TITLE OF THE INVENTION

DIHYDROIMIDAZOTHIAZOLE DERIVATIVES

BACKGROUND OF THE INVENTION

The present invention is directed to dihydroimidazo[2,1-b]thiazole derivatives exhibiting 5-HT_{1A} agonism, in addition to noradrenaline reuptake inhibition and optionally also 5-HT reuptake inhibition, that are useful for the treatment of obesity e.g. as regulators of feeding and/or satiety.

Obesity is characterized by an excessive adipose tissue mass relative to body size. Clinically, body fat mass is estimated by the body mass index (BMI; weight(kg)/height(m)^2), or waist circumference. Individuals are considered obese when the BMI is greater than 30 and there are established medical consequences of being overweight. It has been an accepted medical view for some time that an increased body weight, especially as a result of abdominal body fat, is associated with an increased risk for diabetes, hypertension, heart disease, and numerous other health complications, such as arthritis, stroke, gallbladder disease, muscular and respiratory problems, back pain and even certain cancers.

Pharmacological approaches to the treatment of obesity have been mainly concerned with reducing fat mass by altering the balance between energy intake and expenditure. Many studies have clearly established the link between adiposity and the brain circuitry involved in the regulation of energy homeostasis. Direct and indirect evidence suggest that serotonergic, dopaminergic, adrenergic, cholinergic, endocannabinoid, opioid, and histaminergic pathways in addition to many neuropeptide pathways (e.g. neuropeptide Y and melanocortins) are implicated in the central control of energy intake and expenditure. Hypothalamic centres are also able to sense peripheral hormones involved in the maintenance of body weight and degree of adiposity, such as insulin and leptin, and fat tissue derived peptides.

Drugs aimed at the pathophysiology associated with insulin dependent Type I diabetes and non-insulin dependent Type II diabetes have many potential side effects and do not adequately address the dyslipidaemia and hyperglycaemia in a high proportion of patients. Treatment is often focused at individual patient needs using diet, exercise, hypoglycaemic agents and insulin, but there is a continuing need for novel antidiabetic agents, particularly ones that may be better tolerated with fewer adverse effects.

Similarly, metabolic syndrome (syndrome X) which is characterized by hypertension and its associated pathologies including atherosclerosis, lipidemia, hyperlipidemia and hypercholesterolemia have been associated with decreased insulin sensitivity which can lead to abnormal blood sugar levels when challenged. Myocardial ischemia and microvascular disease is an established morbidity associated with untreated or poorly controlled metabolic syndrome.

A class of compounds called the Serotonin/Noradrenaline Reuptake Inhibitors (SNRI's) are believed to reduce food intake and increase energy expenditure by enhancing central 5-HT and noradrenaline (NA) function. Sibutramine ((+) and (-) enantiomers of 1-(4-chlorophenyl)-N,N-dimethyl-α-(2-methylpropyl)cyclobutanemethanamine) which is a member of this class of compounds has been shown to produce dose-dependant long lasting weight reduction in obese patients by enhancing natural satiety and increasing energy expenditure by stimulating

thermogenesis. The most common side effects associated with Sibutramine therapy include headache, dry mouth, constipation and insomnia. However, it is also associated with dose related increases in heart rate and blood pressure which limit the weight loss that can be achieved and is contraindicated in patients with cardiovascular history.

A SNRI with the addition of 5-HT_{1A} agonist activity is expected to have an improved cardiovascular profile as compared to a SNRI alone, through activation of post-synaptic 5-HT_{1A} receptors thereby reducing sympathetic drive (van den Buuse, M. & Wegener, N., 2005, Eur. J. Pharmacol., Vol. 507(1-3) PP187-98; Chamienia, A.L. & Johns, E.J. 1996. Brit. J. Pharmacol., Vol. 118(8) PP 1891-1898.). 5-HT_{1A} agonists also increase the activity of noradrenergic neurones in the locus coeruleus (Szabo, S.T. & Blier, P., 2001; Eur. J. Neuroscience, Vol. 13, PP 2077-2087) through a reduction in firing of 5-HT neurones in the raphe via 5-HT_{1A} autoreceptor activation thereby removing the 5-HT tonic inhibition in noradrenergic activity throughout the brain (Béïque, J-C., de Montigny, C., Blier, P. & DeBonnel, G. 1999; Synapse, Vol. 32, PP 198-211; Haddjeri, N., de Montigny, C. & Blier, P. 1997 Brit. J. Pharmacol., Vol. 120, PP 865-875). It has been demonstrated that postsynaptic 5-HT_{1A} receptors do not significantly down-regulate after repeated administration of 5-HT_{1A} agonists indicating that there should be no reduction in efficacy with a chronic treatment (Anxiety and the Serotonin1A Receptor, Jeremy D. Coplan, Susan I. Wolk, and Donald F. Klein; Mochizuki, D., Hokonohara, T., Kawasaki, K., & Miki, N. 2002. J. Psychopharmacol., Vol. 16(3) PP 253-260).

WO97/02269 and WO00/71549 disclose condensed thiazole derivatives having 5-HT receptor affinity.

WO98/41528 discloses compounds exhibiting monoamine reuptake inhibition.

WO02/26747 discloses the use of compounds which have dual 5-HT_{1A} agonist / monoamine reuptake inhibitory activity for use in the treatment of obesity.

WO01/62341 discloses a method for the treatment of obesity comprising the administration of a monoamine reuptake inhibitor and a 5-HT_{1A} agonist.

WO01/68653 discloses dihydroimidazo[2,1-b]thiazole and dihydro-5H-thiazolo[3,2-a]pyrimidines which have dual 5-HT_{1A} agonist / monoamine reuptake inhibitory activity for use in the treatment of depression, obesity and other disorders.

Sharpe *et al*, *J. Med. Chem.*, 1971, 14(10), 977 disclose phenacylthioimidazolines and 3-aryl-5,6-dihydroimidazo[2,1-b]thiazoles, including the compounds 3-naphthalen-1-yl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide and 3-naphthalen-2-yl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide, having antidepressant activity. No mechanism of action is disclosed or suggested for these compounds.

USSR Patent Application No. 910637 discloses 3-(3-chloro-4-propoxyphenyl)-5,6-dihydroimidazo[2,1-b]thiazole and 3-(3-chloro-4-butyloxyphenyl)-5,6-dihydroimidazo[2,1-b]thiazole having mutagenic activity.

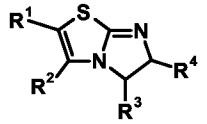
US Patent Nos. 3,671,533 and 3,806,515 disclose the 5,6-dihydroimidazo[2,1-b]thiazole derivatives 3-(4-chlorophenyl)-2-ethyl-5,6-dihydroimidazo[2,1-b]thiazole and 3-(4-chlorophenyl)-2-methyl-5,6-dihydroimidazo[2,1-b]thiazole and certain 2,3,5,6-tetrahydroimidazo[2,1-b]thiazole derivatives. 2,3,5,6-Tetrahydroimidazo[2,1-b]thiazole derivatives are stated to be preferred. The compounds are stated to have CNS stimulant activity and may be useful as antidepressants, anorectics and diuretics.

US Patent No. 3,715,367 discloses the compounds 3-(3,4-dichlorophenyl)-5,6-dihydroimidazo[2,1-b]thiazole, 3-(2-hydroxy-5-methylphenyl)-5,6-dihydroimidazo[2,1-b]thiazole and 3-(4-aminophenyl)-5,6-dihydroimidazo[2,1-b]thiazole having antidepressant activity.

There is a continuing need for novel antiobesity and antidiabetic agents, particularly ones that are well tolerated with few adverse effects.

SUMMARY OF THE INVENTION

Compounds of formula (I):

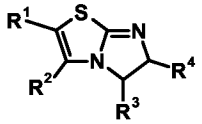


(I)

or pharmaceutically acceptable salts thereof, exhibit 5-HT_{1A} agonism in addition to noradrenaline reuptake inhibition and optionally also 5-HT reuptake inhibition and are useful as for the treatment of obesity e.g. as regulators of feeding and/or satiety.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to a compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof,

wherein R^1 is hydrogen, halo, C_{1-6} alkyl optionally substituted by one or more halo atoms or hydroxy groups, C_{3-6} cycloalkyl optionally substituted by one or more halo atoms or hydroxy groups, C_{1-2} alkylC_{3-6} cycloalkyl optionally substituted by one or more halo atoms or hydroxy groups, C_{1-6} alkoxycarbonyl, cyano, -C=N-OR^7, C_{2-6} alkenyl optionally substituted by one or more halo atoms or hydroxy groups in which hydroxy is not directly attached to either carbon of the double bond, C_{2-6} alkynyl optionally substituted by one or more halo atoms or hydroxy groups in which hydroxy is not directly attached to either carbon of the triple bond, $(CH_2)_mNR^5R^6$, C_{1-3}alkoxy, C_{1-3} alkylthio, C_{1-3} alkoxyC_{1-3} alkyl or C_{1-3} alkylthioC_{1-3} alkyl;

R^2 is an 8- to 10-membered bicyclic aromatic group optionally containing up to 3 heteroatoms selected from N and S, or phenyl, provided that R^2 is not benzo[b]thiophene;

R^2 may be optionally substituted by one or more groups selected from halo, cyano, hydroxy, NR^5R^6, $CONR^5R^6$, or $COOR^7$, or C_{1-3} alkyl, C_{2-3} alkenyl, C_{1-3} alkynyl, C_{3-6} cycloalkyl, C_{1-3} alkoxy, C_{1-3} hydroxyalkyl, C_{2-3} alkoxyalkyl or C_{1-3} alkyl$S(O)_n$ any of which may be optionally substituted by one or more halo atoms; or when R^2 is phenyl two substituents on phenyl may join to form a fused C_{5-6} carbocyclic ring;

R^3 and R^4 are independently hydrogen or C_{1-3} alkyl;

R^5 and R^6 are independently hydrogen or C_{1-3} alkyl, or together with the nitrogen to which they are attached form a 5- or 6-membered heterocyclyl group;

R^7 is hydrogen or C_{1-3} alkyl;

m is 1, 2 or 3; and

n is 0, 1 or 2;

provided that the compound is not:

a) 3-naphthalen-1-yl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide,

b) 3-naphthalen-2-yl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide,

c) 3-(3-chloro-4-propoxyphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

d) 3-(4-chlorophenyl)-2-ethyl-5,6-dihydroimidazo[2,1-b]thiazole,

e) 3-(4-chlorophenyl)-2-methyl-5,6-dihydroimidazo[2,1-b]thiazole,

f) 3-(3,4-dichlorophenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

g) 3-(2-hydroxy-5-methylphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

h) 3-(4-aminophenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

i) 3-(2-chlorophenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

j) 3-(3-chlorophenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

k) 3-(4-chlorophenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

l) 3-(2,4-dichlorophenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

m) 3-(2,5-dichlorophenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

n) 3-(4-bromophenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

o) 3-(2,4-difluorophenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

p) 3-(2-methylphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

q) 3-(3-methylphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

r) 3-(4-methylphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

s) 3-(2,4-dimethylphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

t) 3-(3,4-dimethylphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

u) 3-(4-cyanophenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

v) 3-(4-carboxyphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

w) 3-(2-methoxyphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

x) 3-(3-methoxyphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

y) 3-(4-methoxyphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

z) 3-(2-hydroxyphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

aa) 3-(3-hydroxyphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

ab) 3-(4-hydroxyphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

ac) 3-(3,4-dihydroxyphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

ad) 3-(2-hydroxy-4-methoxyphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

ae) 3-(3-hydroxy-4-methoxyphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

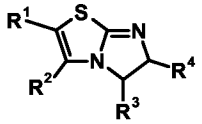
af) 3-(4-hydroxy-3-methoxyphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

ag) 3-(4-hydroxy-3-chlorophenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

ah) 3-(4-hydroxy-3-methylphenyl)-5,6-dihydroimidazo[2,1-b]thiazole, or

ai) 3-(3,4-dichlorophenyl)-2-phenyl-5,6-dihydroimidazo[2,1-b]thiazole.

A preferred group of compounds of the invention are the compounds of formula (Ia):



(Ia)

or a pharmaceutically acceptable salt thereof,

wherein R^1 is hydrogen, halo, C_{1-6} alkyl optionally substituted by one or more halo atoms or hydroxy groups, C_{3-6} cycloalkyl optionally substituted by one or more halo atoms or hydroxy groups, C_{1-2} alkylC_{3-6} cycloalkyl optionally substituted by one or more halo atoms or hydroxy groups, C_{1-6} alkoxycarbonyl, cyano, -C=N-OR^7, C_{2-6} alkenyl optionally substituted by one or more halo atoms or hydroxy groups in which hydroxy is not directly attached to either carbon of the double bond, C_{2-6} alkynyl optionally substituted by one or more halo atoms or hydroxy groups in which hydroxy is not directly attached to either carbon of the triple bond, $(CH_2)_mNR^5R^6$, C_{1-3}alkoxy, C_{1-3} alkylthio, C_{1-3} alkoxyC_{1-3} alkyl or C_{1-3} alkylthioC_{1-3} alkyl;

R^2 is an 8- to 10-membered bicyclic aromatic group optionally containing up to 3 heteroatoms selected from N and S, provided that R^2 is not benzo[b]thiophene;

R^2 may be optionally substituted by one or more groups selected from halo, cyano, hydroxy, NR^5R^6, $CONR^5R^6$, or $COOR^7$, or C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} hydroxyalkyl, C_{2-3} alkoxyalkyl or C_{1-3} alkyl$S(O)_n$ any of which may be optionally substituted by one or more halo atoms;

R^3 and R^4 are independently hydrogen or C_{1-3} alkyl;

R^5 and R^6 are independently hydrogen or C_{1-3} alkyl, or together with the nitrogen to which they are attached form a 5- or 6-membered heterocyclyl group;

R^7 is hydrogen or C_{1-3} alkyl;

m is 1, 2 or 3; and

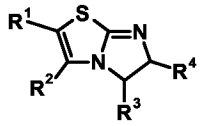
n is 0, 1 or 2;

provided that the compound is not:

a) 3-naphthalen-1-yl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide, or

b) 3-naphthalen-2-yl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide.

A further group of compounds which may be mentioned are the compounds of formula (Ib):



(Ib)

or a pharmaceutically acceptable salt thereof, wherein

R^1 is hydrogen, halo, C_{1-6} alkyl optionally substituted by one or more halo atoms or hydroxy groups, C_{3-6} cycloalkyl optionally substituted by one or more halo atoms or hydroxy groups, C_{1-2} alkylC_{3-6} cycloalkyl optionally substituted by one or more halo atoms or hydroxy groups, C_{1-6} alkoxycarbonyl, cyano, -C=N-OR^7, C_{2-6} alkenyl optionally substituted by one or more halo atoms or hydroxy groups in which hydroxyl is not directly attached to either carbon of the double bond, C_{2-6} alkynyl optionally substituted by one or more halo atoms or hydroxy groups in which hydroxyl is not directly attached to either carbon of the triple bond, $(CH_2)_mNR^5R^6$, C_{1-3}alkoxy, C_{1-3} alkylthio, C_{1-3} alkoxyC_{1-3} alkyl or C_{1-3} alkylthioC_{1-3} alkyl;

R^2 is phenyl substituted by one or more groups selected from halo, cyano, hydroxy, NR^5R^6, $CONR^5R^6$, or $COOR^7$, or C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, C_{3-6} cycloalkyl, C_{1-3} alkoxy, C_{1-3} hydroxyalkyl, C_{2-3} alkoxyalkyl or C_{1-3} alkyl$S(O)_n$ any of which may be optionally substituted by one or more halo atoms;

R^3 and R^4 are independently hydrogen or C_{1-3} alkyl;

R^5 and R^6 are independently hydrogen or C_{1-3} alkyl, or together with the nitrogen to which they are attached form a 5- or 6-membered heterocyclyl group;

R^7 is hydrogen or C_{1-3} alkyl;

m is 1, 2 or 3; and

n is 0, 1 or 2;

provided that the compound is not:

c) 3-(3-chloro-4-propoxyphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

d) 3-(4-chlorophenyl)-2-ethyl-5,6-dihydroimidazo[2,1-b]thiazole,

e) 3-(4-chlorophenyl)-2-methyl-5,6-dihydroimidazo[2,1-b]thiazole,

f) 3-(3,4-dichlorophenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

g) 3-(2-hydroxy-5-methylphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

h) 3-(4-aminophenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

i) 3-(2-chlorophenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

j) 3-(3-chlorophenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

k) 3-(4-chlorophenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

l) 3-(2,4-dichlorophenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

m) 3-(2,5-dichlorophenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

n) 3-(4-bromophenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

o) 3-(2,4-difluorophenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

p) 3-(2-methylphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

q) 3-(3-methylphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

r) 3-(4-methylphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

s) 3-(2,4-dimethylphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

t) 3-(3,4-dimethylphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

u) 3-(4-cyanophenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

v) 3-(4-carboxyphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

w) 3-(2-methoxyphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

x) 3-(3-methoxyphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

y) 3-(4-methoxyphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

z) 3-(2-hydroxyphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

aa) 3-(3-hydroxyphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

ab) 3-(4-hydroxyphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

ac) 3-(3,4-dihydroxyphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

ad) 3-(2-hydroxy-4-methoxyphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

ae) 3-(3-hydroxy-4-methoxyphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

af) 3-(4-hydroxy-3-methoxyphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

ag) 3-(4-hydroxy-3-chlorophenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

ah) 3-(4-hydroxy-3-methylphenyl)-5,6-dihydroimidazo[2,1-b]thiazole, or

ai) 3-(3,4-dichlorophenyl)-2-phenyl-5,6-dihydroimidazo[2,1-b]thiazole.

In the compounds of formulae (I), (Ia) and (Ib):

R^1 is preferably hydrogen, C_{1-6} alkyl optionally substituted by one or more halo atoms or hydroxy groups, C_{3-6} cycloalkyl optionally substituted by one or more halo atoms or hydroxy groups, or C_{1-2} alkylC_{3-6} cycloalkyl optionally substituted by one or more halo atoms or hydroxy groups. R^1 is more preferably C_{1-6} alkyl, especially methyl.

A further specific group of compounds which may be mentioned are those where R^1 is not hydrogen.

When R^1 is C_{1-6} alkyl optionally substituted by one or more halo atoms it may be a fluoroalkyl group.

Examples of 8- to 10-membered bicyclic aromatic groups which R^2 may represent include naphthalenyl, e.g. naphthalen-1-yl or naphthalen-2-yl, thienothiophenyl, e.g. thieno[2,3-b]thiophen-2-yl, indolyl, quinolinyl, e.g. quinolin-2-yl, isoquinolinyl and benzoisothiazole, e.g. benzoisothiaxol-3-yl. R^2 is preferably naphthalenyl, especially naphthalen-1-yl.

When R^2 is a substituted 8- to 10-membered bicyclic aromatic group, e.g. naphthalenyl, it is preferably substituted by one or two substituents preferably selected from halo, e.g. fluoro or chloro, and C_{1-3} alkyl, e.g. methyl. When R^2 is naphthalen-1-yl it is preferably unsubstituted or substituted in one or two of the 4-, 5- or 7-positions by halo, e.g. fluoro or chloro.

When R^2 is phenyl it is preferably substituted in the 3-, 4- and/or 5-positions.

When R^2 is phenyl it is preferably substituted by one or two groups selected from halo and C_{1-3} alkyl optionally substituted by one or more halo atoms.

When R^2 is phenyl a specific group of compounds of the invention which may be mentioned are compounds in which, when R^1 is straight chain unsubstituted C_{1-4} alkyl and R^3 and R^4 are hydrogen, R^2 is not phenyl substituted only by one, two or three fluoro or chloro atoms in the 3-, 4- and/or 5-positions.

R^3 and R^4 are preferably independently hydrogen or methyl, more preferably R^3 and R^4 are both hydrogen.

The molecular weight of the compounds of formulae (I), (Ia) and (Ib) is preferably less than 800, more preferably less than 600, even more preferably less than 500.

Specific compounds of the invention which may be mentioned are those included in the Examples and pharmaceutically acceptable salts thereof.

As used herein, unless stated otherwise, "alkyl" as well as other groups having the prefix "alk" such as, for example, alkenyl, alkynyl, and the like, means carbon chains which may be linear or branched or combinations thereof. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, heptyl and the like. "Alkenyl", "alkynyl" and other like terms include carbon chains having at least one unsaturated carbon-carbon bond.

The term "fluoroalkyl" includes alkyl groups substituted by one or more fluorine atoms, e.g. CH_2F, CHF_2 and CF_3.

The terms "cycloalkyl" and "carbocyclic group" mean carbocycles containing no heteroatoms, and includes monocyclic saturated carbocycles. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "halo" includes fluorine, chlorine, bromine and iodine atoms.

