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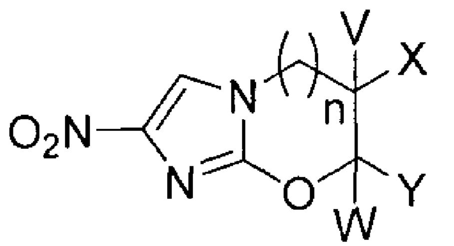
(72) **Inventeurs/Inventors:**
THOMPSON, ANDREW M., NZ;
DENNY, WILLIAM ALEXANDER, NZ;
BLASER, ADRIAN, NZ;
MA, ZHENKUN, US

(73) **Propriétaire/Owner:**
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT, US

(74) **Agent:** KIRBY EADES GALE BAKER

(54) **Titre : ANALOGUES DE NITRO-IMIDAZO-OXAZINE ET DE NITRO-IMIDAZO-OXAZOLE ET LEURS UTILISATIONS**
(54) **Title: NITROIMIDAZOOXAZINE AND NITROIMIDAZOOXAZOLE ANALOGUES AND THEIR USES**



I

(57) **Abrégé/Abstract:**
The current invention pertains to nitroimidazooxazine and nitroimidazooxazole analogues, their methods of preparation, and uses of the compounds as treatment for Mycobacterium tuberculosis, for use as anti-tubercular drugs, for use as anti-protozoal agents with unexpectedly high potency against Trypanosoma cruzi or Leishmania donovani, and for the treatment of other microbial infections.

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(71) Applicant *(for all designated States except US)*: **GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT** [US/US]; 40 Wall Street, 24th Floor, New York, NY 10005 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **THOMPSON, Andrew, M.** [NZ/NZ]; 3-13 Stanhope Road, Mount Wellington, Auckland, 1051 (NZ). **DENNY, William, Alexander** [NZ/NZ]; 165 Gossamer Drive, Pakuranga, Auckland, 2010 (NZ). **BLASER, Adrian** [NZ/NZ]; 157B Colwill Rd., Massey East, Waitakere City, 0614 (NZ). **MA, Zhenkun** [US/US]; 443 Edgewood Ave., Westfield, NJ 07090 (US).

(74) Agents: **CHWANG, T., Ling** et al.; Jackson Walker L.L.P., 901 Main Street, Suite 6000, Dallas, TX 75202 (US).

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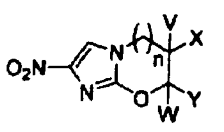
(54) **Title**: NITROIMIDAZOOXAZINE AND NITROIMIDAZOOXAZOLE ANALOGUES AND THEIR USES



(I)

(57) **Abstract**: The current invention pertains to nitroimidazooxazine and nitroimidazooxazole analogues, their methods of preparation, and uses of the compounds as treatment for *Mycobacterium tuberculosis*, for use as anti-tubercular drugs, for use as anti-protozoal agents with unexpectedly high potency against *Trypanosoma cruzi* or *Leishmania donovani*, and for the treatment of other microbial infections.

NITROIMIDAZOOXAZINE AND NITROIMIDAZOOXAZOLE ANALOGUES AND THEIR USES

BACKGROUND

[0002] The present invention relates to nitroimidazooxazine and nitroimidazooxazole analogues, to their preparation, and to their use as drugs effective against *Mycobacterium tuberculosis* and as anti-protozoal agents, either alone or in combination with other treatments.

[0003] Tuberculosis remains a leading infectious cause of death worldwide (having a mortality estimated to be 1.3 million in 2008), with a recent resurgence attributable to an enhanced susceptibility in HIV patients, as well as the increasing incidence of multidrug-resistant strains and the emergence of extensively drug resistant strains. Current drug therapy for tuberculosis is long and complex, involving multidrug combinations (usually isoniazid, rifampin, pyrazinamide and ethambutol) given daily for in excess of 6 months. Furthermore, these drugs are relatively ineffective against the persistent form of the disease, which is suggested to occur in a significant proportion of cases (Ferrara et al., 2006). Second-line drugs used in lengthy combination therapies for multidrug resistant diseases (typically over 2 years) mostly have reduced potency or greater toxicity than existing first-line agents. Frequently, incomplete treatment is administered, leading to high relapse rates and increased drug resistance, underscoring the urgent need for new, more effective drugs.

[0004] Chagas disease affects about 9 million people, principally in South America, and results in about 14,000 deaths annually. It is caused by the protozoan parasite *Trypanosoma cruzi*, which is transmitted to humans by blood-sucking bugs. The two drugs currently available for treatment, nifurtimox and benznidazole, show efficacy that is limited to the acute phase of the disease and to only some pathogen strains. These drugs also give serious side effects, and this, together with the lengthy and expensive treatment required, leads to inadequate patient compliance and the development of drug resistance (Cavalli et al., 2009).

[0005] Leishmaniases affect almost 12 million people in nearly 90 countries and result in about 51,000 deaths annually. They are particularly prevalent on the Indian subcontinent and in east Africa, where the parasite *Leishmania donovani* is the causative agent. This parasite is transmitted to humans through the bite of female sandflies and is responsible for the most severe form, visceral leishmaniasis (kala-azar), which causes chronic disease in the liver and spleen and is fatal unless treated by chemotherapy. First-line treatments are the antimonials meglumine antimoniate (Glucantime) and sodium stibogluconate (Pentostam), discovered more than 50 years ago, which present severe, undesirable side effects. Their administration in low doses over a longer time has resulted in growing drug resistance such that they can no longer be used in India (Cavalli et al., 2009). Second-line agents suffer from similar toxicity concerns, illustrating the real need for safer, more effective treatments.

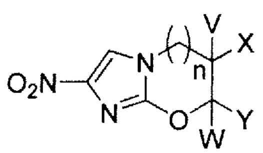
[0006] It is therefore highly desirable to provide new nitroimidazooxazine and nitroimidazooxazole analogues with unexpectedly high potency against both aerobic (replicating) and hypoxic (latent or persistent) cultures of *Mycobacterium tuberculosis*, for use as anti-tubercular drugs, and/or with unexpectedly high potency against *Trypanosoma cruzi* or *Leishmania donovani* for use as anti-protozoal agents, and for the treatment of other microbial infections.

SUMMARY

[0007] The current invention pertains to nitroimidazooxazine and nitroimidazooxazole analogues, their methods of preparation, and uses of the compounds as treatment for *Mycobacterium tuberculosis*, for use as anti-tubercular drugs, for use as anti-protozoal agents with unexpectedly high potency against *Trypanosoma cruzi* or *Leishmania donovani*, and for the treatment of other microbial infections.

[0008] The recent introduction of the nitroimidazooxazine PA-824 to clinical trial is significant, as this compound shows good in vitro and in vivo activity against *Mycobacterium tuberculosis* in both its active and persistent forms (Tyagi et al., 2005). A related 2-nitroimidazo[2,1-*b*]oxazole, OPC-67683 is also in clinical trial (Sasaki et al., 2006). The structures of these compounds are shown in Figure 1. Without wanting to be bound by theory, the mechanism of action of PA-824 is suggested to involve the release of nitric oxide (Singh et al., 2008), following a reductive step, in a process dependent on the bacterial glucose-6-phosphate dehydrogenase (FGD1) and its cofactor F420 (Stover et al., 2000). Microarray studies on mutant strains wild-type for both FGD1 and F420 show that a 151-amino acid (17.37 kDa) protein of unknown function, Rv3547, appears to be critical for this activation (Manjunatha et al., 2006). Recent mechanistic studies of the reductive chemistry of PA-824 support this contention (Anderson et al., 2008). Nitroimidazooxazine analogues and nitroimidazooxazole analogues and their uses in tuberculosis have been previously reported (U.S. Patent Nos. 5,668,127 and 6,087,358; Jiricek et al., WO 2007075872A2; Li et al., 2008; Kim et al., 2009; Nagarajan et al., 1989; Ashtekar et al., 1993; Sasaki et al., 2006; Matsumoto et al., 2006; Tsubochi et al., WO 2005042542A1 and WO 2004033463A1; JP 2005330266A; EP 1555267A1).

[0009] In a first aspect, the present invention pertains to a compound having a general structure of Formula I:

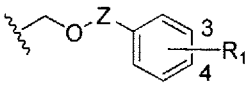


I

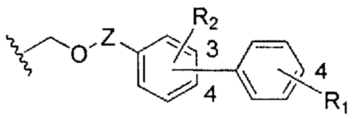
wherein n is 0 or 1,

V and W independently are H or CH_3, and

one of X or Y represents H and the other represents one of Formulae IIa or IIb, wherein Formulae IIa and IIb have the general structures:



IIa



IIb

wherein Formula IIb comprises a first ring labeled at a 3-position and a 4-position and having as substituents both R_2 and a terminal ring labeled at a 4-position and having R_1 as a substituent,

Z in Formulae IIa and IIb represents CH_2 or a direct bond, and

R_1 and R_2 each represents any one or two of H, F, Cl, I, CN, CF_3, OCF_3, OCH_3, OCH_2Ph, aza (-CH= replaced by –N=), or diaza (-CH=CH- replaced by –N=N-, -CH=CH-CH= replaced by –N=CH-N=, or -CH=CH-CH=CH- replaced by –N=CH-CH=N-) at any of the available ring positions;

provided that if n is 0, V, W and X are all H, and Y is Formula IIa wherein Z is either CH_2 or a direct bond, then R_1 is not H;

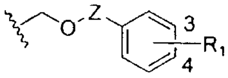
and provided that if n is 0, V and X are both H, W is CH_3, and Y is Formula IIa wherein Z is a direct bond, then R_1 is not H, 4-Cl, 4-I, 4-CF_3, 4-OCH_3, or 4-OCF_3;

and provided that if n is 0, V and X are both H, W is CH_3, and Y is Formula IIb wherein Z is a direct bond, the terminal ring is located at the 4-position on the first ring, and R_2 is H, then R_1 is not H, or 4-aza.

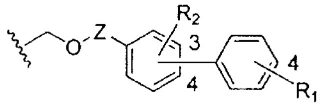
[0010] A more preferred subclass of compounds includes those having a general structure of Formula I as defined above, wherein:

n is 0 or 1,

V and W independently are H or CH_3, and one of X or Y represents H and the other represents one of Formulae IIa or IIb, wherein Formulae IIa and IIb have the general structures:



IIa



IIb

wherein Formula IIb comprises a first ring labeled at a 3-position and a 4-position and having as substituents both R_2 and a terminal ring labeled at a 4-position and having R_1 as a substituent,

Z in Formulae IIa and IIb represents CH_2 or a direct bond,

R_1 represents 4-F, 4-CN, 4-I, 4-CF_3, 3-OCF_3, 4-OCF_3, 4-OCH_2Ph, or 3-aza-4-OMe, and

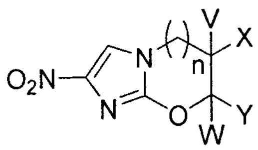
R_2 represents H, aza (-CH= replaced by –N=), or diaza (-CH=CH- replaced by –N=N-, -CH=CH-CH= replaced by –N=CH-N=, or -CH=CH-CH=CH- replaced by –N=CH-CH=N-) at any of the available ring positions;

provided that if n is 0, V, W and X are all H, and Y is Formula IIa wherein Z is either CH_2 or a direct bond, then R_1 is not H;

and provided that if n is 0, V and X are both H, W is CH_3, and Y is Formula IIa wherein Z is a direct bond, then R_1 is not H, 4-Cl, 4-I, 4-CF_3, 4-OCH_3, or 4-OCF_3;

and provided that if n is 0, V and X are both H, W is CH_3, and Y is Formula IIb wherein Z is a direct bond, the terminal ring is located at the 4-position on the first ring, and R_2 is H, then R_1 is not H, or 4-aza.

[0010a] In one particular embodiment the invention provides a compound having a general structure of Formula I:



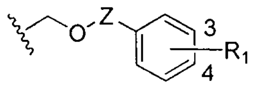
I

wherein

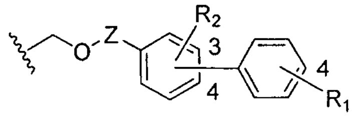
n is 1,

V and W are independently H or CH_3, and

one of X or Y is H and the other is one of Formulae IIa or IIb, wherein Formulae IIa and IIb have general structures of:



IIa



IIb

wherein Formula IIa has a single ring labeled at a 3-position and a 4-position and having R_1 as a substituent, and Formula IIb has a first ring labeled at a 3-position and a 4-position and having as substituents both R_2 and a terminal ring labeled at a 4-position and having R_1 as a substituent,

wherein the single ring of Formula IIa and the first ring and the terminal ring of Formula IIb comprise C, CH, or aza at each ring position, wherein the single ring of Formula IIa and the first ring and the terminal ring of Formula IIb independently comprise no more than two aza,

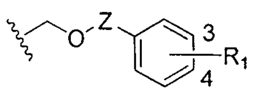
Z in Formulae IIa and IIb is CH_2 or a direct bond, and

R_1 and R_2 are independently any one or two of H, F, Cl, I, CN, CF_3, OCF_3, OCH_3, or OCH_2Ph.

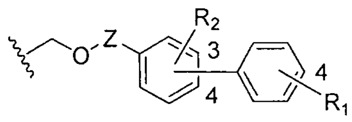
[0010b] In another embodiment the invention provides the compound as set out above wherein:

n is 1,

V and W are independently H or CH_3, and one of X or Y is H and the other is one of Formulae IIa or IIb, wherein Formulae IIa and IIb have general structures of:



IIa



IIb

wherein Formula IIa has a single ring labeled at a 3-position and a 4-position and having R_1 as a substituent, Formula IIb has a first ring labeled at a 3-position and a 4-position and having as substituents both R_2 and a terminal ring labeled at a 4-position and having R_1 as a substituent,

wherein the first ring of Formula IIb comprises C, CH or aza at each ring position, wherein the first ring of Formula IIb comprises no more than two aza, and both the single ring of Formula IIa and the terminal ring of Formula IIb comprise C or CH at each ring position when R_1 is not 4-OMe, or comprise aza at the 3-position and C or CH at each remaining ring position when R_1 is 4-OMe,

Z in Formulae IIa and IIb is CH_2 or a direct bond,

R_1 is 4-F, 4-CN, 4-I, 4-CF_3, 3-OCF_3, 4-OCF_3, 4-OCH_2Ph, or 4-OMe, and

R_2 is H.

[0011] These compounds, as well as mixtures thereof, isomers, physiologically functional salt derivatives, and prodrugs thereof, are useful in prevention of or therapy for treating *Mycobacterium tuberculosis*, for use as anti-tubercular drugs, for use as anti-protozoal agents with unexpectedly high potency against *Trypanosoma cruzi* or *Leishmania donovani*, and for the treatment of other microbial infections.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] Figure 1 shows the structures of compounds PA-824 and OPC-67683;

[0013] Figure 2 shows the general structures of representative compounds referred to in Table 1;

[0014] Figure 3 shows a general synthetic scheme for preparing representative compounds;

[0015] Figure 4 shows a general synthetic scheme for preparing representative compounds;

[0016] Figure 5 shows a general synthetic scheme for preparing representative compounds;

[0017] Figure 6 shows a general synthetic scheme for preparing representative compounds;

[0018] Figure 7 shows a general synthetic scheme for preparing representative compounds;

[0019] Figure 8 shows a general synthetic scheme for preparing representative compounds;

[0020] Figure 9 shows a general synthetic scheme for preparing representative compounds;

[0021] Figure 10 shows a general synthetic scheme for preparing representative compounds;

[0022] Figure 11 shows a general synthetic scheme for preparing representative compounds;

[0023] Figure 12 shows a general synthetic scheme for preparing representative compounds;

[0024] Figure 13 shows a general synthetic scheme for preparing representative compounds;

[0025] Figure 14 shows a general synthetic scheme for preparing representative compounds;

[0026] Figure 15 shows a general synthetic scheme for preparing representative compounds;

[0027] Figure 16 shows a general synthetic scheme for preparing representative compounds;

[0028] Figure 17 shows a general synthetic scheme for preparing representative compounds;

[0029] Figure 18 shows the structures of representative compounds **1-20** referred to in Table 1 and Examples 1-3;

[0030] Figure 19 shows the structures of representative compounds **21-38** referred to in Table 1 and Examples 1-3;

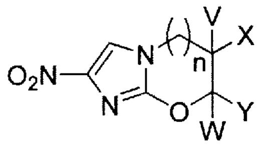
[0031] Figure 20 shows the structures of representative compounds **39-58** referred to in Table 1 and Examples 1-3; and

[0032] Figure 21 shows the structures of representative compounds **59-75** referred to in Table 1 and Examples 1-3.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

[0033] The current invention pertains to nitroimidazooxazine and nitroimidazooxazole analogues, their methods of preparation, and uses of the compounds in prevention of or therapy for treating *Mycobacterium tuberculosis*, for use as anti-tubercular drugs, for use as anti-protozoal agents with unexpectedly high potency against *Trypanosoma cruzi* or *Leishmania donovani*, and for the treatment of other microbial infections.

[0034] In a first aspect, the present invention pertains to a compound having a general structure of Formula I:

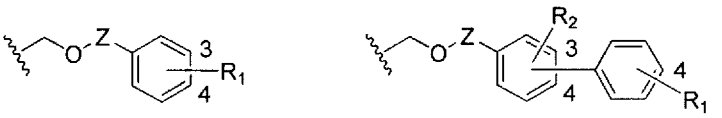


I

wherein n is 0 or 1,

V and W independently are H or CH_3, and

one of X or Y represents H and the other represents one of Formulae IIa or IIb, wherein Formulae IIa and IIb have the general structures:



IIa **IIb**

wherein Formula IIb comprises a first ring labeled at a 3-position and a 4-position and having as substituents both R_2 and a terminal ring labeled at a 4-position and having R_1 as a substituent,

Z in Formulae IIa and IIb represents CH_2 or a direct bond, and

R_1 and R_2 each represents any one or two of H, F, Cl, I, CN, CF_3, OCF_3, OCH_3, OCH_2Ph, aza (-CH= replaced by –N=), or diaza (-CH=CH- replaced by –N=N-, -CH=CH-CH= replaced by –

N=CH-N=, or -CH=CH-CH=CH- replaced by –N=CH-CH=N-) at any of the available ring positions;

provided that if n is 0, V, W and X are all H, and Y is Formula IIa wherein Z is either CH_2 or a direct bond, then R_1 is not H;

and provided that if n is 0, V and X are both H, W is CH_3, and Y is Formula IIa wherein Z is a direct bond, then R_1 is not H, 4-Cl, 4-I, 4-CF_3, 4-OCH_3, or 4-OCF_3;

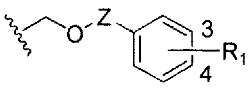
and provided that if n is 0, V and X are both H, W is CH_3, and Y is Formula IIb wherein Z is a direct bond, the terminal ring is located at the 4-position on the first ring, and R_2 is H, then R_1 is not H, or 4-aza.

[0035] A more preferred subclass of compounds includes those having a general structure of Formula I as defined above, wherein:

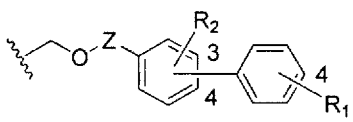
n is 0 or 1,

V and W independently are H or CH_3, and

one of X or Y represents H and the other represents one of Formulae IIa or IIb, wherein Formulae IIa and IIb have the general structures:



IIa



IIb

wherein Formula IIb comprises a first ring labeled at a 3-position and a 4-position and having as substituents both R_2 and a terminal ring labeled at a 4-position and having R_1 as a substituent,

Z in Formulae IIa and IIb represents CH_2 or a direct bond,

R_1 represents 4-F, 4-CN, 4-I, 4-CF_3, 3-OCF_3, 4-OCF_3, 4-OCH_2Ph, or 3-aza-4-OMe, and

R_2 represents H, aza (-CH= replaced by –N=), or diaza (-CH=CH- replaced by –N=N-, -CH=CH-CH= replaced by –N=CH-N=, or -CH=CH-CH=CH- replaced by –N=CH-CH=N-) at any of the available ring positions;

provided that if n is 0, V, W and X are all H, and Y is Formula IIa wherein Z is either CH_2 or a direct bond, then R_1 is not H;

and provided that if n is 0, V and X are both H, W is CH_3, and Y is Formula IIa wherein Z is a direct bond, then R_1 is not H, 4-Cl, 4-I, 4-CF_3, 4-OCH_3, or 4-OCF_3;

and provided that if n is 0, V and X are both H, W is CH_3, and Y is Formula IIb wherein Z is a direct bond, the terminal ring is located at the 4-position on the first ring, and R_2 is H, then R_1 is not H, or 4-aza.

[0036] The most highly preferred of the compounds of Formula I are:

A. 6-Nitro-2-{[4-(trifluoromethoxy)phenoxy]methyl}-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (compound **1** of Table 1 and Figure 18);

B. 2-{[4-(Benzyloxy)phenoxy]methyl}-6-nitro-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (compound **2** of Table 1 and Figure 18);

C. 2-{[(4'-Fluoro[1,1'-biphenyl]-4-yl)oxy]methyl}-6-nitro-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (compound **3** of Table 1 and Figure 18);

D. 6-Nitro-2-({[4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]oxy}methyl)-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (compound **4** of Table 1 and Figure 18);

E. 6-Nitro-2-({[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]oxy}methyl)-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (compound **5** of Table 1 and Figure 18);

F. 6-Nitro-2-[({5-[4-(trifluoromethoxy)phenyl]-2-pyridinyl}oxy)methyl]-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (compound **6** of Table 1 and Figure 18);

G. 2-{[4-(Benzyloxy)phenoxy]methyl}-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (compound **7** of Table 1 and Figure 18);

H. 2-{[4-(6-Methoxy-3-pyridinyl)phenoxy]methyl}-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (compound **8** of Table 1 and Figure 18);

I. 4'-[(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-*b*][1,3]oxazol-2-yl)methoxy][1,1'-biphenyl]-4-carbonitrile (compound **9** of Table 1 and Figure 18);

J. 2-{[(4'-Fluoro[1,1'-biphenyl]-4-yl)oxy]methyl}-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (compound **10** of Table 1 and Figure 18);

K. 2-Methyl-6-nitro-2-({[4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]oxy}methyl)-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (compound **11** of Table 1 and Figure 18);

L. 2-Methyl-6-nitro-2-({[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]oxy}methyl)-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (compound **12** of Table 1 and Figure 18);

M. 2-({[5-(4-Fluorophenyl)-2-pyridinyl]oxy}methyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (compound **13** of Table 1 and Figure 18);

N. 2-Methyl-6-nitro-2-[({5-[4-(trifluoromethoxy)phenyl]-2-pyridinyl}oxy)methyl]-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (compound **14** of Table 1 and Figure 18);

O. 2-({[6-(4-Fluorophenyl)-3-pyridinyl]oxy}methyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (compound **15** of Table 1 and Figure 18);

P. 2-Methyl-6-nitro-2-[({6-[4-(trifluoromethoxy)phenyl]-3-pyridinyl}oxy)methyl]-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (compound **16** of Table 1 and Figure 18);

Q. 2-({[5-(4-Fluorophenyl)-2-pyrimidinyl]oxy}methyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (compound **17** of Table 1 and Figure 18);

R. 2-Methyl-6-nitro-2-[({5-[4-(trifluoromethoxy)phenyl]-2-pyrimidinyl}oxy)methyl]-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (compound **18** of Table 1 and Figure 18);

S. 2-({[2-(4-Fluorophenyl)-5-pyrimidinyl]oxy}methyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (compound **19** of Table 1 and Figure 18);

T. 2-Methyl-6-nitro-2-[({2-[4-(trifluoromethoxy)phenyl]-5-pyrimidinyl}oxy)methyl]-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (compound **20** of Table 1 and Figure 18);

U. 2-({[5-(4-Fluorophenyl)-2-pyrazinyl]oxy}methyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (compound **21** of Table 1 and Figure 19);

V. 2-Methyl-6-nitro-2-[({5-[4-(trifluoromethoxy)phenyl]-2-pyrazinyl}oxy)methyl]-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (compound **22** of Table 1 and Figure 19);

W. 6-Nitro-2-({[4-(trifluoromethoxy)benzyl]oxy}methyl)-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (compound **23** of Table 1 and Figure 19);

X. 2-({[4-(Benzyloxy)benzyl]oxy}methyl)-6-nitro-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (compound **24** of Table 1 and Figure 19);

Y. 2-Methyl-6-nitro-2-({[4-(trifluoromethoxy)benzyl]oxy}methyl)-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (compound **25** of Table 1 and Figure 19);

Z. 2-({[4-(Benzyloxy)benzyl]oxy}methyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (compound **26** of Table 1 and Figure 19);

AA. 2-Nitro-7-{[4-(trifluoromethoxy)phenoxy]methyl}-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound **27** of Table 1 and Figure 19);

BB. 7-{[4-(Benzyloxy)phenoxy]methyl}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound **28** of Table 1 and Figure 19);

CC. 7-{[(4'-Fluoro[1,1'-biphenyl]-4-yl)oxy]methyl}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound **29** of Table 1 and Figure 19);

DD. 2-Nitro-7-({[4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]oxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound **30** of Table 1 and Figure 19);

EE. 2-Nitro-7-({[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]oxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound **31** of Table 1 and Figure 19);

FF. 7-({[5-(4-Fluorophenyl)-2-pyridinyl]oxy}methyl)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound **32** of Table 1 and Figure 19);

GG. 2-Nitro-7-[({5-[4-(trifluoromethoxy)phenyl]-2-pyridinyl}oxy)methyl]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound **33** of Table 1 and Figure 19);

HH. 7-({[6-(4-Fluorophenyl)-3-pyridinyl]oxy}methyl)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound **34** of Table 1 and Figure 19);

II. 2-Nitro-7-[({6-[4-(trifluoromethoxy)phenyl]-3-pyridinyl}oxy)methyl]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound **35** of Table 1 and Figure 19);

JJ. 7-Methyl-2-nitro-7-{[4-(trifluoromethoxy)phenoxy]methyl}-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound **36** of Table 1 and Figure 19);

KK. 7-{[4-(Benzyloxy)phenoxy]methyl}-7-methyl-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound **37** of Table 1 and Figure 19);

LL. 7-{[(4'-Fluoro[1,1'-biphenyl]-4-yl)oxy]methyl}-7-methyl-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound **38** of Table 1 and Figure 19);

MM. 7-Methyl-2-nitro-7-({[4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]oxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound **39** of Table 1 and Figure 20);

NN. 7-Methyl-2-nitro-7-({[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]oxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound **40** of Table 1 and Figure 20);

OO. 7-({[5-(4-Fluorophenyl)-2-pyridinyl]oxy}methyl)-7-methyl-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound **41** of Table 1 and Figure 20);

PP. 7-Methyl-2-nitro-7-[({5-[4-(trifluoromethyl)phenyl]-2-pyridinyl}oxy)methyl]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound **42** of Table 1 and Figure 20);

QQ. 7-Methyl-2-nitro-7-[({5-[4-(trifluoromethoxy)phenyl]-2-pyridinyl}oxy)methyl]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound **43** of Table 1 and Figure 20);

RR. 7-({[6-(4-Fluorophenyl)-3-pyridinyl]oxy}methyl)-7-methyl-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound **44** of Table 1 and Figure 20);

SS. 7-Methyl-2-nitro-7-[({6-[4-(trifluoromethyl)phenyl]-3-pyridinyl}oxy)methyl]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound **45** of Table 1 and Figure 20);

TT. 7-Methyl-2-nitro-7-[({6-[4-(trifluoromethoxy)phenyl]-3-pyridinyl}oxy)methyl]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound **46** of Table 1 and Figure 20);

UU. 2-Nitro-7-({[3-(trifluoromethoxy)benzyl]oxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound **47** of Table 1 and Figure 20);

VV. 2-Nitro-7-({[4-(trifluoromethoxy)benzyl]oxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound **48** of Table 1 and Figure 20);

WW. 7-({[4-(Benzyloxy)benzyl]oxy}methyl)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound **49** of Table 1 and Figure 20);

XX. 2-Nitro-7-({[4'-(trifluoromethoxy)[1,1'-biphenyl]-3-yl]methoxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound **50** of Table 1 and Figure 20);

YY. 2-Nitro-7-({[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]methoxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound **51** of Table 1 and Figure 20);

ZZ. 7-Methyl-2-nitro-7-({[3-(trifluoromethoxy)benzyl]oxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound **52** of Table 1 and Figure 20);

AAA. 7-Methyl-2-nitro-7-({[4-(trifluoromethoxy)benzyl]oxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound **53** of Table 1 and Figure 20);

BBB. 7-({[4-(Benzyloxy)benzyl]oxy}methyl)-7-methyl-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound **54** of Table 1 and Figure 20);

CCC. 7-Methyl-2-nitro-7-({[4'-(trifluoromethoxy)[1,1'-biphenyl]-3-yl]methoxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound **55** of Table 1 and Figure 20);

DDD. 7-Methyl-2-nitro-7-({[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]methoxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound **56** of Table 1 and Figure 20);

EEE. (7*R*)-7-Methyl-2-nitro-7-({[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]methoxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound **57** of Table 1 and Figure 20);

FFF. (7*S*)-7-Methyl-2-nitro-7-({[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]methoxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound **58** of Table 1 and Figure 20);

GGG. 2-Nitro-6-{[4-(trifluoromethoxy)phenoxy]methyl}-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound **59** of Table 1 and Figure 21);

HHH. (6*R*)-2-Nitro-6-{[4-(trifluoromethoxy)phenoxy]methyl}-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound **60** of Table 1 and Figure 21);

III. (6*S*)-2-Nitro-6-{[4-(trifluoromethoxy)phenoxy]methyl}-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound **61** of Table 1 and Figure 21);

JJJ. 6-{[(4'-Fluoro[1,1'-biphenyl]-4-yl)oxy]methyl}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound **62** of Table 1 and Figure 21);

KKK. 2-Nitro-6-({[4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]oxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound **63** of Table 1 and Figure 21);

LLL. 2-Nitro-6-({[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]oxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound **64** of Table 1 and Figure 21);

MMM. 6-({[5-(4-Fluorophenyl)-2-pyridinyl]oxy}methyl)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound **65** of Table 1 and Figure 21);

NNN. 2-Nitro-6-[({5-[4-(trifluoromethyl)phenyl]-2-pyridinyl}oxy)methyl]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound **66** of Table 1 and Figure 21);

OOO. 2-Nitro-6-[({5-[4-(trifluoromethoxy)phenyl]-2-pyridinyl}oxy)methyl]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound **67** of Table 1 and Figure 21);

PPP. 6-({[6-(4-Fluorophenyl)-3-pyridinyl]oxy}methyl)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound **68** of Table 1 and Figure 21);

QQQ. 2-Nitro-6-[({6-[4-(trifluoromethyl)phenyl]-3-pyridinyl}oxy)methyl]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound **69** of Table 1 and Figure 21);

RRR. 2-Nitro-6-[({6-[4-(trifluoromethoxy)phenyl]-3-pyridinyl}oxy)methyl]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound **70** of Table 1 and Figure 21);

SSS. 2-Nitro-6-({[3-(trifluoromethoxy)benzyl]oxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound **71** of Table 1 and Figure 21);

TTT. 2-Nitro-6-({[4-(trifluoromethoxy)benzyl]oxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound **72** of Table 1 and Figure 21);

UUU. 6-({[4-(Benzyloxy)benzyl]oxy}methyl)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound **73** of Table 1 and Figure 21);

VVV. 2-Nitro-6-({[4'-(trifluoromethoxy)[1,1'-biphenyl]-3-yl]methoxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound **74** of Table 1 and Figure 21); and

WWW. 2-Nitro-6-({[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]methoxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound **75** of Table 1 and Figure 21).

[0037] Compounds of Formula I may occur in different geometric and enantiomeric forms, and both pure forms and mixtures of these separate isomers are included in the scope of this invention, as well as any physiologically functional or pharmacologically acceptable salt derivatives or prodrugs thereof. Production of these alternate forms would be well within the capabilities of one skilled in the art.

[0038] The current invention also pertains to methods of prevention or therapy for tubercular, protozoal, and other microbial infections, such as *Mycobacterium tuberculosis*, *Trypanosoma cruzi*, and *Leishmania donovani*, including the step of administering a compound of Formula I.

[0039] In another aspect of the present invention there is provided a pharmaceutical composition including a therapeutically effective amount of a compound of Formula I as defined above and a pharmaceutically acceptable excipient, adjuvant, carrier, buffer or stabiliser. A "therapeutically effective amount" is to be understood as an amount of a compound of Formula I that is sufficient to show anti-bacterial or anti-microbial effects. The actual amount, rate and time-course of administration will depend on the nature and severity of the disease being treated. Prescription of treatment is within the responsibility of general practitioners and other medical doctors. The pharmaceutically acceptable excipient, adjuvant, carrier, buffer or stabiliser should be non-toxic and should not interfere with the efficacy of the active ingredient. The precise nature of the carrier or other material will depend on the route of administration, which may be oral, or by injection, such as cutaneous, subcutaneous, intravenous injection, or by dry powder inhaler.

[0040] Pharmaceutical compositions for oral administration may be in tablet, capsule, powder or liquid form. A tablet may comprise a solid carrier or an adjuvant. Liquid pharmaceutical compositions generally comprise a liquid carrier such as water, petroleum, animal or vegetable oils, mineral oil or synthetic oil. Physiological saline solution, dextrose or other saccharide solution or glycols such as ethylene glycol, propylene glycol or polyethylene glycol may be included. A capsule may comprise a solid carrier such as gelatin. For intravenous, cutaneous or subcutaneous injection, the active ingredient will be in the form of a parenterally acceptable aqueous solution which is pyrogen-free and has a suitable pH, isotonicity and stability. Those of relevant skill in the art are well able to prepare suitable solutions using, for example, isotonic vehicles such as Sodium Chloride injection, Ringer's injection, Lactated Ringer's injection. Preservatives, stabilisers, buffers, antioxidants and/or other additives may be included as required.

[0041] The pharmaceutical composition can further comprise one or more additional anti-infective treatments. These anti-infective treatments can be any suitable treatment available commercially or from other sources that are known to effectively prevent or treat microbial infections, such as *Mycobacterium tuberculosis*, *Trypanosoma cruzi*, and/or *Leishmania donovani*.

[0042] In another aspect, there is provided the use in the manufacture of a medicament of a therapeutically effective amount of a compound of Formula I as defined above for administration to a subject. There is also provided a method of making a compound of Formula I.

[0043] The term "pharmacologically acceptable salt" used throughout the specification is to be taken as meaning any acid or base derived salt formed from hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic, isoethonic acids and the like, and potassium carbonate, sodium or potassium hydroxide, ammonia, triethylamine, triethanolamine and the like.

[0044] The term "prodrug" means a pharmacological substance that is administered in an inactive, or significantly less active, form. Once administered, the prodrug is metabolised *in vivo* into an active metabolite.

[0045] The term "therapeutically effective amount" means a nontoxic but sufficient amount of the drug to provide the desired therapeutic effect. The amount that is "effective" will vary from subject to subject, depending on the age and general condition of the individual, the particular concentration and composition being administered, and the like. Thus, it is not always possible to specify an exact effective amount. However, an appropriate effective amount in any individual case may be determined by one of ordinary skill in the art using routine experimentation. Furthermore, the effective amount is the concentration that is within a range sufficient to permit ready application of the formulation so as to deliver an amount of the drug that is within a therapeutically effective range.

[0046] The term "aza" means -CH= replaced by –N= within the compound. The term "diaza" means -CH=CH- replaced by –N=N-, -CH=CH-CH= replaced by –N=CH-N=, or -CH=CH-CH=CH- replaced by –N=CH-CH=N- within the compound.

[0047] Further aspects of the present invention will become apparent from the following description given by way of example only and with reference to the accompanying synthetic schemes.

EXAMPLE 1. GENERAL SYNTHETIC SCHEMES

[0048] The compounds can be prepared by the general methods outlined in Schemes 1-15, shown in Figures 3-17, or by any other suitable method. In the description of Schemes 1-15 below, reference is made to representative compounds shown in Table 1 below and in Figures 2 and 18-21.

Table 1. Representative Compounds

No	Fig. 2 Struct	R	Formula	Mp (°C)	Analysis
1	A	4-OCF_3 (X=H)	$C_{13}H_{10}F_3N_3O_5$	170-172	C,H,N
2	A	4-OCH_2Ph (X=H)	$C_{19}H_{17}N_3O_5$	208-210	C,H,N
3	A	4-[(4-F)phenyl] (X=H)	$C_{18}H_{14}FN_3O_4$	224-226	
4	A	4-[(4-CF_3)phenyl] (X=H)	$C_{19}H_{14}F_3N_3O_4$	210-211	
5	A	4-[(4-OCF_3)phenyl] (X=H)	$C_{19}H_{14}F_3N_3O_5$	200-201	C,H,N
6	A	2-aza, 4-[(4-OCF_3)phenyl] (X=H)	$C_{18}H_{13}F_3N_4O_5$	127-130	
7	A	4-OCH_2Ph (X=Me)	$C_{20}H_{19}N_3O_5$	162-165	C,H,N
8	A	4-[(6-OMe)3-pyridyl)] (X=Me)	$C_{19}H_{18}N_4O_5$	217-219	C,H,N
9	A	4-[(4-CN)phenyl] (X=Me)	$C_{20}H_{16}N_4O_4$	180-181	C,H,N
10	A	4-[(4-F)phenyl] (X=Me)	$C_{19}H_{16}FN_3O_4$	180-181	C,H,N
11	A	4-[(4-CF_3)phenyl] (X=Me)	$C_{20}H_{16}F_3N_3O_4$	219-220	C,H,N
12	A	4-[(4-OCF_3)phenyl] (X=Me)	$C_{20}H_{16}F_3N_3O_5$	209-211	C,H,N
13	A	2-aza, 4-[(4-F)phenyl] (X=Me)	$C_{18}H_{15}FN_4O_4$	162-164	
14	A	2-aza, 4-[(4-OCF_3)phenyl] (X=Me)	$C_{19}H_{15}F_3N_4O_5$	172-174	C,H,N
15	A	3-aza, 4-[(4-F)phenyl] (X=Me)	$C_{18}H_{15}FN_4O_4$	180-181	
16	A	3-aza, 4-[(4-OCF_3)phenyl] (X=Me)	$C_{19}H_{15}F_3N_4O_5$	209-211	C,H,N
17	A	2,6-diaza, 4-[(4-F)phenyl] (X=Me)	$C_{17}H_{14}FN_5O_4$	196 dec	C,H,N
18	A	2,6-diaza, 4-[(4-OCF_3)phenyl] (X=Me)	$C_{18}H_{14}F_3N_5O_5$	227 dec	C,H,N
19	A	3,5-diaza, 4-[(4-F)phenyl] (X=Me)	$C_{17}H_{14}FN_5O_4$	201-203	
20	A	3,5-diaza, 4-[(4-OCF_3)phenyl] (X=Me)	$C_{18}H_{14}F_3N_5O_5$	223-225	C,H,N
21	A	2,5-diaza, 4-[(4-F)phenyl] (X=Me)	$C_{17}H_{14}FN_5O_4$	200-201	C,H,N
22	A	2,5-diaza, 4-[(4-OCF_3)phenyl)] (X=Me)	$C_{18}H_{14}F_3N_5O_5$	222-224	C,H,N
23	B	4-OCF_3 (X=H)	$C_{14}H_{12}F_3N_3O_5$	134-135	C,H,N
24	B	4-OCH_2Ph (X=H)	$C_{20}H_{19}N_3O_5$	123-124	C,H,N

25	B	4-OCF_3 (X=Me)	$C_{15}H_{14}F_3N_3O_5$	110-111	C,H,N
26	B	4-OCH_2Ph (X=Me)	$C_{21}H_{21}N_3O_5$	130-131	C,H,N
27	C	4-OCF_3 (X=H)	$C_{14}H_{12}F_3N_3O_5$	138-140	C,H,N
28	C	4-OCH_2Ph (X=H)	$C_{20}H_{19}N_3O_5$ ·0.25H_2O	222-224	C,H,N
29	C	4-[(4-F)phenyl] (X=H)	$C_{19}H_{16}FN_3O_4$	217-219	C,H,N
30	C	4-[(4-CF_3)phenyl] (X=H)	$C_{20}H_{16}F_3N_3O_4$	242-245	C,H,N
31	C	4-[(4-OCF_3)phenyl] (X=H)	$C_{20}H_{16}F_3N_3O_5$	197-199	C,H,N
32	C	2-aza, 4-[(4-F)phenyl] (X= H)	$C_{18}H_{15}FN_4O_4$	180-181	
33	C	2-aza, 4-[(4-OCF_3)phenyl] (X= H)	$C_{19}H_{15}F_3N_4O_5$	161-163	C,H,N
34	C	3-aza, 4-[(4-F)phenyl] (X= H)	$C_{18}H_{15}FN_4O_4$	204-206	
35	C	3-aza, 4-[(4-OCF_3)phenyl] (X= H)	$C_{19}H_{15}F_3N_4O_5$	161-163	C,H,N
36	C	4-OCF_3 (X=Me)	$C_{15}H_{14}F_3N_3O_5$	134-136	C,H,N
37	C	4-OCH_2Ph (X=Me)	$C_{21}H_{21}N_3O_5$	174-176	C,H,N
38	C	4-[(4-F)phenyl] (X=Me)	$C_{20}H_{18}FN_3O_4$	160-162	C,H,N
39	C	4-[(4-CF_3)phenyl] (X= Me)	$C_{21}H_{18}F_3N_3O_4$	196-198	C,H,N
40	C	4-[(4-OCF_3)phenyl] (X= Me)	$C_{21}H_{18}F_3N_3O_5$	186-188	C,H,N
41	C	2-aza, 4-[(4-F)phenyl] (X=Me)	$C_{19}H_{17}FN_4O_4$	145-147	C,H,N
42	C	2-aza, 4-[(4-CF_3)phenyl] (X= Me)	$C_{20}H_{17}F_3N_4O_4$	212-214	C,H,N
43	C	2-aza, 4-[(4-OCF_3)phenyl] (X= Me)	$C_{20}H_{17}F_3N_4O_5$	195-198	C,H,N
44	C	3-aza, 4-[(4-F)phenyl] (X=Me)	$C_{19}H_{17}FN_4O_4$	203-204	C,H,N
45	C	3-aza, 4-[(4-CF_3)phenyl] (X= Me)	$C_{20}H_{17}F_3N_4O_4$	215-217	C,H,N
46	C	3-aza, 4-[(4-OCF_3)phenyl] (X= Me)	$C_{20}H_{17}F_3N_4O_5$	202-203	C,H,N
47	D	3-OCF_3 (X=H)	$C_{15}H_{14}F_3N_3O_5$	100-112	C,H,N
48	D	4-OCF_3 (X=H)	$C_{15}H_{14}F_3N_3O_5$	158-160	C,H,N
49	D	4-OCH_2Ph (X=H)	$C_{21}H_{21}N_3O_5$	151-153	C,H,N
50	D	3-[(4-OCF_3)phenyl] (X=H)	$C_{21}H_{18}F_3N_3O_5$	117-119	C,H,N
51	D	4-[(4-OCF_3)phenyl] (X=H)	$C_{21}H_{18}F_3N_3O_5$	159-161	C,H,N
52	D	3-OCF_3 (X=Me)	$C_{16}H_{16}F_3N_3O_5$	108-110	C,H,N
53	D	4-OCF_3 (X=Me)	$C_{16}H_{16}F_3N_3O_5$	100-101	C,H,N
54	D	4-OCH_2Ph (X=Me)	$C_{22}H_{23}N_3O_5$	109-111	C,H,N
55	D	3-[(4-OCF_3)phenyl] (X=Me)	$C_{22}H_{20}F_3N_3O_5$	80-82	C,H,N
56	D	4-[(4-OCF_3)phenyl] (X=Me) (rac)	$C_{22}H_{20}F_3N_3O_5$	150-152	C,H,N
57	D	4-[(4-OCF_3)phenyl] (X=Me) (7-*R*)	$C_{22}H_{20}F_3N_3O_5$	165-167	C,H,N
58	D	4-[(4-OCF_3)phenyl] (X=Me) (7-*S*)	$C_{22}H_{20}F_3N_3O_5$	162-164	C,H,N

59	E	4-OCF$_3$ (rac)	$C_{14}H_{12}F_3N_3O_5$	141-143	C,H,N
60	E	4-OCF$_3$ (6-*R*)	$C_{14}H_{12}F_3N_3O_5$	138-139	C,H,N
61	E	4-OCF$_3$ (6-*S*)	$C_{14}H_{12}F_3N_3O_5$	139-140	C,H,N
62	E	4-[(4-F)phenyl]	$C_{19}H_{16}FN_3O_4$	201-203	C,H,N
63	E	4-[(4-CF$_3$)phenyl]	$C_{20}H_{16}F_3N_3O_4$	218-221	C,H,N
64	E	4-[(4-OCF$_3$)phenyl]	$C_{20}H_{16}F_3N_3O_5$	192-194	C,H,N
65	E	2-aza, 4-[(4-F)phenyl]	$C_{18}H_{15}FN_4O_4$	160-161	C,H,N
66	E	2-aza, 4-[(4-CF$_3$)phenyl]	$C_{19}H_{15}F_3N_4O_4$	180-182	C,H,N
67	E	2-aza, 4-[(4-OCF$_3$)phenyl]	$C_{19}H_{15}F_3N_4O_5$	182-183	C,H,N
68	E	3-aza, 4-[(4-F)phenyl]	$C_{18}H_{15}FN_4O_4$	214-216	C,H,N
69	E	3-aza, 4-[(4-CF$_3$)phenyl]	$C_{19}H_{15}F_3N_4O_4$	233-235	C,H,N
70	E	3-aza, 4-[(4-OCF$_3$)phenyl]	$C_{19}H_{15}F_3N_4O_5$	180-181	C,H,N
71	F	3-OCF$_3$	$C_{15}H_{14}F_3N_3O_5$	60-61	C,H,N
72	F	4-OCF$_3$	$C_{15}H_{14}F_3N_3O_5$	92-93	C,H,N
73	F	4-OCH$_2$Ph	$C_{21}H_{21}N_3O_5$	150-151	C,H,N
74	F	3-[(4-OCF$_3$)phenyl]	$C_{21}H_{18}F_3N_3O_5$	78-80	C,H,N
75	F	4-[(4-OCF$_3$)phenyl]	$C_{21}H_{18}F_3N_3O_5$	135-138	C,H,N

[0049] In Scheme 1, shown in Figure 3, reagents and conditions were (i) RPhOH, K_2CO_3, acetone, reflux, 36-52 h; (ii) **77**, **78**, or **79**, DIPEA, 105 °C, 6.5-12 h; (iii) NaH, DMF, 0 °C, 45 min; (iv) NaH, DMF, 0 °C, 80 min, then 17 °C, 60 min; (v) $ArB(OH)_2$, 2M Na_2CO_3, toluene, EtOH, DMF, Pd(dppf)Cl_2 under N_2, 88-90 °C, 50-90 min. Base-catalysed reactions of 2-bromo-4(5)-nitroimidazole (**80**) or 2-chloro-4(5)-nitroimidazole (**81**) with epoxides **77-79** [prepared by alkylation of the appropriate 4-substituted phenols with 2-(bromomethyl)oxirane (**76**)] gave alcohols **82-84**, which underwent NaH-assisted ring closure reactions to give compounds **1** and **2** of Table 1, and iodide **85**, respectively. Suzuki couplings of **85** with arylboronic acids then gave compounds **3-5** of Table 1.

[0050] In Scheme 2, shown in Figure 4, reagents and conditions were (i) 70 °C, 16 h; (ii) NaH, DMF, -20 to -10 °C, 50 min; (iii) 1% HCl in 95% EtOH, 20 °C, 6 h, then 4 °C, 2.5 d; (iv) 4-$OCF_3PhB(OH)_2$, 2M Na_2CO_3, toluene, EtOH, Pd(dppf)Cl_2 under N_2, 85-88 °C, 3 h; (v) **90**, NaH, DMF, 0-20 °C, 2.5 h. Reaction of 2,4-dinitroimidazole (**86**) with epoxide **87** gave alcohol **88**, which underwent NaH-assisted ring closure, followed by acid-catalysed desilylation, to give alcohol **90**. NaH-assisted alkylation of **90** with fluoropyridine **92** [prepared by Suzuki coupling of 5-bromo-2-fluoropyridine (**91**) with 4-(trifluoromethoxy)phenylboronic acid] then gave compound **6** of Table 1.

[0051] In Scheme 3, shown in Figure 5, reagents and conditions were (i) 4-BnOPhOH, K_2CO_3, acetone, reflux, 24 h; (ii) *m*-CPBA, Na_2HPO_4, CH_2Cl_2, 0-20 °C, 3.5 h; (iii) 4-IPhOH, K_2CO_3, NaI, DMF, 70-73 °C, 32 h; (iv) **80**, DIPEA, 107 °C, 14-15 h; (v) NaH, DMF, 0 °C, 50-75 min; (vi) $ArB(OH)_2$, 2M Na_2CO_3, toluene, EtOH, Pd(dppf)Cl_2 under N_2, 90 °C, 45 min. Base-catalysed reactions of 2-bromo-4(5)-nitroimidazole (**80**) with epoxides **95** and **96** [prepared by methallylation of 4-(benzyloxy)phenol with chloride **93**, followed by epoxidation, or by alkylation of 4-iodophenol with 2-(chloromethyl)-2-methyloxirane (**97**)] gave alcohols **98** and **99**, which underwent NaH-assisted ring closure reactions to give compound **7** of Table 1, and iodide **100**, respectively. Suzuki couplings of **100** with arylboronic acids then gave compounds **8-12** of Table 1.

[0052] In Scheme 4, shown in Figure 6, reagents and conditions were (i) TFA, anisole, CH_2Cl_2, 20 °C, 4 h; (ii) **91** or 5-Br,2-Clpyrimidine or 2,5-diBrpyrazine, NaH, DMF, 0-20 °C, 2-3 h; (iii) $ArB(OH)_2$, 2M Na_2CO_3, toluene, EtOH, (DMF), Pd(dppf)Cl_2 under N_2, 89-90 °C, 1.8-3 h. NaH-assisted alkylations of alcohol **101** [prepared from compound **26** by acid-catalysed cleavage of the 4-(benzyloxy)benzyl ether side chain] with 5-bromo-2-fluoropyridine (**91**), 5-bromo-2-chloropyrimidine, and 2,5-dibromopyrazine gave bromides **102-104**, which underwent Suzuki couplings with arylboronic acids to give compounds **13**, **14**, **17**, **18**, **21** and **22** of Table 1.

[0053] In Scheme 5, shown in Figure 7, reagents and conditions were (i) 6-Br-3-pyridinol, NaH, DMF, 0-20 °C, 10 min, then 50 °C, 4 h; (ii) $ArB(OH)_2$, 2M Na_2CO_3, toluene, EtOH, DMF, Pd(dppf)Cl_2 under N_2, 90 °C, 3 h; (iii) $EtOCH_2Cl$, K_2CO_3, DMF, 20 °C, 16 h; (iv) $ArB(OH)_2$, 2M Na_2CO_3, toluene, EtOH, Pd(dppf)Cl_2 under N_2, 86 °C, 2-2.5 h; (v) 1.25M HCl in MeOH, 20 °C, 0-12 h, then 53 °C, 2-4 h; (vi) **111** or **112**, NaH, DMF, 0-20 °C, 10-30 min, then 50-60 °C, 3 h; (vii) NaH, DMF, 0 °C, 35-80 min. Base-catalysed reaction of epoxide **105** (obtained in 2 steps from **80**, via epoxidation of the corresponding alkene, as reported by Ding et al., WO 2008008480A2) with 6-bromo-3-pyridinol gave bromide **106**, which underwent Suzuki couplings with arylboronic acids to give compounds **15** and **16** of Table 1. Similar reactions of **105** with arylpyrimidinols **111** and **112** [prepared from 2-chloro-5-pyrimidinol (**107**) via successive ethoxymethyl protection of the hydroxyl group, Suzuki couplings with arylboronic acids, followed by acid-catalysed removal of the protecting group] gave mixtures of the precursor alcohols (**113** or **114**) and final compounds **19** or **20** of Table 1. NaH-assisted ring closure of these mixtures (or preferably of the purified alcohols **113** or **114**) then gave compounds **19** and **20** of Table 1.

[0054] In Scheme 6, shown in Figure 8, reagents and conditions were (i) 4-OCF_3BnBr or 4-BnOBnCl, NaH, DMF, 0-20 °C, 7-21 h; (ii) **80**, DIPEA, 107-108 °C, 13-16 h; (iii) NaH, DMF, 0 °C, 65-80 min; (iv) *m*-CPBA, Na_2HPO_4, CH_2Cl_2, 0-20 °C, 2.5-3.5 h. NaH-assisted alkylations of glycidol (**115**) with substituted benzyl halides gave epoxides **116** and **117**, which underwent successive base-catalysed reaction with 2-bromo-4(5)-nitroimidazole (**80**), followed by NaH-assisted ring closure of the intermediate alcohols (**118** and **119**), to give compounds **23** and **24** of Table 1. Similar reactions of epoxides **123** and **124** [prepared from 2-methyl-2-propen-1-ol (**120**) via alkylation with substituted benzyl halides, followed by epoxidation] with **80** gave the alcohols **125** and **126**, which also underwent NaH-assisted ring closure reactions to give compounds **25** and **26** of Table 1.

