl]-6-(2-piperazin-1-yl-ethoxy)-1H-benzoimidazole
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-benzoimidazole
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-benzoimidazole
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-benzoimidazol-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-benzoimidazole
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-benzoimidazol-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

Example 31

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



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 $(M+H)^+$

Example 32

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

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)-1*H*-benzimidazol-2-yl}piperidine-1-carboxylate.

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 $(M+H)^+$

Example 33

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

A solution of 1-(t-butyloxycarbonyl)piperdine-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 $(M+H)^+$

Example 34

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

A solution of 1-(t-butyloxycarbonyl)piperdine-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 $(M+H)^+$

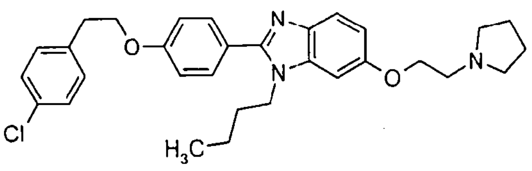
Example 35

(3-(3-butyl-2-(3-(4-tert-butyl-phenoxy)-phenyl)-7-(2-pyrrolidin-1-yl-ethoxy)-3H-benzimidazol-5-yloxy-propyl)-diiethyl-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)-1H-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 N^2-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)$^+$

Example 37

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

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)$^+$

Example 38

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

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.

To a solution of the aryl bromide (0.07 mmol) in pyridine (1 mL) was added copper powder (0.14 mmol) followed by K_2CO_3 (0.35 mmol) and the respective substituted phenol (0.14 mmol). The mixture was heated at 110 ^{0}C overnight, then diluted with water (2 mL) and extracted with EtOAc (3 x 2mL). The combined organic extract was dried over Na_2SO_4, 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.
MS (m/z): 547 (M+H)$^+$

Example 39

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-benzoimidazole
43	1-butyl-2-{3-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-(2-piperazin-1-yl-ethoxy)-1H-benzoimidazole
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-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-

2007202350 24 May 2007

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-propioinamide
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-benzoimidazole
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-benzoimidazole
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-benzoimidazole
153	2-[4-(biphenyl-4-yloxy)-phenyl]-1-butyl-6-(2-piperazin-1-yl-ethoxy)-1H-benzoimidazole
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-benzoimidazole
156	1-butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-5-(1H-imidazol-4-ylmethoxy)-1H-benzoimidazole
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-benzoimidazol-4-yloxy]-propyl}-diethyl-amine
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-fluoro-benzyloxy)-phenyl]-propyl}-3H-

Example	Name
	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-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

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

This compound was prepared according to General Procedure K by refluxing a mixture of 4-[2-(4-chloro-phenyl)-ethoxy]-bezaldehyde (300 mg) and N^1-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).
MS: *m/z* 663 $(M+H)^+$

Example 167

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

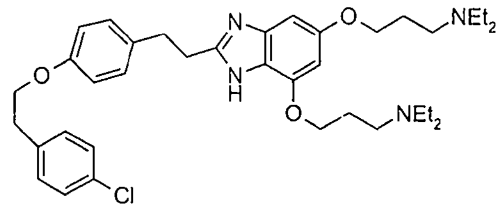
{3-[1-Butyl-2-[3-(4-tert-butyl-phenoxy)-phenyl]-6--(3-diethylaminopropoxy)-1H-benzimidazole-4-yloxy]-propyl}diethyl-amine was formed employing 3(4-t-butyl-phenoxy)benzaldehyde (127 mg; 0.50 mmol) and 2-butylamino-4,6-di(3-diethylaminopropoxy)aniline (synthesized via General Procedures J1 and J2 and I)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

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-diethylamino-propxy)-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

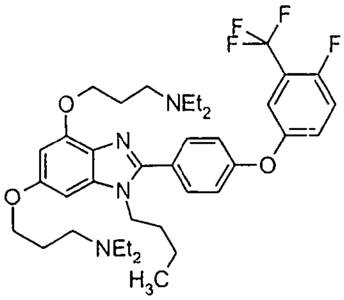
(3-(1-Butyl-6-(3-diethylaminopropoxy)-2-[4-(4-chloro-3-trifluoromethyl-phenoxy)-phenyl]-1H-benzimidazole-4-yloxy)-propyl)diethyl-amine

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-



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).

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-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-benzoimidazole
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
175	{3-[1-Butyl-2-[3-(3,4-dichloro-phenoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzoimidazol-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-benzoimidazole
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-pyrrolodin-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-

2007202350 24 May 2007

Example	Name
	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
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-benzoimidazole-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-benzoimidazole
225	{3-[2-[4-(4-tert-Butyl-phenoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine
226	{3-[3-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-7-[2-(tetrahydro-furan-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-benzoimidazole
228	[3-(7-Butoxy-3-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-3H-benzoimidazol-5-yloxy)-propyl]-diethyl-amine
229	4-{3-[4,6-Bis-(3-diethylamino-propoxy)-1H-benzoimidazol-2-yl]-phenoxy}-benzonitrile
230	2-[3-(3,5-Dichloro-phenoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazole
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-benzoimidazol-4-yloxy]-propyl}-diethyl-amine
234	2-[4-(4-Chloro-3-trifluoromethyl-phenoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazole
235	{3-[1-Butyl-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-6-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazol-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-benzoimidazlo-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

Example 255

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

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 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.

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 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 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.

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 Et_3N (0.5 to 1%), to afford the desired benzimidazole (100 mg).
MS m/z 657 $(M+H)^+$
^{1}H NMR (400 MHz, $CDCl_3$) 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 Cs_2CO_3 (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

24 May 2007 2007202350

mixture and heated to 90 °C until the reaction was complete. 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 with brine (3X50 mL) and dried (anhydrous Na_2SO_4). 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% Et_3N) 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 H_2O (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 Na_2SO_4). 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 K_2CO_3 (9 mmol) and DMF (15 mL) was heated with stirring at 90°C for 15h. The reaction was quenched by cold H_2O (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 Na_2SO_4). 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 Et_3N (0.5 to 1%), to afford the desired benzimidazole (80 mg).
MS m/z 657 $(M+H)^+$

[1]H NMR (400 MHz, $CDCl_3$) 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.

Example 258

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

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 Et_3N (0.5 to 1%), to afford the desired benzimidazole (50 mg).

MS m/z 653 $(M+H)^+$

[1]H NMR (400 MHz, $CDCl_3$):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.

Example 259

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

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 Et_3N (0.5 to 1%), to afford the desired benzimidazole (80 mg).

MS m/z 625 $(M+H)^+$

[1]H NMR (400 MHz, $CDCl_3$):δ0.73 (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.

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

2007202350 24 May 2007

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-benzoimidazlo-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-benzoimidazlo-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-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
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-benzoimidazole
326	[2-(1-butyl-2-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-6-fluoro-1H-benzoimidazol-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%Et_3N, yield 0.025 g .LC/MS (m/z): 776 $(M+H)^+$

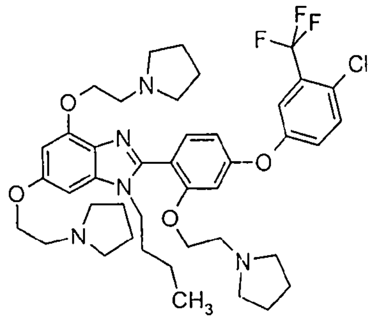
Example 328

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



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)
MS m/z 784 $(M+H)^+$

Example 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

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.
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 was diluted with DCM (200 mL), washed with cold H_2O 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 $KHCO_3$ (12.0g, 120 mmol) in anhydrous DMF(150 mL) was heated at 130°C for 4h following the general procedure described for disubstitued 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 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), Cs_2CO_3 (20.4g, 62.5 mmol) and anhydrous DMSO (100 mL), and the whole mixture was heated at 90°C for 6h. following the general procedure described for disubstitued 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 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 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 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-chloro-phenyl)-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 disubstitued 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 pyrrolidineehanol (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 µL; 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 proiduct 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 (10ml) 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 (1.97g, 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 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.

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 μL; 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.

A solution of 3-diethylaminopropanol (516 □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.

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.

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.
MS m/z 800 $(M+H)^+$

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}-

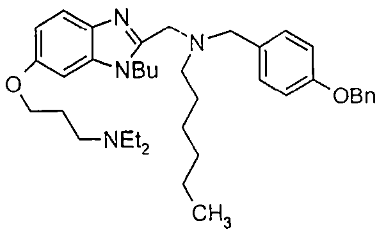
Example	Name
	diethyl-amine
363	{3-[2-[4-[2-(4-Chloro-phenyl)-ethoxy]-2-(pyridin-4-ylmethoxy)-phenyl]-6-(3-diethylamino-propoxy)-1H-benzoimidazol-4-yloxy]-propyl}-diethyl-amine
364	1-Butyl-2-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-2-(pyridin-2-ylmethoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazole
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-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
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
374	2-[4-(4-Chloro-3-trifluoromethyl-phenoxy)-2-cyclopentylmethoxy-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazole
375	2-[4-(4-Fluoro-3-trifluoromethyl-phenoxy)-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-4,6-bis-(2-pyrrolidin-1-yl-ethoxy)-1H-benzoimidazole
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-benzoimidazole-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

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

2007202350 24 May 2007



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-diethylaminopropxy)-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-diethylaminopropxy)-1-H-benzimidazole hydrochloride.

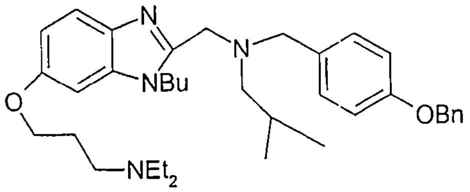
To 1-butyl-2-aminomethyl-6-(3-diethylaminopropxy)-1-H-benzimidazole (1.0 mmol) in DCM (8 mL) were added Et_3N (3.0 mmol) and 4-benzoxybenzaldehyde (1.0 mmol) and the mixture was stirred for 4h, then $NaBH(OAc)_3$ (4.0 mmol) was added and stirred for another 4 h, then sodium bicarbonate was added and 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-diethylaminopropxy)-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

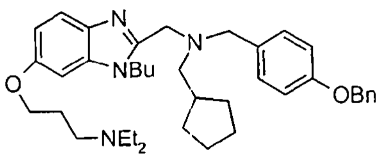
(4-benzyloxy-benzyl)-[1-butyl-6-(3-diethylaminopropoxy)-1-H-benzimidazol-2-ylmethyl]-isobutyl-amine



To 1-butyl-2-(4-benzyloxy-benzyl)-aminomethyl-6-(3-diethylaminopropxy)-1-H-benzimidazole (16 mg, 0.03 mmol) in DCM (2 mL) were added isbutrylaldehyde (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.
MS m/z 585 $[M+H]^+$

Example 395

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

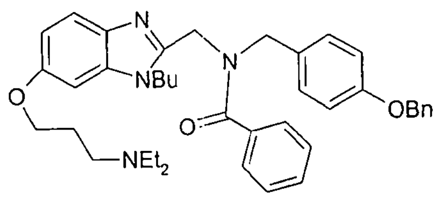


To 1-butyl-2-(4-benzyloxy-benzyl)-aminomethyl-6-(3-diethylaminopropxy)-1-H-benzimidazole (16 mg, 0.03 mmol) in DCM (2 mL) were added cyclopentyl carboxaldehyde (11 mg, 0.10 mmol) and the mixture was stirred for 10 min, then NaBH(OAc)3 (32 mg, 0.15 mmol) was added and stirred for 3 h, then sodium bicarbonate 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 $[M+H]^+$

Example 396

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

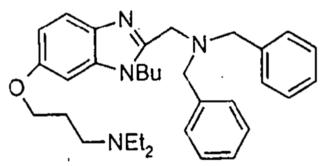


To 1-butyl-2-(4-benzyloxy-benzyl)-aminomethyl-6-(3-diethylaminopropxy)-1-H-benzimidazole (32 mg, 0.06 mmol) in DCM (3 mL) were added benzoyl chloride (34 mg, 0.24 mmol), TEA (24 mg, 0.24 mmol), DMAP (catalytic amount) and the mixture was stirred for 12 h, then sodium bicarbonate was added and the mixture 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 $[M+H]^+$

Example 397

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



To 1-butyl-2-aminomethyl-6-(3-diethylaminopropxy)-1-H-benzimidazole (15 mg, 0.034 mmol) in DCM (2 mL) were added Et_3N (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;

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}-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 H_2O and extracted with EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of the solvent *in vacuuo* 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 General Procedure H. The reaction mixture was then filtered to remove the catalyst. The solvent was removed *in vacuuo* 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. 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 vacuuo* 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 solvent was then removed *in vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo*, 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 $(M+H)^+$:

^{1}H 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 H_2O (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 vacuuo* 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 vacuuo* 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 vacuuo* and treating the residue with saturated sodium bicarbonate. The aqueous layer was poured into EtOAc (20ml) and washed with H_2O (2X10 ml) and brine (15 ml). The organic layer was dried over magnesium sulfate, and the solvent was removed *in vacuuo* 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 vacuuo* and the crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was used for further transformation.

2007202350 24 May 2007

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 H_2O and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuuo* 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 vacuuo*, 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 $(M+H)^+$

^{1}H 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]-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 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 vacuuo.*

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 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 vacuuo* 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 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 vacuuo* 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 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 product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuuo* 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)-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 vacuuo*, 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 $(M+H)^+$:

^{1}H NMR ($CDCl_3$): 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 H_2O (2X50 ml), brine (30 ml) and dried with magnesium sulfate. The solvent was then removed *in vacuuo* 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 H_2O and the product was isolated in Et_2O. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuuo* 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 vacuuo*, 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 vacuuo*, 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. Et_2O (30 mL) was added to the reaction mixture followed by H_2O (10 mL). The organic layer was washed with H_2O (2x15 mL) and brine, and dried over sodium sulfate. The solvent was removed *in vacuuo*. 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 H_2O (2X50 ml), brine (30 ml) and dried with magnesium sulfate. The solvent was then removed *in vacuuo* 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 H_2O and the product was isolated in Et_2O. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuuo* 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 vacuuo*, 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 vacuuo*, 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, Et_2O (30 mL) was added to the reaction mixture followed by H_2O (10 mL). The organic layer was washed with H_2O (2x15 mL) and brine, and dried over sodium sulfate. The solvent was removed *in vacuuo.* Pure imidazole was obtained from chromatography in 5-10% MeOH/DCM (yield 14 mg).

MS m/z value $(M+H)^+$: 569

^1H NMR ($CDCl_3$): 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

1-[5-(4-{2-butyl-1-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-pentyl]-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 H_2O (2X50 ml), brine (30 ml) and dried with magnesium sulfate. The solvent was then removed *in vacuuo* 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 H_2O and the product was isolated in Et_2O. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuuo* afforded the desired product. The crude alkylated aniline was purified by chromatography (Silica gel). Pure product was obtained from 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 ambient temperature until completion, as indicated by TLC and HPLC. The solvent was removed *in vacuuo*, 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 vacuuo*, 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. Et_2O (30 mL) was added to the reaction mixture followed by H_2O (10 mL). The organic layer was washed with H_2O (2x15 mL) and brine, and dried over sodium sulfate. The solvent was removed *in vacuuo*. Pure product was obtained after chromatography on slilca 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 H_2O (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 vacuuo* 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 vacuuo* to afford the desired N,N-diethyl-N-[3-(4-nitrophenoxy)propyl]amine, 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 vacuuo* and treating the residue with saturated sodium bicarbonate. The aqueous layer was poured into EtOAc (20ml) and washed with H_2O (2X10 ml) and brine (15 ml). The organic layer was dried over magnesium sulfate, and the solvent was removed *in vacuuo* 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, 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 vacuuo* 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 H_2O and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuuo* 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 ($CDCl_3$): 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 H_2O (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 vacuuo* 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 vacuuo* 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-chlorophenethoxy)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 H_2O and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuuo* afforded the desired product. The crude alkylated aniline was purified by chromatography on silica gel (elutiion 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 ($CDCl_3$): δ7.89 (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-phenoxide (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 H_2O (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 vacuuo* 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 vacuuo* 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 K_2CO_3 (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 H_2O 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 vacuuo* 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 H_2O (2X15 ml) and brine (15 ml). The organic layer was dried over magnesium sulfate, and the solvent was removed *in vacuuo* 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 $(M+H)^+$

^{1}H NMR ($CDCl_3$): δ7.64 (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. The reaction mixture was stirred at 0°C until completion, as indicated by TLC or HPLC. The solvent was then removed *in vacuuo* and the reaction mixture was treated with cold H_2O (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 vacuuo* afforded the desired 1-fluoro-4-(4-nitrophenoxy)-2-(trifluoromethyl)benzene. The crude product could be 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 vacuuo* 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 potassium carbonate (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 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 vacuuo* 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 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) 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 vacuuo* 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 vacuuo* to afford the desired product.

2007202350 24 May 2007

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 vacuuo* 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 vacuuo*, 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-phenoxide (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

2007202350 24 May 2007

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 H_2O (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 vacuuo* 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 K_2CO_3 (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 H_2O and the product was isolated in EtOAc. The combined organic layers were washed with saturated sodium bicarbonate (2X15 ml), H_2O (2X15 ml) and brine (15 ml). The organic layer was dried over magnesium sulfate, and the solvent was removed *in vacuuo* 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 vacuuo* 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-trifluoromethoxy-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 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 $(M+H)^+$

^{1}H NMR ($CDCl_3$): δ7.91 (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

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 vacuuo*.

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 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 vacuuo* and the 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was purified by flash chromatography (going by increasing gradient up to 10% MeOH in DCM).

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 anhydrous sodium sulfate and filtered, after which the solvent was removed *in vacuuo*.

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 vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo*, 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, $CDCl_3$): 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

[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 Procedure L1. After cooling to rt, the reaction mixture was poured into cold H_2O (60 mL). The resulting mixture was extracted with EtOAc (3×100 mL). The combined EtOAc extracts were washed with H_2O (2×40 mL) and brine (50 mL), and dried over anhydrous sodium sulfate. The solvent was removed *in vacuuo* 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 vacuuo* 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), methanesulfonyl chloride (60 mmol) was added dropwise and the reaction mixture was stirred for 2h at 0°C, followed by additional 1h at rt. After the removal of the solvents *in vacuuo*, 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 H_2O (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 vacuuo*, 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 vacuuo* 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 vacuuo*, 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 vacuuo*, 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 vacuuo*, 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, $CDCl_3$): δ1.05 (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.

2007202350 24 May 2007

Example 417

[3-(4-{2-cyclopentyl-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 H_2O (60 mL). The resulting mixture was extracted with EtOAc (3×100 mL). The combined EtOAc extracts were washed with H_2O (2×40 mL) and brine (50 mL), and dried over anhydrous sodium sulfate. The solvent was removed *in vacuuo* 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 vacuuo* 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 vacuuo*, 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 H_2O (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 vacuuo*, 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 vacuuo* 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 vacuuo*, 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 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 vacuuo*, 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 vacuuo*, 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 $(M+H)^+$:

^{1}H NMR (400 MHz, $CDCl_3$): 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, 2H) ppm.

Example 418

2007202350 24 May 2007

[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 H_2O (60 mL). The resulting mixture was extracted with EtOAc (3×100 mL). The combined EtOAc extracts were washed with H_2O (2×40 mL) and brine (50 mL), and dried over anhydrous sodium sulfate. The solvent was removed *in vacuuo* 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 vacuuo* 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 vacuuo*, 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 H_2O (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 vacuuo*, 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 vacuuo* 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 vacuuo*, 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 vacuuo*, 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 vacuuo*, 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 $(M+H)^+$:

^{1}H NMR (400 MHz, $CDCl_3$): δ1.02-2.00 (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 H_2O (60 mL). The resulting mixture was extracted with EtOAc (3×100 mL). The combined EtOAc extracts were washed with H_2O (2×40 mL) and brine (50 mL), and dried over anhydrous sodium sulfate. The solvent was removed *in vacuuo* 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 vacuuo* 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 vacuuo*, 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 H_2O (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 vacuuo*, 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 vacuuo* 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

2007202350 24 May 2007

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 vacuuo*, 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 vacuuo*, 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 vacuuo*, 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, $CDCl_3$): δ0.86 (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 H_2O (60 mL). The resulting mixture was extracted with EtOAc (3×100 mL). The combined EtOAc extracts were washed with H_2O (2×40 mL) and brine (50 mL), and dried over anhydrous sodium sulfate. The solvent was removed *in vacuuo* 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 vacuuo* 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 vacuuo*, 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 H_2O (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 vacuuo*, 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 vacuuo* 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 vacuuo*, 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 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 vacuuo*, 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 vacuuo*, 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)$^+$:

^{1}H NMR (400 MHz, $CDCl_3$): 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

[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 Procedure L1. After cooling to rt, the reaction mixture was poured into cold H_2O (60 mL). The resulting mixture was extracted with EtOAc (3×100 mL). The combined EtOAc extracts were washed with H_2O (2×40 mL) and brine (50 mL), and dried over anhydrous sodium sulfate. The solvent was removed *in vacuuo* 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 vacuuo* 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 vacuuo*, 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 H_2O (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 vacuuo*, 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 vacuuo* 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 vacuuo*, 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 vacuuo*, 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 vacuuo*, 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, $CDCl_3$): δ1.09 (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 H_2O (60 mL). The resulting mixture was extracted with EtOAc (3×100 mL). The combined EtOAc extracts were washed with H_2O (2×40 mL) and brine (50 mL), and dried over anhydrous sodium sulfate. The solvent was removed *in vacuuo* 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 vacuuo* 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 vacuuo*, 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 H_2O (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 vacuuo*, 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 vacuuo* 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 vacuuo*, 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 vacuuo*, 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 vacuuo*, 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 $(M+H)^+$:

^1H NMR (400 MHz, $CDCl_3$): δ1.11 (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

[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 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 vacuuo.*

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 vacuuo* 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%.

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 vacuuo*.

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 vacuuo* to afford the desired 4-(3,5-bis-trifluoromethyl)phenoxyaniline, 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 vacuuo* and the crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was used for further transformation.