The term "aryl" includes phenyl and naphthyl, in particular phenyl.

The term "heterocyclyl" includes 5- and 6-membered saturated rings containing one or two nitrogen atoms. Examples of heterocyclyl groups rings include azetidine, pyrrolidine, piperidine and piperazine. Heterocyclyl groups may also contain additional heteroatoms, e.g. morpholine.

Compounds described herein may contain one or more asymmetric centers and may thus give rise to enantiomers, diastereomers and optical isomers. The present invention includes all

such possible enantiomers, diastereomers as well as their racemic mixtures, their substantially pure resolved enantiomers, all possible geometric isomers, and pharmaceutically acceptable salts thereof. The above formula (I) is shown without a definitive stereochemistry at certain positions. The present invention includes all stereoisomers of formula (I) and pharmaceutically acceptable salts thereof. Further, mixtures of stereoisomers as well as isolated specific stereoisomers are also included. During the course of the synthetic procedures used to prepare such compounds, or in using racemization or epimerization procedures known to those skilled in the art, the products of such procedures can be a mixture of stereoisomers.

The compounds of the invention may also exhibit atropisomerism, the present invention includes all atropisomers of formula (I) and mixtures thereof.

When a tautomer of the compound of formula (I) exists, the present invention includes any possible tautomers and pharmaceutically acceptable salts thereof, and mixtures thereof, except where specifically drawn or stated otherwise.

When the compound of formula (I) and pharmaceutically acceptable salts thereof exist in the form of solvates or polymorphic forms, the present invention includes any possible solvates and polymorphic forms. A type of a solvent that forms the solvate is not particularly limited so long as the solvent is pharmacologically acceptable. For example, water, ethanol, propanol, acetone or the like can be used.

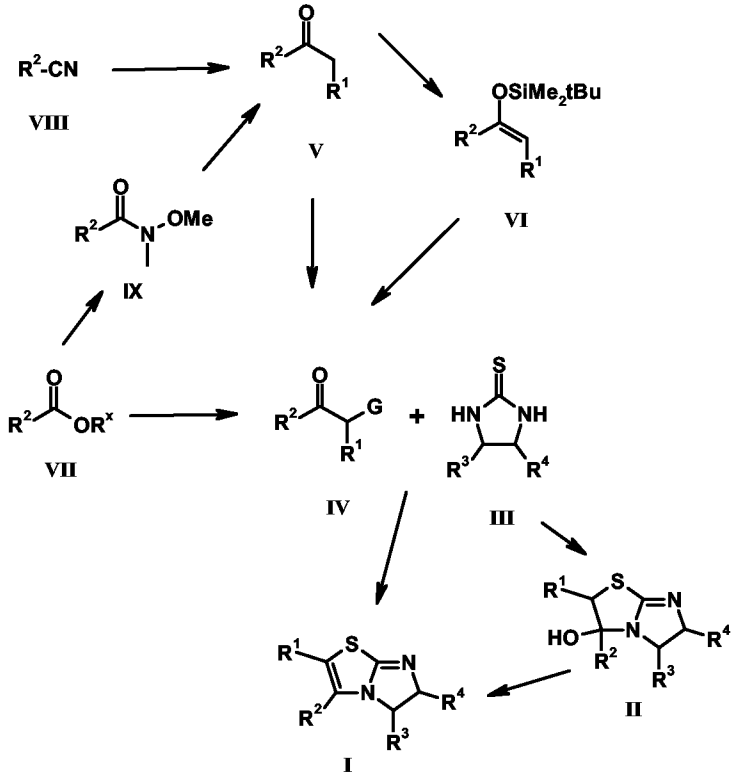
The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids. When the compound of the present invention is acidic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic bases, including inorganic bases and organic bases. Salts derived from such inorganic bases include aluminum, ammonium, calcium, copper (ic and ous), ferric, ferrous, lithium, magnesium, potassium, sodium, zinc and the like salts. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, as well as cyclic amines and substituted amines such as naturally occurring and synthesized substituted amines. Other pharmaceutically acceptable organic non-toxic bases from which salts can be formed include arginine, betaine, caffeine, choline, *N'*,*N'*-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, *N*-ethylmorpholine, *N*-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

When the compound of the present invention is basic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include, for example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, oxalic, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like.

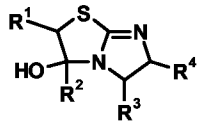
Since the compounds of formula (I) are intended for pharmaceutical use they are preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure, especially at least 98% pure (% are on a weight for weight basis).

The compounds of formula (I) can be prepared as described below and as summarized in Scheme 1, wherein R^1, R^2, R^3 and R^4 are hereinbefore defined, R^x is hydrogen or C_{1-6} alkyl and G is a leaving group or hydrogen.

Scheme 1



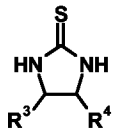
Compounds of formula (I) may be prepared by dehydrating a compound of formula (II):



II

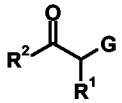
optionally in the presence of an acid, for example acetic or sulfuric acid, at a temperature in the range 0-200°C; preferably in the range 20-150°C.

Compounds of formula (II) may be prepared by reacting a compound of formula (III):



III

with a compound of formula (IV):



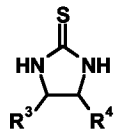
IV

in which G is a leaving group, for example, halo such as bromo or chloro, at a temperature in the range 0-150°C, in the presence of a solvent such as ethanol or acetone, preferably ethanol, in the presence of an acid such as acetic acid; preferably by heating at a temperature in the range 20-120°C.

Compounds of formula (I) may also be prepared by reacting a compound of formula (IV) with a compound of formula (III) at a temperature in the range 0-200°C, preferably in the range 20-120°C, optionally in the presence of an acid, for example acetic acid, and optionally in the presence of a solvent, for example ethanol, without isolation of the intermediate of formula (II).

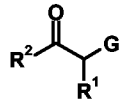
Compounds of formula (I) may also be prepared by reacting a compound of formula (III) with a compound of formula (IV) where G is H, in the presence of a solvent, for example acetic acid, and an acid, for example sulfuric or hydrochloric acid, and optionally in the presence of a second dehydrating agent, for example acetic anhydride, at a temperature in the range 0-200°C, preferably in the range 20-150°C.

According to a further aspect of the invention there is provided a process for the production of a compound of formula (I) which comprises the step of reacting a compound of formula (III):



III

with a compound of formula (IV):



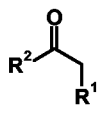
IV

wherein R^1 to R^4 are as defined for formula (I) and G is hydrogen or a leaving group.

Compounds of formula (I) in which is R^1 is bromo or chloro, may be prepared by reaction of a compound of formula (I) in which R^1 is H with a halogenating agent for example bromine or benzyltrimethylammonium tetrachloroiodate at a temperature in the range of -50-150°C optionally in the presence of a solvent for example dichloromethane, tetrahydrofuran or acetone.

Compounds of formula (I) in which is R^1 is ethoxycarbonyl may be prepared by reaction of a compound of formula (IV) in which R^1 is ethoxycarbonyl and G is bromo and a compound of formula (III) as described above. Compounds of formula (IV) in which R^1 is ethoxycarbonyl and G is bromo may be prepared from compounds of formula (V) in which R^1 is ethoxycarbonyl by the halogenation methods described below. Compounds of formula (V) in which R^1 is alkoxycarbonyl, e.g. ethoxycarbonyl, may be prepared from compounds of formula (V) in which R^1 is H by reacting with e.g. diethylcarbonate in the presence of a base such as sodium hydride. Compounds of formula (III) are generally commercially available.

Compounds of formula (IV) in which G is halo may be prepared by reaction of a compound of formula (V):

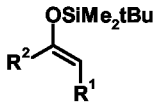


V

with a halogenating agent, for example a brominating agent such as phenyltrimethylammonium tribromide (PTAT), sodium bromate, bromine or copper(II)bromide in the range 0-200°C in the presence of a solvent, for example tetrahydrofuran; preferably by heating at a temperature in the range 20-120°C.

Alternatively compounds of formula (IV) in which G is bromo and R^2 contains basic atoms, e.g. R^2 is a quinoline or isoquinoline group, may be more suitably prepared by reaction of a compound of formula (V) with pyridinium tribromide in a solvent such as acetic acid at a temperature in the range 20-120°C.

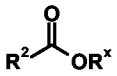
Additionally compounds of formula (IV) in which G is halo and R^2 contains basic atoms, e.g. R^2 is a quinoline group, may be more suitably prepared by reaction of a compound of formula (V) with tertbutyldimethylsilyl triflate and a base such as triethylamine in a solvent such as dichloromethane in a solvent, such as acetic acid, at a temperature in the range 0-120°C to give compounds of formula (VI):



VI

which can then undergo reaction with a halogenating agent, for example a brominating agent such as phenyltrimethylammonium tribromide (PTAT), at a temperarture in the range 0-200°C in the presence of a solvent, for example tetrahydrofuran; preferably by heating at a temperature in the range 20-120°C to give compounds of formula (IV) after acidic work-up at -78°C using a mixture of mineral acid e.g. hydrobromic acid and acetic acid.

Compounds of formula (IV) where G is bromo and R^1 is hydrogen may also be prepared by reacting a compound of formula (VII):



VII

in which R^x is C_{1-6} alkyl, with dibromomethane and an organolithium reagent such as methyllithium in a solvent such as tetrahydrofuran, at a temperature in the range of -78°C to the boiling point of the chosen solvent, or by using dibromomethane and a base such as lithium diisopropylamine (LDA) in a solvent such as tetrahydrofuran at a temperature in the range of -78°C to the boiling point of the chosen solvent

Compounds of formula (VII) are generally commercially available.

Compounds of formula (V) may be prepared directly by reacting a compound of formula (VIII):



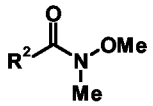
VIII

with an organometallic reagent, for example a compound of formula R^1CH_2MgX in which X is halo, for example chloro, in the presence of a solvent, for example tetrahydrofuran or ether, at a temperature in the range of -50°C to the boiling point of the chosen solvent, followed by hydrolysis of the intermediate imine salt optionally in the presence of an acid, for example hydrochloric acid.

Compounds of formula (VIII) may be prepared by methods known to those skilled in the art or are commercially available.

Additionally compounds of formula (V) in which R^1 is H may also be prepared by reacting a compound of formula (VII) wherein R^x is hydrogen with dibromomethane and an organolithium reagent such as methyllithium in a solvent such as tetrahydrofuran at a temperature in the range of -50°C to the boiling point of the chosen solvent.

Compounds of formula (V) may also be prepared by reacting a compound of formula (IX):



IX

commonly known as a Weinreb amide, with an organometallic reagent, for example a compound of formula R^1CH_2MgX in which X is halo, for example chloro, in the presence of a solvent, for example tetrahydrofuran or ether, at a temperature in the range of -50°C to the boiling point of the chosen solvent, followed by hydrolysis of the intermediate imine salt optionally in the presence of an acid, for example hydrochloric acid.

Additionally compounds of formula (V) may also be prepared directly from compounds of formula (VII) (where R^x =H) by reacting firstly with oxalyl chloride in dichloromethane containing N,N-dimethylformamide (DMF) to give the intermediate acid chloride which is then reacted further with an organometallic reagent, for example a compound of formula R^1CH_2MgX in which X is halo, for example chloro, in the presence of a solvent, for example tetrahydrofuran in the presence of iron (III) acetylacetonate.

Compounds of formula (IX) may be prepared by reacting a compound of formula (VII), where R^x is hydrogen, and methoxymethylamine under standard amide coupling conditions known to those skilled in the art.

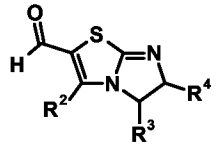
Further details for the preparation of the compounds of formula (I) are found in the examples.

The compounds of formula (I) may be prepared singly or as compound libraries comprising at least 2, for example 5 to 1,000, compounds and more preferably 10 to 100 compounds of formula (I). Compound libraries may be prepared by a combinatorial "split and mix" approach or by multiple parallel synthesis using either solution or solid phase chemistry, using procedures known to those skilled in the art.

During the synthesis of the compounds of formula (I), labile functional groups in the intermediate compounds, e.g. hydroxy, carboxy and amino groups, may be protected. The protecting groups may be removed at any stage in the synthesis of the compounds of formula (I) or may be present on the final compound of formula (I). A comprehensive discussion of the ways in which various labile functional groups may be protected and methods for cleaving the resulting protected derivatives is given in, for example, Protective Groups in Organic Chemistry, T.W. Greene and P.G.M. Wuts, (1991) Wiley-Interscience, New York, 2nd edition.

Any novel intermediates as defined above, such as the compounds of formula (II) are also included within the scope of the invention.

Other novel intermediates which are included within the scope of the invention are the compounds of formula (X):



X

wherein R^2, R^3 and R^4 are hereinbefore defined. Compounds of formula (X) are useful intermediates for the production of compounds of formula (I) wherein R^1 is e.g. cyano or C_{1-6} alkyl substituted by hydroxy.

The preferences recited above for the compounds of formulae (I), (Ia) and (Ib) also apply to any intermediate compounds such as those of formulae (II) and (X).

As indicated above the compounds of formula (I) are useful as Noradrenaline and optionally also Serotonin reuptake inhibitors e.g. for the treatment of obesity. For such use the compounds of formula (I) will generally be administered in the form of a pharmaceutical composition.

The invention also encompasses a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable carrier.

Preferably the composition is comprised of a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

Moreover, the invention also provides a pharmaceutical composition for the treatment of disease by inhibiting Noradrenalin and optionally also Serotonin reuptake, e.g. resulting in the treatment of obesity, comprising a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of compound of formula (I), including the compounds of provisos a) and b), or a pharmaceutically acceptable salt thereof.

The pharmaceutical compositions may optionally comprise other therapeutic ingredients or adjuvants. The compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

In practice, the compounds of formula (I), or pharmaceutically acceptable salts thereof, can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g. oral or parenteral (including intravenous).

Thus, the pharmaceutical compositions can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a powder, as granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion, or as a water-in-oil liquid emulsion. In addition to the common dosage forms set out above, the compound of formula (I), or a pharmaceutically acceptable salt thereof, may also be administered by controlled release means and/or delivery devices. The compositions may be prepared by any of the methods of pharmacy. In general, such methods include a step of

bringing into association the active ingredient with the carrier that constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both. The product can then be conveniently shaped into the desired presentation.

The compounds of formula (I), or pharmaceutically acceptable salts thereof, can also be included in pharmaceutical compositions in combination with one or more other therapeutically active compounds.

The pharmaceutical carrier employed can be, for example, a solid, liquid, or gas. Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid carriers are sugar syrup, peanut oil, olive oil, and water. Examples of gaseous carriers include carbon dioxide and nitrogen.

In preparing the compositions for oral dosage form, any convenient pharmaceutical media may be employed. For example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like may be used to form oral liquid preparations such as suspensions, elixirs and solutions; while carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like may be used to form oral solid preparations such as powders, capsules and tablets. Because of their ease of administration, tablets and capsules are the preferred oral dosage units whereby solid pharmaceutical carriers are employed. Optionally, tablets may be coated by standard aqueous or nonaqueous techniques.

A tablet containing the composition of this invention may be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Each tablet preferably contains from about 0.05mg to about 5g of the active ingredient and each cachet or capsule preferably containing from about 0.05mg to about 5g of the active ingredient.

For example, a formulation intended for the oral administration to humans may contain from about 0.5mg to about 5g of active agent, compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Unit dosage forms will generally contain between from about 1mg to about 2g of the active ingredient, typically 25mg, 50mg, 100mg, 200mg, 300mg, 400mg, 500mg, 600mg, 800mg, or 1000mg.

Pharmaceutical compositions of the present invention suitable for parenteral administration may be prepared as solutions or suspensions of the active compounds in water. A suitable surfactant can be included such as, for example, hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Further, a preservative can be included to prevent the detrimental growth of microorganisms.

Pharmaceutical compositions of the present invention suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of

manufacture and storage; thus, preferably should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, dusting powder, or the like. Further, the compositions can be in a form suitable for use in transdermal devices. These formulations may be prepared, using a compound of formula (I), or a pharmaceutically acceptable salt thereof, via conventional processing methods. As an example, a cream or ointment is prepared by admixing hydrophilic material and water, together with about 5wt% to about 10wt% of the compound, to produce a cream or ointment having a desired consistency.

Pharmaceutical compositions of this invention can be in a form suitable for rectal administration wherein the carrier is a solid. It is preferable that the mixture forms unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories may be conveniently formed by first admixing the composition with the softened or melted carrier(s) followed by chilling and shaping in molds.

In addition to the aforementioned carrier ingredients, the pharmaceutical formulations described above may include, as appropriate, one or more additional carrier ingredients such as diluents, buffers, flavoring agents, binders, surface-active agents, thickeners, lubricants, preservatives (including anti-oxidants) and the like. Furthermore, other adjuvants can be included to render the formulation isotonic with the blood of the intended recipient.

Compositions containing a compound of formula (I), or pharmaceutically acceptable salts thereof, may also be prepared in powder or liquid concentrate form.

Generally, dosage levels on the order of 0.01mg/kg to about 150mg/kg of body weight per day are useful in the treatment of the above-indicated conditions, or alternatively about 0.5mg to about 7g per patient per day. For example, obesity may be effectively treated by the administration of from about 0.01 to 50mg of the compound per kilogram of body weight per day, or alternatively about 0.5mg to about 3.5g per patient per day.

It is understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The compounds of formula (I), including the compounds of provisos a), b) and f) to ai), may be used in the treatment of diseases or conditions in which Noradrenaline and optionally also Serotonin reuptake plays a role. The 5-HT_{1A} agonist activity exhibited by the compounds of formula (I) means that such compounds should provide greater efficacy and lower side effects than a SNRI alone in the treatment of these diseases or conditions.

Thus the invention also provides a method for the treatment of a disease or condition in which Noradrenaline and optionally also Serotonin reuptake plays a role comprising a step of administering to a subject in need thereof an effective amount of a compound of formula (I), including the compounds of provisos a), b) and f) to ai), or a pharmaceutically acceptable salt thereof.

The invention also provides a method for the treatment of a disease or condition in which Noradrenaline and optionally also Serotonin reuptake plays a role and in which 5-HT_{1A}

agonism is desirable comprising a step of administering to a subject in need thereof an effective amount of a compound of formula (I), including the compounds of provisos a), b) and f) to ai), or a pharmaceutically acceptable salt thereof.

Diseases or conditions in which Noradrenaline and optionally also Serotonin reuptake plays a role include obesity. In the context of the present application the treatment of obesity is intended to encompass the treatment of diseases or conditions such as obesity and other eating disorders associated with excessive food intake e.g. by reduction of appetite and body weight, maintenance of weight reduction and prevention of rebound.

The compounds of the invention may also be used for treating of other diseases in which obesity is a factor including metabolic diseases such as Type II diabetes, metabolic syndrome (syndrome X), impaired glucose tolerance, dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL levels and hypertension.

Other diseases or conditions in which Noradrenaline and optionally also Serotonin reuptake play a role include those described in WO01/68653, for example depression, anxiety, psychoses (e.g. schizophrenia), tardive dyskinesia, drug addiction, drug abuse, cognitive disorders, Alzheimer's disease, obsessive compulsive behaviour, panic attacks, social phobias, eating disorders such as bulimia, anorexia, snacking and binge eating, stress, as an aid to smoking cessation, seizures, neurological disorders such as epilepsy and/or conditions in which there is neurological damage such a stroke, brain trauma, cerebral ischaemia, heads injuries and haemorrhage. Other indications include urinary stress incontinence, neuropathic pain and chronic pain associated with drug therapy or radiation therapy.

The invention also provides a method for the regulation of feeding and/or satiety comprising a step of administering to a subject in need thereof an effective amount of a compound of formula (I), including the compounds of provisos a), b) and f) to ai), or a pharmaceutically acceptable salt thereof.

The invention also provides a method for the treatment of obesity comprising a step of administering to a subject in need thereof an effective amount of a compound of formula (I), including the compounds of provisos a), b) and f) to ai), or a pharmaceutically acceptable salt thereof.

The invention also provides a method for reducing the potential for cardiovascular side effects in the treatment of a disease or condition as defined above comprising a step of administering to a subject in need thereof an effective amount of a compound of formula (I), including the compounds of provisos a), b) and f) to ai), or a pharmaceutically acceptable salt thereof.

The invention also provides a method for the treatment of a metabolic disease selected from Type II diabetes, metabolic syndrome (syndrome X), impaired glucose tolerance, dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL levels and hypertension, comprising a step of administering to a subject in need thereof an effective amount of a compound of formula (I), including the compounds of provisos a), b) and f) to ai), or a pharmaceutically acceptable salt thereof.