[0055] In Scheme 7, shown in Figure 9, reagents and conditions were (i) $Br(CH_2)_2CH{=}CH_2$, K_2CO_3, DMF, 66-73 °C, 4.5-12 h; (ii) *m*-CPBA, Na_2HPO_4, CH_2Cl_2, 0-20 °C, 50 h; (iii) 4-OCF_3PhOH, K_2CO_3, MEK, 81 °C, 12 h; (iv) NaH, DMF, 0-20 °C, 2-2.5 h; (v) OsO_4, NMO, CH_2Cl_2, 20 °C, 4 h; (vi) TIPSCl, imidazole, DMF, 20 °C, 18 h; (vii) 1% HCl in 95% EtOH, 20 °C, 35 h; (viii) 4-BnOPhOH or 4-IPhOH, DEAD, PPh_3, THF, 0-20 °C, 32-51 h; (ix) $ArB(OH)_2$, 2M Na_2CO_3, toluene, EtOH, DMF, Pd(dppf)Cl_2 under N_2, 90 °C, 90 min. Base-catalysed reaction of epoxide **129** [prepared from 2-chloro-4(5)-nitroimidazole (**81**) via alkylation with 4-bromo-1-butene, followed by epoxidation] with 4-trifluoromethoxyphenol gave alcohol **130**, which underwent NaH-assisted ring closure to give compound **27** of Table 1. Similar ring closure of mono-protected diol **132** [prepared from 2-bromo-4(5)-nitroimidazole (**80**) via alkylation with 4-bromo-1-butene, followed by dihydroxylation and TIPS protection of the primary alcohol] and acid-catalysed desilylation yielded alcohol **134**. Mitsunobu reactions of **134** with the appropriate phenols gave compound **28** of Table 1 and iodide **135**. Suzuki couplings of **135** with arylboronic acids then gave compounds **29-31** of Table 1.

[0056] In Scheme 8, shown in Figure 10, reagents and conditions were (i) **91**, NaH, DMF, 0-20 °C, 2.5 h; (ii) $ArB(OH)_2$, 2M Na_2CO_3, toluene, EtOH, DMF, Pd(dppf)Cl_2 under N_2, 90 °C, 2.5 h; (iii) 6-Br-3-pyridinol, K_2CO_3, MEK, 82-85 °C, 28 h; (iv) NaH, DMF, 0-20 °C, 2.5 h. NaH-assisted alkylation of alcohol **134** with 5-bromo-2-fluoropyridine (**91**) gave bromide **136**, which underwent Suzuki couplings with arylboronic acids to give compounds **32** and **33** of Table 1. Alternatively, base-catalysed reaction of epoxide **129** with 6-bromo-3-pyridinol, followed by NaH-assisted ring closure of the resulting alcohol **137**, gave bromide **138**, which also underwent Suzuki couplings with arylboronic acids to give compounds **34** and **35** of Table 1.

[0057] In Scheme 9, shown in Figure 11, reagents and conditions were (i) $I(CH_2)_2C(CH_3)=CH_2$, K_2CO_3, DMF, 61 °C, 20 h; (ii) *m*-CPBA, Na_2HPO_4, CH_2Cl_2, 0-20 °C, 4 h; (iii) RPhOH, K_2CO_3, MEK, 82-83 °C, 8-10 h; (iv) NaH, DMF, 0-20 °C, 2-2.5 h; (v) $ArB(OH)_2$, 2M Na_2CO_3, toluene, EtOH, DMF, Pd(dppf)Cl_2 under N_2, 90 °C, 100-105 min. Base-catalysed reactions of epoxide **140** [prepared from 2-chloro-4(5)-nitroimidazole (**81**) via alkylation with 4-iodo-2-methyl-1-butene (obtained by iodination of 3-methyl-3-buten-1-ol, as reported by Helmboldt et al., 2006), followed by epoxidation] with the appropriate phenols gave alcohols **141-143**, which underwent NaH-assisted ring closure reactions to give compounds **36** and **37** of Table 1 and iodide **144**, respectively. Suzuki couplings of **144** with arylboronic acids then gave compounds **38-40** of Table 1.

[0058] In Scheme 10, shown in Figure 12, reagents and conditions were (i) $I(CH_2)_2C(CH_3)=CH_2$, K_2CO_3, DMF, 60 °C, 11 h; (ii) OsO_4, NMO, CH_2Cl_2, 20 °C, 4 h; (iii) TIPSCl, imidazole, DMF, 20 °C, 6 d; (iv) NaH, DMF, 0-20 °C, 2.5 h, then 46 °C, 3.2 h; (v) 1% HCl in 95% EtOH, 44 °C, 3 d; (vi) **91**, NaH, DMF, 0-20 °C, 2.5 h; (vii) $ArB(OH)_2$, 2M Na_2CO_3, toluene, EtOH, DMF, Pd(dppf)Cl_2 under N_2, 90 °C, 120-135 min; (viii) 6-Br-3-pyridinol, K_2CO_3, MEK, 84 °C, 18.5 h; (ix) NaH, DMF, 0-20 °C, 2.5 h. NaH-assisted ring closure of mono-protected diol **147** [prepared from 2-bromo-4(5)-nitroimidazole (**80**) via alkylation with 4-iodo-2-methyl-1-butene (obtained by iodination of 3-methyl-3-buten-1-ol, as reported by Helmboldt et al., 2006), followed by dihydroxylation and TIPS protection of the primary alcohol] and acid-catalysed desilylation yielded alcohol **149**. NaH-assisted alkylation of **149** with 5-bromo-2-fluoropyridine (**91**) gave bromide **150**, which underwent Suzuki couplings with arylboronic acids to give compounds **41-43** of Table 1. Alternatively, base-catalysed reaction of epoxide **140** with 6-bromo-3-pyridinol, followed by NaH-assisted ring closure of the resulting alcohol **151**, gave bromide **152**, which also underwent Suzuki couplings with arylboronic acids to give compounds **44-46** of Table 1.

[0059] In Scheme 11, shown in Figure 13, reagents and conditions were (i) RBnBr or 4-BnOBnCl, NaH, DMF, 0-20 °C, 2.5-7 h; (ii) 4-$OCF_3PhB(OH)_2$, 2M Na_2CO_3, toluene, EtOH, Pd(dppf)Cl_2 under N_2, 90 °C, 20-25 min. NaH-assisted alkylations of alcohols **134** and **149** with substituted benzyl halides gave compounds **47-49** and **52-54** of Table 1 and iodides **153-156**. Suzuki couplings of **153-156** with 4-trifluoromethoxyphenylboronic acid then gave compounds **50**, **51**, **55** and **56** of Table 1.

[0060] In Scheme 12, shown in Figure 14, reagents and conditions were (i) Ac_2O, pyridine, 20 °C, 38 h; (ii) preparative chiral HPLC (ChiralPak IA, 40% EtOH/hexane); (iii) K_2CO_3, aq MeOH, 20 °C, 4 h; (iv) 4-BrBnBr, NaH, DMF, 0-20 °C, 3 h; (v) 4-$OCF_3PhB(OH)_2$, 2M Na_2CO_3, toluene, EtOH, Pd(dppf)Cl_2 under N_2, 88 °C, 75 min. Preparative chiral HPLC of racemic acetate **157** [obtained from alcohol **149** by acetylation] gave the enantiomers **158** and **161**, which were hydrolysed to the enantiomeric alcohols **159** and **162**. NaH-assisted alkylations of these alcohols with 4-bromobenzyl bromide gave the bromides **160** and **163**, which were Suzuki coupled with 4-trifluoromethoxyphenylboronic acid to give compounds **57** and **58** of Table 1.

[0061] In Scheme 13, shown in Figure 15, reagents and conditions were (i) I_2, PPh_3, imidazole, CH_2Cl_2, 0-8 °C, 5 h; (ii) RPhOH, K_2CO_3, acetone, 50 °C, 6-11 h; (iii) I_2, $NaBH_4$, THF, 0 °C, 3-4 h, then 20 °C, 13 h, then 30% H_2O_2, 3N NaOH, 0-20 °C, 3 h; (iv) I_2, PPh_3, imidazole, CH_2Cl_2, 20 °C, 12-15 h; (v) **80**, K_2CO_3, DMF, 84-88 °C, 33-37 h; (vi) 1% HCl in 95% EtOH, 20 °C, 7-12 h; (vii) NaH, DMF, 0-20 °C, 4-5 h; (viii) preparative chiral HPLC (ChiralPak IA, 27% EtOH/hexane); (ix) $ArB(OH)_2$, 2M Na_2CO_3, toluene, EtOH, DMF, Pd(dppf)Cl_2 under N_2, 90 °C, 90 min. Hydroboration of alkenes **166** and **167** [prepared by alkylation of the appropriate phenols with iodide **165**, obtained by iodination of 2-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-2-propen-1-ol (**164**) (reported by Chen et al., US 2007213341 A1, by monosilylation of 2-methylene-1,3-

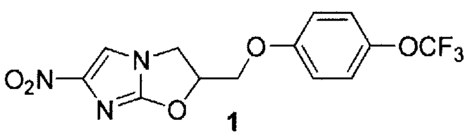
propanediol)] gave the alcohols **168** and **169**, which were converted into iodides **170** and **171**. Alkylation of 2-bromo-4(5)-nitroimidazole (**80**) with these iodides, acid-catalysed desilylation, and NaH-assisted ring closure of the resulting alcohols **174** and **175** then gave compound **59** of Table 1 and iodide **176**, respectively. Suzuki couplings of **176** with arylboronic acids also gave compounds **62-64** of Table 1.

[0062] In Scheme 14, shown in Figure 16, reagents and conditions were (i) **80**, K_2CO_3, DMF, 82 °C, 24 h; (ii) 1% HCl in 95% EtOH, 20 °C, 4 h, then 4 °C, 12 h; (iii) NaH, DMF, 0-20 °C, 3.5 h; (iv) **91**, NaH, DMF, 0-20 °C, 3 h; (v) $ArB(OH)_2$, 2M Na_2CO_3, toluene, EtOH, DMF, $Pd(dppf)Cl_2$ under N_2, 90 °C, 2-2.5 h; (vi) RBnBr or 4-BnOBnI, NaH, DMF, 0-20 °C, 0.5-3 h; (vii) 4-$OCF_3PhB(OH)_2$, 2M Na_2CO_3, toluene, EtOH, $Pd(dppf)Cl_2$ under N_2, 90 °C, 20 min. Alkylation of 2-bromo-4(5)-nitroimidazole (**80**) with known iodide **177** (reported by Curran et al., 1998 in 4 steps from 2-methylene-1,3-propanediol) and acid-catalysed desilylation of the product (**178**) gave the diol **179**, which underwent NaH-assisted ring closure to give alcohol **180**. NaH-assisted alkylation of **180** with 5-bromo-2-fluoropyridine (**91**) gave bromide **181**, which underwent Suzuki couplings with arylboronic acids to give compounds **65-67** of Table 1. Similar alkylations of alcohol **180** with the appropriately substituted benzyl halides gave compounds **71-73** of Table 1, as well as iodobenzyl ethers **182** and **183**. Suzuki couplings of **182** and **183** with 4-(trifluoromethoxy)phenylboronic acid then gave compounds **74** and **75** of Table 1.

[0063] In Scheme 15, shown in Figure 17, reagents and conditions were (i) 6-Br-3-pyridinol, DEAD, PPh_3, THF, 0 °C, 1 h, then 20 °C, 41 h; (ii) 1% HCl in 95% EtOH, 20 °C, 13 h; (iii) NaH, THF, 20 °C, 1 h, then TBDMSCl, 20 °C, 100 min; (iv) I_2, PPh_3, imidazole, CH_2Cl_2, 20 °C, 18 h; (v) **80**, K_2CO_3, DMF, 87 °C, 42 h; (vi) TBAF, THF, 20 °C, 4 h; (vii) NaH, DMF, 0-20 °C, 200 min; (viii) $ArB(OH)_2$, 2M Na_2CO_3, toluene, EtOH, DMF, $Pd(dppf)Cl_2$ under N_2, 90 °C, 140 min. Mitsunobu reaction of 6-bromo-3-pyridinol with known alcohol **184** (reported by Kim et al., 2001, via silylation and hydroboration of 2-methylene-1,3-propanediol), and acid-catalysed desilylation of the product (**185**) gave the diol **186**. Monosilylation of **186** gave alcohol **187**, which was converted into iodide **188**. Alkylation of 2-bromo-4(5)-nitroimidazole (**80**) with **188**, desilylation, and NaH-assisted ring closure of the resulting alcohol **190** gave bromide **191**. Suzuki couplings of **191** with arylboronic acids then gave compounds **68-70** of Table 1.

EXAMPLE 2. METHODS OF PREPARATION

[0064] A. Synthesis of 6-nitro-2-{[4-(trifluoromethoxy)phenoxy]methyl}-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (compound 1 of Table 1) by the method of Scheme 1.



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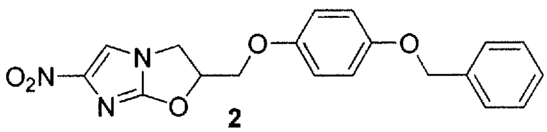
[0065] A mixture of 4-trifluoromethoxyphenol (0.152 mL, 1.17 mmol), K_2CO_3 (260 mg, 1.17 mmol) and 2-(bromomethyl)oxirane (**76**) (0.30 mL, 3.51 mmol) in anhydrous acetone (3 mL) was stirred in a sealed vial at 59 °C for 36 h. The resulting mixture was filtered, washing with CH_2Cl_2, and then the filtrate was evaporated to dryness and the residue was chromatographed on silica gel. Elution with 0-15% CH_2Cl_2/pentane firstly gave foreruns, and then further elution with 20-25% CH_2Cl_2/pentane gave 2-{[4-(trifluoromethoxy)phenoxy]methyl}oxirane (**77**) (similarly prepared by Cao et al., WO 2008112483A2 using epichlorohydrin) (260 mg, 95%) as an oil; ^{1}H NMR ($CDCl_3$) δ 7.14 (br dd, *J* = 9.0, 0.6 Hz, 2 H), 6.91 (dt, *J* = 9.1, 3.0 Hz, 2 H), 4.23 (dd, *J* = 11.1, 3.1 Hz, 1 H), 3.94 (dd, *J* = 11.1, 5.7 Hz, 1 H), 3.34 (m, 1 H), 2.91 (dd, *J* = 4.8, 4.2 Hz, 1 H), 2.75 (dd, *J* = 4.9, 2.6 Hz, 1 H).

[0066] A mixture of epoxide **77** (200 mg, 0.854 mmol), 2-bromo-4(5)-nitroimidazole (**80**) (180 mg, 0.938 mmol) and diisopropylethylamine (0.75 mL, 4.31 mmol) was stirred in a sealed vial at 105 °C for 6.5 h, and then cooled. The product was dissolved in CH_2Cl_2 (15 mL), washed with aqueous $NaHCO_3$ (15 mL) and the aqueous portion was further extracted with CH_2Cl_2 (4x 15 mL). The combined organic extracts were evaporated to dryness and the residue was chromatographed on silica gel. Elution with CH_2Cl_2 firstly gave foreruns, and then further elution with 0-1% EtOAc/CH_2Cl_2 gave 1-(2-bromo-4-nitro-1*H*-imidazol-1-yl)-3-[4-(trifluoromethoxy)phenoxy]-2-propanol (**82**) (255 mg, 70%) as a white solid: mp (MeOH/CH_2Cl_2/hexane) 139-141 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.52 (s, 1 H), 7.30 (br dd, *J* = 9.1, 0.7 Hz, 2 H), 7.05 (dt, *J* = 9.2, 3.1 Hz, 2 H), 5.66 (br s, 1 H), 4.28 (dd, *J* = 13.3, 3.3 Hz, 1 H), 4.21 (m, 1 H), 4.13 (dd, *J* = 13.3, 8.0 Hz, 1 H), 4.01 (d, *J* = 5.0 Hz, 2 H). Anal. ($C_{13}H_{11}BrF_3N_3O_5$) C, H, N.

[0067] A solution of alcohol **82** (242 mg, 0.568 mmol) in anhydrous DMF (5 mL) under N_2 at 0 °C was treated with 60% NaH (36 mg, 0.90 mmol), then quickly degassed and resealed under N_2. After stirring at 0 °C for 45 min, the reaction was cooled (CO_2/acetone), quenched with ice/aqueous $NaHCO_3$ (15 mL), added to brine (40 mL), and extracted with CH_2Cl_2 (6x 50 mL). The combined extracts were evaporated to dryness and the residue was chromatographed on silica gel, eluting with CH_2Cl_2, to give **1** (171 mg, 87%) as a cream solid: mp ($MeOH/CH_2Cl_2$/hexane) 170-172 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.16 (s, 1 H), 7.31 (br dd, J = 9.1, 0.8 Hz, 2 H), 7.05 (dt, J = 9.2, 3.1 Hz, 2 H), 5.74 (m, 1 H), 4.50 (dd, J = 10.8, 8.9 Hz, 1 H), 4.46 (dd, J = 11.5, 2.8 Hz, 1 H), 4.39 (dd, J = 11.5, 5.2 Hz, 1 H), 4.22 (dd, J = 10.8, 6.5 Hz, 1 H). Anal. ($C_{13}H_{10}F_3N_3O_5$) C, H, N.

[0068] B. Synthesis of 2-{[4-(benzyloxy)phenoxy]methyl}-6-nitro-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (compound 2 of Table 1) by the method of Scheme 1.



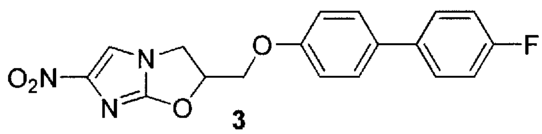
2

[0069] Alkylation of 4-(benzyloxy)phenol with 2-(bromomethyl)oxirane (**76**) as in Example 2A, followed by chromatography of the product on silica gel, eluting with 0-25% CH_2Cl_2/petroleum ether (foreruns) and then with 25% CH_2Cl_2/petroleum ether, gave 2-{[4-(benzyloxy)phenoxy]methyl}oxirane (**78**) (reported by Kopka et al., 2003 using epichlorohydrin) (79%) as a white solid: mp (CH_2Cl_2/pentane) 61-62 °C; ^{1}H NMR ($CDCl_3$) δ 7.44-7.28 (m, 5 H), 6.90 (dt, J = 9.3, 2.8 Hz, 2 H), 6.85 (dt, J = 9.3, 2.8 Hz, 2 H), 4.16 (dd, J = 11.1, 3.3 Hz, 1 H), 3.92 (dd, J = 11.1, 5.6 Hz, 1 H), 3.32 (m, 1 H), 2.89 (dd, J = 4.8, 4.3 Hz, 1 H), 2.73 (dd, J = 5.0, 2.7 Hz, 1 H).

[0070] Reaction of epoxide **78** with 2-bromo-4(5)-nitroimidazole (**80**) as in Example 2A for 12 h, followed by chromatography of the product on silica gel, eluting with CH_2Cl_2 (foreruns) and then with 1-2% EtOAc/CH_2Cl_2, gave 1-[4-(benzyloxy)phenoxy]-3-(2-bromo-4-nitro-1*H*-imidazol-1-yl)-2-propanol (**83**) (74%) as a pale yellow solid: mp ($MeOH/CH_2Cl_2$/hexane) 160-162 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.50 (s, 1 H), 7.46-7.28 (m, 5 H), 6.94 (dt, J = 9.2, 2.9 Hz, 2 H), 6.88 (dt, J = 9.2, 2.9 Hz, 2 H), 5.60 (br d, J = 4.6 Hz, 1 H), 5.04 (s, 2 H), 4.27 (dd, J = 13.0, 2.7 Hz, 1 H), 4.16 (m, 1 H), 4.11 (dd, J = 13.1, 8.2 Hz, 1 H), 3.93 (dd, J = 10.0, 4.8 Hz, 1 H), 3.89 (dd, J = 10.1, 5.3 Hz, 1 H). Anal. ($C_{19}H_{18}BrN_3O_5$) C, H, N.

[0071] Ring closure of alcohol **83** with NaH as in Example 2A, followed by chromatography of the product on silica gel, eluting with CH_2Cl_2 (foreruns) and then with 1-2% MeOH/CH_2Cl_2, gave **2** (94%) as a cream solid: mp (CH_2Cl_2/hexane) 208-210 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.15 (s, 1 H), 7.45-7.28 (m, 5 H), 6.95 (dt, J = 9.2, 3.0 Hz, 2 H), 6.88 (dt, J = 9.2, 3.0 Hz, 2 H), 5.70 (m, 1 H), 5.05 (s, 2 H), 4.48 (dd, J = 10.7, 8.9 Hz, 1 H), 4.35 (dd, J = 11.6, 2.8 Hz, 1 H), 4.28 (dd, J = 11.6, 5.1 Hz, 1 H), 4.20 (dd, J = 10.8, 6.5 Hz, 1 H). Anal. ($C_{19}H_{17}N_3O_5$) C, H, N.

[0072] C. Synthesis of 2-{[(4'-fluoro[1,1'-biphenyl]-4-yl)oxy]methyl}-6-nitro-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (compound 3 of Table 1) by the method of Scheme 1.



3

[0073] Alkylation of 4-iodophenol with 2-(bromomethyl)oxirane (**76**) as in Example 2A for 52 h, followed by chromatography of the product on silica gel, eluting with 0-10% CH_2Cl_2/petroleum ether (foreruns) and then with 20-25% CH_2Cl_2/petroleum ether, gave 2-[(4-iodophenoxy)methyl]oxirane (**79**) (reported by Apparu et al., 2000 using glycidyl tosylate) (89%) as a white solid: mp (CH_2Cl_2/ petroleum ether) 67-68 °C; ^{1}H NMR ($CDCl_3$) δ 7.56 (dt, J = 9.0, 2.7 Hz, 2 H), 6.70 (dt, J = 9.0, 2.7 Hz, 2 H), 4.20 (dd, J = 11.1, 3.1 Hz, 1 H), 3.92 (dd, J = 11.1, 5.7 Hz, 1 H), 3.33 (m, 1 H), 2.90 (dd, J = 4.8, 4.3 Hz, 1 H), 2.74 (dd, J = 4.9, 2.6 Hz, 1 H).

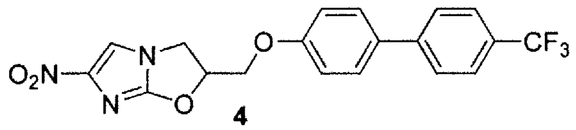
[0074] Reaction of epoxide **79** with 2-chloro-4(5)-nitroimidazole (**81**) and diisopropylethylamine as in Example 2A (but extracting the aqueous wash 6 times with 10% MeOH/CH_2Cl_2), followed by chromatography of the product on silica gel, eluting with 0-0.5% MeOH/CH_2Cl_2 (foreruns) and then with 0.5-1% MeOH/CH_2Cl_2, gave 1-(2-chloro-4-nitro-1*H*-imidazol-1-yl)-3-(4-iodophenoxy)-2-propanol (**84**) (83%) as a yellow solid: mp (MeOH/H_2O)

174-176 °C; [1]H NMR [$(CD_3)_2SO$] δ 8.49 (s, 1 H), 7.60 (dt, *J* = 8.9, 2.7 Hz, 2 H), 6.81 (dt, *J* = 9.0, 2.7 Hz, 2 H), 5.66 (br s, 1 H), 4.28 (dd, *J* = 12.8, 2.6 Hz, 1 H), 4.19 (m, 1 H), 4.14 (dd, *J* = 12.9, 8.0 Hz, 1 H), 3.97 (d, *J* = 4.6 Hz, 2 H); HRESIMS calcd for $C_{12}H_{11}ClIN_3NaO_4$ *m/z* $[M + Na]^+$ 447.9346, 445.9375, found 447.9322, 445.9366.

[0075] Ring closure of alcohol **84** with NaH as in Example 2A at 0 °C for 80 min and then at 17 °C for 60 min, followed by chromatography of the product on silica gel, eluting with 0-40% EtOAc/petroleum ether (foreruns) and then with 40% EtOAc/petroleum ether and 0-0.5% $MeOH/CH_2Cl_2$, gave 2-[(4-iodophenoxy)methyl]-6-nitro-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (**85**) (77%) as a pale yellow solid: mp ($MeOH/CH_2Cl_2$/hexane) 198-199 °C ; [1]H NMR [$(CD_3)_2SO$] δ 8.15 (s, 1 H), 7.61 (dt, *J* = 8.9, 2.6 Hz, 2 H), 6.80 (dt, *J* = 9.0, 2.6 Hz, 2 H), 5.72 (m, 1 H), 4.49 (dd, *J* = 10.7, 9.0 Hz, 1 H), 4.41 (dd, *J* = 11.6, 2.7 Hz, 1 H), 4.35 (dd, *J* = 11.6, 5.2 Hz, 1 H), 4.20 (dd, *J* = 10.8, 6.5 Hz, 1 H). Anal. ($C_{12}H_{10}IN_3O_4$) C, H, N.

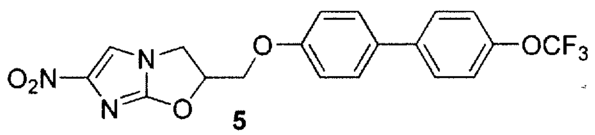
[0076] A stirred mixture of iodide **85** (250 mg, 0.646 mmol), 4-fluorophenylboronic acid (163 mg, 1.16 mmol) and $Pd(dppf)Cl_2$ (95 mg, 0.13 mmol) in DMF (5.6 mL), toluene (4.4 mL) and EtOH (2.5 mL) was degassed for 11 min (vacuum pump) and then N_2 was added. An aqueous solution of 2M Na_2CO_3 (1.3 mL, 2.6 mmol) was added by syringe and the stirred mixture was again degassed for 11 min, and then N_2 was added. The resulting mixture was stirred at 88 °C for 70 min, and then cooled, diluted with aqueous $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (6x 50 mL). The extracts were evaporated to dryness and the residue was chromatographed on silica gel, eluting with 0-0.5% $MeOH/CH_2Cl_2$ (foreruns) and then with 0.5% $MeOH/CH_2Cl_2$, to give **3** (191 mg, 83%) as a pale brown solid: mp ($MeOH/CH_2Cl_2$/hexane) 224-226 °C; [1]H NMR [$(CD_3)_2SO$] δ 8.18 (s, 1 H), 7.65 (ddt, *J* = 8.9, 5.4, 2.7 Hz, 2 H), 7.59 (dt, *J* = 8.8, 2.6 Hz, 2 H), 7.25 (tt, *J* = 8.9, 2.7 Hz, 2 H), 7.03 (dt, *J* = 8.8, 2.6 Hz, 2 H), 5.76 (m, 1 H), 4.51 (dd, *J* = 10.8, 9.0 Hz, 1 H), 4.47 (dd, *J* = 11.6, 2.8 Hz, 1 H), 4.41 (dd, *J* = 11.6, 5.3 Hz, 1 H), 4.23 (dd, *J* = 10.8, 6.5 Hz, 1 H); APCI MS *m/z* 356 $[M + H]^+$.

[0077] D. Synthesis of 6-nitro-2-({[4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]oxy}methyl)-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (compound 4 of Table 1) by the method of Scheme 1.


4

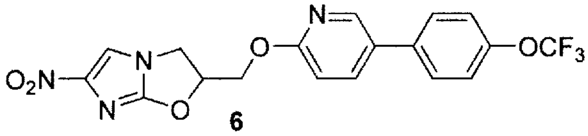
[0078] Suzuki coupling of iodide **85** and 4-(trifluoromethyl)phenylboronic acid as in Example 2C for 90 min, followed by chromatography of the product on silica gel, eluting with 0-0.5% MeOH/CH_2Cl_2 (foreruns) and then with 0.5% MeOH/CH_2Cl_2, gave **4** (77%) as a cream solid: mp (MeOH/CH_2Cl_2/hexane) 210-211 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.19 (s, 1 H), 7.86 (br d, *J* = 8.2 Hz, 2 H), 7.77 (br d, *J* = 8.4 Hz, 2 H), 7.71 (dt, *J* = 8.8, 2.5 Hz, 2 H), 7.09 (dt, *J* = 8.9, 2.6 Hz, 2 H), 5.77 (m, 1 H), 4.52 (dd, *J* = 10.7, 9.0 Hz, 1 H), 4.50 (dd, *J* = 11.6, 2.8 Hz, 1 H), 4.43 (dd, *J* = 11.6, 5.3 Hz, 1 H), 4.24 (dd, *J* = 10.8, 6.5 Hz, 1 H); APCI MS *m/z* 406 $[M + H]^+$.

[0079] E. Synthesis of 6-nitro-2-({[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]oxy}methyl)-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (compound 5 of Table 1) by the method of Scheme 1.


5

[0080] Suzuki coupling of iodide **85** and 4-(trifluoromethoxy)phenylboronic acid as in Example 2C for 50 min, followed by chromatography of the product on silica gel, eluting with CH_2Cl_2, gave **5** (83%) as a pale pink solid: mp (CH_2Cl_2/hexane) 200-201 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.18 (s, 1 H), 7.74 (br d, *J* = 8.8 Hz, 2 H), 7.64 (br d, *J* = 8.8 Hz, 2 H), 7.41 (br d, *J* = 8.1 Hz, 2 H), 7.06 (br d, *J* = 8.8 Hz, 2 H), 5.76 (m, 1 H), 4.52 (dd, *J* = 10.5, 9.0 Hz, 1 H), 4.49 (dd, *J* = 11.6, 2.6 Hz, 1 H), 4.42 (dd, *J* = 11.6, 5.2 Hz, 1 H), 4.23 (dd, *J* = 10.7, 6.5 Hz, 1 H). Anal. ($C_{19}H_{14}F_3N_3O_5$) C, H, N.

[0081] F. Synthesis of 6-nitro-2-[({5-[4-(trifluoromethoxy)phenyl]-2-pyridinyl}oxy)methyl]-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (compound 6 of Table 1) by the method of Scheme 2.


6

[0082] A mixture of 2,4-dinitroimidazole (**86**) (2.02 g, 12.8 mmol) and *tert*-butyl(dimethyl)silyl 2-oxiranylmethyl ether (**87**) (3.84 g, 20.4 mmol) was stirred at 70 °C for 16 h. The resulting cooled mixture was diluted with EtOAc (300 mL) and washed with aqueous $NaHCO_3$ (3x 50 mL), water (2x 50 mL) and brine (50 mL), and then the solvent was removed. Chromatography of the residue on silica gel, eluting with 10-20% EtOAc/petroleum ether, gave 1-{[*tert*-butyl(dimethyl)silyl]oxy}-3-(2,4-dinitro-1*H*-imidazol-1-yl)-2-propanol (**88**) (reported by Otera et al., US 2006063929A1, starting from 2,4-dinitroimidazole and glycidol) (2.63 g, 60%) as a yellow oil; ^{1}H NMR ($CDCl_3$) δ 8.01 (s, 1 H), 4.78 (dd, J = 13.9, 2.9 Hz, 1 H), 4.46 (dd, J = 14.0, 8.3 Hz, 1 H), 4.08 (m, 1 H), 3.76 (dd, J = 10.4, 4.6 Hz, 1 H), 3.67 (dd, J = 10.5, 5.0 Hz, 1 H), 2.60 (br s, 1 H), 0.92 (s, 9 H), 0.11 (s, 6 H); APCI MS *m/z* 300 $[M + H - HNO_2]^+$.

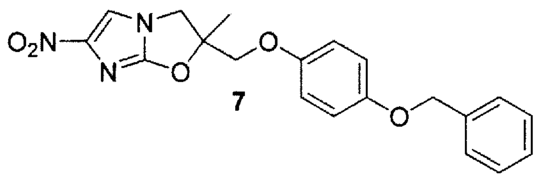
[0083] A solution of alcohol **88** (2.04 g, 5.89 mmol) in anhydrous DMF (20 mL) under N_2 at -20 °C was treated with 60% NaH (0.34 g, 8.50 mmol). After stirring at -20 to -10 °C for 50 min, the reaction was quenched with EtOAc and water (150 mL), and extracted with EtOAc (500 mL). The extract was washed with water (2x 100 mL) and brine (100 mL), backextracting with EtOAc (100 mL), and then the solvent was removed. Chromatography of the residue on silica gel, eluting with 40-67% EtOAc/petroleum ether, gave 2-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-6-nitro-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (**89**) (1.13 g, 64%) as a pale yellow solid: mp (EtOAc/petroleum ether) 142-144 °C ; ^{1}H NMR ($CDCl_3$) δ 7.52 (s, 1 H), 5.33 (m, 1 H), 4.29 (d, J = 7.2 Hz, 2 H), 4.05 (dd, J = 11.9, 3.5 Hz, 1 H), 3.86 (dd, J = 11.9, 2.8 Hz, 1 H), 0.81 (s, 9 H), 0.08, 0.03 (2s, 2x 3 H). Anal. ($C_{12}H_{21}N_3O_4Si$) C, H, N.

[0084] A suspension of silyl ether **89** (503 mg, 1.68 mmol) in a solution of 1% HCl in 95% EtOH (desilylation conditions described by Cunico et al., 1980) (27 mL) was stirred at room temperature for 6 h, and then stored at 4 °C for 2.5 d. The resulting solution was neutralised by dropwise addition of 7M NH_3 in MeOH (2 mL) with stirring, and then concentrated to dryness and the residue was chromatographed on silica gel. Elution with 0-2% MeOH/CH_2Cl_2 firstly gave foreruns, and then further elution with 2-5% MeOH/CH_2Cl_2 gave (6-nitro-2,3-dihydroimidazo[2,1-*b*][1,3]oxazol-2-yl)methanol (**90**) (reported by Sehgal et al., 1981 via reaction of 2,4-dinitroimidazole and glycidol) (299 mg, 97%) as a white solid (after trituration with CH_2Cl_2): mp (CH_2Cl_2) 166-169 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.10 (s, 1 H), 5.40 (m, 1 H), 5.27 (t, J = 5.6 Hz, 1 H), 4.36 (dd, J = 10.5, 8.8 Hz, 1 H), 4.11 (dd, J = 10.5, 6.4 Hz, 1 H), 3.80 (ddd, J = 12.8, 5.4, 3.0 Hz, 1 H), 3.65 (dd, J = 12.8, 5.8, 3.9 Hz, 1 H). Anal. ($C_6H_7N_3O_4$) C, H, N.

[0085] A stirred mixture of 4-(trifluoromethoxy)phenylboronic acid (1.55 g, 7.53 mmol) and Pd(dppf)Cl_2 (367 mg, 0.502 mmol) in toluene (50 mL) and EtOH (25 mL) was degassed for 15 min (vacuum pump) and then N_2 was added. An aqueous solution of 2M Na_2CO_3 (12.5 mL, 25.0 mmol) was added by syringe and the stirred mixture was again degassed for 15 min, and then N_2 was added, followed by 5-bromo-2-fluoropyridine (**91**) (0.53 mL, 5.15 mmol). The resulting mixture was stirred at 85-88 °C for 3 h, and then cooled, diluted with aqueous $NaHCO_3$ (100 mL) and extracted with CH_2Cl_2 (4x 100 mL). The extracts were evaporated to dryness and the residue was chromatographed on silica gel. Elution with 0-10% CH_2Cl_2/petroleum ether firstly gave foreruns, and then further elution with 10-20% CH_2Cl_2/petroleum ether gave 2-fluoro-5-[4-(trifluoromethoxy)phenyl]pyridine (**92**) (1.32 g, 100%) as a white solid: mp (CH_2Cl_2/petroleum ether) 58-60 °C; ^{1}H NMR ($CDCl_3$) δ 8.40 (d, J = 2.5 Hz, 1 H), 7.94 (ddd, J = 8.4, 7.6, 2.6 Hz, 1 H), 7.55 (dt, J = 8.8, 2.5 Hz, 2 H), 7.33 (br d, J = 8.0 Hz, 2 H), 7.02 (dd, J = 8.5, 3.0 Hz, 1 H); HRESIMS calcd for $C_{12}H_8F_4NO$ *m/z* (MH^+) 258.0537, found 258.0531.

[0086] A mixture of alcohol **90** (300 mg, 1.62 mmol) and fluoropyridine **92** (1.255 g, 4.88 mmol) in anhydrous DMF (6 mL) under N_2 at 0 °C was treated with 60% NaH (96 mg, 2.40 mmol), then quickly degassed and resealed under N_2. After stirring at room temperature for 2.5 h, the reaction was cooled (CO_2/acetone), quenched with ice/aqueous $NaHCO_3$ (10 mL), added to brine (40 mL), and extracted with CH_2Cl_2 (6x 50 mL). The combined extracts were evaporated to dryness and the residue was chromatographed on silica gel. Elution with 0-20% CH_2Cl_2/petroleum ether firstly gave foreruns (including recovered **92**), and then further elution with CH_2Cl_2 gave **6** (5.5 mg, 0.8%) as a cream solid: mp (CH_2Cl_2/pentane) 127-130 °C; ^{1}H NMR ($CDCl_3$) δ 8.32 (dd, J = 2.5, 0.7 Hz, 1 H), 7.80 (dd, J = 8.5, 2.5 Hz, 1 H), 7.58 (s, 1 H), 7.53 (dt, J = 8.8, 2.5 Hz, 2 H), 7.31 (br dd, J = 8.7, 0.8 Hz, 2 H), 6.83 (dd, J = 8.6, 0.7 Hz, 1 H), 5.69 (m, 1 H), 4.80 (dd, J = 12.4, 4.0 Hz, 1 H), 4.75 (dd, J = 12.4, 4.1 Hz, 1 H), 4.45 (dd, J = 10.2, 8.7Hz, 1 H), 4.35 (dd, J = 10.2, 6.5 Hz, 1 H); APCI MS m/z 423 $[M + H]^+$.

[0087] G. Synthesis of 2-{[4-(benzyloxy)phenoxy]methyl}-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (compound 7 of Table 1) by the method of Scheme 3.



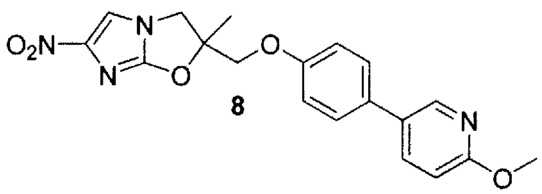
[0088] A mixture of 4-(benzyloxy)phenol (2.01 g, 10.1 mmol), K_2CO_3 (1.60 g, 11.6 mmol) and 3-chloro-2-methylpropene (**93**) (2.00 mL, 20.4 mmol) in anhydrous acetone (2.5 mL) was stirred in a sealed vial at 58 °C for 24 h. The resulting mixture was filtered, washing with CH_2Cl_2, and then the filtrate was evaporated to dryness and the residue was chromatographed on silica gel. Elution with petroleum ether firstly gave foreruns, and then further elution with 25% CH_2Cl_2/petroleum ether gave 1-(benzyloxy)-4-[(2-methyl-2-propenyl)oxy]benzene (**94**) (Karrer, F. DE 2312518) (1.74 g, 68%) as a white solid: mp (CH_2Cl_2/hexane) 62-64 °C; ^1H NMR ($CDCl_3$) δ 7.45-7.29 (m, 5 H), 6.90 (dt, J = 9.3, 2.8 Hz, 2 H), 6.85 (dt, J = 9.3, 2.8 Hz, 2 H), 5.08 (m, 1 H), 5.01 (s, 2 H), 4.79 (m, 1 H), 4.38 (s, 2 H), 1.82 (s, 3 H).

[0089] 3-Chloroperbenzoic acid (1.43 g of 50%, 4.14 mmol) was added to an ice-cooled mixture of **94** (500 mg, 1.97 mmol) and powdered Na_2HPO_4 (974 mg, 6.86 mmol) in CH_2Cl_2 (20 mL), and the resulting mixture was stirred at room temperature for 3.5 h. Cold aqueous Na_2SO_3 (50 mL of 10%) was added, and the mixture was extracted with CH_2Cl_2 (3x 50 mL). The extracts were sequentially washed with cold aqueous Na_2SO_3 (50 mL of 10%), aqueous $NaHCO_3$ (50 mL) and brine (50 mL). The combined extracts were then evaporated to dryness and the residue was chromatographed on silica gel. Elution with 25% CH_2Cl_2/petroleum ether firstly gave foreruns, and then further elution with 25-33% CH_2Cl_2/petroleum ether gave 2-{[4-(benzyloxy)phenoxy]methyl}-2-methyloxirane (**95**) (460 mg, 87%) as a white solid: mp (CH_2Cl_2/pentane) 105-107 °C; ^1H NMR ($CDCl_3$) δ 7.44-7.28 (m, 5 H), 6.90 (dt, J = 9.3, 2.9 Hz, 2 H), 6.85 (dt, J = 9.3, 2.9 Hz, 2 H), 5.01 (s, 2 H), 3.97 (d, J = 10.5 Hz, 1 H), 3.90 (d, J = 10.5 Hz, 1 H), 2.85 (d, J = 4.8 Hz, 1 H), 2.71 (d, J = 4.8 Hz, 1 H), 1.47 (s, 3 H). Anal. ($C_{17}H_{18}O_3$) C, H, N.

[0090] Reaction of epoxide **95** with 2-bromo-4(5)-nitroimidazole (**80**) as in Example 2A at 107 °C for 14 h, followed by chromatography of the product on silica gel, eluting with CH_2Cl_2 (foreruns) and then with 0-1% EtOAc/CH_2Cl_2, gave 1-[4-(benzyloxy)phenoxy]-3-(2-bromo-4-nitro-1*H*-imidazol-1-yl)-2-methyl-2-propanol (**98**) (86%) as a pale yellow solid: mp (MeOH/CH_2Cl_2/hexane) 148-150 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.31 (s, 1 H), 7.45-7.28 (m, 5 H), 6.94 (dt, J = 9.2, 3.0 Hz, 2 H), 6.87 (dt, J = 9.2, 3.0 Hz, 2 H), 5.41 (s, 1 H), 5.04 (s, 2 H), 4.22 (d, J = 14.3 Hz, 1 H), 4.15 (d, J = 14.3 Hz, 1 H), 3.76 (d, J = 9.5 Hz, 1 H), 3.72 (d, J = 9.4 Hz, 1 H), 1.19 (s, 3 H). Anal. ($C_{20}H_{20}BrN_3O_5$) C, H, N.

[0091] Ring closure of alcohol **98** with NaH as in Example 2A for 50 min, followed by chromatography of the product on silica gel, eluting with CH_2Cl_2 (foreruns) and then with 0-1% EtOAc/CH_2Cl_2, gave **7** (92%) as a pale yellow solid: mp (CH_2Cl_2/hexane) 162-165 °C; ^{1}H NMR ($CDCl_3$) δ 7.54 (s, 1 H), 7.43-7.28 (m, 5 H), 6.89 (dt, J = 9.1, 3.0 Hz, 2 H), 6.78 (dt, J = 9.1, 3.1 Hz, 2 H), 5.01 (s, 2 H), 4.48 (d, J = 10.2 Hz, 1 H), 4.17 (d, J = 10.1 Hz, 1 H), 4.03 (d, J = 10.2 Hz, 1 H), 4.00 (d, J = 10.2 Hz, 1 H), 1.76 (s, 3 H). Anal. ($C_{20}H_{19}N_3O_5$) C, H, N.

[0092] H. Synthesis of 2-{[4-(6-methoxy-3-pyridinyl)phenoxy]methyl}-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (compound 8 of Table 1) by the method of Scheme 3.



[0093] A mixture of 4-iodophenol (2.00 g, 9.09 mmol), powdered K_2CO_3 (2.54 g, 18.4 mmol), NaI (364 mg, 2.43 mmol) and 2-(chloromethyl)-2-methyloxirane (**97**) (0.90 mL, 9.31 mmol) in anhydrous DMF (5 mL) was stirred in a sealed vial at 70 °C for 15 h. Further 2-

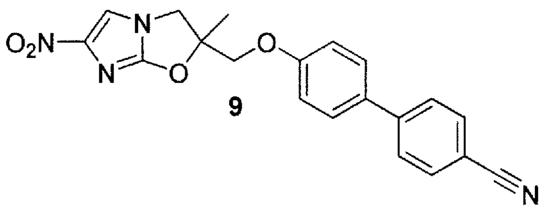
(chloromethyl)-2-methyloxirane (**97**) (0.18 mL, 1.86 mmol) was added and the mixture was then stirred at 73 °C for 17 h. The cooled mixture was added to ice/aqueous $NaHCO_3$ (100 mL) and extracted with Et_2O (5x 100 mL). The extracts were washed with water (100 mL) and then evaporated to dryness and the residue was chromatographed on silica gel. Elution with 0-15% CH_2Cl_2/petroleum ether firstly gave foreruns, and then further elution with 15-20% CH_2Cl_2/petroleum ether gave 2-[(4-iodophenoxy)methyl]-2-methyloxirane (**96**) (1.81 g, 69%) as a white solid: mp (CH_2Cl_2/pentane) 40-41 °C; ^{1}H NMR ($CDCl_3$) δ 7.55 (dt, J = 9.0, 2.7 Hz, 2 H), 6.70 (dt, J = 9.0, 2.7 Hz, 2 H), 4.01 (d, J = 10.5 Hz, 1 H), 3.90 (d, J = 10.5 Hz, 1 H), 2.85 (d, J = 4.7 Hz, 1 H), 2.72 (d, J = 4.7 Hz, 1 H), 1.47 (s, 3 H). Anal. ($C_{10}H_{11}IO_2$) C, H, N.

[0094] Reaction of epoxide **96** with 2-bromo-4(5)-nitroimidazole (**80**) as in Example 2A at 107 °C for 15 h, followed by chromatography of the product on silica gel, eluting with CH_2Cl_2 (foreruns) and then with 0-1% EtOAc/CH_2Cl_2, gave 1-(2-bromo-4-nitro-1*H*-imidazol-1-yl)-3-(4-iodophenoxy)-2-methyl-2-propanol (**99**) (85%) as a foam (after trituration in Et_2O/pentane); ^{1}H NMR ($CDCl_3$) δ 8.04 (s, 1 H), 7.59 (dt, J = 9.0, 2.7 Hz, 2 H), 6.66 (dt, J = 9.0, 2.7 Hz, 2 H), 4.27 (d, J = 14.5 Hz, 1 H), 4.16 (d, J = 14.5 Hz, 1 H), 3.86 (d, J = 9.2 Hz, 1 H), 3.82 (d, J = 9.2 Hz, 1 H), 2.44 (s, 1 H), 1.35 (s, 3 H). Anal. ($C_{13}H_{13}BrIN_3O_4 \cdot 0.1Et_2O$) C, H, N.

[0095] Ring closure of alcohol **99** with NaH as in Example 2A for 75 min, followed by chromatography of the product on silica gel, eluting with CH_2Cl_2, gave 2-[(4-iodophenoxy)methyl]-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (**100**) (92%) as a cream solid: mp (MeOH/CH_2Cl_2/hexane) 181-183 °C; ^{1}H NMR ($CDCl_3$) δ 7.57 (dt, J = 9.0, 2.7 Hz, 2 H), 7.54 (s, 1 H), 6.63 (dt, J = 9.0, 2.7 Hz, 2 H), 4.46 (d, J = 10.2 Hz, 1 H), 4.20 (d, J = 10.1 Hz, 1 H), 4.05 (d, J = 9.9 Hz, 1 H), 4.03 (d, J = 10.1 Hz, 1 H), 1.78 (s, 3 H). Anal. ($C_{13}H_{12}IN_3O_4$) C, H, N.

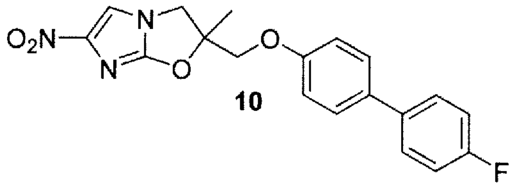
[0096] A stirred mixture of iodide **100** (40.1 mg, 0.100 mmol), 6-methoxy-3-pyridinylboronic acid (23.8 mg, 0.156 mmol) and Pd(dppf)Cl_2 (7.3 mg, 9.98 μmol) in toluene (1.7 mL) and EtOH (0.6 mL) was degassed for 4 min (vacuum pump) and then N_2 was added. An aqueous solution of 2M Na_2CO_3 (0.30 mL, 0.60 mmol) was added by syringe and the stirred mixture was again degassed for 4 min, and then N_2 was added. The resulting mixture was stirred at 90 °C for 45 min, and then cooled, diluted with aqueous $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (4x 50 mL). The extracts were evaporated to dryness and the residue was chromatographed on silica gel. Elution with 0-3% EtOAc/CH_2Cl_2 firstly gave foreruns, and then further elution with 4% EtOAc/CH_2Cl_2 gave **8** (32 mg, 84%) as a cream solid: mp (MeOH/CH_2Cl_2/pentane) 217-219 °C; ^{1}H NMR ($CDCl_3$) δ 8.32 (br d, *J* = 2.2 Hz, 1 H), 7.72 (dd, *J* = 8.6, 2.6 Hz, 1 H), 7.56 (s, 1 H), 7.44 (dt, *J* = 8.8, 2.5 Hz, 2 H), 6.92 (dt, *J* = 8.8, 2.5 Hz, 2 H), 6.79 (d, *J* = 8.5 Hz, 1 H), 4.51 (d, *J* = 10.2 Hz, 1 H), 4.27 (d, *J* = 10.1 Hz, 1 H), 4.13 (d, *J* = 10.1 Hz, 1 H), 4.05 (d, *J* = 10.2 Hz, 1 H), 3.97 (s, 3 H), 1.80 (s, 3 H). Anal. ($C_{19}H_{18}N_4O_5$) C, H, N.

[0097] I. Synthesis of 4'-[(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-*b*][1,3]oxazol-2-yl)methoxy][1,1'-biphenyl]-4-carbonitrile (compound 9 of Table 1) by the method of Scheme 3.



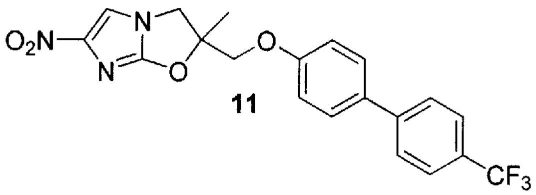
[0098] Suzuki coupling of iodide **100** and 4-cyanophenylboronic acid as in Example 2H, followed by chromatography of the product on silica gel, eluting with 0-0.5% EtOAc/CH_2Cl_2 (foreruns) and then with 0.5-1% EtOAc/CH_2Cl_2, gave **9** (45%) as a cream solid: mp (CH_2Cl_2/pentane) 180-181 °C; ^{1}H NMR ($CDCl_3$) δ 7.70 (dt, *J* = 8.6, 1.8 Hz, 2 H), 7.62 (dt, *J* = 8.6, 1.8 Hz, 2 H), 7.56 (s, 1 H), 7.53 (dt, *J* = 8.9, 2.6 Hz, 2 H), 6.95 (dt, *J* = 8.9, 2.6 Hz, 2 H), 4.51 (d, *J* = 10.2 Hz, 1 H), 4.30 (d, *J* = 10.2 Hz, 1 H), 4.15 (d, *J* = 10.2 Hz, 1 H), 4.06 (d, *J* = 10.2 Hz, 1 H), 1.81 (s, 3 H). Anal. ($C_{20}H_{16}N_4O_4$) C, H, N.

[0099] J. Synthesis of 2-{[(4'-fluoro[1,1'-biphenyl]-4-yl)oxy]methyl}-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (compound 10 of Table 1) by the method of Scheme 3.


10

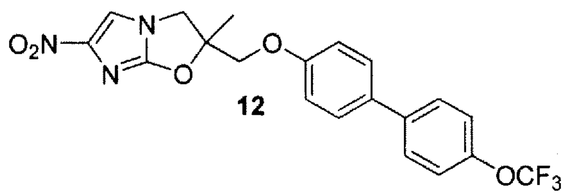
[00100] Suzuki coupling of iodide **100** and 4-fluorophenylboronic acid as in Example 2H, followed by chromatography of the product on silica gel, eluting with CH_2Cl_2 (foreruns) and then with 0-1% EtOAc/CH_2Cl_2, gave **10** (84%) as a cream solid: mp (MeOH/CH_2Cl_2/pentane) 180-181 °C; ^{1}H NMR ($CDCl_3$) δ 7.56 (s, 1 H), 7.50-7.43 (m, 4 H), 7.10 (tt, J = 8.7, 2.6 Hz, 2 H), 6.91 (dt, J = 8.8, 2.6 Hz, 2 H), 4.51 (d, J = 10.2 Hz, 1 H), 4.27 (d, J = 10.1 Hz, 1 H), 4.13 (d, J = 10.1 Hz, 1 H), 4.05 (d, J = 10.2 Hz, 1 H), 1.80 (s, 3 H). Anal. ($C_{19}H_{16}FN_3O_4$) C, H, N.

[0100] K. Synthesis of 2-methyl-6-nitro-2-({[4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]oxy}methyl)-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (compound 11 of Table 1) by the method of Scheme 3.


11

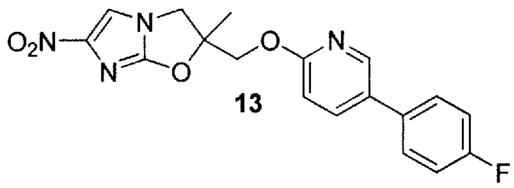
[0101] Suzuki coupling of iodide **100** and 4-(trifluoromethyl)phenylboronic acid as in Example 2H, followed by chromatography of the product on silica gel, eluting with 0-0.5% EtOAc/CH_2Cl_2 (foreruns) and then with 0.5% EtOAc/CH_2Cl_2, gave **11** (88%) as a cream solid: mp (CH_2Cl_2/pentane) 219-220 °C; ^{1}H NMR ($CDCl_3$) δ 7.67 (d, J = 8.5 Hz, 2 H), 7.63 (d, J = 8.5 Hz, 2 H), 7.56 (s, 1 H), 7.53 (dt, J = 8.8, 2.5 Hz, 2 H), 6.95 (dt, J = 8.8, 2.5 Hz, 2 H), 4.51 (d, J = 10.2 Hz, 1 H), 4.29 (d, J = 10.1 Hz, 1 H), 4.14 (d, J = 10.1 Hz, 1 H), 4.06 (d, J = 10.2 Hz, 1 H), 1.81 (s, 3 H). Anal. ($C_{20}H_{16}F_3N_3O_4$) C, H, N.

[0102] L. Synthesis of 2-methyl-6-nitro-2-({[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]oxy}methyl)-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (compound 12 of Table 1) by the method of Scheme 3.



[0103] Suzuki coupling of iodide **100** and 4-(trifluoromethoxy)phenylboronic acid as in Example 2H, followed by chromatography of the product on silica gel, eluting with CH_2Cl_2, gave **12** (90%) as a cream solid: mp ($MeOH/CH_2Cl_2$/pentane) 209-211 °C; ^1H NMR ($CDCl_3$) δ 7.56 (s, 1 H), 7.53 (dt, *J* = 8.8, 2.5 Hz, 2 H), 7.48 (dt, *J* = 8.8, 2.5 Hz, 2 H), 7.26 (m, 2 H), 6.92 (dt, *J* = 8.8, 2.5 Hz, 2 H), 4.51 (d, *J* = 10.2 Hz, 1 H), 4.28 (d, *J* = 10.1 Hz, 1 H), 4.13 (d, *J* = 10.1 Hz, 1 H), 4.05 (d, *J* = 10.2 Hz, 1 H), 1.81 (s, 3 H). Anal. ($C_{20}H_{16}F_3N_3O_5$) C, H, N.