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 vacuuo* 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 vacuuo*, 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 $(M+H)^+$:

^{1}H NMR (400 MHz, $CDCl_3$): 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 vacuuo*.

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 vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo*, 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 $(M+H)^+$;

^{1}H NMR ($CDCl_3$): 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

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 H_2O (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 vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo* and the residue was treated with saturated sodium

2007202350 24 May 2007

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 vacuuo* 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 vacuuo* 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 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 vacuuo*, 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: 270 mg).

MS m/z 561 $(M+H)^+$:

^{1}H NMR (400 MHz, $CDCl_3$): 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 H_2O (2X50 ml), brine (30 ml) and dried with magnesium sulfate. The solvent was then removed *in vacuuo* 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 H_2O and the product was isolated in Et_2O. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuuo* 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 vacuuo*, 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 vacuuo*, 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, Et_2O (30 mL) was added to the reaction mixture followed by H_2O (10 mL). The organic layer was washed with H_2O (2x15 mL) and brine, and dried over sodium sulfate. The solvent was removed *in vacuuo*. Pure product was obtained from 5-10% MeOH/DCM (yield 65.0 mg).

MS m/z 557 $(M+H)^+$:

^1H NMR ($CDCl_3$): 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 H_2O and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuuo* 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

2007202350 24 May 2007

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^{0}C overnight, then diluted with H_2O (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 $(M+H)^+$:

^{1}H NMR (400 MHz, $CDCl_3$): 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 H_2O (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 vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo*, 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: 334 mg).

MS m/z 598 $(M+H)^+$:

^1H NMR (400 MHz, $CDCl_3$): δ7.76 (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

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 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 H_2O (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 vacuuo* 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 vacuuo* to afford the desired 4-alkoxyaniline, which was used directly for further transformation without further purification.

2007202350 24 May 2007

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 vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo* 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

2007202350 24 May 2007

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 vacuuo*, 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, $CDCl_3$): δ7.65 (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 H_2O (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 vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo*, 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: 366 mg)

MS m/z 572 $(M+H)^+$:

Example 431

[3-(4-{4-[4-(biphenyl-4-yloxy)-phenyl]-imidazol-1-yl}-phenoxy)-propyl]-diethyl-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 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 H_2O and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuuo* 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 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), followed by potassium carbonate (0.35 mmol) and 1,1'-biphenyl-4-ol (0.14 mmol). The mixture was heated at 110^{0}C overnight, then diluted with H_2O (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 $(M+H)^+$:

^{1}H NMR (400 MHz, $CDCl_3$): 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 H_2O and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuuo* 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^{0}C overnight, then diluted with H_2O (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).

MS m/z 510 $(M+H)^+$:

Example 433

[3-(4-{4-[4-(3,4-dichloro-phenoxy)-phenyl]-imidazol-1-yl}-phenoxy)-propyl]-diethyl-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 H_2O and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuuo* 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 3,4-dichlorophenol (0.14 mmol). The mixture was heated at 110^{0}C overnight, then diluted with H_2O (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 15 mg).

MS m/z 510 $(M+H)^+$:

Example 434

[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 vacuuo.*

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 vacuuo* 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%.

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 vacuuo.*

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 vacuuo* to afford the desired 4-(4-

2007202350 24 May 2007

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 vacuuo* 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 vacuuo* 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 vacuuo*, 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 $(M+H)^+$:

^{1}H NMR ($CDCl_3$): 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 (5.0mL) 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 H_2O (2X50 ml), brine (30 ml) and dried with magnesium sulfate. The solvent was then removed *in vacuuo* 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 H_2O and the product was isolated in Et_2O. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuuo* 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 vacuuo*, 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 vacuuo*, 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, Et_2O (30 mL) was added to the reaction mixture followed by H_2O (10 mL). The organic layer was washed with H_2O (2x15 mL) and brine, and dried over sodium sulfate. The solvent was removed *in vacuuo*. 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 vacuuo* to give the title compound as white solid (yield 37 mg).

MS m/z 584 $(M+H)^+$:

^1H NMR ($CDCl_3$): 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 vacuuo*. The resulting solid was dissolved in EtOAc (30 mL), washed with H_2O (2X20 mL) and brine (20 mL) and dried over sodium sulfate. Evaporation of solvent *in vacuuo* 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 resuting 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 ($CDCl_3$): δ7.76 (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 vacuuo*. The resulting solid was dissolved in EtOAc (30 mL), washed with H_2O (2X20 mL) and brine (20 mL) and dried over sodium sulfate. Evaporation of solvent *in vacuuo* 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 resuting 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 was by obtained by elution with 4-6% MeOH/DCM (yield 125 mg)

MS m/z 503 $(M+H)^+$:

^{1}H NMR ($CDCl_3$): 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.

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 heated to reflux for 45 min. The reaction mixture was then cooled to rt and the solvent was removed *in vacuuo*. The resulting solid was dissolved in EtOAc (30 mL), washed with H_2O(2X20 mL) and brine (20 mL) and dried over sodium sulfate. Evaporation of solvent *in vacuuo* 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 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 resuting 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 vacuuo* afforded the desired product.

MS m/z 503 $(M+H)^+$:

^1H NMR (CD_3OD): 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 H_2O (60 mL). The resulting mixture was extracted with EtOAc (3×100 mL). The combined EtOAc extracts were washed with H_2O (2×40 mL) and brine (50 mL), and dried over anhydrous sodium sulfate. The solvent was removed *in vacuuo* 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 vacuuo* to afford 4-(4'-fluoro-3'-

2007202350 24 May 2007

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 vacuuo*, 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 H_2O (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 vacuuo*, 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 vacuuo* 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 vacuuo*, 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 vacuuo*, 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 vacuuo*, 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 $(M+H)^+$:

^{1}H NMR (400 MHz, $CDCl_3$): 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 H_2O (60 mL). The resulting mixture was extracted with EtOAc (3×100 mL). The combined EtOAc extracts were washed with H_2O (2×40 mL) and brine (50 mL), and dried over anhydrous sodium sulfate. The solvent was removed *in vacuuo* 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 vacuuo* to afford 4-(4'-fluoro-3'-trifluoromethyl-phenoxy)aniline, which was used directly for further transformation without purification (overall yield: 95%).

2007202350 24 May 2007

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 vacuuo*, 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 H_2O (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 vacuuo*, 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 vacuuo* 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 vacuuo*, 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 vacuuo*, 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 vacuuo*, 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 $(M+H)^+$:

^{1}H NMR (400 MHz, $CDCl_3$): δ1.06 (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 H_2O (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 vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo*, 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 $(M+H)^+$:

^{1}H NMR (400 MHz, $CDCl_3$): δ7.67 (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 H_2O (2X50 ml), brine (30 ml) and dried with magnesium sulfate. The solvent was then removed *in vacuuo* 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 H_2O and the product was isolated in Et_2O. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuuo* 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 vacuuo*, 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 vacuuo*, 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, Et_2O (30 mL) was added to the reaction mixture followed by H_2O (10 mL). The organic layer was washed with H_2O (2x15 mL) and brine, and dried over sodium sulfate. The solvent was removed *in vacuuo*. Pure imidazole was obtained by elution with chromatography in 5-10% MeOH/DCM (yield 52.0 mg)

MS m/z 583 $(M+H)^+$:

^{1}H NMR ($CDCl_3$): 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-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. The reaction mixture was stirred at 0°C until completion, as indicated by TLC or HPLC. The solvent was then removed *in vacuuo* and the reaction mixture was treated with cold H_2O (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 vacuuo* 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 vacuuo* 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-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 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 vacuuo* 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 vacuuo*, 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 vacuuo* 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 vacuuo* 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 vacuuo*, 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 $(M+H)^+$:

^{1}H NMR (400 MHz, $CDCl_3$): 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 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 H_2O (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 vacuuo* 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 vacuuo* 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 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 vacuuo* 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 mL), water (2X10 mL) and brine (15 mL). The organic layer was dried over magnesium sulfate, and the solvent was removed *in vacuuo* 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 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 vacuuo* 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 vacuuo*, 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 (yield179 mg).

MS m/z 512 $(M+H)^+$:

^{1}H NMR ($CDCl_3$): δ7.69 (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 vacuuo.*

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 vacuuo* 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 H_2O (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 vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo* afforded the desired product. The crude alkylated aniline was purified by chromatography (Silica gel). Pure product by 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 solvent was removed *in vacuuo*, 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 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 ($CDCl_3$): 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.

Example 446

3-(S)-(4-{2-butyl-1-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxymethyl)-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 H_2O (2X50 ml), brine (30 ml) and dried with magnesium sulfate. The solvent was then removed *in vacuuo* to give a white solid. The alpha-bromoacetophenone was used for further transformation without further purification.

2007202350 24 May 2007

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 H_2O and the product was isolated in Et_2O. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuuo* 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 vacuuo*, 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 vacuuo*, 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, Et_2O (30 mL) was added to the reaction mixture followed by H_2O (10 mL). The organic layer was washed with H_2O (2x15 mL) and brine, and dried over sodium sulfate. The solvent was removed *in* *vacuuo.* Pure imidazole was obtained by elution with chromatography in 5-10% MeOH/DCM (yield 50.0 mg).

MS m/z 597 $(M+H)^+$:

^{1}H NMR ($CDCl_3$): 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

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 H_2O (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 vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo*, 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

^{1}H NMR (400 MHz, $CDCl_3$): δ7.69 (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}-phenoxymethyl)-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 H_2O (2X50 ml), brine (30 ml) and dried with magnesium sulfate. The solvent was then removed *in vacuuo* 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 H_2O and the product was isolated in Et_2O. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuuo* 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 vacuuo*, 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 vacuuo*, 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, Et_2O (30 mL) was added to the reaction mixture followed by H_2O (10 mL). The organic layer was washed with H_2O (2x15 mL) and brine, and dried over sodium sulfate. The solvent was removed *in vacuuo*. Pure imidazole was obtained by elution with chromatography in 5-10% MeOH/DCM (yield 50.0 mg).

MS m/z 597 $(M+H)^+$:

^{1}H NMR ($CDCl_3$): 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]-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

2007202350 24 May 2007

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 vacuuo*.

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 vacuuo* 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%.

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 vacuuo*.

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 vacuuo* to afford the desired 4-(3-tert-butyl-phenoxy)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 vacuuo* 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 vacuuo* 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 vacuuo*, 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, $CDCl_3$): 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 H_2O (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 vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo* 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 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 or HPLC. The reaction mixture was then diluted with cold water and the product was isolated in DCM. The solvent was removed *in vacuuo*, 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: 265 mg).

MS m/z 549 $(M+H)^+$:

^{1}H NMR (400 MHz, $CDCl_3$): δ7.72 (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

(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 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 H_2O (15 mL), and extracted with

2007202350 24 May 2007

EtOAc (2x15 mL). The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of the solvent *in vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo*, 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 $(M+H)^+$:

^{1}H NMR (400 MHz, $CDCl_3$): δ7.71 (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 vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo*, 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, $CDCl_3$): δ7.69 (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 H_2O (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 vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo*, 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 $(M+H)^+$:

^{1}H NMR (400 MHz, $CDCl_3$): δ7.69 (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-phenoxymethyl)-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 H_2O (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 vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo*, 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 $(M+H)^+$:

^{1}H NMR (400 MHz, $CDCl_3$): δ7.72 (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 H_2O (15 mL), and extracted with EtOAc (2x15 mL). The combined organic layers were washed with brine and dried over

2007202350 24 May 2007

sodium sulfate. Evaporation of the solvent *in vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo*, 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: 350 mg).

MS m/z 624 $(M+H)^+$:

^{1}H NMR (400 MHz, $CDCl_3$): δ7.71 (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

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

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 H_2O (2X50 ml), brine (30 ml) and dried with magnesium sulfate, The solvent was then removed *in vacuuo* 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 H_2O and the product was isolated in Et_2O. The combined organic layers were washed with brine and dried over sodium sulfate. The solvent was removed *in vacuuo* 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 vacuuo*, 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 H_2O (2X50 ml), brine (30 ml) and dried with magnesium sulfate. The solvent was then removed *in vacuuo* 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 H_2O and the product was isolated in Et_2O. The combined organic layers were washed with brine and dried over sodium sulfate. The solvent was removed *in vacuuo* 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 vacuuo*, 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 ($CDCl_3$): δ7.58 (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 H_2O (2X50 ml), brine (30 ml) and dried with magnesium sulfate. The solvent was then removed *in vacuuo* to give a white solid. The alpha-bromophenone was used for further transformation.

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 H_2O and the product was isolated in Et_2O. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuuo* 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 ~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 at 0°C for 1h and allowed to warm to ambient temperature until completion, as indicated by HPLC. The solvent was removed *in vacuuo*, 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 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 ($CDCl_3$): δ7.6 (d, 2H), 7.28 (d, 2H), 7.21 (d, 2H), 7.11 (d, 2H), 7.00 (d, 2H), 6.90 (d, 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

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 H_2O (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 vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo*, 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 $(M+H)^+$:

^{1}H NMR (400 MHz, $CDCl_3$): δ7.66 (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

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 H_2O and the product was isolated in Et_2O. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuuo* 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 vacuuo*, 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 H_2 atmosphere using a balloon, according to General Procedure T2. The Pd/C was removed by filtration. The solvent was removed *in vacuuo*, 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 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. Et_2O (30 mL) was added to the reaction mixture followed by H_2O (10 mL). The organic layer was washed with H_2O (2x15 mL) and brine, and dried over sodium sulfate. The solvent was removed *in vacuuo.* Pure imidazole was obtained by elution with chromatography in 5-10% MeOH/DCM (yield 70.0 mg).

MS m/z 604 $(M+H)^+$:

^{1}H NMR ($CDCl_3$): 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.

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-(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 H_2O and the product was isolated in Et_2O. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuuo* 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 vacuuo*, 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 H_2 atmosphere using a balloon, according to General Procedure T2. The Pd/C was removed by filtration. The solvent was removed *in vacuuo*, 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. Et_2O (30 mL) was added to the reaction mixture followed by H_2O (10 mL). The organic layer was washed with H_2O (2x15 mL) and brine, and dried over sodium sulfate. The solvent was removed *in vacuuo*. Pure imidazole was obtained from chromatography with 5-10% MeOH/DCM (yield 70.0 mg)

MS m/z 618 $(M+H)^+$:

^1H NMR ($CDCl_3$): 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 H_2O and the product was isolated in Et_2O. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuuo* 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 vacuuo*, 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 H_2 atmosphere using a balloon, according to General Procedure T2. The Pd/C was removed by filtration. The solvent was removed *in vacuuo*, 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. Et_2O (30 mL) was added to the reaction mixture followed by H_2O (10 mL). The organic layer was washed with H_2O (2x15 mL) and brine, and dried over sodium sulfate. The solvent was removed *in vacuuo*. Pure imidazole was obtained from chromatography with 5-10% MeOH/DCM (yield 77 mg).

MS m/z 666 $(M+H)^+$:

^1H NMR ($CDCl_3$): 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 H_2O and the product was isolated in Et_2O. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuuo* 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 vacuuo*, 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 H_2 atmosphere using a balloon, according to General Procedure T2. The Pd/C was removed by filtration. The solvent was removed *in vacuuo*, 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. Et_2O (30 mL) was added to the reaction mixture followed by H_2O (10 mL). The organic layer was washed with H_2O (2x15 mL) and brine, and dried over sodium sulfate.

The solvent was removed *in vacuuo*. Pure imidazole was obtained from chromatography with 5-10% MeOH/DCM (yield 66 mg).

MS m/z 602 $(M+H)^+$:

^{1}H NMR ($CDCl_3$): δ7.71 (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, 2 H), 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]-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 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 H_2O (2X50 mL) and brine (50 mL). The organic layer was dried over sodium sulfate, and the solvent was removed *in vacuuo* 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 vacuuo* 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 H_2O and the

2007202350 24 May 2007

product was extracted in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuuo* 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 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 vacuuo*, 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 H_2O (2x15 mL) and brine, and dried over sodium sulfate. Evaporation of the solvent *in vacuuo* afforded the desired N-aryl imidazole. The crude product was purified using silica gel column chromatography (2-5% MeOH/DCM) (yield 117 mg).

MS m/z 532 $(M+H)^+$:

^1H NMR ($CDCl_3$): 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.

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 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 H_2O (2X50 mL) and brine (50 mL). The organic layer was dried over sodium sulfate, and the solvent was removed *in vacuuo* 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 vacuuo* 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 H_2O and the product was extracted in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuuo* 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 vacuuo*, 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 H_2O (2x15 mL) and brine, and dried over sodium sulfate. Evaporation of the solvent *in vacuuo* afforded the desired N-aryl imidazole. The crude product was purified using silica gel column chromatography (2-5% MeOH/DCM) (yield 180 mg).

MS m/z 572 $(M+H)^+$:

^{1}H NMR ($CDCl_3$): 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

[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 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 H_2O (2X50 mL) and brine (50 mL). The organic layer was dried over sodium sulfate, and the solvent was removed *in vacuuo* 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 vacuuo* 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 H_2O and the

2007202350 24 May 2007

product was extracted in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuuo* 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 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 vacuuo*, 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 H_2O (2x15 mL) and brine, and dried over sodium sulfate. Evaporation of the solvent *in vacuuo* afforded the desired N-aryl imidazole. The crude product was purified using silica gel column chromatography (2-4% MeOH/DCM) (yield 50 mg).

MS m/z 580 $(M+H)^+$:

^{1}H NMR ($CDCl_3$): 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.

Example 467

[3-(4-{2-(4-tert-butyl-phenoxymethyl)-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) 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 vacuuo*.

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 vacuuo* 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 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 vacuuo* 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 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 product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuuo* 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 solution of 2-[4-(4-chlorophenoxy)-phenylamino]-1-[4-(3-diethylamino-propoxy)-phenyl]-ethanone described above (2 mmol) in anhydrous DCM (5 mL), PS-carbodimide (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 (CDCl$_3$): δ7.72 (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]-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 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 H_2O (100ml), extracted with EtOAc (2X50 mL), washed with H_2O (2X50 ml) and brine (50 ml), and dried over sodium sulfate. The solvent was removed *in vacuuo* 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 $SnCl_2 \cdot 2H_2O$ (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 vacuuo* 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 vacuuo* 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 H_2O (2X50 mL) and brine (50 mL). The organic layer was dried over sodium sulfate, and the solvent was removed *in vacuuo* 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 vacuuo* 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 H_2O and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuuo* 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 vacuuo*, 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 H_2O (2x15 mL) and brine, and dried over sodium sulfate. Evaporation of the solvent *in vacuuo* afforded the desired N-aryl imidazole. The crude product was purified using silica gel column chromatography (2-5% MeOH/DCM).

MS m/z 566 $(M+H)^+$:

^1H NMR ($CDCl_3$): 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

[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 was then removed *in vacuuo* 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 Et_2O (100 mL) and washed with sodium bicarbonate (10%, 30 ml), H_2O (2X30mL), brine (30mL) and dried with magnesium sulfate. Evaporation of solvent *in vacuuo* 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 vacuuo*, 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 66 mg).

MS m/z 546 $(M+H)^+$:

^{1}H NMR ($CDCl_3$): δ7.59 (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 vacuuo* 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 Et_2O (100 mL) and washed with sodium bicarbonate (10%, 30 ml), H_2O (2X30mL), brine (30mL) and dried with magnesium sulfate. Evaporation of solvent *in vacuuo* 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 vacuuo*, 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 ($CDCl_3$): 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]-diethyl-amine

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 vacuuo* 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 Et_2O (100 mL) and washed with sodium bicarbonate (10%, 30 ml), H_2O (2X30mL), brine (30mL) and dried with magnesium sulfate. Evaporation of solvent *in vacuuo* 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 vacuuo*, 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 67.0 mg).

MS m/z 588 $(M+H)^+$:

^{1}H NMR ($CDCl_3$): 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.

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) 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 vacuuo* 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 Et_2O (100 mL) and washed with sodium bicarbonate (10%, 30 ml), H_2O (2X30mL), brine (30mL) and dried with magnesium sulfate. Evaporation of solvent *in vacuuo* 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 vacuuo*, 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 ($CDCl_3$): 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 vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo*, 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 $(M)^+$:

^{1}H NMR (400 MHz, $CDCl_3$): 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 vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo*, 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, $CDCl_3$): δ7.49 (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 vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo*, 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 $(M+H)^+$:

^{1}H NMR (400 MHz, $CDCl_3$): 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

2007202350 24 May 2007

[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 vacuuo* 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 vacuuo* 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 vacuuo* 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 vacuuo* 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

2007202350 24 May 2007

HPLC. The reaction mixture was then diluted with water and the product was isolated in DCM. The solvent was removed *in vacuuo*, 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 H_2O and the product was isolated in Et_2O. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuuo* 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 vacuuo*, 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

2007202350 24 May 2007

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 H_2 atmosphere using a balloon, according to General Procedure T2. The Pd/C was removed by filtration. The solvent was removed *in vacuuo*, 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 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. Et_2O (30 mL) was added to the reaction mixture followed by H_2O (10 mL). The organic layer was washed with H_2O (2x15 mL) and brine, and dried over sodium sulfate. The solvent was removed *in vacuuo*. Pure imidazole was obtained from chromatography with 5-10% MeOH/DCM (yield 60 mg).

MS m/z 570 $(M+H)^+$:

^{1}H NMR ($CDCl_3$): 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) 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

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 H_2O and the product was isolated in Et_2O. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuuo* 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 vacuuo*, 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 H_2 atmosphere using a balloon, according to General Procedure T2. The Pd/C was removed by filtration. The solvent was removed *in vacuuo*, 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. Et_2O (30 mL) was added to the reaction mixture followed by H_2O (10 mL). The organic layer was washed with H_2O (2x15 mL) and brine, and dried over sodium sulfate. The solvent was removed *in vacuuo*. Pure product was obtained from 5-10% MeOH/DCM (yield 57 mg).