The invention also provides the use of a compound of formula (I), including the compounds of provisos a), b) and f) to ai), or a pharmaceutically acceptable salt thereof, in the treatment of a condition as defined above.

The invention also provides the use of a compound of formula (I), including the compounds of provisos a), b) and f) to ai), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a condition as defined above.

In the methods of the invention the term "treatment" includes both therapeutic and prophylactic treatment.

The compounds of formula (I), or pharmaceutically acceptable salts thereof, may be administered alone or in combination with one or more other therapeutically active compounds. The other therapeutically active compounds may be for the treatment of the same disease or condition as the compounds of formula (I), or a different disease or condition. The therapeutically active compounds may be administered simultaneously, sequentially or separately.

The compounds of formula (I), may be administered with other active compounds for the treatment of obesity and/or diabetes, for example insulin and insulin analogs, gastric lipase inhibitors, pancreatic lipase inhibitors, sulfonyl ureas and analogs, biguanides, α2 agonists, glitazones, PPAR-γ agonists, RXR agonists, fatty acid oxidation inhibitors, α-glucosidase inhibitors, β-agonists, phosphodiesterase inhibitors, lipid lowering agents, glycogen phosphorylase inhibitors, MCH-1 antagonists and CB-1 antagonists, amylin antagonists, lipoxygenase inhibitors, somostatin analogs, glucokinase activators, glucagon antagonists, insulin signalling agonists, PTP1B inhibitors, gluconeogenesis inhibitors, antilypolitic agents, GSK inhibitors, galanin receptor agonists, anorectic agents, CCK receptor agonists, leptin, serotonergic/dopaminergic antiobesity drugs, CRF antagonists, CRF binding proteins, thyromimetic compounds, aldose reductase inhibitors, glucocorticoid receptor antagonists, NHE-1 inhibitors or sorbitol dehydrogenase inhibitors.

When used in combination therapy, the compounds of formula (I) are preferably administered in combination with other non-central approaches to obesity e.g. with orlistat (Xenical®) or a with an agonist of GPR119 (GPR119 is identified as SNORF25 in WO00/50562 which discloses both the human and rat receptors and in US 6,468,756 which also discloses the mouse receptor) if peripherally acting.

All publications, including, but not limited to, patents and patent application cited in this specification, are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as fully set forth.

The invention will now be described by reference to the following examples which are for illustrative purposes and are not to be construed as a limitation of the scope of the present invention.

EXAMPLES

Materials and methods

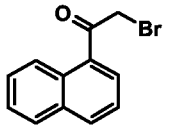
Column chromatography was carried out on SiO_2 (40-63 mesh) unless specified otherwise. LCMS data were obtained as follows: Atlantis 3μ C_{18} column (3.0 × 20.0 mm, flow rate = 0.85 mL/min) eluting with a H_2O-CH_3CN solution, containing 0.1% HCO_2H, over 6 min with UV detection at 220 nm. Gradient information: 0.0-0.3 mi n 100% H_2O; 0.3-4.25 min: Ramp up to 10% H_2O-90% CH_3CN; 4.25-4.4 min: Ramp up to 100% CH_3CN; 4.4-4.9 min: Hold at 100% CH_3CN; 4.9-5.0 min: Return to 100% H_2O; 5.0-6.0 min: Hold at 100% H_2O. The mass spectra were obtained using an electrospray ionisation source in either the positive (ES^+) or

negative (ES^-) ion modes. NMR spectra were acquired at 27°C on a Varian Mercury 400 spectrometer operating at 400 MHz or on a Bruker AMX2 500 spectrometer operating at 500 MHz.

Abbreviations and acronyms

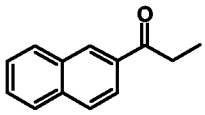
Ac: Acetyl; AIBN; 2,2'-Azobisisobutyronitrile; DCM: Dichloromethane; DIPEA: *N,N'*-Diisopropylethylamine; DMF: *N,N*-Dimethylformamide; DMSO: Dimethylsulfoxide; EDCI: 1-Ethyl-3-(3'-dimethylaminopropyl)carbodiimide; Et: Ethyl; HOBt: 1-Hydroxybenzotriazole; Me: Methyl; ^{i}Pr: iso-Propyl; PTAT: Phenyltrimethylammonium tribromide; RT: Retention time; rt: Room temperature; TFA; Trifluoroacetic acid; THF: Tetrahydrofuran.

Preparation 1: 2-Bromo-1-naphthalen-1-ylethanone



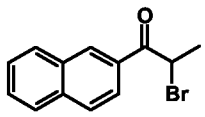
To a stirred solution of 1'-acetonaphthone (0.452g, 2.66mmol) in THF (20mL) was added PTAT (1.10g, 2.92mmol) and the reaction was stirred at rt for 16hr. The reaction mixture was filtered and the solid washed with THF (2 x 20mL). The filtrate was concentrated *in vacuo* and the residue partitioned between water (30mL) and DCM (2 x 30mL). The combined organics were dried ($MgSO_4$), concentrated *in vacuo* and chromatographed on silica gel eluting with EtOAc:hexanes (1:9) to afford the title compound. δ_H ($CDCl_3$): 4.56 (2H, s), 7.50 (1H, m), 7.55 (1H, m), 7.63 (1H, m), 7.88 (1H, m), 7.92 (1H, m), 8.01 (1H, m), 8.63 (1H, m).

Preparation 2: 1-Naphthalen-2-ylpropan-1-one



2-Naphthonitrile (3g, 19.6mmol) was dissolved in Et_2O (20mL) followed by addition of ethylmagnesium chloride (2.0M in Et_2O, 9.8mL, 19.6mmol) and the reaction was heated to reflux for 5hr, then stirred at rt for 16hr. The reaction was quenched with 2N HCl (20mL) and water (20mL) then extracted into DCM (3 x 40mL). The combined organic fractions were dried ($MgSO_4$), concentrated *in vacuo* and purified by chromatography on silica gel eluting with EtOAc:hexanes (1:9) to afford the title compound. δ_H ($CDCl_3$): 1.30 (3H, t), 3.13 (2H, q), 7.57 (2H, m), 7.88 (2H, m), 7.96 (1H, d), 8.05 (1H, dd), 8.47 (1H, s).

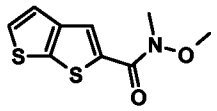
Preparation 3: 2-Bromo-1-naphthalen-2-ylpropan-1-one



1-Naphthalen-2-ylpropan-1-one (Preparation 2, 3.5g, 19.0mmol) was dissolved in THF (50mL) followed by addition of PTAT (7.1g, 19.0mmol) and the reaction stirred at rt for 16hr. The solid was filtered and the filtrate concentrated *in vacuo* and purified on silica gel eluting

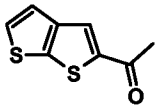
with EtOAc:hexanes (1:9) to afford the title compound. δ_H ($CDCl_3$): 1.98 (3H, d), 5.47 (1H, q), 7.57 (1H, m), 7.63 (1H, m), 7.91 (2H, m), 7.99 (1H, d), 8.08 (1H, dd), 8.57 (1H, s).

Preparation 4: Thieno[2,3-b]thiophene-2-carboxylic acid methoxymethylamide



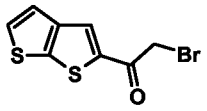
Thieno[2,3-b]thiophene-2-carboxylic acid (1g, 5.43mmol), N,O-dimethylhydroxylamine hydrochloride (0.53g, 5.43mmol) and HOBt (0.73g, 5.43mmol) were dissolved in DMF (20mL) and DIPEA (2.9mL, 16.8mmol). After 5min, EDCI (1.35g, 7.1mmol) was added and the reaction stirred at rt for 24hr. The solvent was removed *in vacuo* and the residue partitioned between water (30mL) and EtOAc (3 x 30mL). The combined organic fractions were washed with 1N NaOH (2 x 20mL), 1N HCl (2 x 20mL), brine (20mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography on silica gel eluting with EtOAc:hexanes (2:3) to afford the title compound. δ_H ($CDCl_3$): 3.40 (3H, s), 3.82 (3H, s), 7.28 (1H, d), 7.39 (1H, d), 8.13 (1H, s).

Preparation 5: 1-Thieno[2,3-b]thiophen-2-ylethanone



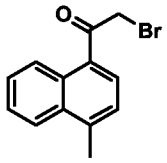
Thieno[2,3-b]thiophene-2-carboxylic acid methoxymethylamide (Preparation 4, 0.958g, 4.21mmol) was dissolved in THF (20mL) under an argon atmosphere and cooled to 0°C. Methylmagnesium bromide (1.4M in toluene:THF, 6.3mL, 8.85mmol) was added dropwise and the reaction stirred at 0°C for 2hr, then rt for 16hr. The reaction was quenched with 5% HCl in MeOH then the solvent removed *in vacuo*. The residue was partitioned between 10% $NaHCO_3$ solution (50mL) and EtOAc (3 x 40mL). The combined organic fractions were dried ($MgSO_4$), concentrated *in vacuo* and chromatographed on silica gel eluting with EtOAc:hexanes (1:3) to afford the title compound. δ_H ($CDCl_3$): 2.60 (3H, s), 7.28 (1H, d), 7.41 (1H, d), 7.83 (1H, s).

Preparation 6: 2-Bromo-1-thieno[2,3-b]thiophen-2-ylethanone



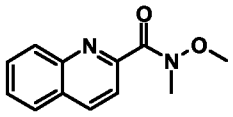
1-Thieno[2,3-b]thiophen-2-ylethanone (Preparation 5, 400mg, 2.2mmol) was dissolved in THF (20mL) followed by addition of PTAT (825mg, 2.2mmol). The reaction was stirred at rt for 16hr and the precipitated solid was filtered and washed with THF (2 x 20mL). The filtrate was concentrated *in vacuo* and the residue partitioned between water (30mL) and EtOAc (3 x 30mL). The combined organic fractions were dried ($MgSO_4$), concentrated *in vacuo* and chromatographed on silica gel eluting with EtOAc:hexanes (1:4) to afford the title compound. δ_H ($CDCl_3$): 4.39 (2H, s), 7.32 (1H, d), 7.45 (1H, d), 7.96 (1H, s).

Preparation 7: 2-Bromo-1-(4-methylnaphthalen-1-yl)ethanone



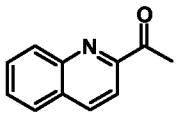
A mixture of 4-methyl-1-acetophone (0.5g, 2.7mmol) and PTAT (1.1g, 3.0mmol) in anhydrous THF (20mL) was stirred at rt under argon for 3hr. The reaction mixture was filtered and washed several times with THF. The filtrate was concentrated *in vacuo* and the residue partitioned between water (30mL) and EtOAc (3 x 30mL). The combined organic phase was dried ($MgSO_4$), concentrated *in vacuo*, and purified by chromatography on silica gel eluting with EtOAc:hexane (1:10) to afford the title compound. δ_H ($CDCl_3$): 2.77 (3H, s) 4.57 (2H, s), 7.37 (1H, d), 7.63 (2H, m), 7.86 (1H, d), 8.07 (1H, d), 8.71 (1H, d).

Preparation 8: Quinoline-2-carboxylic acid methoxymethylamide



To a suspension of quinoline-2-carboxylic acid (2.5g, 14.4mmol), O,N-dimethyl-hydroxylamine hydrochloride (2.9g, 29.7mmol), EDCI (3.4g, 17.7mmol) and HOBt monohydrate (2.25g, 14.7mmol) in DMF (55mL) was added DIPEA (10.5mL, 61.3mmol). The resulting solution was stirred for 12hr at rt before the reaction mixture was partitioned between EtOAc (100mL) and water:brine (200mL, 1:1). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 50mL). After washing with dilute NaOH solution (1M, 50mL) and brine (50mL) the combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by flash-chromatography on silica gel (eluent: EtOAc) gave the title compound. δ_H (DMSO): 3.34, 3.36 (6H, 2s), 7.71 (2H, m), 7.86 (1H, m), 8.08 (2H, m), 8.52 (1H, d); m/z (ES^+) = 217.09 $[M+H]^+$; RT = 2.79 min.

Preparation 9: 1-Quinolin-2-ylethanone

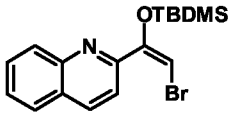


Method A: Methylmagnesium bromide (1.4M solution in toluene : THF, 3:1, 8mL) was added to a solution of quinoline-2-carboxylic acid methoxymethyl amide (Preparation 8, 2.0g, 9.25mmol) in THF at 0°C under an atmosphere of argon. After stirring in the cold for 2hr the reaction mixture was added to conc. NH_4Cl solution (400mL). Extraction with EtOAc (4 x 100mL) followed by washing of the combined extracts with brine (150mL), drying ($MgSO_4$), concentration *in vacuo* and purification of the residue by flash-chromatography on silica gel (eluent, hexane:EtOAc, 2:1) gave the title compound.

Method B: Methyl lithium (1.6M solution in diethyl ether, 10mL) was added to a solution of quinoline-2-carboxylic acid (1.40g, 8.1mmol) in THF (40mL) at 0°C under an

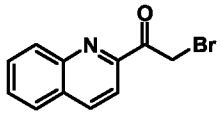
atmosphere of argon. After 2hr successively chlorotrimethylsilane (10mL, 79mmol) and then after a period of 10min dilute hydrochloric acid (1M, 30mL) were added under vigorous stirring. The aqueous layer was separated, further diluted with water (200mL) and neutralised with solid $NaHCO_3$. Similar work-up and purification to Method A gave the title compound. δ_H (DMSO): 2.80 (3H, s), 7.78 (1H, m), 7.90 (1H, m), 8.07 (1H, d), 8.81 (1H, d), 8.20 (1H, d), 8.57 (1H, d); m/z (ES^+) = 172.10 $[M+H]^+$; RT = 3.34 min.

Preparation 10: 2-[2-Bromo-1-(isopropyldimethylsilanyloxy)vinyl]quinoline



Triethylamine (0.40mL, 2.85mmol) and *tert*-butyldimethylsilyl chloride (0.35mL, 1.52mmol) were added to a solution of 1-quinolin-2-ylethanone (Preparation 9, 240mg, 1.40mol) in dry DCM (10mL) at 0°C under an atmosphere of argon. After 1hr PTAT (535mg, 1.42mmol) was added, the ice bath was removed and the resulting mixture was stirred for an additional 2hr. Partitioning between EtOAc (100mL) and a mixture of dilute $Na_2S_2O_3$ solution (10%, 50mL) and $NaHCO_3$ solution (50mL) was followed by further extraction of the aqueous phase with EtOAc (3 x 50mL). After washing with brine (50mL) the combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by flash-chromatography on silica gel (eluent, hexane:EtOAc, 4:1) gave the title compound. δ_H (DMSO): 0.19 (6H, s), 1.01 (9H, s), 6.91 (1H, s), 7.42 (1H, m), 7.60 (1H, m), 7.63 (1H, d), 7.78 (1H, d), 7.80 (1H, d), 8.38 (1H, d); m/z (ES^+) = 364.09, 364.09 $[M+H]^+$; RT = 4.95 min.

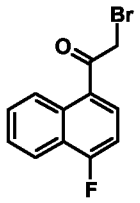
Preparation 11: 2-Bromo-1-quinolin-2-ylethanone



Method A: A suspension of pyridinium tribromide (420mg, 1.31mmol) in AcOH (10mL) was treated with hydrobromic acid (30% in AcOH, 0.26mL) and then stirred for 30min at rt. A solution of 1-quinolin-2-yl-ethanone (Preparation 9, 200mg, 1.08mmol) was added and the mixture was stirred for 12hr at rt. After removal of the solvent the residue was partitioned between EtOAc (100mL) and conc. $NaHCO_3$ solution (100mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 50mL). Washing of the combined extracts with brine (100mL), drying ($MgSO_4$) and concentration *in vacuo* followed by recrystallisation from hexane gave the title compound.

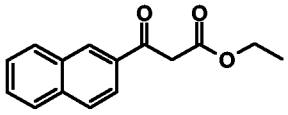
Method B: Hydrobromic acid (30% in AcOH, 0.46mL) was added to a solution of 2-[2-bromo-1-(isopropyldimethylsilanyloxy)vinyl]quinoline (Preparation 10, 420mg, 1.15mmol) in THF (20mL) at –78°C under an atmosphere of argon. The IPA/dry-ice bath was removed and the mixture was stirred for 12hr at rt. Similar work-up and purification to Method A gave the title compound. δ_H (DMSO): 5.24 (2H, s), 7.82 (1H, m), 7.94 (1H, m), 8.14 (2H, m), 8.21 (1H, d), 8.63 (1H, d); m/z (ES^+) = 249.98, 251.98 $[M+H]^+$; RT = 3.65 min.

Preparation 12: 2-Bromo-1-(4-fluoronaphthalen-1-yl)ethanone



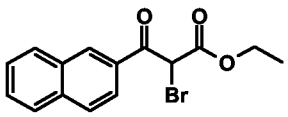
4-Fluoro-1-acetonaphthone (500mg, 2.66mmol) was dissolved in THF (20mL) followed by addition of PTAT (1.1g, 2.92mmol). The reaction was stirred at rt for 16hr then the precipitated solid was filtered and washed with THF (2 x 20mL). The filtrate was concentrated *in vacuo* and purified by chromatography on silica gel eluting with EtOAc:hexanes (1:9) to afford the title compound. δ_H ($CDCl_3$): 4.55 (2H, s), 7.19 (1H, m), 7.64 (1H, m), 7.72 (1H, m), 7.99 (1H, m), 8.19 (1H, d), 8.79 (1H, d).

Preparation 13: 3-Naphthalen-2-yl-3-oxopropionic acid ethyl ester



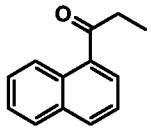
Methyl β-naphthylketone (5g, 29.4mmol) was dissolved in diethyl carbonate (50mL) under an argon atmosphere and sodium hydride (60% in mineral oil, 2.35g, 58.8mmol) was added portionwise over 10min. The reaction mixture was heated to 100°C for 4hr then stirred at rt for 16hr. The solvent was removed *in vacuo* and the residue partitioned between AcOH (5mL) in water (200mL) and Et_2O (3 x 100mL). The combined organic fractions were washed with brine (50mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography on silica gel eluting with EtOAc:hexanes (1:9 to 1:4) to afford the title compound. δ_H ($CDCl_3$): 1.27 (3H, t), 4.12 (2H, s), 4.24 (2H, q), 7.58 (2H, m), 7.88 (2H, m), 7.96 (1H, d), 8.02 (1H, m), 8.45 (1H, s).

Preparation 14: 2-Bromo-3-naphthalen-2-yl-3-oxopropionic acid ethyl ester



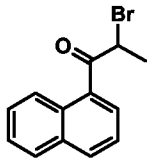
3-Naphthalen-2-yl-3-oxopropionic acid ethyl ester (Preparation 13, 6.33g, 26.1mmol) was dissolved in THF (100mL) and cooled to 0°C. PTAT (9.82g, 26.1mmol) was added and the reaction was stirred at 0°C for 2hr then at rt for 16hr. The precipitated solid was filtered and washed with THF (2 x 30mL). The filtrate was concentrated *in vacuo* and purified by chromatography on silica gel eluting with EtOAc:hexanes (1:9) to afford the title compound. δ_H ($CDCl_3$): 1.25 (3H, t), 4.30 (2H, q), 5.84 (1H, s), 7.58 (1H, m), 7.64 (1H, m), 7.90 (2H, m), 7.97 (1H, d), 8.02 (1H, dd), 8.53 (1H, s).

Preparation 15: 1-Naphthalen-1-ylpropanone



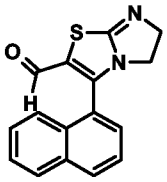
1-Cyanonaphthalene (4.6g, 30mmol) was dissolved in Et_2O (15mL) followed by addition of ethylmagnesium chloride (2.0M in Et_2O, 15mL) and the reaction heated to reflux for 17hr. The reaction was the quenched with dilute HCl (2N, 20mL) and the mixture heated for a further 1hr before water (20mL) was added and the mixture separated and extracted with DCM (3 x 40mL). The combined organic fractions were dried ($MgSO_4$), concentrated *in vacuo* and purified by chromatography on silica gel eluting with Et_2O:iso-hexane (1:19) to afford the title compound. δ_H ($CDCl_3$): 1.27 (3H, t), 3.12 (2H, q), 7.58 (3H, m), 7.90 (2H, m), 8.02 (1H, d), 8.61 (1H, d); m/z (ES^+) = 184.09 $[M+H]^+$; RT = 2.37 min.