[0104] M. Synthesis of 2-({[5-(4-fluorophenyl)-2-pyridinyl]oxy}methyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (compound 13 of Table 1) by the method of Scheme 4.



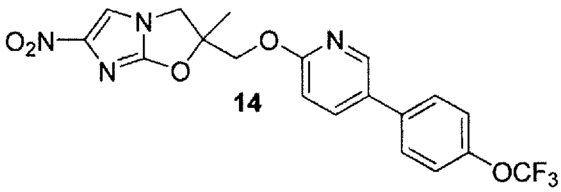
[0105] Trifluoroacetic acid (25.4 mL, 0.342 mol) was added dropwise to a stirred mixture of 2-({[4-(benzyloxy)benzyl]oxy}methyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (**26**) (see Example 2Z) (2.53 g, 6.40 mmol) and anisole (7.0 mL, 64 mmol) in CH_2Cl_2 (100 mL) (water bath cooling). After stirring at room temperature for 4 h, the solvents were removed by blowing under a stream of N_2. The oily residue was treated with excess solid $NaHCO_3$, then diluted with 15% $MeOH/CH_2Cl_2$ (100 mL), and the mixture was stirred at room temperature for 30 min and then filtered. The filtrate was evaporated to dryness and the residue was chromatographed on silica gel. Elution with 0-1% $MeOH/CH_2Cl_2$ firstly gave foreruns, and then further elution with 1-2% $MeOH/CH_2Cl_2$ gave (2-methyl-6-nitro-2,3-dihydroimidazo[2,1-*b*][1,3]oxazol-2-yl)methanol (**101**) (reported by Tsubouchi et al., WO 2004033463A1 via 3 steps, starting from 2-chloro-4(5)-nitroimidazole (**81**) and 2-[(methoxymethoxy)methyl]-2-methyloxirane) (1.215 g, 95%) as a cream solid: mp ($MeOH/CH_2Cl_2$/hexane) 174-176 °C; ^1H

NMR [$(CD_3)_2SO$] δ 8.09 (s, 1 H), 5.41 (t, *J* = 5.7 Hz, 1 H), 4.24 (d, *J* = 10.6 Hz, 1 H), 4.03 (d, *J* = 10.7 Hz, 1 H), 3.64 (dd, *J* = 12.2, 5.6 Hz, 1 H), 3.54 (dd, *J* = 12.2, 5.9 Hz, 1 H), 1.51 (s, 3 H). Anal. ($C_7H_9N_3O_4$) C, H, N.

[0106] 5-Bromo-2-fluoropyridine (**91**) (0.25 mL, 2.43 mmol) was added to a solution of alcohol **101** (200 mg, 1.01 mmol) in anhydrous DMF (4.5 mL) under N_2 at 0 °C. The resulting mixture was treated with 60% NaH (64 mg, 1.60 mmol), then quickly degassed and resealed under N_2. Further 5-bromo-2-fluoropyridine (**91**) (0.25 mL, 2.43 mmol) was added and the mixture was stirred at room temperature for 2 h, and then cooled (CO_2/acetone), quenched with ice/aqueous $NaHCO_3$ (15 mL), added to brine (40 mL) and extracted with CH_2Cl_2 (8x 40 mL). The combined extracts were evaporated to dryness and the residue was chromatographed on silica gel. Elution with CH_2Cl_2 firstly gave foreruns, and then further elution with 0-1.5% EtOAc/CH_2Cl_2 gave 2-{[(5-bromo-2-pyridinyl)oxy]methyl}-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (**102**) (130 mg, 36%) as a cream solid: mp (CH_2Cl_2/hexane) 151-153 °C; ^{1}H NMR ($CDCl_3$) δ 8.17 (dd, *J* = 2.5, 0.5 Hz, 1 H), 7.68 (dd, *J* = 8.8, 2.5 Hz, 1 H), 7.52 (s, 1 H), 6.60 (dd, *J* = 8.7, 0.6 Hz, 1 H), 4.58 (d, *J* = 12.0 Hz, 1 H), 4.50 (d, *J* = 12.0 Hz, 1 H), 4.41 (d, *J* = 10.2 Hz, 1 H), 4.01 (d, *J* = 10.2 Hz, 1 H), 1.76 (s, 3 H). Anal. ($C_{12}H_{11}BrN_4O_4$) C, H, N.

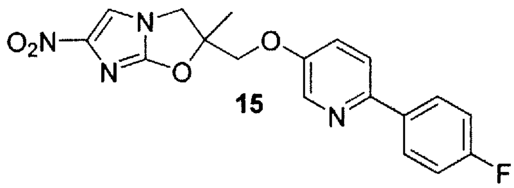
[0107] A stirred mixture of bromide **102** (77.2 mg, 0.217 mmol), 4-fluorophenylboronic acid (58 mg, 0.415 mmol) and Pd(dppf)Cl_2 (43.5 mg, 59.4 μmol) in DMF (2.3 mL), toluene (1.6 mL) and EtOH (1.1 mL) was degassed for 9 min (vacuum pump) and then N_2 was added. An aqueous solution of 2M Na_2CO_3 (0.55 mL, 1.1 mmol) was added by syringe and the stirred mixture was again degassed for 9 min, and then N_2 was added. The resulting mixture was stirred at 90 °C for 3 h, and then cooled, diluted with aqueous $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (6x 50 mL). The extracts were evaporated to dryness and the residue was chromatographed on silica gel. Elution with 0-1% EtOAc/CH_2Cl_2 firstly gave foreruns, and then further elution with 1-2% EtOAc/CH_2Cl_2 gave **13** (60 mg, 74%) as a cream solid: mp (CH_2Cl_2/hexane) 162-164 °C; ^{1}H NMR ($CDCl_3$) δ 8.28 (dd, *J* = 2.5, 0.6 Hz, 1 H), 7.76 (dd, *J* = 8.5, 2.5 Hz, 1 H), 7.55 (s, 1 H), 7.46 (ddt, *J* = 8.9, 5.2, 2.6 Hz, 2 H), 7.14 (tt, *J* = 8.7, 2.6 Hz, 2 H), 6.75 (dd, *J* = 8.5, 0.7 Hz, 1 H), 4.67 (d, *J* = 11.9 Hz, 1 H), 4.58 (d, *J* = 11.9 Hz, 1 H), 4.47 (d, *J* = 10.2 Hz, 1 H), 4.04 (d, *J* = 10.2 Hz, 1 H), 1.79 (s, 3 H); APCI MS *m/z* 371 $[M + H]^+$.

[0108] N. Synthesis of 2-methyl-6-nitro-2-[({5-[4-(trifluoromethoxy)phenyl]-2-pyridinyl}oxy)methyl]-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (compound 14 of Table 1) by the method of Scheme 4.



[0109] Suzuki coupling of bromide **102** and 4-(trifluoromethoxy)phenylboronic acid as in Example 2M, followed by chromatography of the product on silica gel, eluting with CH_2Cl_2, gave **14** (80%) as a cream solid: mp (CH_2Cl_2/pentane) 172-174 °C; ^{1}H NMR ($CDCl_3$) δ 8.31 (d, J = 2.1 Hz, 1 H), 7.78 (dd, J = 8.6, 2.5 Hz, 1 H), 7.55 (s, 1 H), 7.52 (br d, J = 8.8 Hz, 2 H), 7.30 (br d, J = 8.2 Hz, 2 H), 6.76 (d, J = 8.7 Hz, 1 H), 4.68 (d, J = 11.9 Hz, 1 H), 4.58 (d, J = 11.9 Hz, 1 H), 4.47 (d, J = 10.2 Hz, 1 H), 4.04 (d, J = 10.2 Hz, 1 H), 1.80 (s, 3 H). Anal. ($C_{19}H_{15}F_3N_4O_5$) C, H, N.

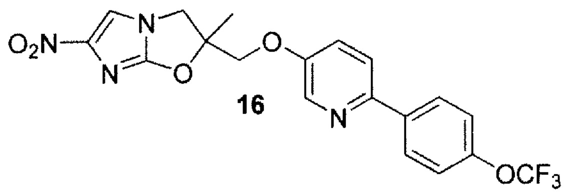
[0110] O. Synthesis of 2-({[6-(4-fluorophenyl)-3-pyridinyl]oxy}methyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (compound 15 of Table 1) by the method of Scheme 5.



[0111] A mixture of 2-bromo-1-[(2-methyl-2-oxiranyl)methyl]-4-nitro-1*H*-imidazole (**105**) (obtained in 2 steps from **80**, via epoxidation of the corresponding alkene, as reported by Ding et al., WO 2008008480A2) (1.011 g, 3.86 mmol) and 6-bromo-3-pyridinol (615 mg, 3.53 mmol) in anhydrous DMF (12 mL) under N_2 at 0 °C was treated with 60% NaH (180 mg, 4.50 mmol), then quickly degassed and resealed under N_2. After stirring at room temperature for 10 min, and then at 50 °C for 4 h, the reaction was cooled (CO_2/acetone), quenched with ice/aqueous $NaHCO_3$ (20 mL), added to brine (100 mL), and extracted with CH_2Cl_2 (6x 100 mL). The combined extracts were evaporated to dryness and the residue was chromatographed on silica gel. Elution with 0-50% EtOAc/petroleum ether firstly gave foreruns, and then further elution with 50-75% EtOAc/petroleum ether and EtOAc gave a crude solid, which was further chromatographed on silica gel. Elution with CH_2Cl_2 firstly gave foreruns, and then further elution with 0.3-0.5% MeOH/CH_2Cl_2 gave 2-{[(6-bromo-3-pyridinyl)oxy]methyl}-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (**106**) (reported by Ding et al., WO 2009120789A1 from **105** via a similar procedure) (564 mg, 45%) as a cream solid: mp (MeOH/CH_2Cl_2/hexane) 148-150 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.14 (s, 1 H), 8.10 (dd, *J* = 3.2, 0.3 Hz, 1 H), 7.56 (dd, *J* = 8.7, 0.4 Hz, 1 H), 7.39 (dd, *J* = 8.8, 3.2 Hz, 1 H), 4.42 (d, *J* = 11.1 Hz, 1 H), 4.39 (d, *J* = 11.1 Hz, 1 H), 4.38 (d, *J* = 11.0 Hz, 1 H), 4.19 (d, *J* = 11.0 Hz, 1 H), 1.68 (s, 3 H). Anal. ($C_{12}H_{11}BrN_4O_4$) C, H, N.

[0112] Suzuki coupling of bromide **106** and 4-fluorophenylboronic acid as in Example 2M, followed by chromatography of the product on silica gel, eluting with 0-0.5% MeOH/CH_2Cl_2 (foreruns) and then with 0.5% MeOH/CH_2Cl_2, gave **15** (74%) as a cream solid: mp (MeOH/CH_2Cl_2/hexane) 180-181 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.32 (d, *J* = 2.8 Hz, 1 H), 8.18 (s, 1 H), 8.05 (ddt, *J* = 8.9, 5.6, 2.6 Hz, 2 H), 7.91 (d, *J* = 8.8 Hz, 1 H), 7.48 (dd, *J* = 8.8, 3.0 Hz, 1 H), 7.27 (tt, *J* = 8.9, 2.6 Hz, 2 H), 4.47 (d, *J* = 11.0 Hz, 1 H), 4.43 (d, *J* = 11.1 Hz, 1 H), 4.41 (d, *J* = 11.0 Hz, 1 H), 4.22 (d, *J* = 11.0 Hz, 1 H), 1.71 (s, 3 H); APCI MS *m/z* 371 $[M + H]^+$.

[0113] P. Synthesis of 2-methyl-6-nitro-2-[({6-[4-(trifluoromethoxy)phenyl]-3-pyridinyl}oxy)methyl]-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (compound 16 of Table 1) by the method of Scheme 5.



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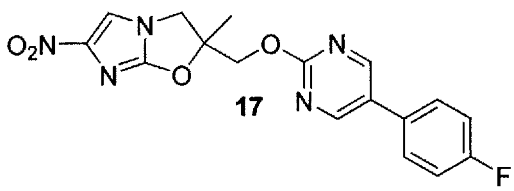
[0114] Suzuki coupling of bromide **106** and 4-(trifluoromethoxy)phenylboronic acid as in Example 2M, followed by chromatography of the product on silica gel, eluting with 0-0.33% MeOH/CH_2Cl_2 (foreruns) and then with 0.33% MeOH/CH_2Cl_2, gave **16** (67%) as a cream solid: mp (MeOH/CH_2Cl_2/hexane) 209-211 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.35 (d, *J* = 2.9 Hz, 1 H), 8.18 (s, 1 H), 8.13 (br d, J = 8.9 Hz, 2 H), 7.97 (d, J = 8.8 Hz, 1 H), 7.51 (dd, J = 8.8, 3.0 Hz, 1 H), 7.44 (br d, J = 8.2 Hz, 2 H), 4.48 (d, J = 11.1 Hz, 1 H), 4.44 (d, J = 11.2 Hz, 1 H), 4.42 (d, J = 11.1 Hz, 1 H), 4.22 (d, J = 11.0 Hz, 1 H), 1.71 (s, 3 H). Anal. ($C_{19}H_{15}F_3N_4O_5$) C, H, N.

[0115] **Q. Synthesis of 7-({[5-(4-fluorophenyl)-2-pyrimidinyl]oxy}methyl)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound 17 of Table 1) by the method of Scheme 4.**

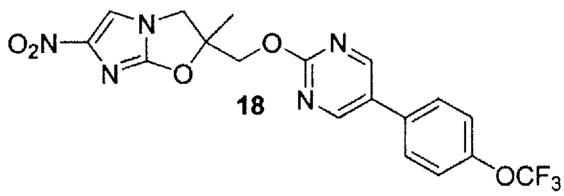


17

[0116] A mixture of alcohol **101** (see Example 2M) (100 mg, 0.502 mmol) and 5-bromo-2-chloropyrimidine (156 mg, 0.806 mmol) in anhydrous DMF (2.5 mL) under N_2 at 0 °C was treated with 60% NaH (32 mg, 0.80 mmol), then quickly degassed and resealed under N_2. After stirring at room temperature for 140 min, the reaction was cooled (CO_2/acetone), quenched with ice/aqueous $NaHCO_3$ (10 mL), added to brine (40 mL), and extracted with CH_2Cl_2 (6x 50 mL). The combined extracts were evaporated to dryness and the residue was chromatographed on silica gel. Elution with 0-0.25% MeOH/CH_2Cl_2 firstly gave foreruns, and then further elution with 0.25-0.5% MeOH/CH_2Cl_2 gave 2-{[(5-bromo-2-pyrimidinyl)oxy]methyl}-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (**103**) (reported by Ding et al., WO 2009120789A1 from **101** via a similar procedure) (163 mg, 91%) as a cream solid: mp (MeOH/CH_2Cl_2/hexane) 224-226 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.77 (s, 2 H), 8.14 (s, 1 H), 4.61 (s, 2 H), 4.41 (d, J = 11.0 Hz, 1 H), 4.20 (d, J = 11.1 Hz, 1 H), 1.70 (s, 3 H). Anal. ($C_{11}H_{10}BrN_5O_4$) C, H, N.

[0117] Suzuki coupling of bromide **103** and 4-fluorophenylboronic acid as in Example 2M, followed by chromatography of the product on silica gel, eluting with CH_2Cl_2 (foreruns) and then with 0.5% MeOH/CH_2Cl_2, gave **17** (22%) as a pale yellow solid: mp (CH_2Cl_2/pentane) 196 °C dec; ^{1}H NMR [$(CD_3)_2SO$] δ 8.92 (s, 2 H), 8.18 (s, 1 H), 7.79 (br dd, J = 8.8, 5.4 Hz, 2 H), 7.34 (br t, J = 8.9 Hz, 2 H), 4.69 (d, J = 12.0 Hz, 1 H), 4.65 (d, J = 12.0 Hz, 1 H), 4.44 (d, J = 11.0 Hz, 1 H), 4.22 (d, J = 11.0 Hz, 1 H), 1.72 (s, 3 H). Anal. ($C_{17}H_{14}FN_5O_4$) C, H, N.

[0118] R. Synthesis of 2-methyl-6-nitro-2-[({5-[4-(trifluoromethoxy)phenyl]-2-pyrimidinyl}oxy)methyl]-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (compound 18 of Table 1) by the method of Scheme 4.



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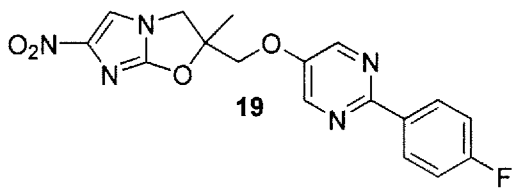
[0119] Suzuki coupling of bromide **103** and 4-(trifluoromethoxy)phenylboronic acid as in Example 2M for 2 h, followed by chromatography of the product on silica gel, eluting with CH_2Cl_2 (foreruns) and then with 0.25% MeOH/CH_2Cl_2, gave **18** (80%) as a cream solid: mp (CH_2Cl_2/hexane) 227 °C dec; ^{1}H NMR [$(CD_3)_2SO$] δ 8.96 (s, 2 H), 8.18 (s, 1 H), 7.87 (br d, *J* = 8.7 Hz, 2 H), 7.50 (br d, *J* = 8.2 Hz, 2 H), 4.70 (d, *J* = 12.0 Hz, 1 H), 4.67 (d, *J* = 12.0 Hz, 1 H), 4.44 (d, *J* = 11.0 Hz, 1 H), 4.22 (d, *J* = 11.0 Hz, 1 H), 1.72 (s, 3 H). Anal. ($C_{18}H_{14}F_3N_5O_5$) C, H, N.

[0120] S. Synthesis of 2-({[2-(4-fluorophenyl)-5-pyrimidinyl]oxy}methyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (compound 19 of Table 1) by the method of Scheme 5.



19

[0121] A stirred mixture of 2-chloro-5-pyrimidinol (**107**) (1.00 g, 7.66 mmol) and chloromethyl ethyl ether (1.75 mL, 18.9 mmol) in anhydrous DMF (2.5 mL) was treated with K_2CO_3 (2.15 g, 15.6 mmol). After stirring at room temperature for 16 h, the mixture was added to ice/aqueous $NaHCO_3$ (100 mL) and extracted with 50% Et_2O/petroleum ether (5x 100 mL). The combined extracts were evaporated to dryness and the residue was chromatographed on silica gel. Elution with 0-1% Et_2O/petroleum ether firstly gave foreruns, and then further elution with 1-10% Et_2O/petroleum ether gave 2-chloro-5-(ethoxymethoxy)pyrimidine (**108**) (1.27 g, 88%) as an oil;

^{1}H NMR ($CDCl_3$) δ 8.43 (s, 2 H), 5.27 (s, 2 H), 3.74 (q, *J* = 7.1 Hz, 2 H), 1.23 (t, *J* = 7.1 Hz, 3 H); HRESIMS calcd for $C_7H_{10}ClN_2O_2$ *m/z* $[M + H]^+$ 191.0396, 189.0425, found 191.0397, 189.0426.

[0122] A stirred mixture of 4-fluorophenylboronic acid (282 mg, 2.02 mmol) and Pd(dppf)Cl_2 (199 mg, 0.272 mmol) in toluene (14 mL) and EtOH (7 mL) was degassed for 10 min (vacuum pump) and then N_2 was added. An aqueous solution of 2M Na_2CO_3 (3.3 mL, 6.6 mmol) was added by syringe and the stirred mixture was again degassed for 10 min, and then N_2 was added, followed by chloropyrimidine **108** (260 mg, 1.38 mmol). The resulting mixture was stirred at 86 °C for 2.5 h, and then cooled, diluted with aqueous $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (5x 50 mL). The extracts were evaporated to dryness and the residue was chromatographed on silica gel. Elution with 0-2% Et_2O/petroleum ether firstly gave foreruns, and then further elution with 2% Et_2O/petroleum ether gave 5-(ethoxymethoxy)-2-(4-fluorophenyl)pyrimidine (**109**) (312 mg, 91%) as a white solid: mp (petroleum ether) 42-44 °C; ^{1}H NMR ($CDCl_3$) δ 8.58 (s, 2 H), 8.36 (ddt, *J* = 9.0, 5.6, 2.5 Hz, 2 H), 7.14 (tt, *J* = 8.8, 2.5 Hz, 2 H), 5.30 (s, 2 H), 3.77 (q, *J* = 7.1 Hz, 2 H), 1.25 (t, *J* = 7.1 Hz, 3 H); HRESIMS calcd for $C_{13}H_{13}FN_2O_2$ *m/z* $[M + H]^+$ 249.1034, found 249.1039.

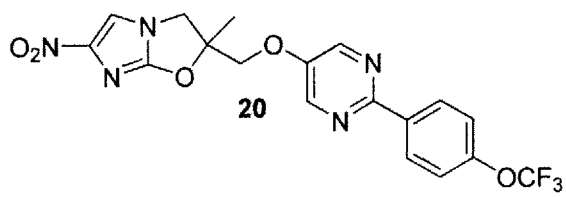
[0123] Ether **109** (301 mg, 1.21 mmol) was treated with 1.25M HCl in MeOH (10 mL) and the mixture was stirred at 53 °C for 4 h. The resulting cooled solution was diluted with ice-water (100 mL) and extracted with CH_2Cl_2 (5x 80 mL). The combined extracts were evaporated to dryness and the residue was triturated in pentane to give 2-(4-fluorophenyl)-5-pyrimidinol (**111**) (225 mg, 98%) as a white solid: mp (pentane) 200-202 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.55 (v br s, 1 H), 8.42 (s, 2 H), 8.29 (ddt, *J* = 9.1, 5.7, 2.6 Hz, 2 H), 7.28 (tt, *J* = 9.0, 2.6 Hz, 2 H); HRESIMS calcd for $C_{10}H_8FN_2O$ *m/z* $[M + H]^+$ 191.0615, found 191.0616.

[0124] A mixture of 2-bromo-1-[(2-methyl-2-oxiranyl)methyl]-4-nitro-1*H*-imidazole (**105**) (obtained in 2 steps from **80**, via epoxidation of the corresponding alkene, as reported by Ding et al., WO 2008008480A2) (279.5 mg, 1.07 mmol) and pyrimidinol **111** (201 mg, 1.06 mmol) in anhydrous DMF (3 mL) under N_2 at 0 °C was treated with 60% NaH (54 mg, 1.35 mmol), then quickly degassed and resealed under N_2. After stirring at room temperature for 30 min, and then at 60 °C for 3 h, the reaction was cooled (CO_2/acetone), quenched with ice/aqueous $NaHCO_3$ (5 mL), added to brine (50 mL), and extracted with CH_2Cl_2 (8x 50 mL). The combined extracts were evaporated to dryness and the residue was chromatographed on silica gel. Elution with 0-33% EtOAc/petroleum ether firstly gave foreruns, and then further elution with 50% EtOAc/petroleum ether gave 1-(2-bromo-4-nitro-1*H*-imidazol-1-yl)-3-{[2-(4-fluorophenyl)-5-pyrimidinyl]oxy}-2-methyl-2-propanol (**113**) (76 mg, 16%) as an oil; ^{1}H NMR ($CDCl_3$) δ 8.46 (s, 2 H), 8.36 (ddt, J = 9.0, 5.5, 2.5 Hz, 2 H), 8.09 (s, 1 H), 7.15 (tt, J = 8.7, 2.5 Hz, 2 H), 4.32 (d, J = 14.6 Hz, 1 H), 4.21 (d, J = 14.5 Hz, 1 H), 4.03 (d, J = 9.2 Hz, 1 H), 3.99 (d, J = 9.1 Hz, 1 H), 2.59 (s, 1 H), 1.43 (s, 3 H); HRESIMS calcd for $C_{17}H_{16}BrFN_5O_4$ *m/z* $[M + H]^+$ 454.0345, 452.0364, found 454.0342, 452.0358.

[0125] Further elution of the above column with EtOAc gave a crude solid, which was further chromatographed over silica gel. Elution with 0-2% EtOAc/CH_2Cl_2 firstly gave foreruns, and then further elution with 2-5% EtOAc/CH_2Cl_2 gave **19** (135 mg, 34%) as a cream solid: mp (MeOH/CH_2Cl_2/hexane) 201-203 °C; ^{1}H NMR 8.63 (s, 2 H), 8.33 (ddt, J = 9.0, 5.7, 2.6 Hz, 2 H), 8.18 (s, 1 H), 7.32 (tt, J = 8.9, 2.6 Hz, 2 H), 4.57 (d, J = 11.1 Hz, 1 H), 4.53 (d, J = 11.1 Hz, 1 H), 4.42 (d, J = 11.0 Hz, 1 H), 4.22 (d, J = 11.0 Hz, 1 H), 1.71 (s, 3 H); APCI MS *m/z* 372 $[M + H]^+$.

[0126] Ring closure of alcohol **113** with NaH (1.8 equiv.) as in Example 2A for 35 min, followed by chromatography of the product on silica gel, eluting with 0-2% EtOAc/CH_2Cl_2 (foreruns) and then with 2-5% EtOAc/CH_2Cl_2, gave additional **19** (67%).

[0127] T. Synthesis of 2-methyl-6-nitro-2-[({2-[4-(trifluoromethoxy)phenyl]-5-pyrimidinyl}oxy)methyl]-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (compound 20 of Table 1) by the method of Scheme 5.



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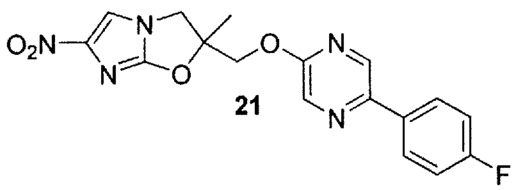
[0128] Suzuki coupling of chloropyrimidine **108** (see Example 2S) and 4-(trifluoromethoxy)phenylboronic acid as in Example 2S above for 2 h, followed by chromatography of the product on silica gel, eluting with 0-2% Et_2O/petroleum ether (foreruns) and then with 2% Et_2O/petroleum ether, gave 5-(ethoxymethoxy)-2-[4-(trifluoromethoxy)phenyl]pyrimidine (**110**) (91%) as a white solid: mp (petroleum ether) 41-43 °C; ^1H NMR ($CDCl_3$) δ 8.60 (s, 2 H), 8.41 (dt, *J* = 9.0, 2.4 Hz, 2 H), 7.30 (br dd, *J* = 9.0, 0.9 Hz, 2 H), 5.31 (s, 2 H), 3.77 (q, *J* = 7.1 Hz, 2 H), 1.25 (t, *J* = 7.1 Hz, 3 H); HRESIMS calcd for $C_{14}H_{14}F_3N_2O_3$ *m/z* $[M + H]^+$ 315.0951, found 315.0944.

[0129] Ether **110** (379 mg, 1.21 mmol) was treated with 1.25M HCl in MeOH (11 mL) and the mixture was stirred at room temperature for 12 h, and then at 53 °C for 2 h. The resulting cooled solution was diluted with water (50 mL) and extracted with CH_2Cl_2 (5x 50 mL). The combined extracts were evaporated to dryness and the residue was triturated in pentane to give 2-[4-(trifluoromethoxy)phenyl]-5-pyrimidinol (**112**) (305 mg, 99%) as a white solid: mp (pentane) 156-157 °C; ^1H NMR ($CDCl_3$) δ 8.45 (s, 2 H), 8.38 (dt, *J* = 8.9, 2.4 Hz, 2 H), 7.29 (br dd, *J* = 8.9, 0.7 Hz, 2 H), 5.60 (br s, 1 H); HRESIMS calcd for $C_{11}H_8F_3N_2O_2$ *m/z* $[M + H]^+$ 257.0532, found 257.0526.

[0130] A mixture of 2-bromo-1-[(2-methyl-2-oxiranyl)methyl]-4-nitro-1*H*-imidazole (**105**) (obtained in 2 steps from **80**, via epoxidation of the corresponding alkene, as reported by Ding et al., WO 2008008480A2) (165 mg, 0.630 mmol) and pyrimidinol **112** (160 mg, 0.625 mmol) in anhydrous DMF (2 mL) under N_2 at 0 °C was treated with 60% NaH (33.5 mg, 0.838 mmol), then quickly degassed and resealed under N_2. After stirring at room temperature for 10 min, and then at 50 °C for 3 h, the reaction was cooled (CO_2/acetone), quenched with ice/aqueous $NaHCO_3$ (5 mL), added to brine (50 mL), and extracted with CH_2Cl_2 (6x 50 mL). The combined extracts were evaporated to dryness and the residue was chromatographed on silica gel. Elution with 0-33% EtOAc/petroleum ether firstly gave foreruns, and then further elution with EtOAc gave a crude mixture of **20** and the non ring-closed alcohol **114** (95 mg). A solution of this mixture in anhydrous DMF (2 mL) under N_2 at 0 °C was treated with 60% NaH (6.3 mg, 0.158 mmol), then degassed and resealed under N_2, and stirred at 0 °C for 80 min. The reaction was quenched and worked up as before, and then chromatography of the product on silica gel, eluting with 0-2%

$EtOAc/CH_2Cl_2$ (foreruns) and then with 3-5% $EtOAc/CH_2Cl_2$, gave **20** (62 mg, 23%) as a cream solid: mp ($MeOH/CH_2Cl_2$/hexane) 223-225 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.66 (s, 2 H), 8.40 (dt, *J* = 8.9, 2.4 Hz, 2 H), 8.18 (s, 1 H), 7.49 (br d, *J* = 8.2 Hz, 2 H), 4.59 (d, *J* = 11.1 Hz, 1 H), 4.55 (d, *J* = 11.1 Hz, 1 H), 4.43 (d, *J* = 11.1 Hz, 1 H), 4.23 (d, *J* = 11.0 Hz, 1 H), 1.72 (s, 3 H). Anal. ($C_{18}H_{14}F_3N_5O_5$) C, H, N.

[0131] U. Synthesis of 2-({[5-(4-fluorophenyl)-2-pyrazinyl]oxy}methyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (compound 21 of Table 1) by the method of Scheme 4.



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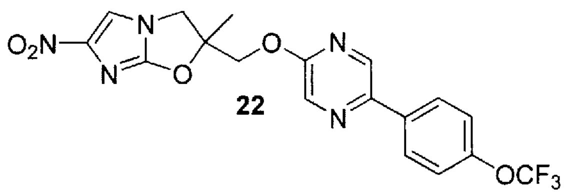
[0132] A solution of alcohol **101** (see Example 2M) (350 mg, 1.76 mmol) in anhydrous DMF (7 mL) under N_2 at 0 °C was treated with 60% NaH (104 mg, 2.60 mmol) and 2,5-dibromopyrazine (837 mg, 3.52 mmol), then quickly degassed and resealed under N_2. After stirring at room temperature for 3 h, the reaction was cooled (CO_2/acetone), quenched with ice/aqueous $NaHCO_3$ (20 mL), added to brine (80 mL), and extracted with CH_2Cl_2 (6x 100 mL). The combined extracts were evaporated to dryness and the residue was chromatographed on silica gel. Elution with CH_2Cl_2 firstly gave foreruns, and then further elution with 0-2% $EtOAc/CH_2Cl_2$ gave 2-{[(5-bromo-2-pyrazinyl)oxy]methyl}-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (**104**) (428 mg, 68%) as a white solid: mp ($MeOH/CH_2Cl_2$/hexane) 198-200 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.44 (d, *J* = 1.3 Hz, 1 H), 8.16 (d, *J* = 1.3 Hz, 1 H), 8.14 (s, 1 H), 4.62 (s, 2 H), 4.40 (d, *J* = 11.0 Hz, 1 H), 4.19 (d, *J* = 11.0 Hz, 1 H), 1.70 (s, 3 H). Anal. ($C_{11}H_{10}BrN_5O_4$) C, H, N.

[0133] A stirred mixture of bromide **104** (140.2 mg, 0.394 mmol), 4-fluorophenylboronic acid (104 mg, 0.743 mmol) and Pd(dppf)Cl_2 (29.8 mg, 40.7 μmol) in toluene (6 mL) and EtOH (2.4 mL) was degassed for 8 min (vacuum pump) and then N_2 was added. An aqueous solution of 2M Na_2CO_3 (1.0 mL, 2.0 mmol) was added by syringe and the stirred mixture was again degassed for 8 min, and then N_2 was added. The resulting mixture was stirred at 89 °C for 110 min, and then cooled, diluted with aqueous $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (5x 50 mL). The extracts were evaporated to dryness and the residue was chromatographed on silica gel. Elution with CH_2Cl_2 firstly gave foreruns, and then further elution with 2-3% EtOAc/CH_2Cl_2 gave **21** (112 mg, 77%) as a cream solid: mp (MeOH/CH_2Cl_2/hexane) 200-201 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.80 (d, J = 1.2 Hz, 1 H), 8.33 (d, J = 1.3 Hz, 1 H), 8.17 (s, 1 H), 8.08 (br dd, J = 8.8, 5.5 Hz, 2 H), 7.33 (br t, J = 8.9 Hz, 2 H), 4.70 (d, J = 12.5 Hz, 1 H), 4.66 (d, J = 12.5 Hz, 1 H), 4.43 (d, J = 11.1 Hz, 1 H), 4.22 (d, J = 11.0 Hz, 1 H), 1.72 (s, 3 H). Anal. ($C_{17}H_{14}FN_5O_4$) C, H, N.

[0134] V. Synthesis of 2-methyl-6-nitro-2-[({5-[4-(trifluoromethoxy)phenyl]-2-pyrazinyl}oxy)methyl]-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (compound 22 of Table 1) by the method of Scheme 4.



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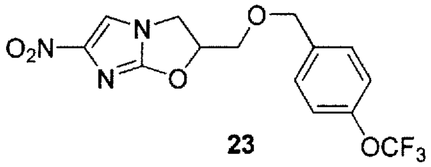
[0135] Suzuki coupling of bromide **104** and 4-(trifluoromethoxy)phenylboronic acid as in Example 2U, followed by chromatography of the product on silica gel, eluting with CH_2Cl_2 (foreruns) and then with 1-2.5% EtOAc/CH_2Cl_2 gave **22** (81%) as a cream solid: mp (MeOH/CH_2Cl_2/hexane) 222-224 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.85 (d, J = 1.3 Hz, 1 H), 8.36 (d, J = 1.4 Hz, 1 H), 8.17 (s, 1 H), 8.16 (br d, J = 9.1 Hz, 2 H), 7.49 (br d, J = 8.2 Hz, 2 H), 4.69 (s, 2 H), 4.44 (d, J = 11.0 Hz, 1 H), 4.22 (d, J = 11.0 Hz, 1 H), 1.73 (s, 3 H). Anal. ($C_{18}H_{14}F_3N_5O_5$) C, H, N.

[0136] W. Synthesis of 6-nitro-2-({[4-(trifluoromethoxy)benzyl]oxy}methyl)-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (compound 23 of Table 1) by the method of Scheme 6.



23

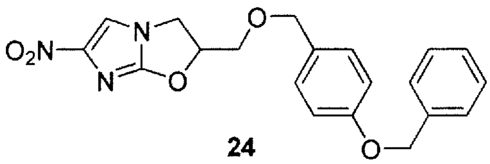
[0137] A mixture of glycidol (**115**) (303 mg, 4.09 mmol) and 4-(trifluoromethoxy)benzyl bromide (0.810 mL, 5.06 mmol) in anhydrous DMF (6 mL) under N_2 at 0 °C was treated with 60% NaH (246 mg, 6.15 mmol), then quickly degassed and resealed under N_2. After stirring at room temperature for 7 h, the mixture was cooled (CO_2/acetone), quenched with ice/aqueous $NaHCO_3$ (20 mL), added to water (100 mL) and extracted with EtOAc (4x 100 mL). The extracts were washed with brine (100 mL) and evaporated to dryness and the residue was chromatographed on silica gel. Elution with 0-5% Et_2O/petroleum ether firstly gave foreruns, and then further elution with 5-10% Et_2O/petroleum ether gave 2-({[4-(trifluoromethoxy)benzyl]oxy}methyl)oxirane (**116**) (625 mg, 62%) as an oil; ^{1}H NMR ($CDCl_3$) δ 7.38 (dt, *J* = 8.7, 2.3 Hz, 2 H), 7.20 (br dd, *J* = 8.7, 0.7 Hz, 2 H), 4.62 (d, *J* = 12.0 Hz, 1 H), 4.56 (d, *J* = 12.0 Hz, 1 H), 3.82 (dd, *J* = 11.5, 2.8 Hz, 1 H), 3.43 (dd, *J* = 11.5, 6.0 Hz, 1 H), 3.21 (m, 1 H), 2.82 (dd, *J* = 4.9, 4.2 Hz, 1 H), 2.63 (dd, *J* = 5.0, 2.7 Hz, 1 H); HRESIMS calcd for $C_{11}H_{11}F_3NaO_3$ *m/z* $[M + Na]^+$ 271.0552, found 271.0557.

[0138] Reaction of epoxide **116** with 2-bromo-4(5)-nitroimidazole (**80**) as in Example 2A at 107 °C for 13 h, followed by chromatography of the product on silica gel, eluting with 0-1% EtOAc/CH_2Cl_2 (foreruns) and then with 1-2% EtOAc/CH_2Cl_2, gave 1-(2-bromo-4-nitro-1*H*-imidazol-1-yl)-3-{[4-(trifluoromethoxy)benzyl]oxy}-2-propanol (**118**) (61%) as a white solid: mp (CH_2Cl_2/pentane) 80-81 °C; ^{1}H NMR ($CDCl_3$) δ 7.95 (s, 1 H), 7.35 (dt, *J* = 8.7, 2.3 Hz, 2 H), 7.23 (br d, *J* = 8.7 Hz, 2 H), 4.57 (s, 2 H), 4.20 (dd, *J* = 13.6, 2.9 Hz, 1 H), 4.14 (m, 1 H), 4.07 (dd, *J* = 13.4, 7.1 Hz, 1 H), 3.59 (dd, *J* = 9.6, 4.2 Hz, 1 H), 3.46 (dd, *J* = 9.6, 5.3 Hz, 1 H), 2.61 (d, *J* = 5.0 Hz, 1 H); HRESIMS calcd for $C_{14}H_{14}BrF_3N_3O_5$ *m/z* $[M + H]^+$ 442.0044, 440.0063, found 442.0044, 440.0061. Anal. ($C_{14}H_{13}BrF_3N_3O_5$) H, N. C: calcd, 38.20; found, 38.61.

[0139] Ring closure of alcohol **118** with NaH as in Example 2A for 65 min, followed by chromatography of the product on silica gel, eluting with CH_2Cl_2, gave **23** (90%) as a cream solid: mp (CH_2Cl_2/hexane) 134-135 °C; ^{1}H NMR ($CDCl_3$) δ 7.53 (s, 1 H), 7.29 (dt, *J* = 8.7, 2.1

Hz, 2 H), 7.20 (br d, J = 8.0 Hz, 2 H), 5.42 (m, 1 H), 4.32 (dd, J = 10.0, 8.6 Hz, 1 H), 4.26 (dd, J = 10.0, 6.5 Hz, 1 H), 3.89 (dd, J = 11.3, 3.9 Hz, 1 H), 3.78 (dd, J = 11.3, 3.5 Hz, 1 H). Anal. ($C_{14}H_{12}F_3N_3O_5$) C, H, N.

[0140] X. Synthesis of 2-({[4-(benzyloxy)benzyl]oxy}methyl)-6-nitro-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (compound 24 of Table 1) by the method of Scheme 6.



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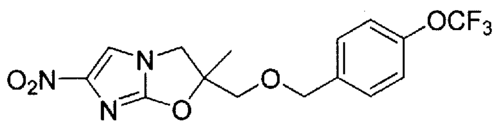
[0141] Alkylation of glycidol (**115**) with 4-(benzyloxy)benzyl chloride as in Example 2W for 10 h, followed by chromatography of the product on silica gel, eluting with 0-7.5% Et_2O/petroleum ether (foreruns) and then with 7.5-10% Et_2O/petroleum ether, gave a crude oil, which was further chromatographed on silica gel. Elution with 0-50% CH_2Cl_2/petroleum ether firstly gave foreruns, and then further elution with 50-66% CH_2Cl_2/petroleum ether gave 2-({[4-(benzyloxy)benzyl]oxy}methyl)oxirane (**117**) (32%) (reported by Cousse et al., EP 187096A1 from epichlorohydrin and 4-(benzyloxy)benzyl alcohol) as an oil; ^{1}H NMR ($CDCl_3$) δ 7.45-7.29 (m, 5 H), 7.27 (dt, J = 8.8, 2.3 Hz, 2 H), 6.95 (dt, J = 8.7, 2.5 Hz, 2 H), 4.54 (d, J = 11.6 Hz, 1 H), 4.48 (d, J = 11.6 Hz, 1 H), 3.72 (dd, J = 11.5, 3.2 Hz, 1 H), 3.42 (dd, J = 11.4, 5.8 Hz, 1 H), 3.17 (m, 1 H), 2.79 (dd, J = 5.0, 4.2 Hz, 1 H), 2.60 (dd, J = 5.1, 2.7 Hz, 1 H); HRESIMS calcd for $C_{17}H_{18}NaO_3$ m/z $[M + Na]^+$ 293.1148, found 293.1143.

[0142] Reaction of epoxide **117** with 2-bromo-4(5)-nitroimidazole (**80**) as in Example 2A at 108 °C for 14 h, followed by chromatography of the product on silica gel, eluting with 0-1% EtOAc/CH_2Cl_2 (foreruns) and then with 2-4% EtOAc/CH_2Cl_2, gave 1-{[4-(benzyloxy)benzyl]oxy}-3-(2-bromo-4-nitro-1*H*-imidazol-1-yl)-2-propanol (**119**) (73%) as a white solid: mp (CH_2Cl_2/hexane) 122-123 °C; ^{1}H NMR ($CDCl_3$) δ 7.88 (s, 1 H), 7.46-7.30 (m, 5 H), 7.24 (dt, J = 8.6, 2.4 Hz, 2 H), 6.98 (dt, J = 8.7, 2.4 Hz, 2 H), 5.08 (s, 2 H), 4.52 (d, J = 11.5 Hz, 1 H), 4.48 (d, J = 11.5 Hz, 1 H), 4.18-4.01 (m, 3 H), 3.55 (dd, J = 9.7, 4.0 Hz, 1 H), 3.39 (dd, J = 9.6, 5.1 Hz, 1 H), 2.48 (d, J = 5.3 Hz, 1 H). Anal. ($C_{20}H_{20}BrN_3O_5$) C, H, N.

[0143] Ring closure of alcohol **119** with NaH as in Example 2A for 80 min, followed by chromatography of the product on silica gel, eluting with CH_2Cl_2 (foreruns) and then with 1-2% EtOAc/CH_2Cl_2, gave **24** (88%) as a cream solid: mp (CH_2Cl_2/hexane) 123-124 °C; ^{1}H NMR ($CDCl_3$) δ 7.50 (s, 1 H), 7.45-7.29 (m, 5 H), 7.19 (dt, J = 8.7, 2.4 Hz, 2 H), 6.95 (dt, J = 8.6, 2.4 Hz, 2 H), 5.37 (m, 1 H), 4.54 (d, J = 11.7 Hz, 1 H), 4.50 (d, J = 11.7 Hz, 1 H), 4.27 (dd, J = 10.0, 8.5 Hz, 1 H), 4.22 (dd, J = 10.0, 6.5 Hz, 1 H), 3.82 (dd, J = 11.2, 4.2 Hz, 1 H), 3.73 (dd, J = 11.2, 3.6 Hz, 1 H). Anal. ($C_{20}H_{19}N_3O_5$) C, H, N.

[0144] Y. Synthesis of 2-methyl-6-nitro-2-({[4-(trifluoromethoxy)benzyl]oxy}methyl)-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (compound 25 of Table 1) by the method of Scheme 6.



25

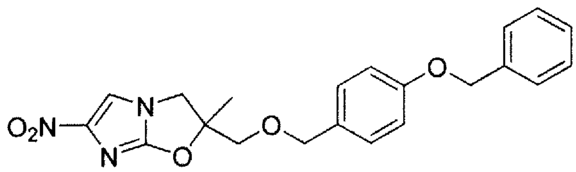
[0145] A solution of 2-methyl-2-propen-1-ol (**120**) (2.34 mL, 27.8 mmol) in anhydrous DMF (10 mL, then 2x 2mL to rinse) was added to a suspension of 60% NaH (1.32 g, 33.1 mmol) in anhydrous DMF (10 mL) under N_2 at 0 °C and the mixture was stirred at 0 °C for 30 min. 4-(Trifluoromethoxy)benzyl bromide (5.1 mL, 31.9 mmol) was added and the mixture was stirred at room temperature for 21 h. The resulting mixture was added to ice/aqueous $NaHCO_3$ (200 mL) and extracted with 25% EtOAc/petroleum ether (2x 200 mL) and 50% EtOAc/petroleum ether (3x 200 mL). The extracts were washed with water (200 mL), the volatile solvents were removed, and the residual oil was chromatographed on silica gel. Elution with petroleum ether firstly gave foreruns, then further elution with 0-15% CH_2Cl_2/petroleum ether gave 1-{[(2-methyl-2-propenyl)oxy]methyl}-4-(trifluoromethoxy)benzene (**121**) (6.57 g, 96%) as an oil that was used directly in the next step; ^{1}H NMR ($CDCl_3$) δ 7.37 (dt, J = 8.7, 2.3 Hz, 2 H), 7.19 (br d, J = 8.0 Hz, 2 H), 5.00 (m, 1 H), 4.94 (m, 1 H), 4.48 (s, 2 H), 3.94 (s, 2 H), 1.77 (s, 3 H).

[0146] Epoxidation of alkene **121** with 3-chloroperbenzoic acid as in Example 2G, followed by chromatography of the product on silica gel, eluting with 0-15% CH_2Cl_2/petroleum ether (foreruns) and then with 15-75% CH_2Cl_2/petroleum ether and CH_2Cl_2, gave 2-methyl-2-({[4-(trifluoromethoxy)benzyl]oxy}methyl)oxirane (**123**) (93%) as an oil; [1]H NMR ($CDCl_3$) δ 7.37 (dt, J = 8.7, 2.4 Hz, 2 H), 7.19 (br d, J = 7.9 Hz, 2 H), 4.59 (d, J = 12.1 Hz, 1 H), 4.54 (d, J = 12.1 Hz, 1 H), 3.61 (d, J = 11.1 Hz, 1 H), 3.44 (d, J = 11.1 Hz, 1 H), 2.75 (d, J = 4.9 Hz, 1 H), 2.64 (d, J = 4.9 Hz, 1 H), 1.40 (s, 3 H); HRCIMS (NH_3) calcd for $C_{12}H_{17}F_3O_3N$ m/z $[M + H + NH_3]^+$ 280.1161, found 280.1144.

[0147] Reaction of epoxide **123** with 2-bromo-4(5)-nitroimidazole (**80**) as in Example 2A at 108 °C for 15 h, followed by chromatography of the product on silica gel, eluting with CH_2Cl_2, gave 1-(2-bromo-4-nitro-1*H*-imidazol-1-yl)-2-methyl-3-{[4-(trifluoromethoxy)benzyl]oxy}-2-propanol (**125**) (94%) as a pale yellow oil; [1]H NMR ($CDCl_3$) δ 8.00 (s, 1 H), 7.33 (dt, J = 8.6, 2.3 Hz, 2 H), 7.22 (br d, J = 8.0 Hz, 2 H), 4.56 (s, 2 H), 4.15 (d, J = 14.8 Hz, 1 H), 4.04 (d, J = 14.5 Hz, 1 H), 3.39 (s, 2 H), 2.51 (s, 1 H), 1.22 (s, 3 H); HRESIMS calcd for $C_{15}H_{16}BrF_3N_3O_5$ m/z $[M + H]^+$ 456.0200, 454.0220, found 456.0197, 454.0221.

[0148] Ring closure of alcohol **125** with NaH as in Example 2A for 80 min, followed by chromatography of the product on silica gel, eluting with CH_2Cl_2 (foreruns) and then with 0-1% EtOAc/CH_2Cl_2, gave **25** (87%) as a pale yellow solid: mp (CH_2Cl_2/hexane) 110-111 °C; [1]H NMR ($CDCl_3$) δ 7.50 (s, 1 H), 7.26 (br d, J= 8.4 Hz, 2 H), 7.19 (br d, J= 8.3 Hz, 2 H), 4.59 (d, J = 12.3 Hz, 1 H), 4.56 (d, J= 12.3 Hz, 1 H), 4.36 (d, J= 10.0 Hz, 1 H), 3.91 (d, J= 10.0 Hz, 1 H), 3.72 (d, J= 10.7 Hz, 1 H), 3.59 (d, J= 10.6 Hz, 1 H), 1.65 (s, 3 H). Anal. ($C_{15}H_{14}F_3N_3O_5$) C, H, N.

[0149] Z. Synthesis of 2-({[4-(benzyloxy)benzyl]oxy}methyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole (compound 26 of Table 1) by the method of Scheme 6.



26

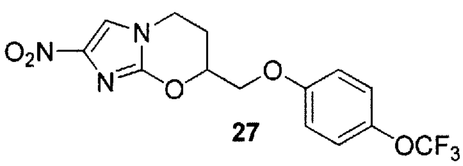
[0150] A solution of 2-methyl-2-propen-1-ol (**120**) (1.17 mL, 13.9 mmol) in anhydrous DMF (5 mL, then 2x 1mL to rinse) was added to a suspension of 60% NaH (674 mg, 16.9 mmol) in anhydrous DMF (5 mL) under N_2 at 0 °C and the mixture was stirred at 0 °C for 30 min. A solution of 4-(benzyloxy)benzyl chloride (3.87 g, 16.6 mmol) in anhydrous DMF (6 mL, then 2x 2 mL to rinse) was added and the mixture was stirred at room temperature for 16 h. The resulting mixture was added to ice/aqueous $NaHCO_3$ (100 mL) and extracted with EtOAc (4x 100 mL). The extracts were washed with water (100 mL), the EtOAc was removed, and the residual oil was chromatographed on silica gel. Elution with petroleum ether firstly gave foreruns, then further elution with 0-25% CH_2Cl_2/petroleum ether gave 1-(benzyloxy)-4-{[(2-methyl-2-propenyl)oxy]methyl}benzene (**122**) (reported by Wennerberg et al., 1999 via alkylation of 4-(benzyloxy)benzyl alcohol) (3.48 g, 93%) as an oil that was used directly in the next step; ^{1}H NMR ($CDCl_3$) δ 7.45-7.28 (m, 5 H), 7.27 (dt, J = 8.5, 2.4 Hz, 2 H), 6.95 (dt, J = 8.7, 2.4 Hz, 2 H), 5.07 (s, 2 H), 4.99 (m, 1 H), 4.91 (m, 1 H), 4.42 (s, 2 H), 3.91 (s, 2 H), 1.76 (s, 3 H).

[0151] Epoxidation of alkene **122** with 3-chloroperbenzoic acid as in Example 2G for 2.5 h, followed by chromatography of the product on silica gel, eluting with 50% CH_2Cl_2/petroleum ether (foreruns) and then with 50-80% CH_2Cl_2/petroleum ether and CH_2Cl_2, gave 2-({[4-(benzyloxy)benzyl]oxy}methyl)-2-methyloxirane (**124**) (95%) as an oil; ^{1}H NMR ($CDCl_3$) δ 7.45-7.29 (m, 5 H), 7.26 (dt, J = 8.7, 2.4 Hz, 2 H), 6.95 (dt, J = 8.7, 2.5 Hz, 2 H), 5.07 (s, 2 H), 4.52 (d, J = 11.6 Hz, 1 H), 4.47 (d, J = 11.6 Hz, 1 H), 3.54 (d, J = 11.0 Hz, 1 H), 3.42 (d, J = 11.0 Hz, 1 H), 2.73 (d, J = 4.9 Hz, 1 H), 2.62 (d, J = 4.9 Hz, 1 H), 1.39 (s, 3 H); HREIMS calcd for $C_{18}H_{20}O_3$ m/z (M^+) 284.1412, found 284.1416.

[0152] Reaction of epoxide **124** with 2-bromo-4(5)-nitroimidazole (**80**) as in Example 2A at 108 °C for 16 h, followed by chromatography of the product on silica gel, eluting with CH_2Cl_2 (foreruns) and then with 0-2% EtOAc/CH_2Cl_2 gave 1-{[4-(benzyloxy)benzyl]oxy}-3-(2-bromo-4-nitro-1*H*-imidazol-1-yl)-2-methyl-2-propanol (**126**) (100%) as a light yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.94 (s, 1 H), 7.46-7.30 (m, 5 H), 7.22 (dt, J = 8.6, 2.4 Hz, 2 H), 6.98 (dt, J = 8.7, 2.5 Hz, 2 H), 5.08 (s, 2 H), 4.50 (d, J = 11.5 Hz, 1 H), 4.47 (d, J = 11.5 Hz, 1 H), 4.11 (d, J = 14.4 Hz, 1 H), 4.00 (d, J = 14.4 Hz, 1 H), 3.34 (s, 2 H), 2.55 (s, 1 H), 1.17 (s, 3 H); HRESIMS calcd for $C_{21}H_{23}BrN_3O_5$ m/z $[M + H]^+$ 478.0796, 476.0816, found 478.0792, 476.0809.

[0153] Ring closure of alcohol **126** with NaH (1.5 equiv.) as in Example 2A for 80 min, followed by chromatography of the product on silica gel, eluting with CH_2Cl_2, gave **26** (97%) as a cream solid: mp (CH_2Cl_2/hexane) 130-131 °C; ^{1}H NMR ($CDCl_3$) δ 7.48 (s, 1 H), 7.45-7.29 (m, 5 H), 7.16 (dt, *J* = 8.7, 2.4 Hz, 2 H), 6.94 (dt, *J* = 8.7, 2.4 Hz, 2 H), 5.06 (s, 2 H), 4.52 (d, *J* = 11.7 Hz, 1 H), 4.47 (d, *J* = 11.7 Hz, 1 H), 4.32 (d, *J* = 10.0 Hz, 1 H), 3.86 (d, *J* = 10.0 Hz, 1 H), 3.67 (d, *J* = 10.6 Hz, 1 H), 3.53 (d, *J* = 10.6 Hz, 1 H), 1.62 (s, 3 H). Anal. ($C_{21}H_{21}N_3O_5$) C, H, N.