MS m/z 661 $(M+H)^+$:

^{1}H NMR ($CDCl_3$): δ 7.65 (d, 2H), 7.2-7.44 (m, 5H), 7.08 (s, 1H), 6.96 (d, 2H), .677 (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

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 H_2O and the product was isolated in Et_2O. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuuo* 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 vacuuo*, 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 H_2 atmosphere using a balloon, according to General Procedure T2. The Pd/C was removed by filtration. The solvent was removed *in vacuuo*, 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 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. Et_2O (30 mL) was added to the reaction mixture followed by H_2O (10 mL).

2007202350 24 May 2007

The organic layer was washed with H_2O (2x15 mL) and brine, and dried over sodium sulfate. The solvent was removed *in vacuuo*. Pure imidazole was obtained from chromatography with 5-10% MeOH/DCM (yield 95 mg).

MS m/z 591 $(M+H)^+$:

^{1}H NMR ($CDCl_3$): 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

[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 H_2O (100 mL), extracted with EtOAc (2X50 mL), washed with H_2O (2X50 mL) and brine (50 mL), and dried over sodium sulfate. The solvent was removed *in vacuuo* to afford the desired 4-(6-methoxy-naphthalen-2-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 vacuuo* to afford the desired 4-(6-methoxy-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-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 H_2O (2X50 mL) and brine (50 mL). The organic layer was dried over sodium sulfate, and the solvent was removed *in vacuuo* 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 vacuuo* 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 H_2O and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuuo* 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 vacuuo*, 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 H_2O (2x40 mL) and brine, and dried over sodium sulfate. Evaporation of the solvent *in vacuuo* 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 ($CDCl_3$): δ8.51 (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]-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 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 H_2O (100 mL), extracated with EtOAc (2X50 mL), washed with H_2O (2X50 mL) and brine (50 mL), and dried over sodium sulfate. The solvent was removed *in vacuuo* 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 remove the catalyst. The solvent was removed *in vacuuo* 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-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 H_2O (2X50 mL) and brine (50 mL). The organic layer was dried over sodium sulfate, and the solvent was removed *in vacuuo* 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 vacuuo* 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 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 H_2O and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuuo* afforded the desired product. The crude alkylated aniline was used for further transformation without additional 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 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 vacuuo*, 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 (2X50 mL). The combined organic layers was washed with H_2O (50 mL) and brine, and dried over sodium sulfate. Evaporation of the solvent *in vacuuo* afforded the desired N-aryl imidazole. The crude product was purified using silica gel column chromatography (2-5% MeOH/DCM) (yield 170 mg).

MS m/z 548 $(M+H)^+$:

^{1}H NMR ($CDCl_3$): 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.

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 H_2O (100 mL), extracted with EtOAc (2X50 mL), washed with H_2O (2X50 mL) and brine (50 mL), and dried over sodium sulfate. The solvent was removed *in vacuuo* 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 vacuuo* 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 H_2O (2X50 mL) and brine (50 mL). The organic layer was dried over sodium sulfate, and the solvent was removed *in vacuuo* 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 vacuuo* 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 H_2O and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuuo* 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 vacuuo*, 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 H_2O (2x30 mL) and brine, and dried over sodium sulfate. Evaporation of the solvent *in vacuuo* 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 $(M+H)^+$:

^{1}H NMR ($CDCl_3$): 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

[3-(4-{2-butyl-1-[4-(dibenzofuran-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 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 H_2O (100 mL), extracted with EtOAc (2X50 mL), washed with H_2O (2X50 mL) and brine (50 mL), and dried over sodium sulfate. The solvent was removed *in vacuuo* to afford the desired 4-(dibenzofuran-2-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 vacuuo* 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 H_2O (2X50 mL) and brine (50 mL). The organic layer was dried over sodium sulfate, and the solvent was removed *in vacuuo* 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 vacuuo* and the crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was used for further transformation.

To a stirred solution of 4-(dibenzofuran-2-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 H_2O and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuuo* afforded the desired product. The crude alkylated aniline was used for further transformation .

To a stirred solution of alkylated 4-(dibenzofuran-2-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 vacuuo*, 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 H_2O (2x30 mL) and brine, and dried over sodium sulfate. Evaporation of the solvent *in vacuuo* afforded the desired N-aryl imidazole. The crude product was purified using silica gel column chromatography (2-5% MeOH/DCM) (yield 164 mg).

MS m/z 588 $(M+H)^+$:

^{1}H NMR ($CDCl_3$): δ7.92 (d, 1H), 7.71 (m, 2H), 7.62 (d, 2H), 7.51 (t, 1H), 7.37 (t, 1H), 7.32-7.26 (m, 3H), 7.23 (m, 2H), 7.16 (s, 1H), 7.13-7.09 (m, 1H), 6.91 (d, 2H), 4.08 (t, 2H), 2.97-2.75 (m, 6H), 2.69 (t, 2H), 2.19 (m, 2H), 1.69 (m, 2H), 1.39-1.25 (m, 2H), 1.29 (t, 6H), 0.89 (t, 3H) ppm.

2007202350 24 May 2007

Example 484

6-(4-{2-butyl-4-[4-(3-diethylamino-propoxy)-phenyl]-imidazol-1-yl}-phenoxy)-naphthalen-2-ol

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 H_2O (100 mL), extracted with EtOAc (2X50 mL), washed with H_2O (2X50 mL) and brine (50 mL), and dried over sodium sulfate. The solvent was removed *in vacuuo* to afford the desired 4-(6-methoxy-2-naphthalen-2-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 vacuuo* to afford the desired 4-(6-methoxy-naphthalen-2-yloxy)aniline, which was used directly for further transformation without additional 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 H_2O (2X50 mL) and brine (50 mL). The organic layer was dried over sodium sulfate, and the solvent was removed *in vacuuo* 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., 5.2 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 vacuuo* 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 H_2O and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuuo* 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-2-naphthalenoxy)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 vacuuo*, 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 H_2O (2x40 mL) and brine, and dried over sodium sulfate. Evaporation of the solvent *in vacuuo* afforded the desired N-aryl imidazole. The crude product was purified using silica gel column chromatography (2-5% MeOH/DCM) (Yield: 19 %).

The N-aryl imidazole (0.12 mmol) previously described was dissolved in 5 mL of 48% aqueous HBr and heated to 90°C for 36 h until the reaction was complete by HPLC. The reaction mixture was cooled to rt and treated with ice-cold saturated aqueous sodium bicarbonate solution until pH 8. The mixture was extracted with with EtOAc (2X15 mL). The combined organic layers was washed with H_2O (2x15 mL) and brine, and dried over sodium sulfate. Evaporation of the solvent *in vacuuo* afforded the demethylated N-aryl imidazole. The crude product was purified using silica gel column chromatography (2-5% MeOH/DCM) (yield 20 mg).

MS m/z 564 $(M+H)^+$:

^{1}H NMR ($CDCl_3$): δ7.62 (d, 2H), 7.60 (s, 1H), 7.58-7.54 (m, 2H), 7.32 (d, 1H), 7.18 (s, 1H), 7.16 (d, 1H), 7.15-7.10 (m, 2H), 7.08 (s, 1H), 7.02 (d, 2H), 6.78 (d, 2H), 3.95 (t, 2H), 3.00-2.81 (m, 6H), 2.60 (t, 2H), 2.12 (m, 2H), 1.56 (m, 2H), 1.30 (t, 2H), 1.21 (t, 6H), 0.75 (t, 3H) ppm.

Example 485

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

A mixture of 4-fluoroacetophone (50 mmol), 4-chlorophenol (75 mmol, 1.5 eq), cesium carbonate (150 mmol, 3 eq) and anhydrous DMSO (80 mL) was heated with stirring at 90°C for 20h (monitored by TLC). After cooling to rt, the reaction mixture was treated with cold H_2O (150 mL), and the resulting mixture was extracted with ether (4×100 mL). The combined organic layers were washed with 2N NaOH (4×100 mL), H_2O (2×100 mL) and brine (100 mL), and dried over anhydrous sodium sulfate. The crude 1-[4-(4-chlorophenoxy)phenyl]ethanone was purified by flash chromatography (eluting with 5-10% EtOAc in hexane) to give 4-(4'-chlorophenoxy)acetophone as an almost colorless solid (yield: 80%).

To a stirred solution of 4-fluoronitrobenzene (50 mmol) and 3-diethylaminoproanol (70 mmol) dissolved in anhydrous THF (50 mL) at 0°C and under a nitrogen stream was added $KOBu^t$ (70 mmol) in portions, and the reaction mixture was allowed to warm to rt, and stirred overnight, according to General Procedure L1. The reaction mixture was then treated with cold H_2O (80 mL), and extracted with EtOAc (3×100 mL). The combined organic layers were washed with brine (2×60 mL) and dried over anhydrous sodium sulfate. Evaporation of the solvent *in vacuuo* afforded the desired N,N-diethyl-N-[3-(4-nitrophenoxy)propyl]amine, which was used for further transformation without further purification (yield: ~98%).

The crude N,N-diethyl-N-[3-(4-nitrophenoxy)propyl]amine (~33 mmol) was dissolved in MeOH (50 mL), and hydrogenated in the presence of 10% Pd/C (0.8g) until the reaction was complete as indicated by LC-MS (~4h), according to General Procedure H. The reaction mixture was then filtered to remove the catalyst. The solvent was removed under high vacuum to afford N,N-diethyl-N-[3-(4-nitrophenoxy)propyl]amine which was used directly for further transformation without further purification (yield: ~96%).

1-[4-(4-chlorophenoxy)phenyl]ethanone (24 mmol) was dissolved in 1,4-dioxane (100 mL), and pyridine hydrotribromide (25.2 mmol, 1.05 eq) was added, according to General

Procedure R1. After being stirred at rt for 7h (monitored by TLC), the reaction was quenched with cold H_2O (100 mL). The resulting mixture was extracted with ether (4×100 mL). The combined ether extracts were washed with brine (3×50 mL), and dried over anhydrous sodium sulfate. The solvent was then removed *in vacuuo* and the crude 2-bromo-1-[4-(4-chlorophenoxy)phenyl]ethanone was directly used for further transformation.

To a stirred solution of ice-cold N,N-diethyl-N-[3-(4-nitrophenoxy)propyl]amine (22 mmol, 1.1 eq) dissolved in DCM (40 mL) was added dropwise a solution of the 2-bromo-1-[4-(4-chlorophenoxy)phenyl]ethanone (20 mmol) dissolved in DMF (30 mL), according to General Procedure R2. The mixture was stirred at 0°C for 3h, and then allowed to warm to rt, continuing the stirring for additional 2h (monitored by LC-MS). The reaction mixture was treated with saturated sodium bicarbonate (100 mL), and the resulting mixture was extracted with EtOAc (4×100 mL). The combined EtOAc extracts were washed with brine (3×50 mL), and dried over anhydrous sodium sulfate. The solvent was removed *in vacuuo*, and the crude product was purified by silica gel column chromatography eluting with 10% MeOH in EtOAc + 0.2% TEA (overall yield from 1-[4-(4-chlorophenoxy)phenyl]ethanone: 60%).

To a stirred solution of the alkylated aniline described above (10 mmol) dissolved in anhydrous DCM (100 mL) at 0°C, TEA (40 mmol, 4 eq) was added, followed by a slow addition of valeryl chloride (20 mmol, 2 eq), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 2h and allowed to warm to rt until completion, as indicated by LC-MS. The solvent was removed *in vacuuo*, and the crude amide was used directly for further transformation.

The crude amide described above (~6 mmol) was suspended in acetic acid (10 mL), and ammonium acetate (excess, ~30 eq) was added, according to General Procedure R4. The reaction mixture was stirred at 90°C for 6h (as monitored by LC-MS). The reaction mixture was then cooled down and neutralized with saturated sodium bicarbonate and solid sodium carbonate. The resulting mixture was extracted with EtOAc (4×100 mL). The combined EtOAc extracts were washed with H_2O (2×60 mL) and brine (2×60 mL), and dried over anhydrous sodium sulfate. The solvent was removed *in vacuuo*, and the crude product was purified by silica gel column chromatography eluting with 10% MeOH in EtOAc + 0.2% TEA affording Example 485.

MS m/z 532 $(M+H)^+$:

^{1}H NMR (400 MHz, $CDCl_3$): δ0.83 (t, 3H), 1.04 (t, 6H), 1.28 (m, 2H), 1.63 (m, 2H), 1.96 (m, 2H), 2.56 (q, 4H), 2.61-2.65 (m, 4H), 4.06 (t, 2H), 6.93 (d, 2H), 6.98 (d, 2H), 7.00 (d, 2H), 7.16 (s, 1H), 7.22 (d, 2H), 7.26 (d, 2H), 7.76 (d, 2H) ppm.

Example 486

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

To a stirred solution of 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone (80 mmol) in MeOH (200 mL) at rt, pyrrolidone hydrotribromide (96 mmol, 1.2 eq) was added in portions at rt, according to General Procedure R1. The reaction mixture was stirred at rt for 2h (monitored by LC-MS). The solvent was then removed *in vacuuo* and the crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was directly used for further transformation.

The solution of the crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone dissolved in anhydrous DMF (180 mL) was chilled to 0°C, and 4-(4'-chlorophenoxy)aniline (88 mmol, 1.1 eq) was added, followed by slowly adding DIEA (240 mmol, 3 eq), according to General Procedure R2. After being stirred at 0°C for 1h and at rt for additional 4h, the reaction mixture was treated with saturated sodium bicarbonate (250 mL). The resulting mixture was extracted with EtOAc (4×200 mL). The combined EtOAc extracts were washed with brine (3×100 mL), and dried over anhydrous sodium sulfate. The solvent was removed *in vacuuo*, and the crude product was purified by silica gel column chromatography eluting with 10% MeOH in EtOAc + 0.2% TEA.

Oxayl chloride (420 mmol, 3 eq) was added slowly to an ice-cold solution of 4-t-butylcyclohexanecarboxylic acid (140 mmol) dissolved in anhydrous DCM (80 mL), and the reaction mixture was stirred at 0°C for 3h and at rt for additional 3h. The solvent was removed *in vacuuo*, and the resulting acid chloride was pumped under high vacuum for about 30 min, and used for next step reaction without further purification.

To a stirred solution of the 2-[4-(4-chlorophenoxy)-phenylamino]-1-[4-(3-diethylamino-propoxy)-phenyl]-ethanone described above (35 mmol) dissolved in anhydrous DCM (200 mL) at 0°C, TEA (140 mmol, 4 eq) was added, followed by a slow addition of the freshly prepared acid chloride (70 mmol, 2 eq). The reaction mixture was stirred under nitrogen at 0°C for 2h and allowed to warm to rt until completion, as indicated by LC-MS. The solvent was removed *in vacuuo*, and the crude amide was used directly for further transformation.

The crude amide described above (~35 mmol) was suspended in acetic acid (50 mL), and ammonium acetate (excess, ~30 eq) was added, according to General Procedure R4. The reaction mixture was stirred at 100°C for 6h (as monitored by LC-MS). The reaction mixture was then cooled down and neutralized with saturated sodium bicarbonate and solid sodium carbonate. The resulting mixture was extracted with EtOAc (4×200 mL). The combined EtOAc extracts were washed with H_2O (2×100 mL) and brine (2×100 mL), and dried over anhydrous sodium sulfate. The solvent was removed *in vacuuo*, and the crude product was purified by silica gel column chromatography eluting with 10% MeOH in EtOAc + 0.2% TEA affording the title compound as cis/trans (1:2 ratio) mixture (yield 14.5 g).

LC: 1.06 min; MS: *m/z* 614 $(M+H)^+$

Example 487

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

To a stirred solution of 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone (80 mmol) in MeOH (200 mL) at rt, pyrrolidone hydrotribromide (96 mmol, 1.2 eq) was added in portions at rt, according to General Procedure R1. The reaction mixture was stirred at rt for 2h (monitored by LC-MS). The solvent was then removed *in vacuuo* and the crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was directly used for further transformation.

The solution of the crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone dissolved in anhydrous DMF (180 mL) was chilled to 0°C, and 4-(4'-chlorophenoxy)aniline (88 mmol, 1.1 eq) was added, followed by slowly adding DIEA (240 mmol, 3 eq), according to General Procedure R2. After being stirred at 0°C for 1h and at rt for additional 4h, the reaction mixture was treated with saturated sodium bicarbonate (250 mL). The resulting mixture was extracted with EtOAc (4×200 mL). The combined EtOAc extracts were washed with brine (3×100 mL), and dried over anhydrous sodium sulfate. The solvent was removed *in vacuuo*, and the crude product was purified by silica gel column chromatography eluting with 10% MeOH in EtOAc + 0.2% TEA (yield: 45%).

Oxayl chloride (3 mmol, 3 eq) was added slowly to an ice-cold solution of *trans*-4-ethylcyclohexanecarboxylic acid (1 mmol) dissolved in anhydrous DCM (5 mL), and the reaction mixture was stirred at 0°C for 2h and at rt for additional 1h. The solvent was removed *in vacuuo*, and the resulting acid chloride was pumped under high vacuum for about 30 min, and used without further purification.

To a stirred solution of the 2-[4-(4-chlorophenoxy)-phenylamino]-1-[4-(3-diethylamino-propoxy)-phenyl]-ethanone (0.3 mmol) described above dissolved in anhydrous DCM (10 mL) at 0°C, TEA (1.2 mmol, 4 eq) was added, followed by slow addition of the freshly prepared acid chloride (~1 mmol, ~3 eq). The reaction mixture was stirred under nitrogen at 0°C for 2h and allowed to warm to rt until completion, as indicated by LC-MS. The solvent was removed *in vacuuo*, and the crude amide was used directly for further transformation.

To a stirred solution of the amide described above (~0.3 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 3h (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 vacuuo*, and the pure product was obtained by silica gel column chromatography eluting with 10% MeOH/EtOAc + 0.2% Et_3N (yield 123 mg).

MS m/z 586 $(M+H)^+$:

^{1}H NMR (400 MHz, $CDCl_3$): δ0.85 (t, 3H), 1.06 (t, 6H), 1.16-1.82 (m, 12H), 1.96 (m, 2H), 2.61 (q, 4H), 2.68 (t, 2H), 4.01 (t, 2H), 6.89 (d, 2H), 7.03 (d, 2H), 7.06 (d, 2H), 7.08 (s, 1H), 7.27 (d, 2H), 7.35 (d, 2H), 7.68 (d, 2H) ppm.

Example 488

[4-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-phenyl]-(1-ethyl-piperidin-4ylmethyl)-amine

To a stirred solution of the 4'-(4-nitro-phenoxy)acetophenone (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 vacuuo* 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 vacuuo* to afford the desired product. The crude alpha-bromoacetophenone was used for further transformation.

To a stirred solution of the 4-chloro-phenoxy aniline (1.2 eq., 2.2 mmol) in anhydrous DMF (10 mL) DIEA (3 eq. 6 mmol) was added, followed by slow addition of the alpha-bromoacetophenone 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 vacuuo* 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 water and the product was isolated in DCM. The solvent was removed *in vacuuo*, 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 cyclized imidazole, which was purified by column chromatography (Silica gel). Pure product was obtained from 30-40% ethylacetate/hexane (yield 50-55%).

The cyclized imidazole intermediate obtained above (0.5 mmol) obtained above was dissolved in MeOH (5 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 vacuuo* to afford the desired reduced imidazole, which was used directly for further transformation without further purification.

To a stirred solution of N-Boc-4-piperidineacetic acid (1.2 eq., 0.6 mmol) in anhydrous DCM (2 mL) was added DCC-PS (1.5 eq., 0.75 mmol). The solution was allowed to shake at rt for 20-30 min. This was followed by addition of the reduced cyclized imidazole described above (0.5 mmol). The reaction mixture was shaken overnight at rt until completion, as indicated by TLC or HPLC. The reaction mixture was then filtered and the product was isolated in DCM. The solvent was removed *in vacuuo*, and the crude amide was used for further transformation.

To a stirred solution of the amide described above (0.5 mmol) in anhydrous THF (2 mL) at 0°C, borane/THF (3 eq, 1.5 mmol) was added. 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 cooled to rt and the solvent was removed *in vacuuo* to give the product imidazole, which was purified by column chromatography (Silica gel). Pure product was obtained from 3-4% MeOH/DCM (yield 150 mg).

MS m/z 635 $(M+H)^+$:

^1H NMR (400 MHz, $CDCl_3$): δ 8.01 (s, 1H), 7.84 (d, 2H), 7.65 (d, 2H), 7.59 (d, 2H), 7.44 (d, 2H), 7.22 (m, 6H), 7.12 (d, 2H), 3.65 (d, 2H), 3.45 (d, 2H), 3.03 (t, 2H), 3.18 (m, 2H), 2.98 (m, 4H), 2.15 (m, 2H), 1.71 (m, 3H), 1.39 (m, 5H), 0.85 (t, 3H) ppm

Example 489

[4-{1-[4-(4-chloro-phenoxy)-phenyl]-4-[4-(3-diethylaminopropoxy)-phenyl]-1H-imidazol-2-yl}-butyric acid methyl ester

As described in Example 406, 2-[4-(4-chlorophenoxy)-phenylamino]-1-[4-(3-diethylamino-propoxy)-phenyl]-ethanone (0.5 mmol) was dissolved in anhydrous DCM (10 mL) and cooled to 0°C. TEA (2 mmol, 4 eq) was added to the reaction mixture, followed by slow addition of methyl 4-(chloroformyl)butyrate (1.5 mmol, 3 eq), according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 2h and allowed to warm to rt until completion, as indicated by LC-MS. The solvent was removed *in vacuuo*, and the crude amide was used directly for further transformation.

To a stirred solution of the amide described above 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 3h (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 vacuuo*, and the pure product was obtained by silica gel column chromatography eluting with 10% MeOH in EtOAc + 0.2% TEA (yield: ~70%) (yield 202 mg).

MS m/z 576 $(M+H)^+$:

^1H NMR (400 MHz, $CDCl_3$): δ1.04 (t, 6H), 1.94 (m, 2H), 2.02 (m, 2H), 2.39 (t, 2H), 2.56 (q, 4H), 2.63 (t, 2H), 2.72 (t, 2H), 3.59 (s, 3H), 4.02 (t, 2H), 6.91 (d, 2H), 7.03 (d, 2H), 7.07 (d, 2H), 7.14 (s, 1H), 7.29 (d, 2H), 7.35 (d, 2H), 7.68 (d, 2H) ppm.