Preparation 16: 2-Bromo-1-naphthalen-1-ylpropanone



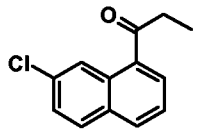
To a stirred solution of 1-naphthalen-1-ylpropanone (Preparation 15, 3.0g, 16.3mmol) in THF (20mL) was added PTAT (6.3g, 16.3mmol) and the reaction was stirred at rt for 16hr. The reaction mixture was filtered and the solid washed with THF (2 x 20mL). The filtrate was concentrated *in vacuo* and the residue partitioned between EtOAc (50mL) and saturated sodium bicarbonate solution (50mL). The combined organics were dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound. δ_H ($CDCl_3$): 2.0 (3H, d), 5.4 (1H, q), 7.60 (3H, m), 7.90 (2H, m), 8.06 (1H, d), 8.49 (1H, d).

Preparation 17: 3-Naphthalen-1-yl-5,6-dihydroimidazo[2,1-b]thiazole-2-carbaldehyde



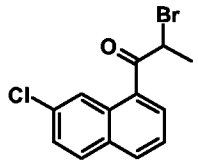
To a solution of ethylmagnesium chloride (2.0M in Et_2O, 3.6mL, 7.28mmol) in THF (20mL) cooled to 0°C was added 2-bromo-3-naphthalen-1-yl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide (Example 4, 1g, 2.43mmol) portionwise over 10min, and the reaction was stirred at 0°C for 2hr. DMF (0.75mL, 9.71mmol) was added over 5min and the reaction stirred at 0°C for 30min then rt for 16hr. The reaction was quenched with saturated NH_4Cl solution (40mL) and water (20mL) then extracted into EtOAc (3 x 40mL). The combined organic fractions were dried ($MgSO_4$), concentrated *in vacuo* and purified by chromatography on silica gel eluting with MeOH:DCM (1:19) to afford the title compound. δ_H ($CDCl_3$): 3.55 (2H, m), 4.31 (2H, t), 7.63 (4H, m), 7.79 (1H, m), 7.99 (1H, m), 8.07 (1H, m), 9.13 (1H, s).

Preparation 18: 1-(7-Chloronaphthalen-1-yl)propan-1-one



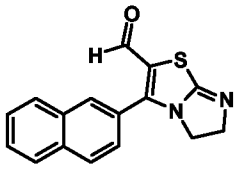
Aluminium chloride (12.5g, 93.7mmol) was added to a solution of 2-chloronaphthalene (5.0g, 30.7mmol) in DCM (50mL) at –10°C. After stirring for 20min the mixture was cooled to –78°C and propionyl chloride (5.5mL, 63.3mmol) was added dropwise. The resulting suspension was maintained at –78°C for 4hr before being added to dilute HCl (0.3M, 300mL). The layers were separated and the aqueous layer was further extracted with EtOAc (2 x 100mL). The extracts were combined, washed with brine (100mL) and dried ($MgSO_4$). Concentration followed by purification of the residue by flash chromatography on silica gel (eluent, hexane: EtOAc, 10:1) gave the title compound. δ_H (DMSO): 1.16 (3H, t), 3.15 (2H, q), 7.62-7.67 (2H, m), 8.07 (1H, d), 8.19-8.21 (2H, m), 8.62 (1H, s); m/z (ES^+) = 219.01 $[M+H]^+$; RT = 4.02 min.

Preparation 19: 2-Bromo-1-(7-chloronaphthalen-1-yl)propan-1-one



PTAT (2.21g, 5.88mmol) was added to a solution of 1-(7-chloronaphthalen-1-yl)propan-1-one (Preparation 18, 1.28g, 5.85mmol) in THF (50mL). Whilst stirring at rt for 2hr the bright orange solution was almost completely decolorized and a precipitate was formed. The mixture was filtered through Celite and the filtrate diluted with EtOAc (300mL) and washed with dilute $Na_2S_2O_3$ solution (10%, 100mL) and brine (100mL). Drying ($MgSO_4$) and concentration *in vacuo*, followed by recrystallisation from EtOH gave the title compound. δ_H (DMSO): 1.98 (3H, d), 5.94 (1H, q), 7.67-7.71 (2H, m), 8.12 (1H, d), 8.26 (1H, d), 8.31 (1H, d), 8.42 (1H, s); m/z (ES^+) = 298.94 $[M+H]^+$; RT = 4.12 min.

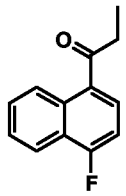
Preparation 20: 3-Naphthalen-2-yl-5,6-dihydroimidazo[2,1-b]thiazole-2-carbaldehyde



2-Bromo-3-naphthalen-2-yl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide (Example 11, 4.0g, 9.7mmol) was suspended in THF (50mL) under an argon atmosphere and cooled to 0°C. Ethylmagnesium chloride (2.0M in Et_2O, 14.6mL, 29.1mmol) was added and the reaction stirred at 0°C for 1hr then rt for 1hr. The reaction was cooled to 0°C and DMF (3.0mL, 38.8mmol) was added. The reaction was stirred at 0°C for 1hr then rt for 16hr. The reaction was quenched with saturated NH_4Cl solution (50mL) and water (25mL) then extracted into EtOAc (3 x 50mL). The combined organic fractions were dried ($MgSO_4$), concentrated *in vacuo* and

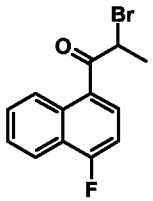
purified by chromatography on silica gel eluting with MeOH:DCM (1:19) to afford the title compound. δ_H ($CDCl_3$): 3.87 (2H, m), 4.35 (2H, m), 7.54 (1H, dd), 7.64 (2H, m), 7.94 (2H, m), 8.02 (2H, m), 9.36 (1H, s).

Preparation 21: 1-(4-Fluoronaphthalen-1-yl)propan-1-one



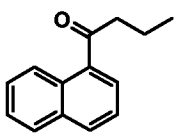
1-Cyano-4-fluoronaphthalene (1g, 5.8mmol) was dissolved in Et_2O (10mL) followed by addition of ethylmagnesium chloride (2.0M in Et_2O, 2.9mL, 5.8mmol) and the reaction was heated to reflux for 16hr. The reaction was quenched with 2N HCl (20mL) then extracted into DCM (3 x 40mL). The combined organic fractions were dried ($MgSO_4$), concentrated *in vacuo* and purified by chromatography on silica gel eluting with EtOAc:hexanes (1:9) to afford the title compound. δ_H ($CDCl_3$): 1.29 (3H, t), 3.08 (2H, q), 7.16 (1H, m), 7.60 (1H, m), 7.66 (1H, m), 7.89 (1H, m), 8.16 (1H, d), 8.74 (1H, d).

Preparation 22: 2-Bromo-1-(4-fluoronaphthalen-1-yl)propan-1-one



1-(4-Fluoronaphthalen-1-yl)propan-1-one (Preparation 21, 3.30g, 16.3mmol) was dissolved in THF (50mL) and cooled to 0°C. PTAT (6.14g, 16.3mmol) was added and the reaction mixture stirred at rt for 16hr. The solid was filtered and washed with THF (2 x 20mL). The filtrate was concentrated *in vacuo* and the residue partitioned between water (30mL) and EtOAc (2 x 50mL). The combined organic fractions were washed with brine (3 x 20mL) dried ($MgSO_4$), concentrated *in vacuo* and purified by chromatography on silica gel eluting with DCM to afford the title compound. δ_H ($CDCl_3$): 1.98 (3H, d), 5.36 (1H, q), 7.18 (1H, m), 7.63 (1H, m), 7.70 (1H, m), 7.92 (1H, m), 8.18 (1H, d), 8.59 (1H, d).

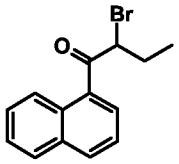
Preparation 23: 1-Naphthalen-1-ylbutan-1-one



1-Cyanonaphthalene (1g, 6.5mmol) was dissolved in THF (20mL) under an argon atmosphere and cooled to 0°C. Ethylmagnesium chloride (2.0M in Et_2O, 9.8mL, 19.6mmol) was added and the reaction stirred at 0°C for 1hr then rt for 16hr. The reaction was quenched with 1N HCl (40mL) and extracted into DCM (3 x 30mL). The combined organic fractions were dried ($MgSO_4$), concentrated *in vacuo* and purified on silica gel eluting with EtOAc:hexanes

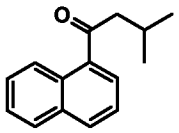
(1:4) to afford the title compound. δ_H ($CDCl_3$): 1.05 (3H, t), 1.84 (2H, m), 3.04 (2H, t), 7.48 – 7.71 (3H, m), 7.87 (2H, m), 7.98 (1H, d), 8.57 (1H, d).

Preparation 24: 2-Bromo-1-naphthalen-1-ylbutan-1-one



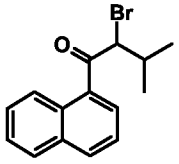
1-Naphthalen-1-ylbutan-1-one (Preparation 23, 0.99g, 5.0mmol) was dissolved in THF (20mL) and cooled to 0°C. PTAT (1.88g, 5.0mmol) was added and the reaction stirred at rt for 16hr. The precipitated solid was filtered and washed with THF (2 x 10mL). The filtrate was concentrated *in vacuo* and the residue partitioned between water (40mL) and EtOAc (2 x 40mL). The combined organic fractions were washed with brine (20mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by chromatography on silica gel eluting with EtOAc:hexanes (1:9) to afford the title compound. δ_H ($CDCl_3$): 1.15 (3H, t), 2.20 (1H, m), 2.33 (1H, m), 5.16 (1H, t), 7.50 – 7.65 (3H, m), 7.89 (2H, m), 8.03 (1H, d), 8.47 (1H, d).

Preparation 25: 3-Methyl-1-naphthalen-1-ylbutan-1-one



1-Cyanonaphthalene (1g, 6.5mmol) was dissolved in THF (20mL) under an argon atmosphere and cooled to 0°C. Isobutylmagnesium bromide (2.0M in Et_2O, 9.8mL, 19.6mmol) was added and the reaction stirred at 0°C for 1hr then rt for 16hr. The reaction was quenched with 1N HCl (30mL) then extracted into DCM (3 x 30mL). The combined organic fractions were dried ($MgSO_4$), concentrated *in vacuo* and purified by chromatography on silica gel eluting with EtOAc:hexanes (1:9) to afford the title compound. δ_H ($CDCl_3$): 1.04 (6H, d), 2.35 (1H, m), 2.95 (2H, d), 7.48 – 7.62 (3H, m), 7.83 (1H, d), 7.89 (1H, d), 7.98 (1H, d), 8.56 (1H, d).

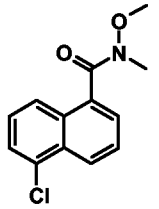
Preparation 26: 2-Bromo-3-methyl-1-naphthalen-1-ylbutan-1-one



3-Methyl-1-naphthalen-1-ylbutan-1-one (Preparation 25, 0.36g, 1.7mmol) was dissolved in THF (10mL) and cooled to 0°C. PTAT (0.64g, 1.7mmol) was added and the reaction stirred at rt for 72hr. The solid was filtered and washed with THF (2 x 20mL). The filtrate was concentrated *in vacuo* and the residue partitioned between water (40mL) and EtOAc (2 x 40mL). The combined organic fractions were washed with brine (2 x 20mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by chromatography on silica gel eluting with EtOAc:hexanes

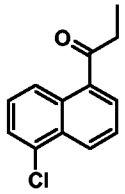
(1:9) to afford the title compound. δ_H ($CDCl_3$): 1.13 (3H, d), 1.24 (3H, d), 2.53 (1H, m), 5.03 (1H, d), 7.52 (1H, m), 7.57 (1H, m), 7.63 (1H, m), 7.89 (2H, m), 8.03 (1H, d), 8.46 (1H, d).

Preparation 27: 5-Chloronaphthalene-1-carboxylic acid methoxymethylamide



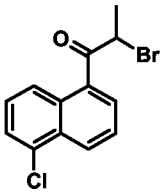
To a solution of 5-chloro-1-naphthoic acid (1.12g, 5.4mmol) in DMF (10mL), N,O-dimethylhydroxylamine (0.53g, 5.4mmol), HOBt (0.73g, 5.4mmol) and DIPEA (2.9mL, 17.0mmol) were added. After 5min EDCI (1.35g, 7.0mmol) was added and the reaction mixture stirred at rt under argon for 96hr. The solvent was removed *in vacuo* and the oil partitioned between water (100mL) and EtOAc (3 x 100mL). The combined organic phase was dried ($MgSO_4$), concentrated *in vacuo* and purified by chromatography on silica gel eluting with EtOAc:hexane (1:1) to afford the title compound. δ_H (CD_3OD): 3.42 (6H, br s), 7.51 (1H, m), 7.62 (1H, d), 7.68 (2H, m), 7.79 (1H, d), 8.37 (1H, d).

Preparation 28: 1-(5-Chloronaphthalen-1-yl)propan-1-one



A stirred solution of 5-chloronaphthalene-1-carboxylic acid methoxymethylamide (Preparation 27, 0.89g, 3.6mmol) and THF (50mL) was cooled to 0°C under an argon atmosphere. Ethylmagnesium bromide (2.0M in Et_2O, 1.2mL, 3.6mmol) was added dropwise and stirred at rt for 24hr. Further ethylmagnesium bromide (1.2mL, 3.6mmol) was added and the reaction stirred at rt for a further 24hr. The reaction was acidified with conc. HCl (5mL) in methanol (40mL) and concentrated *in vacuo*. The residue was partitioned between water (100mL) and EtOAc (3 x 100mL). The combined organic phase was dried ($MgSO_4$), concentrated *in vacuo* and purified by chromatography on silica gel eluting with EtOAc:hexane (1:9) to give the title compound. δ_H ($CDCl_3$): 1.29 (3H, t), 3.08 (2H, q), 7.48 (1H, m), 7.63 (2H, m), 7.88 (1H, d), 8.44 (1H, d), 8.48 (1H, d).

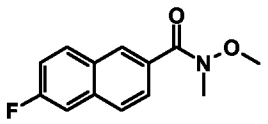
Preparation 29: 2-Bromo-1-(5-chloronaphthalen-1-yl)propan-1-one



A mixture of 1-(5-chloronaphthalen-1-yl)propan-1-one (Preparation 28, 0.13g, 0.6mmol) and PTAT (0.25g, 0.66mmol) in anhydrous THF (10mL) was stirred at rt under argon for 48hr. The reaction mixture was filtered and washed several times with THF. The filtrate was

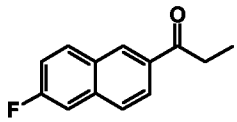
concentrated *in vacuo* giving an oil which was partitioned between water (100mL) and EtOAc (3 x 100mL). The combined organic phase was dried ($MgSO_4$), concentrated *in vacuo* and purified by chromatography on silica gel eluting with EtOAc:hexane (1:19) to give the title compound. δ_H ($CDCl_3$): 1.99 (3H, d), 5.35 (1H, q), 7.53 (1H, m), 7.65 (2H, m), 7.89 (1H, d), 8.31 (1H, d), 8.53 (1H, d).

Preparation 30: 6-Fluoronaphthalene-2-carboxylic acid methoxymethylamide



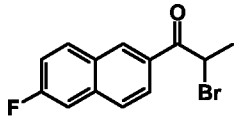
To a solution of 6-fluoro-2-naphthoic acid (1.13g, 5.9mmol) in DMF (10mL) was added N,O-dimethylhydroxylamine (0.58g 5.9mmol), HOBt (0.80g, 5.9mmol) and DIPEA (3.2mL, 18.2mmol). After 5min, EDCI (1.47g, 7.7mmol) was added and the reaction mixture stirred at rt under argon for 24hr. The solvent was removed *in vacuo* and the residue partitioned between EtOAc (3 x 50mL) and water (50mL). The combined organic phase was dried ($MgSO_4$), concentrated *in vacuo* and purified by chromatography on silica gel eluting with EtOAc:hexane (1:1) to give the title compound. δ_H ($CDCl_3$): 3.42 (3H, s), 3.57 (3H, s), 7.31 (1H, m), 7.48 (1H, dd), 7.80 (2H, s), 7.91 (1H, m), 8.24 (1H, s).

Preparation 31: 1-(6-Fluoronaphthalen-2-yl)propan-1-one



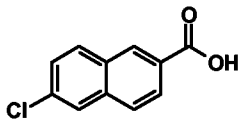
Ethylmagnesium chloride (2.0M in Et_2O, 5.5mL, 11mmol) was added dropwise to a solution of 6-fluoronaphthalene-2-carboxylic acid methoxymethylamide (Preparation 30, 0.18g, 5.0mmol) in THF (50mL) at 0°C under an argon atmosphere. The reaction mixture was warmed to rt and stirred for 24hr. The reaction was acidified with conc. HCl (5mL) in methanol (40mL) and concentrated *in vacuo* the resulting solid was partitioned between EtOAc (3 x 100mL) and water (100mL). The combined organic phase was dried ($MgSO_4$), concentrated *in vacuo* affording the title compound. δ_H ($CDCl_3$): 1.30 (3H, t), 3.14 (2H, q), 7.33 (1H, td), 7.50 (1H, dd), 7.84 (1H, d), 7.97 (1H, m), 8.08 (1H, d), 8.48 (1H, s).

Preparation 32: 2-Bromo-1-(6-fluoronaphthalen-2-yl)propan-1-one



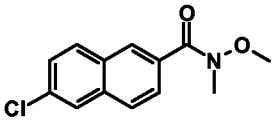
A mixture of 1-(6-fluoronaphthalen-2-yl)propan-1-one (Preparation 31, 0.84g, 4.0mmol) and PTAT (1.72g, 4.6mmol) in anhydrous THF (10mL) was left to stir at rt for 24hr. The reaction mixture was filtered and washed several times with THF. The filtrate was concentrated *in vacuo* to afford the title compound. δ_H ($CDCl_3$): 1.98 (3H, d), 5.44 (1H, q), 7.36 (1H, td), 7.51 (1H, dd), 7.88 (1H, d), 8.00 (1H, m), 8.10 (1H, d), 8.57 (1H, s).

Preparation 33: 6-Chloronaphthalene-2-carboxylic acid



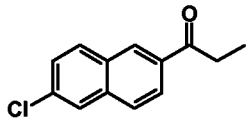
A stirred solution of 6-amino-2-naphthoic acid (3.14g, 17.0mmol) in water (10mL) and conc. HCl (20mL) was cooled to 0°C and a solution of sodium nitrite (1.17g.17.0mmol) in water (10mL) was added dropwise. After 1hr a solution of copper(I)chloride (3.36g, 34.0mmol) in conc. HCl (10mL) at 0°C was added portionwise. The reaction mixture was diluted with water (400mL) and stirred for 30min. The precipitated solid was collected by filtration, washed several times with water and dried to afford the title compound. δ_H (DMSO): 7.63 (1H, dd), 8.03 (2H, m), 8.17 (2H, m), 8.64 (1H, s).

Preparation 34: 6-Chloronaphthalene-2-carboxylic acid methoxymethylamide



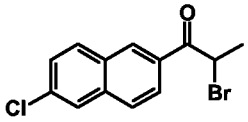
To a solution of 6-chloronaphthalene-2-carboxylic acid (Preparation 33, 1.65g, 8.0mmol) in DMF (10mL) was added N,O-dimethylhydroxylamine (0.78g 8mmol), HOBt (1.08g, 8mmol) and DIPEA (4.3mL, 25mmol). After 5min EDCI (2.0g, 10.0mmol) was added and the reaction mixture stirred at rt under argon for 24hr. The solvent was removed *in vacuo* and the residue partitioned between EtOAc (3 x 100mL) and water (100mL). The combined organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in EtOAc (100mL) and washed with HCl (2M, 50mL). The organic layer was washed with sodium hydroxide (2M, 50mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound. δ_H ($CDCl_3$): 3.42 (3H, s), 3.56 (3H, s), 7.48 (1H, dd), 7.83, (4H, m), 8.21 (1H, s).

Preparation 35: 1-(6-Chloronaphthalen-2-yl)propan-1-one



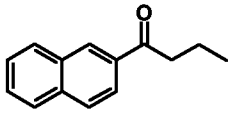
A stirred solution of 6-chloronaphthalene-2-carboxylic acid methoxymethylamide (Preparation 34, 1.84g, 7.4mmol) and THF (50mL) was cooled to 0°C under an argon atmosphere. Ethylmagnesium chloride (2M in Et_2O, 7.7mL, 15.4mmol) was added dropwise and stirred at rt for 24hr. The reaction mixture was acidified with conc. HCl (5mL) in methanol (40mL) and concentrated *in vacuo*. The residue was partitioned between EtOAc (3 x 100mL) and sodium bicarbonate (100mL). The combined organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound. δ_H ($CDCl_3$): 1.30 (3H, t), 3.14 (2H, q), 7.51 (1H, dd), 7.82 (1H, d), 7.90 (2H, m), 8.08 (1H, dd), 8.46 (1H, s).