[0154] AA. Synthesis of 2-nitro-7-{[4-(trifluoromethoxy)phenoxy]methyl}-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound 27 of Table 1) by the method of Scheme 7.



27

[0155] 4-Bromo-1-butene (2.65 mL, 26.1 mmol) was added to a mixture of 2-chloro-4(5)-nitroimidazole (**81**) (2.50 g, 17.0 mmol) and K_2CO_3 (7.88 g, 57.0 mmol) in anhydrous DMF (12 mL) under N_2, and the mixture was stirred at 66 °C for 12 h. The resulting cooled mixture was added to ice/aqueous $NaHCO_3$ (140 mL) and extracted with 50% EtOAc/petroleum ether (5x 100 mL). The extracts were washed with water (100 mL) and then evaporated to dryness and the residue was chromatographed on silica gel. Elution with 0-10% EtOAc/petroleum ether firstly gave foreruns, and then further elution with 10-20% EtOAc/petroleum ether gave 1-(3-butenyl)-2-chloro-4-nitro-1*H*-imidazole (**127**) (2.82 g, 82%) as a cream solid: mp (Et_2O/pentane) 56-58 °C; ^{1}H NMR ($CDCl_3$) δ 7.72 (s, 1 H), 5.74 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1 H), 5.18 (dq, *J* = 10.3, 1.0 Hz, 1 H), 5.12 (dq, *J* = 17.1, 1.3 Hz, 1 H), 4.09 (t, *J* = 6.9 Hz, 2 H), 2.58 (qt, *J* = 6.9, 1.1 Hz, 2 H); HRESIMS calcd for $C_7H_9ClN_3O_2$ *m/z* $[M + H]^+$ 204.0349, 202.0378, found 204.0350, 202.0377.

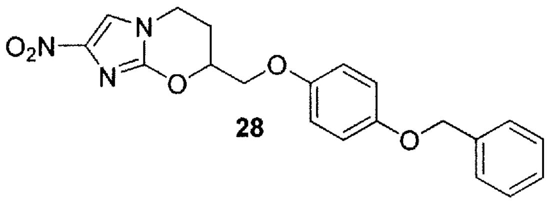
[0156] Epoxidation of alkene **127** with 3-chloroperbenzoic acid as in Example 2G for 50 h, followed by chromatography of the product on silica gel, eluting with 0-10% EtOAc/petroleum ether (foreruns) and then with 20-30% EtOAc/petroleum ether, firstly gave recovered alkene **127** (0.49 g, 17%). Elution with 0-5% Et_2O/CH_2Cl_2 gave a crude product, which was further chromatographed on silica gel, eluting with CH_2Cl_2 (foreruns) and then with 0-5% Et_2O/CH_2Cl_2, to give 2-chloro-4-nitro-1-[2-(2-oxiranyl)ethyl]-1*H*-imidazole (**129**) (73%) as a pale yellow solid: mp (CH_2Cl_2/hexane) 51-52 °C; ^{1}H NMR ($CDCl_3$) δ 7.81 (s, 1 H), 4.28-4.16 (m, 2 H), 2.98-2.92 (m, 1 H), 2.85 (dd, *J* = 4.7, 4.0 Hz, 1 H), 2.53 (dd, *J* = 4.8, 2.6 Hz, 1 H), 2.35-2.25 (m, 1 H), 1.87-1.77 (m, 1 H); HRESIMS calcd for $C_7H_9ClN_3O_3$ *m/z* $[M + H]^+$ 220.0298, 218.0327, found 220.0297, 218.0322.

[0157] 4-Trifluoromethoxyphenol (0.375 mL, 2.89 mmol) was added to a mixture of epoxide **129** (250 mg, 1.15 mmol) and powdered K_2CO_3 (558 mg, 4.04 mmol) in anhydrous 2-butanone (3 mL) under N_2, and the mixture was stirred at 81 °C for 12 h. The resulting cooled mixture was diluted with water (50 mL) and extracted with CH_2Cl_2 (4x 50 mL). The extracts were evaporated to dryness and the residue was chromatographed on silica gel. Elution with 0-25% EtOAc/petroleum ether firstly gave foreruns, and then further elution with 25-33% EtOAc/petroleum ether gave 4-(2-chloro-4-nitro-1*H*-imidazol-1-yl)-1-[4-(trifluoromethoxy)phenoxy]-2-butanol (**130**) (306 mg, 67%) as a pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.85 (s, 1 H), 7.16 (br dd, *J* = 9.1, 0.8 Hz, 2 H), 6.88 (dt, *J* = 9.2, 3.0 Hz, 2 H), 4.37-4.24 (m, 2 H), 4.02-3.93 (m, 2 H), 3.86 (dd, *J* = 10.0, 7.8 Hz, 1 H), 2.47 (dd, *J* = 4.2, 1.1 Hz, 1 H), 2.13-1.98 (m, 2 H); HRESIMS calcd for $C_{14}H_{14}ClF_3N_3O_3$ *m/z* $[M + H]^+$ 398.0540, 396.0569, found 398.0538, 396.0567.

[0158] Further elution of the above column with 66% EtOAc/petroleum ether gave a crude solid (72 mg), which was further chromatographed on silica gel. Elution with CH_2Cl_2 gave foreruns and then further elution with 0-3% $EtOAc/CH_2Cl_2$ gave **27** (61 mg, 15%) as a cream solid: mp (CH_2Cl_2/hexane) 138-140 °C; ^{1}H NMR ($CDCl_3$) δ 7.45 (s, 1 H), 7.17 (br dd, *J* = 9.1, 0.7 Hz, 2 H), 6.91 (dt, *J* = 9.2, 3.0 Hz, 2 H), 4.75 (m, 1 H), 4.31 (dd, *J* = 10.2, 4.3 Hz, 1 H), 4.26-4.09 (m, 3 H), 2.52-2.32 (m, 2 H). Anal. ($C_{14}H_{12}F_3N_3O_5$) C, H, N.

[0159] A stirred solution of alcohol **130** (305 mg, 0.771 mmol) in anhydrous DMF (5 mL) under N_2 at 0 °C was treated with 60% NaH (49 mg, 1.23 mmol), then quickly degassed and resealed under N_2. After stirring at room temperature for 2.5 h, the reaction was cooled (CO_2/acetone), quenched with ice/aqueous $NaHCO_3$ (10 mL), added to brine (40 mL), and extracted with CH_2Cl_2 (6x 50 mL). The combined extracts were evaporated to dryness and the residue was chromatographed on silica gel. Elution with 25-40% EtOAc/petroleum ether firstly gave foreruns, and then further elution with 50-66% EtOAc/petroleum ether gave additional **27** (217 mg, 78%) as a pale yellow solid (see data above).

[0160] BB. Synthesis of 7-{[4-(benzyloxy)phenoxy]methyl}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound 28 of Table 1) by the method of Scheme 7.


28

[0161] A mixture of 2-bromo-4(5)-nitroimidazole (**80**) (2.50 g, 13.0 mmol), 4-bromo-1-butene (2.00 mL, 19.7 mmol) and K_2CO_3 (5.39 g, 39.0 mmol) in anhydrous DMF (25 mL) under N_2 was stirred at 73 °C for 4.5 h. The resulting cooled mixture was added to ice/aqueous $NaHCO_3$ (200 mL) and extracted with EtOAc (4x 200 mL). The extracts were washed with water (200 mL) and then evaporated to dryness and the residue was chromatographed on silica gel. Elution with 0-10% EtOAc/petroleum ether firstly gave foreruns, and then further elution with 20% EtOAc/petroleum ether gave 2-bromo-1-(3-butenyl)-4-nitro-1*H*-imidazole (**128**) (2.96 g, 92%) as a pale yellow waxy solid: mp 28-30 °C; ^1H NMR ($CDCl_3$) δ 7.77 (s, 1 H), 5.75 (ddt, J = 17.1, 10.2, 6.9 Hz, 1 H), 5.18 (dq, J = 10.2, 1.1 Hz, 1 H), 5.12 (dq, J = 17.1, 1.4 Hz, 1 H), 4.09 (t, J = 7.0 Hz, 2 H), 2.59 (qt, J = 6.9, 1.2 Hz, 2 H); HRFABMS calcd for $C_7H_9BrN_3O_2$ m/z $[M + H]^+$ 247.9858, 245.9878, found 247.9860, 245.9882.

[0162] Osmium tetroxide (3.75 mL of a 4% aqueous solution, 0.614 mmol) was added to a solution of alkene **128** (3.00 g, 12.2 mmol) and 4-methylmorpholine *N*-oxide (2.16 g, 18.4 mmol) in CH_2Cl_2 (75 mL), and then the mixture was stirred at room temperature for 4 h. The resulting precipitate was isolated by filtration, washed with CH_2Cl_2 and water, and then dried to give 4-(2-bromo-4-nitro-1*H*-imidazol-1-yl)-1,2-butanediol (**131**) (2.39 g, 70%) as a cream solid: mp (THF/Et_2O/pentane) 99-101 °C; ^1H NMR [$(CD_3)_2SO$] δ 8.55 (s, 1 H), 4.77 (d, J = 5.0 Hz, 1 H), 4.58 (t, J = 5.6 Hz, 1 H), 4.14 (m, 2 H), 3.42 (m, 1 H), 3.34 (dt, J = 10.7, 5.4 Hz, 1 H), 3.24

(dt, J = 10.7, 5.9 Hz, 1 H), 1.98 (dtd, J = 13.7, 7.9, 3.2 Hz, 1 H), 1.69 (dddd, J = 13.6, 9.1, 7.4, 6.0 Hz, 1 H). Anal. ($C_7H_{10}BrN_3O_4$) C, H, N.

[0163] The filtrate above was added to ice/aqueous Na_2SO_3 (100 mL) and extracted with EtOAc (3x 100 mL). The aqueous portion was saturated with salt and further extracted with EtOAc (7x 100 mL). The combined extracts were evaporated to dryness and the residue was chromatographed on silica gel. Elution with 50-67% EtOAc/petroleum ether firstly gave foreruns, and then further elution with 67% EtOAc/petroleum ether and EtOAc gave additional diol **131** (728 mg, 21%).

[0164] Triisopropylsilyl chloride (2.50 mL, 11.7 mmol) was added to a solution of diol **131** (3.11 g, 11.1 mmol) and imidazole (1.66 g, 24.4 mmol) in anhydrous DMF (30 mL) under N_2 and then the mixture was stirred at room temperature for 18 h. The resulting mixture was added to ice-water (200 mL) and extracted with EtOAc (4x 200 mL). The extracts were washed with water (200 mL) and then evaporated to dryness and the residue was chromatographed on silica gel. Elution with 0-20% EtOAc/petroleum ether firstly gave foreruns, and then further elution with 20-33% EtOAc/petroleum ether gave 4-(2-bromo-4-nitro-1*H*-imidazol-1-yl)-1-[(triisopropylsilyl)oxy]-2-butanol (**132**) (4.60 g, 95%) as a white solid: mp (CH_2Cl_2/pentane) 90-91 °C; ^{1}H NMR ($CDCl_3$) δ 7.89 (s, 1 H), 4.24 (dd, J = 7.7, 6.2 Hz, 2 H), 3.74 (dd, J = 9.6, 3.5 Hz, 1 H), 3.62 (m, 1 H), 3.53 (dd, J = 9.6, 6.8 Hz, 1 H), 2.59 (d, J = 3.8 Hz, 1 H), 1.95-1.82 (m, 2 H), 1.17-1.03 (m, 21 H). Anal. ($C_{16}H_{30}BrN_3O_4Si$) C, H, N.

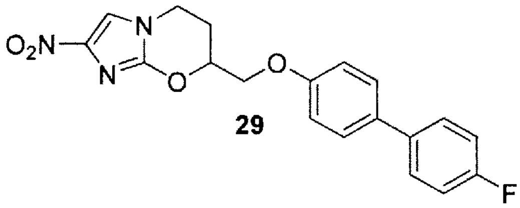
[0165] A stirred solution of alcohol **132** (2.45 g, 5.61 mmol) in anhydrous DMF (25 mL) under N_2 at 0 °C was treated with 60% NaH (388 mg, 9.70 mmol), then quickly degassed and resealed under N_2. After stirring at room temperature for 2 h, the reaction was cooled (CO_2/acetone), quenched with ice/aqueous $NaHCO_3$ (20 mL), diluted with ice-water (150 mL) and extracted with EtOAc (8x 80 mL). The extracts were washed with brine (100 mL) and then evaporated to dryness and the residue was chromatographed on silica gel. Elution with 0-25% EtOAc/petroleum ether firstly gave foreruns, and then further elution with 25% EtOAc/petroleum ether gave 2-nitro-7-{[(triisopropylsilyl)oxy]methyl}-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (**133**) (1.77 g, 89%) as a pale yellow solid: mp (CH_2Cl_2/pentane) 121-123 °C; ^{1}H NMR ($CDCl_3$) δ

7.42 (s, 1 H), 4.45 (m, 1 H), 4.17 (ddd, *J* = 12.3, 5.8, 3.7 Hz, 1 H), 4.06 (ddd, *J* = 12.3, 10.3, 5.4 Hz, 1 H), 4.03 (dd, *J* = 10.7, 4.1 Hz, 1 H), 3.95 (dd, *J* = 10.7, 5.8 Hz, 1 H), 2.37 (dddd, *J* = 14.5, 5.5, 3.6, 2.8 Hz, 1 H), 2.27 (dtd, *J* = 14.5, 10.1, 5.8 Hz, 1 H), 1.17-1.03 (m, 21 H). Anal. ($C_{16}H_{29}N_3O_4Si$) C, H, N.

[0166] A suspension of silyl ether **133** (1.627 g, 4.58 mmol) in a solution of 1% HCl in 95% EtOH (desilylation conditions described by Cunico et al., 1980) (58 mL) was stirred at room temperature for 35 h. The resulting solution was cooled (CO_2/acetone), neutralised by dropwise addition of 7M NH_3 in MeOH (7 mL) with stirring, and then concentrated to dryness and the residue was chromatographed on silica gel. Elution with 0-2% MeOH/CH_2Cl_2 firstly gave foreruns, and then further elution with 2% MeOH/CH_2Cl_2 gave (2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazin-7-yl)methanol (**134**) (877 mg, 96%) as a pale yellow solid: mp (THF/MeOH/CH_2Cl_2/hexane) 179-181 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.04 (s, 1 H), 5.12 (t, *J* = 5.8 Hz, 1 H), 4.48 (dtd, *J* = 10.2, 4.7, 2.5 Hz, 1 H), 4.13 (ddd, *J* = 12.5, 5.8, 3.0 Hz, 1 H), 4.04 (ddd, *J* = 12.4, 11.0, 5.1 Hz, 1 H), 3.64 (m, 2 H), 2.18 (dtd, *J* = 14.4, 5.0, 2.8 Hz, 1 H), 2.03 (dtd, *J* = 14.4, 10.6, 5.7 Hz, 1 H). Anal. ($C_7H_9N_3O_4$) C, H, N.

[0167] Diethylazodicarboxylate (0.070 mL, 0.45 mmol) was added dropwise to a suspension of alcohol **134** (52.4 mg, 0.263 mmol), triphenylphosphine (104 mg, 0.397 mmol), and 4-(benzyloxy)phenol (79.5 mg, 0.397 mmol) in anhydrous THF (1.0 mL) and the resulting mixture was stirred at room temperature for 51 h. The solvent was removed and the residue was chromatographed on silica gel. Elution with 0-1% EtOAc/CH_2Cl_2 firstly gave foreruns, and then further elution with 4% EtOAc/CH_2Cl_2 gave a crude solid, which was further chromatographed on silica gel. Elution with 0-33% EtOAc/petroleum ether firstly gave foreruns, and then further elution with 4% MeOH/CH_2Cl_2 gave **28** (36 mg, 36%) as a cream solid: mp (MeOH/CH_2Cl_2/hexane) 222-224 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.07 (s, 1 H), 7.46-7.28 (m, 5 H), 6.99-6.89 (m, 4 H), 4.86 (m, 1 H), 4.27-4.14 (m, 3 H), 4.09 (ddd, *J* = 12.5, 10.9, 5.2 Hz, 1 H), 2.35-2.25 (m, 1 H), 2.25-2.12 (m, 1 H). Anal. ($C_{20}H_{19}N_3O_5 \cdot 0.25H_2O$) C, H, N.

[0168] CC. Synthesis of 7-{[(4'-fluoro[1,1'-biphenyl]-4-yl)oxy]methyl}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound 29 of Table 1) by the method of Scheme 7.



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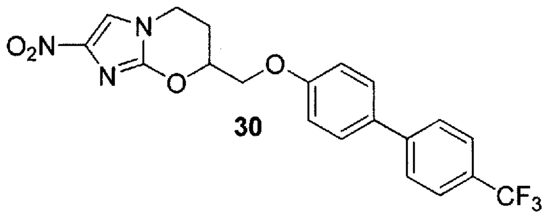
[0169] Diethylazodicarboxylate (0.070 mL, 0.45 mmol) was added dropwise to a suspension of oxazine alcohol **134** (see Example 2BB above) (251 mg, 1.26 mmol), triphenylphosphine (448 mg, 1.71 mmol), and 4-iodophenol (377 mg, 1.71 mmol) in anhydrous THF (3.0 mL) at 0 °C under N_2, and the resulting mixture was stirred at room temperature for 32 h. The solvent was removed and the residue was chromatographed on silica gel. Elution with CH_2Cl_2 firstly gave foreruns, and then further elution with 0-2% EtOAc/CH_2Cl_2 gave a crude solid, which was further chromatographed on silica gel. Elution with 0-50% EtOAc/petroleum ether firstly gave foreruns, and then further elution with 10% MeOH/CH_2Cl_2 gave 7-[(4-iodophenoxy)methyl]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (**135**) (433 mg, 86%) as a cream solid: mp (MeOH/CH_2Cl_2/hexane) 224-227 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.08 (s, 1 H), 7.62 (dt, *J* = 9.0, 2.7 Hz, 2 H), 6.86 (dt, *J* = 9.0, 2.7 Hz, 2 H), 4.89 (m, 1 H), 4.31 (dd, *J* = 11.1, 3.4 Hz, 1 H), 4.25 (dd, *J* = 11.1, 5.8 Hz, 1 H), 4.18 (ddd, *J* = 12.6, 5.8, 3.0 Hz, 1 H), 4.09 (ddd, *J* = 12.5, 10.8, 5.2 Hz, 1 H), 2.35-2.26 (m, 1 H), 2.25-2.12 (m, 1 H). Anal. ($C_{13}H_{12}IN_3O_4$) C, H, N.

[0170] A stirred mixture of iodide **135** (50.1 mg, 0.125 mmol), 4-fluorophenylboronic acid (31.5 mg, 0.225 mmol) and Pd(dppf)Cl_2 (14.1 mg, 0.019 mmol) in toluene (1 mL), EtOH (0.6 mL) and DMF (1.5 mL) was degassed for 5 min (vacuum pump) and then N_2 was added. An aqueous solution of 2M Na_2CO_3 (0.40 mL, 0.80 mmol) was added by syringe and the stirred mixture was again degassed for 5 min, and then N_2 was added. The resulting mixture was stirred at 90 °C for 90 min, and then cooled, diluted with aqueous $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (4x 50 mL). The extracts were evaporated to dryness and the residue was chromatographed on silica gel. Elution with 0-1% EtOAc/CH_2Cl_2 firstly gave foreruns, and then further elution with 1-2% EtOAc/CH_2Cl_2 gave **29** (42 mg, 91%) as a cream solid: mp (MeOH/CH_2Cl_2/pentane) 217-219 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.09 (s, 1 H), 7.66 (ddt, *J* = 8.9, 5.4, 2.7 Hz, 2 H), 7.60 (dt, *J* = 8.8, 2.6 Hz, 2 H), 7.25 (tt, *J* = 8.9, 2.7 Hz, 2 H), 7.09 (dt, *J* = 8.8, 2.6 Hz, 2 H), 4.93 (m, 1 H), 4.37 (dd, *J* = 11.1, 3.4 Hz, 1 H), 4.32 (dd, *J* = 11.1, 5.7 Hz, 1 H), 4.20 (ddd, *J* = 12.6, 5.8, 3.0 Hz, 1 H), 4.11 (ddd, *J* = 12.5, 10.8, 5.2 Hz, 1 H), 2.38-2.30 (m, 1 H), 2.29-2.16 (m, 1 H). Anal. ($C_{19}H_{16}FN_3O_4$) C, H, N.

[0171] DD. Synthesis of 2-nitro-7-({[4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]oxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound 30 of Table 1) by the method of Scheme 7.



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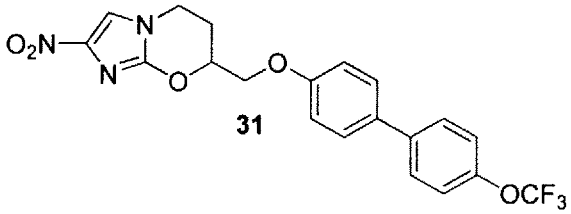
[0172] Suzuki coupling of iodide **135** and 4-(trifluoromethyl)phenylboronic acid as in Example 2CC above, followed by chromatography of the product on silica gel, eluting with 0-1% EtOAc/CH_2Cl_2 (foreruns) and then with 1-2% EtOAc/CH_2Cl_2, gave **30** (88%) as a cream solid: mp (MeOH/CH_2Cl_2/pentane) 242-245 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.09 (s, 1 H), 7.86 (br d, *J* = 8.2 Hz, 2 H), 7.77 (br d, *J* = 8.3 Hz, 2 H), 7.72 (dt, *J* = 8.9, 2.5 Hz, 2 H), 7.14 (dt, *J* = 8.8, 2.5 Hz, 2 H), 4.94 (m, 1 H), 4.40 (dd, *J* = 11.1, 3.4 Hz, 1 H), 4.34 (dd, *J* = 11.1, 5.8 Hz, 1 H), 4.21 (ddd, *J* = 12.5, 5.8, 3.0 Hz, 1 H), 4.12 (ddd, *J* = 12.5, 10.9, 5.2 Hz, 1 H), 2.39-2.30 (m, 1 H), 2.29-2.17 (m, 1 H). Anal. ($C_{20}H_{16}F_3N_3O_4$) C, H, N.

[0173] EE. Synthesis of 2-nitro-7-({[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]oxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound 31 of Table 1) by the method of Scheme 7.



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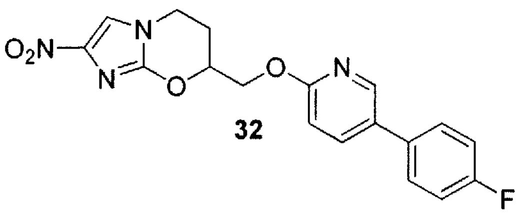
[0174] Suzuki coupling of iodide **135** and 4-(trifluoromethoxy)phenylboronic acid as in Example 2CC above, followed by chromatography of the product on silica gel, eluting with 0-1% EtOAc/CH_2Cl_2 (foreruns) and then with 1-2% EtOAc/CH_2Cl_2, gave **31** (89%) as a cream solid: mp (CH_2Cl_2/pentane) 197-199 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.12 (s, 1 H), 7.75 (dt, *J* = 8.8, 2.5 Hz, 2 H), 7.65 (dt, *J* = 8.9, 2.5 Hz, 2 H), 7.42 (br d, *J* = 8.0 Hz, 2 H), 7.11 (dt, *J* = 8.9, 2.5 Hz, 2 H), 4.94 (m, 1 H), 4.38 (dd, *J* = 11.1, 3.3 Hz, 1 H), 4.32 (dd, *J* = 11.1, 5.8 Hz, 1 H), 4.20 (ddd, *J* = 12.5, 5.7, 2.8 Hz, 1 H), 4.11 (ddd, *J* = 12.4, 11.0, 5.1 Hz, 1 H), 2.38-2.29 (m, 1 H), 2.28-2.15 (m, 1 H). Anal. ($C_{20}H_{16}F_3N_3O_5$) C, H, N.

[0175] **FF. Synthesis of 7-({[5-(4-fluorophenyl)-2-pyridinyl]oxy}methyl)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound 32 of Table 1) by the method of Scheme 8.**



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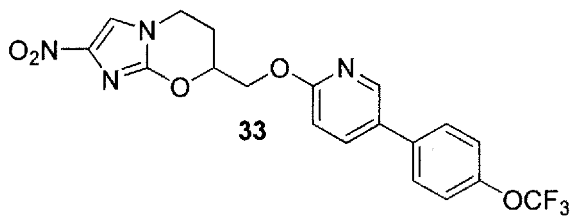
[0176] 5-Bromo-2-fluoropyridine (**91**) (0.52 mL, 5.05 mmol) was added to a solution of oxazine alcohol **134** (see Example 2BB) (500 mg, 2.51 mmol) in anhydrous DMF (10 mL) under N_2 at 0 °C. The resulting mixture was treated with 60% NaH (151 mg, 3.78 mmol), then quickly degassed and resealed under N_2. Further 5-bromo-2-fluoropyridine (**91**) (0.52 mL, 5.05 mmol) was added and the mixture was stirred at room temperature for 2.5 h, and then cooled (CO_2/acetone), quenched with ice/aqueous $NaHCO_3$ (30 mL), added to brine (100 mL) and extracted with CH_2Cl_2 (8x 100 mL). The combined extracts were evaporated to dryness and the residue was chromatographed on silica gel. Elution with 0-1% EtOAc/CH_2Cl_2 firstly gave foreruns, and then further elution with 2-4% EtOAc/CH_2Cl_2 gave 7-{[(5-bromo-2-pyridinyl)oxy]methyl}-2-nitro-

6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (**136**) (778 mg, 87%) as a white solid: mp ($MeOH/CH_2Cl_2$/hexane) 182-184 °C; ^1H NMR [$(CD_3)_2SO$] δ 8.30 (dd, *J* = 2.6, 0.5 Hz, 1 H), 8.07 (s, 1 H), 7.95 (dd, *J* = 8.8, 2.6 Hz, 1 H), 6.91 (dd, *J* = 8.8, 0.6 Hz, 1 H), 4.90 (m, 1 H), 4.58 (dd, *J* = 12.0, 3.3 Hz, 1 H), 4.52 (dd, *J* = 12.0, 6.0 Hz, 1 H), 4.17 (ddd, *J* = 12.6, 5.8, 2.8 Hz, 1 H), 4.09 (ddd, *J* = 12.5, 11.0, 5.2 Hz, 1 H), 2.34-2.26 (m, 1 H), 2.23-2.11 (m, 1 H). Anal. ($C_{12}H_{11}BrN_4O_4$) C, H, N.

[0177] Suzuki coupling of bromide **136** and 4-fluorophenylboronic acid (2.0 equiv.) as in Example 2M for 2.5 h, followed by chromatography of the product on silica gel, eluting with 0-3% $EtOAc/CH_2Cl_2$ (foreruns) and then with 3% $EtOAc/CH_2Cl_2$, gave **32** (91%) as a cream solid: mp ($MeOH/CH_2Cl_2$/hexane) 180-181 °C; ^1H NMR [$(CD_3)_2SO$] δ 8.47 (dd, *J* = 2.5, 0.5 Hz, 1 H), 8.09 (s, 1 H), 8.05 (dd, *J* = 8.6, 2.6 Hz, 1 H), 7.72 (ddt, *J* = 8.9, 5.4, 2.7 Hz, 2 H), 7.30 (tt, *J* = 8.9, 2.7 Hz, 2 H), 6.98 (dd, *J* = 8.6, 0.6 Hz, 1 H), 4.94 (m, 1 H), 4.64 (dd, *J* = 12.0, 3.4 Hz, 1 H), 4.58 (dd, *J* = 12.0, 6.1 Hz, 1 H), 4.19 (ddd, *J* = 12.6, 5.8, 2.7 Hz, 1 H), 4.10 (ddd, *J* = 12.4, 11.1, 5.1 Hz, 1 H), 2.37-2.28 (m, 1 H), 2.26-2.13 (m, 1 H); APCI MS *m/z* 371 $[M + H]^+$.

[0178] GG. Synthesis of 2-nitro-7-[({5-[4-(trifluoromethoxy)phenyl]-2-pyridinyl}oxy)methyl]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound 33 of Table 1) by the method of Scheme 8.



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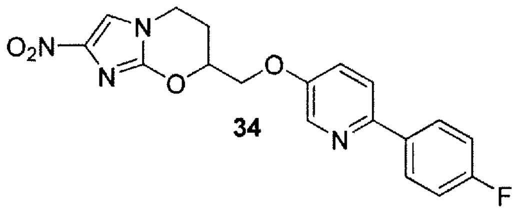
[0179] Suzuki coupling of bromide **136** and 4-(trifluoromethoxy)phenylboronic acid as in Example 2M for 2.5 h, followed by chromatography of the product on silica gel, eluting with CH_2Cl_2 (foreruns) and then with 0-2.5% $EtOAc/CH_2Cl_2$, gave **33** (90%) as a cream solid: mp (CH_2Cl_2/hexane) 161-163 °C; ^1H NMR ($CDCl_3$) δ 8.32 (d, *J* = 2.0 Hz, 1 H), 7.79 (dd, *J* = 8.5, 2.5 Hz, 1 H), 7.53 (br d, *J* = 8.7 Hz, 2 H), 7.45 (s, 1 H), 7.30 (br d, *J* = 8.1 Hz, 2 H), 6.86 (d, *J* = 8.6 Hz, 1 H), 4.84 (m, 1 H), 4.72 (dd, *J* = 11.7, 5.1 Hz, 1 H), 4.66 (dd, *J* = 11.7, 4.9 Hz, 1 H), 4.21

(ddd, J = 12.4, 5.8, 3.4 Hz, 1 H), 4.13 (ddd, J = 12.4, 10.4, 5.5 Hz, 1 H), 2.48-2.30 (m, 2 H). Anal. ($C_{19}H_{15}F_3N_4O_5$) C, H, N.

[0180] HH. Synthesis of 7-({[6-(4-fluorophenyl)-3-pyridinyl]oxy}methyl)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound 34 of Table 1) by the method of Scheme 8.



[0181] A mixture of epoxide **129** (see Example 2AA) (1.004 g, 4.61 mmol), 6-bromo-3-pyridinol (4.015 g, 23.1 mmol) and powdered K_2CO_3 (3.319 g, 24.0 mmol) in anhydrous 2-butanone (10 mL) under N_2 was stirred at 82-85 °C for 28 h. The resulting cooled mixture was diluted with water (100 mL) and extracted with 25% EtOAc/CH_2Cl_2 (3x 100 mL). The extracts were evaporated to dryness and the residue was chromatographed on silica gel. Elution with 0-40% EtOAc/petroleum ether firstly gave foreruns, and then further elution with 40% EtOAc/petroleum ether gave 1-[(6-bromo-3-pyridinyl)oxy]-4-(2-chloro-4-nitro-1*H*-imidazol-1-yl)-2-butanol (**137**) (667 mg, 37%) as a cream solid: mp (MeOH/CH_2Cl_2/pentane) 112-114 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.56 (s, 1 H), 8.12 (d, J = 3.1 Hz, 1 H), 7.53 (d, J = 8.8 Hz, 1 H), 7.39 (dd, J = 8.8, 3.2 Hz, 1 H), 5.28 (br d, J = 4.5 Hz, 1 H), 4.24 (dd, J = 14.0, 5.8 Hz, 1 H), 4.18 (dd, J = 14.2, 7.3 Hz, 1 H), 3.99 (dd, J = 10.0, 4.9 Hz, 1 H), 3.96 (dd, J = 10.0, 5.5 Hz, 1 H), 3.82 (m, 1 H), 2.06 (dtd, J = 13.9, 7.7, 3.4 Hz, 1 H), 1.90 (ddt, J = 13.7, 9.2, 6.7 Hz, 1 H); HRESIMS calcd for $C_{12}H_{13}BrClN_4O_4$ m/z $[M + H]^+$ 394.9754, 392.9782, 390.9803, found 394.9753, 392.9777, 390.9797.

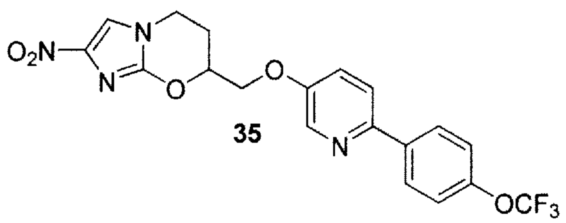
[0182] Further elution of the above column with EtOAc gave crude ring-closed material, which was further chromatographed on silica gel. Elution with 0-0.5% MeOH/CH_2Cl_2 firstly gave foreruns and then further elution with 0.5% MeOH/CH_2Cl_2 gave 7-{[(6-bromo-3-pyridinyl)oxy]methyl}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (**138**) (51 mg, 3%) as a cream solid: mp (MeOH/CH_2Cl_2/hexane) 200-202 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.19 (d, J = 3.2

Hz, 1 H), 8.08 (s, 1 H), 7.58 (d, *J* = 8.7 Hz, 1 H), 7.47 (dd, *J* = 8.8, 3.2 Hz, 1 H), 4.92 (m, 1 H), 4.43 (dd, *J* = 11.2, 3.3 Hz, 1 H), 4.37 (dd, *J* = 11.2, 5.8 Hz, 1 H), 4.19 (ddd, *J* = 12.5, 5.8, 3.0 Hz, 1 H), 4.10 (ddd, *J* = 12.5, 10.9, 5.2 Hz, 1 H), 2.36-2.27 (m, 1 H), 2.26-2.13 (m, 1 H). Anal. ($C_{12}H_{11}BrN_4O_4$) C, H, N.

[0183] Ring closure of alcohol **137** with NaH (1.6 equiv.) as in Example 2AA followed by chromatography of the product on silica gel, eluting with 0-0.5% $MeOH/CH_2Cl_2$ (foreruns) and then with 0.5-0.75% $MeOH/CH_2Cl_2$, gave additional **138** (87%) as a pale yellow solid (see above).

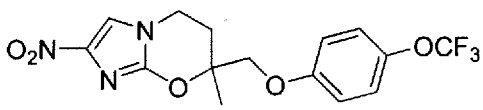
[0184] Suzuki coupling of bromide **138** and 4-fluorophenylboronic acid as in Example 2M for 2.5 h, followed by chromatography of the product on silica gel, eluting with 0-0.5% $MeOH/CH_2Cl_2$ (foreruns) and then with 0.5% $MeOH/CH_2Cl_2$, gave **34** (87%) as a cream solid: mp ($MeOH/CH_2Cl_2$/hexane) 204-206 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.43 (br d, *J* = 2.7 Hz, 1 H), 8.11 (s, 1 H), 8.07 (ddt, *J* = 8.9, 5.6, 2.7 Hz, 2 H), 7.94 (br d, *J* = 8.7 Hz, 1 H), 7.56 (dd, *J* = 8.8, 3.0 Hz, 1 H), 7.28 (tt, *J* = 8.9, 2.6 Hz, 2 H), 4.96 (m, 1 H), 4.47 (dd, *J* = 11.2, 3.2 Hz, 1 H), 4.41 (dd, *J* = 11.2, 5.8 Hz, 1 H), 4.20 (ddd, *J* = 12.5, 5.7, 2.9 Hz, 1 H), 4.11 (ddd, *J* = 12.4, 11.0, 5.1 Hz, 1 H), 2.38-2.30 (m, 1 H), 2.29-2.16 (m, 1 H); APCI MS *m/z* 371 $[M + H]^+$.

[0185] II. Synthesis of 2-nitro-7-[({6-[4-(trifluoromethoxy)phenyl]-3-pyridinyl}oxy)methyl]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound 35 of Table 1) by the method of Scheme 8.



[0186] Suzuki coupling of bromide **138** and 4-(trifluoromethoxy)phenylboronic acid as in Example 2M for 2.5 h, followed by chromatography of the product on silica gel, eluting with 0-0.33% $MeOH/CH_2Cl_2$ (foreruns) and then with 0.33% $MeOH/CH_2Cl_2$, gave **35** (87%) as a cream solid: mp ($MeOH/CH_2Cl_2$/hexane) 161-163 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.46 (d, *J* = 2.9 Hz, 1 H), 8.15 (br d, *J* = 8.8 Hz, 2 H), 8.11 (s, 1 H), 7.99 (d, *J* = 8.8 Hz, 1 H), 7.59 (dd, *J* = 8.8, 3.0 Hz, 1 H), 7.45 (br d, *J* = 8.2 Hz, 2 H), 4.96 (m, 1 H), 4.49 (dd, *J* = 11.2, 3.2 Hz, 1 H), 4.43 (dd, *J* = 11.2, 5.8 Hz, 1 H), 4.20 (ddd, *J* = 12.5, 5.6, 2.7 Hz, 1 H), 4.12 (ddd, *J* = 12.4, 11.0, 5.2 Hz, 1 H), 2.39-2.30 (m, 1 H), 2.29-2.16 (m, 1 H). Anal. ($C_{19}H_{15}F_3N_4O_5$) C, H, N.

[0187] JJ. Synthesis of 7-methyl-2-nitro-7-{[4-(trifluoromethoxy)phenoxy]methyl}-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound 36 of Table 1) by the method of Scheme 9.



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[0188] A solution of 4-iodo-2-methyl-1-butene (obtained by iodination of 3-methyl-3-buten-1-ol, as reported by Helmboldt et al., 2006) (2.01 g, 10.3 mmol) in anhydrous DMF (3 mL, then 3x 1 mL to rinse) was added to a stirred mixture of 2-chloro-4(5)-nitroimidazole (**81**) (1.00 g, 6.80 mmol) and powdered K_2CO_3 (2.83 g, 20.5 mmol) in anhydrous DMF (6.5 mL) under N_2, and the mixture was stirred at 61 °C for 20 h. The resulting cooled mixture was added to ice/aqueous $NaHCO_3$ (100 mL) and extracted with EtOAc (4x 100 mL). The extracts were washed with dilute brine (100 mL) and then evaporated to dryness and the residue was chromatographed on silica gel. Elution with 0-10% EtOAc/petroleum ether firstly gave foreruns, and then further elution with 10-15% EtOAc/petroleum ether gave 2-chloro-1-(3-methyl-3-butenyl)-4-nitro-1*H*-imidazole (**139**) (1.15 g, 78%) as a white solid: mp (CH_2Cl_2/pentane) 68-69 °C; ^{1}H NMR ($CDCl_3$) δ 7.71 (s, 1 H), 4.90 (m, 1 H), 4.69 (m, 1 H), 4.13 (t, *J* = 7.1 Hz, 2 H), 2.52 (br t, *J* = 7.1 Hz, 2 H), 1.80 (s, 3 H); HRFABMS calcd for $C_8H_{11}ClN_3O_2$ *m/z* $[M + H]^+$ 218.0510, 216.0540, found 218.0512, 216.0544.

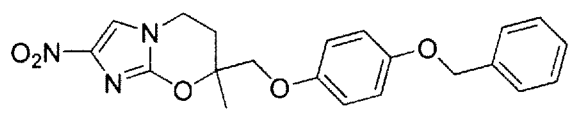
[0189] Epoxidation of alkene **139** with 3-chloroperbenzoic acid as in Example 2G for 4 h, followed by chromatography of the product on silica gel, eluting with CH_2Cl_2 (foreruns) and then with 0-5% EtOAc/CH_2Cl_2, gave 2-chloro-1-[2-(2-methyl-2-oxiranyl)ethyl]-4-nitro-1*H*-imidazole (**140**) (88%) as a cream solid: mp (CH_2Cl_2/pentane) 82-85 °C; ^{1}H NMR ($CDCl_3$) δ 7.78 (s, 1 H), 4.12 (t, *J* = 7.6 Hz, 1 H), 2.66 (d, *J* = 4.4 Hz, 1 H), 2.62 (d, *J* = 4.4 Hz, 1 H), 2.19 (dt, *J*

= 14.3, 7.7 Hz, 1 H), 2.04 (dt, *J* = 14.3, 7.4 Hz, 1 H), 1.39 (s, 3 H); HRFABMS calcd for $C_8H_{11}ClN_3O_3$ *m/z* [M + H]$^+$ 234.0459, 232.0489, found 234.0466, 232.0488.

[0190] Reaction of epoxide **140** with 4-trifluoromethoxyphenol as in Example 2AA at 82 °C for 10 h, followed by chromatography of the product on silica gel, eluting with CH_2Cl_2 (foreruns) and then with 0-2% EtOAc/CH_2Cl_2, gave 4-(2-chloro-4-nitro-1*H*-imidazol-1-yl)-2-methyl-1-[4-(trifluoromethoxy)phenoxy]-2-butanol (**141**) (77%) as a pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.81 (s, 1 H), 7.17 (br dd, *J* = 9.1, 0.7 Hz, 2 H), 6.90 (dt, *J* = 9.2, 3.1 Hz, 2 H), 4.29 (ddd, *J*= 14.1, 9.5, 6.3 Hz, 1 H), 4.24 (ddd, *J*= 14.1, 9.6, 6.5 Hz, 1 H), 3.85 (d, *J* = 9.0 Hz, 1 H), 3.82 (d, *J* = 9.0 Hz, 1 H), 2.23 (ddd, *J* = 13.8, 9.3, 6.5 Hz, 1 H), 2.21 (s, 1 H), 1.40 (s, 3 H); HRESIMS calcd for $C_{15}H_{16}ClF_3N_3O_5$ *m/z* [M + H]$^+$ 412.0697, 410.0725, found 412.0700, 410.0722.

[0191] Ring closure of alcohol **141** with NaH as in Example 2AA for 2 h, followed by chromatography of the product on silica gel, eluting with 25-33% EtOAc/petroleum ether (foreruns) and then with 50% EtOAc/petroleum ether, gave **36** (61%) as a cream solid: mp (CH_2Cl_2/pentane) 134-136 °C; ^{1}H NMR ($CDCl_3$) δ 7.45 (s, 1 H), 7.16 (br dd, *J* = 9.1, 0.8 Hz, 2 H), 6.87 (dt, *J* = 9.2, 3.0 Hz, 2 H), 4.21-4.02 (m, 4 H), 2.51 (ddd, *J* = 14.5, 7.4, 6.0 Hz, 1 H), 2.25 (dt, *J* = 14.5, 6.2 Hz, 1 H), 1.60 (s, 3 H). Anal. ($C_{15}H_{14}F_3N_3O_5$) C, H, N.

[0192] KK. Synthesis of 7-{[4-(benzyloxy)phenoxy]methyl}-7-methyl-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound 37 of Table 1) by the method of Scheme 9.



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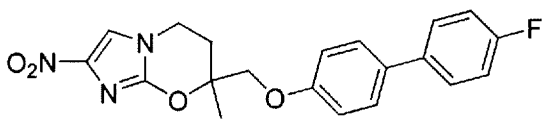
[0193] Reaction of epoxide **140** (see Example 2JJ) with 4-(benzyloxy)phenol as in Example 2AA at 82 °C for 10 h, followed by chromatography of the product on silica gel, eluting with CH_2Cl_2 (foreruns) and then with 2% EtOAc/CH_2Cl_2, gave 1-[4-(benzyloxy)phenoxy]-4-(2-chloro-4-nitro-1*H*-imidazol-1-yl)-2-methyl-2-butanol (**142**) (79%) as an oil; ^{1}H NMR ($CDCl_3$) δ

7.79 (s, 1 H), 7.44-7.29 (m, 5 H), 6.92 (dt, J = 9.2, 3.0 Hz, 2 H), 6.83 (dt, J = 9.2, 3.0 Hz, 2 H), 4.28 (ddd, J= 14.0, 9.7, 6.1 Hz, 1 H), 4.23 (ddd, J= 14.0, 9.7, 6.3 Hz, 1 H), 3.81 (d, J = 9.1 Hz, 1 H), 3.77 (d, J = 9.0 Hz, 1 H), 2.29 (s, 1 H), 2.22 (ddd, J = 13.8, 9.6, 6.2 Hz, 1 H), 2.02 (ddd, J = 13.6, 9.7, 6.5 Hz, 1 H), 1.38 (s, 3 H); HRESIMS calcd for $C_{21}H_{23}ClN_3O_5$ m/z $[M + H]^+$ 434.1293, 432.1321, found 434.1298, 432.1319.

[0194] Ring closure of alcohol **142** with NaH (1.4 equiv.) as in Example 2AA, followed by chromatography of the product on silica gel, eluting with 0-33% EtOAc/petroleum ether (foreruns) and then with EtOAc, gave the crude product, which was further chromatographed on silica gel. Elution with 0-2.5% EtOAc/CH_2Cl_2 firstly gave foreruns, then further elution with 2.5% EtOAc/CH_2Cl_2 gave **37** (53%) as a cream solid: mp (CH_2Cl_2/hexane) 174-176 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.07 (s, 1 H), 7.45-7.28 (m, 5 H), 6.94 (dt, J = 9.3, 2.9 Hz, 2 H), 6.89 (dt, J = 9.3, 2.9 Hz, 2 H), 5.04 (s, 2 H), 4.21-4.06 (m, 2 H), 4.10 (s, 2 H), 2.37 (ddd, J = 14.5, 7.9, 6.2 Hz, 1 H), 2.17 (dt, J = 14.4, 5.8 Hz, 1 H), 1.48 (s, 3 H). Anal. ($C_{21}H_{21}N_3O_5$) C, H, N.

[0195] LL. Synthesis of 7-{[(4'-fluoro[1,1'-biphenyl]-4-yl)oxy]methyl}-7-methyl-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound 38 of Table 1) by the method of Scheme 9.



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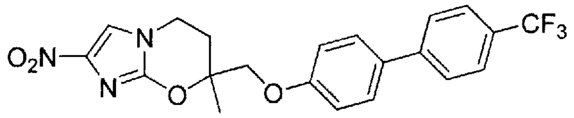
[0196] Reaction of epoxide **140** (see Example 2JJ) with 4-iodophenol as in Example 2AA at 83 °C for 8 h, followed by chromatography of the product on silica gel, eluting with 0-2% EtOAc/CH_2Cl_2 (foreruns) and then with 5% EtOAc/CH_2Cl_2, gave 4-(2-chloro-4-nitro-1*H*-imidazol-1-yl)-1-(4-iodophenoxy)-2-methyl-2-butanol (**143**) (81%) as a cream solid: mp (CH_2Cl_2/pentane) 91-93 °C; ^{1}H NMR ($CDCl_3$) δ 7.80 (s, 1 H), 7.59 (dt, J = 8.9, 2.6 Hz, 1 H), 6.69 (dt, J = 8.9, 2.6 Hz, 1 H), 4.28 (ddd, J= 14.1, 9.6, 6.3 Hz, 1 H), 4.23 (ddd, J= 14.1, 9.4, 6.5 Hz, 1 H), 3.82 (d, J= 9.0 Hz, 1 H), 3.79 (d, J= 9.0 Hz, 1 H), 2.22 (ddd, J = 13.8, 9.2, 6.5 Hz, 1

H), 2.20 (s, 1 H), 2.02 (ddd, J = 13.8, 9.6, 6.6 Hz, 1 H), 1.39 (s, 3 H); HRESIMS calcd for $C_{14}H_{16}ClIN_3O_4$ m/z $[M + H]^+$ 453.9840, 451.9869, found 453.9832, 451.9857.

[0197] Ring closure of alcohol **143** with NaH (1.5 equiv.) as in Example 2AA, followed by chromatography of the product on silica gel, eluting with 0-33% EtOAc/petroleum ether (foreruns) and then with 0-5% EtOAc/CH_2Cl_2, gave 7-[(4-iodophenoxy)methyl]-7-methyl-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (**144**) (74%) as a pale yellow solid: mp (CH_2Cl_2/hexane) 170-172 °C; ^{1}H NMR ($CDCl_3$) δ 7.57 (dt, J = 9.0, 2.7 Hz, 2 H), 7.44 (s, 1 H), 6.64 (dt, J = 9.0, 2.7 Hz, 2 H), 4.19-4.05 (m, 2 H), 4.07 (d, J = 9.6 Hz, 1 H), 4.02 (d, J = 9.6 Hz, 1 H), 2.49 (ddd, J = 14.5, 7.4, 6.0 Hz, 1 H), 2.24 (ddd, J = 14.5, 6.4, 5.9 Hz, 1 H), 1.58 (s, 3 H). Anal. ($C_{14}H_{14}IN_3O_4$) C, H, N.

[0198] Suzuki coupling of iodide **144** and 4-fluorophenylboronic acid as in Example 2CC for 100 min, followed by chromatography of the product on silica gel, eluting with 0-1% EtOAc/CH_2Cl_2 (foreruns) and then with 1-2% EtOAc/CH_2Cl_2, gave **38** (90%) as a pale yellow-orange solid: mp (CH_2Cl_2/pentane) 160-162 °C; ^{1}H NMR ($CDCl_3$) δ 7.51-7.44 (m, 5 H), 7.10 (tt, J = 8.7, 2.6 Hz, 2 H), 6.92 (dt, J = 8.8, 2.6 Hz, 2 H), 4.23-4.06 (m, 4 H), 2.53 (ddd, J = 14.4, 7.2, 6.0 Hz, 1 H), 2.28 (ddd, J = 14.5, 6.8, 5.9 Hz, 1 H), 1.62 (s, 3 H). Anal. ($C_{20}H_{18}FN_3O_4$) C, H, N.

[0199] MM. Synthesis of 7-methyl-2-nitro-7-({[4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]oxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound 39 of Table 1) by the method of Scheme 9.



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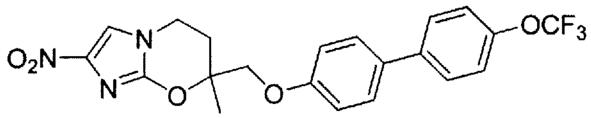
[0200] Suzuki coupling of iodide **144** (see Example 2LL) and 4-(trifluoromethyl)phenylboronic acid as in Example 2CC for 100 min, followed by chromatography of the product on silica gel, eluting with 0-1% EtOAc/CH_2Cl_2 (foreruns) and then with 1% EtOAc/CH_2Cl_2, gave **39** (87%) as a cream solid: mp (CH_2Cl_2/pentane) 196-198 °C; ^{1}H NMR ($CDCl_3$) δ 7.67 (br d, J = 8.5 Hz, 2 H), 7.63 (br d, J = 8.4 Hz, 2 H), 7.54 (dt, J = 8.8, 2.6 Hz, 2 H), 7.46 (s, 1 H), 6.96 (dt, J = 8.8, 2.6 Hz, 2 H), 4.23-4.08 (m, 4 H), 2.54 (ddd, J = 14.5, 7.3, 6.0 Hz, 1 H), 2.28 (ddd, J = 14.5, 6.6, 5.9 Hz, 1 H), 1.62 (s, 3 H). Anal. ($C_{21}H_{18}F_3N_3O_4$) C, H, N.

[0201] NN. Synthesis of 7-methyl-2-nitro-7-({[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]oxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound 40 of Table 1) by the method of Scheme 9.



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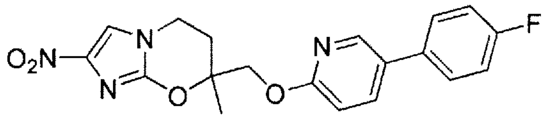
[0202] Suzuki coupling of iodide **144** (see Example 2LL) and 4-(trifluoromethoxy)phenylboronic acid as in Example 2CC for 105 min, followed by chromatography of the product on silica gel, eluting with 0-1% EtOAc/CH_2Cl_2 (foreruns) and then with 1% EtOAc/CH_2Cl_2, gave **40** (89%) as a pale yellow-pink solid: mp (CH_2Cl_2/pentane) 186-188 °C; ^{1}H NMR ($CDCl_3$) δ 7.53 (dt, J = 8.8, 2.5 Hz, 2 H), 7.49 (dd, J = 8.8, 2.6 Hz, 2 H), 7.46 (s, 1 H), 7.26 (br dd, J = 8.7, 0.8 Hz, 2 H), 6.94 (dt, J = 8.8, 2.6 Hz, 2 H), 4.23-4.07 (m, 4 H), 2.53 (ddd, J = 14.5, 7.2, 6.0 Hz, 1 H), 2.28 (ddd, J = 14.5, 6.7, 5.9 Hz, 1 H), 1.62 (s, 3 H). Anal. ($C_{21}H_{18}F_3N_3O_5$) C, H, N.

[0203] OO. Synthesis of 7-({[5-(4-fluorophenyl)-2-pyridinyl]oxy}methyl)-7-methyl-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound 41 of Table 1) by the method of Scheme 10.



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[0204] A solution of 4-iodo-2-methyl-1-butene (obtained by iodination of 3-methyl-3-buten-1-ol, as reported by Helmboldt et al., 2006) (2.68 g, 13.7 mmol) in anhydrous DMF (5 mL, then 2x 2 mL + 1 mL to rinse) was added to a stirred mixture of 2-bromo-4(5)-nitroimidazole

(**80**) (2.00 g, 10.4 mmol) and powdered K_2CO_3 (4.35 g, 31.5 mmol) in anhydrous DMF (10 mL) under N_2, and the resulting mixture was stirred at 60 °C for 11 h. The resulting cooled mixture was added to ice/aqueous $NaHCO_3$ (120 mL) and extracted with EtOAc (3x 100 mL). The extracts were washed with dilute brine (100 mL) and then evaporated to dryness and the residue was chromatographed on silica gel. Elution with 0-10% EtOAc/petroleum ether firstly gave foreruns, and then further elution with 20-25% EtOAc/petroleum ether gave 2-bromo-1-(3-methyl-3-butenyl)-4-nitro-1*H*-imidazole (**145**) (2.296 g, 85%) as a white solid: mp (CH_2Cl_2/pentane) 90-92 °C; ^{1}H NMR ($CDCl_3$) δ 7.76 (s, 1 H), 4.90 (m, 1 H), 4.70 (m, 1 H), 4.12 (t, *J* = 7.2 Hz, 2 H), 2.52 (br t, *J* = 7.1 Hz, 2 H), 1.81 (s, 3 H). Anal. ($C_8H_{10}BrN_3O_2$) C, H, N.