Example 490

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

To a stirred solution of 1-fluoro-4-nitrobenzene (10 mmol) in DMF (10 mL) at rt, solid potassium carbonate (30 mmol) was added followed by addition of 4-chloro-2-cyclohexylphenol (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 EtOAc (80ml), washed with H_2O (2X40 ml) and brine (60 mL), and dried over sodium sulfate. The solvent was removed *in vacuuo* to afford the desired 4-(4-chloro-2-cyclohexylphenoxy)-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 $SnCl_2{\cdot}2H_2O$ (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 vacuuo* 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, brine and dried over sodium sulfate. The solvent was removed *in vacuuo* to afford the desired 4-(4-chloro-2-cyclohexylphenoxy) 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

2007202350 24 May 2007

washed with H_2O (2X50 mL) and brine (50 mL). The organic layer was dried over sodium sulfate, and the solvent was removed *in vacuuo* 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 (2.4 mmol) in anhydrous MeOH (5 mL) at 0°C, pyrrolidone hydrotribromide (1.2 eq, 2.9 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 vacuuo* and the crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was used for further transformation.

To a stirred solution of 4-(4-chloro-2-cyclohexylphenoxy) aniline (1.2 eq., 2.5 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 (2.4 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 H_2O and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuuo* afforded the desired product. The crude alkylated aniline was purified by chromatography (Silica gel). Pure product obtained from 2-4% MeOH/DCM (yield ~50-60%).

To a stirred solution of alkylated 4-(4-chloro-2-cyclohexylphenoxy) aniline described above (2.4 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 vacuuo*, and the crude amide was used for further transformation.

To a stirred solution of the N-alkylated anilide (~2.4 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 H_2O (2x30 mL) and brine, and dried over sodium sulfate. Evaporation of the solvent *in vacuuo* afforded the desired N-aryl imidazole. The crude product was purified using silica gel column chromatography (2-5% MeOH/DCM) (yield 118 mg).

MS m/z 614 $(M+H)^+$:

^{1}H NMR ($CDCl_3$) δ7.86 (d, 1H), 7.63 (d, 2H), 7.25 (d, 2H), 7.18 (s, 1H), 7.08 (s, 1H), 6.94 (d, 2H), 6.81 (d, 2H), 6.80 (d, 1H, 6.8 Hz), 4.12 (m, 2H), 3.20 (m, 2H), 2.98-2.79 (m, 6H), 2.60 (t, 2H), 2.21-2.19 (m, 2H), 2.15-2.05 (m, 1H), 1.78-1.72 (m, 2H), 1.59-1.50 (m, 2H), 1.36-1.24 (m, 4H), 1.21 (t, 6H), 0.84 (m, 4H), 0.79 (m, 3H) ppm.

Example 491

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

To a stirred solution of 1-fluoro-4-nitrobenzene (10 mmol) in DMF (20 mL) at room temperature, solid K_2CO_3 (30 mmol) was added followed by addition of 4-hydroxybiphenyl (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 room temperature to room temperature, the reaction mixture was poured into EtOAc (100 mL), washed with water (2X50 mL) and brine (50 mL), and dried over sodium sulfate. The solvent was removed *in vacuo* to afford the desired 4-(biphenyl-4-oxy)-1-nitrobenzene. The crude product was used for further transformation .

The nitro intermediate (10 mmol) obtained above was dissolved in EtOAc (40 mL) and hydrogenated in the presence of 10% Pd/C (360 mg) until completion, 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-(biphenyl-4-oxy)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 room temperature, solid K_2CO_3 (153 mmol) was added. The mesylate of 3-diethylamino-1-propanol and methanesulfonyl chloride (76 mmol) was added to the reaction mixture and heated to 80 °C until completion, as indicated by TLC or HPLC. After cooling to room temperature, 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 water (2X50 mL) and brine (50 mL). The organic layer was dried over sodium sulfate, and the solvent was removed *in vacuuo* to afford the desired product. The crude alkylated product was used for further transformation after purifying using silica gel column chromatography (1-4% methanol/DCM).

To a stirred solution of 1-{4-[3-(diethylamino)propoxy]phenyl}ethanone (2.4 mmol) in anhydrous MeOH (5 mL) at 0°C, pyrrolidone hydrotribromide (1.2 eq., 2.9 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 vacuuo* and the crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was used for further transformation.

To a stirred solution of 4-(biphenyl-4-oxy)aniline (1.2 eq., 2.5 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 (2.4 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 H_2O and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuuo* afforded the desired product. The crude alkylated aniline was purified by chromatography (Silica gel). Pure product obtained from 2-4% MeOH/DCM (yield ~13%

To a stirred solution of alkylated 4-(biphenyl-4-oxy)aniline described above (0.3 mmol) in anhydrous DCM (3 mL) at 0°C, TEA (3eq., 0.9 mmol) was added, followed by slow addition of valeryl chloride (3 eq., 0.9 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 vacuuo*, and the crude amide was used for further transformation.

To a stirred solution of the N-alkylated anilide (~0.3 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 H_2O (2x15 mL) and brine, and dried over sodium sulfate. Evaporation of the solvent *in vacuuo* afforded the desired N-aryl imidazole. The crude product was purified using silica gel column chromatography (2-5% MeOH/DCM).

MS m/z 574 $(M+H)^+$

[1]H NMR ($CDCl_3$) δ7.86 (d, 1H), 7.63 (d, 2H), 7.25 (d, 2H), 7.18 (s, 1H), 7.08 (s, 1H), 6.94 (d, 2H), 6.81 (d, 2H), 6.80 (d, 1H), 4.12 (m, 2H), 3.20 (m, 2H), 2.98-2.79 (m, 6H), 2.60 (t, 2H), 2.21-2.19 (m, 2H), 2.15-2.05 (m, 1H), 1.78-1.72 (m, 2H), 1.59-1.50 (m, 2H), 1.36-1.24 (m, 4H), 1.21 (t, 6H), 0.84 (m, 4H), 0.79 (m, 3H) ppm

Example 492

[3-(4-{1-[4-(4-bromo-phenoxy)-phenyl]-2-butyl-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 4-bromophenol (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 EtOAc (100 mL), washed with H_2O (2X50 mL) and brine (50 mL), and dried over sodium sulfate. The solvent was removed *in vacuuo* to afford the desired 4-bromophenoxy-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 vacuuo* to afford the desired 4-bromophenoxyaniline, which was used directly for further transformation without additional 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 H_2O (2X50 mL) and brine (50 mL). The organic layer was dried over sodium sulfate, and the solvent was removed *in vacuuo* 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 (2.4 mmol) in anhydrous MeOH (5 mL) at 0°C, pyrrolidone hydrotribromide (1.2 eq., 2.9 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 vacuuo* and the crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was used for further transformation.

To a stirred solution of 4-bromophenoxyaniline (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 (2.4 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 H_2O and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuuo* 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 4-bromophenoxyaniline described above (0.45 mmol) in anhydrous DCM (5 mL) at 0°C, TEA (3eq., 1.35 mmol) was added, followed by slow addition of valeryl chloride (3 eq., 1.35 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 vacuuo*, and the crude amide was used for further transformation.

To a stirred solution of the N-alkylated anilide (~0.45 mmol) obtained as above in acetic acid (3 mL), solid ammonium acetate (9 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 H_2O (2x15 mL) and brine, and dried over sodium sulfate. Evaporation of the solvent *in vacuuo* afforded the desired N-aryl imidazole. The crude product was purified using silica gel column chromatography (2-5% MeOH/DCM) (yield 66 mg).

MS m/z 577 $(M+H)^+$:

^{1}H NMR ($CDCl_3$):δ7.63 (d, 2H), 7.43 (d, 2H), 7.23 (d, 2H), 7.08 (s, 1H), 7.02 (d, 2H), 6.90 (d, 2H), 6.83 (d, 2H) 4.05 (t, 2H), 2.92-2.72 (m, 6H), 2.60 (t, 2H), 2.05-2.15 (m, 2H), 1.60 (m, 2H), 1.33 (m, 2H), 1.20 (t, 6H), 0.80 (t, 3H) ppm

Example 493

N-[4-(4-{2-butyl-4-[4-(3-diethylamino-porpoxy)-phenyl]-imidazol-1-yl}-phenoxy)-phenyl]-acetamide

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 1 h and at rt for 1 h (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 vacuuo*.

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 vacuuo* 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%.

4-Acetamidophenol (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. EtOAc layer was dried over anhydrous sodium sulfate and filtered, after which the solvent was removed *in vacuuo*.

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 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 vacuuo* to afford the desired 4-(3,4-dichlorophenoxy)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 vacuuo* and the crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was used for further transformation.

To a solution of 4-(4-acetamidophenoxy) 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 vacuuo* afforded the desired product. The crude alkylated aniline was purified by chromatography (Silica gel). Pure product obtained from 2-4% MeOH/DCM (yield 54%).

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 vacuuo*, 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 210 mg).

MS m/z 555 $(M+H)^+$:

^1H NMR: ($CDCl_3$): δ7.68 (d, 2H), 7.51 (d, 2H), 7.25 (d, 2H), 7.13 (s, 1H), 6.88-7.00 (m, 6H), 4.02 (t, 2H), 2.62-2.70 (m, 8H), 2.20 (s, 3H), 2.16 (m, 2H), 1.97 (m, 2H), 1.16 (m, 2H), 1.05 (t, 6H), 0.83 (t, 3H) ppm

Example 494

(3-{4-[2-butyl-1-(4-p-tolyloxy-phenyl)-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 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 vacuuo*.

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

To a solution of 4-tolyloxy 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 vacuuo* 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 vacuuo*, and the crude amide was used for further transformation.

To a stirred solution of the amide described above (1 mmol) in acetic acid (4mL), 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 204 mg).

MS m/z 512 $(M+H)^+$:

^{1}H NMR ($CDCl_3$): δ 7.68 (d, 2H), 7.23 (d, 2H), 7.19 (d, 2H), 7.13 (s, 1H), 7.04 (d, 2H), 6.97 (d, 2H), 6.87 (d, 2H) 4.04 (t, 2H), 2.88-2.96 (m, 8H), 2.36 (s, 3H), 2.12 (m, 2H), 1.59 (m, 2H), 1.23(m, 2H), 1.18 (t, 6H), 0.83 (t, 3H) ppm

Example 495

[3-(4-{2-butyl-1-[4-(4-fluoro-phenoxy)-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 4-fluorophenol (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 EtOAc (100 mL), washed with H_2O (2X50 mL) and brine (50 mL), and dried over sodium sulfate. The solvent was removed *in vacuuo* to afford the desired 4-fluorophenoxy-1-nitrobenzene. The crude product may be used for further transformation .

The nitro intermediate (10 mmol) obtained above was dissolved in EtOAc (30 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 vacuuo* to afford the desired 4-fluorophenoxyaniline, which was used directly for further transformation without additional 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 H_2O (2X50 mL) and brine (50 mL). The organic layer was dried over sodium sulfate, and the solvent was removed *in vacuuo* 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., 2.8 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 vacuuo* and the crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was used for further transformation.

To a stirred solution of 4-fluorophenoxyaniline (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 H_2O and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuuo* afforded the desired product. The crude alkylated aniline was purified by chromatography (Silica gel). Pure product obtained from 2-4% MeOH/DCM (yield ~30%).

To a stirred solution of alkylated 4-fluorophenoxyaniline described above (0.8 mmol) in anhydrous DCM (5 mL) at 0°C, TEA (3eq., 2.4 mmol) was added, followed by slow addition of valeryl chloride (3 eq., 2.4 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 vacuuo*, and the crude amide was used for further transformation.

To a stirred solution of the N-alkylated anilide (~0.8 mmol) obtained as above in acetic acid (3 mL), solid ammonium acetate (16 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 H_2O (2x15 mL) and brine, and dried over sodium sulfate. Evaporation of the solvent *in vacuuo* afforded the desired N-aryl imidazole. The crude product was purified using silica gel column chromatography (2-5% MeOH/DCM) (yield 214 mg).

MS m/z 516 $(M+H)^+$:

^{1}H NMR ($CDCl_3$): δ7.88 (d, 2H), 7.46 (d, 2H), 7.23 (d, 2H), 7.31 (s, 1H), 7.22 (d, 2H), 7.09 (d, 2H), 7.06 (d, 2H) 4.22 (t, 2H), 3.16 (m, 2H), 3.21 (q, 4H), 2.84 (t, 2H), 2.39-2.19 (m, 2H), 1.83 (m, 2H), 1.50 (m, 2H), 1.35 (t, 6H), 1.03 (t, 3H) ppm

Example 496

[3-(4-{2-butyl-1-[4-(4-chloro-3-ethyl-phenoxy)-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 4-chloro-3-ethylphenol (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 EtOAc (100 mL), washed with H_2O (2X50 mL) and brine (50 mL), and dried over sodium sulfate. The solvent was removed *in vacuuo* to afford the desired 4-(4-chloro-3-ethylphenoxy)-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 $SnCl_2 \cdot 2H_2O$ (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 vacuuo* 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 and dried over sodium sulfate. The solvent was removed *in vacuuo* to afford the desired 4-chloro-3-ethylphenoxyaniline, which was used directly for further transformation without additional 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 H_2O (2X50 mL) and brine (50 mL). The organic layer was dried over sodium sulfate, and the solvent was removed *in vacuuo* 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 (2.4 mmol) in anhydrous MeOH (5 mL) at 0°C, pyrrolidone hydrotribromide (1.2 eq., 2.9 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 vacuuo* and the crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was used for further transformation.

To a stirred solution of 4-(4-chloro-3-ethylphenoxy)-1-nitrobenzene (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 (2.4 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 H_2O and the product was isolated in EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuuo* afforded the desired product. The crude alkylated aniline was used for further transformation .

To a stirred solution of alkylated 4-(4-chloro-3-ethylphenoxy)-1-nitrobenzene described above (~2.4 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 vacuuo*, and the crude amide was used for further transformation.

To a stirred solution of the N-alkylated anilide (~2.4 mmol) obtained as above in acetic acid (3 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 H_2O (2x30 mL) and brine, and dried over sodium sulfate. Evaporation of the solvent *in vacuuo* afforded the desired N-aryl imidazole. The crude product was purified using silica gel column chromatography (2-5% MeOH/DCM) (yield 60 mg).

MS m/z 560 $(M+H)^+$:

^1H NMR ($CDCl_3$): δ8.30 (d, 1H), 7.64 (d, 2H), 7.28 (d, 2H), 7.21 (s, 1H), 7.18 (s, 1H), 7.03 (d, 2H), 6.90 (m, 1H), 6.83 (d, 2H) 4.22 (t, 2H), 2.85-2.75 (m, 2H), 2.89 (q, 4H), 2.61 (m, 2H), 2.24 (t, 2H), 2.14 (d, 3H), 2.09-1.98 (m, 2H), 1.58 (m, 2H), 1.28 (m, 2H), 1.25 (t, 6H), 0.93 (t, 3H) ppm.

Example 497

{2-[4-(2-butyl-4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-imidazol-1-yl)-phenoxy]-ethyl}-ethyl-amine

To a stirred solution of 4'-hydroxyacetophenone (4 mmol) in DMF (10 mL) at rt, solid potassium carbonate (12.0 mmol) was added. 4-chlorophenthoxy mesylate (prepwered from the 4-chlorophenethanol and methanesulfonyl chloride) (4.4 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 with saturated sodium bicarbonate. The aqueous layer was poured into EtOAc (30ml) and washed with water (2X15 ml) and brine (15 ml). The organic layer was dried over magnesium sulfate, and the solvent was removed *in vacuuo* to afford the desired 1-{4-[2-(4-chlorophenyl)ethoxy]phenyl}ethanone. The crude alkylated product was purified by silica gel chromatography and the pure product obtained from 10% EtOAc/hexanes (yield 70%).

To a stirred solution of 4-fluoronitrobenzene (4.0 mmol) in anhydrous THF (12 mL) at 0°C, a 1M solution of a potassium alkoxide (4.4 mmol) in THF (may be generated by adding the N-Boc,N-ethyl ethanolamine 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

2007202350 24 May 2007

0°C until completion, as indicated by TLC or HPLC. The solvent was removed and the reaction mixture was then treated with cold H_2O (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 vacuuo* afforded the desired 4-alkoxynitrobenzene. The crude product could be used directly for further transformation .

The nitro intermediate (2 mmol) obtained above was dissolved in EtOH (8mL) and hydrogenated in the presence of 10% Pd/C (10 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 vacuuo* to afford 4-(N-Boc-N-ethylaminoethoxy)aniline, which was used directly for further transformation without further purification (yield 80%).

To a stirred solution of 1-{4-[2-(4-chlorophenyl)ethoxy]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 vacuuo* and the crude 2-bromo-1-{4-[3-(diethylamino)propoxy]phenyl}ethanone was used for further transformation.

To a solution of 4-(N-Boc-N-ethylethoxy)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 vacuuo* 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 vacuuo*, 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 obtained from 4-6% MeOH/DCM was treated with HCl in dioxane for 2h to give the hydrochloride salt of {2-[4-(2-butyl-4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-imidazol-1-yl)-phenoxy]-ethyl}-ethyl-amine (yield 177mg).

MS m/z 518 $(M+H)^+$:

^1H NMR (400 MHz, $CDCl_3$): δ 7.7 (d, 2H), 7.2 (m, 4H), 7.1 (m, 3H), 6.8-7.0 (m, 4H), 4.0-4.3 (m, 6H), 3.0-3.2 (m, 6H), 2.9 (m, 2H), 2.6 (m, 2H), 1.2 (t, 3H), 0.8 (t, 3H) ppm

Example 498

[3-(4-{5-butyl-4-[4-(3,3-diphenyl-propoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenoxy)-2,2-dimethyl-propyl]-dimethyl-amine

To a stirred solution of ice-cold 4-hydroxy-*n*-hexanophenone (18 mmol), 3,3-diphenyl-1-propanol (22.6 mmol, 1.25 eq), triphenylphosphine (22.6 mmol, 1.25 eq) dissolved in anhydrous THF (100 mL) was added dropwise diisopropyl azodicarboxylate (DIAD) (22.6 mmol, 1.25 eq). The reaction mixture was stirred at 0°C for 1h, and then allowed to warm to rt, continuing the stirring for additional 6h (monitored by TLC). The solvent was removed *in vacuuo*, and the crude product was purified by silica gel column chromatography eluting with 10% EtOAc in hexane (yield: 100%).

The acetophone described as above (18 mmol) was dissolved in 1,4-dioxane (100 mL), and treated with pyridine hydrotribromide (18.9 mmol, 1.05 eq), according to General Procedure R1. After stirring at rt for 6h (monitored by TLC), the reaction was quenched with cold H_2O (100 mL). The resulting mixture was extracted with EtOAc (4×100 mL). The combined EtOAc extracts were washed with brine (3×50 mL), and dried over anhydrous sodium sulfate. The solvent was then removed *in vacuuo* and the crude alpha-bromoacetophenone was directly used for further transformation.

To a stirred solution of the crude alpha-bromoacetophenone described as above (~12 mmol) and 4-benzyloxyaniline (12 mmol) dissolved in DMF (40 mL), DIEA (36 mmol, 3 eq) was added at rt, and the mixture was stirred at the same temperature for 12h, according to General Procedure R2 (monitored by TLC and LC-MS). The reaction mixture was treated

2007202350 24 May 2007

with saturated sodium bicarbonate (100 mL), and the resulting mixture was extracted with EtOAc (4×100 mL). The combined EtOAc extracts were washed with brine (3×50 mL), and dried over anhydrous sodium sulfate. The solvent was removed *in vacuuo*, and the crude product was purified by silica gel column chromatography eluting with 10-15% EtOAc in hexane (overall yield from the acetophone: ~50%).

To a stirred solution of ice-cold the alkylated aniline (1.7 mmol) obtained above and DMAP (3.4 mmol, 2 eq) dissolved in anhydrous DCM (200 mL), isovaleryl chloride (6.8 mmol, 4 eq) was added, according to General Procedure R3. The reaction mixture was stirred under nitrogen at 0°C for 3h and allowed to warm to rt until completion, as indicated by LC-MS. The solvent was removed *in vacuuo*, and the crude amide was used directly for further transformation.

The crude amide described above (~3.7 mmol) was suspended in acetic acid (10 mL), and ammonium acetate (excess, ~30 eq) was added, according to General Procedure R4. The reaction mixture was stirred at 120°C for 20h (as monitored by TLC and LC-MS). The reaction mixture was then cooled to rt and neutralized with saturated sodium bicarbonate and solid sodium carbonate. The resulting mixture was extracted with EtOAc (4×100 mL). The combined EtOAc extracts were washed with H_2O (2×60 mL) and brine (2×60 mL), and dried over anhydrous sodium sulfate. The solvent was removed *in vacuuo*, and the crude product was purified by silica gel column chromatography eluting with 10-20% EtOAc in hexane (overall yield from the alkylated aniline: 62%).

The product (2.9 mmol) obtained above was dissolved in MeOH (50 mL) and hydrogenated in the presence of 10% Pd/C (0.5g) until completion as indicated by LC-MS (~2h) , according to General Procedure H. The reaction mixture was then filtered to remove the catalyst. The solvent was removed *in vacuuo* to afford the desired 1-(4'-hydroxyphenyl) imidazole, which was used directly for further transformation without purification (yield: 100%).

To a stirred solution of ice-cold 3-dimethylamino-2,2-dimethyl-1-propanol (1 mmol) and TEA (1.5 mmol) dissolved in anhydrous DCM (8 mmol) was added dropwise methanesulfonyl chloride (1.05 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 vacuuo*, the crude mesylate was dissolved in DMF (10 mL). 1-(4'-hydroxyphenyl) imidazole (0.5 mmol) obtained above and cesium carbonate (3 mmol) were added, and the mixture was heated with stirring at 90°C for 3 h (monitored by LC-MS). After cooling to rt, the reaction was quenched with saturated sodium bicarbonate (20 mL), and the resulting mixture was extracted with EtOAc (3×50 mL).