Preparation 36: 2-Bromo-1-(6-chloronaphthalen-2-yl)propan-1-one



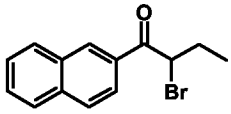
A mixture of 1-(6-chloronaphthalen-2-yl)propan-1-one (Preparation 35, 1.39g, 6.4mmol) and PTAT (2.64g, 7.0mmol) in anhydrous THF (40mL) was stirred at rt under argon for 24hr. The reaction mixture was filtered and the solid washed several times with THF. The filtrate was then concentrated *in vacuo*. The residue was purified by chromatography on silica gel eluting with EtOAc:hexane (8:92) to afford the title compound. δ_H ($CDCl_3$): 1.98 (3H, d), 5.43 (1H, q), 7.53 (1H, dd), 7.89 (3H, m), 8.11 (1H, dd), 8.55 (1H, s).

Preparation 37: 1-Naphthalen-2-ylbutan-1-one



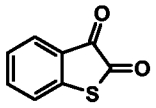
Propylmagnesium chloride (2.0M in Et_2O, 3.3mL, 6.5mmol) was added dropwise to a stirred solution of 2-naphthonitrile (1.0g, 6.5mmol) in Et_2O (20mL) at 0°C under an argon atmosphere. The reaction was warmed to rt and stirred for 48hr. The reaction was acidified with HCl (2M, 15mL) and concentrated *in vacuo* to afford the title compound. δ_H ($CDCl_3$): 1.06 (3H, t), 1.85 (2H, m), 3.09 (2H, t), 7.61 (2H, m), 7.90 (2H, m), 7.98 (1H, d), 8.05 (1H, d), 8.48 (1H, s).

Preparation 38: 2-Bromo-1-naphthalen-2-ylbutan-1-one



A mixture of 1-naphthalen-2-ylbutan-1-one (Preparation 37, 1.26g, 6.4mmol) and PTAT (2.65g, 7.0mmol) in anhydrous THF (20mL) was stirred at rt under argon for 48hr. The reaction mixture was filtered and the solid washed several times with THF. The filtrate was concentrated *in vacuo* giving a solid which was purified by chromatography on silica gel eluting with EtOAc:hexane (1:19) to afford the title compound. δ_H ($CDCl_3$): 1.14 (3H, t), 2.23 (1H, m), 2.30 (1H, m), 5.25 (1H, t), 7.61 (2H, m), 7.92 (2H, m), 8.00 (1H, d), 8.08 (1H, dd), 8.56 (1H, s).

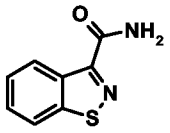
Preparation 39: Benzo[b]thiophene-2,3-dione



Oxalyl chloride (3.8mL, 43.0mmol) was added dropwise to a stirred solution of benzenethiol (3g, 27.0mmol) in Et_2O (20mL) and the mixture heated under reflux for 1.5hr. The solution was cooled to rt then concentrated *in vacuo*. The residue was dissolved in DCM (50mL) and cooled to 0°C. Aluminium chloride (2.3g, 32.0mmol) was added portionwise to the reaction

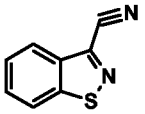
mixture and the solution heated under reflux for 1hr. The solution was cooled to rt and poured onto ice. The organic layer was separated and washed successively with saturated aqueous sodium bicarbonate (100mL), water (100mL) and brine (100mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. With the addition of hexane a precipitate was formed which was collected by filtration to afford the title compound. δ_H ($CDCl_3$): 7.38 (1H, t), 7.43 (1H, d), 7.70 (1H, t), 7.84 (1H, d).

Preparation 40: Benzo[d]isothiazole-3-carboxylic acid amide



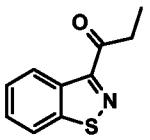
To a stirred solution of benzo[b]thiophene-2,3-dione (Preparation 39, 0.73g, 4.4mmol) in ammonium hydroxide (28% in H_2O, 14mL) was added hydrogen peroxide (30% volume, 1.4mL) dropwise over 5min and stirred for 96hr. The precipitate was collected by filtration to afford the title compound. δ_H ($CDCl_3$): 5.62 (1H, br s) 7.27 (1H, br s), 7.57 (2H, m), 7.97 (1H, d), 8.98 (1H, d).

Preparation 41: Benzo[d]isothiazole-3-carbonitrile



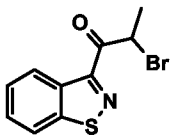
Benzo[d]isothiazole-3-carboxylic acid amide (Preparation 40, 0.52g, 3.0mmol) was dissolved in phosphorus oxylchloride (10mL) at 0°C, warmed to rt then heated under reflux for 3hr. The solvent was removed *in vacuo* and the residue partitioned between ice water (100mL) and EtOAc (3x100mL). The combined organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound. δ_H ($CDCl_3$): 7.67 (2H, m), 8.06 (1H, d), 8.26 (1H, d).

Preparation 42: 1-Benzo[d]isothiazol-3-ylpropan-1-one



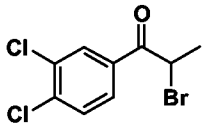
Ethylmagnesium bromide (3.0M in Et_2O, 0.83mL, 2.5mmol) was added dropwise to a stirred solution of benzo[d]isothiazole-3-carbonitrile (Preparation 41, 0.39g, 2.5mmol) in Et_2O (20mL) at 0°C and stirred for 24hr under an argon atmosphere. The reaction was acidified with HCl (2M, 15mL) and concentrated *in vacuo* the resulting solid was partitioned between water (100mL) and EtOAc (3 x 100mL). The combined organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound. δ_H ($CDCl_3$): 1.29 (3H, t), 3.33 (2H, q), 7.56 (2H, m), 7.98 (1H, d), 8.88 (1H, d).

Preparation 43: 1-Benzo[d]isothiazol-3-yl-2-bromopropan-1-one



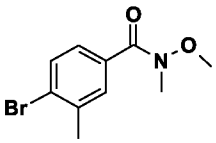
A mixture of 1-benzo[d]isothiazol-3-ylpropan-1-one (Preparation 42, 0.35g, 1.8mmol) and PTAT (0.74g, 2.0mmol) in anhydrous THF (10mL) was stirred at rt under argon for 72hr. The reaction mixture was filtered and washed several times with THF. The filtrate was concentrated *in vacuo* giving an oil which was partitioned between EtOAc (3 x 100mL), water (100mL) and brine (50mL). The combined organic phase was dried ($MgSO_4$), concentrated *in vacuo* and purified by chromatography on silica gel eluting with EtOAc:hexane (1:19) to afford the title compound. δ_H ($CDCl_3$): 1.97 (3H, d), 5.99 (1H, q), 7.60 (2H, m), 8.00 (1H, dd), 8.85 (1H, dd); m/z (ES^+) = 274 $[M+H]^+$; RT = 2.12min.

Preparation 44: 2-Bromo-1-(3,4-dichlorophenyl)propan-1-one



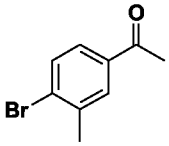
To a stirred solution of 1-(3,4-dichlorophenyl)propan-1-one (1.0g, 4.924mmol) in THF (30mL) was added PTAT (1.94g, 5.170mmol) and the reaction was stirred at rt for 16hr. The reaction mixture was filtered and the solid washed with THF (2 x 20mL). The filtrate was concentrated in vacuo and the residue partitioned between a saturated solution of $NaHCO_3$ (30mL) and DCM (2 x 30mL). The combined organics were dried ($MgSO_4$), concentrated *in vacuo* and chromatographed on silica gel eluting with ethyl acetate:hexanes (1:4) to afford the title compound as a pale yellow oil. δ_H ($CDCl_3$): 8.20 (1H, s), 7.90 (1H, d), 7.60 (1H, d), 5.20 (1H, q), 1.95 (3H, m).

Preparation 45: 4-Bromo-N-methoxy-3,N-dimethylbenzamide



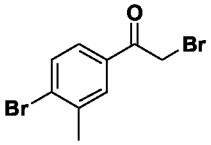
Diisopropylethylamine (7.3mL, 0.042mol) was added to a solution of 4-bromo-3-methylbenzoic acid (3g, 0.014mol), N,O-dimethylhydroxylamine hydrochloride (1.36g, 0.014mol), EDCI (4.01g, 0.021mol) and HOBt (1.94g, 0.01395mol) in DMF (20ml) at rt. After 24hr the solvent was removed *in vacuo* and the residue purified on silica by elution with DCM to yield the title compound. m/z (ES^+) = 257.93 $[M+H]^+$; RT = 3.31 min.

Preparation 46: 1-(4-Bromo-3-methylphenyl)ethanone



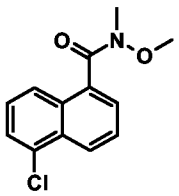
Methyllithium (3.7mL, 5.93mmol) was added to a solution of 4-bromo-N-methoxy-3,N-dimethylbenzamide (Preparation 45, 1.53g, 5.93mmol) in THF at –70°C. After warming to rt overnight the solvent was partially removed and the residue partitioned between dichloromethane (50mL) and saturated ammonium chloride (50mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified on silica gel by elution with hexane : DCM (4:1) to yield the title compound. δ_H ($CDCl_3$): 7.90 (1H, br s), 7.70 (2H, br s), 2.65 (3H, s), 2.45 (3H, s).

Preparation 47: 2-Bromo-1-(4-bromo-3-methylphenyl)ethanone



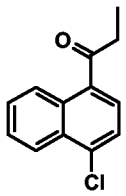
1-(4-Bromo-3-methylphenyl)ethanone (Preparation 46, 0.58g, 2.732 mmol) and PTAT (1.027g, 2.732mmol) were added together in THF (30ml) at rt. After overnight reaction the solid was filtered off and the filtrate concentrated to leave a brown oil. Purification on silica gel by elution with hexane:EtOAc (25:1) yielded the title compound. m/z (ES^+) = 292.97 $[M+H]^+$; RT = 2.60min.

Preparation 48: 5-Chloronaphthalene-1-carboxylic acid methoxymethylamide



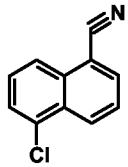
5-Chloro-1-naphthoic acid (1.12g, 5.4mmol), N,O-dimethylhydroxylamine hydrochloride (0.53g, 5.4mmol) and HOBt (0.73g, 5.4mmol) were dissolved in DMF (15mL) and DIPEA (2.9mL, 17.0mmol). After 5min, EDCI (1.35g, 7mmol) was added and the reaction was stirred at rt for 96hr. The solvent was removed *in vacuo* and the residue partitioned between water (100mL) and EtOAc (3 x 100mL). The combined organic fractions were dried ($MgSO_4$), concentrated *in vacuo* and chromatographed on silica gel eluting with EtOAc:hexanes 1:1 affording the title compound. δ_H ($CDCl_3$): 3.41 (6H, br s), 7.44 (1H, t), 7.61 (3H, m), 7.83 (1H, d), 8.37 (1H, m).

Preparation 49: 1-(4-Chloronaphthalen-1-yl)propan-1-one



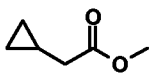
To a stirred solution of 1-chloronaphthalene (10g, 61.5mmol) in DCM (150mL) at -10°C was added aluminium chloride (24.6g, 184.5mmol) portionwise over 5min, and the reaction mixture was cooled to -78°C. Propionyl chloride (10.7mL, 123.0mmol) was added dropwise over 10min and the reaction stirred at -78°C for 16hr. The reaction mixture was warmed to 0°C and quenched with 1M HCl, followed by addition of water (200mL). The organic layer was separated and the aqueous layer extracted into DCM (2 x 125mL). The combined organic fractions were washed with 1M NaOH solution (2 x 50mL), brine (50mL), dried ($MgSO_4$) and concentrated *in vacuo* affording the title compound. δ_H ($CDCl_3$): 1.28 (3H, t), 3.04 (2H, q), 7.58 (1H, d), 7.64 (2H, m), 7.73 (1H, d), 8.34 (1H, m), 8.59 (1H, m).

Preparation 50: 5-Chloronaphthalene-1-carbonitrile



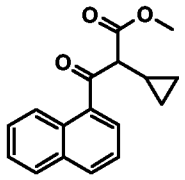
A solution of 5-chloro-1-naphthoic acid (2.08g, 10.1mmol) in thionyl chloride (10mL) was refluxed for 3hr, then cooled to rt and concentrated *in vacuo*. Concentrated ammonia solution (10mL) was added cautiously to the residue at 0°C, and the reaction mixture was warmed to rt and stirred for 30min. The reaction mixture was diluted with water (50mL) and the solid was filtered, washed with water and dried under vacuum. The solid was dissolved in phosphorus oxychloride (10mL) and heated to reflux for 4hr, then cooled to rt and poured slowly into warm water (50mL). The precipitated solid was filtered, washed with water (2 x 20mL) and dried under vacuum affording the title compound. δ_H ($CDCl_3$): 7.64 (2H, m), 7.73 (1H, m), 8.00 (1H, m), 8.20 (1H, d), 8.56 (1H, d).

Preparation 51: Cyclopropylacetic acid methyl ester



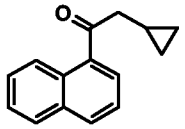
To a solution of cyclopropylacetic acid (2g, 20.0mmol) in MeOH (10mL) was added concentrated H_2SO_4 (5 drops) and the reaction mixture was heated to reflux for 16hr. The reaction mixture was cooled to rt and concentrated *in vacuo*. The residue was partitioned between saturated $NaHCO_3$ solution (30mL) and Et_2O (2 x 30mL). The combined organic fractions were washed with brine (2 x 20mL), dried ($MgSO_4$) and concentrated *in vacuo* affording the title compound. δ_H ($CDCl_3$): 0.15 (2H, m), 0.54 (2H, m), 1.04 (1H, m), 2.21 (2H, d), 3.68 (3H, s).

Preparation 52: 2-Cyclopropyl-3-naphthalen-1-yl-3-oxopropionic acid methyl ester



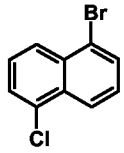
n-Butyllithium (2.5M, 8.3mL, 20.9mmol) was added to a solution of diisopropylamine (2.9mL, 20.9mmol) in THF (20mL) at 0°C under an argon atmosphere. The reaction mixture was stirred at 0°C for 1hr, and then cooled to -78°C. A solution of cyclopropylacetic acid methyl ester (Preparation 51, 1.19g, 10.4mmol) in THF (15mL) was added dropwise and the reaction was stirred at -78°C for 20min. A solution of 1-naphthaldehyde (1.56mL, 11.5mmol) in THF (15mL) was then added, and the reaction was warmed to rt and stirred for 16hr. Water (50mL) was added and the reaction mixture was extracted into Et_2O (3 x 50mL). The combined organic fractions were dried ($MgSO_4$), concentrated *in vacuo* and chromatographed on silica gel eluting with EtOAc:hexanes 1:9. The product eluted was dissolved in DCM (50mL) and Dess-Martin periodinane (3.30g, 7.8mmol) was added. The reaction was stirred at rt for 16hr. The reaction mixture was diluted with DCM (50mL) and water (100mL) was added. The precipitate was filtered and the layers separated. The aqueous layer was extracted into DCM (2 x 50mL), the combined organic fractions were dried ($MgSO_4$), concentrated *in vacuo* and chromatographed on silica gel eluting with EtOAc:hexanes 1:9 affording the title compound. δ_H ($CDCl_3$): 0.17 (1H, m), 0.40 (1H, m), 0.63 (1H, m), 0.73 (1H, m), 1.58 (1H, m), 3.60 (1H, d), 3.72 (3H, s), 7.50 (1H, m), 7.56 (1H, m), 7.61 (1H, m), 7.82 (1H, d), 7.89 (1H, d), 8.00 (1H, d), 8.55 (1H, d).

Preparation 53: 2-Cyclopropyl-1-naphthalen-1-ylethanone



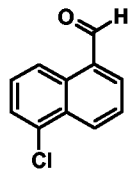
A suspension of cyclopropyl-3-naphthalen-1-yl-3-oxo propionic acid methyl ester (Preparation 52, 0.61g, 2.3mmol) and NaCl (0.13g, 2.3mmol) in DMSO (15mL) and water (0.5mL) was heated to 160°C for 24hr. The reaction mixture was cooled to rt and partitioned between water (50mL) and EtOAc (3 x 40mL). The combined organic fractions were dried ($MgSO_4$), concentrated *in vacuo* and chromatographed on silica gel eluting with EtOAc:hexanes 1:9 affording the title compound. δ_H ($CDCl_3$): 0.23 (2H, m), 0.61 (2H, m), 1.19 (1H, m), 2.97 (2H, d), 7.50 (1H, m), 7.54 (1H, m), 7.60 (1H, m), 7.82 (1H, m), 7.89 (1H, d), 7.98 (1H, d), 8.60 (1H, d).

Preparation 54: 1-Bromo-5-chloronaphthalene



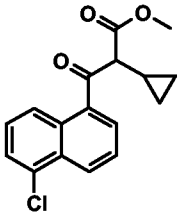
The title compound was prepared according to the method of Robert F. O'Malley et al, *J. Org. Chem.*, 1994, 59, 7335 -7340.

Preparation 55: 5-Chloronaphthalene-1-carbaldehyde



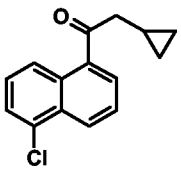
A solution of 1-bromo-5-chloronaphthalene (Preparation 54, 1g, 4.14mmol) in THF (20mL) was cooled to -78°C under an argon atmosphere. n-Butyllithium (2.5M, 1.8mL, 4.55mmol) was added dropwise and the reaction stirred at -78°C for 1hr. DMF (0.96mL, 12.4mmol) was added and the reaction stirred at -78°C for 2hr, then warmed to rt and quenched with 1M HCl (30mL). The reaction mixture was extracted into EtOAc (3 x 30mL) and the combined organic fractions were dried ($MgSO_4$), concentrated *in vacuo* and chromatographed on silica gel eluting with EtOAc:hexanes 1:9 affording the title compound. δ_H ($CDCl_3$): 7.60 (1H, m), 7.70 (1H, d), 7.75 (1H, m), 8.05 (1H, d), 8.61 (1H, d), 9.22 (1H, d), 10.41 (1H, s).

Preparation 56: 3-(5-Chloronaphthalen-1-yl)-2-cyclopropyl-3-oxopropionic acid methyl ester



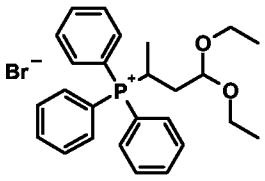
The title compound was prepared using an identical method to that for Preparation 52 starting from 5-chloronaphthalene-1-carbaldehyde (Preparation 55). δ_H ($CDCl_3$): 0.15 (1H, m), 0.40 (1H, m), 0.62 (1H, m), 0.73 (1H, m), 1.54 (1H, m), 3.56 (1H, d), 7.51 (1H, m), 7.62 (1H, m), 7.66 (1H, m), 7.84 (1H, d), 8.40 (1H, d), 8.50 (1H, d).

Preparation 57: 1-(5-Chloronaphthalen-1-yl)-2-cyclopropylethanone



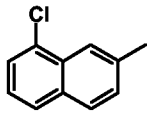
The title compound was prepared using an identical method to that for Preparation 53 starting from 3-(5-chloronaphthalen-1-yl)-2-cyclopropyl-3-oxopropionic acid methyl ester (Preparation 56). δ_H ($CDCl_3$): 0.22 (2H, m), 0.60 (2H, m), 1.16 (1H, m), 2.95 (2H, d), 7.49 (1H, m), 7.62 (2H, m), 7.83 (1H, m), 8.47 (2H, m).

Preparation 58: (3,3-Diethoxy-1-methylpropyl)triphenylphosphonium bromide



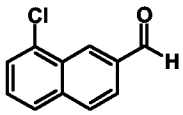
The title compound was prepared according to the method of Henri Brunner et al., *Synthesis*, 1997, 79 -86.