[0205] Osmium tetroxide (2.55 mL of a 4% aqueous solution, 0.417 mmol) was added to a solution of alkene **145** (2.15 g, 8.27 mmol) and 4-methylmorpholine *N*-oxide (1.49 g, 12.7 mmol) in CH_2Cl_2 (55 mL), and then the mixture was stirred at room temperature for 4 h. The mixture was cooled (-20 °C), slowly diluted with petroleum ether (70 mL) and recooled (-20 °C) and the resulting precipitate was isolated by filtration, washed with petroleum ether and water, and dried to give 4-(2-bromo-4-nitro-1*H*-imidazol-1-yl)-2-methyl-1,2-butanediol (**146**) (1.53 g, 63%) as a pale grey-brown solid: mp (MeOH/CH_2Cl_2/pentane) 121-123 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.58 (s, 1 H), 4.69 (br t, *J* = 5.3 Hz, 1 H), 4.41 (br s, 1 H), 4.13 (t, *J* = 8.1 Hz, 2 H), 3.24 (dd, *J* = 10.6, 5.6 Hz, 1 H), 3.18 (dd, *J* = 10.7, 5.6 Hz, 1 H), 1.89 (dt, *J* = 13.3, 8.1 Hz, 1 H), 1.82 (dt, *J* = 13.3, 8.1 Hz, 1 H), 1.09 (s, 3 H). Anal. ($C_8H_{12}BrN_3O_4$) C, H, N.

[0206] The aqueous portion above was saturated with salt and extracted with EtOAc (6x 100 mL). The combined extracts were evaporated to dryness and the residue was chromatographed on silica gel. Elution with 50-67% EtOAc/petroleum ether firstly gave foreruns, and then further elution with 67-80% EtOAc/petroleum ether gave additional **146** (882 mg, 36%).

[0207] Triisopropylsilyl chloride (2.00 mL, 9.35 mmol) was added to a solution of diol **146** (2.507 g, 8.52 mmol) and imidazole (1.278 g, 18.8 mmol) in anhydrous DMF (25 mL) under N_2 and then the mixture was stirred at room temperature for 3 d. Further triisopropylsilyl chloride (0.50 mL, 2.34 mmol) was added and the mixture was stirred at room temperature for 3 d. The resulting mixture was added to ice-water (130 mL) and extracted with EtOAc (4x 100 mL).

The extracts were washed with water (100 mL) and then evaporated to dryness and the residue was chromatographed on silica gel. Elution with 0-10% EtOAc/petroleum ether firstly gave foreruns, and then further elution with 33% EtOAc/petroleum ether gave 4-(2-bromo-4-nitro-1*H*-imidazol-1-yl)-2-methyl-1-[(triisopropylsilyl)oxy]-2-butanol (**147**) (3.658 g, 95%) as a white solid: mp (CH_2Cl_2/pentane) 73-75 °C; ^{1}H NMR ($CDCl_3$) δ 7.85 (s, 1 H), 4.26 (ddd, *J* = 14.1, 10.3, 5.8 Hz, 1 H), 4.19 (ddd, *J* = 14.1, 10.3, 6.0 Hz, 1 H), 3.56 (s, 2 H), 2.52 (s, 1 H), 2.11 (ddd, *J* = 13.6, 10.3, 5.8 Hz, 1 H), 1.87 (ddd, *J* = 13.6, 10.3, 6.0 Hz, 1 H), 1.25 (s, 3 H), 1.21-1.04 (m, 21 H). Anal. ($C_{17}H_{32}BrN_3O_4Si$) C, H, N.

[0208] A stirred solution of alcohol **147** (3.60 g, 8.00 mmol) in anhydrous DMF (35 mL) under N_2 at 0 °C was treated with 60% NaH (550 mg, 13.8 mmol), then quickly degassed and resealed under N_2. After stirring at room temperature for 2.5 h and then at 46 °C for 190 min, the reaction was cooled (CO_2/acetone), quenched with ice/aqueous $NaHCO_3$ (40 mL), diluted with ice-water (140 mL) and extracted with EtOAc (5x 80 mL). The combined extracts were washed with brine (80 mL) and then evaporated to dryness and the residue was chromatographed on silica gel. Elution with 0-15% EtOAc/petroleum ether firstly gave foreruns, and then further elution with 15-25% EtOAc/petroleum ether gave 7-methyl-2-nitro-7-{[(triisopropylsilyl)oxy]methyl}-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (**148**) (2.599 g, 88%) as a pale yellow solid: mp (CH_2Cl_2/pentane) 112-114 °C; ^{1}H NMR ($CDCl_3$) δ 7.41 (s, 1 H), 4.14 (ddd, *J* = 12.4, 6.9, 5.8 Hz, 1 H), 4.03 (ddd, *J* = 12.4, 7.3, 5.8 Hz, 1 H), 3.84 (d, *J* = 10.2 Hz, 1 H), 3.77 (d, *J* = 10.2 Hz, 1 H), 2.37 (ddd, *J* = 14.4, 7.2, 5.8 Hz, 1 H), 2.11 (ddd, *J* = 14.4, 6.9, 5.9 Hz, 1 H), 1.45 (s, 3 H), 1.16-0.97 (m, 21 H). Anal. ($C_{17}H_{31}N_3O_4Si$) C, H, N.

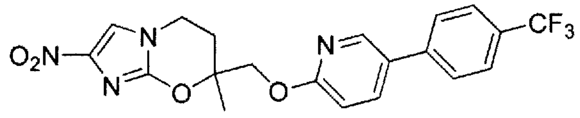
[0209] A suspension of silyl ether **148** (2.518 g, 6.81 mmol) in a solution of 1% HCl in 95% EtOH (desilylation conditions described by Cunico et al., 1980) (90 mL) was stirred at 44 °C for 3 days. The resulting solution was cooled (CO_2/acetone), neutralised by dropwise addition of 7M NH_3 in MeOH (8 mL) and $NaHCO_3$ (0.10 g, 1.19 mmol) with stirring, and then concentrated to dryness and the residue was chromatographed on silica gel. Elution with 0-1% MeOH/CH_2Cl_2 firstly gave foreruns, and then further elution with 1.5% MeOH/CH_2Cl_2 gave (7-methyl-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazin-7-yl)methanol (**149**) (1.285 g, 88%) as a pale yellow solid: mp (MeOH/CH_2Cl_2/hexane) 199-201 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.03 (s, 1 H), 5.22 (t, *J* =

5.7 Hz, 1 H), 4.13 (dt, *J* = 12.9, 6.0 Hz, 1 H), 4.05 (ddd, *J* = 13.0, 8.1, 5.6 Hz, 1 H), 3.54 (dd, *J* = 11.6, 5.5 Hz, 1 H), 3.48 (dd, *J* = 11.6, 5.8 Hz, 1 H), 2.21 (ddd, *J* = 14.4, 8.1, 5.9 Hz, 1 H), 2.00 (dt, *J* = 14.4, 5.8 Hz, 1 H), 1.32 (s, 3 H). Anal. ($C_8H_{11}N_3O_4$) C, H, N.

[0210] A solution of alcohol **149** (200 mg, 0.938 mmol) in anhydrous DMF (4 mL) under N_2 at 0 °C was treated with 60% NaH (53.8 mg, 1.35 mmol), then quickly degassed and resealed under N_2. 5-Bromo-2-fluoropyridine (**91**) (0.245 mL, 2.38 mmol) was added and the mixture was stirred at room temperature for 2.5 h, and then cooled (CO_2/acetone), quenched with ice/aqueous $NaHCO_3$ (10 mL), added to brine (40 mL), and extracted with CH_2Cl_2 (10x 50 mL). The combined extracts were evaporated to dryness and the residue was chromatographed on silica gel. Elution with CH_2Cl_2 firstly gave foreruns, and then further elution with 1-3% EtOAc/CH_2Cl_2 gave 7-{[(5-bromo-2-pyridinyl)oxy]methyl}-7-methyl-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (**150**) (269 mg, 78%) as a cream solid: mp (CH_2Cl_2/pentane) 172-174 °C; ^{1}H NMR ($CDCl_3$) δ 8.17 (br d, *J* = 2.2 Hz, 1 H), 7.67 (dd, *J* = 8.8, 2.5 Hz, 1 H), 6.64 (dd, *J* = 8.7, 0.4 Hz, 1 H), 4.49 (d, *J* = 11.5 Hz, 1 H), 4.42 (d, *J* = 11.4 Hz, 1 H), 4.17 (dt, *J* = 12.7, 6.1 Hz, 1 H), 4.09 (ddd, *J* = 12.6, 7.7, 5.8 Hz, 1 H), 2.45 (ddd, *J* = 14.5, 7.6, 5.9 Hz, 1 H), 2.18 (dt, *J* = 14.6, 6.1 Hz, 1 H), 1.57 (s, 3 H). Anal. ($C_{13}H_{13}BrN_4O_4$) C, H, N.

[0211] Suzuki coupling of bromide **150** and 4-fluorophenylboronic acid as in Example 2M for 135 min, followed by chromatography of the product on silica gel, eluting with 0-3% EtOAc/CH_2Cl_2 (foreruns) and then with 3-5% EtOAc/CH_2Cl_2, gave **41** (92%) as a cream solid: mp (CH_2Cl_2/pentane) 145-147 °C; ^{1}H NMR ($CDCl_3$) δ 8.28 (d, *J* = 2.5 Hz, 1 H), 7.76 (dd, *J* = 8.6, 2.5 Hz, 1 H), 7.46 (ddt, *J* = 8.8, 5.1, 2.6 Hz, 2 H), 7.45 (s, 1 H), 7.14 (tt, *J* = 8.6, 2.6 Hz, 2 H), 6.88 (d, *J* = 8.6 Hz, 1 H), 4.58 (d, *J* = 11.4 Hz, 1 H), 4.50 (d, *J* = 11.4 Hz, 1 H), 4.20 (ddd, *J* = 12.6, 6.5, 6.1 Hz, 1 H), 4.10 (ddd, *J* = 12.6, 7.3, 5.8 Hz, 1 H), 2.49 (ddd, *J* = 14.4, 7.3, 6.0 Hz, 1 H), 2.21 (ddd, *J* = 14.4, 6.6, 6.0 Hz, 1 H), 1.61 (s, 3 H). Anal. ($C_{19}H_{17}FN_4O_4$) C, H, N.

[0212] PP. Synthesis of 7-methyl-2-nitro-7-[({5-[4-(trifluoromethyl)phenyl]-2-pyridinyl}oxy)methyl]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound 42 of Table 1) by the method of Scheme 10.



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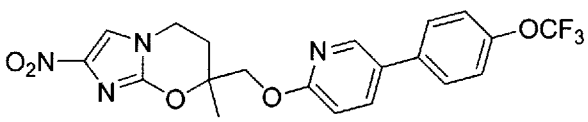
[0213] Suzuki coupling of bromide **150** and 4-(trifluoromethyl)phenylboronic acid as in Example 2M for 2 h, followed by chromatography of the product on silica gel, eluting with 0-2% EtOAc/CH_2Cl_2 (foreruns) and then with 3-5% EtOAc/CH_2Cl_2, gave **42** (91%) as a cream solid: mp (CH_2Cl_2/pentane) 212-214 °C; ^1H NMR ($CDCl_3$) δ 8.35 (dd, *J* = 2.5, 0.4 Hz, 1 H), 7.82 (dd, *J* = 8.6, 2.5 Hz, 1 H), 7.71 (br d, *J* = 8.2 Hz, 2 H), 7.62 (br d, *J* = 8.1 Hz, 2 H), 7.46 (s, 1 H), 6.82 (dd, *J* = 8.7, 0.4 Hz, 1 H), 4.60 (d, *J* = 11.4 Hz, 1 H), 4.52 (d, *J* = 11.4 Hz, 1 H), 4.21 (ddd, *J* = 12.6, 6.5, 6.0 Hz, 1 H), 4.11 (ddd, *J* = 12.7, 7.4, 5.8 Hz, 1 H), 2.50 (ddd, *J* = 14.6, 7.4, 5.9 Hz, 1 H), 2.22 (ddd, *J* = 14.5, 6.5, 6.0 Hz, 1 H), 1.61 (s, 3 H). Anal. ($C_{20}H_{17}F_3N_4O_4$) C, H, N.

[0214] QQ. Synthesis of 7-methyl-2-nitro-7-[({5-[4-(trifluoromethoxy)phenyl]-2-pyridinyl}oxy)methyl]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound 43 of Table 1) by the method of Scheme 10.



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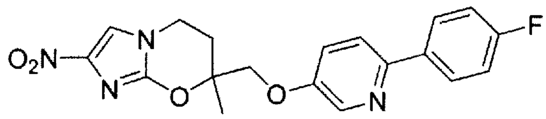
[0215] Suzuki coupling of bromide **150** and 4-(trifluoromethoxy)phenylboronic acid as in Example 2M for 2 h, followed by chromatography of the product on silica gel, eluting with 0-2% EtOAc/CH_2Cl_2 (foreruns) and then with 2-3.5% EtOAc/CH_2Cl_2, gave **43** (92%) as a cream solid: mp (CH_2Cl_2/pentane) 195-198 °C; ^1H NMR ($CDCl_3$) δ 8.31 (dd, *J* = 2.5, 0.7 Hz, 1 H), 7.78 (dd, *J* = 8.5, 2.6 Hz, 1 H), 7.52 (dt, *J* = 8.8, 2.5 Hz, 2 H), 7.45 (s, 1 H), 7.30 (br dd, *J* = 8.7, 0.8 Hz, 2 H), 6.79 (dd, *J* = 8.6, 0.7 Hz, 1 H), 4.59 (d, *J* = 11.4 Hz, 1 H), 4.50 (d, *J* = 11.4 Hz, 1 H), 4.20 (ddd, *J* = 12.6, 6.7, 5.9 Hz, 1 H), 4.10 (ddd, *J* = 12.6, 7.4, 5.8 Hz, 1 H), 2.49 (ddd, *J* = 14.5, 7.4, 5.9 Hz, 1 H), 2.21 (ddd, *J* = 14.5, 6.6, 5.9 Hz, 1 H), 1.61 (s, 3 H). Anal. ($C_{20}H_{17}F_3N_4O_5$) C, H, N.

[0216] RR. Synthesis of 7-({[6-(4-fluorophenyl)-3-pyridinyl]oxy}methyl)-7-methyl-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound 44 of Table 1) by the method of Scheme 10.



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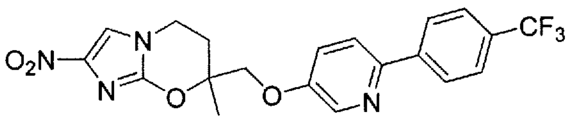
[0217] Reaction of epoxide **140** (see Example 2JJ) with 6-bromo-3-pyridinol as in Example 2AA at 84 °C for 18.5 h, followed by chromatography of the product on silica gel, eluting with 25-40% EtOAc/petroleum ether (foreruns) and then with 40-50% EtOAc/petroleum ether, gave 1-[(6-bromo-3-pyridinyl)oxy]-4-(2-chloro-4-nitro-1*H*-imidazol-1-yl)-2-methyl-2-butanol (**151**) (70%) as a pale yellow-brown foam; ^{1}H NMR ($CDCl_3$) δ 8.09 (dd, *J* = 3.0, 0.3 Hz, 1 H), 7.80 (s, 1 H), 7.41 (dd, *J* = 8.7, 0.4 Hz, 1 H), 7.13 (dd, *J* = 8.7, 3.2 Hz, 1 H), 4.29 (ddd, *J* = 14.2, 9.4, 6.4 Hz, 1 H), 4.25 (ddd, *J* = 14.1, 9.4, 6.7 Hz, 1 H), 3.89 (d, *J* = 8.9 Hz, 1 H), 3.86 (d, *J* = 9.0 Hz, 1 H), 2.22 (ddd, *J* = 13.9, 9.3, 6.5 Hz, 1 H), 2.18 (s, 1 H), 2.04 (ddd, *J* = 13.8, 9.4, 6.7 Hz, 1 H), 1.42 (s, 3 H); HRESIMS calcd for $C_{13}H_{15}BrClN_4O_4$ *m/z* $[M + H]^+$ 408.9910, 406.9939, 404.9960, found 408.9920, 406.9945, 404.9966.

[0218] Ring closure of alcohol **151** with NaH (1.5 equiv.) as in Example 2AA, followed by chromatography of the product on silica gel, eluting with 0-50% EtOAc/petroleum ether (foreruns) and then with 0-2% MeOH/CH_2Cl_2, gave 7-{[(6-bromo-3-pyridinyl)oxy]methyl}-7-methyl-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (**152**) (66%) as a light yellow solid: mp (CH_2Cl_2/hexane) 170-171 °C; ^{1}H NMR ($CDCl_3$) δ 8.06 (dd, *J* = 3.1, 0.3 Hz, 1 H), 7.46 (s, 1 H), 7.40 (dd, *J* = 8.7, 0.3 Hz, 1 H), 7.11 (dd, *J* = 8.7, 3.2 Hz, 1 H), 4.21-4.07 (m, 4 H), 2.52 (ddd, *J* = 14.5, 8.1, 6.3 Hz, 1 H), 2.24 (dt, *J* = 14.5, 5.7 Hz, 1 H), 1.60 (s, 3 H). Anal. ($C_{13}H_{13}BrN_4O_4$) C, H, N.

[0219] Suzuki coupling of bromide **152** and 4-fluorophenylboronic acid as in Example 2M for 2 h, followed by chromatography of the product on silica gel, eluting with 0-3% EtOAc/CH_2Cl_2 (foreruns) and then with 3-7% EtOAc/CH_2Cl_2, gave **44** (88%) as a cream solid: mp (CH_2Cl_2/hexane) 203-204 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.39 (d, *J* = 2.8 Hz, 1 H), 8.10 (s, 1 H), 8.06 (ddt, J = 9.0, 5.6, 2.6 Hz, 2 H), 7.92 (d, J = 8.8 Hz, 1 H), 7.53 (dd, J = 8.8, 3.0 Hz, 1 H), 7.27 (tt, J = 8.9, 2.6 Hz, 2 H), 4.33 (s, 2 H), 4.25-4.11 (m, 2 H), 2.42 (ddd, J = 14.5, 8.2, 6.2 Hz, 1 H), 2.21 (dt, J = 14.4, 5.7 Hz, 1 H), 1.52 (s, 3 H). Anal. ($C_{19}H_{17}FN_4O_4$) C, H, N.

[0220] SS. Synthesis of 7-methyl-2-nitro-7-[({6-[4-(trifluoromethyl)phenyl]-3-pyridinyl}oxy)methyl]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound 45 of Table 1) by the method of Scheme 10.



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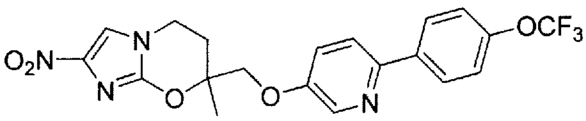
[0221] Suzuki coupling of bromide **152** (see Example 2RR) and 4-(trifluoromethyl)phenylboronic acid as in Example 2M for 130 min, followed by chromatography of the product on silica gel, eluting with 0-3% EtOAc/CH_2Cl_2 (foreruns) and then with 4-7% EtOAc/CH_2Cl_2, gave **45** (65%) as a cream solid: mp (CH_2Cl_2/hexane) 215-217 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.46 (d, J = 2.9 Hz, 1 H), 8.25 (br d, J = 8.1 Hz, 2 H), 8.10 (s, 1 H), 8.06 (d, J = 8.8 Hz, 1 H), 7.81 (br d, J = 8.3 Hz, 2 H), 7.59 (dd, J = 8.8, 3.0 Hz, 1 H), 4.36 (s, 2 H), 4.26-4.11 (m, 2 H), 2.42 (ddd, J = 14.5, 8.1, 6.0 Hz, 1 H), 2.21 (dt, J = 14.4, 5.7 Hz, 1 H), 1.53 (s, 3 H). Anal. ($C_{20}H_{17}F_3N_4O_4$) C, H, N.

[0222] TT. Synthesis of 7-methyl-2-nitro-7-[({6-[4-(trifluoromethoxy)phenyl]-3-pyridinyl}oxy)methyl]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound 46 of Table 1) by the method of Scheme 10.



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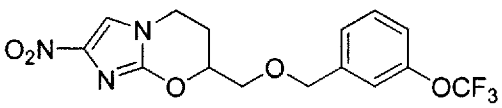
[0223] Suzuki coupling of bromide **152** (see Example 2RR) and 4-(trifluoromethoxy)phenylboronic acid as in Example 2M for 130 min, followed by chromatography of the product on silica gel, eluting with 0-4% EtOAc/CH_2Cl_2 (foreruns) and then with 5-7% EtOAc/CH_2Cl_2, gave **46** (84%) as a cream solid: mp (CH_2Cl_2/pentane) 202-203 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.42 (d, *J* = 2.8 Hz, 1 H), 8.14 (dt, *J* = 8.9, 2.6 Hz, 2 H), 8.10 (s, 1 H), 7.97 (d, *J* = 8.8 Hz, 1 H), 7.56 (dd, *J* = 8.8, 3.0 Hz, 1 H), 7.44 (br dd, *J* = 8.8, 0.8 Hz, 2 H), 4.34 (s, 2 H), 4.25-4.11 (m, 2 H), 2.42 (ddd, *J* = 14.5, 8.2, 6.1 Hz, 1 H), 2.21 (dt, *J* = 14.4, 5.7 Hz, 1 H), 1.52 (s, 3 H). Anal. ($C_{20}H_{17}F_3N_4O_5$) C, H, N.

[0224] UU. Synthesis of 2-nitro-7-({[3-(trifluoromethoxy)benzyl]oxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound 47 of Table 1) by the method of Scheme 11.



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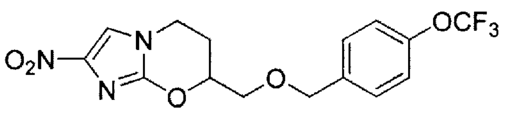
[0225] A mixture of oxazine alcohol **134** (see Example 2BB above) (31.8 mg, 0.160 mmol) and 3-(trifluoromethoxy)benzyl bromide (0.040 mL, 0.247 mmol) in anhydrous DMF (3 mL) under N_2 at 0 °C was treated with 60% NaH (9.5 mg, 0.238 mmol), then quickly degassed and resealed under N_2. After stirring at room temperature for 2.5 h, the mixture was cooled (CO_2/acetone), quenched with ice/aqueous $NaHCO_3$ (10 mL), added to brine (40 mL) and extracted with CH_2Cl_2 (4x 50 mL). The combined extracts were evaporated to dryness and the residue was chromatographed on silica gel. Elution with 0-1% EtOAc/CH_2Cl_2 firstly gave foreruns, and then further elution with 1-2% EtOAc/CH_2Cl_2 gave **47** (44 mg, 74%) as a cream solid: mp (CH_2Cl_2/pentane) 110-112 °C; ^{1}H NMR ($CDCl_3$) δ 7.41 (s, 1 H), 7.41-7.35 (m, 1 H), 7.23 (br d, *J* = 7.8 Hz, 1 H), 7.19-7.13 (m, 2 H), 4.62 (s, 2 H), 4.58 (m, 1 H), 4.15 (ddd, *J* = 12.4, 5.8, 3.7 Hz, 1 H), 4.06 (ddd, *J* = 12.3, 10.1, 5.6 Hz, 1 H), 3.84 (dd, *J* = 10.6, 4.3 Hz, 1 H), 3.78 (dd, *J* = 10.6, 5.1 Hz, 1 H), 2.40-2.21 (m, 2 H). Anal. ($C_{15}H_{14}F_3N_3O_5$) C, H, N.

[0226] VV. Synthesis of 2-nitro-7-({[4-(trifluoromethoxy)benzyl]oxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound 48 of Table 1) by the method of Scheme 11.



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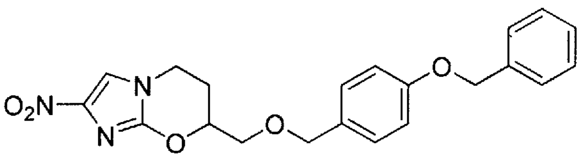
[0227] Alkylation of oxazine alcohol **134** (see Example 2BB above) with 4-(trifluoromethoxy)benzyl bromide (1.9 equiv.) and NaH (1.7 equiv.) as in Example 2UU above for 165 min, followed by chromatography of the product on silica gel, eluting with 0-0.5% MeOH/CH_2Cl_2 (foreruns) and then with 0.5% MeOH/CH_2Cl_2, gave **48** (69%) as a cream solid: mp (CH_2Cl_2/hexane) 158-160 °C; ^{1}H NMR ($CDCl_3$) δ 7.41 (s, 1 H), 7.34 (dt, J = 8.8, 2.3 Hz, 2 H), 7.20 (br d, J = 7.9 Hz, 2 H), 4.61 (s, 2 H), 4.61-4.54 (m, 1 H), 4.14 (ddd, J = 12.4, 5.7, 3.7 Hz, 1 H), 4.06 (ddd, J = 12.3, 10.0, 5.8 Hz, 1 H), 3.82 (dd, J = 10.7, 4.4 Hz, 1 H), 3.78 (dd, J = 10.7, 4.9 Hz, 1 H), 2.38-2.21 (m, 1 H). Anal. ($C_{15}H_{14}F_3N_3O_5$) C, H, N.

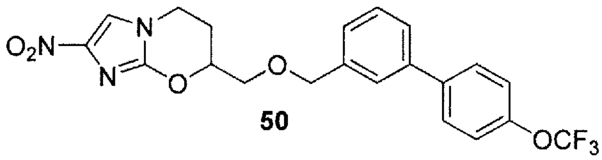
[0228] WW. Synthesis of 7-({[4-(benzyloxy)benzyl]oxy}methyl)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound 49 of Table 1) by the method of Scheme 11.



49

[0229] Alkylation of oxazine alcohol **134** (see Example 2BB above) with 4-(benzyloxy)benzyl chloride (3.0 equiv.) and NaH (1.5 equiv.) as in Example 2UU above for 3 h, followed by chromatography of the product on silica gel, eluting with 0-1% EtOAc/CH_2Cl_2 (foreruns) and then with 1% EtOAc/CH_2Cl_2, gave **49** (20 mg, 25%) as a cream solid: mp (CH_2Cl_2/hexane) 151-153 °C; ^{1}H NMR ($CDCl_3$) δ 7.45-7.29 (m, 6 H), 7.22 (dt, J = 8.7, 2.4 Hz, 2 H), 6.95 (dt, J = 8.7, 2.4 Hz, 2 H), 5.07 (s, 2 H), 4.54 (m, 1 H), 4.52 (s, 2 H), 4.11 (ddd, J = 12.3, 5.8, 3.9 Hz, 1 H), 4.02 (ddd, J = 12.3, 10.0, 5.5 Hz, 1 H), 3.78 (dd, J = 10.5, 4.3 Hz, 1 H), 3.71 (dd, J = 10.5, 5.5 Hz, 1 H), 2.33 (dddd, J = 14.5, 5.4, 3.8, 3.0 Hz, 1 H), 2.23 (dtd, J = 14.6, 9.8, 5.9 Hz, 1 H). Anal. ($C_{21}H_{21}N_3O_5$) C, H, N.

[0230] XX. Synthesis of 2-nitro-7-({[4'-(trifluoromethoxy)[1,1'-biphenyl]-3-yl]methoxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound 50 of Table 1) by the method of Scheme 11.

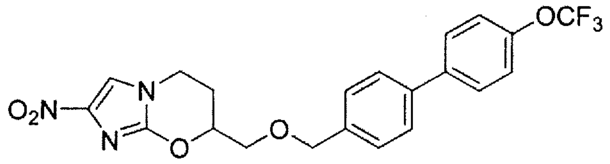


50

[0231] Alkylation of oxazine alcohol **134** (see Example 2BB above) with 3-iodobenzyl bromide (1.36 equiv.) and NaH (1.5 equiv.) as in Example 2UU above for 3 h, followed by chromatography of the product on silica gel, eluting with 0-1% EtOAc/CH_2Cl_2 (foreruns) and then with 1.5-2% EtOAc/CH_2Cl_2, gave 7-{[(3-iodobenzyl)oxy]methyl}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (**153**) (65%) as a cream solid: mp (CH_2Cl_2/hexane) 131-133 °C; ^{1}H NMR ($CDCl_3$) δ 7.65 (br s, 1 H), 7.64 (br d, *J* = 7.5 Hz, 1 H), 7.41 (s, 1 H), 7.26 (m, 1 H), 7.09 (td, *J* = 7.4, 1.0 Hz, 1 H), 4.57 (m, 1 H), 4.54 (s, 2 H), 4.15 (ddd, *J* = 12.3, 5.8, 3.8 Hz, 1 H), 4.06 (ddd, *J* = 12.3, 10.0, 5.5 Hz, 1 H), 3.82 (dd, *J* = 10.6, 4.3 Hz, 1 H), 3.76 (dd, *J* = 10.6, 5.1 Hz, 1 H), 2.39-2.21 (m, 2 H). Anal. ($C_{14}H_{14}IN_3O_4$) C, H, N.

[0232] A stirred mixture of iodide **153** (30.2 mg, 0.0727 mmol), 4-(trifluoromethoxy)phenylboronic acid (20.8 mg, 0.101 mmol) and Pd(dppf)Cl_2 (2.3 mg, 3.14 μmol) in toluene (1.7 mL) was degassed for 4 min (vacuum pump) and then N_2 was added. EtOH (0.6 mL) and aqueous 2M Na_2CO_3 (0.30 mL, 0.60 mmol) were added by syringe and the resulting mixture was stirred at 90 °C for 20 min, and then cooled, diluted with aqueous $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (4x 50 mL). The extracts were evaporated to dryness and the residue was chromatographed on silica gel. Elution with 0-1% EtOAc/CH_2Cl_2 firstly gave foreruns, and then elution with 1-1.5% EtOAc/CH_2Cl_2 gave **50** (30 mg, 92%) as a cream solid: mp (CH_2Cl_2/pentane) 117-119 °C; ^{1}H NMR ($CDCl_3$) δ 7.60 (dt, *J* = 8.7, 2.4 Hz, 2 H), 7.52-7.47 (m, 2 H), 7.44 (t, *J* = 7.8 Hz, 1 H), 7.40 (s, 1 H), 7.32-7.26 (m, 3 H), 4.67 (s, 2 H), 4.59 (m, 1 H), 4.14 (ddd, *J* = 12.3, 5.7, 3.8 Hz, 1 H), 4.05 (ddd, *J* = 12.3, 10.0, 5.6 Hz, 1 H), 3.86 (dd, *J* = 10.7, 4.3 Hz, 1 H), 3.80 (dd, *J* = 10.7, 5.0 Hz, 1 H), 2.40-2.22 (m, 2 H). Anal. ($C_{21}H_{18}F_3N_3O_5$) C, H, N.

[0233] YY. Synthesis of 2-nitro-7-({[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]methoxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound 51 of Table 1) by the method of Scheme 11.

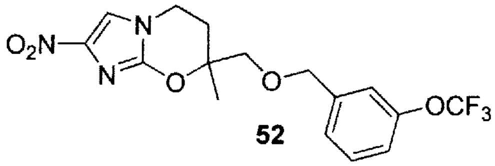


51

[0234] Alkylation of oxazine alcohol **134** (see Example 2BB above) with 4-iodobenzyl bromide (1.35 equiv.) and NaH (1.5 equiv.) as in Example 2UU above, followed by chromatography of the product on silica gel, eluting with CH_2Cl_2 (foreruns) and then with 1-1.5% EtOAc/CH_2Cl_2, gave 7-{[(4-iodobenzyl)oxy]methyl}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (**154**) (61%) as a cream solid: mp (CH_2Cl_2/hexane) 169-171 °C; ^{1}H NMR ($CDCl_3$) δ 7.68 (dt, J = 8.3, 2.0 Hz, 2 H), 7.41 (s, 1 H), 7.05 (br d, J = 8.3 Hz, 2 H), 4.56 (m, 1 H), 4.54 (s, 2 H), 4.14 (ddd, J = 12.3, 5.7, 3.8 Hz, 1 H), 4.05 (ddd, J = 12.3, 10.0, 5.6 Hz, 1 H), 3.80 (dd, J = 10.6, 4.3 Hz, 1 H), 3.75 (dd, J = 10.6, 5.0 Hz, 1 H), 2.37-2.20 (m, 2 H); HRFABMS calcd for $C_{14}H_{15}IN_3O_4$ *m/z* $[M + H]^+$ 416.0107, found 416.0105.

[0235] Suzuki coupling of iodide **154** and 4-(trifluoromethoxy)phenylboronic acid as in Example 2XX above, followed by chromatography of the product on silica gel, eluting with 0-1% EtOAc/CH_2Cl_2 (foreruns) and then with 1-1.5% EtOAc/CH_2Cl_2, gave **51** (85%) as a cream solid: mp (CH_2Cl_2/pentane) 159-161 °C; ^{1}H NMR ($CDCl_3$) δ 7.59 (dt, J = 8.8, 2.5 Hz, 2 H), 7.54 (br d, J = 8.2 Hz, 2 H), 7.41 (s, 1 H), 7.39 (br d, J = 8.3 Hz, 2 H), 7.29 (br d, J = 8.0 Hz, 2 H), 4.65 (s, 2 H), 4.59 (m, 1 H), 4.15 (ddd, J = 12.3, 5.8, 3.8 Hz, 1 H), 4.06 (ddd, J = 12.3, 10.0, 5.6 Hz, 1 H), 3.85 (dd, J = 10.6, 4.3 Hz, 1 H), 3.80 (dd, J = 10.6, 5.1 Hz, 1 H), 2.41-2.23 (m, 2 H). Anal. ($C_{21}H_{18}F_3N_3O_5$) C, H, N.

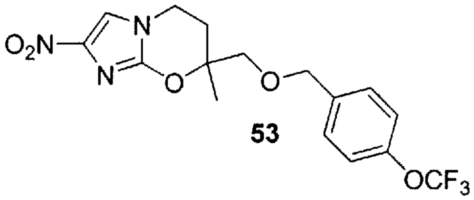
[0236] ZZ. Synthesis of 7-methyl-2-nitro-7-({[3-(trifluoromethoxy)benzyl]oxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound 52 of Table 1) by the method of Scheme 11.



52

[0237] Alkylation of oxazine alcohol **149** (see Example 2OO) with 3-(trifluoromethoxy)benzyl bromide (1.6 equiv.) and NaH (2.0 equiv.) as in Example 2UU above for 3 h, followed by chromatography of the product on silica gel, eluting with 0-1% EtOAc/CH_2Cl_2 (foreruns) and then with 1-1.5% EtOAc/CH_2Cl_2, gave **52** (83%) as a cream solid: mp (CH_2Cl_2/pentane) 108-110 °C; ^{1}H NMR ($CDCl_3$) δ 7.38 (s, 1 H), 7.36 (t, *J* = 8.0 Hz, 1 H), 7.19-7.10 (m, 3 H), 4.58 (s, 2 H), 4.10 (ddd, *J* = 12.5, 6.9, 5.9 Hz, 1 H), 4.02 (ddd, *J* = 12.5, 7.1, 5.9 Hz, 1 H), 3.65 (d, *J* = 10.2 Hz, 1 H), 3.61 (d, *J* = 10.2 Hz, 1 H), 2.38 (ddd, *J* = 14.4, 7.1, 6.0 Hz, 1 H), 2.12 (ddd, *J* = 14.5, 6.9, 6.0 Hz, 1 H), 1.48 (s, 3 H). Anal. ($C_{16}H_{16}F_3N_3O_5$) C, H, N.

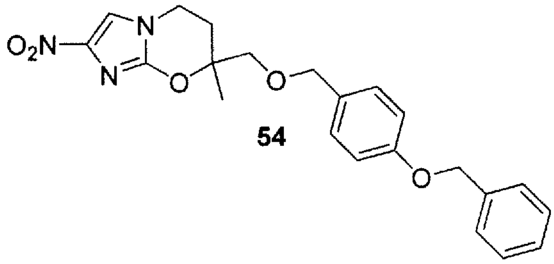
[0238] AAA. Synthesis of 7-methyl-2-nitro-7-({[4-(trifluoromethoxy)benzyl]oxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound 53 of Table 1) by the method of Scheme 11.



53

[0239] Alkylation of oxazine alcohol **149** (see Example 2OO) with 4-(trifluoromethoxy)benzyl bromide (1.6 equiv.) and NaH (1.8 equiv.) as in Example 2UU above for 3 h, followed by chromatography of the product on silica gel, eluting with CH_2Cl_2 (foreruns) and then with 1.5% EtOAc/CH_2Cl_2, gave **53** (83%) as a cream solid: mp (CH_2Cl_2/pentane) 100-101 °C; ^{1}H NMR ($CDCl_3$) δ 7.39 (s, 1 H), 7.28 (br d, *J* = 8.7 Hz, 2 H), 7.18 (br d, *J* = 8.0 Hz, 2 H), 4.56 (s, 2 H), 4.09 (ddd, *J* = 12.5, 6.8, 5.9 Hz, 1 H), 4.02 (ddd, *J* = 12.5, 7.3, 5.9 Hz, 1 H), 3.64 (d, *J* = 10.2 Hz, 1 H), 3.60 (d, *J* = 10.2 Hz, 1 H), 2.38 (ddd, *J* = 14.5, 7.2, 5.9 Hz, 1 H), 2.11 (ddd, *J* = 14.5, 6.7, 6.0 Hz, 1 H), 1.47 (s, 3 H). Anal. ($C_{16}H_{16}F_3N_3O_5$) C, H, N.

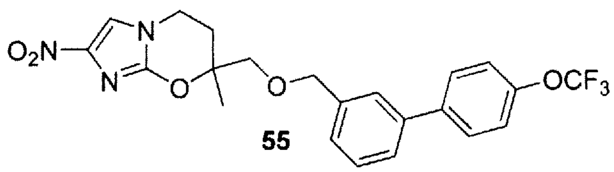
[0240] BBB. Synthesis of 7-({[4-(benzyloxy)benzyl]oxy}methyl)-7-methyl-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound 54 of Table 1) by the method of Scheme 11.



54

[0241] Alkylation of oxazine alcohol **149** (see Example 2OO) with 4-(benzyloxy)benzyl chloride (2.8 equiv.) and NaH (1.6 equiv.) as in Example 2UU above for 7 h, followed by chromatography of the product on silica gel, eluting with 0-1% EtOAc/CH_2Cl_2 (foreruns) and then with 1% EtOAc/CH_2Cl_2, gave **54** (41%) as a cream solid: mp (CH_2Cl_2/pentane) 109-111 °C; ^{1}H NMR ($CDCl_3$) δ 7.45-7.29 (m, 6 H), 7.16 (dt, *J* = 8.6, 2.3 Hz, 2 H), 6.93 (dt, *J* = 8.6, 2.4 Hz, 2 H), 5.06 (s, 2 H), 4.48 (d, *J* = 11.5 Hz, 1 H), 4.45 (d, *J* = 11.6 Hz, 1 H), 4.03 (ddd, *J* = 12.5, 7.6, 5.8 Hz, 1 H), 3.95 (dt, *J* = 12.5, 6.2 Hz, 1 H), 3.58 (d, *J* = 10.1 Hz, 1 H), 3.54 (d, *J* = 10.1 Hz, 1 H), 2.34 (dt, *J* = 14.5, 6.2 Hz, 1 H), 2.08 (ddd, *J* = 14.4, 7.6, 6.0 Hz, 1 H), 1.45 (s, 3 H). Anal. ($C_{22}H_{23}N_3O_5$) C, H, N.

[0242] CCC. Synthesis of 7-methyl-2-nitro-7-({[4'-(trifluoromethoxy)[1,1'-biphenyl]-3-yl]methoxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound 55 of Table 1) by the method of Scheme 11.



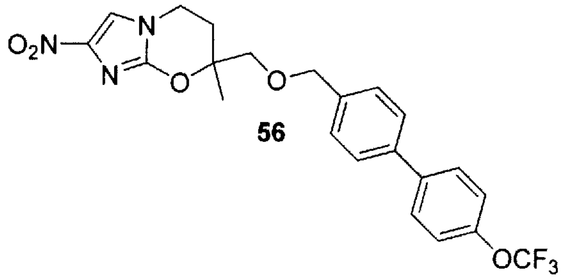
55

[0243] Alkylation of oxazine alcohol **149** (see Example 2OO) with 3-iodobenzyl bromide (1.6 equiv.) and NaH (1.8 equiv.) as in Example 2UU above for 3.5 h, followed by chromatography of the product on silica gel, eluting with CH_2Cl_2 (foreruns) and then with 0-2% EtOAc/CH_2Cl_2, gave 7-{[(3-iodobenzyl)oxy]methyl}-7-methyl-2-nitro-6,7-dihydro-5*H*-

imidazo[2,1-*b*][1,3]oxazine (**155**) (69%) as a cream solid: mp (CH_2Cl_2/pentane) 122-125 °C (dec); ^{1}H NMR ($CDCl_3$) δ 7.63 (br d, *J* = 7.9 Hz, 1 H), 7.58 (m, 1 H), 7.40 (s, 1 H), 7.19 (br d, *J* = 7.7 Hz, 1 H), 7.06 (t, *J* = 7.7 Hz, 1 H), 4.49 (s, 2 H), 4.11 (ddd, *J* = 12.4, 7.3, 5.8 Hz, 1 H), 4.01 (ddd, *J* = 12.5, 6.7, 6.0 Hz, 1 H), 3.63 (d, *J* = 10.2 Hz, 1 H), 3.60 (d, *J* = 10.2 Hz, 1 H), 2.37 (ddd, *J* = 14.4, 6.7, 6.0 Hz, 1 H), 2.12 (ddd, *J* = 14.4, 7.3, 6.0 Hz, 1 H), 1.47 (s, 3 H). Anal. ($C_{15}H_{16}IN_3O_4$) C, H, N.

[0244] Suzuki coupling of iodide **155** and 4-(trifluoromethoxy)phenylboronic acid as in Example 2H for 25 min, followed by chromatography of the product on silica gel, eluting with 0-0.5% EtOAc/CH_2Cl_2 (foreruns) and then with 1% EtOAc/CH_2Cl_2, gave **55** (94%) as a cream solid: mp (CH_2Cl_2/pentane) 80-82 °C; ^{1}H NMR ($CDCl_3$) δ 7.58 (dt, *J* = 8.8, 2.5 Hz, 2 H), 7.49 (br dt, *J* = 6.4, 1.5 Hz, 1 H), 7.43 (br s, 1 H), 7.41 (t, *J* = 7.6 Hz, 1 H), 7.37 (s, 1 H), 7.30 (br dd, *J* = 8.7, 0.8 Hz, 2 H), 7.25 (m, 1 H), 4.62 (s, 2 H), 4.11 (ddd, *J* = 12.4, 7.1, 5.8 Hz, 1 H), 4.00 (ddd, *J* = 12.5, 6.9, 5.9 Hz, 1 H), 3.68 (d, *J* = 10.2 Hz, 1 H), 3.63 (d, *J* = 10.2 Hz, 1 H), 2.39 (ddd, *J* = 14.4, 6.9, 6.0 Hz, 1 H), 2.12 (ddd, *J* = 14.4, 7.1, 6.0 Hz, 1 H), 1.48 (s, 3 H). Anal. ($C_{22}H_{20}F_3N_3O_5$) C, H, N.

[0245] DDD. Synthesis of 7-methyl-2-nitro-7-({[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]methoxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound 56 of Table 1) by the method of Scheme 11.



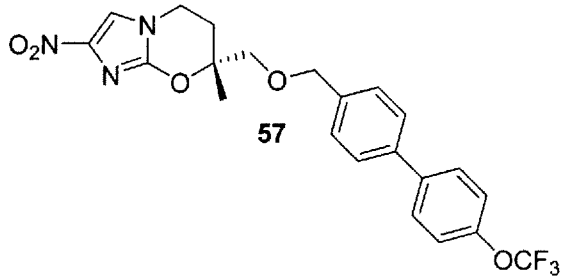
56

[0246] Alkylation of oxazine alcohol **149** (see Example 2OO) with 4-iodobenzyl bromide (1.7 equiv.) and NaH (1.9 equiv.) as in Example 2UU above for 3 h, followed by chromatography of the product on silica gel, eluting with CH_2Cl_2 (foreruns) and then with 1% EtOAc/CH_2Cl_2, gave 7-{[(4-iodobenzyl)oxy]methyl}-7-methyl-2-nitro-6,7-dihydro-5*H*-

imidazo[2,1-*b*][1,3]oxazine (**156**) (54%) as a cream solid: mp (CH_2Cl_2/pentane) 130-132 °C; ^1H NMR ($CDCl_3$) δ 7.67 (dt, *J* = 8.3, 2.0 Hz, 2 H), 7.39 (s, 1 H), 6.99 (br d, *J* = 8.3 Hz, 2 H), 4.49 (s, 2 H), 4.09 (ddd, *J* = 12.5, 7.0, 5.9 Hz, 1 H), 4.01 (ddd, *J* = 12.5, 7.1, 5.9 Hz, 1 H), 3.62 (d, *J* = 10.2 Hz, 1 H), 3.58 (d, *J* = 10.2 Hz, 1 H), 2.37 (ddd, *J* = 14.4, 7.0, 6.0 Hz, 1 H), 2.10 (ddd, *J* = 14.4, 6.9, 6.0 Hz, 1 H), 1.46 (s, 3 H). Anal. ($C_{15}H_{16}IN_3O_4$) C, H, N.

[0247] Suzuki coupling of iodide **156** and 4-(trifluoromethoxy)phenylboronic acid as in Example 2H for 25 min, followed by chromatography of the product on silica gel, eluting with 0-0.5% EtOAc/CH_2Cl_2 (foreruns) and then with 0.5-1% EtOAc/CH_2Cl_2, gave **56** (92%) as a cream solid: mp (CH_2Cl_2/pentane) 150-152 °C; ^1H NMR ($CDCl_3$) δ 7.58 (dt, *J* = 8.8, 2.5 Hz, 2 H), 7.52 (dt, *J* = 8.3, 1.9 Hz, 2 H), 7.38 (s, 1 H), 7.32 (br d, *J* = 8.3 Hz, 2 H), 7.28 (br dd, *J* = 8.8, 0.8 Hz, 2 H), 4.61 (d, *J* = 12.0 Hz, 1 H), 4.58 (d, *J* = 12.0 Hz, 1 H), 4.11 (ddd, *J* = 12.4, 7.3, 5.8 Hz, 1 H), 4.01 (ddd, *J* = 12.5, 6.7, 6.0 Hz, 1 H), 3.67 (d, *J* = 10.2 Hz, 1 H), 3.63 (d, *J* = 10.2 Hz, 1 H), 2.40 (ddd, *J* = 14.5, 6.7, 6.0 Hz, 1 H), 2.13 (ddd, *J* = 14.5, 7.3, 6.0 Hz, 1 H), 1.48 (s, 3 H). Anal. ($C_{22}H_{20}F_3N_3O_5$) C, H, N.

[0248] EEE. Synthesis of (7*R*)-7-methyl-2-nitro-7-({[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]methoxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound 57 of Table 1) by the method of Scheme 12.



57

[0249] Ac_2O (3.6 mL, 38.1 mmol) was added to a stirred suspension of alcohol **149** (see Example 2OO) (807 mg, 3.79 mmol) in anhydrous pyridine (7.0 mL). After stirring at room temperature for 38 h, the mixture was diluted with CH_2Cl_2, added to ice-water (150 mL) and extracted with CH_2Cl_2 (5x 100 mL). The extracts were evaporated to dryness and the residue was chromatographed on silica gel. Elution with CH_2Cl_2 firstly gave foreruns, and then further elution with 1-6% EtOAc/CH_2Cl_2 gave 7-methyl-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazin-7-yl]methyl acetate (**157**) (962 mg, 100%) as a cream solid: mp (CH_2Cl_2/hexane) 145-147 °C; ^{1}H NMR ($CDCl_3$) δ 7.44 (s, 1 H), 4.27 (d, *J* = 11.9 Hz, 1 H), 4.20 (d, *J* = 11.9 Hz, 1 H), 4.14 (dt, *J* = 12.7, 5.9 Hz, 1 H), 4.08 (ddd, *J* = 12.7, 8.3, 5.6 Hz, 1 H), 2.32 (ddd, *J* = 14.5, 8.3, 6.1 Hz, 1 H), 2.10 (dt, *J* = 14.5, 5.7 Hz, 1 H), 2.09 (s, 3 H), 1.50 (s, 3 H); HRFABMS calcd for $C_{10}H_{14}N_3O_5$ *m/z* $[M + H]^+$ 256.0934, found 256.0941.

[0250] Racemic acetate **157** (990 mg) was separated into pure enantiomers by preparative chiral HPLC, using a ChiralPak™ IA column and an isocratic solvent system of 40% EtOH in hexane at a flow rate of 6 mL/min, to firstly give [(7*S*)-7-methyl-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazin-7-yl]methyl acetate (**161**) (427 mg, 43%) as a cream solid that was used directly in the next step; ^{1}H NMR ($CDCl_3$) δ 7.44 (s, 1 H), 4.27 (d, *J* = 11.9 Hz, 1 H), 4.20 (d, *J* = 11.9 Hz, 1 H), 4.14 (dt, *J* = 12.7, 5.9 Hz, 1 H), 4.08 (ddd, *J* = 12.7, 8.3, 5.6 Hz, 1 H), 2.32 (ddd, *J* = 14.5, 8.3, 6.1 Hz, 1 H), 2.10 (dt, *J* = 14.5, 5.7 Hz, 1 H), 2.09 (s, 3 H), 1.50 (s, 3 H); $[\alpha]_D^{26}$ -6.0° (*c* 1.00, $CHCl_3$).

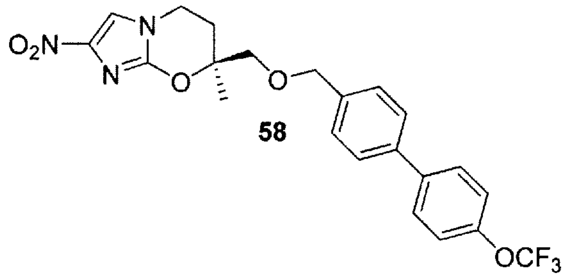
[0251] The above preparative chiral HPLC of racemic acetate **157** secondly gave [(7*R*)-7-methyl-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazin-7-yl]methyl acetate (**158**) (428 mg, 43%) as a cream solid that was used directly in the next step; ^{1}H NMR ($CDCl_3$) δ 7.44 (s, 1 H), 4.27 (d, *J* = 11.9 Hz, 1 H), 4.20 (d, *J* = 11.8 Hz, 1 H), 4.14 (dt, *J* = 12.7, 5.9 Hz, 1 H), 4.08 (ddd, *J* = 12.7, 8.3, 5.6 Hz, 1 H), 2.32 (ddd, *J* = 14.5, 8.3, 6.1 Hz, 1 H), 2.10 (dt, *J* = 14.5, 5.7 Hz, 1 H), 2.09 (s, 3 H), 1.50 (s, 3 H); $[\alpha]_D^{26}$ 6.0° (*c* 1.00, $CHCl_3$).

[0252] Water (4 mL) was added dropwise to a stirred mixture of (*R*)-acetate **158** (427 mg, 1.67 mmol) and K_2CO_3 (256 mg, 1.85 mmol) in MeOH (36 mL). After stirring at room temperature for 4 h, the mixture was cooled in ice and treated with 0.1M HCl (37 mL, 3.70 mmol). The solvents were removed under reduced pressure and the residue was chromatographed on silica gel. Elution with 0-1% MeOH/CH_2Cl_2 firstly gave foreruns, and then further elution with 1-2.5% MeOH/CH_2Cl_2 gave [(7*R*)-7-methyl-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazin-7-yl]methanol (**159**) (343 mg, 96%) as a pale yellow solid that was used directly in the next step; ^{1}H NMR [$(CD_3)_2SO$] δ 8.03 (s, 1 H), 5.23 (br t, *J* = 5.4 Hz, 1 H), 4.13 (dt, *J* = 13.0, 6.0 Hz, 1 H), 4.05 (ddd, J = 12.9, 8.1, 5.6 Hz, 1 H), 3.54 (dd, J = 11.6, 4.9 Hz, 1 H), 3.48 (dd, J = 11.6, 5.2 Hz, 1 H), 2.21 (ddd, J = 14.4, 8.1, 5.9 Hz, 1 H), 2.00 (dt, J = 14.4, 5.8 Hz, 1 H), 1.32 (s, 3 H); $[\alpha]_D^{27}$ -16.0° (c 1.00, DMF).

[0253] Alkylation of (R)-alcohol **159** with 4-bromobenzyl bromide (1.3 equiv.) and NaH (1.5 equiv.) as in Example 2UU above for 3 h, followed by chromatography of the product on silica gel, eluting with CH_2Cl_2 (foreruns) and then with 1% EtOAc/CH_2Cl_2, gave (7R)-7-{[(4-bromobenzyl)oxy]methyl}-7-methyl-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine (**160**) (349 mg, 57%) as a white solid: mp (CH_2Cl_2/hexane) 157-159 °C; ^{1}H NMR ($CDCl_3$) δ 7.46 (dt, J = 8.3, 2.0 Hz, 2 H), 7.39 (s, 1 H), 7.12 (br d, J = 8.3 Hz, 2 H), 4.50 (s, 2 H), 4.09 (ddd, J = 12.5, 6.9, 6.0 Hz, 1 H), 4.01 (ddd, J = 12.5, 7.0, 6.0 Hz, 1 H), 3.62 (d, J = 10.2 Hz, 1 H), 3.58 (d, J = 10.2 Hz, 1 H), 2.37 (ddd, J = 14.4, 7.0, 6.0 Hz, 1 H), 2.10 (ddd, J = 14.4, 6.9, 6.1 Hz, 1 H), 1.46 (s, 3 H); $[\alpha]_D^{27}$ 30.0° (c 1.00, $CHCl_3$); HRFABMS calcd for $C_{15}H_{17}BrN_3O_4$ m/z $[M + H]^+$ 384.0382, 382.0402, found 384.0385, 382.0398.