The combined EtOAc extracts were washed with brine (3×30 mL), and dried over anhydrous sodium sulfate. The solvent was removed *in vacuuo*, and the pure product was obtained by silica gel column chromatography eluting with 5-10% MeOH in EtOAc (yield 252 mg).

MS m/z 672 $(M+H)^+$:

^{1}H NMR (400 MHz, $CDCl_3$): δ0.70 (t, 3H), 0.83 (d, 6H), 1.03 (s, 6H), 1.13 (m, 2H), 1.28 (m, 2H), 1.96 (m, 1H), 2.29 (s, 6H), 2.31 (s, 2H), 2.36 (d, 2H), 2.47-2.56 (m, 4H), 3.77 (s, 2H), 3.91 (t, 2H), 4.26 (t, 1H), 6.86 (d, 2H), 7.00 (d, 2H), 7.11 (d, 2H), 7.19-7.28 (m, 10H), 7.56 (d, 2H) ppm

Example 499

[3-(4-{4-[4-(3,3-diphenyl-propoxy)-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 H_2O and the product was isolated in Et_2O. The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent *in vacuuo* 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 vacuuo*, 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 H_2 atmosphere using a balloon, according to General Procedure T2. The Pd/C was removed by filtration. The solvent was removed *in vacuuo*, 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 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 3,3-diphenylpropan-1-ol (1.1eq) was added to the reaction mixture, and stirred at rt overnight, according to General Procedure T3. Et_2O (30 mL) was added to the reaction mixture followed by H_2O (10 mL). The organic layer was washed with H_2O (2x15 mL) and brine, and dried over sodium sulfate. The solvent was removed *in vacuuo*. Pure imidazole was obtained from chromatography with 5-10% MeOH/DCM (yield 73 mg).

MS m/z 616 $(M+H)^+$:

^1H NMR ($CDCl_3$): δ7.67 (d, 2H), 7.15-7.3, (m, 12H), 7.09 (s, 1H), 6.96 (d, 2H), 6.84 (d, 2H), 4.25 (t, 1H), 4.07 (t, 2H), 3.9 (t, 2H), 3.74 (t, 1H), 2.46-2.75 (m, 10 H), 2.0 (m, 3H), 1.0 (t, 6H), 0.84 (d, 6H) ppm.

Example 500

7-{2-butyl-4-[4-(4-chloro-phenoxy)-naphthalen-1-yl]-imidazol-1-yl}-1,2,3,4-tetrahydro-isoquinoline hydrochloride

7-Nitro-1,2,3,4-tetrahydroisoquinoline hydrochloride (8.2g, 42% yield) was prepared by slightly modifying the published procedure (*J. Med. Chem.*, 1997, *40*, 3997-4005).

Di-tert-butyl dicarbonate (7.5g, 33.8 mmol) was added to a solution of 7-nitro-1,2,3,4-tetrahydroisoquinoline hydrochloride (3.8g, 16.9 mmol), Et_3N (9.42 mL, 67.6 mmol) and DMAP (0.1g) dissolved in anhydrous THF (60 mL). After being stirred overnight at rt, the reaction mixture was treated with saturated $NaHCO_3$ (50 mL), and the resulting mixture was extracted with EtOAc (3×100 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). The crude products were purified by flash chromatography (eluting with 10-20% EtOAc in hexanes) to give 2-BOC-7-nitro-1,2,3,4-tetrahydroisoquinoline (4.1g).

The nitro compound obtained above (4.1g, 14.7 mmol) was dissolved in MeOH (80 mL) and hydrogenated in the presence of 10% Pd/C (0.3g), according to General Procedure H. Workup afforded afforded 7-amino-2-Boc-1,2,3,4-tetrahydroisoquinoline (2-Boc-TIQ aniline (3.6g, 98% yield) as a light-brown solid.

4'-(4-chlorophenoxy)-1'-acetonaphthone was prepared from 4'-fluoro-1'acetonaphthone and 4-chlorophenol following general procedure Q2. 4'-(4-chlorophenoxy)-1'-acetonaphthone was brominated following general procedure R1. The bromo ketone was condensed with 7-amino-2-Boc-1,2,3,4-tetrahydroisoquinoline following general procedure R2. The aminoketone intermediate was treated with n-penatnoyl chloride accoding to general procedure R3. The product amide was then subjected to imidazole formation employing general procedure R4. The BOC group of the product was removed cmploying general procedure T1 to afford 7-{2-Butyl-4-[4-(4-chloro-phenoxy)-naphthalen-1-yl]-imidazol-1-yl}-1,2,3,4-tetrahydro-isoquinoline hydrochloride.

LC-MS (*m/z*): 508 $(M+H)^+$.

Example 501

2-biphenyl-4-yl-N-{4-[2-butyl-1-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-1H-imidazol-4-yl]-phenyl}-acetamide hydrochloride

4-Nitrophenacyl bromide (5 mmol) was added to a stirred mixture of 2-BOC-7-nitro-1,2,3,4-tetrahydroisoquinoline (5 mmol) in DCM (20 mL) at rt, and the mixture was stirred at rt overnight. The reaction mixture was treated with sat. $NaHCO_3$ (30 mL), the resulting mixture was extracted with EtOAc (200 mL), washed with brine and dried. The crude product was purified by silica gel column chromatography (eluting with 8% EtOAc in hexane to give the amino ketone intermediate (0.33g).

Following the general procedures R2, R3, and R4 as for Example 500, the amino ketone intermediate (330 mg, 0.8 mmol) was converted into a 4-nitrophenyl - substituted imidazole. The imidazole was reduced by Pd-carbon catalytic hydrogenation following general procedure H to the corresponding 4-aminophenyl imidazole.

PS-carbodiimide (1,27 mmol/g, 310 mg, 0.4 mmol) was added to a mixture of the 4-aminophenyl imidazole obtained above (45 mg, 0.1 mmol) and biphenylacetic acid (43 mg, 0.2 mmol) in anhydrous DCM (6 mL), and the mixture was slowly shaken at rt overnight. The pure product (25 mg, 40% yield) was obtained after silica gel column chromatography (20% EtOAc in hexane). 2-Biphenyl-4-yl-N-{4-[2-butyl-1-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-1H-imidazol-4-yl]-phenyl}-acetamide hydrochloride (20 mg) was obtained by treating the product with 4N hydrogen chloride in dioxane solution, following the General Procedure T1.

LC-MS (*m/z*): 541 $(M+1)^+$.

Example 502

7-{2-butyl-4-[4-(2,4-dichloro-phenoxy)-phenyl]-imidazol-1-yl}-1,2,3,4-tetrahydro-isoquinoline hydrochloride

1-[4-(2,4-Dichlorophenoxy)phenyl]ethan-1-one (282 mg, 1 mmol) was brominated by General Procedure R1. The bromo ketone was condensed with 7-amino-2-Boc-1,2,3,4-tetrahydroisoquinoline following general procedure R2. The aminoketone intermediate was treated with n-penatnoyl chloride accoding to General Procedure R3. The product amide was then subjected to imidazole formation employing general procedure R4. The BOC group of the product was removed employing general procedure T1 to afford 7-{2-butyl-4-[4-(2,4-dichloro-phenoxy)-phenyl]-imidazol-1-yl}-1,2,3,4-tetrahydro-isoquinoline hydrochloride (150 mg).

LC-MS (*m/z*): 493 $(M+1)^+$.

Example 503

7-(2-butyl-4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-isobutyl-imidazol-1-yl)-1,2,3,4-tetrahydro-isoquinoline hydrochloride

1-[4-(4-chlorophenylethoxy)]ethan-1-one (1 mmol) was brominated by General Procedure R1. The bromo ketone was condensed with 7-amino-2-Boc-1,2,3,4-tetrahydroisoquinoline following general procedure R2. The aminoketone intermediate was treated with n-pentanoyl chloride accoding to General Procedure R3. The product amide was then subjected to imidazole formation employing general procedure R4. The BOC group of the product was removed employing general procedure T1 to afford 7-(2-Butyl-4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-isobutyl-imidazol-1-yl)-1,2,3,4-tetrahydro-isoquinoline hydrochloride (145mg).

LC-MS (*m/z*): 486 $(M+H)^+$.

Example 504

7-[4-(4-benzyloxy-phenyl)-2-butyl-imidazol-1-yl]-1,2,3,4-tetrahydro-isoquinoline hydrochloride

4-benzyloxyacetophone was brominated by General Procedure R1. The bromo ketone was condensed with 7-amino-2-Boc-1,2,3,4-tetrahydroisoquinoline following general procedure R2. The aminoketone intermediate was treated with n-pentanoyl chloride accoding to General Procedure R3. The product amide was then subjected to imidazole formation employing general procedure R4 to afford 7-[4-(4-Benzyloxy-phenyl)-2-butyl-imidazol-1-yl]-2-Boc-1,2,3,4-tetrahydro-isoquinoline. The BOC group of the product was removed employing general procedure T1 to afford 7-[4-(4-Benzyloxy-phenyl)-2-butyl-imidazol-1-yl]-1,2,3,4-tetrahydro-isoquinoline hydrochloride (170 mg).

LC-MS (*m/z*): 438 $(M+1)^+$.

Example 505

9-(2-{4-[2-butyl-1-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-1H-imidazol-4-yl]-phenoxy}-ethyl-9H-carbazole hydrochloride

7-[4-(4-Benzyloxy-phenyl)-2-butyl-imidazol-1-yl]-2-Boc-1,2,3,4-tetrahydro-isoquinoline was debenzylated according to General Procedure T2 to afford 7-[4-(4-hydroxyphenyl)-2-butyl-imidazol-1-yl]-2-Boc-1,2,3,4-tetrahydro-isoquinoline. The phenol was condensed with the mesylate of 9H-carbazole-9-ethanol following general procedure T3 to afford the ethylcarbazole ether intermediate. This ethylcarbazole intermediate was deprotected employing general procedure T1 to afford 9-(2-{4-[2-butyl-1-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-1H-imidazol-4-yl]-phenoxy}-ethyl-9H-carbazole hydrochloride (55mg).

LC-MS (*m/z*): 541 $(M+1)^+$.

Example 506

7-{2-butyl-4-[4-(4-methoxy-phenoxy)-phenyl]-imidazol-1-yl}-1,2,3,4-tetrahydro-isoquinoline hydrochloride

1-[4-(4-methoxyphenoxy)phenyl]ethan-1-one (1 mmol) was brominated by General Procedure R1. The bromo ketone was condensed with 7-amino-2-Boc-1,2,3,4-tetrahydroisoquinoline following general procedure R2. The aminoketone intermediate was treated with n-pentanoyl chloride accoding to General Procedure R3. The product amide was then subjected to imidazole formation employing general procedure R4. The BOC group of the product was removed employing general procedure T1 to afford 7-{2-butyl-4-[4-(4-methoxy-phenoxy)-phenyl]-imidazol-1-yl}-1,2,3,4-tetrahydro-isoquinoline hydrochloride (yield 135 mg)
LC-MS (*m/z*): 454 $(M+1)^+$.

Example 507

7-(2-butyl-4-{4-[2-(4-tert-butyl-phenyl)-ethoxy]-phenyl}-imidazol-1-yl)-1,2,3,4-tetrahydro-isoquinoline hydrochloride

7-[4-(4-hydroxyphenyl)-2-butyl-imidazol-1-yl]-2-Boc-1,2,3,4-tetrahydro-isoquinoline was condensed with the mesylate of 2-(4-t-butylphenyl)ethanol according to General Procedure T3 to afford the phenyl ether intermediate, which was deprotected according to general procedure T1 to afford 7-(2-butyl-4-{4-[2-(4-tert-butyl-phenyl)-ethoxy]-phenyl}-imidazol-1-yl)-1,2,3,4-tetrahydro-isoquinoline hydrochloride (35mg).

LC-MS (*m/z*): 508 $(M+1)^+$.

Example 508

7-{2-butyl-4-[4-(naphthalen-2-ylmethoxy)-phenyl]-imidazol-1-yl}-1,2,3,4-tetrahydro-isoquinoline hydrochloride

7-[4-(4-hydroxyphenyl)-2-butyl-imidazol-1-yl]-2-Boc-1,2,3,4-tetrahydro-isoquinoline was condensed with 2-(bromomethyl)naphthalene according to general procedure T3 to afford the phenyl ether intermediate, which was deprotected according to general procedure T1 to afford 7-{2-butyl-4-[4-(naphthalen-2-ylmethoxy)-phenyl]-imidazol-1-yl}-1,2,3,4-tetrahydro-isoquinoline hydrochloride (32 mg).

LC-MS (*m/z*): 488 (M+1)$^+$.

Example 509

7-{2-butyl-4-[4-(4-trifluoromethyl-phenoxy)-phenyl]-imidazol-1-yl}-1,2,3,4-tetrahydro-isoquinoline hydrochloride

7-[4-(4-hydroxyphenyl)-2-butyl-imidazol-1-yl]-2-Boc-1,2,3,4-tetrahydro-isoquinoline was condensed with 4-trifluoromethylbenzyl bromide according to general procedure T3 to afford the phenyl ether intermediate, which was deprotected according to general procedure T1 to afford 77-{2-butyl-4-[4-(4-trifluoromethyl-phenoxy)-phenyl]-imidazol-1-yl}-1,2,3,4-tetrahydro-isoquinoline hydrochloride (45 mg).

LC-MS (*m/z*): 506 (M+1)$^+$.

Example 510

7-(2-butyl-4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-imidazol-1-yl)-1,2,3,4-tetrahydro-isoquinoline hydrochloride

1-[4-(4-chlorophenylethoxy)]ethan-1-one (1 mmol) was brominated by General Procedure R1. The bromo ketone was condensed with 7-amino-2-Boc-1,2,3,4-tetrahydroisoquinoline following general procedure R2. The aminoketone intermediate was treated with n-pentanoyl chloride accoding to General Procedure R3.
The product amide was then subjected to imidazole formation employing general procedure R4. The BOC group of the product was removed employing general procedure T1 to afford 7-(2-Butyl-4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-imidazol-1-yl)-1,2,3,4-tetrahydro-isoquinoline hydrochloride (170mg).
LC-MS (*m/z*): 486 (M+1)$^+$.

Example 511

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

Example 511 was synthesized by the method established for Example 406, using 4-butylcyclohexanecarbonyl chloride in place of valeryl chloride (yield 300 mg).
MS: m/z 614 $(M+H)^+$

Example 512

2-(4-{1-[4-(4-Chloro-phenoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenoxy)-ethylamine

Example 512 was synthesized by the method established for Example 464, utilizing N-BOC-ethanolamine in plase of 3-dimethylamino-1-propanol to produce 2-(4-{1-[4-(4-chloro-phenoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenoxy)-ethylamino tert-butyl carbamate as an intermediate. This intermediate was deprotected employing general procedure T1 to afford Example 512 as the hydrochloride salt. (Yield: 115 mg).
MS: m/z 462 $(M+H)^+$

Example 513

[3-(4-{2-(trans-4-tert-Butyl-cyclohexyl)-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine

Example 513 was prepared by chromatographic purification on silica gel of the compound of Example 486. 500 mg of Example 486 was separated by silica gel column chromatography, eluting with 5-10% MeOH in DCM, to give the cis-isomer (120 mg) followed by trans-isomer Example 513 (200 mg).
^{1}H NMR (400 MHz, $CDCl_3$): δ 0.82 (s, 9H), 1.08 (t, 6H), 1.50-2.50 (m, 12H), 2.66 (q, 4H), 2.73 (t, 2H), 4.02 (t, 2H), 6.89 (d, 2H), 7.04 (d, 2H), 7.07 (d, 2H), 7.08 (s, 1H), 7.27 (d, 2H), 7.36 (d, 2H), 7.69 (d, 2H) ppm
MS: m/z 614 $(M+H)^+$

Example 514

[3-(4-{2-(cis-4-tert-Butyl-cyclohexyl)-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine

Example 514 was prepared by chromatographic purification on silica gel of the compound of Example 486. 500 mg of Example 486 was separated by silica gel column

chromatography, eluting with 5-10% MeOH in DCM, to give the cis-isomer Example 514 (120 mg) followed by trans-isomer (200 mg).
MS: m/z 614 $(M+H)^+$

Example 515

[2-(4-{2-Butyl-1-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-ethyl]-methyl-pyridin-4-yl-amine

A mixture of 4-chloropyridine hydrochloride salt (15.0 g) and 2-methylaminoethanol (30 mL) was refluxed for 48 hour. After cooling to rt the crude mixture was added slowly to saturated solution of sodium bicarbonate (150 mL). The product was extracted with EtOAc (3X100 mL), the combined EtOAc was washed with brine (50mL), dried (Na_2SO_4) and removed in vacuo to give the desired product 2-[methyl(pyridin-4-yl)amino]ethanol as yellow solid (7.0g).

2-[methyl(pyridin-4-yl)amino]ethyl methanesulfonate was prepared according to general procedure P2.

4-{2-butyl-1-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-1H-imidazole-4-yl}-phenol was prepared via a modification of the procedure employed to synthesize {1-[4-(4-chloro-phenoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}phenol.

Sodium hydride (50.0 mg, 60% dispersion in oil) was added to a mixture of 100 mg of 4-{2-butyl-1-[4-(4-fluoro-3-trifluoromethyl-phenoxy)-phenyl]-1H-imidazole-4-yl}-phenol and 200 mg 2-[methyl(pyridin-4-yl)amino]ethyl methanesulfonate in DMF (5 mL). After 24 h of stirring at rt, the mixture was added to ether (50mL) and the ether was washed with water and dried (Na_2SO_4). The solvent was removed *in vacuo*. Silica gel chromatography afforded 150 mg of Example 515.

MS: *m/z* 605 $(M+H)^+$

Example 516

[2-(4-{1-[4-(4-Fluoro-phenoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenoxy)-ethyl]-methyl-pyridin-4-yl-amine

4-{1-[4-(4-fluoro-phenoxy)-phenyl]-2-isobutyl-1H-imidazole-4-yl}phenol was prepared in analogous fashion to 4-{1-[4-(4-chloro-phenoxy)-phenyl]-2-isobutyl-1H-imidazole-4-yl}phenol. Alkylation opf the phenol proceeded as for Example 515 to afford Example 516 (47mg).

MS: m/z 537 $(M+H)^+$

^{1}H NMR ($CDCl_3$): δ 8.23 (d, 2H), 7.70 (d, 2H), 7.53 (d, 2H,), 7.24 (s, 1H), 7.12 (d, 2H), 7.07 (m, 2H), 7.04 (d, 2H), 6.87 (d, 2H), 6.58 (d, 2H) 4.17 (t, 2H), 3.81 (t, 2H), 3.11 (s, 3H), 2.54 (d, 2H), 2.06 (m, 1H), 0.87 (d, 6H) ppm

Example 517

[2-(4-{1-[4-(4-Fluoro-phenoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenoxy)-ethyl]-methyl-(3-methyl-pyridin-4-yl)-amine

Example 517 was prepared in analogous fashion to Example 516, with the use of 3-methyl-4-chloropyridine in place of 4-chloropyridine. (Yield: 110 mg)

MS: m/z 551 $(M+H)^+$

Example 518

[2-(4-{1-[4-(4-Chloro-phenoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenoxy)-ethyl]-ethyl-pyridin-4-yl-amine

2-[Ethyl(pyridin-4-yl)amino]ethanol was synthesized via an analogous methd as that employed for 2-[methyl(pyridin-4-yl)amino]ethanol.

2-[Ethyl(pyridin-4-yl)amino]ethanol was converted to the methanesulfonate via a modification of General Procedure P2.

{1-[4-(4-Chloro-phenoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}phenol was synthesized by an analogous series of procedures as for Example 77.

Another procedure was below;

4-Acetoxyacetophenone (10.7g, 60 mmol) in dioxane (200 mL) was treated with pyridinium hydrotribromide (21g, 66 mmol, 1.1 eq) added in portions at rt, according to General Procedure R1. The reaction mixture was stirred at rt for 6h. The reaction was quenched by adding cold H_2O (100 mL), and extracted with ether (4×100 mL). The ethereal solution was washed with H_2O (100 mL) and dried (anhydrous Na_2SO_4). The solvent was then removed *in vacuo* and the α-bromoacetophenone obtained above was added to a stirred solution of 4-(4'-chlorophenoxy)aniline (13.2g, 60 mmol, 1.1 eq) and anhydrous DMF (100 mL) at rt, and the mixture was stirred at the same temperature for 5h (monitored by LC-MS). The reaction mixture was treated with sat. $NaHCO_3$ (100 mL), and the resulting mixture was extracted with EtOAc (4×100 mL). The combined EtOAc extracts were washed with H_2O (2×100 mL) and brine (2×100 mL), and dried (Na_2SO_4). The solvent was removed *in vacuo*, and the alkylated aniline was used for next step

To a stirred solution of the c alkylated aniline dissolved in anhydrous DCM (250 mL) at 0°C, triethylamine (15.2 mL, 180 mmol) was added, followed by slow addition of isovaleryl chloride (14.7 mL, 120 mmol), according to General Procedure R3. The reaction mixture was stirred under N_2 at 0°C for 0.5h and then at rt for another 2h (or monitored by LC-MS). The solvent was removed *in vacuo*, and the crude amide was used directly for further transformation.

To a stirred suspension of the amide described above in AcOH (30 mL), ammonium acetate (80g) was added, according to General Procedure R4. The reaction mixture was stirred at 100°C for 2h (as monitored by LC-MS). The reaction mixture was then cooled down and neutralized with sat. $NaHCO_3$ (100 mL) and solid Na_2CO_3. The resulting mixture was extracted with EtOAc (4×150 mL) and the organic phase was concentrated. The light-yellow solid product was collected after fiiltration. The filtrate was concentrated *in vacuo* to about 150 mL volume andafter standing at rt the solid product was collected and dried, overall yield 11 g of {1-[4-(4-chloro-phenoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}phenol.