Preparation 59: 1-Chloro-7-methylnaphthalene



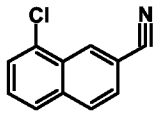
(3,3-Diethoxy-1-methylpropyl)triphenylphosphonium bromide (30g, 61.6mmol) was suspended in THF (90mL) under an argon atmosphere and cooled to -78°C. n-Butyllithium (2.5M, 27mL, 67.7mmol) was added dropwise over 15min, and the reaction stirred at -78°C for 1.5hr. A solution of 2-chlorobenzaldehyde (6.9mL, 61.6mmol) in THF (10mL) was added and the reaction warmed to rt and stirred for 16hr. EtOH (20mL) and triethylamine (2mL) were added and the reaction mixture partitioned between water (100mL) and Et_2O (3 x 100mL). The combined organic fractions were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in glacial acetic acid (100mL) and 48% HBr in water (100mL) and heated to 100°C for 16hr. The reaction was cooled to rt and partitioned between water (150mL) and Et_2O (3 x 100mL). The combined organic fractions were dried ($MgSO_4$), concentrated *in vacuo* and chromatographed on silica gel eluting with hexanes affording the title compound. δ_H ($CDCl_3$): 2.59 (3H, s), 7.33 (1H, m), 7.39 (1H, m), 7.56 (1H, m), 7.73 (1H, d), 7.77 (1H, d), 8.07 (1H, s).

Preparation 60: 8-Chloronaphthalene-2-carbaldehyde



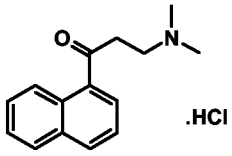
To a refluxing solution of N-bromosuccinimide (1.20g, 6.7mmol) and AIBN (84mg, 0.5mmol) in CCl_4 (25mL) was added a solution of 1-chloro-7-methylnaphthalene (Preparation 59, 1.13g, 6.4mmol) in CCl_4 (25mL). The reaction was refluxed for 3hr, then cooled to rt and the solid filtered and discarded. The filtrate was concentrated *in vacuo* and dissolved in $CHCl_3$ (50mL). Hexamethylenetetramine (1.08g, 7.7mmol) was added and the reaction was refluxed for 3hr, then stirred at rt for 72hr. The reaction mixture was concentrated *in vacuo* and the residue dissolved in acetic acid:water (1:1, 40mL) and concentrated HCl (10mL). The reaction mixture was refluxed for 3hr, then cooled to rt and partitioned between water (100mL) and EtOAc (3 x 100mL). The combined organic fractions were dried ($MgSO_4$), concentrated *in vacuo* and chromatographed on silica gel eluting with EtOAc:hexanes 1:9 affording the title compound. δ_H ($CDCl_3$): 7.56 (1H, t), 7.68 (1H, m), 7.84 (1H, d), 7.98 (1H, d), 8.03 (1H, dd), 8.77 (1H, s), 10.23 (1H, s).

Preparation 61: 8-Chloronaphthalene-2-carbonitrile



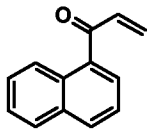
A solution of 8-chloronaphthalene-2-carbaldehyde (Preparation 60, 117mg, 0.61mmol) and hydroxylamine hydrochloride (51mg, 0.74mmol) in formic acid (5mL) was heated to reflux for 24hr. The reaction was cooled to rt and partitioned between water (30mL) and EtOAc (3 x 30mL). The combined organic fractions were dried ($MgSO_4$), concentrated *in vacuo* and chromatographed on silica gel eluting with EtOAc:hexanes 1:9 affording the title compound. δ_H ($CDCl_3$): 7.57 (1H, m), 7.70 (2H, m), 7.83 (1H, d), 7.98 (1H, d), 8.69 (1H, s).

Preparation 62: 3-Dimethylamino-1-naphthalen-1-ylpropan-1-one hydrochloride



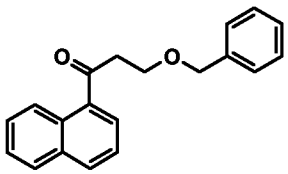
To a solution of 1-acetonaphthone (10g, 59mmol), paraformaldehyde (2.3g, 78mmol) and dimethylamine hydrochloride (6.36g, 78mmol) in ethanol (20mL) was added concentrated HCl (0.5mL). The reaction was heated to reflux for 10hr, then cooled to rt and concentrated *in vacuo*. The residue was triturated with Et_2O (20mL) affording the title compound. m/z (ES^+) = 228 $[M+H]^+$; RT = 2.22min.

Preparation 63: 1-Naphthalen-1-ylpropenone



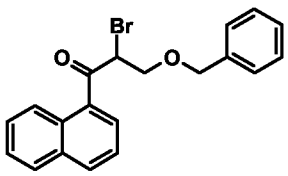
3-Dimethylamino-1-naphthalen-1-ylpropan-1-one hydrochloride (Preparation 62, 15.47g, 59mmol) was dissolved in water (400mL) and basified to pH9 with saturated Na_2CO_3 solution. The free base was extracted into EtOAc (3 x 150mL), and the combined organic fractions were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in MeOH (25mL) and cooled to 0°C and iodomethane (8.4mL, 135mmol) was added. The reaction mixture was warmed to rt and stirred for 1hr. The resulting solid was filtered and washed with Et_2O (2 x 20mL). The solid was stirred vigorously between Et_2O (100mL) and saturated $NaHCO_3$ solution (100mL) for 16hr. The layers were separated and the aqueous extracted into EtOAc (2 x 100mL). The combined organic fractions were washed with 1M HCl (100mL), brine (150mL), dried ($MgSO_4$) and concentrated *in vacuo* affording the title compound. δ_H ($CDCl_3$): 6.06 (1H, d), 6.28 (1H, d), 6.97 (1H, dd), 7.55 (3H, m), 7.74 (1H, m), 7.91 (1H, m), 8.00 (1H, d), 8.35 (1H, m).

Preparation 64: 3-Benzyloxy-1-naphthalen-1-ylpropan-1-one



1-Naphthalen-1-ylpropenone (Preparation 63, 3.78g, 20.7mmol) and benzyl alcohol (3.35g, 31mmol) were dissolved in DCM (40mL) and to this was added concentrated H_2SO_4 (4 drops). The reaction was stirred at rt for 16hr, then diluted with DCM (40mL) and washed with saturated $NaHCO_3$ solution (50mL) and water (50mL). The organic layer was dried ($MgSO_4$), concentrated *in vacuo* and chromatographed on silica gel eluting with EtOAc:hexanes 1:9. The product was further chromatographed on silica gel eluting with DCM affording the title compound. δ_H ($CDCl_3$): 3.37 (2H, t), 3.99 (2H, t), 4.57 (2H, s), 7.32 (4H, m), 7.56 (4H, m), 7.90 (2H, m), 8.00 (1H, d), 8.63 (1H, d).

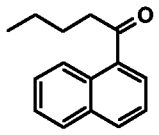
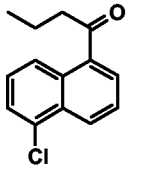
Preparation 65: 3-Benzyloxy-2-bromo-1-naphthalen-1-ylpropan-1-one

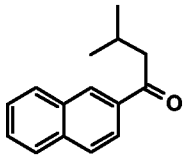
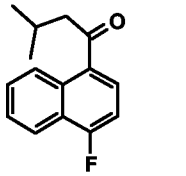
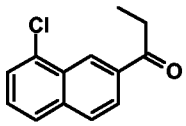


3-Benzyloxy-1-naphthalen-1-ylpropan-1-one (Preparation 64, 2.89g, 9.9mmol) and PTAT (4.12g, 10.9mmol) were dissolved in THF (40mL) and stirred at rt for 72hr. The precipitate was filtered and washed with THF (10mL) and discarded. The filtrate was concentrated *in vacuo* and chromatographed on silica gel eluting with EtOAc:hexanes 1:19 affording the title compound. δ_H (DMSO): 3.95 (1H, dd), 4.20 (1H, dd), 4.60 (2H, d), 5.96 (1H, t), 7.31 (4H, m), 7.65 (4H, m), 8.07 (1H, d), 8.22 (2H, m), 8.38 (1H, d).

Preparations 66 – 70

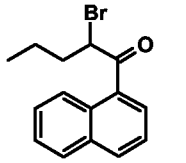
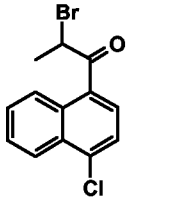
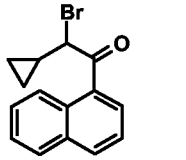
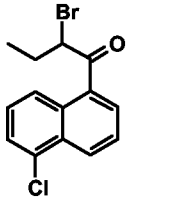
The procedure described in Preparation 15 was used to prepare the compounds of Preparations 66 – 70 from the appropriate nitrile and Grignard reagent.

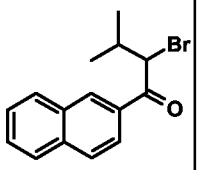
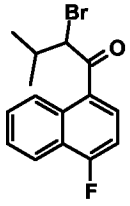
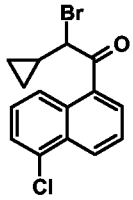
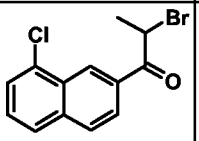
Prep	Structure	Name	^{1}H-NMR data
66		1-Naphthalen-1-ylpentan-1-one	δ_H ($CDCl_3$): 0.97 (3H, t), 1.46 (2H, m), 1.79 (2H, m), 3.06 (2H, t), 7.48 – 7.61 (3H, m), 7.85 (1H, m), 7.89 (1H, m), 7.98 (1H, d), 8.55 (1H, d)
67		1-(5-Chloronaphthalen-1-yl)-butan-1-one	δ_H ($CDCl_3$): 1.04 (3H, t), 1.83 (2H, m), 3.03 (2H, t), 7.48 (1H, m), 7.64 (2H, m), 7.87 (1H, m), 8.43 (1H, d), 8.48 (1H, d)

68		3-Methyl-1-naphthalen-2-yl-butan-1-one	δ_H ($CDCl_3$): 1.05 (6H, d), 2.38 (1H, m), 2.98 (2H, d), 7.61 (2H, m), 7.91 (2H, m), 7.98 (1H, d), 8.04 (1H, m), 8.47 (1H, s)
69		1-(4-Fluoronaphthalen-1-yl)-3-methylbutan-1-one	δ_H ($CDCl_3$): 1.03 (6H, d), 2.34 (1H, m), 2.92 (2H, d), 7.16 (1H, m), 7.64 (1H, m), 7.66 (1H, m), 7.87 (1H, m), 8.17 (1H, d), 8.69 (1H, d)
70		1-(8-Chloronaphthalen-2-yl)-propan-1-one	δ_H ($CDCl_3$): 1.32 (3H, t), 3.20 (2H, q), 7.50 (1H, t), 7.64 (1H, d), 7.80 (1H, d), 7.92 (1H, d), 8.11 (1H, m), 8.89 (1H, s)

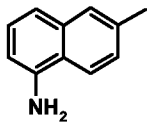
Preparations 71 – 79

The procedure described in Preparation 1 was used to prepare the compounds of Preparations 71 – 79 from the appropriate ketone.

Prep	**Structure**	**Name**	**^{1}H-NMR data**
71		2-Bromo-1-naphthalen-1-yl-pentan-1-one	δ_H ($CDCl_3$): 1.02 (3H, t), 1.54 (1H, m), 1.63 (1H, m), 2.17 (1H, m), 2.28 (1H, m), 5.23 (1H, t), 7.52 (1H, t), 7.57 (1H, m), 7.64 (1H, m), 7.89 (2H, m), 8.03 (1H, d), 8.47 (1H, d)
72		2-Bromo-1-(4-chloro-naphthalen-1-yl)propan-1-one	δ_H ($CDCl_3$): 1.99 (3H, d), 5.33 (1H, q), 7.63 (1H, d), 7.69 (2H, m), 7.77 (1H, d), 8.38 (1H, m), 8.45 (1H, m)
73		2-Bromo-2-cyclopropyl-1-naphthalen-1-ylethanone	δ_H ($CDCl_3$): 0.57 (2H, m), 0.95 (2H, m), 1.86 (1H, m), 4.55 (1H, d), 7.50 (1H, t), 7.57 (1H, t), 7.64 (1H, t), 7.82 (1H, d), 7.90 (1H, d), 8.02 (1H, d), 8.48 (1H, d)
74		2-Bromo-1-(5-chloro-naphthalen-1-yl)butan-1-one	δ_H ($CDCl_3$): 1.15 (3H, t), 2.19 (1H, m), 2.34 (1H, m), 5.12 (1H, t), 7.52 (1H, m), 7.64 (2H, m), 7.89 (1H, d), 8.32 (1H, d), 8.52 (1H, d)

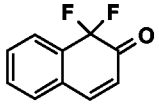
75		2-Bromo-3-methyl-1-naphthalen-2-ylbutan-1-one	δ_H ($CDCl_3$): 1.08 (3H, d), 1.28 (3H, d), 2.57 (1H, m), 5.11 (1H, d), 7.59 (1H, m), 7.64 (1H, m), 7.90 (1H, d), 7.94 (1H, d), 8.00 (1H, d), 8.07 (1H, m), 8.53 (1H, s)
76		2-Bromo-1-(4-fluoro-naphthalen-1-yl)-3-methyl-butan-1-one	δ_H ($CDCl_3$): 1.28 (6H, m), 2.54 (1H, m), 4.98 (1H, d), 7.18 (1H, m), 7.64 (1H, m), 7.70 (1H, m), 7.90 (1H, m), 8.19 (1H, d), 8.57 (1H, d)
77		2-Bromo-1-(5-chloro-naphthalen-1-yl)-2-cyclopropylethanone	δ_H ($CDCl_3$): 0.57 (2H, m), 0.96 (2H, m), 1.83 (1H, m), 4.51 (1H, d), 7.53 (1H, t), 7.62 (1H, m), 7.67 (1H, d), 7.83 (1H, d), 8.33 (1H, d), 8.51 (1H, d)
78		2-Bromo-1-(8-chloro-naphthalen-2-yl)propan-1-one	δ_H ($CDCl_3$): 2.00 (3H, d), 5.52 (1H, q), 7.53 (1H, t), 7.66 (1H, d), 7.82 (1H, d), 7.95 (1H, d), 8.13 (1H, d), 8.99 (1H, s)

Preparation 79: 6-Methylnaphthalen-1-ylamine



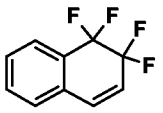
6-Methylnaphthalene-1-carboxylic acid (2.50g, 13.4mmol) was mixed with polyphosphoric acid (~50mL) and hydroxylamine hydrochloride (990mg, 14.2mmol). The mixture was heated to 80°C and stirred for 30min. The temperature was slowly raised to 160°C (froth!) and the stirring was continued for 1hr before the hot solution was added to a water/ice mixture (~1.5L). The resulting solution was washed with EtOAc (200mL) and then made alkaline with solid NaOH. Extraction with EtOAc (3 x 300mL), washing of the combined extracts with water (200mL) and brine (200mL), drying ($MgSO_4$) and concentration *in vacuo* afforded the title compound. δ_H (DMSO): 2.44 (3H, s), 5.63 (2H, br s), 6.60 (1H, d), 7.01 (1H, d), 7.16 (1H, dd), 7.20 (1H, d), 7.50 (1H, s), 7.97 (1H, d); m/z (ES^+) = 158.12 $[M+H]^+$; RT = 2.31 min.

Preparation 80: 1,1-Difluoro-1H-naphthalen-2-one



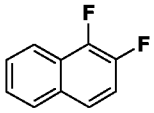
2-Naphthol (4.5g, 31.21mmol) was dissolved in DMF (50mL) and then Selectfluor (22.11g, 62.42mmol) was added slowly. The mixture was stirred for 1hr at rt before the organics were diluted with EtOAc (2 × 50mL) and washed with brine (100mL). The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound. δ_H (DMSO): 6.38 (1H, m), 7.60-7.72 (3H, m), 7.89 (2H, m).

Preparation 81: 1,1,2,2-Tetrafluoro-1,2-dihydronaphthalene



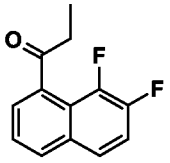
1,1-Difluoro-1H-naphthalen-2-one (Preparation 80, 6.9g, 31.21mmol) was dissolved in toluene (5mL). $BF_3.Et_2O$ (0.44mL) and then Deoxyfluor (10mL, 54.61mmol) were added under an inert atmosphere and the mixture stirred at 60°C for 2hr before being cooled to rt and stirred for a further 16hr. The mixture was cooled to 0°C and methanol (0.5mL) added before $NaHCO_3$ (100mL) was added dropwise. The organic layer was then diluted with toluene (2 × 50mL). The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound. δ_H (DMSO): 6.37-6.40 (1H, m), 7.15 (1H, d), 7.54-7.58 (2H, m), 7.68 (1H, t), 7.82 (1H, d).

Preparation 82: 1,2 Difluoronaphthalene



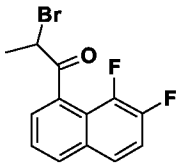
1,1,2,2-Tetrafluoro-1,2-dihydronaphthalene (Preparation 81, 3.9g, 19.29mmol) was dissolved in THF (15mL) and ammonium hydroxide (30mL) and zinc (6.29g, 96.30mmol) were then added. The mixture was stirred at rt under an inert atmosphere for 4hr then filtered and washed with hexane. The washings were filtered through a short silica column with hexane and concentrated *in vacuo* to give the title compound. δ_H (DMSO): 7.58-7.62 (3H, m), 7.81 (1H, m), 8.01 (2H, t).

Preparation 83: 1-(7,8-Difluoronaphthalene-1-yl)propan-1-one



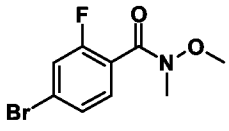
1,2-Difluoronaphthalene (Preparation 82, 1.2g, 7.3 mmol) was dissolved in DCM (15mL) and cooled to -15°C. Aluminium chloride (2.9g, 21.9mmol) was added portionwise and the mixture was stirred at -15 °C for 15min. The solution was cooled to -78°C and propionyl chloride (1.27mL, 14.6mmol) was then added dropwise. The mixture was stirred for 16hr and HCl (20mL) added slowly. The organics were diluted with EtOAc (100mL), washed with 1M HCl solution (2x50mL) dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound. δ_H ($CDCl_3$) 1.25 (3H, t), 2.86 (2H, m), 7.40-7.45 (3H, m), 7.64 (1H,m), 7.90 (1H, d).

Preparation 84: 2-Bromo-1-(7,8-difluoronaphthalene-1-yl)propan-1-one



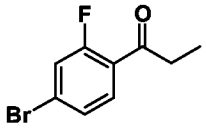
The title compound was prepared from 1-(7,8-difluoronaphthalene-1-yl)propan-1-one (Preparation 83) under similar conditions as described in Preparation 1. δ_H ($CDCl_3$): 2.00 (3H, m), 5.01 (1H, m), 7.25 (1H, q), 7.38 (1H, t), 7.64 (1H, d), 7.73 (1H, m), 7.98 (1H, d).

Preparation 85: 4-Bromo-2-fluoro-N-methoxy-N-methylbenzamide



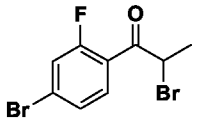
The title compound was prepared from 4-bromo-2-fluorobenzoic acid (9.4g, 42.9mmol) under similar conditions as described in Preparation 27. δ_H ($CDCl_3$): 3.40 (3H, s), 3.60 (3H, s), 7.35 (3H, m).

Preparation 86: 1-(4-Bromo-2-fluorophenyl)propan-1-one



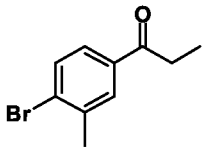
The title compound was prepared from 4-bromo-2-fluoro-N-methoxy-N-methyl-benzamide (Preparation 85, 5.62g, 21.45mmol) under similar conditions as described in Preparation 28. δ_H ($CDCl_3$): 1.20 (3H, t), 3.00 (3H, q), 7.40 (2H, m), 7.80 (1H, t).

Preparation 87: 2-Bromo-1-(4-bromo-2-fluorophenyl)propan-1-one



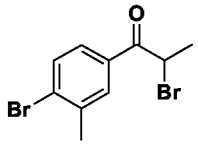
The title compound was prepared from 1-(4-bromo-2-fluorophenyl)propan-1-one (Preparation 86, 1.64g, 7.1mmol) under similar conditions as described in Preparation 29. δ_H ($CDCl_3$): 1.90 (3H, d), 5.30 (1H, q), 7.35 (1H, d), 7.45 (1H, d), 7.80 (1H, t).