[0254] A stirred mixture of bromide **160** (347.5 mg, 0.909 mmol), 4-(trifluoromethoxy)phenylboronic acid (283 mg, 1.37 mmol) and Pd(dppf)Cl_2 (101 mg, 0.138 mmol) in toluene (16 mL) and EtOH (6 mL) was degassed for 10 min (vacuum pump) and then N_2 was added. An aqueous solution of 2M Na_2CO_3 (3.0 mL, 6.0 mmol) was added by syringe and the stirred mixture was again degassed for 10 min, and then N_2 was added. The resulting mixture was stirred at 88 °C for 75 min, and then cooled, diluted with aqueous $NaHCO_3$ (100 mL) and extracted with CH_2Cl_2 (6x 100 mL). The extracts were evaporated to dryness and the residue was chromatographed on silica gel. Elution with 0-0.5% EtOAc/CH_2Cl_2 firstly gave foreruns, and then further elution with 0.5-1.5% EtOAc/CH_2Cl_2 gave **57** (381 mg, 90%) as a cream solid: mp (CH_2Cl_2/hexane) 165-167 °C; ^{1}H NMR ($CDCl_3$) δ 7.58 (dt, J = 8.7, 2.4 Hz, 2 H), 7.52 (br d, J = 8.2 Hz, 2 H), 7.38 (s, 1 H), 7.32 (br d, J = 8.1 Hz, 2 H), 7.28 (br d, J = 8.1 Hz, 2 H), 4.61 (d, J = 12.1 Hz, 1 H), 4.58 (d, J = 12.1 Hz, 1 H), 4.11 (ddd, J = 12.4, 7.2, 5.8 Hz, 1 H), 4.01 (ddd, J = 12.6, 6.5, 6.1 Hz, 1 H), 3.67 (d, J = 10.2 Hz, 1 H), 3.63 (d, J = 10.2 Hz, 1 H), 2.40 (ddd, J = 14.4, 6.6, 6.1 Hz, 1 H), 2.13 (ddd, J = 14.5, 7.3, 6.0 Hz, 1 H), 1.48 (s, 3 H); $[\alpha]_D^{27}$ 37.0° (c 1.00, $CHCl_3$). Anal. ($C_{22}H_{20}F_3N_3O_5$) C, H, N.

[0255] FFF. Synthesis of (7*S*)-7-methyl-2-nitro-7-({[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]methoxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound 58 of Table 1) by the method of Scheme 12.

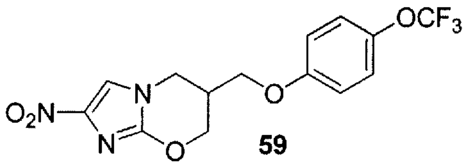


[0256] Hydrolysis of (*S*)-acetate **161** (426 mg, 1.67 mmol) with K_2CO_3 in MeOH/water as in Example 2EEE above, followed by chromatography of the product on silica gel, eluting with 0-1% MeOH/CH_2Cl_2 (forerun), and then with 1-2.5% MeOH/CH_2Cl_2, gave [(7*S*)-7-methyl-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazin-7-yl]methanol (**162**) (343 mg, 96%) as a pale yellow solid that was used directly in the next step; ^{1}H NMR [$(CD_3)_2SO$] δ 8.03 (s, 1 H), 5.22 (br t, *J* = 5.7 Hz, 1 H), 4.13 (dt, *J* = 13.0, 6.0 Hz, 1 H), 4.05 (ddd, *J* = 12.9, 8.1, 5.6 Hz, 1 H), 3.54 (dd, *J* = 11.6, 5.4 Hz, 1 H), 3.48 (dd, *J* = 11.6, 5.7 Hz, 1 H), 2.21 (ddd, *J* = 14.4, 8.1, 5.9 Hz, 1 H), 2.00 (dt, *J* = 14.4, 5.8 Hz, 1 H), 1.32 (s, 3 H); $[\alpha]_D^{27}$ 18.0° (*c* 1.00, DMF).

[0257] Alkylation of (*S*)-alcohol **162** with 4-bromobenzyl bromide (1.35 equiv.) and NaH (1.55 equiv.) as in Example 2UU above for 3 h, followed by chromatography of the product on silica gel, eluting with CH_2Cl_2 (foreruns) and then with 1% EtOAc/CH_2Cl_2, gave (7*S*)-7-{[(4-bromobenzyl)oxy]methyl}-7-methyl-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (**163**) (373 mg, 61%) as a white solid: mp (CH_2Cl_2/hexane) 159-161 °C; ^{1}H NMR ($CDCl_3$) δ 7.46 (dt, *J* = 8.4, 2.1 Hz, 2 H), 7.39 (s, 1 H), 7.12 (dt, *J* = 8.4, 2.1 Hz, 2 H), 4.50 (s, 2 H), 4.09 (ddd, *J* = 12.5, 7.0, 5.8 Hz, 1 H), 4.01 (ddd, *J* = 12.5, 7.1, 5.9 Hz, 1 H), 3.62 (d, *J* = 10.2 Hz, 1 H), 3.58 (d, *J* = 10.2 Hz, 1 H), 2.37 (ddd, *J* = 14.4, 7.1, 5.9 Hz, 1 H), 2.10 (ddd, *J* = 14.5, 7.0, 5.9 Hz, 1 H), 1.46 (s, 3 H); $[\alpha]_D^{27}$ -32.0° (*c* 1.00, $CHCl_3$); HRFABMS calcd for $C_{15}H_{17}BrN_3O_4$ *m*/*z* $[M + H]^+$ 384.0382, 382.0402, found 384.0374, 382.0393.

[0258] Suzuki coupling of bromide **163** and 4-(trifluoromethoxy)phenylboronic acid as in Example 2EEE, followed by chromatography of the product on silica gel, eluting with 0-0.5% EtOAc/CH_2Cl_2 (foreruns) and then with 0.5-1% EtOAc/CH_2Cl_2, gave **58** (415 mg, 92%) as a cream solid: mp (CH_2Cl_2/hexane) 162-164 °C; ^{1}H NMR ($CDCl_3$) δ 7.58 (dt, J = 8.8, 2.5 Hz, 2 H), 7.52 (br d, J = 8.3 Hz, 2 H), 7.38 (s, 1 H), 7.32 (br d, J = 8.3 Hz, 2 H), 7.28 (br dd, J = 8.8, 0.8 Hz, 2 H), 4.61 (d, J = 12.1 Hz, 1 H), 4.58 (d, J = 12.1 Hz, 1 H), 4.11 (ddd, J = 12.4, 7.3, 5.8 Hz, 1 H), 4.01 (ddd, J = 12.5, 6.6, 6.1 Hz, 1 H), 3.67 (d, J = 10.2 Hz, 1 H), 3.63 (d, J = 10.2 Hz, 1 H), 2.40 (ddd, J = 14.4, 6.7, 6.0 Hz, 1 H), 2.13 (ddd, J = 14.4, 7.3, 6.0 Hz, 1 H), 1.48 (s, 3 H). $[\alpha]_D^{27}$ -36.0° (c 1.00, $CHCl_3$). Anal. ($C_{22}H_{20}F_3N_3O_5$) C, H, N.

[0259] GGG. Synthesis of 2-nitro-6-{[4-(trifluoromethoxy)phenoxy]methyl}-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound 59 of Table 1) by the method of Scheme 13.



59

[0260] A solution of iodine (1.49 g, 5.85 mmol) in anhydrous CH_2Cl_2 (3x 10 mL, then 4x 1 mL to rinse) was added dropwise to a stirred mixture of imidazole (0.441 g, 6.48 mmol) and triphenylphosphine (1.50 g, 5.71 mmol) in anhydrous CH_2Cl_2 (3 mL) at 0 °C under N_2. After stirring at 0 °C for 30 min, a solution of 2-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-2-propen-1-ol (**164**) (reported by Chen et al., US 2007213341 A1, by monosilylation of 2-methylene-1,3-propanediol) (1.00 g, 4.94 mmol) in anhydrous CH_2Cl_2 (4 mL, then 4x 1 mL to rinse) was added, and the mixture was stirred at 0-8 °C for 5 h. The resulting mixture was concentrated carefully under reduced pressure, and the residual oil was chromatographed on silica gel. Elution with pentane firstly gave foreruns, and then further elution with 10% CH_2Cl_2/pentane gave *tert*-butyl(dimethyl)silyl 2-(iodomethyl)-2-propenyl ether (**165**) (1.46 g, 95%) as a volatile pink oil that was used directly in the next step; ^{1}H NMR ($CDCl_3$) δ 5.31 (br s, 1 H), 5.19 (d, J = 1.3 Hz, 1 H), 4.31 (s, 2 H), 3.95 (s, 2 H), 0.92 (s, 9 H), 0.10 (s, 6 H).

[0261] A mixture of iodide **165** (4.63 g, 14.8 mmol), 4-(trifluoromethoxy)phenol (3.10 mL, 23.9 mmol) and powdered K_2CO_3 (3.56 g, 25.8 mmol) in acetone (10 mL) was stirred at 50 °C for 11 h. The resulting cooled mixture was diluted with ice-water (100 mL) and extracted with CH_2Cl_2 (4x 100 mL). The combined extracts were evaporated to dryness and the residue was chromatographed on silica gel. Elution with 0-3% CH_2Cl_2/petroleum ether firstly gave foreruns, and then further elution with 5-10% CH_2Cl_2/petroleum ether gave *tert*-butyl(dimethyl)[(2-{[4-(trifluoromethoxy)phenoxy]methyl}-2-propenyl)oxy]silane (**166**) (3.12 g, 58%) as a colourless oil; ^{1}H NMR ($CDCl_3$) δ 7.12 (br d, *J* = 9.0 Hz, 2 H), 6.90 (dt, *J* = 9.1, 2.9 Hz, 2 H), 5.27 (d, *J* = 0.7 Hz, 1 H), 5.20 (d, *J* = 1.1 Hz, 1 H), 4.54 (s, 2 H), 4.24 (s, 2 H), 0.91 (s, 9 H), 0.07 (s, 6 H); HRFABMS calcd for $C_{17}H_{26}F_3O_3Si$ *m/z* $[M + H]^+$ 363.1603, found 363.1604.

[0262] A solution of iodine (825 mg, 3.25 mmol) in anhydrous THF (5 mL, then 2x 3mL to rinse) was added dropwise (over 70 min) to a stirred mixture of alkene **166** (5.21 g, 14.4 mmol) and powdered $NaBH_4$ (257 mg, 6.79 mmol) in anhydrous THF (18 mL) at 0 °C under N_2. After stirring at 0 °C for 3 h, and then at room temperature for 13 h, the mixture was again cooled to 0 °C, treated with 30% H_2O_2 (6.8 mL) and 3N NaOH (6.8 mL), and then stirred at room temperature for 3 h. Water (160 mL) was then added, and the mixture was extracted with EtOAc (4x 160 mL). The extracts were washed with brine (80 mL) and evaporated to dryness and the residue was chromatographed on silica gel. Elution with 0-3.5% EtOAc/petroleum ether firstly gave foreruns, and then further elution with 4-8% EtOAc/petroleum ether gave 3-{[*tert*-butyl(dimethyl)silyl]oxy}-2-{[4-(trifluoromethoxy)phenoxy]methyl}-1-propanol (**168**) (3.32 g, 61%) as a colourless oil; ^{1}H NMR ($CDCl_3$) δ 7.13 (br d, *J* = 9.0 Hz, 2 H), 6.89 (dt, *J* = 9.1, 3.0 Hz, 2 H), 4.08 (dd, *J* = 9.3, 6.6 Hz, 1 H), 4.04 (dd, *J* = 9.3, 6.0 Hz, 1 H), 3.94-3.81 (m, 4 H), 2.36 (dd, *J* = 6.1, 5.2 Hz, 1 H), 2.19 (m, 1 H), 0.89 (s, 9 H), 0.07, 0.05 (2s, 6 H); HRFABMS calcd for $C_{17}H_{28}F_3O_4Si$ *m/z* $[M + H]^+$ 381.1709, found 381.1707.

[0263] A solution of iodine (2.89 g, 11.4 mmol) in anhydrous CH_2Cl_2 (6x 10 mL, then 5mL + 2 mL to rinse) was added dropwise (over 100 min) to a stirred mixture of alcohol **168** (3.28 g, 8.62 mmol), imidazole (1.50 g, 22.0 mmol) and triphenylphosphine (2.83 g, 10.8 mmol) in anhydrous CH_2Cl_2 (20 mL) under N_2. After stirring at room temperature for 15 h, the resulting mixture was concentrated under reduced pressure, and the residue was chromatographed on silica gel. Elution with petroleum ether firstly gave foreruns, and then further elution with 5-20% CH_2Cl_2/petroleum ether gave *tert*-butyl(3-iodo-2-{[4-(trifluoromethoxy)phenoxy]methyl}propoxy)dimethylsilane (**170**) (3.90 g, 92%) as a pale brown oil; ^{1}H NMR ($CDCl_3$) δ 7.13 (br dd, *J* = 9.1, 0.7 Hz, 2 H), 6.89 (dt, *J* = 9.1, 3.0 Hz, 2 H), 4.01 (dd, *J* = 9.3, 5.7 Hz, 1 H), 3.94 (dd, *J* = 9.3, 6.2 Hz, 1 H), 3.75 (dd, *J* = 10.1, 5.6 Hz, 1 H), 3.70 (dd, *J* = 10.1, 5.6 Hz, 1 H), 3.39 (dd, *J* = 10.1, 5.9 Hz, 1 H), 3.37 (dd, *J* = 10.1, 6.0 Hz, 1 H), 2.10 (sept, *J* = 5.8 Hz, 1 H), 0.89 (s, 9 H), 0.07, 0.06 (2s, 6 H); HRCIMS calcd for $C_{17}H_{27}F_3IO_3Si$ *m/z* $[M + H]^+$ 491.0726, found 491.0721.

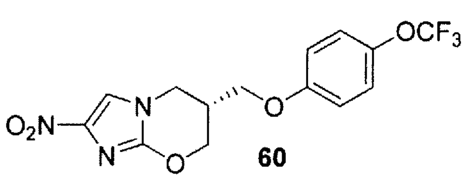
[0264] A mixture of iodide **170** (3.89 g, 7.93 mmol), 2-bromo-4(5)-nitroimidazole (**80**) (1.68 g, 8.77 mmol) and powdered K_2CO_3 (1.90 g, 13.7 mmol) in anhydrous DMF (20 mL) was stirred at 84-88 °C for 37 h. The resulting cooled mixture was diluted with ice-water (100 mL) and extracted with EtOAc (5x 100 mL). The extracts were washed with brine (100 mL), backextracting with EtOAc (50 mL), and then evaporated to dryness and the residue was chromatographed on silica gel. Elution with 0-7% EtOAc/petroleum ether firstly gave foreruns, and then further elution with 7-15% EtOAc/petroleum ether gave 2-bromo-1-(3-{[*tert*-butyl(dimethyl)silyl]oxy}-2-{[4-(trifluoromethoxy)phenoxy]methyl}propyl)-4-nitro-1*H*-imidazole (**172**) (3.57 g, 81%) as a pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.82 (s, 1 H), 7.16 (br dd, *J* = 9.1, 0.7 Hz, 2 H), 6.85 (dt, *J* = 9.1, 3.0 Hz, 2 H), 4.26 (d, *J* = 7.1 Hz, 2 H), 3.96 (d, *J* = 5.6 Hz, 2 H), 3.77 (dd, *J* = 10.6, 5.1 Hz, 1 H), 3.67 (dd, *J* = 10.6, 4.7 Hz, 1 H), 2.51 (m, 1 H), 0.92 (s, 9 H), 0.08, 0.07 (s, 6 H); HRFABMS calcd for $C_{20}H_{28}BrF_3N_3O_5Si$ *m/z* $[M + H]^+$ 556.0913, 554.0934, found 556.0921, 554.0938.

[0265] Silyl ether **172** (3.42 g, 6.17 mmol) was treated with a solution of 1% HCl in 95% EtOH (desilylation conditions described by Cunico et al., 1980) (31 mL), and the mixture was stirred at room temperature for 12 h. The resulting solution was cooled (CO_2/acetone), neutralised by dropwise addition of 7M NH_3 in MeOH (6.6 mL) with stirring, and then concentrated to dryness and the residue was chromatographed on silica gel. Elution with 0-30% EtOAc/petroleum ether firstly gave foreruns, and then further elution with 40-50% EtOAc/petroleum ether gave 3-(2-bromo-4-nitro-1*H*-imidazol-1-yl)-2-{[4-

(trifluoromethoxy)phenoxy]methyl}-1-propanol (**174**) (2.48 g, 91%) as a white solid: mp (CH_2Cl_2/pentane) 97-99 °C; ^{1}H NMR ($CDCl_3$) δ 7.88 (s, 1 H), 7.17 (br d, *J* = 8.5 Hz, 2 H), 6.88 (dt, *J* = 9.1, 3.0 Hz, 2 H), 4.34 (dd, *J* = 14.4, 7.4 Hz, 1 H), 4.31 (dd, *J* = 14.4, 7.1 Hz, 1 H), 4.06 (dd, *J* = 9.6, 5.7 Hz, 1 H), 4.03 (dd, *J* = 9.6, 4.8 Hz, 1 H), 3.88 (dt, *J* = 10.8, 4.4 Hz, 1 H), 3.76 (dt, *J* = 10.8, 4.9 Hz, 1 H), 2.54 (m, 1 H), 1.72 (t, *J* = 4.4 Hz, 1 H); HRFABMS calcd for $C_{14}H_{14}BrF_3N_3O_5$ *m/z* $[M + H]^+$ 442.0049, 440.0069, found 442.0053, 440.0063.

[0266] A stirred solution of alcohol **174** (2.48 g, 5.64 mmol) in anhydrous DMF (50 mL) under N_2 at 0 °C was treated with 60% NaH (345 mg, 8.63 mmol), then quickly degassed and resealed under N_2. After stirring at room temperature for 4 h, the reaction was cooled (CO_2/acetone), quenched with ice/aqueous $NaHCO_3$ (30 mL), added to brine (200 mL), and extracted with CH_2Cl_2 (8x 100 mL). The combined extracts were evaporated to dryness and the residue was chromatographed on silica gel. Elution with 0-1% EtOAc/CH_2Cl_2 firstly gave foreruns, and then further elution with 1.5-2% EtOAc/CH_2Cl_2 gave **59** (1.407 g, 69%) as a pale yellow solid: mp (CH_2Cl_2/hexane) 141-143 °C; ^{1}H NMR ($CDCl_3$) δ 7.45 (s, 1 H), 7.17 (br dd, *J* = 9.1, 0.7 Hz, 2 H), 6.88 (dt, *J* = 9.2, 3.0 Hz, 2 H), 4.62 (ddd, *J* = 11.5, 3.2, 0.8 Hz, 1 H), 4.50 (dd, *J* = 11.6, 7.3 Hz, 1 H), 4.27 (ddd, *J* = 12.5, 5.6, 0.7 Hz, 1 H), 4.17 (dd, *J* = 12.4, 7.1 Hz, 1 H), 4.13 (dd, *J* = 9.6, 5.7 Hz, 1 H), 4.07 (dd, *J* = 9.6, 6.7 Hz, 1 H), 2.88 (m, 1 H). Anal. ($C_{14}H_{12}F_3N_3O_5$) C, H, N.

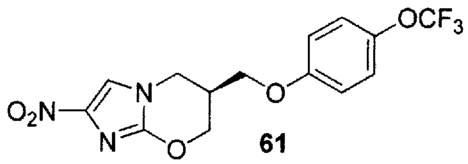
[0267] HHH. Synthesis of (6*R*)-2-nitro-6-{[4-(trifluoromethoxy)phenoxy]methyl}-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound 60 of Table 1) by the method of Scheme 13.



60

[0268] Racemic ether **59** (1.18 g) was separated into pure enantiomers by preparative chiral HPLC, using a ChiralPak IA column and an isocratic solvent system of 27% EtOH in hexane, to firstly give **60** (510 mg, 43%) as a white solid: mp (CH_2Cl_2/hexane) 138-139 °C; ^{1}H NMR ($CDCl_3$) δ 7.45 (s, 1 H), 7.17 (br dd, *J* = 9.0, 0.6 Hz, 2 H), 6.88 (dt, *J* = 9.2, 3.0 Hz, 2 H), 4.62 (ddd, J = 11.5, 3.2, 0.7 Hz, 1 H), 4.50 (dd, J = 11.5, 7.3 Hz, 1 H), 4.27 (br dd, J = 12.4, 5.6 Hz, 1 H), 4.17 (dd, J = 12.4, 7.0 Hz, 1 H), 4.13 (dd, J = 9.6, 5.7 Hz, 1 H), 4.07 (dd, J = 9.6, 6.7 Hz, 1 H), 2.88 (m, 1 H); $[\alpha]^{26}$ 14° (c, 1.00, $CHCl_3$). Anal. ($C_{14}H_{12}F_3N_3O_5$) C, H, N.

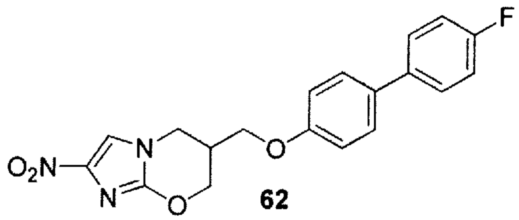
[0269] III. Synthesis of (6*S*)-2-nitro-6-{[4-(trifluoromethoxy)phenoxy]methyl}-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound 61 of Table 1) by the method of Scheme 13.



61

[0270] Preparative chiral HPLC of ether **59** (see Example 2HHH above) secondly gave **61** (509 mg, 43%) as a white solid: mp (CH_2Cl_2/hexane) 139-140 °C; ^1H NMR ($CDCl_3$) δ 7.45 (s, 1 H), 7.17 (br dd, J = 9.1, 0.6 Hz, 2 H), 6.88 (dt, J = 9.1, 3.0 Hz, 2 H), 4.62 (ddd, J = 11.5, 3.2, 0.6 Hz, 1 H), 4.50 (dd, J = 11.5, 7.3 Hz, 1 H), 4.27 (br dd, J = 12.4, 5.2 Hz, 1 H), 4.17 (dd, J = 12.5, 7.1 Hz, 1 H), 4.13 (dd, J = 9.6, 5.7 Hz, 1 H), 4.07 (dd, J = 9.6, 6.7 Hz, 1 H), 2.88 (m, 1 H); $[\alpha]^{26}$ -14° (c, 1.00, $CHCl_3$). Anal. ($C_{14}H_{12}F_3N_3O_5$) C, H, N.

[0271] JJJ. Synthesis of 6-{[(4'-fluoro[1,1'-biphenyl]-4-yl)oxy]methyl}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound 62 of Table 1) by the method of Scheme 13.



62

[0272] Alkylation of 4-iodophenol with iodide **165** (see Example 2GGG) and K_2CO_3 as in Example 2GGG above for 6 h, followed by chromatography of the product on silica gel, eluting with petroleum ether (foreruns) and then with 5% CH_2Cl_2/petroleum ether, gave *tert*-butyl({2-[(4-iodophenoxy)methyl]-2-propenyl}oxy)dimethylsilane (**167**) (94%) as an oil; ^1H

NMR ($CDCl_3$) δ 7.54 (dt, *J* = 8.9, 2.7 Hz, 2 H), 6.70 (dt, *J* = 8.9, 2.7 Hz, 2 H), 5.25 (d, *J* = 1.0 Hz, 1 H), 5.19 (d, *J* = 1.2 Hz, 1 H), 4.51 (s, 2 H), 4.23 (s, 2 H), 0.91 (s, 9 H), 0.07 (2 s, 6 H); HRFABMS calcd for $C_{16}H_{26}IO_2Si$ *m/z* $[M + H]^+$ 405.0747, found 405.0739.

[0273] A solution of iodine (282 mg, 1.11 mmol) in anhydrous THF (1.5 mL, then 2x 0.75 mL to rinse) was added dropwise (over 40 min) to a stirred mixture of alkene **167** (1.71 g, 4.23 mmol) and powdered $NaBH_4$ (90 mg, 2.38 mmol) in anhydrous THF (5.5 mL) at 0 °C under N_2. After stirring at 0 °C for 4 h, and then at room temperature for 13 h, the mixture was again cooled to 0 °C, treated with 30% H_2O_2 (2.4 mL) and 3N NaOH (2.4 mL), and then stirred at room temperature for 3 h. Water (50 mL) was then added, and the mixture was extracted with EtOAc (4x 50 mL). The extracts were washed with brine (50 mL) and evaporated to dryness and the residue was chromatographed on silica gel. Elution with 0-2% EtOAc/petroleum ether firstly gave foreruns, and then further elution with 4-5% EtOAc/petroleum ether gave 3-{[*tert*-butyl(dimethyl)silyl]oxy}-2-[(4-iodophenoxy)methyl]-1-propanol (**169**) (1.26 g, 71%) as a pale yellow oil; ^1H NMR ($CDCl_3$) δ 7.55 (dt, *J* = 9.0, 2.7 Hz, 2 H), 6.69 (dt, *J* = 9.0, 2.7 Hz, 2 H), 4.06 (dd, *J* = 9.3, 6.7 Hz, 1 H), 4.01 (dd, *J* = 9.3, 5.9 Hz, 1 H), 3.93-3.80 (m, 4 H), 2.36 (dd, *J* = 6.3, 5.1 Hz, 1 H), 2.17 (sept, *J* = 5.4 Hz, 1 H), 0.89 (s, 9 H), 0.06, 0.05 (2 s, 6 H); HRFABMS calcd for $C_{16}H_{28}IO_3Si$ *m/z* $[M + H]^+$ 423.0853, found 423.0849.

[0274] Iodination of alcohol **169** with I_2, PPh_3 and imidazole as in Example 2GGG above for 12 h, followed by chromatography of the product on silica gel, eluting with 0-5% CH_2Cl_2/petroleum ether (foreruns) and then with 5-10% CH_2Cl_2/petroleum ether, gave *tert*-butyl{3-iodo-2-[(4-iodophenoxy)methyl]propoxy}dimethylsilane (**171**) (94%) as a colourless oil; ^1H NMR ($CDCl_3$) δ 7.55 (dt, *J* = 9.0, 2.7 Hz, 2 H), 6.68 (dt, *J* = 9.0, 2.7 Hz, 2 H), 3.98 (dd, *J* = 9.4, 5.7 Hz, 1 H), 3.92 (dd, *J* = 9.4, 6.2 Hz, 1 H), 3.74 (dd, *J* = 10.1, 5.6 Hz, 1 H), 3.69 (dd, *J* = 10.1, 5.6 Hz, 1 H), 3.38 (dd, *J* = 10.0, 5.9 Hz, 1 H), 3.35 (dd, *J* = 10.0, 6.1 Hz, 1 H), 2.09 (sept, *J* = 5.8 Hz, 1 H), 0.89 (s, 9 H), 0.06 (2 s, 6 H); HRFABMS calcd for $C_{16}H_{27}I_2O_2Si$ *m/z* $[M + H]^+$ 532.9870, found 532 9864.

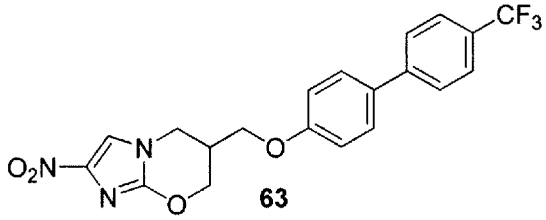
[0275] Alkylation of 2-bromo-4(5)-nitroimidazole (**80**) with iodide **171** and K_2CO_3 as in Example 2GGG above for 33 h, followed by chromatography of the product on silica gel, eluting with 0-7% EtOAc/petroleum ether (foreruns) and then with 8-15% EtOAc/petroleum ether, gave 2-bromo-1-{3-{[*tert*-butyl(dimethyl)silyl]oxy}-2-[(4-iodophenoxy)methyl]propyl}-4-nitro-1*H*-imidazole (**173**) (80%) as a white solid: mp (CH_2Cl_2/pentane) 81-83 °C; ^1H NMR ($CDCl_3$) δ 7.81 (s, 1 H), 7.57 (dt, J = 9.0, 2.7 Hz, 2 H), 6.64 (dt, J = 9.0, 2.6 Hz, 2 H), 4.24 (d, J = 7.1 Hz, 1 H), 3.93 (d, J = 5.6 Hz, 1 H), 3.76 (dd, J = 10.6, 5.1 Hz, 1 H), 3.66 (dd, J = 10.6, 4.7 Hz, 1 H), 2.50 (m, 1 H), 0.91 (s, 9 H), 0.07 (2 s, 6 H); HRFABMS calcd for $C_{19}H_{28}BrIN_3O_4Si$ m/z $[M + H]^+$ 598.0057, 596.0077, found 598.0070, 596.0082.

[0276] Hydrolysis of silyl ether **173** with 1% HCl in 95% EtOH as in Example 2GGG above for 7 h, followed by chromatography of the product on silica gel, eluting with 0-30% EtOAc/petroleum ether (foreruns) and then with 40-50% EtOAc/petroleum ether, gave 3-(2-bromo-4-nitro-1*H*-imidazol-1-yl)-2-[(4-iodophenoxy)methyl]-1-propanol (**175**) (86%) as a white solid: mp (CH_2Cl_2/pentane) 109-111 °C; ^1H NMR ($CDCl_3$) δ 7.87 (s, 1 H), 7.58 (dt, J = 9.0, 2.7 Hz, 2 H), 6.66 (dt, J = 9.0, 2.7 Hz, 2 H), 4.33 (dd, J = 14.4, 7.3 Hz, 1 H), 4.29 (dd, J = 14.4, 7.1 Hz, 1 H), 4.03 (dd, J = 9.6, 5.7 Hz, 1 H), 4.00 (dd, J = 9.6, 7.8 Hz, 1 H), 3.86 (ddd, J = 10.9, 4.6, 4.3 Hz, 1 H), 3.75 (dt, J = 10.8, 4.9 Hz, 1 H), 2.52 (m, 1 H), 1.72 (t, J = 4.4 Hz, 1 H); HRFABMS calcd for $C_{13}H_{14}BrIN_3O_4$ m/z $[M + H]^+$ 483.9192, 481.9212, found 483.9200, 481.9211.

[0277] Ring closure of alcohol **175** with NaH as in Example 2GGG for 5 h, followed by chromatography of the product on silica gel, eluting with 0-1% EtOAc/CH_2Cl_2 (foreruns) and then with 1.5-2% EtOAc/CH_2Cl_2, gave 6-[(4-iodophenoxy)methyl]-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (**176**) (78%) as a pale yellow solid: mp (CH_2Cl_2/pentane triturate) 239-240 °C; ^1H NMR [$(CD_3)_2SO$] δ 8.09 (s, 1 H), 7.60 (dt, J = 9.0, 2.7 Hz, 2 H), 6.82 (dt, J = 9.0, 2.7 Hz, 2 H), 4.59 (dd, J = 10.9, 2.9 Hz, 1 H), 4.44 (dd, J = 11.0, 7.2 Hz, 1 H), 4.28 (dd, J = 12.5, 5.4 Hz, 1 H), 4.09 (dd, J = 10.0, 6.7 Hz, 1 H), 4.06 (dd, J = 10.0, 6.7 Hz, 1 H), 4.03 (dd, J = 12.5, 7.0 Hz, 1 H), 2.82 (m, 1 H). Anal. ($C_{13}H_{12}IN_3O_4$) C, H, N.

[0278] Suzuki coupling of iodide **176** and 4-fluorophenylboronic acid as in Example 2CC above, followed by chromatography of the product on silica gel, eluting with 0-1% EtOAc/CH_2Cl_2 (foreruns) and then with 1-2% EtOAc/CH_2Cl_2, gave **62** (92%) as a pale pink solid: mp (CH_2Cl_2/pentane) 201-203 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.11 (s, 1 H), 7.65 (dt, *J* = 8.9, 2.7 Hz, 2 H), 7.64 (dt, *J* = 8.8, 2.7 Hz, 2 H), 7.59 (dt, *J* = 8.8, 2.5 Hz, 2 H), 7.25 (tt, 8.9, 2.7 Hz, 2 H), 7.05 (dt, *J* = 8.8, 2.6 Hz, 2 H), 4.63 (dd, *J* = 10.9, 2.9 Hz, 1 H), 4.48 (dd, *J* = 11.0, 7.3 Hz, 1 H), 4.31 (dd, *J* = 12.5, 5.4 Hz, 1 H), 4.16 (dd, *J* = 10.0, 6.7 Hz, 1 H), 4.12 (dd, *J* = 10.0, 6.7 Hz, 1 H), 4.07 (dd, *J* = 12.6, 7.0 Hz, 1 H), 2.86 (m, 1 H). Anal. ($C_{19}H_{16}FN_3O_4$) C, H, N.

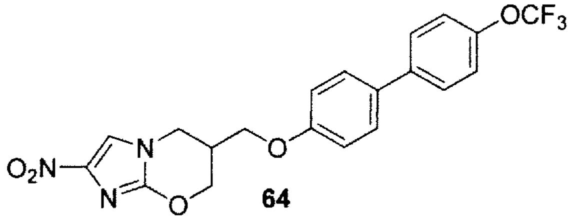
[0279] KKK. Synthesis of 2-nitro-6-({[4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]oxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound 63 of Table 1) by the method of Scheme 13.



63

[0280] Suzuki coupling of iodide **176** (see Example 2JJJ above) and 4-(trifluoromethyl)phenylboronic acid as in Example 2CC above, followed by chromatography of the product on silica gel, eluting with 0-1% EtOAc/CH_2Cl_2 (foreruns) and then with 1-2% EtOAc/CH_2Cl_2, gave **63** (90%) as a cream solid: mp (CH_2Cl_2/pentane) 218-221 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.11 (s, 1 H), 7.85 (br d, *J* = 8.2 Hz, 2 H), 7.77 (br d, *J* = 8.3 Hz, 2 H), 7.71 (dt, *J* = 8.8, 2.5 Hz, 2 H), 7.10 (dt, *J* = 8.8, 2.5 Hz, 2 H), 4.63 (dd, *J* = 10.9, 2.9 Hz, 1 H), 4.48 (dd, *J* = 11.0, 7.2 Hz, 1 H), 4.32 (dd, *J* = 12.5, 5.5 Hz, 1 H), 4.18 (dd, *J* = 10.0, 6.7 Hz, 1 H), 4.15 (dd, *J* = 10.0, 6.7 Hz, 1 H), 4.08 (dd, *J* = 12.6, 7.0 Hz, 1 H), 2.87 (m, 1 H). Anal. ($C_{20}H_{16}F_3N_3O_4$) C, H, N.

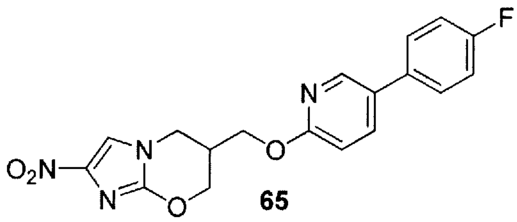
[0281] LLL. Synthesis of 2-nitro-6-({[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]oxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound 64 of Table 1) by the method of Scheme 13.



64

[0282] Suzuki coupling of iodide **176** (see Example 2JJJ above) and 4-(trifluoromethoxy)phenylboronic acid as in Example 2CC above, followed by chromatography of the product on silica gel, eluting with CH_2Cl_2, gave **64** (93%) as a cream solid: mp (CH_2Cl_2/pentane) 192-194 °C; ^{1}H NMR ($CDCl_3$) δ 7.54 (dt, *J* = 8.7, 2.4 Hz, 2 H), 7.50 (dt, *J* = 8.7, 2.5 Hz, 2 H), 7.46 (s, 1 H), 7.26 (m, 2 H), 6.96 (dt, *J* = 8.7, 2.4 Hz, 2 H), 4.63 (dd, *J* = 11.5, 3.1 Hz, 1 H), 4.52 (dd, *J* = 11.5, 7.4 Hz, 1 H), 4.28 (dd, *J* = 12.4, 5.6 Hz, 1 H), 4.20 (m, 1 H), 4.18 (dd, *J* = 10.0, 5.7 Hz, 1 H), 4.12 (dd, *J* = 9.7, 6.7 Hz, 1 H), 2.91 (m, 1 H). Anal. ($C_{20}H_{16}F_3N_3O_5$) C, H, N.

[0283] MMM. Synthesis of 6-({[5-(4-fluorophenyl)-2-pyridinyl]oxy}methyl)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound 65 of Table 1) by the method of Scheme 14.



65

[0284] A mixture of 2-bromo-4(5)-nitroimidazole (**80**) (3.373 g, 17.6 mmol), 6-(iodomethyl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecane (**177**) (reported by Curran et al., 1998 in 4 steps from 2-methylene-1,3-propanediol) (6.79 g, 15.3 mmol) and powdered K_2CO_3 (5.10 g, 36.9 mmol) in anhydrous DMF (40 mL) under N_2 was stirred at 82 °C for 24 h. The resulting cooled mixture was added to ice-water (200 mL) and extracted with EtOAc (3x 200 mL). The extracts were washed with water (200 mL), back-extracting with EtOAc (200 mL), and then further washed with brine (150 mL). The combined extracts were evaporated to dryness and the residue was chromatographed on silica gel. Elution with 0-2% EtOAc/petroleum ether firstly gave foreruns, and then further elution with 3-5% EtOAc/petroleum ether gave 2-bromo-1-[3-{[*tert*-butyl(dimethyl)silyl]oxy}-2-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)propyl]-4-nitro-1*H*-imidazole (**178**) (7.35 g, 95%) as a white solid: mp (pentane) 51-53 °C; ^{1}H NMR ($CDCl_3$) δ 7.83 (s, 1 H), 4.12 (d, *J* = 7.2 Hz, 2 H), 3.61 (dd, *J* = 10.4, 5.5 Hz, 2 H), 3.56 (dd, *J* =

10.4, 5.0 Hz, 2 H), 2.15 (m, 1 H), 0.91 (s, 18 H), 0.07 (2s, 2x 6 H). Anal. ($C_{19}H_{38}BrN_3O_4Si_2$) C, H, N.

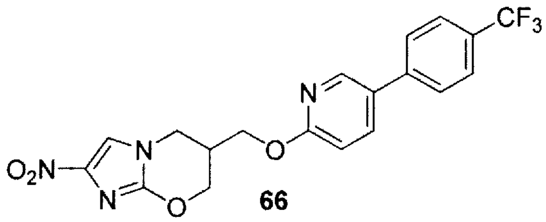
[0285] A suspension of silyl ether **178** (7.35 g, 14.5 mmol) in a solution of 1% HCl in 95% EtOH (desilylation conditions described by Cunico et al., 1980) (150 mL) was stirred at room temperature for 4 h, and then kept at 4 °C for 12 h. The resulting solution was cooled (CO_2/acetone), neutralised by dropwise addition of 7M NH_3 in MeOH (9.8 mL) with stirring, and then concentrated to dryness and the residue was chromatographed on silica gel. Elution with 33-75% EtOAc/petroleum ether firstly gave foreruns, and then further elution with 75% EtOAc/petroleum ether and EtOAc gave 2-[(2-bromo-4-nitro-1*H*-imidazol-1-yl)methyl]-1,3-propanediol (**179**) (3.42, 85%) as a white solid: mp (MeOH/CH_2Cl_2/hexane) 110-112 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.50 (s, 1 H), 4.65 (t, *J* = 5.0 Hz, 2 H), 4.07 (d, *J* = 7.3 Hz, 2 H), 3.41 (m, 4 H), 2.06 (m, 1 H). Anal. ($C_7H_{10}BrN_3O_4$) C, H, N.

[0286] A stirred solution of diol **179** (3.44 g, 12.3 mmol) in anhydrous DMF (30 mL) under N_2 at 0 °C was treated with 60% NaH (1.72 g, 43.0 mmol), then quickly degassed and resealed under N_2. After stirring at room temperature for 3.5 h, the reaction was cooled (CO_2/acetone), quenched with ice/aqueous NH_4Cl (20 mL) and aqueous $NaHCO_3$ (20 mL), added to brine (150 mL) and extracted with CH_2Cl_2 (3x 150 mL), 10% MeOH/CH_2Cl_2 (6x 150 mL), and EtOAc (15x 150 mL). The combined extracts were evaporated to dryness and the residue was chromatographed on silica gel. Elution with 0-2% MeOH/CH_2Cl_2 firstly gave foreruns, and then further elution with 2-3% MeOH/CH_2Cl_2 gave the crude product (1.88 g), which was further chromatographed on silica gel. Elution with 50-90% EtOAc/petroleum ether firstly gave foreruns, and then further elution with 90% EtOAc/petroleum ether and EtOAc gave (2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazin-6-yl)methanol (**180**) (1.649 g, 67%) as a pale yellow solid: mp (MeOH/CH_2Cl_2/hexane) 130-131 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.06 (s, 1 H), 4.96 (t, *J* = 5.1 Hz, 1 H), 4.49 (ddd, *J* = 10.9, 3.3, 0.9 Hz, 1 H), 4.30 (dd, *J* = 10.9, 7.9 Hz, 1 H), 4.15 (ddd, *J* = 12.5, 5.4, 0.8 Hz, 1 H), 3.90 (dd, *J* = 12.5, 7.7 Hz, 1 H), 3.47 (m, 2 H), 2.40 (m, 1 H). Anal. ($C_7H_9N_3O_4$) C, H, N.

[0287] Alkylation of oxazine alcohol **180** with 5-bromo-2-fluoropyridine (**91**) (2.0 equiv.) and NaH (1.74 equiv.) as in Example 2OO for 3 h, followed by chromatography of the product on silica gel, eluting with 0-0.25% MeOH/CH_2Cl_2 (foreruns) and then with 0.25-0.5% MeOH/CH_2Cl_2, gave 6-{[(5-bromo-2-pyridinyl)oxy]methyl}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (**181**) (67%) as a white solid: mp (MeOH/CH_2Cl_2/hexane) 233-235 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.27 (dd, *J* = 2.5, 0.4 Hz, 1 H), 8.07 (s, 1 H), 7.93 (dd, *J* = 8.8, 2.6 Hz, 1 H), 6.85 (dd, *J* = 8.9, 0.5 Hz, 1 H), 4.60 (dd, *J* = 11.0, 2.7 Hz, 1 H), 4.44 (dd, *J* = 11.1, 7.4 Hz, 1 H), 4.36 (dd, *J* = 11.0, 6.7 Hz, 1 H), 4.33 (dd, *J* = 11.0, 6.7 Hz, 1 H), 4.27 (dd, *J* = 12.5, 5.4 Hz, 1 H), 4.04 (dd, *J* = 12.6, 7.1 Hz, 1 H), 2.85 (m, 1 H). Anal. ($C_{12}H_{11}BrN_4O_4$) C, H, N.

[0288] Suzuki coupling of bromide **181** and 4-fluorophenylboronic acid (2.0 equiv.) as in Example 2M for 2.5 h, followed by chromatography of the product on silica gel, eluting with 0-5% EtOAc/CH_2Cl_2 (foreruns) and then with 5-6% EtOAc/CH_2Cl_2, gave **65** (93%) as a cream solid: mp (CH_2Cl_2/pentane) 160-161 °C; ^{1}H NMR ($CDCl_3$) δ 8.29 (dd, *J* = 2.5, 0.6 Hz, 1 H), 7.78 (dd, *J* = 8.8, 2.5 Hz, 1 H), 7.46 (ddt, *J* = 8.9, 5.2, 2.6 Hz, 2 H), 7.44 (s, 1 H), 7.14 (tt, *J* = 6.5, 2.6 Hz, 2 H), 6.83 (dd, *J* = 8.6, 0.7 Hz, 1 H), 4.64 (ddd, *J* = 11.4, 3.3, 1.0 Hz, 1 H), 4.54 (dd, *J* = 11.3, 6.2 Hz, 1 H), 4.49 (dd, *J* = 11.3, 6.5 Hz, 1 H), 4.45 (dd, *J* = 11.5, 7.9 Hz, 1 H), 4.26 (ddd, *J* = 12.4, 5.6, 0.9 Hz, 1 H), 4.10 (dd, *J* = 12.4, 7.7 Hz, 1 H), 2.94 (m, 1 H). Anal. ($C_{18}H_{15}FN_4O_4$) C, H, N.

[0289] NNN. Synthesis of 2-nitro-6-[({5-[4-(trifluoromethyl)phenyl]-2-pyridinyl}oxy)methyl]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound 66 of Table 1) by the method of Scheme 14.

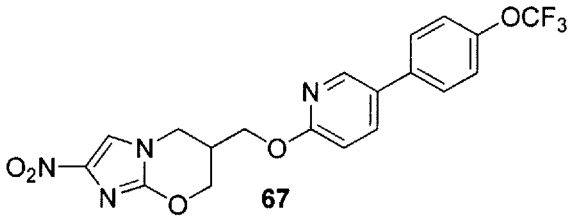


66

[0290] Suzuki coupling of bromide **181** (see Example 2MMM) and 4-(trifluoromethyl)phenylboronic acid as in Example 2M for 130 min, followed by chromatography of the product on silica gel, eluting with 0-4% EtOAc/CH_2Cl_2 (foreruns) and then with 5-6%

$EtOAc/CH_2Cl_2$, gave **66** (94%) as a cream solid: mp (CH_2Cl_2/pentane) 180-182 °C; ^1H NMR ($CDCl_3$) δ 8.38 (dd, J = 2.5, 0.5 Hz, 1 H), 7.87 (dd, J = 8.6, 2.6 Hz, 1 H), 7.73 (br d, J = 8.2 Hz, 2 H), 7.64 (br d, J = 8.1 Hz, 2 H), 7.48 (s, 1 H), 6.89 (dd, J = 8.6, 0.6 Hz, 1 H), 4.66 (ddd, J = 11.4, 3.3, 0.9 Hz, 1 H), 4.57 (dd, J = 11.3, 6.3 Hz, 1 H), 4.52 (dd, J = 11.3, 6.4 Hz, 1 H), 4.49 (dd, J = 11.5, 7.9 Hz, 1 H), 4.29 (ddd, J = 12.4, 5.6, 0.8 Hz, 1 H), 4.13 (dd, J = 12.4, 7.6 Hz, 1 H), 2.98 (m, 1 H). Anal. ($C_{19}H_{15}F_3N_4O_4$) C, H, N.

[0291] OOO. Synthesis of 2-nitro-6-[({5-[4-(trifluoromethoxy)phenyl]-2-pyridinyl}oxy)methyl]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound 67 of Table 1) by the method of Scheme 14.



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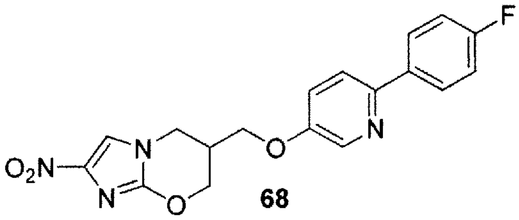
[0292] Suzuki coupling of bromide **181** (see Example 2MMM) and 4-(trifluoromethoxy)phenylboronic acid as in Example 2M for 2 h, followed by chromatography of the product on silica gel, eluting with 0-4% $EtOAc/CH_2Cl_2$ (foreruns) and then with 4-5% $EtOAc/CH_2Cl_2$, gave **67** (93%) as a cream solid: mp (CH_2Cl_2/pentane) 182-183 °C; ^1H NMR ($CDCl_3$) δ 8.31 (dd, J = 2.5, 0.7 Hz, 1 H), 7.80 (dd, J = 8.6, 2.6 Hz, 1 H), 7.52 (dt, J = 8.8, 2.6 Hz, 2 H), 7.44 (s, 1 H), 7.30 (br dd, J = 8.7, 0.8 Hz, 2 H), 6.84 (dd, J = 8.6, 0.6 Hz, 1 H), 4.64 (ddd, J = 11.5, 3.3, 0.9 Hz, 1 H), 4.54 (dd, J = 11.3, 6.2 Hz, 1 H), 4.50 (dd, J = 11.2, 6.4 Hz, 1 H), 4.46 (dd, J = 11.4, 7.9 Hz, 1 H), 4.26 (ddd, J = 12.4, 5.6, 0.8 Hz, 1 H), 4.10 (dd, J = 12.4, 7.6 Hz, 1 H), 2.95 (m, 1 H). Anal. ($C_{19}H_{15}F_3N_4O_5$) C, H, N.

[0293] PPP. Synthesis of 6-({[6-(4-fluorophenyl)-3-pyridinyl]oxy}methyl)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound 68 of Table 1) by the method of Scheme 15.



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[0294] Diethylazodicarboxylate (3.445 mL, 22.2 mmol) was added dropwise to a stirred mixture of 3-{[*tert*-butyl(dimethyl)silyl]oxy}-2-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-1-propanol (**184**) (reported by Kim et al., 2001, via silylation and hydroboration of 2-methylene-1,3-propanediol) (5.706 g, 17.1 mmol), 6-bromo-3-pyridinol (3.571 g, 20.5 mmol) and triphenylphosphine (5.386 g, 20.5 mmol) in anhydrous THF (55 mL) at 0 °C under N_2. After stirring at 0 °C for 1 h, and then at room temperature for 41 h, the mixture was concentrated under reduced pressure and the residue was chromatographed on silica gel. Elution with 0-5% Et_2O/petroleum ether firstly gave foreruns, and then further elution with 5% Et_2O/petroleum ether gave 2-bromo-5-[3-{[*tert*-butyl(dimethyl)silyl]oxy}-2-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)propoxy]pyridine (**185**) (8.09 g, 97%) as a colourless oil; ^{1}H NMR ($CDCl_3$) δ 8.06 (d, J = 3.0 Hz, 1 H), 7.35 (dd, J = 8.7, 0.3 Hz, 1 H), 7.11 (dd, J = 8.7, 3.2 Hz, 1 H), 4.03 (d, J = 5.9 Hz, 2 H), 3.73 (dd, J = 10.1, 5.7 Hz, 1 H), 3.69 (dd, J = 10.0, 6.0 Hz, 1 H), 2.16 (sept, J = 5.8 Hz, 1 H), 0.88 (s, 18 H), 0.03 (2 s, 12 H); HRESIMS calcd for $C_{21}H_{41}BrNO_3Si_2$ *m/z* $[M + H]^+$ 492.1783, 490.1803, found 492.1786, 490.1804.

[0295] Silyl ether **185** (11.06 g, 22.5 mmol) was treated with a solution of 1% HCl in 95% EtOH (desilylation conditions described by Cunico et al., 1980) (200 mL), and the mixture was stirred at room temperature for 13 h. The resulting solution was cooled (CO_2/acetone), neutralised by dropwise addition of 7M NH_3 in MeOH (10 mL) with stirring, and then concentrated to dryness and the residue was chromatographed on silica gel. Elution with 0-3% MeOH/CH_2Cl_2 firstly gave foreruns, and then further elution with 5% MeOH/CH_2Cl_2 gave 2-{[(6-bromo-3-pyridinyl)oxy]methyl}-1,3-propanediol (**186**) (5.56 g, 94%) as a white solid: mp (CH_2Cl_2) 90-91 °C; ^{1}H NMR ($CDCl_3$) δ 8.07 (d, J = 3.1 Hz, 1 H), 7.36 (d, J = 8.7 Hz, 1 H), 7.12 (dd, J = 8.7, 3.1 Hz, 1 H), 4.15 (d, J = 6.1 Hz, 1 H), 3.95 (dt, J = 10.8, 4.9 Hz, 1 H), 3.92 (dt, J = 10.8, 5.3 Hz, 1 H), 2.24 (m, 1 H), 1.99 (t, J = 5.1 Hz, 2 H). Anal. ($C_9H_{12}BrNO_3$) C, H, N.

[0296] A suspension of diol **186** (5.25 g, 20.0 mmol) in anhydrous THF (66 mL) under N_2 was stirred at room temperature until the solid had completely dissolved (~10 min), and then treated with 60% NaH (0.829 g, 20.7 mmol) and quickly degassed and resealed under N_2. After stirring at room temperature for 60 min (to give a white precipitate), *tert*-butyldimethylsilyl chloride (3.21 g, 21.3 mmol) was added, and the mixture was stirred at room temperature for 100 min. The resulting mixture was concentrated under reduced pressure and the residue was chromatographed on silica gel. Elution with 0-33% Et_2O/petroleum ether firstly gave foreruns, and then further elution with 33-50% Et_2O/petroleum ether gave 3-[(6-bromo-3-pyridinyl)oxy]-2-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-1-propanol (**187**) (5.97 g, 79%) as a colourless oil; ^1H NMR ($CDCl_3$) δ 8.07 (d, J = 3.1 Hz, 1 H), 7.36 (d, J = 8.7 Hz, 1 H), 7.12 (dd, J = 8.7, 3.1 Hz, 1 H), 4.12 (dd, J = 9.2, 6.6 Hz, 1 H), 4.09 (dd, J = 9.2, 5.9 Hz, 1 H), 3.94-3.80 (m, 4 H), 2.27 (dd, J = 6.3, 4.8 Hz, 1 H), 2.18 (sept, J = 5.4 Hz, 1 H), 0.89 (s, 9 H), 0.06, 0.05 (2 s, 6 H); HRESIMS calcd for $C_{15}H_{27}BrNO_3Si$ *m/z* $[M + H]^+$ 378.0918, 376.0938, found 378.0912, 376.0931.

[0297] Iodination of alcohol **187** with I_2, PPh_3 and imidazole as in Example 2GGG above for 18 h, followed by chromatography of the product on silica gel, eluting with petroleum ether and pentane (foreruns) and then with 5-25% Et_2O/pentane, gave 2-bromo-5-[3-{[*tert*-butyl(dimethyl)silyl]oxy}-2-(iodomethyl)propoxy]pyridine (**188**) (97%) as a colourless oil; ^1H NMR ($CDCl_3$) δ 8.07 (d, J = 3.0 Hz, 1 H), 7.37 (dd, J = 8.7, 0.3 Hz, 1 H), 7.11 (dd, J = 8.7, 3.2 Hz, 1 H), 4.06 (dd, J = 9.2, 5.7 Hz, 1 H), 3.99 (dd, J = 9.2, 6.1 Hz, 1 H), 3.74 (dd, J = 10.1, 5.6 Hz, 1 H), 3.70 (dd, J = 10.1, 5.5 Hz, 1 H), 3.36 (d, J = 6.0 Hz, 2 H), 2.12 (sept, J = 5.8 Hz, 1 H), 0.89 (s, 9 H), 0.06 (2 s, 6 H); HRESIMS calcd for $C_{15}H_{26}BrINO_2Si$ *m/z* $[M + H]^+$ 487.9935, 485.9955, found 487.9931, 485.9952.