Sodium hydride (50.0 mg,60% dispersion in oil) was added to mixture of 100 mg of 4-{1-[4-(4-chloro-phenoxy)-phenyl]-2-isobutyl-1H-imidazole-4-yl}phenol and 180 mg of 2-[ethyl(pyridin-4-yl)amino]ethyl methanesulfonate in DMF (5 mL). After 24 h of stirring at rt, the mixture was added to ether (50mL) and washed with water and dried (Na_2SO_4). The solvent was removed *in vacuo*. Chromatography on silica gel afforded Example 518 (36 mg).

MS: m/z 567 $(M+H)^+$

Example 519

[2-(4-{1-[4-(4-Chloro-phenoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenoxy)-ethyl]-pyridin-4-yl-amine

2-(4-{1-[4-(4-Chloro-phenoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenoxy)-ethylamine, the product of Example 512, was treated with 4-chloropyridine in DMF and was heated at 100 °C. Aqueous workup and chromatography on silica gel afforded Example 519. (Yield: 80 mg)

MS: m/z 539 $(M+H)^+$

Example 520

[2-(4-{1-[4-(4-Chloro-phenoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenoxy)-ethyl]-bis-pyridin-2-ylmethyl-amine

The methanesulfonate of N-Boc-glycinol was synthesized by modifying the general procedure P2.

{1-[4-(4-Chloro-phenoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}phenol (2 mmol) was added to a solution of Cs_2CO_3 (10 eq., 20 mmol) in anhydrous DMF (5 ml). This was followed by addition of the mesylate obtained above and the reaction mixture was heated to 90°C for 2-3 h. The reaction mixture was then cooled to rt, diluted with cold water and the product was extracted with DCM. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo to give desired product, which was BOC – deprotected according to general procedure T1. The HCl salt was dissolved in water, neutralized with 4N NaOH solution and the crude product was extracted with EtOAc. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo to give desired product amine.

The crude product obtained above was taken in anhydrous DCM (5 ml). 2-pyridylcarboxaldehyde (2.5 eq.) and $Na(OAc)_3BH$ (2.5 eq.) was added to this solution and the reaction mixture was stirred at rt for 2-3 h. The product was concentrated in vacuo and extracted with EtOAc and the organic layer was washed with saturated sodium bicarbonate solution. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo to give desired product, Example 520 (yield 96 mg).

MS: m/z 644 $(M+H)^+$

Example 521

N-[2-(4-{1-[4-(4-Chloro-phenoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenoxy)-ethyl]-guanidine

2-(4-{1-[4-(4-Chloro-phenoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenoxy)-ethylamine, the product of Example 512, was treated in acetonitile with DIEA and N,N'-bis-BOC-1-guanylpyrazole. The resulting mixture was then refluxed. The reaction mixture was then cooled to rt and diluted with EtOAc. The mixture was washed with water and brine and dried over anhydrous sodium sulfate. Solvent was removed in vacuo and the residue obtained was purified by silica gel column chromatography to afford the BOC-protected guanadino intermediate. The BOC-protected guanadino intermediate was treated with 4M HCl/dioxane to remove the BOC group as described in general procedure T1, affording Example 521.

MS: m/z 504 $(M+H)^+$

Example 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

To a stirred solution of 4-pyridyl-piperazine (2 mmol) in DCM (4 mL) at 0°C, triethylamine (6.0 mmol) was added followed by addition of 2-chloroacetyl chloride (4mmol). The reaction mixture was stirred under nitrogen at rt until completion, as indicated by TLC or HPLC. The reaction mixture was treated with saturated aqueous sodium bicarbonate solution (5 mL), then extracted with EtOAc (2X15 mL). The combined organic layers were washed with H_2O (2x15 mL) and brine, and dried over sodium sulfate. Evaporation of the solvent *in vacuo* afforded the amide. The crude product was used for further transformation .

To the above amide (2mmol) in DMF (5ml) was added Cesium carbonate (10mmol, 5eq), followed by the addition of {1-[4-(4-chloro-phenoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}phenol (1.5mmol) and the reaction was heated to 90 °C until completion, as indicated by TLC or HPLC. After cooling to rt, the reaction mixture was treated with saturated sodium bicarbonate (150 ml). The aqueous layer was extracted with EtOAc (4X100ml). The organic layer was washed with 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 imidazole which was purified by was purified by chromatography over silica gel to afford Example 522.

MS: m/z 622 $(M+H)^+$

Example 523

5-(4-{1-[4-(4-Chloro-phenoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenoxymethyl)-pyrrolidin-3-ol

Sodium borohydride (227 mg, 6 mmol) was added at 0°C to a stirred solution of (2S,4R)-N-BOC-4-(*t*-butyldimethylsilyloxy)prolinaldehyde (522 mg, 1.58 mmol) in MeOH (10 mL), and the mixture was stirred at rt for 3h. The reaction was quenched by adding sat. $NaHCO_3$ (20 mL), and the resulting mixture was extracted with EtOAc (3×50 mL). The EtOAc extracts were washed with brine (2×50 mL), and dried (Na_2SO_4). The solvent was removed *in vacuo* to give (2S,4R)-N-BOC-4-(*t*-butyldimethylsilylhydroxy)prolinol (550 mg).

The acohol obtained above was converted to the methanesulfonate according to general procedure P2.

4-{1-[4-Chlorophenoxy)phenyl]-2-isobutyl-1*H*-imidazol-4-yl}phenol described above (840 mg, 2 mmol) was added to a stirred mixture of the mesylate obtained in the previous step, Cs_2CO_3 (1.95g, 6 mmol) in anhydrous DMF (20 mL), and the mixture was heated with stirring at 90 °C for 15 h. The reaction was quenched by adding sat. $NaHCO_3$ and the resulting mixture was extracted with EtOAc. The EtOAc extracts were washed with brine and dried (Na_2SO_4). The solvent was removed *in vacuo* to give crude alkylated product.

2N hydrogen chloride in ethereal solution (2 mL) was added to a stirred mixture of the alkylated imidazole obtained above (150 mg) in DCM (8 mL) at rt. After being stirred at rt for 4 h, the reaction mixture was treated with sat. $NaHCO_3$. The resulting mixture was extracted with EtOAc. The EtOAc extracts were washed with brine and dried (Na_2SO_4). The solvent was removed *in vacuo*, and the residue was purified by silica gel column chromatography to give 5-(4-{1-[4-(4-chlorophenoxy)phenyl]-2-isobutyl-1H-imidazol-4-yl}phenoxymethyl)pyrrolidin-3-ol (50 mg).

LC-MS: *m/z* 518 $(M+H)^+$

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.84 (d, 6H), 1.25-3.20 (m, 6H), 2.53 (d, 2H), 4.05 (m, 3H), 4.50 (m, 1H), 6.91 (d, 2H), 7.01 (d, 2H), 7.05 (d, 2H), 7.10 (s, 1H), 7.24 (d, 2H), 7.34 (d, 2H), 7.66 (d, 2H) ppm.

Example 524

3-(4-{1-[4-(4-Fluoro-phenoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenoxy)-pyridin-4-ylamine

To an ice-cold solution of 3-bromopyridine-N-oxide (4 mmol) in concentrated H_2SO_4 (4 ml), concentrated HNO_3 (0.5 ml) was added gradually. The reaction mixture was heated at 90°C for 48 h. The reaction mixture was then cooled to rt, diluted with cold water and the product was extracted with EtOAc. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo to give desired product, 3-bromo-4-nitropyridine N-oxide.

{1-[4-(4-Chloro-phenoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}phenol (1.1 eq. 4.4 mmol) was added slowly to a solution of NaH (8 mmol) in anhydrous DMF (6ml) at 0°C. This was followed by addition of 3-bromo-4-nitropyridine-N-oxide (4 mmol) and the reaction mixture was heated to 90°C for 2-3 h or until the completion of reaction. The reaction mixture was then cooled to rt, diluted with cold water and the product was extracted with DCM. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo to give desired product, which was taken up in acetic acid (4 ml). Powdered iron (2 eq., 8 mmol) was added and the reaction was heated to 90°C for 2-3 h. The reaction mixture was then cooled to rt, diluted with cold water and the product was extracted with EtOAc. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo to give desired product, Example 524. (Yield: 60 mg)

MS: *m/z* 495 $(M+1)^+$

Example 525

(4-{1-[4-(4-Chloro-phenoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenyl)-pyridin-4-yl-amine

[4-(4-Chloro-phenoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-aniline was synthesized by procedures analogous to those for the similar 4-(4-aminophenyl)1H-imidazole intermediate in the preparation of Example 501.

A mixture of 200 mg of 4-{1-[4-(4-chloro-phenoxy)-phenyl]-2-isobutyl-1H-imidazole-4-yl}aniline (200 mg, 0.47 mmole), 4-chloropyridine hydrochloride (0.5 g, 3.2 mmole) and potassium carbonate (0.5 g, 3.6 mmole) were heated at 100 °C in DMF (10 mL) for 24 h. After cooling to rt the mixture was diluted with ether, washed with water) and dried (Na_2SO_4). Silica gel chromatography of the crude material afforded Example 525 (50 mg).

MS: m/z 495 $(M+H)^+$

Example 526

2-(4-{1-[4-(4-Fluoro-phenoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenoxymethyl)-3,5-dimethyl-pyridin-4-ylamine

(3, 5-dimethyl-4-nitro-2-pyridyl)methyl mesylate was synthesized by the general procedure P2.

{1-[4-(4-Chloro-phenoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}phenol (2 mmol) was added to a solution of Cs_2CO_3 (10 eq., 20 mmol) in anhydrous DMF (5 ml). This was followed by addition of the mesylate obtained above and the reaction mixture was heated to 90°C for 2-3 h. The reaction mixture was then cooled to rt, diluted with cold water and the product was extracted with DCM. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo to give desired phenyl ether.

The crude product obtained above was taken in acetic acid (5 ml). Powdered iron (2 eq., 8 mmol) was added to the reaction mixture and the reaction was heated to 90°C for 2-3 h or until the completion of reaction. The reaction mixture was then cooled to rt, diluted with cold water and the product was extracted with EtOAc. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo to give desired product., Example 526. (Yield: 80 mg)

MS: m/z 537 $(M+H)^+$

Example 527

1-[2-(4-{1-[4-(4-Chloro-phenoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenoxy)-ethyl]-4-pyridin-4-yl-piperazine

The product of Example 522 was taken in 4ml of THF to which was added 5 eq. of BH3-THF solution and the reaction was heated to reflux until the reaction was complete. The crude product was purified by silica gel chromatography to afford Example 527.

MS: m/z 608 $(M+H)^+$

Example 528

4-(4-{2-Butyl-4-[4-(3-diethylamino-propoxy)-phenyl]-imidazol-1-yl}-phenoxy)-phenylamine

Example 528 was prepared by modifying the procedures utilized in the synthesis of Example 493, with utilization of 4-tert-butoxycarbonylaminophenol in place of 4-acetamidophenol. The BOC group was removed from the intermediate utilizing general procedure T1 to afford the product, Example 528, as the HCl salt.

MS: m/z 513 $(M+H)^+$

Example 529

{3-[4-(2-Butyl-4-dibenzofuran-2-yl-imidazol-1-yl)-phenoxy]-propyl}-diethyl-amine

A solution of dibenzofuran (0.5 mmol) in anhydrous DCM was cooled to 0°C. $AlCl_3$ (1.5 eq., 0.75 mmol) was added followed by a slow addition of acetyl chloride (1.5 eq., 0.75 mmol). The reaction mixture was stirred at 0°C for 2-3h or until the completion of reaction. The product was extracted with DCM and washed with saturated sodium bicarbonate solution. The organic layer was dried over anhydrous sodium sulfate and concenterated in vacuo to give dibenzofuran-2-ylethan-2-one.

Example 529 was prepared by modifying the procedures utilized for the synthesis of Example 463, utilizing dibenzofuran-2-ylethan-2-one as the aryl ketone starting material. (Yield: 75 mg)

MS: m/z 496 $(M+H)^+$

Example 530

N-[4-(4-{2-Butyl-4-[4-(3-diethylamino-propoxy)-phenyl]-imidazol-1-yl}-phenoxy)-phenyl]-benzamide

2007202350 24 May 2007

Example 530 was prepared by modifying the procedures utilized in the synthesis of Example 493, with utilization of 4-(tert-butoxycarbonylamino)phenol in place of 4-acetamidophenol. The BOC group was removed from the intermediate utilizing general procedure T1 to afford the product, Example 528, as the HCl salt. The product was treated with benzoyl chloride and TEA in DCM to afford, after aqueous workup and purification by silica gel chromatography, Example 530.

MS: m/z 617 $(M+H)^+$

Example 531

N-[4-(4-{2-Butyl-4-[4-(3-diethylamino-propoxy)-phenyl]-imidazol-1-yl}-phenoxy)-phenyl]-isonicotinamide

Example 530 was prepared by modifying the procedures utilized in the synthesis of Example 493, with utilization of 4-(tert-butoxycarbonylamino)phenol in place of 4-acetamidophenol. The BOC group was removed from the intermediate utilizing general procedure T1 to afford the product, Example 528, as the HCl salt. The product was treated with 4-pyridylcarbonyl chloride and TEA in DCM to afford, after aqueous workup and purification by silica gel chromatography, Example 531.

MS: m/z 618 $(M+H)^+$

Example 532

[2-(4-{1-[4-(4-Chloro-phenoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenoxy)-ethyl]-methyl-pyridin-4-yl-amine

A mixture of 4-chloropyridine hydrochloride salt (15.0 g) and 2-methylaminoethanol (30 mL) was refluxed for 48 hour. After cooling to rt the crude mixture was added slowly to saturated solution of sodium bicarbonate (150 mL). The product was extracted with EtOAc (3X100 mL), the combined EtOAc was washed with brine (50mL), dried (Na_2SO_4) and removed in vacuo to give the desired product 2-[methyl(pyridin-4-yl)amino]ethanol as yellow solid (7.0g).

2-[methyl(pyridin-4-yl)amino]ethyl methanesulfonate was synthesized as described for Example 515.

Sodium hydride (50.0 mg, 60% dispersion in oil) was added to mixture of 150 mg of 4-{1-[4-(4-chloro-phenoxy)-phenyl]-2-isobutyl-1H-imidazole-4-yl}phenol and 2-[methyl(pyridin-4-

2007202350 24 May 2007

yl)amino]ethyl methanesulfonate (75 mg) in DMF (5 mL). After 24 h of stirring at rt, the mixture was added to ether (50mL) and the organic phase was washed with water and dried (Na_2SO_4). The solvent was removed *in vacuo* and the product purified by silica gel chromatography to afford 80 mg of Example 532.

MS: m/z 553 $(M+H)^+$

Example 533

N-(4-{1-[4-(4-Chloro-phenoxy)-phenyl]-2-isobutyl-1H-imidazol-4-yl}-phenyl)-2-dimethylamino-acetamide

1-[4-(4-Chloro-phenoxy)-phenyl]-2-isobutyl-4-(4-nitrophenyl)-1H-imidazole was synthesized following the general procedures utilized in example 501. The nitro group was reduced accorgding to general procedure H to afford 1-[4-(4-chloro-phenoxy)-phenyl]-2-isobutyl-4-(4-aminophenyl)-1H-imidazole, which was coupled with N,N-dimethylglycine using PS-carbodiimide according to the procedure utilized in Example 502 to afford Example 533.

MS: m/z 503 $(M+H)^+$

Example 534

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

Example 534 was synthesized by modification of the procedures utilized for the synthesis of example 459. 3,3(4-chlorophenyl)-2-propene-1-ol was converted to the methanesulfonate and utilized in condensation with 4'-hydroxyacetophenone. Isovaleryl chloride was utilized in place of benzyloxyacetyl chloride (yield 35mg).

MS: m/z 682 $(M+H)^+$

Example 535

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

The intermediate phenol 4-(4-hydroxyphenyl)-2-isobutyl-imidazol-1-yl)-phenoxy]-propyl}-diethyl-amine utilized in the synthesis of Example 477 was condensed with the methanesulfonate of 3,3(4-fluorophenyl)-1-propanol (synthesized according to general procedure P2). The condensation was conducted in accord with similar operation in the preparation of Example 477 to provide Example 535.

MS: m/z 652 $(M+H)^+$

Example 536

[2-(4-{4-[4-(4-Chloro-phenoxy)-phenyl]-2-isobutyl-imidazol-1-yl}-phenoxy)-ethyl]-methyl-pyridin-4-yl-amine

4-Fluoronitrobenzene was condensed with 2-[methyl(pyridin-4-yl)amino]ethanol according to general procedure C and the nitro group was then reduced according to general procedure H to afford the aniline intermediate. This aniline was utilized in modification of the procedure for preparation of Example 485 to afford Example 536.

MS: m/z 553 $(M+H)^+$

Example 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 aminonium iodide

{4-{4-[2-(4-Chloro-phenyl)-ethoxy]-phenyl}-2-[2-(pyridin-3-yl)-ethyl]-imidazol-1-yl}-phenoxy)-propyl]-diethyl-amine was synthesized modifying the procedures utilized in the preparation of Example 485, where 3-(3-pyridyl)-propionyl chloride was utilized in place of valeryl chloride. The product {4-{4-[2-(4-Chloro-phenyl)-ethoxy]-phenyl}-2-[2-(pyridin-3-yl)-ethyl]-imidazol-1-yl}-phenoxy)-propyl]-diethyl-amine was treated with excess methyl iodide, concentrated in vacuo, and the solid collected to afford the product, Example 537 (Yield: 37 mg)

MS: m/z 625 $(M+H)^+$

Example 538

[3-(4-{2-(N-BOC-piperidine-4-ylmethyl)-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine

2007202350 24 May 2007

The procedure utilized for the preparation of Example 486 was modified, employing N-BOC-piperidine-4-acetic acid in place of 4-tert-butylcyclohexanecarboxylic acid, to afford 270 mg of Example 538.

MS: m/z 673 $(M+H)^+$

Example 539

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

The compound of Example 538 was deprotected according to General Procedure T1 to afford 116 mg of Example 539 as the HCl salt.

MS: m/z 573 $(M+H)^+$

Example 540

[3-(4-{2-(N-ethyl-piperidine-4-ylmethyl)-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine

[3-(4-{2-(Piperidine-4-ylmethyl)-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl-amine (Example 539) (0.1 mmol) was treated in anhydrous DCM (2 ml) with acetaldehyde (1.2 eq.,) followed by addition of $Na(OAc)_3BH$ (1.5 eq.). The reaction mixture was stirred at rt. Crude product was extracted into EtOAc and washed with saturated sodium bicarbonate solution. The organic layer was dried over anhydrous sodium sulfate and concenterated in vacuo to give desired product, which was purified by column chromatography on silica gel to afford 49 mg of Example 540.

MS: m/z 601 $(M+H)^+$

Example 541

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

The procedure of Example 485 was adapted, using 4-BOC-piperidine-1-acetic acid in place of valeryl chloride. The resulting imidazole was deprotected using General Procedure T1 to afford Example 541 (48 mg) as the HCl salt.

MS: m/z 602 $(M+H)^+$

Example 542

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

The product of Example 541 was treated in anhydrous DCM (2 ml) with acetaldehyde (1.2 eq.,) followed by addition of $Na(OAc)_3BH$ (1.5 eq.). The reaction mixture was stirred at rt. Crude product was extracted into EtOAc and washed with saturated sodium bicarbonate solution. The organic layer was dried over anhydrous sodium sulfate and concenterated in vacuo to give desired product, which was purified by column chromatography on silica gel to afford 50 mg of Example 542.

^{1}H NMR: δ 7.68 (d, 2H), 7.23 (m, 6H), 7.16 (s, 1H), 6.95 (m, 2H), 6.88 (d, 2H), 4.17 (t, 2H), 4.06 (t, 2H), 3.06 (t, 2H),2.91 (d, 2H), 2.81 (broad, 1H), 2.57 (m, 6H), 2.43 (m, 6H), 1.95-2.05 (m, 6H), 1.09 (t, 9H) ppm

MS: m/z 629 $(M+H)^+$

Example 543

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

The procedure of Example 485 was adapted, using 4-acetyl-piperidine-1-carbonyl chloride in place of valeryl chloride, to afford Example 543 (40 mg).

MS: m/z 629 $(M+H)^+$

Example 544

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

Example 543 (1 mmol, 125 mg) was taken in 6 N HCl (5 ml) and the reaction was refluxed. The reaction mixture was then cooled to rt, diluted with water and neutralized with 3N NaOH solution. Product was extracted with EtOAc and the organic layer was dried over anhydrous sodium sulfate, concenterated in vacuo to give crude product, which was purified by column chromatography on silica gel to afford 290 mg of Example 544.

MS: m/z 587 $(M+H)^+$

Example 545

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

The product of Example 544 was treated in anhydrous DCM (2 ml) with benzaldehyde (1.2 eq.,) followed by addition of $Na(OAc)_3BH$ (1.5 eq.). The reaction mixture was stirred at rt. Crude product was extracted into EtOAc and washed with saturated sodium bicarbonate solution. The organic layer was dried over anhydrous sodium sulfate and concenterated in vacuo to give desired product, which was purified by column chromatography on silica gel to afford 50 mg of Example 545.

^1H NMR: δ 7.68 (d, 2H), 7.28 (d, 2H), 7.21-7.26 (m, 9H), 7.17 (s, 1H), 6.97 (d, 2H), 6.87 (d, 2H), 4.16 (t, 2H), 4.07 (t, 2H), 3.48 (s, 2H), 3.05 (t, 2H), 2.91 (broad, 1H), 2.74 (t, 2H), 2.66 (m, 8H), 2.05 (m, 6H), 1.11 (t, 6H) ppm

MS: m/z 677 $(M+H)^+$

Example 546

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

The product of Example 544 was treated in anhydrous DCM (2 ml) with pyridine-2-carboxaldehyde(1.2 eq.,) followed by addition of $Na(OAc)_3BH$ (1.5 eq.). The reaction mixture was stirred at rt. Crude product was extracted into EtOAc and washed with saturated sodium bicarbonate solution. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo to give desired product, which was purified by column chromatography on silica gel to afford 40 mg of Example 546.