Preparation 88: 1-(4-Bromo-3-methylphenyl)propan-1-one



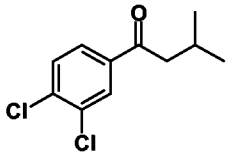
The title compound was prepared from 4-bromo-3-methylbenzonitrile (7.7g, 39.3mmol) under similar conditions as described in Preparation 42. δ_H ($CDCl_3$): 1.20 (3H, t), 3.00 (2H, q), 7.60 (2H, s), 7.80 (1H, s).

Preparation 89: 2-Bromo-1-(4-bromo-3-methylphenyl)propan-1-one



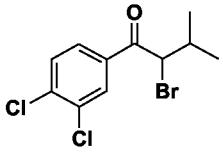
The title compound was prepared from 1-(4-bromo-3-methylphenyl)propan-1-one (Preparation 88, 2.31g, 10.13mmol) under similar conditions as described in Preparation 16. δ_H ($CDCl_3$): 1.97 (3H, d), 2.50 (3H, s), 5.25 (1H, q), 7.70 (2H, m), 7.80 (1H, s).

Preparation 90: 1-(3,4-Dichlorophenyl)-3-methylbutan-1-one



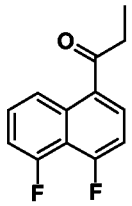
The title compound was prepared from 3,4-dichlorobenzonitrile (5g, 29.1mmol) under similar conditions as described in Preparation 42. δ_H ($CDCl_3$): 1.05 (6H, d), 2.30 (1H, m), 2.80 (2H, d), 7.60 (1H, d), 7.80 (1H, d), 8.05 (1H, s).

Preparation 91: 2-Bromo-1-(3,4-dichlorophenyl)-3-methylbutan-1-one



The title compound was prepared from 1-(3,4-dichlorophenyl)-3-methylbutan-1-one (Preparation 90, 1.6g, 6.9mmol) under similar conditions as described in Preparation 16. δ_H ($CDCl_3$): 1.05 (3H, d), 1.10 (3H, d), 2.50 (1H, m), 4.80 (1H, d), 7.60 (1H, d), 7.80 (1H, d), 8.15 (1H, s).

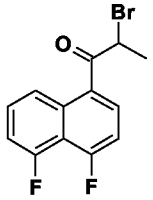
Preparation 92: 1-(4,5-Difluoronaphthalen-1-yl)propan-1-one



A solution of 1,8-difluoronaphthalene (1g, 6.1mmol) (prepared by the procedure of Mallory F. B, *J. Amer. Chem. Soc.* 1974, 96, 3536) and propionyl chloride (0.54mL, 6.16mmol) in DCM (20mL) was added to a suspension of aluminium trichloride (2.44g, 18.3mmol) in DCM (5mL) at -40°C. After 1hr the reaction was warmed to rt and quenched with hydrochloric acid 2N HCl (10mL). The mixture was extracted with EtOAc (3 x 10mL). The combined organic layers were washed with sodium hydroxide (2N, 10mL), dried ($MgSO_4$) and

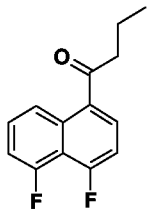
concentrated *in vacuo*. Purification by flash-chromatography on silica gel (eluent: hexane/EtOAc, 98:2) gave the title compound. δ_H ($CDCl_3$): 1.30 (3H, t), 3.10 (2H, q), 7.20 (2H, m), 7.60 (1H, m), 7.90 (1H, m), 8.50 (1H, d).

Preparation 93: 2-Bromo-1-(4,5-difluoronaphthalen-1-yl)propan-1-one



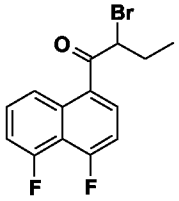
The title compound was prepared from 1-(4,5-difluoronaphthalen-1-yl)propan-1-one (Preparation 92, 0.86g, 3.91mmol) under similar conditions as described in Preparation 16. δ_H (DMSO): 1.80 (3H, d), 5.90 (1H, q), 7.45 (2H, m), 7.80 (1H, d), 8.20 (1H, d), 8.30 (1H, m).

Preparation 94: 1-(4,5-Difluoronaphthalen-1-yl)butan-1-one



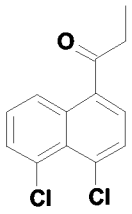
A solution of 1,8-difluoronaphthalene (1.0g, 6.1mmol) and butyryl chloride (0.72g, 6.16mmol) in DCM (20mL) was added to a suspension of aluminium trichloride (2.44g, 18.3mmol) in DCM (5mL) at -40°C. After 1hr the reaction was warmed to rt and quenched with hydrochloric acid 2N HCl (10mL). The mixture was extracted with EtOAc (3 x 10mL). The combined organic layers were washed with sodium hydroxide (2N, 10mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash-chromatography on silica gel (eluent: hexane/EtOAc 98:2) gave the title compound. δ_H ($CDCl_3$): 1.05 (3H, t), 1.80 (2H, m), 3.00 (2H, t), 7.20 (2H, m), 7.60(1H, m), 7.90 (1H, m), 8.50 (1H, d).

Preparation 95: 2-Bromo-1-(4,5-difluoronaphthalen-1-yl)butan-1-one



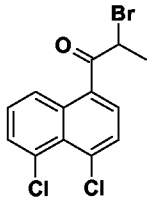
The title compound was prepared from 1-(4,5-difluoronaphthalen-1-yl)butan-1-one (Preparation 94, 0.8g, 3.41mmol) under similar conditions as described in Preparation 16. δ_H ($CDCl_3$): 1.20 (3H, t), 2.2 (1H, m), 2.4 (1H, m), 5.1 (1H, t), 7.2 (2H, m), 7.6 (1H, m), 7.9 (1H, m), 8.3 (1H, d).

Preparation 96: 1-(4,5-Dichloronaphthalen-1-yl)propan-1-one



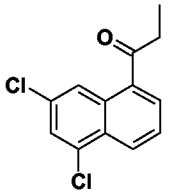
The title compound was prepared from 1,8-dichloronaphthalene (0.8g, 4.1mmol) (prepared by the procedure of Hodgson *J.Chem. Soc.* 1947, 80) under similar conditions as described in Preparation 92. δ_H ($CDCl_3$): 1.30 (3H, t), 3.00 (2H, q), 7.50 (1H, t), 7.60-7.80 (3H, m), 8.40 (1H, d).

Preparation 97: 2-Bromo-1-(4,5-dichloronaphthalen-1-yl)propan-1-one



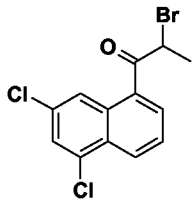
The title compound was prepared from 1-(4,5-dichloronaphthalen-1-yl)propan-1-one (Preparation 96, 0.84g, 2.53mmol) under similar conditions as described in Preparation 16. δ_H ($CDCl_3$): 2.00 (3H, d), 5.25 (1H, q), 7.45 (1H, t), 7.60-7.80 (3H, m), 8.20 (1H, d).

Preparation 98: 1-(5,7-Dichloronaphthalen-1-yl)propan-1-one



5,7-Dichloronaphthalene-1-carboxylic acid (1.5g, 6.25mmol) (Sestanj, Kazimir Eur. Pat. Appl. (1982), EP 59596 A1 19820908), oxalyl chloride (0.6mL, 6.87mmol), DMF (1 drop) were combined in DCM (50mL) and stirred for 12hr. The mixture was concentrated *in vacuo*, solubilised in THF (40mL) and cooled to -78°C. Iron(III)acetylacetonate (66mg, 0.19mmol) was added followed by dropwise addition of ethylmagnesium bromide (2.7mL, 3M solution, 8.12mmol). After 1hr the reaction was warmed to rt and saturated ammonium chloride solution (30mL) was added. The mixture was extracted with DCM (3 x 50mL) and the combined organics dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash-chromatography on silica gel (eluent: hexane/ethyl acetate 99:1) gave the title compound. δ_H ($CDCl_3$): 1.10 (3H, t), 3.00 (2H, q), 7.60 (2H, m), 7.09 (1H, d), 8.40 (1H, d), 8.50 (1H, s).

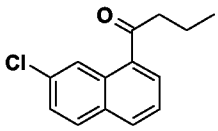
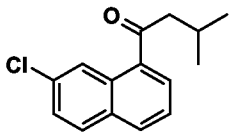
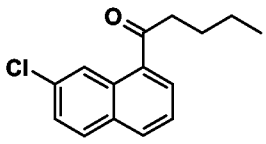
Preparation 99: 2-Bromo-1-(5,7-dichloronaphthalen-1-yl)propan-1-one

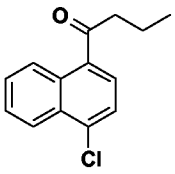
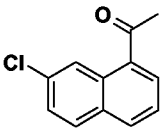
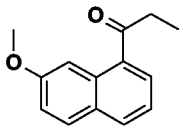
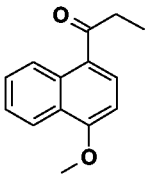


The title compound was prepared from 1-(5,7-dichloronaphthalen-1-yl)propan-1-one (Preparation 98, 0.719g, 2.84mmol) under similar conditions as described in Preparation 16. δ_H ($CDCl_3$): 2.00 (3H, d), 5.40 (1H, q), 7.70 (2H, m), 8.00 (1H, d), 8.42 (1H, s), 8.50 (1H, d).

Preparations 100 – 106:

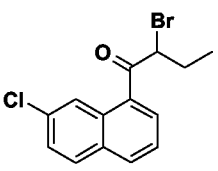
The procedure described in Preparation 18 was used to prepare the compounds of Preparations 100 – 104 and the procedure described in Preparation 23 was used to prepare the compounds of Preparations 105 and 106.

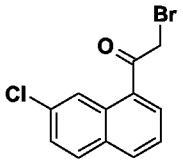
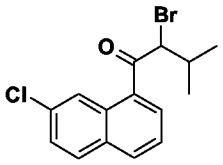
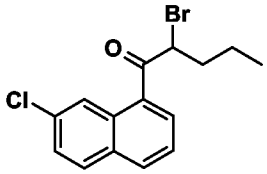
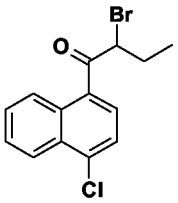
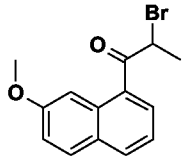
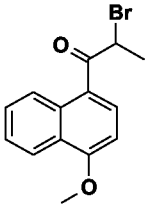
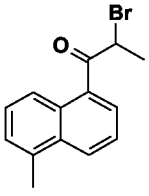
Prep	Structure	Name	LCMS	^{1}H-NMR data
100		1-(7-Chloronaphthalen-1-yl)butan-1-one	m/z (ES^+) = 233.10 $[M+H]^+$; RT = 4.18 min	δ_H ($CDCl_3$): 1.08 (3H, t), 1.86 (2H, m), 3.07 (2H, t), 7.50-7.56 (2H, m), 7.84 (1H, d), 7.95-8.00 (2H, m), 8.74 (1H, s)
101		1-(7-Chloronaphthalen-1-yl)-3-methylbutan-1-one	m/z (ES^+) = 247.08 $[M+H]^+$; RT = 4.32 min	δ_H ($CDCl_3$): 1.07 (6H, d), 2.34-2.41 (1H, m), 2.96 (2H, d), 7.51-7.56 (2H, m), 7.84 (1H, d), 7.94 (1H, d), 7.98 (1H, d), 8.72 (1H, s)
102		1-(7-Chloronaphthalen-1-yl)pentan-1-one	m/z (ES^+) = 247.09 $[M+H]^+$; RT = 4.39 min	δ_H ($CDCl_3$): 1.00 (3H, t), 1.45-1.50 (2H, m), 1.77-1.85 (2H, m) 3.08 (2H, t), 7.49-7.54 (2H, m), 7.82 (1H, d), 7.96 (2H, m), 8.73 (1H, s)

103		1-(4-Chloronaphthalen-1-yl)butan-1-one	m/z (ES^+) = 233.14 $[M+H]^+$; RT = 4.09 min	δ_H ($CDCl_3$): 1.04 (3H, t), 1.83 (2H, m), 3.01 (2H, t), 7.60 (1H, d), 7.64-7.66 (2H, m), 7.74 (1H, d), 8.34-8.37 (1H, m), 8.56 (1H, m)
104		(7-Chloronaphthalen-1-yl)ethanone	_	δ_H ($CDCl_3$): 2.77 (3H, s), 7.50-7.55 (2H, m), 7.82 (1H, d), 7.99-8.04 (2H, m), 8.92 (1H, s)
105		1-(7-Methoxynaphthalen-1-yl)propan-1-one	_	δ_H ($CDCl_3$): 1.33 (3H, t), 3.14 (2H, q), 3.99 (3H, s), 7.22-7.25 (1H, m), 7.36-7.40 (1H, m), 7.79 (1H, d), 7.94-7.99 (2H, m), 8.30 (1H, s)
106		1-(4-Methoxynaphthalen-1-yl)propan-1-one	m/z (ES^+) = 215.10 $[M+H]^+$; RT = 3.76 min	δ_H ($CDCl_3$): 1.31 (3H, t), 3.09 (2H, q), 4.07 (3H, s), 6.79 (1H, d), 7.53-7.57 (1H, t), 7.62-7.68 (1H, t), 7.97 (1H, d), 8.35 (1H, d), 8.93 (1H, d)

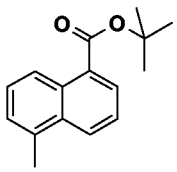
Preparations 107 – 114:

The procedure described in Preparation 16 was used to prepare the compounds of Preparations 107 – 114 from the appropriate ketone.

Prep	**Structure**	**Name**	**^{1}H NMR data**
107		2-Bromo-1-(7-chloro-naphthalen-1-yl)butan-1-one	δ_H ($CDCl_3$): 1.17 (3H, t), 2.18-2.25 (1H, m), 2.34-2.41 (1H, m), 5.17 (1H, t), 7.51-7.55 (2H, m), 7.84 (1H, d), 7.97 (1H, d) 8.02 (1H, d), 8.62 (1H, s)

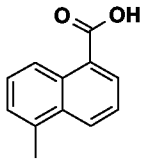
108		2-Bromo-1-(7-chloro-naphthalen-1-yl)ethanone	δ_H ($CDCl_3$): 4.59 (2H, s), 7.52-7.57 (2H, m), 7.84 (1H, d), 8.02-8.06 (2H, m), 8.80 (1H, s)
109		2-Bromo-1-(7-chloro-naphthalen-1-yl)-3-methyl-butan-1-one	δ_H ($CDCl_3$): 1.16 (3H, d), 1.28 (3H, d), 2.54-2.59 (1H, m), 5.03 (1H, d), 7.52-7.56 (2H, m), 7.85 (1H, d), 7.96 (1H, d), 8.03 (1H, d), 8.59 (1H, s)
110		2-Bromo-1-(7-chloro-naphthalen-1-yl)pentan-1-one	δ_H ($CDCl_3$): 1.06 (3H, t), 1.51-1.69 (2H, m), 2.18-2.34 (2H, m), 5.24 (1H, t), 7.55 (2H, m), 7.85 (1H, d), 7.98 (1H, d), 8.03 (1H, d), 8.61 (1H, s)
111		2-Bromo-1-(4-chloro-naphthalen-1-yl)butan-1-one	δ_H ($CDCl_3$): 1.16 (3H, t), 2.15-2.23 (1H, m), 2.32-2.39 (1H, m), 5.11 (1H, m), 7.62 (1H, d), 7.68-7.72 (2H, m), 7.78 (1H, d), 8.37-8.39 (1H, m), 8.46-8.48 (1H, m)
112		2-Bromo-1-(7-methoxy-naphthalen-1-yl)propan-1-one	δ_H ($CDCl_3$): 2.01 (3H, d), 4.00 (3H, s), 5.47 (1H, q), 7.24-7.27 (1H, m), 7.40 (1H, t), 7.81 (1H, d), 7.97-8.00 (2H, m), 8.12 (1H, s)
113		2-Bromo-1-(4-methoxy-naphthalen-1-yl)propan-1-one	δ_H ($CDCl_3$): 1.99 (3H, d), 4.11 (3H, s), 5.46 (1H, q), 6.84 (1H, d), 7.57 (1H, t), 7.68 (1H, t), 8.04 (1H, d), 8.37 (1H, d), 8.81 (1H, d)
114		2-Bromo-1-(5-methyl-naphthalen-1-yl)propan-1-one	δ_H ($CDCl_3$): 2.01 (3H, d), 2.76 (3H, s), 5.38 (1H, q), 7.44 (1H, d), 7.51-7.60 (2H, m), 7.85 (1H, d), 8.22-8.25 (2H, m)

Preparation 115: 5-Methylnaphthalene-1-carboxylic acid tert-butyl ester



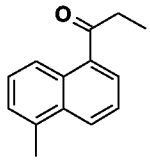
To a solution of 5-bromo-l-naphthalene-1-carboxylic acid tert-butyl ester (*J. Org. Chem.;* 2002; *67*(4); 1171-1177) (1.00g, 3.26mmol) in THF (10mL) at -78 °C was added butyl lithium (2.5M, 1.56mL) over a period of 2min. After stirring for 40min methyl iodide (0.55g) was added and the reaction allowed to warm to rt over 1.5hr. The reaction was quenched water (10mL) and partitioned between water and diethyl ether (3 x 50mL). The combined extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by flash-chromatography (eluent: isohexane/EtOAc : 98:2) gave the title compound. δ_H ($CDCl_3$): 1.70 (9H, s), 2.78 (3H, s), 7.37 (d, 1H), 7.46-7.54 (m, 2H), 8.04 (d, 1H), 8.18 (d, 1H), 8.66 (d, 1H); m/z (ES^+) = 242.23 $[M+H]^+$; RT = 2.86 min.

Preparation 116: 5-Methylnaphthalene-1-carboxylic acid



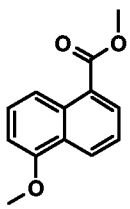
5-Methylnaphthalene-1-carboxylic acid tert-butyl ester (Preparation 115, 1.37g, 4.45mmol) was dissolved in DCM (10mL) and TFA (3mL) was added. After stirring for 16hr, the reaction was concentrated in vacuo to give the title compound. δ_H (DMSO): 2.71 (3H, s), 7.45 (1H, d), 7.53 (1H, m), 7.64 (1H, m), 8.13 (1H, d), 8.28 (1H, d), 8.68 (1H, d).

Preparation 117: 1-(5-Methylnaphthalen-1-yl)propan-1-one



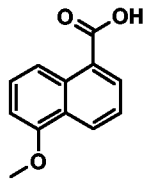
The title compound was prepared from 5-methylnaphthalene-1-carboxylic acid (Preparation 116) *via* acid chloride under similar conditions as described in Preparation 98. δ_H ($CDCl_3$): 1.20 (3H, t), 2.63 (3H, s), 2.97 (2H, q), 7.29 (1H, d), 7.35-7.46 (2H, m), 7.69 (1H, d), 8.07 (1H, d), 8.22 (1H, d); m/z (ES^+) = 199.07 $[M+H]^+$; RT = 3.86 min.

Preparation 118: 5-Methoxynaphthalene-1-carboxylic acid methyl ester



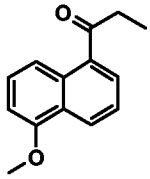
The title compound was prepared according to the method of Can. J. Chem. (2004), 240-253.

Preparation 119: 5-Methoxynaphthalene-1-carboxylic acid



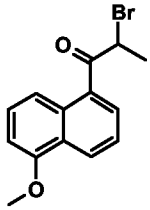
5-Methoxynaphthalene-1-carboxylic acid methyl ester (Preparation 118, 1.43g) was dissolved in methanol (30mL) and 2M sodium hydroxide solution added and stirred for 16hr then concentrated *in vacuo*. 1M NaOH (50mL) was added, washed EtOAc (50mL), acidified using concentrated HCl then extracted into DCM (3 x 50mL). The combined organic fractions were dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound. δ_H (DMSO): 4.00 (3H, s), 7.06 (1H, d), 7.60 (2H, m), 8.16 (1H, d), 8.42 (2H, m), 13.10 (1H, s).

Preparation 120: 1-(5-Methoxynaphthalen-1-yl)propan-1-one



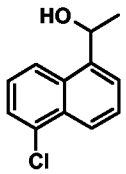
The title compound was prepared from 5-methoxynaphthalene-1-carboxylic acid (Preparation 119) *via* the acid chloride as described in Preparation 98. δ_H (DMSO): 1.18 (3H, t), 3.10 (2H, q), 3.98 (3H, s), 7.08 (1H, d), 7.55 (2H, m), 7.96 (1H, d), 8.04 (1H, d), 8.40 (1H, d).