[0298] Alkylation of 2-bromo-4(5)-nitroimidazole (**80**) with iodide **188** and K_2CO_3 as in Example 2GGG above for 42 h, followed by chromatography of the product on silica gel, eluting with 0-20% EtOAc/petroleum ether (foreruns) and then with 20-33% EtOAc/petroleum ether, gave 2-bromo-5-[3-(2-bromo-4-nitro-1*H*-imidazol-1-yl)-2-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)propoxy]pyridine (**189**) (73%) as a cream solid: mp (CH_2Cl_2/hexane) 132-134 °C; ^1H NMR ($CDCl_3$) δ 8.05 (d, J = 3.0 Hz, 1 H), 7.82 (s, 1 H), 7.40 (dd, J = 8.7, 0.4 Hz, 1 H), 7.06 (dd, J = 8.7, 3.2 Hz, 1 H), 4.25 (d, J = 7.2 Hz, 2 H), 4.01 (d, J =

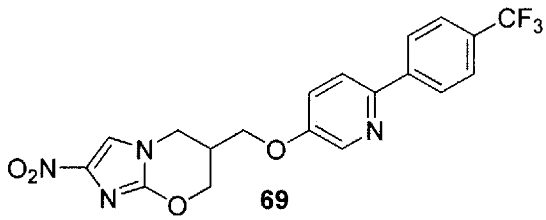
5.7 Hz, 2 H), 3.77 (dd, J = 10.7, 4.9 Hz, 1 H), 3.66 (dd, J = 10.6, 4.6 Hz, 1 H), 2.53 (m, 1 H), 0.91 (s, 9 H), 0.08, 0.07 (2 s, 6 H). Anal. ($C_{18}H_{26}Br_2N_4O_4Si$) C, H, N.

[0299] Tetra-*n*-butylammonium fluoride (13.0 mL of a 1M solution in THF, 13.0 mmol) was added dropwise to a stirred solution of silyl ether **189** (6.78 g, 12.3 mmol) in anhydrous THF (140 mL) and the mixture was stirred at room temperature for 4 h. The resulting solution was concentrated under reduced pressure, and then diluted with ice-water (120 mL) and extracted with EtOAc (5x 120 mL). The extracts were washed with brine (100 mL) and then evaporated to dryness and the residue was chromatographed on silica gel. Elution with 0-80% Et_2O/petroleum ether, petroleum ether and 0-1% MeOH/CH_2Cl_2 firstly gave foreruns, and then further elution with 2-3% MeOH/CH_2Cl_2 gave 3-(2-bromo-4-nitro-1*H*-imidazol-1-yl)-2-{[(6-bromo-3-pyridinyl)oxy]methyl}-1-propanol (**190**) (5.36 g, 100%) as a pale yellow foam; ^{1}H NMR ($CDCl_3$) δ 8.07 (d, J = 3.0 Hz, 1 H), 7.89 (s, 1 H), 7.40 (d, J = 8.7 Hz, 1 H), 7.09 (dd, J = 8.7, 3.2 Hz, 1 H), 4.32 (d, J = 7.2 Hz, 2 H), 4.09 (d, J = 5.5 Hz, 2 H), 3.87 (dd, J = 10.7, 4.7 Hz, 1 H), 3.75 (dd, J = 10.8, 4.8 Hz, 1 H), 2.57 (m, 1 H); HRESIMS calcd for $C_{12}H_{13}Br_2N_4O_4$ *m/z* $[M + H]^+$ 438.9258, 436.9278, 434.9298, found 438.9262, 436.9279, 434.9299.

[0300] Ring closure of alcohol **190** with NaH (1.35 equiv.) as in Example 2GGG for 200 min, followed by chromatography of the product on silica gel, eluting with 0-1% MeOH/CH_2Cl_2 (foreruns) and then with 1-3% MeOH/CH_2Cl_2, gave 6-{[(6-bromo-3-pyridinyl)oxy]methyl}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (**191**) (71%) as a pale yellow solid: mp (MeOH/CH_2Cl_2/hexane) 197-199 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.15 (br d, J = 3.0 Hz, 1 H), 8.10 (s, 1 H), 7.56 (dd, J = 8.7, 0.3 Hz, 1 H), 7.42 (dd, J = 8.8, 3.2 Hz, 1 H), 4.60 (dd, J = 11.0, 2.7 Hz, 1 H), 4.45 (dd, J = 11.0, 7.0 Hz, 1 H), 4.29 (dd, J = 12.5, 5.5 Hz, 1 H), 4.20 (dd, J = 10.0, 6.8 Hz, 1 H), 4.17 (dd, J = 10.0, 6.7 Hz, 1 H), 4.05 (dd, J = 12.6, 6.8 Hz, 1 H), 2.85 (m, 1 H). Anal. ($C_{12}H_{11}BrN_4O_4$) C, H, N.

[0301] Suzuki coupling of bromide **191** and 4-fluorophenylboronic acid as in Example 2M for 140 min, followed by chromatography of the product on silica gel, eluting with 0-4% EtOAc/CH_2Cl_2 (foreruns) and then with 5-6% EtOAc/CH_2Cl_2, gave **68** (85%) as a pale yellow-brown solid: mp (MeOH/CH_2Cl_2/hexane) 214-216 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.38 (d, J = 2.8 Hz, 1 H), 8.11 (s, 1 H), 8.06 (ddt, J = 8.9, 5.6, 2.6 Hz, 2 H), 7.91 (d, J = 8.8 Hz, 1 H), 7.51 (dd, J = 8.8, 3.0 Hz, 1 H), 7.27 (dt, J = 8.9, 2.6 Hz, 2 H), 4.63 (dd, J = 11.0, 2.9 Hz, 1 H), 4.49 (dd, J = 11.1, 7.1 Hz, 1 H), 4.32 (dd, J = 12.5, 5.5 Hz, 1 H), 4.25 (dd, J = 10.0, 6.8 Hz, 1 H), 4.22 (dd, J = 10.0, 6.7 Hz, 1 H), 4.08 (dd, J = 12.6, 6.9 Hz, 1 H), 2.89 (m, 1 H). Anal. ($C_{18}H_{15}FN_4O_4$) C, H, N.

[0302] QQQ. Synthesis of 2-nitro-6-[({6-[4-(trifluoromethyl)phenyl]-3-pyridinyl}oxy)methyl]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound 69 of Table 1) by the method of Scheme 15.



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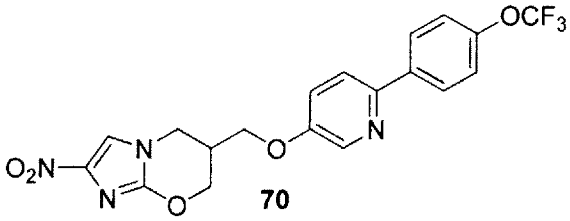
[0303] Suzuki coupling of bromide **191** (see Example 2PPP) and 4-(trifluoromethyl)phenylboronic acid as in Example 2M for 140 min, followed by chromatography of the product on silica gel, eluting with 0-4% EtOAc/CH_2Cl_2 (foreruns) and then with 4-5% EtOAc/CH_2Cl_2, gave **69** (41 mg, 69%) as a pale yellow solid: mp (MeOH/CH_2Cl_2/hexane) 233-235 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.45 (d, J = 2.7 Hz, 1 H), 8.24 (br d, J = 8.1 Hz, 2 H), 8.12 (s, 1 H), 8.05 (d, J = 8.9 Hz, 1 H), 7.81 (br d, J = 8.3 Hz, 2 H), 7.57 (dd, J = 8.8, 3.0 Hz, 1 H), 4.64 (dd, J = 11.0, 2.9 Hz, 1 H), 4.50 (dd, J = 11.1, 7.1 Hz, 1 H), 4.32 (dd, J = 12.5, 5.4 Hz, 1 H), 4.28 (dd, J = 10.0, 6.7 Hz, 1 H), 4.25 (dd, J = 10.1, 6.7 Hz, 1 H), 4.09 (dd, J = 12.6, 6.8 Hz, 1 H), 2.90 (m, 1 H). Anal. ($C_{19}H_{15}F_3N_4O_4$) C, H, N.

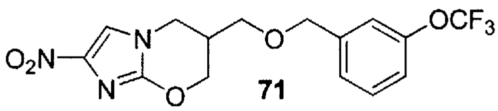
[0304] RRR. Synthesis of 2-nitro-6-[({6-[4-(trifluoromethoxy)phenyl]-3-pyridinyl}oxy)methyl]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound 70 of Table 1) by the method of Scheme 15.



70

[0305] Suzuki coupling of bromide **191** (see Example 2PPP) and 4-(trifluoromethoxy)phenylboronic acid as in Example 2M for 140 min, followed by chromatography of the product on silica gel, eluting with 0-4% EtOAc/CH_2Cl_2 (foreruns) and then with 4-5% EtOAc/CH_2Cl_2, gave **70** (55 mg, 89%) as a cream solid: mp (MeOH/CH_2Cl_2/hexane) 180-181 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.41 (d, J = 2.7 Hz, 1 H), 8.14 (dt, J = 8.9, 2.5 Hz, 2 H), 8.11 (s, 1 H), 7.96 (d, J = 8.7 Hz, 1 H), 7.54 (dd, J = 8.8, 3.0 Hz, 1 H), 7.44 (br dd, J = 8.8, 0.8 Hz, 2 H), 4.64 (dd, J = 10.9, 2.9 Hz, 1 H), 4.49 (dd, J = 11.0, 7.1 Hz, 1 H), 4.32 (dd, J = 12.5, 5.4 Hz, 1 H), 4.26 (dd, J = 10.1, 6.7 Hz, 1 H), 4.23 (dd, J = 10.1, 6.7 Hz, 1 H), 4.09 (dd, J = 12.6, 6.8 Hz, 1 H), 2.89 (m, 1 H). Anal. ($C_{19}H_{15}F_3N_4O_5$) C, H, N.

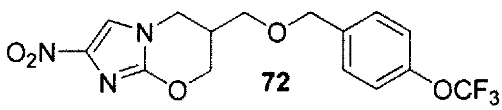
[0306] SSS. Synthesis of 2-nitro-6-({[3-(trifluoromethoxy)benzyl]oxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound 71 of Table 1) by the method of Scheme 14.



71

[0307] Alkylation of oxazine alcohol **180** (see Example 2MMM) with 3-(trifluoromethoxy)benzyl bromide and NaH (1.6 equiv.) as in Example 2UU above, followed by chromatography of the product on silica gel, eluting with 0-1% EtOAc/CH_2Cl_2 (foreruns) and then with 1.5% EtOAc/CH_2Cl_2, gave **71** (56%) as a cream solid: mp (CH_2Cl_2/pentane) 60-61 °C; ^{1}H NMR ($CDCl_3$) δ 7.40 (s, 1 H), 7.39 (t, J = 7.8 Hz, 1 H), 7.21 (br d, J = 7.8 Hz, 1 H), 7.20-7.14 (m, 2 H), 4.54 (s, 2 H), 4.51 (ddd, J = 11.5, 3.4, 0.9 Hz, 1 H), 4.36 (dd, J = 11.4, 7.8 Hz, 1 H), 4.15 (ddd, J = 12.3, 5.6, 0.8 Hz, 1 H), 4.03 (dd, J = 12.3, 7.5 Hz, 1 H), 3.62 (dd, J = 9.6, 5.8 Hz, 1 H), 3.57 (dd, J = 9.6, 6.6 Hz, 1 H), 2.68 (m, 1 H). Anal. ($C_{15}H_{14}F_3N_3O_5$) C, H, N.

[0308] TTT. Synthesis of 2-nitro-6-({[4-(trifluoromethoxy)benzyl]oxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound 72 of Table 1) by the method of Scheme 14.



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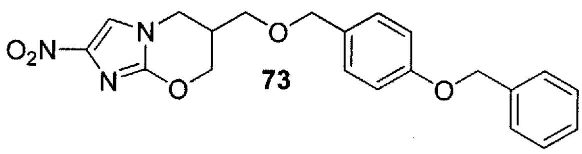
[0309] Alkylation of oxazine alcohol **180** (see Example 2MMM) with 4-(trifluoromethoxy)benzyl bromide (1.9 equiv.) and NaH (1.6 equiv.) as in Example 2UU above for 3 h, followed by chromatography of the product on silica gel, eluting with 0-1% EtOAc/CH_2Cl_2 (foreruns) and then with 2% EtOAc/CH_2Cl_2, gave **72** (59%) as a cream solid: mp (CH_2Cl_2/hexane) 92-93 °C; ^{1}H NMR ($CDCl_3$) δ 7.40 (s, 1 H), 7.32 (dt, J = 8.7, 2.3 Hz, 2 H), 7.21 (br d, J = 8.0 Hz, 2 H), 4.52 (s, 2 H), 4.51 (ddd, J = 11.3, 3.3, 0.9 Hz, 1 H), 4.36 (dd, J = 11.4, 7.8 Hz, 1 H), 4.15 (ddd, J = 12.3, 5.6, 0.8 Hz, 1 H), 4.02 (dd, J = 12.3, 7.5 Hz, 1 H), 3.62 (dd, J = 9.6, 5.9 Hz, 1 H), 3.56 (dd, J = 9.6, 6.5 Hz, 1 H), 2.67 (m, 1 H). Anal. ($C_{15}H_{14}F_3N_3O_5$) C, H, N.

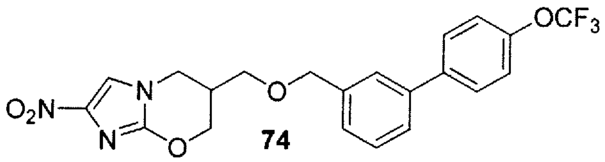
[0310] UUU. Synthesis of 6-({[4-(benzyloxy)benzyl]oxy}methyl)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound 73 of Table 1) by the method of Scheme 14.



[0311] A solution of 4-(benzyloxy)benzyl iodide (reported by Cativiela et al., 1995, via iodination of 4-(benzyloxy)benzyl alcohol) (98 mg, 0.302 mmol) in anhydrous DMF (0.3 mL, then 2x 0.4 mL to rinse) was added to a solution of oxazine alcohol **180** (see Example 2MMM) (30.7 mg, 0.154 mmol) in anhydrous DMF (1 mL) under N_2 at 0 °C. The mixture was treated with 60% NaH (8.8 mg, 0.22 mmol), then quickly degassed and resealed under N_2. After stirring at room temperature for 35 min, the mixture was cooled (CO_2/acetone), quenched with ice/aqueous $NaHCO_3$ (10 mL), added to brine (40 mL) and extracted with CH_2Cl_2 (3x 50 mL) and EtOAc (3x 50 mL). The combined extracts were evaporated to dryness and the residue was chromatographed on silica gel. Elution with 0-2% EtOAc/CH_2Cl_2 firstly gave foreruns, and then elution with 2-3% EtOAc/CH_2Cl_2 gave the crude product (20 mg), which was further chromatographed on silica gel. Elution with 25-40% EtOAc/petroleum ether firstly gave foreruns, and then further elution with EtOAc gave **73** (15 mg, 25%) as a white solid: mp (CH_2Cl_2/hexane) 150-151 °C; ^{1}H NMR ($CDCl_3$) δ 7.46-7.29 (m, 6 H), 7.20 (dt, J = 8.6, 2.4 Hz, 2 H), 6.96 (dt, J = 8.7, 2.4 Hz, 2 H), 5.07 (s, 2 H), 4.48 (ddd, J = 11.4, 3.3, 0.8 Hz, 1 H), 4.46 (d, J = 11.6 Hz, 1 H), 4.43 (d, J = 11.6 Hz, 1

H), 4.32 (dd, J = 11.4, 7.9 Hz, 1 H), 4.09 (br dd, J = 12.3, 5.5 Hz, 1 H), 3.99 (dd, J = 12.3, 7.6 Hz, 1 H), 3.56 (dd, J = 9.6, 5.7 Hz, 1 H), 3.50 (dd, J = 9.6, 6.7 Hz, 1 H), 2.62 (m, 1 H). Anal. ($C_{21}H_{21}N_3O_5$) C, H, N.

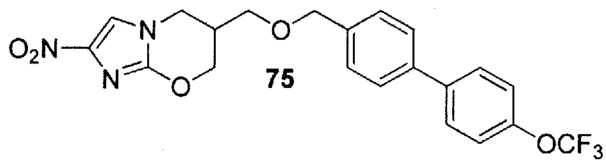
[0312] VVV. Synthesis of 2-nitro-6-({[4'-(trifluoromethoxy)[1,1'-biphenyl]-3-yl]methoxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound 74 of Table 1) by the method of Scheme 14.



[0313] A mixture of oxazine alcohol **180** (see Example 2MMM) (200.3 mg, 1.01 mmol) and 3-iodobenzyl bromide (406 mg, 1.37 mmol) in anhydrous DMF (7.5 mL) under N_2 at 0 °C was treated with 60% NaH (57 mg, 1.43 mmol), then quickly degassed and resealed under N_2. After stirring at room temperature for 140 min, the mixture was cooled (CO_2/acetone), quenched with ice/aqueous $NaHCO_3$ (10 mL) and diluted with water (40 mL) to precipitate a crude solid, which was collected by filtration and washed with water and petroleum ether (0.49 g). The filtrate was extracted with EtOAc (3x 80 mL), and then the extracts were washed with brine (50 mL). The combined extracts were evaporated to dryness and the residue was combined with the solid above and chromatographed on silica gel. Elution with 0-1% EtOAc/CH_2Cl_2 firstly gave foreruns, and then further elution with 1-2% EtOAc/CH_2Cl_2 gave 6-{[(3-iodobenzyl)oxy]methyl}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (**182**) (184 mg, 44%) as a cream solid: mp (CH_2Cl_2/hexane) 127-130 °C; ^{1}H NMR ($CDCl_3$) δ 7.69-7.62 (m, 2 H), 7.40 (s, 1 H), 7.24 (m, 1 H), 7.10 (br t, J = 8.0 Hz, 1 H), 4.51 (dd, J = 11.4, 3.1 Hz, 1 H), 4.48 (d, J = 12.3 Hz, 1 H), 4.44 (d, J = 12.2 Hz, 1 H), 4.35 (dd, J = 11.4, 7.7 Hz, 1 H), 4.14 (dd, J = 12.3, 5.5 Hz, 1 H), 4.02 (dd, J = 12.3, 7.4 Hz, 1 H), 3.60 (dd, J = 9.6, 5.8 Hz, 1 H), 3.54 (dd, J = 9.6, 6.7 Hz, 1 H), 2.66 (m, 1 H). Anal. ($C_{14}H_{14}IN_3O_4$) C, H, N.

[0314] Suzuki coupling of iodide **182** and 4-(trifluoromethoxy)phenylboronic acid as in Example 2XX above, followed by chromatography of the product on silica gel, eluting with 0-1% EtOAc/CH_2Cl_2 (foreruns) and then with 1-1.5% EtOAc/CH_2Cl_2, gave **74** (92%) as a cream solid: mp (CH_2Cl_2/pentane) 78-80 °C; ^{1}H NMR ($CDCl_3$) δ 7.58 (dt, J = 8.8, 2.5 Hz, 2 H), 7.51 (dt, J = 7.8, 1.5 Hz, 1 H), 7.48-7.42 (m, 2 H), 7.37 (s, 1 H), 7.33-7.26 (m, 3 H), 4.61 (d, J = 11.9 Hz, 1 H), 4.57 (d, J = 12.0 Hz, 1 H), 4.51 (ddd, J = 11.4, 3.2, 0.7 Hz, 1 H), 4.37 (dd, J = 11.4, 7.6 Hz, 1 H), 4.13 (dd, J = 12.4, 5.5 Hz, 1 H), 4.03 (dd, J = 12.3, 7.4 Hz, 1 H), 3.64 (dd, J = 9.6, 5.8 Hz, 1 H), 3.58 (dd, J = 9.6, 6.7 Hz, 1 H), 2.67 (m, 1 H). Anal. ($C_{21}H_{18}F_3N_3O_5$) C, H, N.

[0315] WWW. Synthesis of 2-nitro-6-({[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]methoxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (compound 75 of Table 1) by the method of Scheme 14.



[0316] Alkylation of oxazine alcohol **180** (see Example 2MMM) with 4-iodobenzyl bromide and NaH (1.4 equiv.) as in Example 2UU above for 3 h, followed by chromatography of the product on silica gel, eluting with 0-1% EtOAc/CH_2Cl_2 (foreruns) and then with 3% EtOAc/CH_2Cl_2, gave 6-{[(4-iodobenzyl)oxy]methyl}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (**183**) (42%) as a white solid: mp (CH_2Cl_2/hexane) 161-163 °C; ^{1}H NMR ($CDCl_3$) δ 7.70 (dt, J = 8.3, 2.0 Hz, 2 H), 7.40 (s, 1 H), 7.03 (br d, J = 8.3 Hz, 2 H), 4.50 (ddd, J = 11.4, 3.3, 0.8 Hz, 1 H), 4.46 (s, 2 H), 4.34 (dd, J = 11.4, 7.8 Hz, 1 H), 4.13 (ddd, J = 12.3, 5.6, 0.8 Hz, 1 H), 4.00 (dd, J = 12.3, 7.6 Hz, 1 H), 3.59 (dd, J = 9.6, 5.8 Hz, 1 H), 3.53 (dd, J = 9.6, 6.5 Hz, 1 H), 2.65 (m, 1 H); HRFABMS calcd for $C_{14}H_{15}IN_3O_4$ m/z $[M + H]^+$ 416.0107, found 416.0108.

[0317] Suzuki coupling of iodide **183** and 4-(trifluoromethoxy)phenylboronic acid as in Example 2XX above, followed by chromatography of the product on silica gel, eluting with 0-1% EtOAc/CH_2Cl_2 (foreruns) and then with 1-1.5% EtOAc/CH_2Cl_2, gave **75** (95%) as a cream solid: mp (CH_2Cl_2/pentane) 135-138 °C; ^{1}H NMR ($CDCl_3$) δ 7.59 (dt, J = 8.8, 2.5 Hz, 2 H), 7.55 (dt, J = 8.3, 1.9 Hz, 2 H), 7.40 (s, 1 H), 7.37 (br d, J = 8.3 Hz, 2 H), 7.29 (br dd, J = 8.7, 0.8 Hz, 2 H), 4.57 (s, 2 H), 4.52 (ddd, J = 11.4, 3.3, 0.8 Hz, 1 H), 4.37 (dd, J = 11.4, 7.8 Hz, 1 H), 4.15 (ddd, J = 12.3, 5.6, 0.7 Hz, 1 H), 4.04 (dd, J = 12.3, 7.5 Hz, 1 H), 3.64 (dd, J = 9.6, 5.8 Hz, 1 H), 3.58 (dd, J = 9.6, 6.6 Hz, 1 H), 2.68 (m, 1 H). Anal. ($C_{21}H_{18}F_3N_3O_5$) C, H, N.

EXAMPLE 3. BIOLOGICAL ACTIVITIES AND STABILITY

[0318] The biological activity of the compounds of the invention was evaluated as follows. Results are shown below in Table 2.

[0319] (a) Minimum inhibitory concentrations (MICs). Compounds were evaluated for their activity against replicating *Mycobacterium tuberculosis* in an 8 day microplate-based assay using Alamar blue reagent (added on day 7) for determination of growth (MABA) (Collins et al., 1997; Falzari et al., 2005). The lowest compound concentration effecting an inhibition of >90% was considered the MIC. Screening for the activity of the compounds against bacteria in the non-replicating state that models clinical persistence used an 11 day high-throughput, luminescence-based low-oxygen-recovery assay (LORA), where *M. tuberculosis* bacteria containing a plasmid with an acetamidase promoter driving a bacterial luciferase gene were first adapted to low oxygen conditions by extended culture (Cho et al., 2007).

[0320] (b) Mammalian cell cytotoxicity assay. This was assessed against VERO cells (CCL-81, American Type Culture Collection) in a 72 h exposure, using a tetrazolium dye assay (Falzari et al., 2005).

[0321] (c) Antiprotozoal screening. Compounds were evaluated for their activities against both *Trypanosoma cruzi* amastigotes and *Leishmania donovani* amastigotes (free or encapsulated in macrophages), according to the following protocols:

[0322] (i) *Trypanosoma cruzi* assay. L-6 cells ($2x10^3$) in medium (100 μL of RPMI 1640 supplemented with 2 mM L-glutamine plus 10% heat inactivated fetal calf serum) were seeded in 96-well microtitre plates (Costar™) and incubated at 37 °C (5% CO_2) for 1 d. A suspension (50 μL) of *Trypanosoma cruzi* trypomastigotes ($5x10^3$ of Tulahuen C2C4 strain, containing the β-galactosidase gene) was added, and the cells were incubated at 37 °C (5% CO_2) for a further 48 h to establish the infection. The medium was removed and replaced by fresh medium and the infected cells were then incubated at 37 °C (5% CO_2) for 96 h in either medium alone or in the presence of serial (3-fold) dilutions of test compounds (initially prepared as 10 mg/mL stock solutions in DMSO and diluted into medium). Benznidazole was employed as a standard in each assay. Following incubation, chlorophenol red glycoside (100 mM) in 0.1% Nonidet P40/PBS (50 μL) was added, and (after 6 h) the absorbance at 540 nm was measured and used to calculate the IC_{50} values.

[0323] (ii) Axenic *Leishmania donovani* assay. Axenically grown *L. donovani* amastigotes (MHOM-ET-67/L82) from a healthy culture in log phase were seeded at a density of $1x10^6$/mL medium (SM, pH 5.4 plus 10% heat inactivated fetal calf serum) in 96-well microtitre plates (Costar™) and incubated at 37 °C (5% CO_2) for 70 h in either medium alone or in the presence of serial (3-fold) dilutions of test compounds (initially prepared as 10 mg/mL stock solutions in DMSO and diluted into medium). Miltefosin was employed as a standard in each assay. After incubation, Resazurin fluorescent dye was added to each well, and incubation was continued for an additional 2 h. The IC_{50} values were determined from measurements of the fluorescence data.

[0324] (iii) *Leishmania donovani* infected macrophage assay. Freshly harvested mouse macrophages in medium (RPMI 1640 plus 10% heat inactivated fetal calf serum) were incubated at 37 °C (5% CO_2) for 24 h and then infected (1:3 macrophages to amastigotes) with an axenic *L. donovani* amastigote culture (MHOM-ET-67/L82) in medium (SM, pH 5.4 plus 10% heat inactivated fetal calf serum). The infected macrophages were seeded at a density of $1.2x10^6$/mL (by diluting in RPMI + 10% FCS) in 16-well slides (Lab-tek™) and incubated at 37 °C (5% CO_2) for 24 h. The medium was removed and replaced by fresh medium (RPMI 1640 + 10% FCS), and this was repeated following mixing. The infected macrophages were then incubated at 37 °C (5% CO_2) for 96 h in either medium alone or in the presence of serial (3-fold) dilutions of test compounds (initially prepared as 10 mg/mL stock solutions in DMSO and diluted into medium). Miltefosin was employed as a standard in each assay. After removal of the medium and wells, the slides were fixed (5 min in 100% MeOH) and stained (10% Giemsa, 10 min). The ratio of infected to uninfected macrophages was determined by microscopic examination, and the IC_{50} values were then calculated by linear regression analysis.

Table 2. In vitro biological activity of selected compounds of Table 1

No	MIC (μM)	IC_{50} (μM)	IC_{50} (μg/mL)

	MABA (aerobic)	LORA (anaerobic)	VERO	*T. cruzi*	*L. donovani*	
					axen	macro
7	0.53	24	ND	3.2	0.016	0.40
8	0.04	14	>128	4.1	0.017	0.38
9	0.04	3.7	>128	1.2	0.016	0.20
10	0.045	11	>128	2.0	0.040	0.23
11	0.08	>128	>128	18	0.028	0.47
12	0.087	64	>128	9.4	0.016	0.74
25	0.25	34	>128	0.24	0.029	0.22
26	0.30	50	>128	0.34	0.013	0.36
47	3.8	15	ND	1.1	0.041	0.084
49	0.46	3.0	>128	0.55	0.048	0.065
50	0.24	5.1	>128	6.3	0.041	0.15
51	0.055	1.5	>128	15	0.046	0.17
54	0.20	1.4	>128	0.74	0.047	0.095
71	0.33	15	>128	0.56	0.20	0.65
72	2.4	7.9	46	0.62	0.089	0.55
73	3.1	35	113	2.8	0.16	0.53
74	0.22	2.9	>128	0.94	0.16	0.54
75	0.30	>128	>128	0.47	0.20	0.67

[0325] The in vitro microsomal stability and in vivo biological activity of selected compounds of the invention was also evaluated as follows, with results shown in Table 3.

[0326] (a) Stability of the compounds to human and mouse microsomes. Test compounds (1 μM) were incubated at 37 °C with pooled human or CD-1 mouse liver microsome preparations (0.5 mg/mL final protein concentration) and an NADPH regenerating system (MgCl2, 3.3 mM; G6P, 3.3 mM; G6PD, 0.4 U/mL; NADP+, 1.3 mM) in phosphate buffer (75 mM, pH 7.4), with a final volume of 200 μL. The compounds were dissolved in DMSO such that the final DMSO concentration was 0.5%. Reactions were stopped at 0 and 60 min by the addition of MeCN (100 μL) containing 0.2 μM metoprolol as an internal standard. Samples were diluted 10x and centrifuged prior to analysis by LC-MS/MS using electrospray ionization and SRM monitoring using a gradient LC method. LC peak areas were integrated and expressed as analyte/IS peak area ratios (PAR), and a mean value for each time point was calculated from the duplicates. The percent remaining value was calculated as:

$$\% \text{ remaining} = 100 \text{ x } (\text{Mean PAR}_{T60} / \text{Mean PAR}_{T0}).$$

[0327] (b) In vivo mouse acute TB infection assay. BALB/c mice were infected via aerosol with a suspension of ~2 x 106 colony forming units (CFU) of M. tuberculosis Erdman/mL (Falzari et al., 2005). Each compound was given orally to a group of 7 or 8 mice at 100 mg/kg daily for 5 days a week for 3 weeks, beginning on day 11 post-infection. Compounds were administered as a suspension in 0.5% CMC/0.08% Tween 80 in water. Mice were sacrificed on day 31 and the numbers of CFU in the lungs were determined and compared with the CFU for vehicle alone-treated mice at this time. PA-824 was employed as a positive control in each experiment, and the results are recorded as the ratio of the average reduction in CFU in the compound-treated mice/the average CFU reduction in the mice treated with PA-824. In this assay, PA-824 caused up to 2.5-3 log reductions in CFU.

Table 3. Microsomal stability and in vivo biological activity of selected compounds of Table 1

No	Microsomes (% remaining)		In vivo efficacy vs PA-824
	Human	Mouse	
PA-824	82	94	1.00
12	82	81	112
25	68	30	0.025
72	71	41	ND

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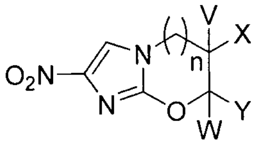
WHAT IS CLAIMED IS:

1. A compound having a general structure of Formula I:



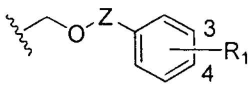
I

wherein

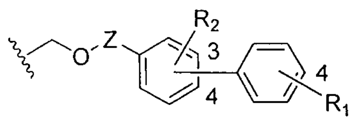
n is 1,

V and W are independently H or CH_3, and

one of X or Y is H and the other is one of Formulae IIa or IIb, wherein Formulae IIa and IIb have general structures of:



IIa



IIb

wherein Formula IIa has a single ring labeled at a 3-position and a 4-position and having R_1 as a substituent, and Formula IIb has a first ring labeled at a 3-position and a 4-position and having as substituents both R_2 and a terminal ring labeled at a 4-position and having R_1 as a substituent,

wherein the single ring of Formula IIa and the first ring and the terminal ring of Formula IIb comprise C, CH, or aza at each ring position, wherein the single ring of Formula IIa and the first ring and the terminal ring of Formula IIb independently comprise no more than two aza,

Z in Formulae IIa and IIb is CH_2 or a direct bond, and

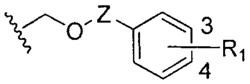
R_1 and R_2 are independently any one or two of H, F, Cl, I, CN, CF_3, OCF_3, OCH_3, or OCH_2Ph.

2. The compound of claim 1 wherein:

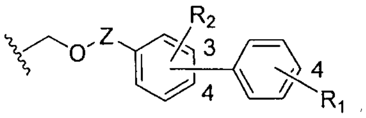
n is 1,

V and W are independently H or CH_3, and

one of X or Y is H and the other is one of Formulae IIa or IIb, wherein Formulae IIa and IIb have general structures of:



IIa



IIb

wherein Formula IIa has a single ring labeled at a 3-position and a 4-position and having R_1 as a substituent, Formula IIb has a first ring labeled at a 3-position and a 4-position and having as substituents both R_2 and a terminal ring labeled at a 4-position and having R_1 as a substituent,

wherein the first ring of Formula IIb comprises C, CH or aza at each ring position, wherein the first ring of Formula IIb comprises no more than two aza, and both the single ring of Formula IIa and the terminal ring of Formula IIb comprise C or CH at each ring position when R_1 is not 4-OMe, or comprise aza at the 3-position and C or CH at each remaining ring position when R_1 is 4-OMe,

Z in Formulae IIa and IIb is CH_2 or a direct bond,

R_1 is 4-F, 4-CN, 4-I, 4-CF_3, 3-OCF_3, 4-OCF_3, 4-OCH_2Ph, or 4-OMe, and

R_2 is H.

3. A pharmaceutical composition for use in preventing or treating microbial infection, comprising a therapeutically effective amount of the compound of claim 1 and further comprising a pharmaceutically acceptable excipient, adjuvant, carrier, buffer, stabilizer, or mixture thereof.

4. The pharmaceutical composition of claim 3, further comprising one or more additional anti-infective compositions.

5. The pharmaceutical composition of claim 3, wherein the microbial infection is caused by *Mycobacterium tuberculosis*, *Trypanosoma cruzi*, or *Leishmania donovani*.

6. A compound selected from the group consisting of:

A. 2-Nitro-7-{[4-(trifluoromethoxy)phenoxy]methyl}-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine;

B. 7-{[4-(Benzyloxy)phenoxy]methyl}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine;

C. 7-{[(4'-Fluoro[1,1'-biphenyl]-4-yl)oxy]methyl}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine;

D. 2-Nitro-7-({[4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]oxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine;

E. 2-Nitro-7-({[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]oxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine;

F. 7-({[5-(4-Fluorophenyl)-2-pyridinyl]oxy}methyl)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine;

G. 2-Nitro-7-[({5-[4-(trifluoromethoxy)phenyl]-2-pyridinyl}oxy)methyl]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine;

H. 7-({[6-(4-Fluorophenyl)-3-pyridinyl]oxy}methyl)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine;

I. 2-Nitro-7-[({6-[4-(trifluoromethoxy)phenyl]-3-pyridinyl}oxy)methyl]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine;

J. 7-Methyl-2-nitro-7-{[4-(trifluoromethoxy)phenoxy]methyl}-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine;

K. 7-{[4-(Benzyloxy)phenoxy]methyl}-7-methyl-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine;

L. 7-{[(4'-Fluoro[1,1'-biphenyl]-4-yl)oxy]methyl}-7-methyl-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine;

M. 7-Methyl-2-nitro-7-({[4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]oxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine;

N. 7-Methyl-2-nitro-7-({[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]oxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine;

O. 7-({[5-(4-Fluorophenyl)-2-pyridinyl]oxy}methyl)-7-methyl-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine;

P. 7-Methyl-2-nitro-7-[({5-[4-(trifluoromethyl)phenyl]-2-pyridinyl}oxy)methyl]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine;

Q. 7-Methyl-2-nitro-7-[({5-[4-(trifluoromethoxy)phenyl]-2-pyridinyl}oxy)methyl]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine;

R. 7-({[6-(4-Fluorophenyl)-3-pyridinyl]oxy}methyl)-7-methyl-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine;

S. 7-Methyl-2-nitro-7-[({6-[4-(trifluoromethyl)phenyl]-3-pyridinyl}oxy)methyl]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine;

T. 7-Methyl-2-nitro-7-[({6-[4-(trifluoromethoxy)phenyl]-3-pyridinyl}oxy)methyl]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine;

U. 2-Nitro-7-({[3-(trifluoromethoxy)benzyl]oxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine;

V. 2-Nitro-7-({[4-(trifluoromethoxy)benzyl]oxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine;

W. 7-({[4-(Benzyloxy)benzyl]oxy}methyl)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine;

X. 2-Nitro-7-({[4'-(trifluoromethoxy)[1,1'-biphenyl]-3-yl]methoxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine;

Y. 2-Nitro-7-({[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]methoxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine;

Z. 7-Methyl-2-nitro-7-({[3-(trifluoromethoxy)benzyl]oxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine;

AA. 7-Methyl-2-nitro-7-({[4-(trifluoromethoxy)benzyl]oxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine;

BB. 7-({[4-(Benzyloxy)benzyl]oxy}methyl)-7-methyl-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine;

CC. 7-Methyl-2-nitro-7-({[4'-(trifluoromethoxy)[1,1'-biphenyl]-3-yl]methoxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine;

DD. 7-Methyl-2-nitro-7-({[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]methoxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine;

EE. (7*R*)-7-Methyl-2-nitro-7-({[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]methoxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine;

FF. (7*S*)-7-Methyl-2-nitro-7-({[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]methoxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine;

GG. 2-Nitro-6-{[4-(trifluoromethoxy)phenoxy]methyl}-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine;

HH. (6*R*)-2-Nitro-6-{[4-(trifluoromethoxy)phenoxy]methyl}-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine;

II. (6*S*)-2-Nitro-6-{[4-(trifluoromethoxy)phenoxy]methyl}-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine;

JJ. 6-{[(4'-Fluoro[1,1'-biphenyl]-4-yl)oxy]methyl}-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine;

KK. 2-Nitro-6-({[4'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]oxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine;

LL. 2-Nitro-6-({[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]oxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine;

MM. 6-({[5-(4-Fluorophenyl)-2-pyridinyl]oxy}methyl)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine;

NN. 2-Nitro-6-[({5-[4-(trifluoromethyl)phenyl]-2-pyridinyl}oxy)methyl]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine;

OO. 2-Nitro-6-[({5-[4-(trifluoromethoxy)phenyl]-2-pyridinyl}oxy)methyl]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine;

PP. 6-({[6-(4-Fluorophenyl)-3-pyridinyl]oxy}methyl)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine;

QQ. 2-Nitro-6-[({6-[4-(trifluoromethyl)phenyl]-3-pyridinyl}oxy)methyl]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine;

RR. 2-Nitro-6-[({6-[4-(trifluoromethoxy)phenyl]-3-pyridinyl}oxy)methyl]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine;

SS. 2-Nitro-6-({[3-(trifluoromethoxy)benzyl]oxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine;

TT. 2-Nitro-6-({[4-(trifluoromethoxy)benzyl]oxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine;

UU. 6-({[4-(Benzyloxy)benzyl]oxy}methyl)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine;

VV. 2-Nitro-6-({[4'-(trifluoromethoxy)[1,1'-biphenyl]-3-yl]methoxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine; and

WW. 2-Nitro-6-({[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]methoxy}methyl)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine; and

mixtures, optical or geometric isomers, and pharmacologically acceptable salt derivatives thereof.

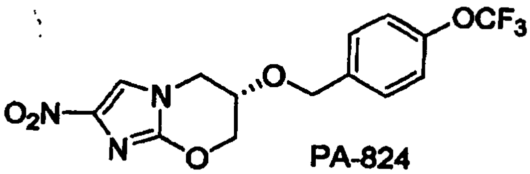
7. Use of the pharmaceutical composition of claim 3 in the manufacture of a medicament for preventing or treating microbial infection.

8. The use of claim 7, wherein the microbial infection is caused by *Mycobacterium tuberculosis*, *Trypanosoma cruzi*, or *Leishmania donovani*.

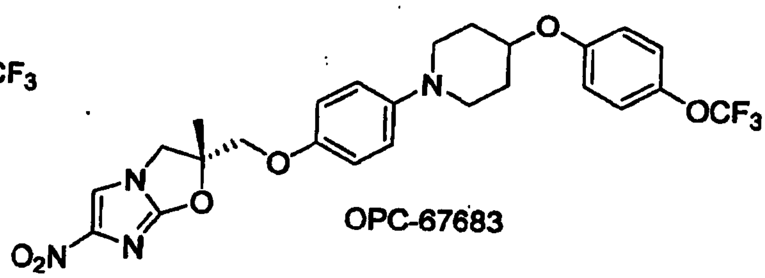
9. Use of the pharmaceutical composition of claim 3 for preventing or treating microbial infection.

10. The use of claim 9, wherein the microbial infection is caused by *Mycobacterium tuberculosis*, *Trypanosoma cruzi*, or *Leishmania donovani*.

Figure 1



PA-824



OPC-67683

Figure 2

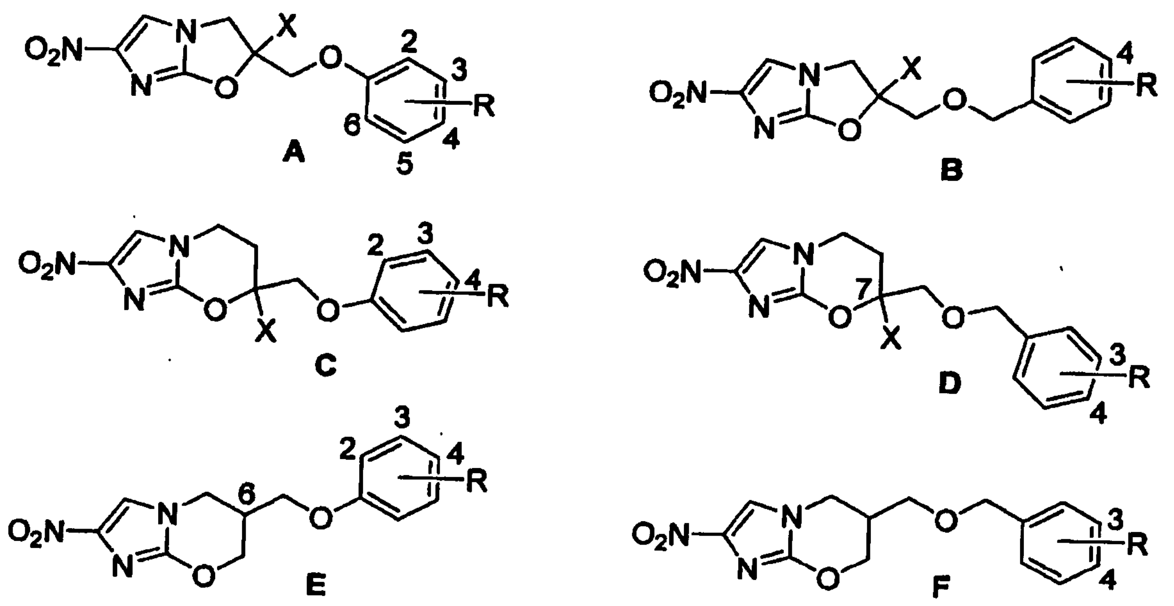


Figure 3

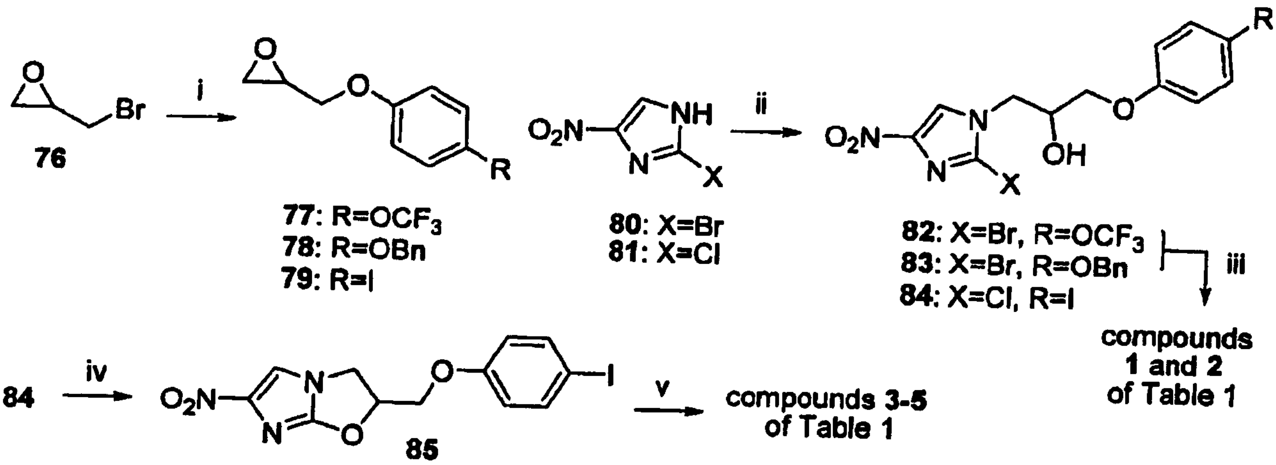

Br
76
i
O
R
77: R=OCF3
78: R=OBn
79: R=I
O2N
NH
N
X
80: X=Br
81: X=Cl
ii
O2N
N
N
X
OH
O
R
82: X=Br, R=OCF3
83: X=Br, R=OBn
84: X=Cl, R=I
iii
compounds
1 and 2
of Table 1
84
iv
O2N
N
N
O
O
I
85
v
compounds 3-5
of Table 1

Figure 4

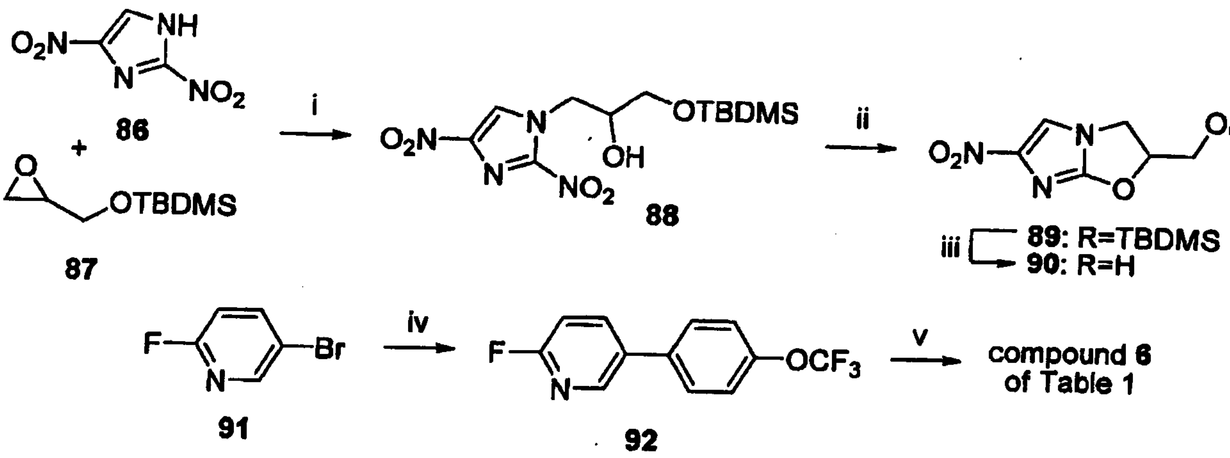

O2N
NH
N
NO2
86
+
O
OTBDMS
87
i
O2N
N
OTBDMS
OH
N
NO2
88
ii
O2N
N
OR
N
O
iii
89: R=TBDMS
90: R=H
F
N
Br
91
iv
F
N
OCF3
92
v
compound 6
of Table 1

Figure 5

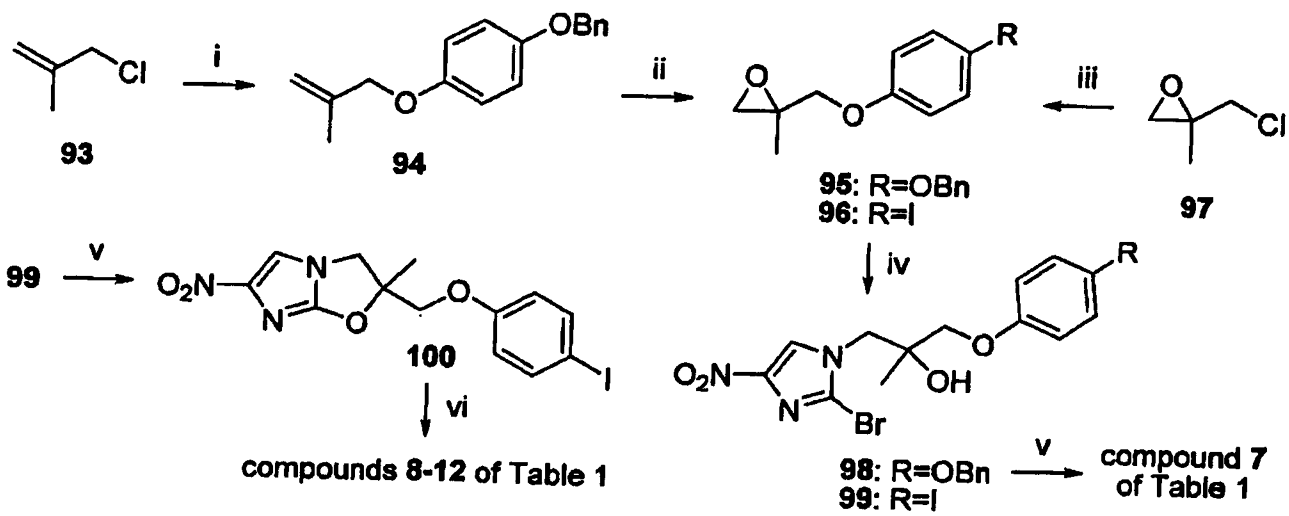

OBn
Cl
i
93
94
ii
O
R
iii
95: R=OBn
96: R=I
97
99
v
O_2N
N
100
vi
compounds 8-12 of Table 1
iv
OH
Br
98: R=OBn
99: R=I
compound 7
of Table 1

Figure 6

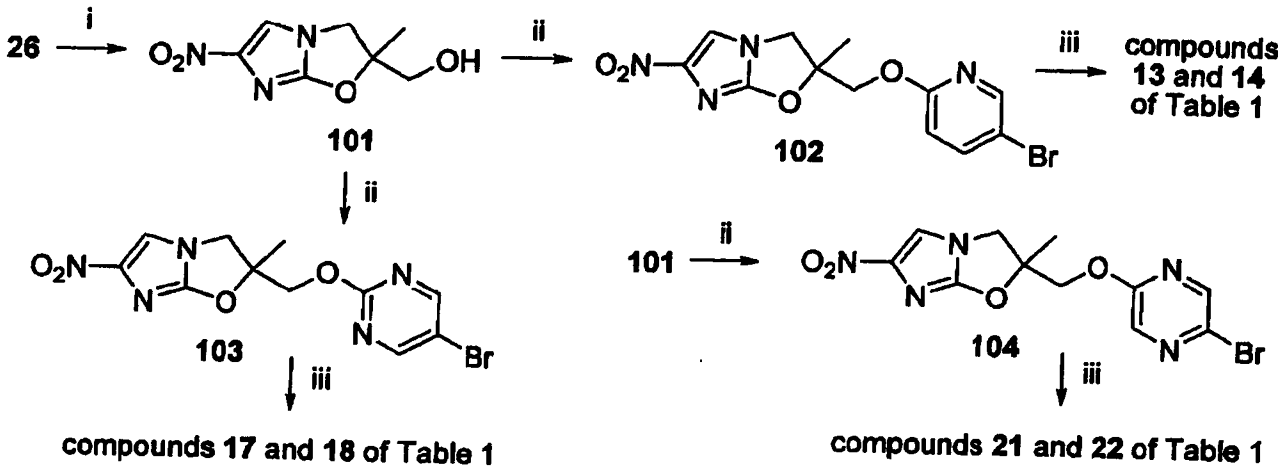
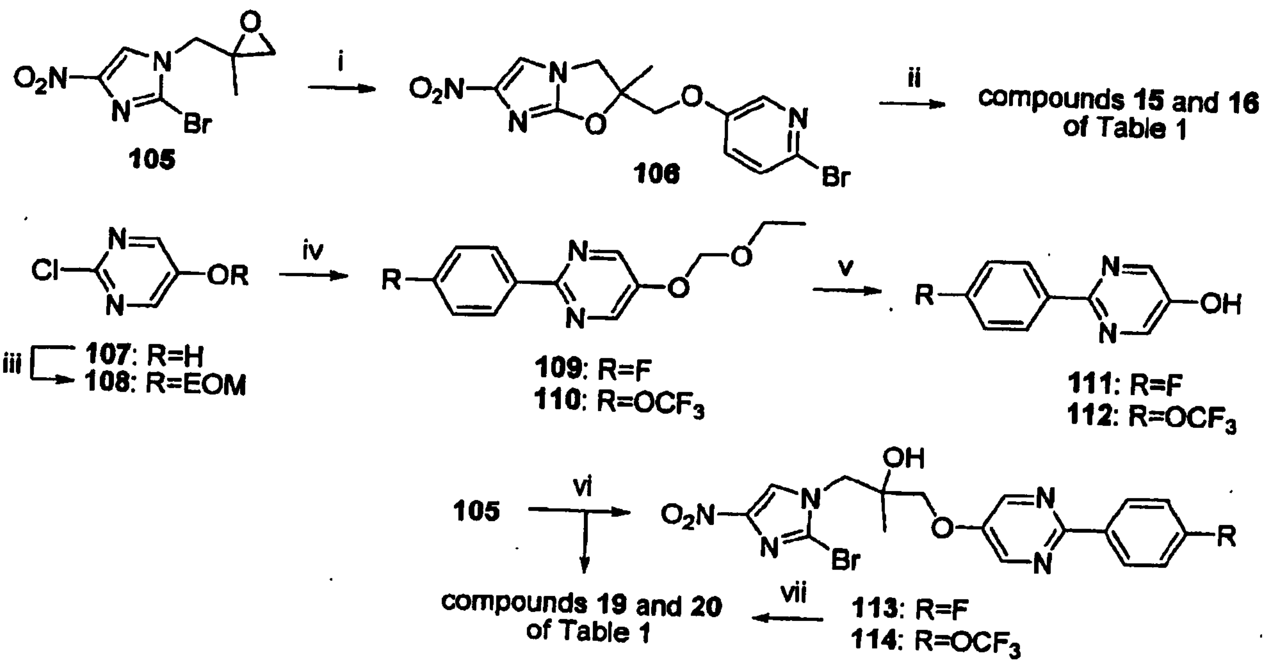