MS: m/z 678 $(M+H)^+$

Example 547

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

The product of Example 544 was treated in anhydrous DCM (2 ml) with imidazole-2-carboxaldehyde(1.2 eq.,) followed by addition of $Na(OAc)_3BH$ (1.5 eq.). The reaction mixture was stirred at rt. Crude product was extracted into EtOAc and washed with saturated sodium bicarbonate solution. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo to give desired product, which was purified by column chromatography on silica gel to afford 40 mg of Example 547.

^1H NMR: δ 7.66 (d, 2H), 7.2-7.3 (m, 7H), 7.06 (s, 1H), 6.98 (m, 3H), 6.88 (d, 2H), 4.18 (t, 2H), 4.05 (t, 2H), 3.65 (s, 2H), 3.08 (t, 2H), 2.81 (broad, 1H), 2.75 (m, 2H), 2.55-2.65 (m, 8H), 1.95-2.08 (m, 6H), 1.09 (t, 6H) ppm

MS: m/z 667 $(M+H)^+$

Example 548

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

The product of Example 544 was treated in anhydrous DCM (2 ml) with 4-biphenylcarboxaldehyde (1.2 eq.,) followed by addition of $Na(OAc)_3BH$ (1.5 eq.). The reaction mixture was stirred at rt. Crude product was extracted into EtOAc and washed with saturated sodium bicarbonate solution. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo to give desired product, which was purified by column chromatography on silica gel to afford 45 mg of Example 548.

2007202350 24 May 2007

[1]H NMR: δ 7.68 (d, 2H), 7.59 (d, 2H), 7.54 (d, 2H), 7.38-7.44 (m, 5H), 7.19-7.29 (m, 6H), 7.09 (s, 1H), 6.79 (d, 2H), 6.88 (d, 2H), 4.18 (t, 2H), 4.08 (t, 2H), 3.55 (s, 2H), 3.08 (t, 2H), 2.98 (broad, 1H), 2.65 (t, 2H), 2.58-2.65 (m, 8H), 1.98-2.09 (m, 6H), 1.12 (t, 6H) ppm.
MS: m/z 753 $(M+H)^+$

Example 549

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

The product of Example 544 was treated in anhydrous DCM (2 ml) with cyclopentanone (1.2 eq.,) followed by addition of $Na(OAc)_3BH$ (1.5 eq.). The reaction mixture was stirred at rt. Crude product was extracted into EtOAc and washed with saturated sodium bicarbonate solution. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo to give desired product, which was purified by column chromatography on silica gel to afford 52 mg of Example 549.

[1]H NMR: δ 7.68 (d, 2H), 7.38 (m, 3H), 7.21 (m, 3H), 7.08 (s, 1H), 6.98 (m, 2H), 6.88 (d, 2H), 4.18 (t, 2H), 4.08 (t, 2H), 3.08 (t, 2H), 2.67 (t, 2H), 2.51-2.55 (m, 8H), 1.99-2.08 (m, 6H), 1.91 (broad, 4H), 1.68 (broad 2H), 1.51 (broad 4H), 1.12 (t, 6H) ppm.
MS: m/z 655 $(M+H)^+$

Example 550

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

The product of Example 544 was treated in anhydrous DCM (2 ml) with 4-cyanobenzaldehyde (1.2 eq.,) followed by addition of $Na(OAc)_3BH$ (1.5 eq.). The reaction mixture was stirred at rt. Crude product was extracted into EtOAc and washed with saturated sodium bicarbonate solution. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo to give desired product, which was purified by column chromatography on silica gel to afford 70 mg of Example 550.

[1]H NMR: δ 7.69 (d, 2H), 7.59 (d, 2H), 7.44 (d, 2H), 7.2-7.3 (m, 6H), 7.09 (s, 1H), 6.99 (d, 2H), 6.88 (d, 2H), 4.18 (t, 2H), 4.09 (t, 2H), 3.55 (s, 2H), 3.08 (t, 2H), 2.85 (broad, 1H), 2.5-2.8 (m, 10H), 1.9-2.1 (m, 6H), 1.09 (t, 6H) ppm.
MS: m/z 702 $(M+H)^+$

Example 551

2007202350 24 May 2007

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

The product of Example 544 was treated in anhydrous DCM (2 ml) with acetaldehyde(1.2 eq.,) followed by addition of $Na(OAc)_3BH$ (1.5 eq.). The reaction mixture was stirred at rt. Crude product was extracted into EtOAc and washed with saturated sodium bicarbonate solution. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo to give desired product, which was purified by column chromatography on silica gel to afford 50 mg of Example 551.

^1H NMR: δ 7.68 (d, 2H), 7.23 (d, 2H), 7.22 (m, 4H), 7.16 (s, 1H), 6.95 (d, 2H), 6.88 (d, 2H), 4.17 (t, 2H), 4.05 (t, 2H), 3.05-3.07 (m, 7H), 2.51-2.61 (m, 6H), 2.39 (q, 2H), 1.89-2.09 (m, 6H), 1.12 (t, 9H) ppm.

MS: m/z 678 $(M+H)^+$

Biological Assay

The following assay method is utilized to identify compounds of Formula (I) which are effective in binding with RAGE, and hence useful as modulators, preferably antagonists of RAGE.

General Assay Procedure

S100b, β-amyloid and CML (500 ng/100μL/well) in 100 mM sodium bicarbonate/sodium carbonate buffer (pH 9.8) is loaded onto the wells of a NUNC Maxisorp flat bottom 96 –well microtitre plate. The plate is incubated at 4°C overnight. The wells are aspirated and treated with 50 mM imidazole buffer saline (pH 7.2) (with 5mM $CaCl_2$/$MgCl_2$) containing 1% bovine serum albumin (BSA) (300 μL/well) for 1 h at RT. The wells are aspirated..

Test compounds are dissolved in nanopure water (concentration: 10-100 μM). DMSO may be used as co-solvent. 25 μL of test compound solution in 4% DMSO is added, along with 75 μL sRAGE (6.75 nM FAC) to each well and samples are incubated for 1 h at 37°C. The wells are washed 4 times with 155 mM NaCl pH 7.2 buffer saline and are soaked 10 seconds between each wash.

Non-radioactive detection is performed by adding:

10μL Biotinylated goat F(ab')2 Anti-mouse IgG. (8.0×10^{-4} mg/mL, FAC)
5μL Alk-phos-Sterptavidin (3×10^{-3} mg/mL FAC)
0.42μL per 5 mL Monoclonal antibody for sRAGE (FAC 6.0×10^{-3} mg/mL)

to 5 mL 50mM imidazole buffer saline (pH 7.2) containing 0.2% bovine serum albumin and 5mM $CaCl_2$. The mixture is incubated for 30 minutes at RT. 100 μL complex is added to each well and incubation is allowed to proceed at rt for 1 h. Wells are washed 4 times with wash buffer and soaked 10 s between each wash. 100 μL 1mg/mL (pNPP) in 1 M diethanolamine (pH adjusted to 9.8 with HCl) is added. Color is allowed to develop in the dark for 30 min to 1 h at rt. The reaction is quenched with 10 μL of stop solution (0.5 N NaOH in 50% ethanol) and the absorbance is measured spectrophotometrically with a microplate reader at 405 nm.

The Examples in Table 1 were tested according to the assay method described above, employing S100b as the RAGE ligand, and were found to possess IC_{50} in the assay of less than 10 μM. IC_{50} (μM) of ELISA assay represents the concentration of compound at which 50% signal has been inhibited.

The invention further provides pharmaceutical compositions comprising the RAGE modulating compounds of the invention. The term "pharmaceutical composition" is used herein to denote a composition that may be administered to a mammalian host, *e.g.*, orally, topically, parenterally, by inhalation spray, or rectally, in unit dosage formulations containing conventional non-toxic carriers, diluents, adjuvants, vehicles and the like. The term "parenteral" as used herein, includes subcutaneous injections, intravenous, intramuscular, intracisternal injection, or by infusion techniques.

The pharmaceutical compositions containing a compound of the invention may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous, or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any known method, and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents, and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets may contain the active ingredient in admixture with non-toxic pharmaceutically-acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example corn starch or alginic acid; binding agents, for example, starch, gelatin or acacia; and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in U.S. Patent Nos. 4,356,108; 4,166,452; and 4,265,874, incorporated herein by reference, to form osmotic therapeutic tablets for controlled release.

Formulations for oral use may also be presented as hard gelatin capsules where the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or a soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions may contain the active compounds in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide such as lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example, heptadecaethyl-eneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

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

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

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

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectible aqueous or oleaginous suspension. This suspension may be formulated according to the known methods using suitable dispersing or wetting agents and suspending agents described above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conveniently employed as solvent or suspending medium. For this purpose, any bland fixed oil may be employed using synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compositions may also be in the form of suppositories for rectal administration of the compounds of the invention. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will thus melt in the rectum to release the drug. Such materials include cocoa butter and polyethylene glycols, for example.

For topical use, creams, ointments, jellies, solutions or suspensions, lotions, eye ointments and eye or ear drops, impregnated dressings and aerosols etc., containing the compounds of the invention are contemplated. These topical formulations may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams. The formulations may also contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions. Such carriers may be present as from about .1% up to about 99% of the formulation. More usually they will form up to about 80% of the formulation.. For the purpose of this application, topical applications shall include mouth washes and gargles.
The compounds of the present invention may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes may be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels. Also provided by the present invention are prodrugs of the invention.

For administration by inhalation the compounds according to the invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, tetrafluoroethane, heptafluoropropane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g. gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

Pharmaceutically acceptable salts of the compounds of the present invention, where a basic or acidic group is present in the structure, are also included within the scope of the invention. The term "pharmaceutically acceptable salts" refers to non-toxic salts of the compounds of this invention which are generally prepared by reacting the free base with a suitable organic or inorganic acid or by reacting the acid with a suitable organic or inorganic base. Representative salts include the following salts: Acetate, Benzenesulfonate, Benzoate, Bicarbonate, Bisulfate, Bitartrate, Borate, Bromide, Calcium Edetate, Camsylate, Carbonate, Chloride, Clavulanate, Citrate, Dihydrochloride, Edetate, Edisylate, Estolate, Esylate, Fumarate, Gluceptate, Gluconate, Glutamate, Glycollylarsanilate, Hexylresorcinate, Hydrabamine, Hydrobromide, Hydrocloride, Hydroxynaphthoate, Iodide, Isethionate, Lactate, Lactobionate, Laurate, Malate, Maleate, Mandelate, Mesylate, Methylbromide, Methyliodide, Methylchloride, Methylnitrate, Methylsulfate, Monopotassium Maleate, Mucate, Napsylate, Nitrate, N-methylglucamine, Oxalate, Pamoate (Embonate), Palmitate, Pantothenate, Phosphate/diphosphate, Polygalacturonate, Potassium, Salicylate, Sodium, Stearate, Subacetate, Succinate, Tannate, Tartrate, Teoclate, Tosylate, Triethiodide, Trimethylammonium and Valerate. When an acidic substituent is present, such as–COOH, there can be formed the ammonium, morpholinium, sodium, potassium, barium, calcium salt, and the like, for use as the dosage form. When a basic group is present, such as amino or a basic heteroaryl radical, such as pyridyl, an acidic salt, such as hydrochloride, hydrobromide, phosphate, sulfate, trifluoroacetate, trichloroacetate, acetate, oxlate, maleate, pyruvate, malonate, succinate, citrate, tartarate, fumarate, mandelate, benzoate, cinnamate, methiodide, methbromide, methchloride, methanesulfonate, ethanesulfonate, picrate and the like, and include acids related to the pharmaceutically-acceptable salts listed in the Journal of Pharmaceutical Science, 66, 2 (1977) p. 1-19.

Other salts which are not pharmaceutically acceptable may be useful in the preparation of compounds of the invention and these form a further aspect of the invention.

In addition, some of the compounds of the present invention may form solvates with water or common organic solvents. Such solvates are also encompassed within the scope of the invention.

Thus, in a further embodiment, there is provided a pharmaceutical composition comprising a compound of the present invention, or a pharmaceutically acceptable salt, solvate, or prodrug therof, and one or more pharmaceutically acceptable carriers, excipients, or diluents.

The compounds of the present invention selectively act as modulators of RAGE binding to a single endogenous ligand, *i.e.*, selective modulators of β-amyloid - RAGE interaction, and therefore are especially advantageous in treatment of Alzheimer's disease and related dementias.

Further, the compounds of the present invention act as modulators of RAGE interaction with two or more endogenous ligands in preference to others. Such compounds are advantageous in treatment of related or unrelated pathologies mediated by RAGE, *i.e.*, Alzheimer's disease and cancer.

Further, the compounds of the present invention act as modulators of RAGE binding to each and every one of its ligands, thereby preventing the generation of oxidative stress and activation of NF-κB regulated genes, such as the cytokines IL-1, and TNF- α. Thus, antagonizing the binding of physiological ligands to RAGE prevent targeted pathophysiological consequences and useful for management or treatment of diseases, *i.e.*, AGE-RAGE interaction leading to diabetic complications, S100/EN-RAGE/calgranulin-RAGE interaction leading to inflammatory diseases, ß-amyloid-RAGE interaction leading to Alzheimer's Disease, and amphoterin-RAGE interaction leading to cancer.

I. RAGE and the Complications of Diabetes

As noted above, the compounds of the present invention are useful in the treatment of the complications of diabetes. It has been shown that nonenzymatic glycoxidation of macromolecules ultimately resulting in the formation of advanced glycation endproducts (AGEs) is enhanced at sites of inflammation, in renal failure, in the presence of hyperglycemia and other conditions associated with systemic or local oxidant stress (Dyer, D., *et al., J. Clin. Invest.,* **91**:2463-2469 (1993); Reddy, S., *et al., Biochem.,* **34**:10872-10878 (1995); Dyer, D., *et al., J. Biol. Chem.,* **266**:11654-11660 (1991); Degenhardt, T., *et al., Cell Mol. Biol.,* **44**:1139-1145 (1998)). Accumulation of AGEs in the vasculature can occur focally, as in the joint amyloid composed of AGE-$ß_2$-microglobulin found in patients with dialysis-related amyloidosis (Miyata, T., *et al., J. Clin. Invest.,* **92**:1243-1252 (1993); Miyata, T., *et al., J. Clin. Invest.,* **98**:1088-1094 (1996)), or generally, as exemplified by the vasculature and tissues of patients with diabetes (Schmidt, A-M., *et al., Nature Med.,* **1**:1002-1004 (1995)). The progressive accumulation of AGEs over time in patients with diabetes suggests that endogenous clearance mechanisms are not able to function effectively at sites of AGE deposition. Such accumulated AGEs have the capacity to alter cellular properties by a number of mechanisms. Although RAGE is expressed at low levels in normal tissues and vasculature, in an environment where the receptor's ligands accumulate, it has been shown that RAGE becomes upregulated (Li, J. *et al., J. Biol. Chem.,* **272**:16498-16506 (1997); Li, J., *et al., J. Biol. Chem.,* **273**:30870-30878 (1998); Tanaka, N., *et al., J. Biol. Chem,.* **275**:25781-25790(2000)). RAGE expression is increased in endothelium, smooth muscle cells and infiltrating mononuclear phagocytes in diabetic vasculature. Also, studies in cell culture have demonstrated that AGE-RAGE interaction caused changes in cellular properties important in vascular homeostasis.

II. RAGE and Cellular Dysfunction in the Amyloidoses

Also as noted above, the compounds of the present invention are useful in treating amyloidoses and Alzheimer's disease. RAGE appears to be a cell surface receptor which binds ß-sheet fibrillar material regardless of the composition of the subunits (amyloid-ß peptide, Aß, amylin, serum amyloid A, prion-derived peptide) (Yan, S. -D., *et al., Nature,* **382**:685-691 (1996); Yan, S-D., *et al., Nat. Med.,* **6**:643-651 (2000)). Deposition of amyloid has been shown to result in enhanced expression of RAGE. For example, in the brains of patients with Alzheimer's disease (AD), RAGE expression increases in neurons and glia (Yan, S. -D., et al., *Nature* **382**:685-691 (1996)). The consequences of Aß interaction with RAGE appear to be quite different on neurons versus microglia. Whereas microglia become activated as a consequence of Aß-RAGE interaction, as reflected by increased motility and expression of cytokines, early RAGE-mediated neuronal activation is superceded by cytotoxicity at later times. Further evidence of a role for RAGE in cellular interactions of Aß concerns inhibition of Aß-induced cerebral vasoconstriction and transfer of the peptide across the blood-brain barrier to brain parenchyma when the receptor was blocked (Kumar, S., et al., *Neurosci. Program,* p141-#275.19 (2000)). Inhibition of RAGE-amyloid interaction has been shown to decrease expression of cellular RAGE and cell stress markers (as well as NF-kB activation), and diminish amyloid deposition (Yan, S-D., *et al., Nat. Med.,* **6**:643-651 (2000)) suggesting a role for RAGE-amyloid interaction in both perturbation of cellular properties in an environment enriched for amyloid (even at early stages) as well as in amyloid accumulation.

III. RAGE and Propagation of the Immune/Inflammatory Response

As noted above, the compounds of the present invention are useful in treating inflammation. For example, S100/calgranulins have been shown to comprise a family of closely related calcium-binding polypeptides characterized by two EF-hand regions linked by a connecting peptide (Schafer, B. *et al., TIBS,* **21**:134-140 (1996); Zimmer, D., *et al., Brain Res. Bull.,* **37**:417-429 (1995); Rammes, A., *et al., J. Biol. Chem.,* **272**:9496-9502 (1997); Lugering, N., *et al., Eur. J. Clin. Invest.,* **25**:659-664 (1995)). Although they lack signal peptides, it has long been known that S100/calgranulins gain access to the extracellular space, especially at sites of chronic immune/inflammatory responses, as in cystic fibrosis and rheumatoid arthritis. RAGE is a receptor for many members of the S100/calgranulin family, mediating their proinflammatory effects on cells such as lymphocytes and mononuclear phagocytes. Also, studies on delayed-type hypersensitivity response, colitis in IL-10 null mice, collagen-induced arthritis, and experimental autoimmune encephalitis models suggest that RAGE-ligand interaction (presumably with S100/calgranulins) has a proximal role in the inflammatory cascade as implicated in the inflammatory diseases such as but not limited to rheumatoid arthritis and multiple sclerosis.

RAGE is also implicated in inflammatory diseases of the skin such as but not limited to atopic dermatitis, eczema, and psoriasis. Psoriasis in particular is characterized by inflamed itchy lesions. Psoriasis may be accompanied by arthropathic symptoms that are similar to those in seen in rheumatoid arthritis.

There is considerable evidence that psoriasis is a polygenic autoimmune disorder. Psoriatic lesions are rich in cytokines, in particular IL-1 and IL-8, both potent proinflammatory mediators. IL-8 in particular is a chemotactic factor for neutrophils; neutrophils are also known to synthesize and secrete S100 proteins, one of the ligands for RAGE which is implicated in propogation of the the immune and inflammatory response. Psoriasin (S100A7) a new member of the S100 gene family, is a secreted protein isolated from psoriatic skin. Semprini et. al. (Hum. Genet. 2002 Oct, 111(4-5), 310-3) have shown a linkage of psoriasis genetic susceptibility to distinct overexpression of S100 proteins in skin. Therefore, a modulator of RAGE would be expected to regulate the immune response in psoriasis.

IV. RAGE and Amphoterin

As noted above, the compounds of the present invention are useful in treating tumor and tumor metastasis. For example, amphoterin is a high mobility group I nonhistone chromosomal DNA binding protein (Rauvala, H., *et al., J. Biol. Chem.*, **262**:16625-16635 (1987); Parkikinen, J., *et al., J. Biol. Chem.* **268**:19726-19738 (1993)) which has been shown to interact with RAGE. It has been shown that amphoterin promotes neurite outgrowth, as well as serving as a surface for assembly of protease complexes in the fibrinolytic system (also known to contribute to cell mobility). In addition, a local tumor growth inhibitory effect of blocking RAGE has been observed in a primary tumor model (C6 glioma), the Lewis lung metastasis model (Taguchi, A., *et al., Nature* **405**:354-360 (2000)), and spontaneously arising papillomas in mice expressing the v-Ha-*ras* transgene (Leder, A., *et al., Proc. Natl. Acad. Sci.,* **87**:9178-9182 (1990)).

Amphoterin is a high mobility group I nonhistone chromosomal DNA binding protein (Rauvala, H. and R. Pihlaskari. 1987. Isolation and some characteristics of an adhesive factor of brain that enhances neurite outgrowth in central neurons. *J. Biol. Chem.* 262:16625-16635. (Parkikinen, J., E. Raulo, J. Merenmies, R. Nolo, E. Kajander, M. Baumann, and H. Rauvala. 1993. Amphoterin, the 30 kDa protein in a family of HIMG1-type polypeptides. *J. Biol. Chem.* 268:19
726-19738).

V. RAGE and Erectile Dysfunction

Relaxation of the smooth muscle cells in the cavernosal arterioles and sinuses results in increased blood flow into the penis, raising corpus cavernosum pressure to culminate in penile erection. Nitric oxide is considered the principle stimulator of cavernosal smooth muscle relaxation (See Wingard CJ, Clinton W, Branam H, Stopper VS, Lewis RW, Mills TM, Chitaley K. Antagonism of Rho-kinase stimulates rat penile erection via a nitric oxide-independent pathway. Nature Medicine 2001 Jan;7(1):119-122). RAGE activation produces oxidants (See Yan, S-D., Schmidt A-M., Anderson, G., Zhang, J., Brett, J., Zou, Y-S., Pinsky, D., and Stern, D. Enhanced cellular oxidant stress by the interaction of advanced glycation endproducts with their receptors/binding proteins. J. Biol. Chem. 269:9889-9887, 1994.) via an NADH oxidase-like enzyme, therefore suppressing the circulation of nitric oxide. Potentially by inhibiting the activation of RAGE signaling pathways by decreasing the intracellular production of AGEs, generation of oxidants will be attenuated. RAGE blockers may promote and facilitate penile erection by blocking the access of ligands to RAGE.