26
i
O_2N
N
N
O
OH
101
ii
O_2N
N
N
O
O
N
Br
102
iii
compounds
13 and 14
of Table 1
ii
O_2N
N
N
O
O
N
N
Br
103
iii
compounds 17 and 18 of Table 1
101
ii
O_2N
N
N
O
O
N
N
Br
104
iii
compounds 21 and 22 of Table 1

Figure 7



i
ii
compounds 15 and 16 of Table 1
105
106
iii
107: R=H
108: R=EOM
iv
v
109: R=F
110: R=OCF3
111: R=F
112: R=OCF3
vi
vii
compounds 19 and 20 of Table 1
113: R=F
114: R=OCF3

Figure 8

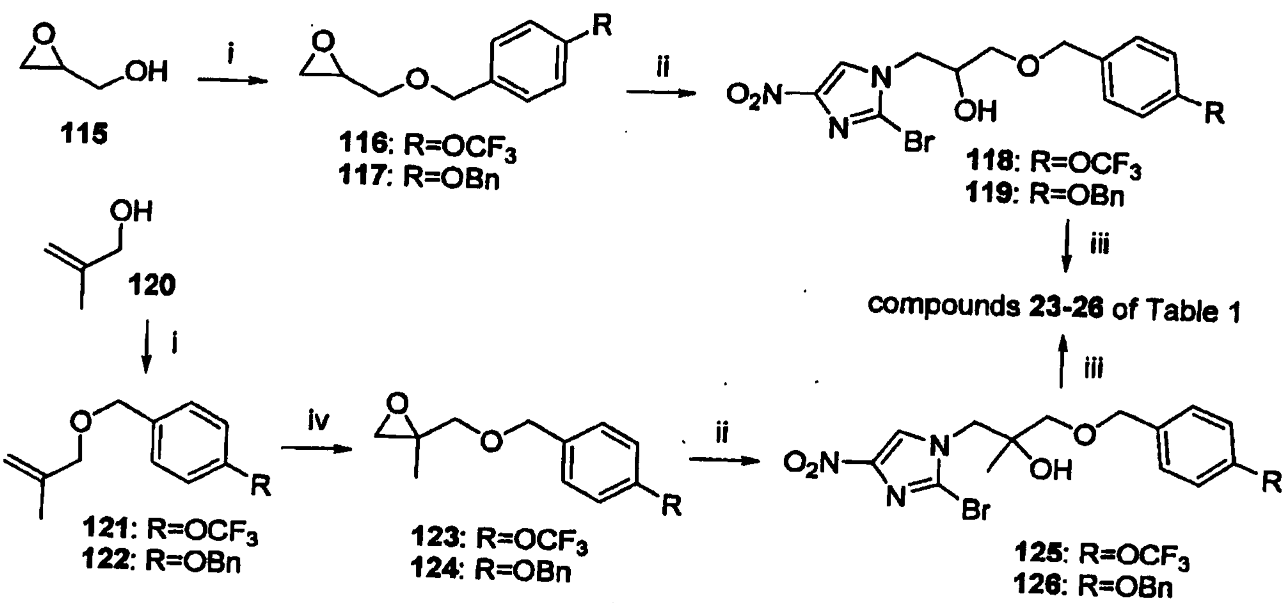

OH
115
R
116: R=OCF3
117: R=OBn
O2N
N
Br
OH
118: R=OCF3
119: R=OBn
i
ii
iii
compounds 23-26 of Table 1
120
121: R=OCF3
122: R=OBn
iv
123: R=OCF3
124: R=OBn
125: R=OCF3
126: R=OBn

Figure 9

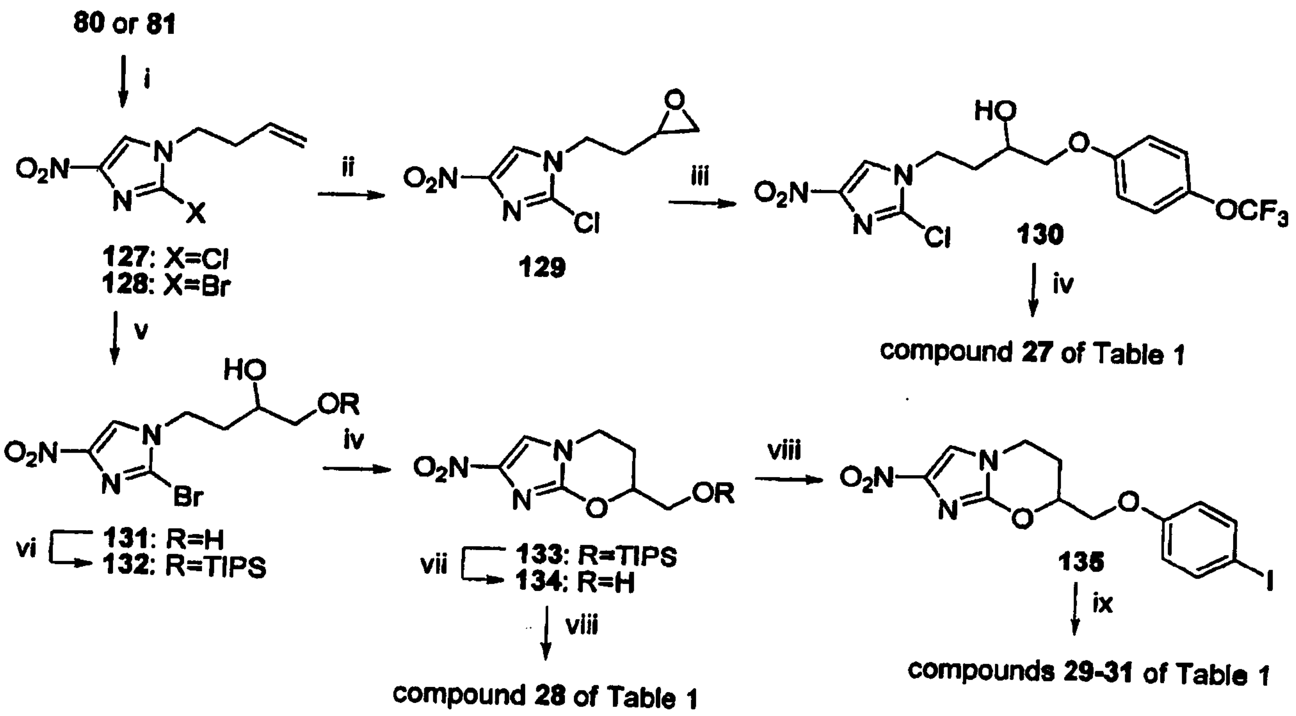

80 or 81
i
O_2N
N
X
127: X=Cl
128: X=Br
ii
Cl
129
iii
HO
O
OCF_3
130
iv
compound 27 of Table 1
v
OR
Br
vi
131: R=H
132: R=TIPS
iv
vii
133: R=TIPS
134: R=H
viii
compound 28 of Table 1
viii
135
I
ix
compounds 29-31 of Table 1

Figure 10

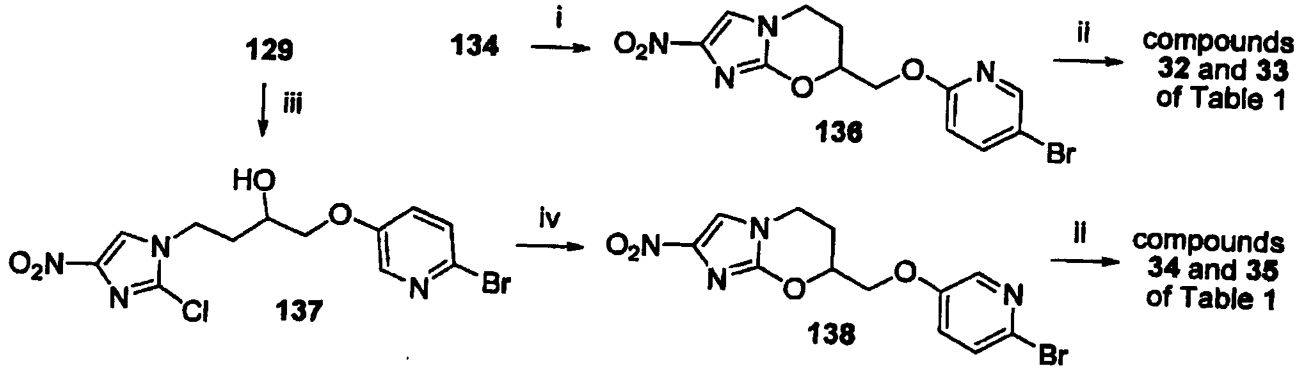

129
iii
134
i
O_2N
N
N
O
O
N
136
Br
ii
compounds
32 and 33
of Table 1
HO
O_2N
N
N
Cl
137
O
N
Br
iv
O_2N
N
N
O
O
N
138
Br
ii
compounds
34 and 35
of Table 1

Figure 11

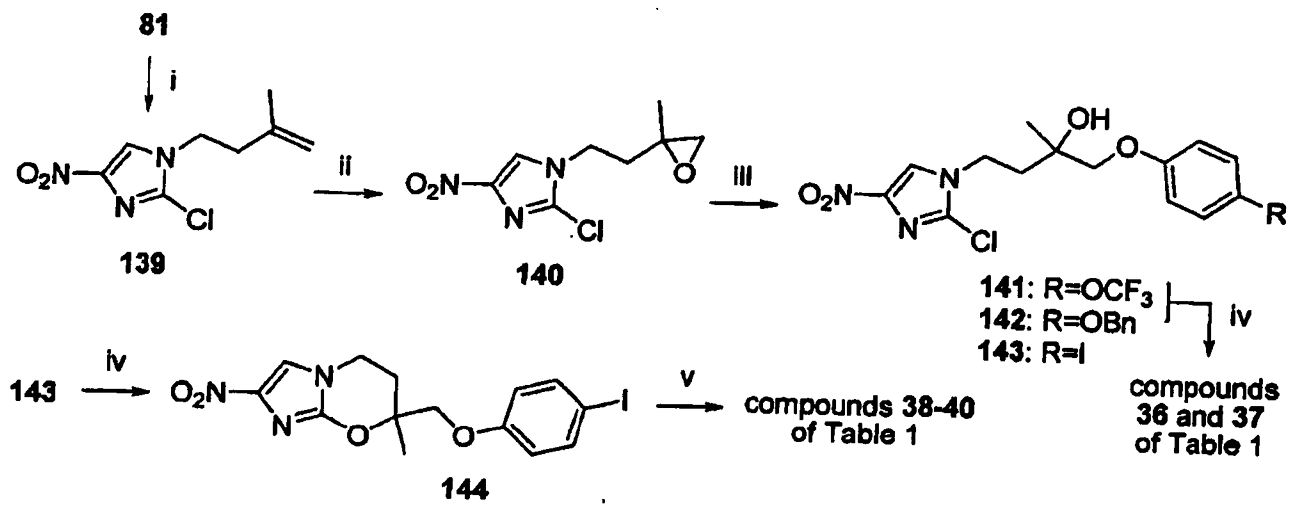

81
i
O_2N
N
N
Cl
139
ii
O_2N
N
N
Cl
O
140
iii
OH
O
O_2N
N
N
Cl
R
141: R=OCF$_3$
142: R=OBn
143: R=I
iv
compounds
36 and 37
of Table 1
143
iv
O_2N
N
N
O
O
I
144
v
compounds 38-40
of Table 1

Figure 12

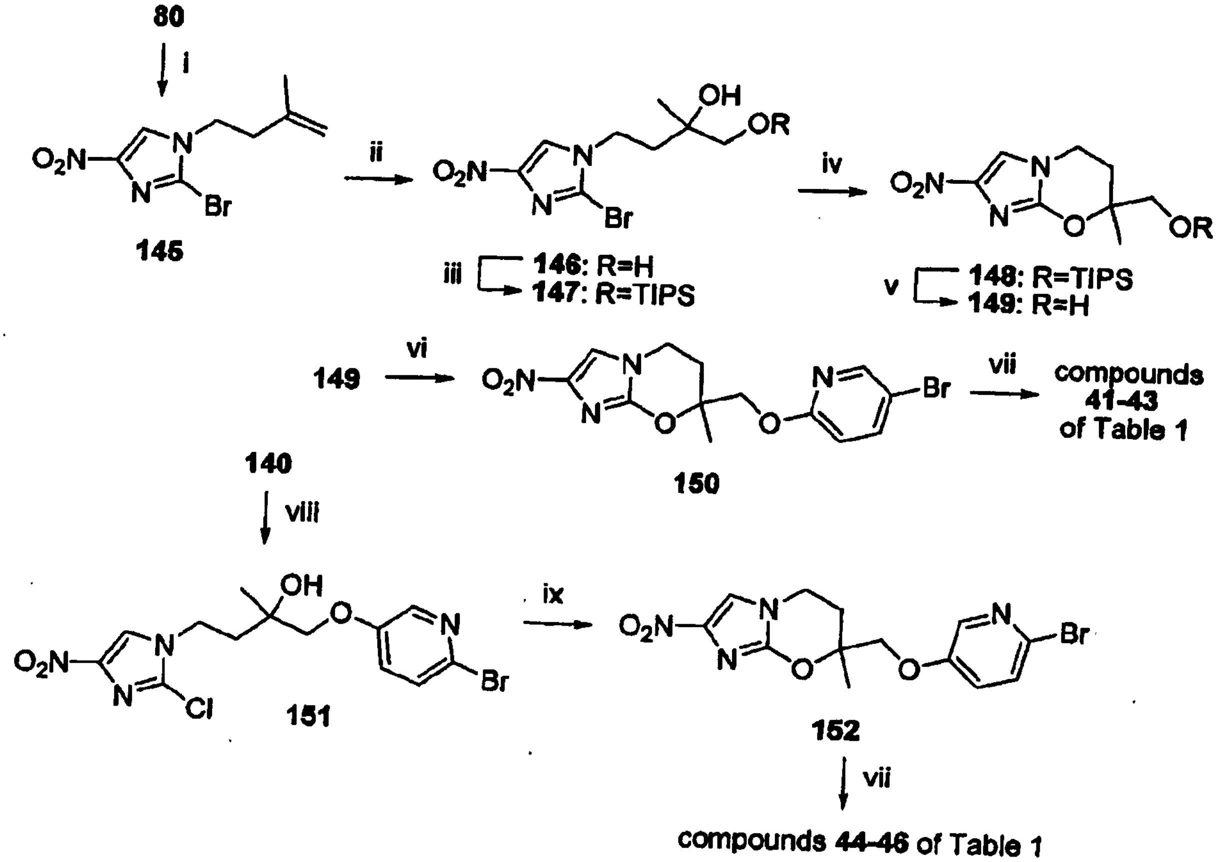

80
i
O_2N
N
N
Br
145
ii
OH
OR
Br
iii
146: R=H
147: R=TIPS
iv
O
OR
v
148: R=TIPS
149: R=H
149
vi
Br
vii
compounds
41-43
of Table 1
150
140
viii
151
Cl
ix
152
compounds 44-46 of Table 1

Figure 13

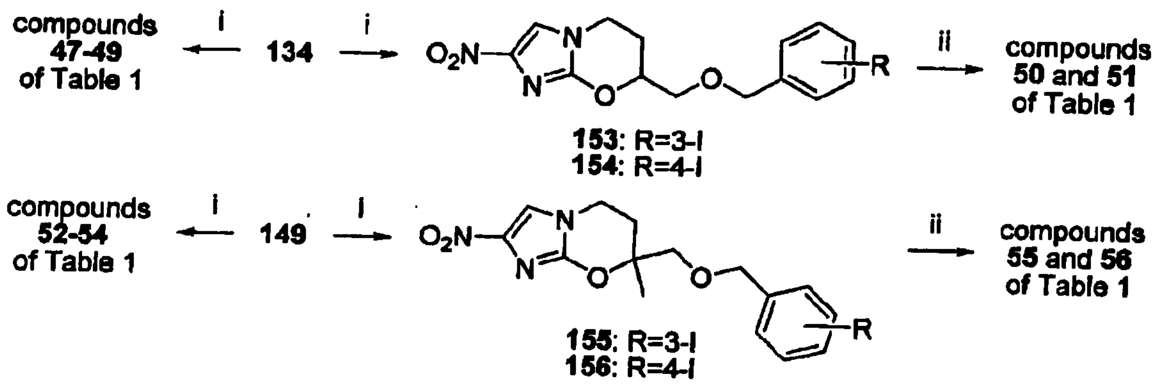

compounds 47-49 of Table 1
i
134
i
O_2N
153: R=3-I
154: R=4-I
ii
compounds 50 and 51 of Table 1
compounds 52-54 of Table 1
i
149
i
O_2N
155: R=3-I
156: R=4-I
ii
compounds 55 and 56 of Table 1

Figure 14

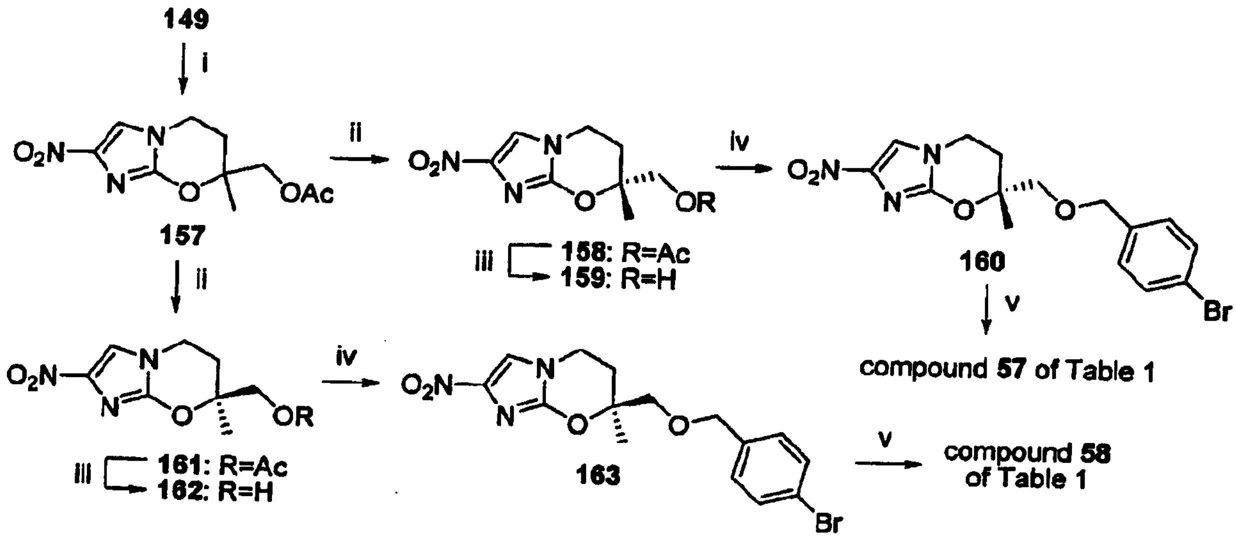

149
i
O_2N
N
N
O
OAc
157
ii
ii
OR
iii
158: R=Ac
159: R=H
iv
160
Br
v
compound 57 of Table 1
161: R=Ac
162: R=H
163
compound 58
of Table 1

Figure 15

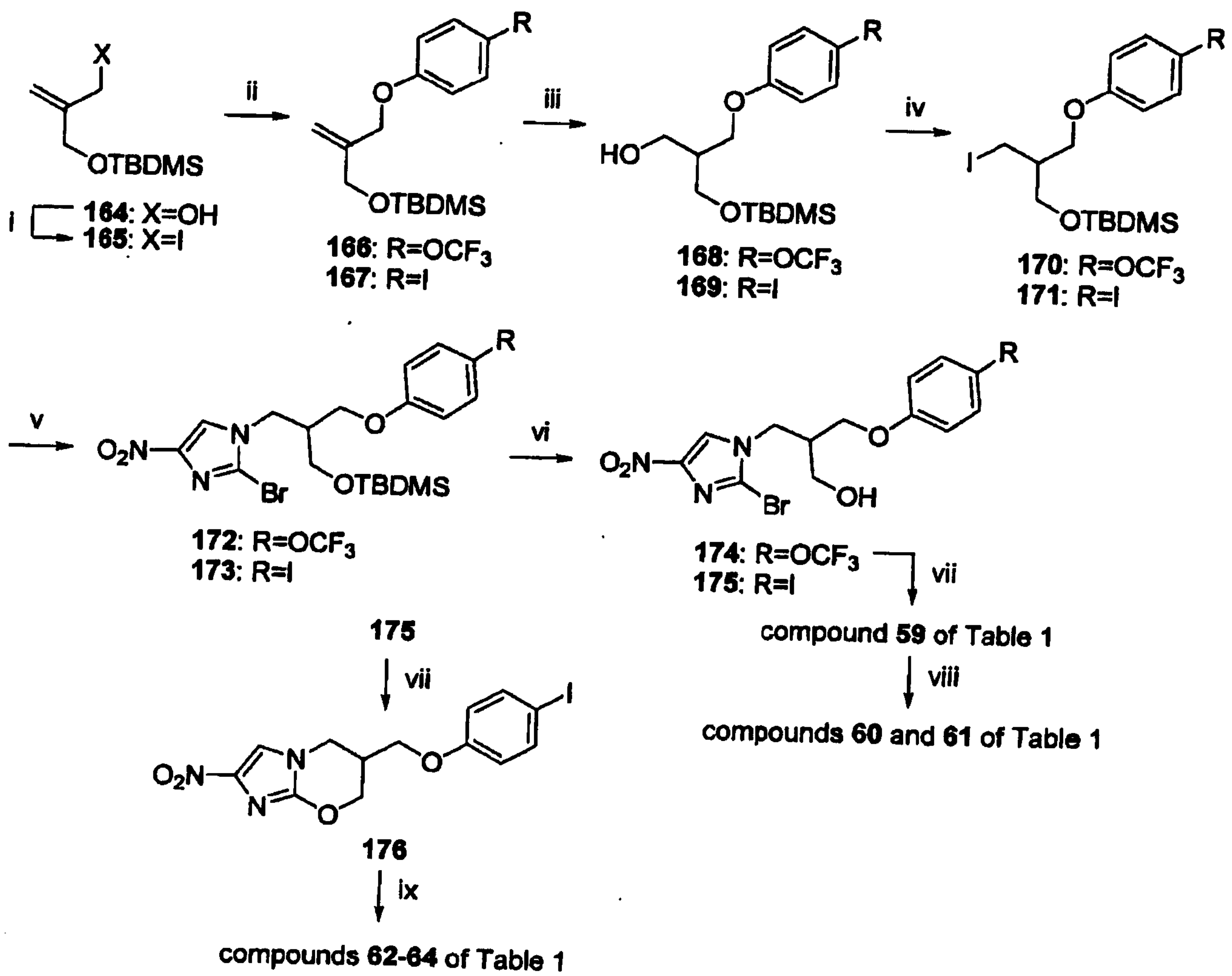

X
OTBDMS
164: X=OH
165: X=I
i
ii
R
O
OTBDMS
166: R=OCF3
167: R=I
iii
HO
168: R=OCF3
169: R=I
iv
I
170: R=OCF3
171: R=I
v
O2N
N
Br
172: R=OCF3
173: R=I
vi
OH
174: R=OCF3
175: R=I
vii
compound 59 of Table 1
viii
compounds 60 and 61 of Table 1
175
vii
176
ix
compounds 62-64 of Table 1

Figure 16

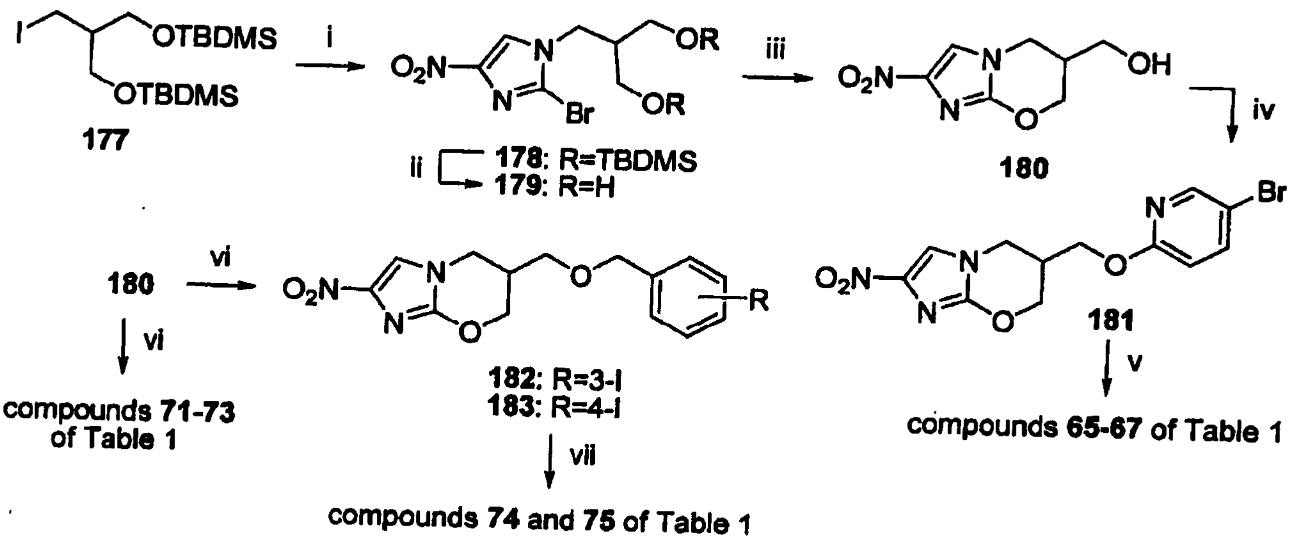

OTBDMS
i
OTBDMS
177
O2N
N
OR
Br
OR
iii
ii
178: R=TBDMS
179: R=H
OH
iv
180
Br
180
vi
O
R
181
vi
182: R=3-I
183: R=4-I
v
compounds 71-73 of Table 1
vii
compounds 65-67 of Table 1
compounds 74 and 75 of Table 1

Figure 17

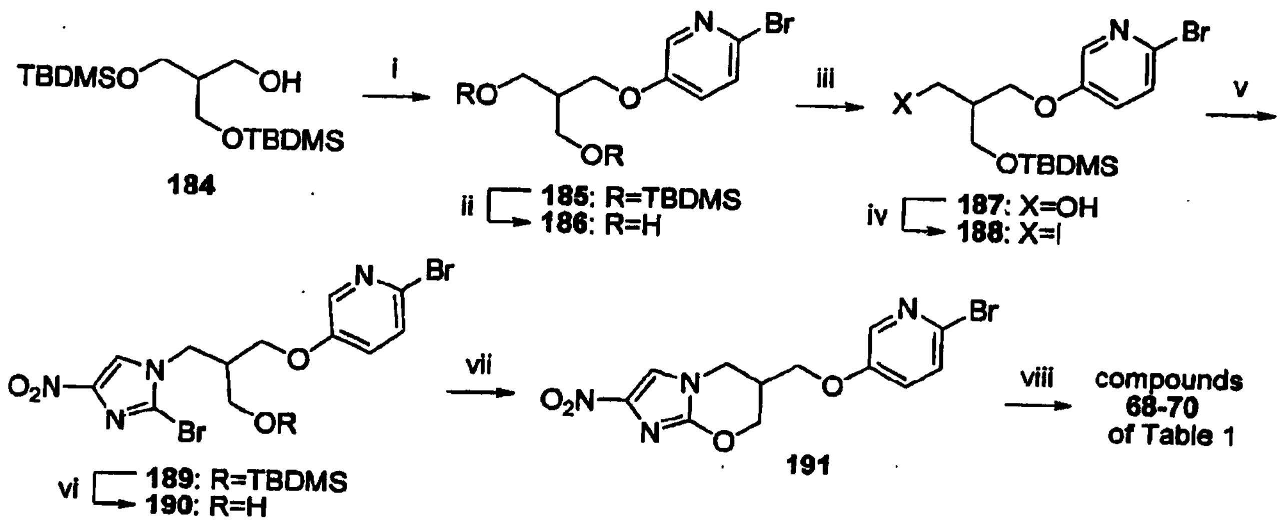
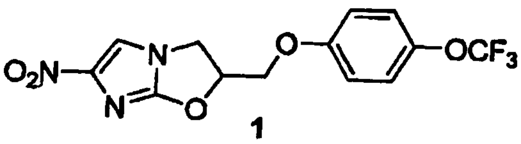

TBDMSO
OH
OTBDMS
184
i
RO
O
N
Br
OR
ii
185: R=TBDMS
186: R=H
iii
X
OTBDMS
iv
187: X=OH
188: X=I
v
O_2N
N
Br
vi
189: R=TBDMS
190: R=H
vii
191
viii
compounds
68-70
of Table 1

Figure 18



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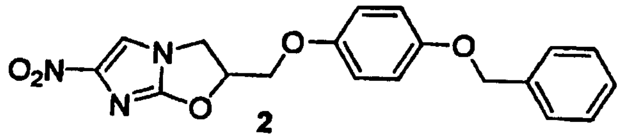

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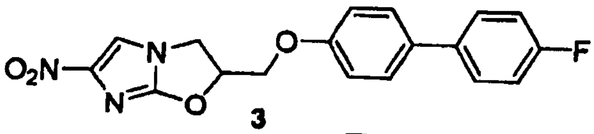

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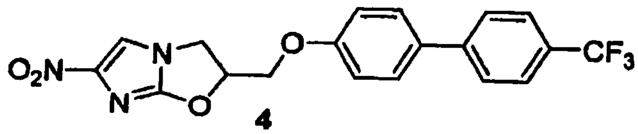

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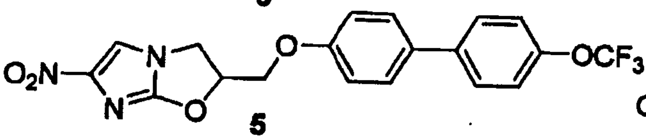

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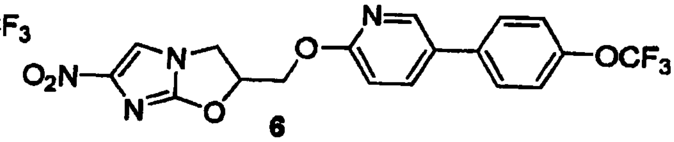

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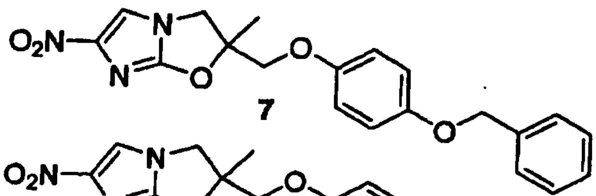

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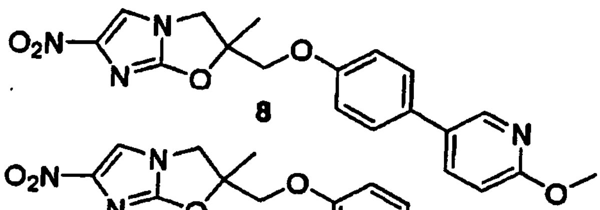

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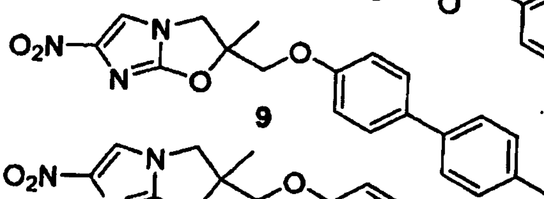

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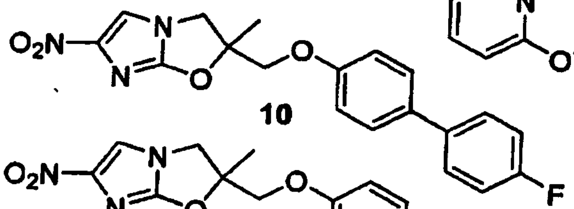

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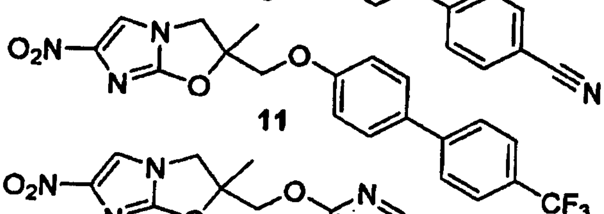

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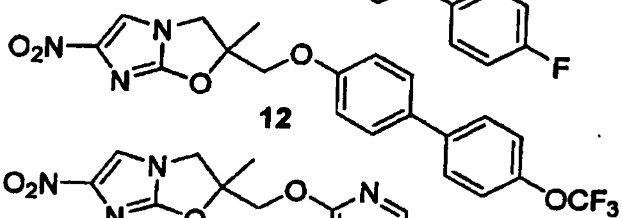

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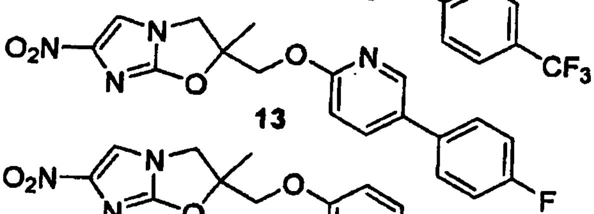

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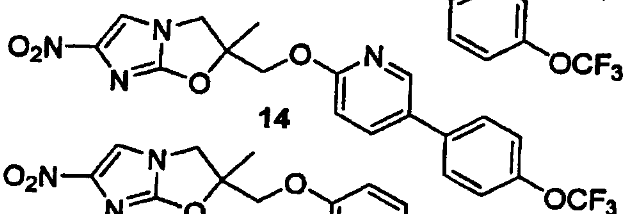

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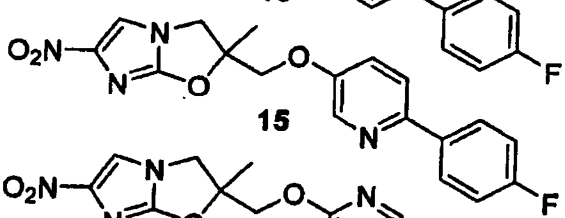

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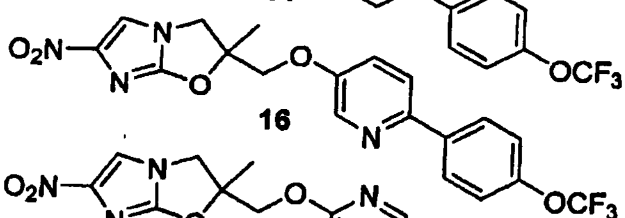

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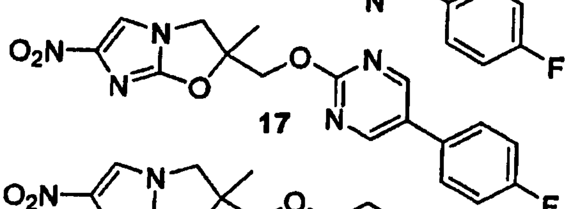

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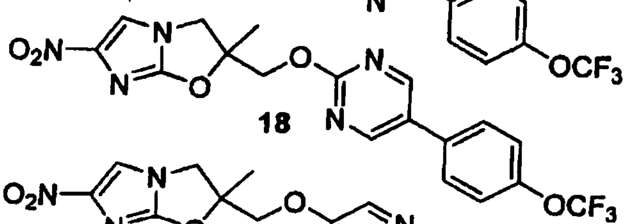

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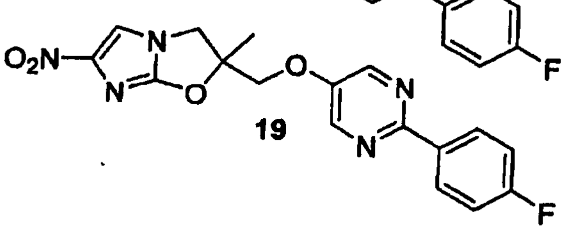

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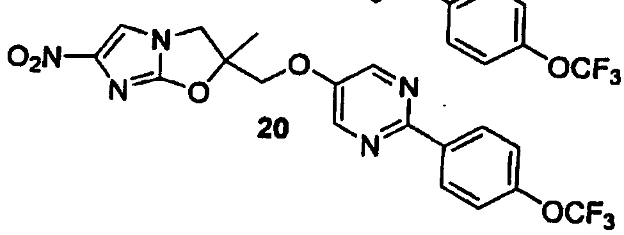
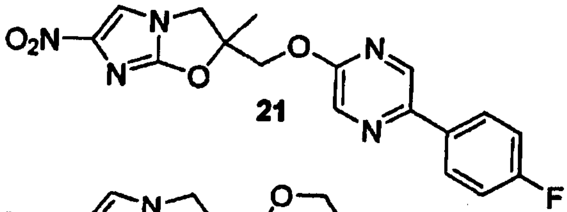


20

11/05/2010 15:41 FAX

Figure 19



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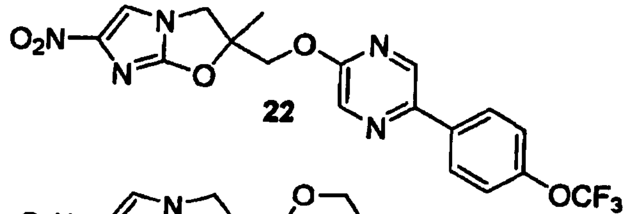

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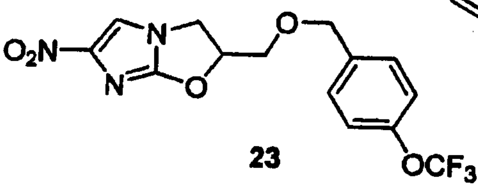

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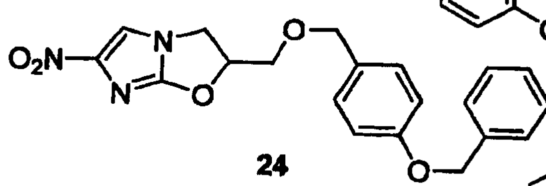

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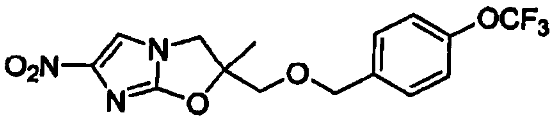

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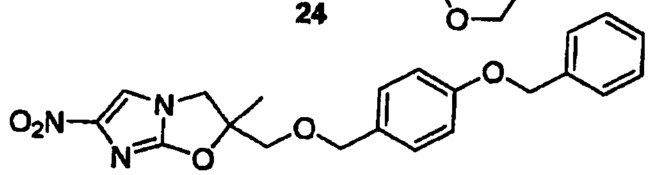

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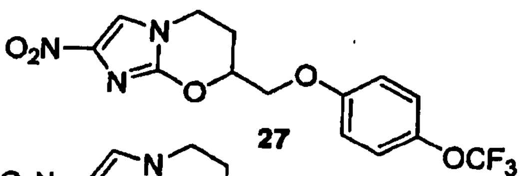

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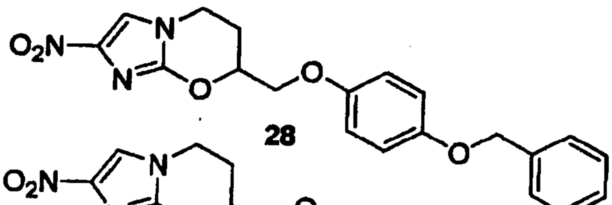

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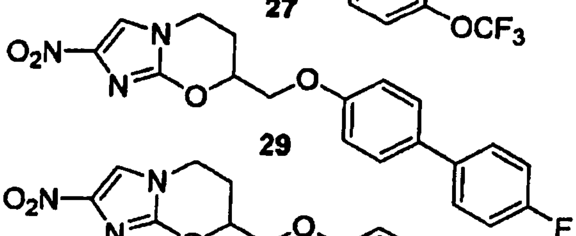

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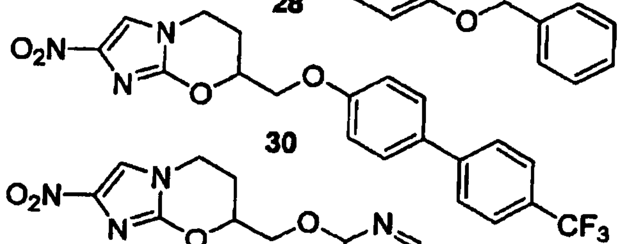

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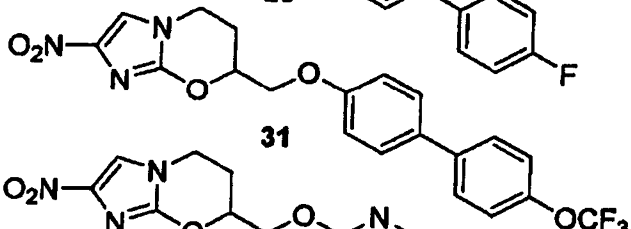

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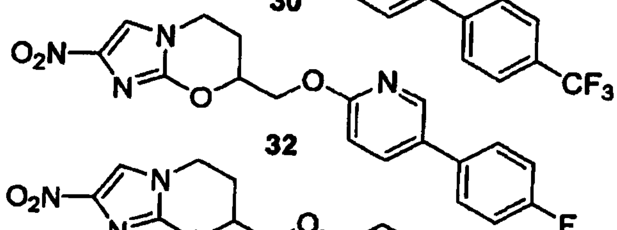

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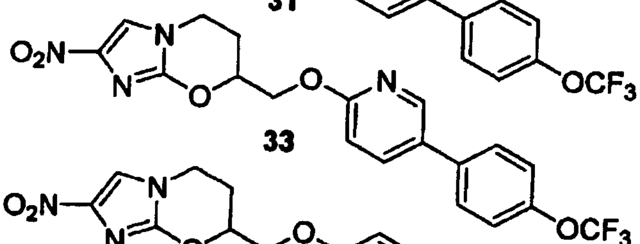

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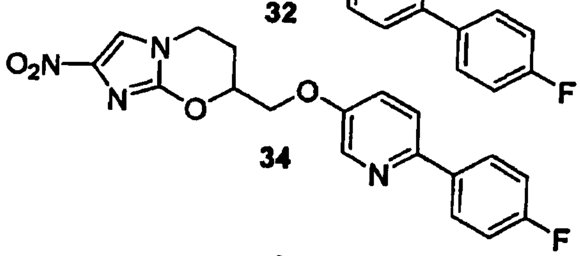

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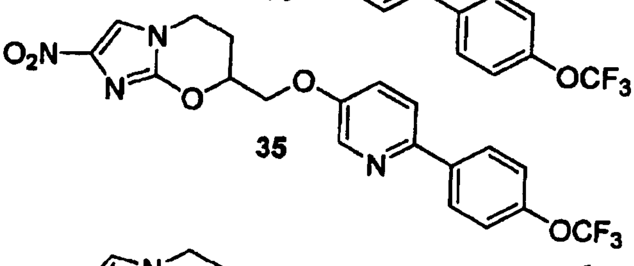

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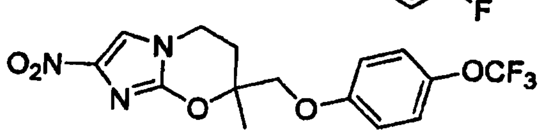

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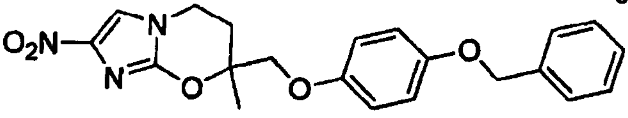

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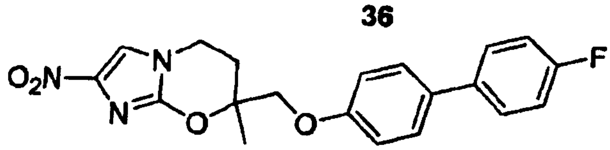

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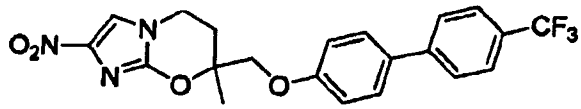
Figure 20



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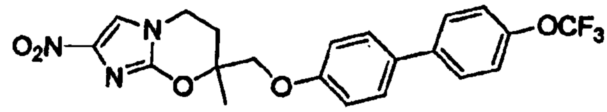

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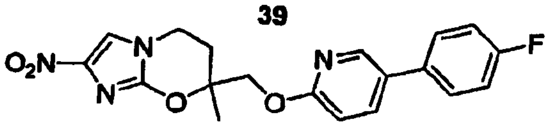

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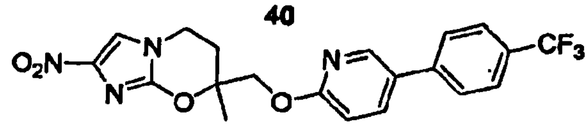

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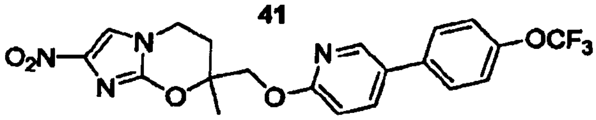

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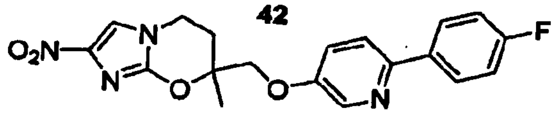

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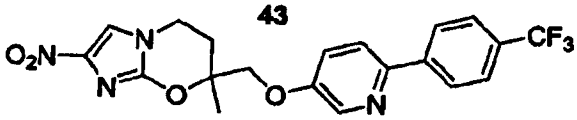

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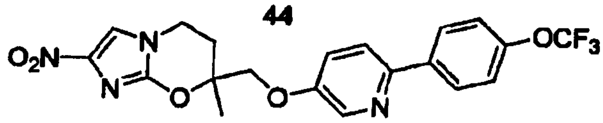

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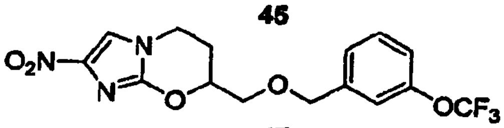

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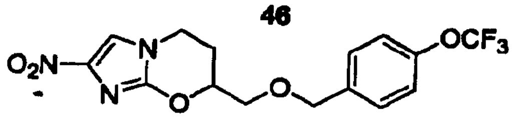

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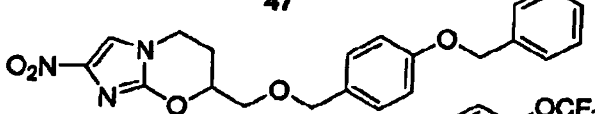

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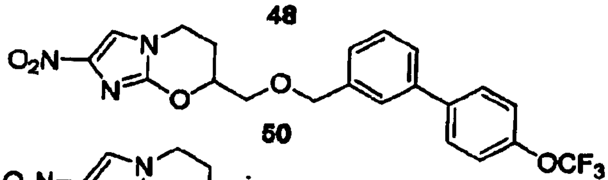

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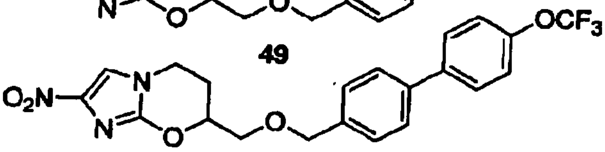

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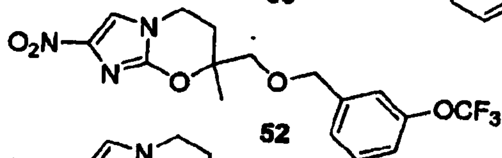

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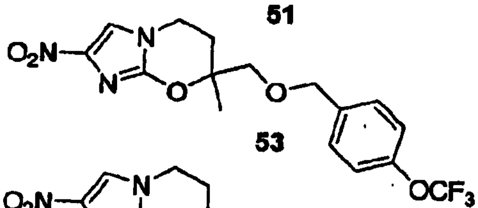

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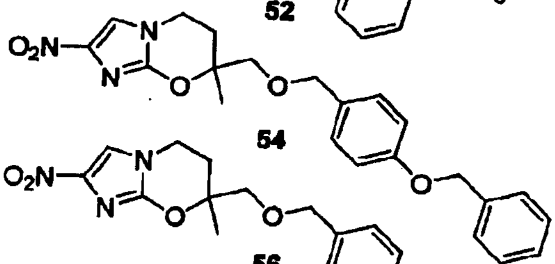

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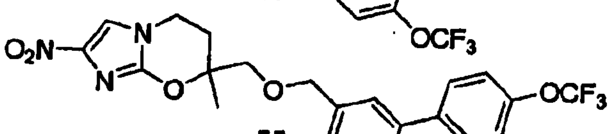

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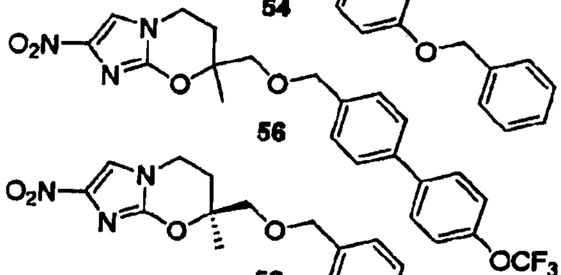

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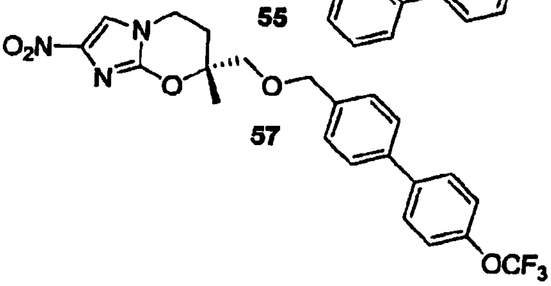

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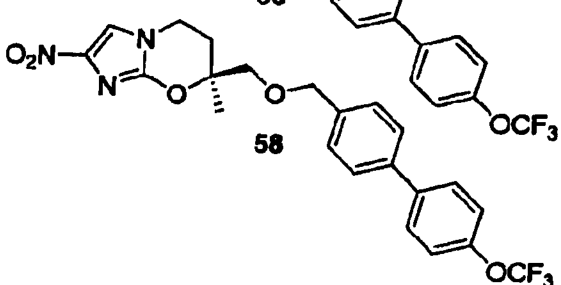

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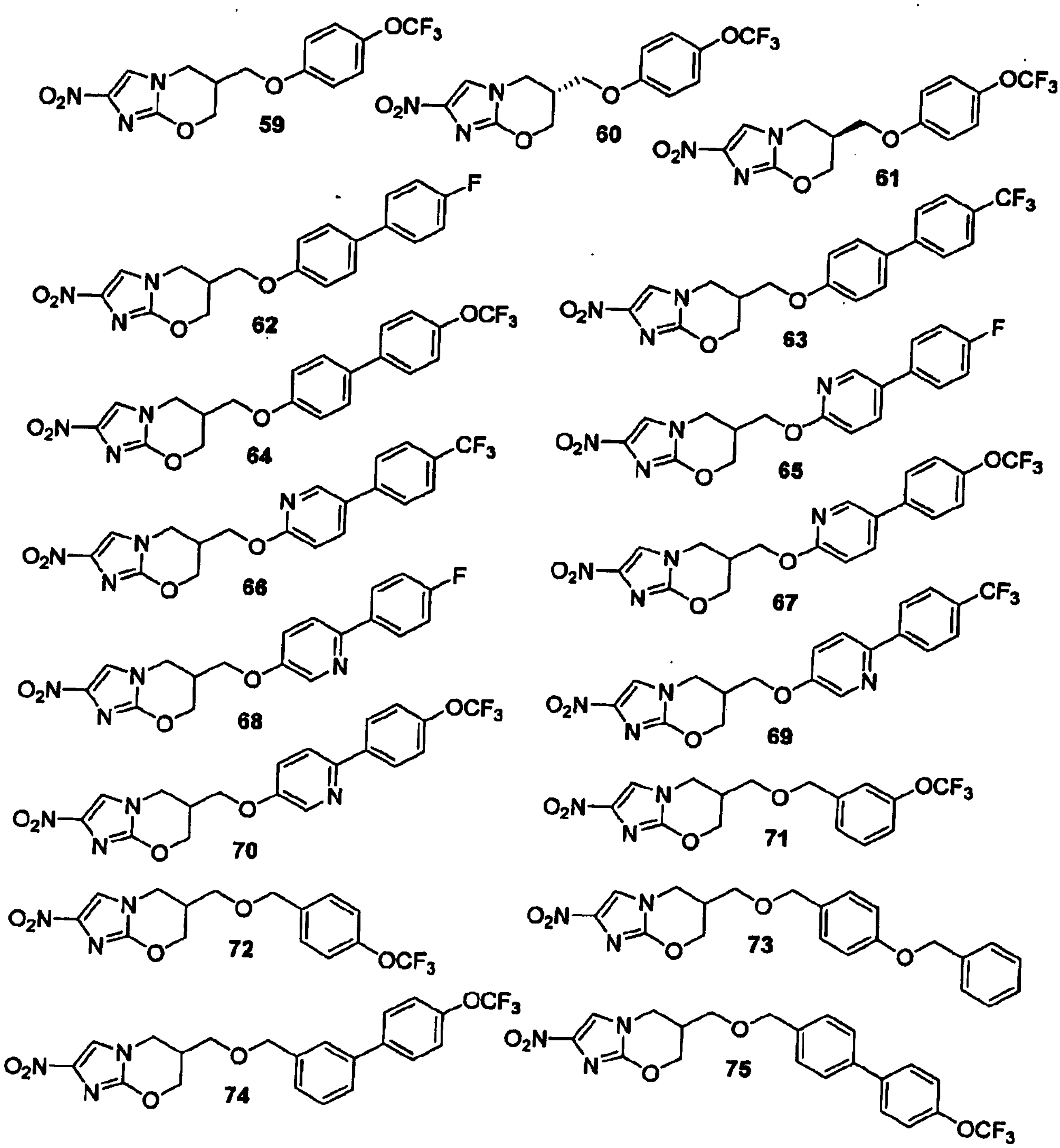
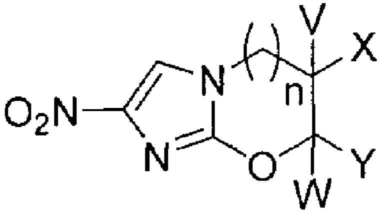
Figure 21





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