The calcium-sensitizing Rho-kinase pathway may play a synergistic role in cavernosal vasoconstriction to maintain penile flaccidity. The antagonism of Rho-kinase results in increased corpus cavernosum pressure, initiating the erectile response independently of nitric oxide (Wingard *et al.*). One of the signaling mechanisms activated by RAGE involves the Rho-kinase family such as cdc42 and rac (See Huttunen HJ, Fages C, Rauvala H. Receptor for advanced glycation end products (RAGE)-mediated neurite outgrowth and activation of NF-kappaB require the cytoplasmic domain of the receptor but different downstream signaling pathways. J Biol Chem 1999 Jul 9;274(28):19919-24). Thus, inhibiting activation of Rho-kinases via suppression of RAGE signaling pathways will enhance and stimulate penile erection independently of nitric oxide.

VI. RAGE and Respiratory Diseases

Airway inflammation is important in the pathogenesis of asthma. Such inflammation may give rise to significant exacerbations and increases in asthma severity, as well as to be a major factor in a decline in asthmatic status. In severe exacerbations of asthma there is an intense, mechanistically heterogeneous inflammatory response involving neutrophil and eosinophil accumulation and activation. Neutrophils are a significant source of S100 proteins, key ligands for RAGE implicated in the propogation of the immune response and inflammation. Therefore, modulators of RAGE would be expected to possess therapeutic value in the treatment of asthma.

Further, the propogation step in the immune response in the lung driven by S100 – RAGE interaction would be expected to lead to the activation and/or recruitment of inflammatory cells, such as neutrophils, which in chronic obstructive pulmonary diseases such as emphysema, are significant sources of damaging proteases. Therefore, a RAGE modulator would be expected possess potential in the treatment of chronic obstructive pulmonary diseases.

Thus, in a further aspect, the present invention provides a method for the inhibition of the interaction of RAGE with physiological ligands. In a preferred embodiment of this aspect, the present invention provides a method for treating a disease state selected from the group consisting of acute and chronic inflammationin cluding but not limited to skin inflammation such as psoriasis nad atopic dermatitis and lung inflammation including asthma and chronic osbtructive pulmonary disease, vascular permeability, nephropathy, atherosclerosis, retinopathy, Alzheimer's disease, erectile dysfunction, and tumor invasion and/or metastasis, which comprises administering to a subject in need thereof a compound of the present invention, preferably a pharmacologically effective amount, more preferably a therapeutically effective amount. In a preferred embodiment, at least one compound of Formula (I) is utilized, either alone or in combination with one or more known therapeutic agents. In a further preferred embodiment, the present invention provides 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 the present invention, preferably a compound of Formula (I).

In this method, factors which will influence what constitutes an effective amount will depend upon the size and weight of the subject, the biodegradability of the therapeutic agent, the activity of the therapeutic agent, as well as its bioavailability. As used herein, the phrase "a subject in need thereof" includes mammalian subjects, preferably humans, who either suffer from one or more of the aforesaid diseases or disease states or are at risk for such. Accordingly, in the context of the therapeutic method of the invention, this method also is comprised of a method for treating a mammalian subject prophylactically, or prior to the onset of diagnosis such disease(s) or disease state(s).

In a further aspect of the present invention, the RAGE modulators of the invention are utilized in adjuvant therapeutic or combination therapeutic treatments with other known therapeutic agents.

The term "treatment" 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.

The following is a non-exhaustive listing of adjuvants and additional therapeutic agents which may be utilized in combination with the RAGE modulators of the present invention:

Pharmacologic classifications of anticancer agents:

1. Alkylating agents: Cyclophosphamide, nitrosoureas, carboplatin, cisplatin, procarbazine
2. Antibiotics: Bleomycin, Daunorubicin, Doxorubicin
3. Antimetabolites: Methotrexate, Cytarabine, Fluorouracil
4. Plant alkaloids: Vinblastine, Vincristine, Etoposide, Paclitaxel,
5. Hormones: Tamoxifen, Octreotide acetate, Finasteride, Flutamide
6. Biologic response modifiers: Interferons, Interleukins, Anti-tumor antibodies

Pharmacologic classifications of treatment for Rheumatoid Arthritis (Inflammation)

1. Analgesics: Aspirin
2. NSAIDs (Nonsteroidal anti-inflammatory drugs): Ibuprofen, Naproxen, Diclofenac
3. DMARDs (Disease-Modifying Antirheumatic drugs): Methotrexate, gold preparations, hydroxychloroquine, sulfasalazine
4. Biologic Response Modifiers, DMARDs: Etanercept, Infliximab Glucocorticoids

Pharmacologic classifications of treatment for Diabetes Mellitus

1. Sulfonylureas: Tolbutamide, Tolazamide, Glyburide, Glipizide
2. Biguanides: Metformin
3. Miscellaneous oral agents: Acarbose, Troglitazone
4. Insulin

Pharmacologic classifications of treatrnent for Alzheimer's Disease

1. Cholinesterase Inhibitor: Tacrine, Donepezil
2. Antipsychotics: Haloperidol, Thioridazine
3. Antidepressants: Desipramine, Fluoxetine, Trazodone, Paroxetine
4. Anticonvulsants: Carbamazepine, Valproic acid

In a further preferred embodiment, the present invention provides 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) in combination with 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. In a further preferred embodiment, the present invention provides the pharmaceutical composition of the invention as described above, 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.

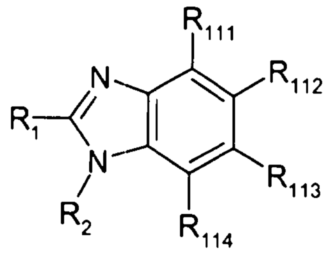
Generally speaking, the compound of the present invention, preferably Formula (I), is administered at a dosage level of from about 0.01 to 500 mg/kg of the body weight of the subject being treated systemically, with a preferred dosage range between 0.01 and 200 mg/kg, most preferably 0.1 to 100mg/kg of body weight per day. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for oral administration to humans may contain 1 mg to 2 grams of a compound of Formula (I) with an appropriate and convenient amount of carrier material which may vary from about 5 to 95 percent of the total composition. Also a dosage form intended for topical administration to the skin may be prepared at .1% to 99% compound to topical excipient ratio and a dosage form intended for inhaled administration of .01 to 200 mg of compound in a suitable carrier to deliver an inhaled dosage of compound. Dosage unit forms of systemically delivered compound will generally contain between from about 5 mg to about 500mg of active ingredient. This dosage has to be individualized by the clinician based on the specific clinical condition of the subject being treated. Thus, it will be understood that the specific dosage level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

While the invention has been described and illustrated with reference to certain preferred embodiments therof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the preferred dosages as set forth herein may be applicable as a consequence of variations in the responsiveness of the mammal being treated for RAGE-mediated disease(s). Likewise, the specific pharmacological responses observed may vary according to and depending on the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention.

2007202350 24 May 2007

Claims

1. A compound of Formula (Ic)



(Ic)

wherein

R_1 is -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 $-G_1-G_2-G_3-R_5$

wherein

G_1 and G_3 are independently selected from the group consisting of alkylene, alkenylene, alkynylene, cycloalkylene, heterocyclylene, arylene, heteroarylene, (aryl)alkylene, (heteroaryl) alkylene, (aryl)alkenylene, (heteroaryl)alkenylene, and a direct bond;

G_2 is -O-, -S-, -S(O)-, $-N(R_6)-$, $-S(O)_2-$, -C(O)-, $-CO_2-$, $-C(O)N(R_6)-$, $N(R_6)C(O)-$, $-S(O_2)N(R_6)-$, $N(R_6)S(O_2)-$, -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_6 is hydrogen, aryl, alkyl, -alkylene-aryl, alkoxy, or –alkylene-O-aryl; and

R_5 is hydrogen, aryl, heteroaryl, cycloalkyl, heterocyclyl, alkyl, alkenyl, alkynyl, -alkylene-aryl, -alkylene-heteroaryl, -alkylene-heterocyclyl,

2007202350 24 May 2007

-alkylene-cycloalkyl, fused cycloalkylaryl, fused cycloalkylheteroaryl, fused heterocyclylaryl, fused heterocyclylheteroaryl;-alkylene-fused cycloalkylaryl, -alkylene-fused cycloalkylheteroaryl, -alkylene-fused heterocyclylaryl, or -alkylene-fused heterocyclylheteroaryl;

R_2 is

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,

R_{111}, R_{112}, R_{113} and R_{114} are independently selected from the group consisting of

a) -hydrogen,
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-W_3-R_{40},

m) –Y_5-Y_6 –$NR_{33}R_{34}$,

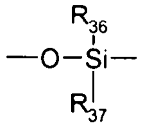
n) –Y_5-Y_6 –NH-C(=NR_{35})$NR_{33}R_{34}$,

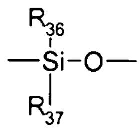
o) –Y_5-Y_6 –C(=NR_{35})$NR_{33}R_{34}$, and

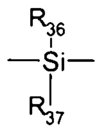
p) –Y_5-Y_6 –Y_7-A_4;

wherein

Y_5 and Y_7 are independently selected from the group consisting of 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-,



,


and


;

wherein R_{36} and R_{37} are independently selected from the group consisting of aryl, alkyl, -alkylene-aryl, alkoxy, and –alkyl-O-aryl;

Y_6 is

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) $-S(O_2)-$; or

s) -S(O)-;

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

A_4 is

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

b) -imidazolyl, or

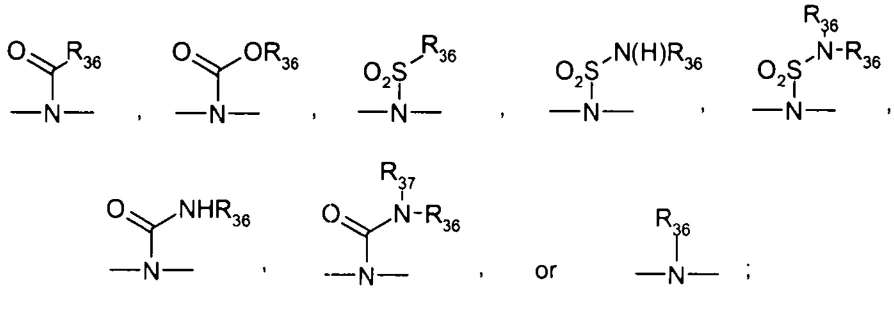
c) -pyridyl;

R_{33}, R_{34} and R_{35} are independently selected from the group consisitng of hydrogen, aryl, heteroaryl, alkyl, -alkylene-aryl, and -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,

wherein

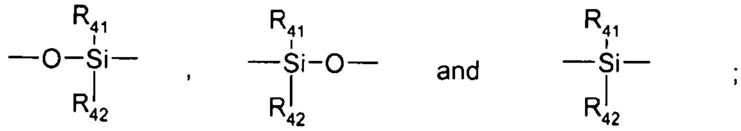
u and v are, independently, 1, 2, 3, or 4;

X_4 is 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} are independently selected from the group consisting of hydrogen, aryl, heteroaryl, alkyl, -alkylene-aryl, and -alkylene-heteroaryl;

Y_8 and W_3 are independently selected from the group consisting of $-CH_2-$, -O-, -N(H), -S-, SO_2-, -CON(H)-, -NHC(O)-, -NHCON(H)-, $-NHSO_2-$, $-SO_2N(H)-$, -C(O)-O-, $-NHSO_2NH-$, -O-CO-,



wherein R_{41} and R_{42} are independently selected from the group consisting of aryl, alkyl, -alkylene-aryl, alkoxy, and -alkyl-O-aryl; and

R_{40} is hydrogen, aryl, alkyl, -alkylene-aryl, -alkylene-heteroaryl, or -alkyene-O-aryl;

wherein at least one of R_{111}, R_{112}, R_{113}, and R_{114} is 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

$-Y_5-Y_6-Y_7-A_4$, and

wherein

the aryl and/or alkyl group(s) in R_1, R_2, R_5, R_6, R_{111}, R_{112}, R_{113}, and R_{114} may be optionally substituted 1-4 times with a substituent selected from the group consisting of:

a) -H,

b) -halogen,

c) -hydroxyl,

d) -cyano,

e) -carbamoyl,

f) -carboxyl,

g) $-Y_2$-alkyl;

h) $-Y_2$-aryl;

i) $-Y_2$-heteroaryl;

2007202350 24 May 2007

j) $-Y_2-$ alkylene-heteroarylaryl;

k) $-Y_2-$alkylene-aryl;

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

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

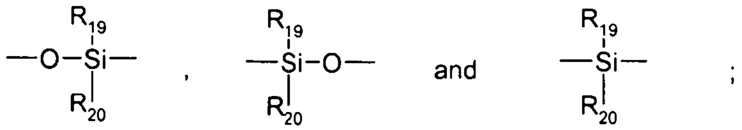
n) $-Y_3-Y_4-NH-C(=NR_{25})NR_{23}R_{24}$,

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

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

wherein

Y_2 and W_2 are independently selected from the group consisting of $-CH_2-$, -O-, -N(H), -S-, SO_2-, -CON(H)-, -NHC(O)-, -NHCON(H)-, $-NHSO_2-$, $-SO_2N(H)-$, -C(O)-O-, $-NHSO_2NH-$, $-O-S(O)_2-$, -O-CO-,

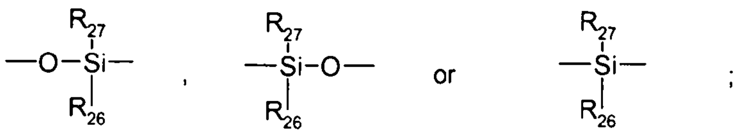


wherein;

R_{19} and R_{20} are independently selected from the group consisting of hydrogen, aryl, alkyl, -alkylene-aryl, alkoxy, and –alkylene-O-aryl; and

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

Y_3 is 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} are independently selected from the group consisting of aryl, alkyl, -alkylene-aryl, alkoxy, and –alkyl-O-aryl;

Y_4 is

a) -alkylene;

b) -alkenylene;

2007202350 24 May 2007

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) $-S(O_2)-$; or
s) -S(O)-;

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

A_2 is

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

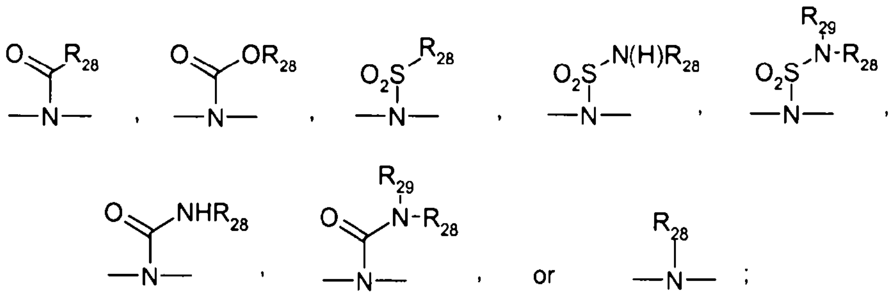
R_{23}, R_{24}, and R_{25} are independently selected from the group consisting of hydrogen, aryl, heteroaryl, -alkylene-heteroaryl, alkyl, -alkylene-aryl, -alkylene-O-aryl, and -alkylene-O-heteroaryl; and R_{23} and R_{24} may be taken together to form a ring having the formula $-(CH_2)_s-X_3-(CH_2)_t-$ 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;

2007202350 24 May 2007

X_3 is 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_{28} and R_{29} are independently selected from the group consisting of hydrogen, aryl, heteroaryl, alkyl, -alkylene-aryl, and -alkylene-heteroaryl;

or a pharmaceutically acceptable salt thereof.

2. The compound of Formula (Ic) of claim 1, wherein R_2 is hydrogen or alkyl, or a pharmaceutically acceptable salt thereof.

3. The compound of Formula (Ic) of claim 1, wherein R_1 is a phenyl group substituted by one or more substituents selected from the group consisting of:

a) $-Y_2$-alkyl;

b) $-Y_2$-aryl;

c) $-Y_2$-heteroaryl;

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 $-C(=NR_{25})NR_{23}R_{24}$, and

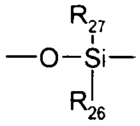
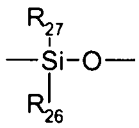
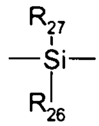
j) $-Y_3$-Y_4 $-Y_5$-A_2

wherein

Y_2 and W_2 are independently selected from the group consisting of $-CH_2-$, and -O-,

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

Y_3 and Y_5 are independently selected from the group consisting of 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-,


,

and

;

wherein R_{27} and R_{26} are independently selected from the group consisting of aryl, alkyl, -alkylene-aryl, alkoxy, and –alkyl-O-aryl;

Y_4 is

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) $-S(O_2)-$; or
s) -S(O)-;

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

A_2 is

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

b) -imidazolyl, or

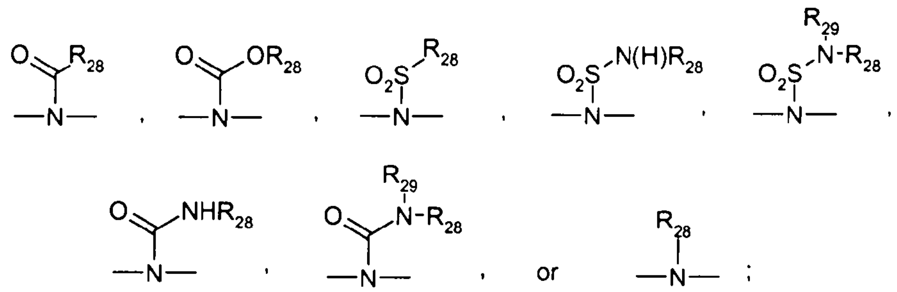
c) -pyridyl;

R_{23}, R_{24}, and R_{25} are independently selected from the group consisting of hydrogen, aryl, heteroaryl, -alkylene-heteroaryl, alkyl, -alkylene-aryl, -alkylene-O-aryl, and -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;

X_3 is 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)-, -$NHSO_2$NH-,



wherein R_{28} and R_{29} are independently selected from the group consisting of hydrogen, aryl, heteroaryl, alkyl, -alkylene-aryl, and -alkylene-heteroaryl,

or a pharmaceutically acceptable salt thereof.

4. The compound of Formula (Ic) of claim 1, wherein R_1 is 2-methoxy-3,5-dimethyoxy-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,

or a pharmaceutically acceptable salt thereof.

5. The compound of Formula (Ic) of claim 1, wherein R_1 is 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,

or a pharmaceutically acceptable salt thereof.

6 The compound of Formula (Ic) of claim 1, wherein R_{111}, R_{112} and R_{114} is hygrogen; and R_{113} is $-Y_3-Y_4-NR_{23}R_{24}$, or $-Y_3-Y_4-Y_5-A_2$,

or a pharmaceutically acceptable salt thereof

7. The compound of Formula (Ic) of claim 1, wherein R_1 is 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 is alkyl; R_{112} and R_{114} are hygrogen; and R_{111} and R_{113} are selected from the group consisting of $-Y_3-Y_4-NR_{23}R_{24}$, and $-Y_3-Y_4-Y_5-A_2$,

or a pharmaceutically acceptable salt thereof

8. A pharmaceutical composition comprising the compound of Formula (Ic) as claimed in claim 1, and one or more pharmaceutically acceptable carriers, excipients, or diluents.

9. The pharmaceutical composition of to claim 8, in the form of an oral dosage or parenteral dosage unit.

10. The pharmaceutical composition of claim 8, wherein said compound is administered as a dose in a range from about 0.01 to 500 mg/kg of body weight per day.

11. The pharmaceutical composition of claim 8, wherein said compound is administered as a dose in a range from about 0.1 to 200 mg/kg of body weight per day.

12. The pharmaceutical composition of claim 8, wherein said compound is administered as a dose in a range from about 0.1 to 100 mg/kg of body weight per day.

13. The pharmaceutical composition of to claim 8, in a topical dosage form.

14. The pharmaceutical composition of claim 8, wherein said compound is administered in a formulation ratio of 0.1% to 99% of compound to topical excipient.

15. The pharmaceutical composition of claim 8, wherein said compound is in an inhaled dosage form.

16. The pharmaceutical composition of claim 15, wherein said composition is an aerosol formulation.

17. The pharmaceutical composition of claim 15, wherein said composition is an inhaled powder dosage form.

18. The pharmaceutical composition of claim 8, further comprising one or more therapeutic agents selected from the group consisting of alkylating agents,

2007202350 24 May 2007

antimetabolites, plant alkaloids, antibiotics, hormones, biologic response modifiers, analgesics, NSAIDs, DMARDs, glucocorticoids, sulfonylureas, biguanides, insulin, cholinesterase inhibitors, antipsychotics, antidepressants, and anticonvulsants.

19. 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 (Ic) as claimed in claim 1.

20. The method of claim 19, wherein the ligand(s) is(are) selected from advanced glycated end products (AGEs), S100/calgranulin/EN-RAGE, β-amyloid and amphoterin.

21. 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 (Ic) as claimed in claim 1.

22. 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 (Ic) as claimed in claim 1.

23. The method of claim 19, further comprising administering to a subject in need thereof at least one adjuvant and/or additional therapeutic agent(s).

24. The method of claim 21, further comprising administering to a subject in need thereof at least one adjuvant and/or additional therapeutic agent(s).

25. The method of claim 22, further comprising administering to a subject in need thereof at least one adjuvant and/or additional therapeutic agent(s).

2007202350 24 May 2007

26. 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 (Ic) 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.

27. 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 (Ic) as defined in claim 1.

28. A pharmaceutical composition comprising a compound of Formula (Ic) as claimed in claim 2 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, excipient, or diluent.

29. A pharmaceutical composition comprising a compound of Formula (Ic) as claimed in claim 3 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, excipient, or diluent.

30. A pharmaceutical composition comprising a compound of Formula (Ic) as claimed in claim 4 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, excipient, or diluent.

31. A pharmaceutical composition comprising a compound of Formula (Ic) as claimed in claim 5 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, excipient, or diluent.

32. A pharmaceutical composition comprising a compound of Formula (Ic) as claimed in claim 6 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, excipient, or diluent.

33. A pharmaceutical composition comprising a compound of Formula (Ic) as claimed in claim 7 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, excipient, or diluent.

34. A compound as claimed in claim 1 and substantially as herein described with reference to the Examples.