Preparation 121: 2-Bromo-1-(5-methoxynaphthalen-1-yl)propan-1-one



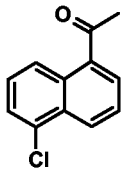
The title compound was prepared from 1-(5-methoxynaphthalen-1-yl)propan-1-one (Preparation 120) under conditions described in Preparation 16. δ_H ($CDCl_3$): 2.01 (3H, d), 4.04 (3H, s), 5.45 (1H, q), 7.14 (1H, d), 7.48 (2H, m), 7.98 (1H, d), 8.10 (1H, d), 8.40 (1H, d).

Preparation 122: 1-(5-Chloronaphthalen-1-yl)ethanol



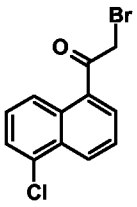
The title compound was prepared from 5-chloronaphthalene-1-carbaldehyde (Preparation 55) with methyl magnesium chloride under similar conditions as described in Preparation 187. δ_H ($CDCl_3$): 1.75 (3H, d), 5.70 (1H, q), 7.45 (1H, m), 7.42 (1H, t), 7.60 (2H, m), 7.78 (2H, d), 8.06 (1H, d), 8.27 (1H, d).

Preparation 123: 1-(5-Chloronaphthalen-1-yl)ethanone



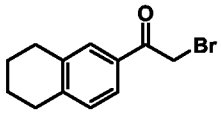
The title compound was prepared from 1-(5-chloronaphthalen-1-yl)ethanol (Preparation 122) under similar conditions as described in Preparation 129. δ_H ($CDCl_3$): 2.75 (3H, s), 7.55 (1H, t), 7.72 (2H, m), 8.04 (1H, m), 8.56 (1H, d), 8.70 (1H, d).

Preparation 124: 2-Bromo-1-(5-Chloronaphthalen-1-yl)ethanone



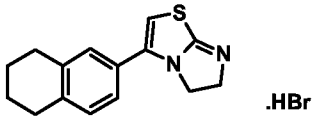
The title compound was prepared from 1-(5-chloronaphthalen-1-yl)ethanone (Preparation 123) under similar conditions as described in Preparation 19. δ_H ($CDCl_3$): 4.60 (2H, d), 7.63 (1H, m), 7.74 (3H, m), 8.04 (2H, m).

Preparation 125: 2-Bromo-1-(5,6,7,8-tetrahydronaphthalen-2-yl)ethanone



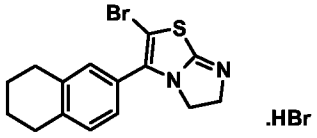
The title compound was prepared from 1-(5,6,7,8-tetrahydronaphthalen-2-yl)ethanone under similar conditions as described in Preparation 44. δ_H (DMSO): 1.77 (4H, m), 2.80 (4H, m), 4.87 (2H, s), 7.24 (1H, d), 7.72 (2H, m).

Preparation 126: 3-(5,6,7,8-Tetrahydronaphthalen-2-yl)-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide



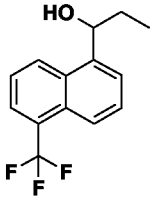
The title compound was prepared from 2-bromo-1-(5,6,7,8-tetrahydronaphthalen-2-yl)ethanone (Preparation 125) and 2-imidazolidinethione under similar conditions as described in Example 66. δ_H (DMSO): 1.77 (4H, m), 2.80 (4H, m), 4.30 (2H, t), 4.53 (2H, t), 6.95 (1H, s), 7.24 (1H, d), 7.34 (2H, d), 9.61 (1H, br); m/z (ES^+) = 257.07 $[M+H]^+$; RT = 2.51 min.

Preparation 127: 2-Bromo-3-(5,6,7,8-tetrahydronaphthalen-2-yl)-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide



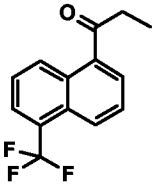
The title compound was prepared from 3-(5,6,7,8-tetrahydronaphthalen-2-yl)-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide (Preparation 126) under similar conditions as described in Example 11. δ_H (DMSO): 1.79 (4H, m), 2.80 (4H, m), 4.23 (2H, m), 4.32 (2H, m), 7.29 (3H, m), 9.60 (1H, br).

Preparation 128: 1-(5-Trifluoromethylnaphthalen-1-yl)propan-1-ol



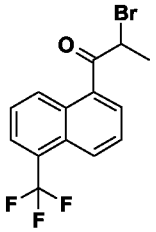
1-Bromo-5-trifluoromethylnaphthalene (4.0g, 14.54mmol) was dissolved in THF (80mL) and cooled under inert atmosphere at -78°C. n-BuLi (6.4mL, 2.5M solution) was then added dropwise over 10min and the solution allowed to stir for further 2hr. Propionaldehyde (3.2mL, 43.62mmol) was then added slowly over 5min and the mixture allowed to stir for 1hr. The cooling bath was removed and the mixture was stirred for 16hr at rt before a 2M HCl solution (50mL) was added. The mixture was stirred for 5min then the aqueous layer was extracted with EtOAc (3 x 60mL). The combined organic layers were washed (brine), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash-chromatography on silica gel (eluent: hexane/EtOAc : 5/1 then 4/1) gave the title compound. δ_H ($CDCl_3$): 1.05 (3H, t), 1.90-2.05 (2H, m), 5.45 (1H, m), 7.55 (1H, t), 7.65 (1H, t), 7.78 (1H, d), 7.90 (1H, d), 8.18 (1H, d), 8.40 (1H, d).

Preparation 129: 1-(5-Trifluoromethylnaphthalen-1-yl)propan-1-one



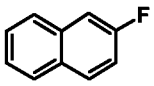
1-(5-Trifluoromethylnaphthalen-1-yl)propan-1-ol (Preparation 128, 2.5g, 9.832mmol) was dissolved in DCM (80mL) and Dess-Martin reagent was added portionwise under inert atmosphere at rt. The mixture was stirred for 16hr at rt before sat. $NaHCO_3$ solution (80mL) was added, extracted with DCM, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash-chromatography on silica gel (eluent: DCM) gave the title compound. δ_H (DMSO): 1.20 (3H, t), 3.17 (2H, q), 7.75 (1H, t), 7.85 (1H, t), 8.10 (1H, d), 8.20 (1H, d), 8.30 (1H, br d), 8.60 (1H, d).

Preparation 130: 2-Bromo-1-(5-trifluoromethylnaphthalen-1-yl)propan-1-one



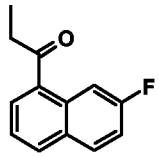
The title compound was prepared from 1,1-(5-trifluoromethylnaphthalen-1-yl)propan-1-one (Preparation 129) under similar conditions as described in Preparation 16. δ_H (DMSO): 1.95 (3H, d), 5.95 (1H, q), 7.80-7.90 (2H, m), 8.15 (1H, d), 8.25-8.35 (2H, m), 8.50 (1H, d).

Preparation 131: 2-Fluoronaphthalene



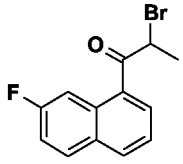
6-Fluoronaphthalene-1-carboxylic acid (15.0g, 78.87mmol) was suspended in Quinidine (35mL) and Cu(0) powder (8.8g, 138.03mmol) was added under inert atmosphere and the reaction was heated under reflux for 48hr. The mixture was allowed to cool to rt and filtered, the filter cake was washed with EtOH (20mL) then ^{i}hexane (20mL). The washings were combined and concentrated *in vacuo*. Organics were diluted with EtOAc (200mL), washed with 2M HCl solution (2 x 50mL) then brine (100mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash-chromatography on silica gel (eluent: hexane) gave the title compound. δ_H (DMSO): 7.40-7.60 (3H, m), 7.72 (1H, d), 7.90-8.10 (3H, m).

Preparation 132: 1-(7-Fluoronaphthalen-1-yl)propan-1-one



2-Fluoronaphthalene (Preparation 131, 8.0g, 55.10mmol) was dissolved in DCM (120mL) under inert atmosphere and the reaction was cooled at 0°C. $AlCl_3$ (22.8g, 170.82mmol) was then added in one portion and the mixture stirred for 15min. The mixture was then cooled at -78°C and propionyl chloride (9.6mL, 110.2mmol) was added slowly over 15min. The mixture was then stirred for 16hr and allowed over this period to reach rt. Organics were diluted with EtOAc (200mL), washed with 1M HCl solution (2 x 50mL) dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound. δ_H (DMSO): 1.15 (3H, t), 3.15 (2H, q), 7.52 (1H, m), 7.61 (1H, m), 8.15 (1H, m), 8.25 (2H, m), 8.35 (1H, m).

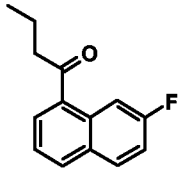
Preparation 133: 2-Bromo-1-(7-fluoronaphthalen-1-yl)propan-1-one



The title compound was prepared from 1-(7-fluoronaphthalen-1-yl)propan-1-one (Preparation 132, 11.7g, 55.10mmol) under similar conditions as described in Preparation 16.

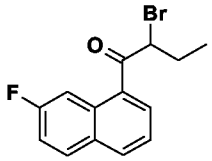
δ_H (DMSO): 1.90 (3H, m), 5.95 (1H, q), 7.55-7.70 (2H, m), 8.10-8.20 (2H, m), 8.25-8.35 (2H, m).

Preparation 134: 1-(7-Fluoronaphthalen-1-yl)butan-1-one



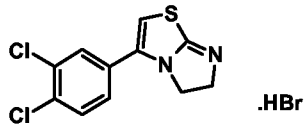
The title compound was prepared from 2-fluoronaphthalene (Preparation 131, 1.0g, 6.88mmol) and butyryl chloride under similar conditions as described in Preparation 18. δ_H (DMSO): 0.95 (3H, t), 1.70 (2H, m), 3.10 (2H, t), 7.55 (1H, m), 7.65 (1H, m), 8.15 (1H, m), 8.22 (2H, m), 8.30 (1H, m).

Preparation 135: 2-Bromo-1-(7-fluoronaphthalen-1-yl)butan-1-one



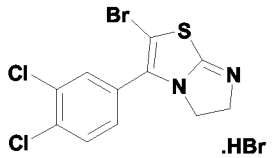
The title compound was prepared from 1-(7-fluoronaphthalen-1-yl)butan-1-one (Preparation 134, 1.47g, 6.88mmol) under similar conditions as described in Preparation 16. δ_H (DMSO): 1.10 (3H, t), 2.05 (1H, m), 2.15 (1H, m), 5.80 (1H, t), 7.55-7.70 (2H, m), 8.10-8.20 (2H, m), 8.25-8.35 (2H, m).

Preparation 136: 3-(3,4-Dichlorophenyl)-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide



The title compound was prepared from 2-bromo-1-(3,4-dichlorophenyl)ethanone and 2-imidazolidinethione under similar conditions as described in Example 1. δ_H (DMSO): 4.30 (2H, m), 4.50 (2H, m), 7.20 (1H, s), 7.60 (1H, d), 7.80 (1H, d), 7.95 (1H, s), 9.60 (1H, br s); m/z (ES^+) = 271.03 $[M+H]^+$; RT = 2.70 min.

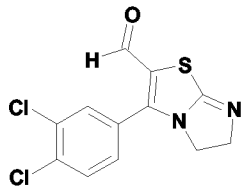
Preparation 137: 2-Bromo-3-(3,4-dichlorophenyl)-5,6-dihydroimidazo[2,1-b]thiazole Hydrobromide



3-(3,4-Dichlorophenyl)-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide (Preparation 136, 5.0g, 13.85mmol) was suspended in DCM (100.0mL) and sat. $NaHCO_3$ solution (100mL)

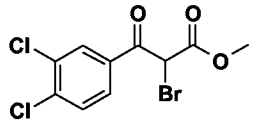
was added. The mixture was stirred vigorously for 15min and the two phases separated; the organic layer was dried by using a phase-separation cartridge and cooled at 0°C by using an ice bath. Bromine (0.71mL, 13.85mmol) was then added over 5min and the mixture was stirred at 0°C under an inert atmosphere for 1hr. After few minutes a yellow precipitate formed, the ice bath was removed and the mixture stirred for 16hr. The suspension was filtered and the solid washed with diethyl ether (30.0mL) to afford the title compound. δ_H (DMSO): 4.35-4.15 (4H, m), 7.60 (1H, d), 7.90 (2H, m), 9.55 (1H, br s).

Preparation 138: 3-(3,4-Dichlorophenyl)-5,6-dihydroimidazo[2,1-b]thiazole-2-carbaldehyde



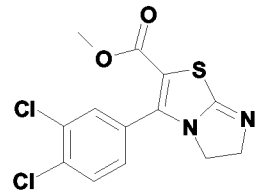
Ethyl magnesium bromide 2.0 M solution in diethyl ether (10.2mL, 20.36mmol) was added to a solution of THF (50.0mL) under inert atmosphere and the mixture cooled at 0°C by using an ice bath. 2-Bromo-3-(3,4-dichlorophenyl)-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide (Preparation 137, 3.0g, 6.79mmol) was added portionwise to the above solution over 5min. After stirring for 2hr, DMF (2.10mL, 27.15mmol) was added to the solution and the mixture stirred for 16hr. Saturated ammonium chloride (50mL) was added slowly to the mixture and then partitioned between EtOAc (150mL) and saturated sodium chloride (100mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound. δ_H (DMSO): 3.90 (2H, m), 4.20 (2H, m), 7.75 (1H, d), 7.85 (1H, d), 8.10 (1H, s), 9.20 (1H, s).

Preparation 139: 2-Bromo-3-(3,4-dichlorophenyl)-3-oxopropionic acid methyl ester



The title compound was prepared from 3-(3,4-dichlorophenyl)-3-oxopropionic acid methyl ester (1.0g, 4.05mmol) under similar conditions as described in Preparation 16. δ_H (DMSO): 3.80 (3H, s), 6.75 (1H, s), 7.90 (1H, d), 8.00 (1H, d), 8.30 (1H, s).

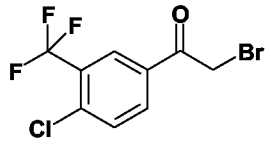
Preparation 140: 3-(3,4-Dichlorophenyl)-5,6-dihydroimidazo[2,1-b]thiazole-2-carboxylic acid methyl ester



The title compound was prepared from 2-bromo-3-(3,4-dichlorophenyl)-3-oxo-propionic acid methyl ester (Preparation 139, 1.40g, 4.05mmol) and 2-imidazolidinethione

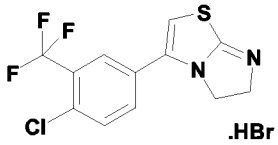
under similar conditions as described in Example 1. δ_H (DMSO): 3.70 (3H, s), 4.30 (4H, m), 7.65 (1H, d), 7.90 (1H, m), 8.00 (1H, s).

Preparation 141: 2-Bromo-1-(4-chloro-3-trifluoromethylphenyl)ethanone



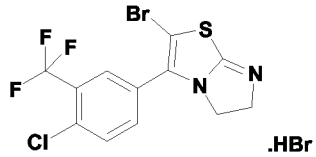
The title compound was prepared from 1-(4-chloro-3-trifluoromethylphenyl)ethanone (5.0g, 22.46mmol) under similar conditions as described in Preparation 16. δ_H (DMSO): 4.40 (2H, s), 7.70 (1H, d), 8.10 (1H, d), 8.35 (1H, s).

Preparation 142: 3-(4-Chloro-3-trifluoromethylphenyl)-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide



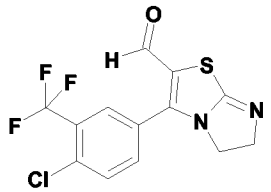
The title compound was prepared from 2-bromo-1-(4-chloro-3-trifluoromethyl-phenyl)ethanone (Preparation 141, 6.44g, 21.32mmol) and 2-imidazolidinethione under similar conditions as described in Example 1. δ_H (DMSO): 4.30 (2H, m), 4.55 (2H, m), 7.30 (1H, s), 7.95 (2H, m), 8.10 (1H, s), 9.65 (1H, br s); m/z (ES^+) = 304.93 $[M+H]^+$; RT = 2.44 min.

Preparation 143: 2-Bromo-3-(4-chloro-3-trifluoromethylphenyl)-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide



The title compound was prepared from 3-(4-chloro-3-trifluoromethylphenyl)-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide (Preparation 142, 5.0g, 12.99mmol) and bromine under similar conditions as described in Example 11. δ_H (DMSO): 4.35-4.20 (4H, m), 7.95 (1H, d), 8.05 (1H, d), 8.10 (1H, s), 9.60 (1H, br s).

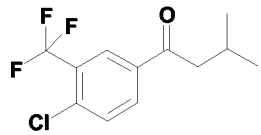
Preparation 144: 3-(4-Chloro-3-trifluoromethylphenyl)-5,6-dihydroimidazo[2,1-b]thiazole-2-carbaldehyde



The title compound was prepared from 2-bromo-3-(4-chloro-3-trifluoromethylphenyl)-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide (Preparation 143, 1.5g, 3.39mmol) under

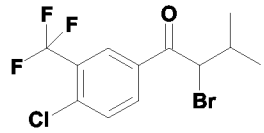
similar conditions as described in Preparation 138. δ_H (DMSO): 3.90 (2H, m), 4.20 (2H, m), 7.95 (1H, m), 8.10 (1H, d), 8.25 (1H, s), 9.20 (1H, s).

Preparation 145: 1-(4-Chloro-3-trifluoromethylphenyl)-3-methylbutan-1-one



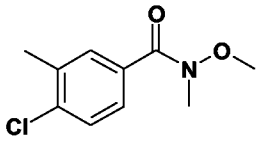
Iso-butyl magnesium bromide 2.0 M solution in diethyl ether (24.0mL, 48.16mmol) was slowly added over 5min to a solution of 4-chloro-3-trifluoromethylbenzonitrile (3.3g, 16.05mmol) in THF (50.0mL) at 0°C under inert atmosphere. The mixture was stirred for 1hr before removing the ice bath and stirred for further 16hr. Saturated ammonium chloride (30mL) was added slowly to the mixture and then partitioned between EtOAc (150mL) and saturated sodium chloride (100mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound. δ_H (DMSO): 0.95 (6H, m), 2.15 (1H, m), 3.00 (2H, m), 7.90 (1H, d), 8.30 (2H, m).

Preparation 146: 2-Bromo-1-(4-chloro-3-trifluoromethylphenyl)-3-methylbutan-1-one



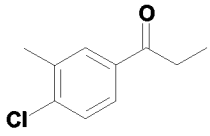
The title compound was prepared from 1-(4-chloro-3-trifluoromethylphenyl)-3-methylbutan-1-one (Preparation 145, 4.0g, 15.15mmol) under similar conditions as described in Preparation 16. δ_H (DMSO): 1.00 (3H, d), 1.15 (3H, d), 2.35 (1H, m), 5.80 (1H, d), 7.95 (1H, d), 8.40 (2H, m).

Preparation 147: 4-Chloro-N-methoxy-3,N-dimethylbenzamide



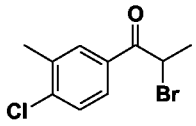
The title compound was prepared from 4-chloro-3-methylbenzoic acid (10.0g, 58.62mmol) under similar conditions as described in Preparation 27. δ_H ($CDCl_3$): 2.42 (3H, s), 3.40 (3H, s), 3.60 (3H, s), 7.40 (1H, d), 7.50 (1H, d), 7.60 (1H, s).

Preparation 148: 1-(4-Chloro-3-methylphenyl)propan-1-one



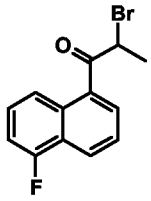
The title compound was prepared from 4-chloro-N-methoxy-3,N-dimethylbenzamide (Preparation 147, 5.0g, 23.40mmol) under similar conditions as described in Preparation 28. δ_H (DMSO): 1.10 (3H, t), 2.40 (3H, s), 3.05 (2H, q), 7.60 (1H, d), 7.80 (1H, d), 8.00 (1H, s).

Preparation 149: 2-Bromo-1-(4-chloro-3-methylphenyl)propan-1-one



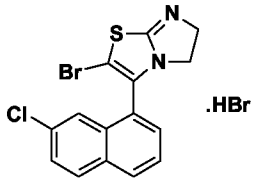
The title compound was prepared from 1-(4-chloro-3-methylphenyl)propan-1-one (4.0g, 21.90mmol) under similar conditions as described in Preparation 16. δ_H (DMSO): 1.80 (3H, d), 2.42 (3H, s), 5.85 (1H, q), 7.62 (1H, d), 7.90 (1H, d), 8.10 (1H, s).

Preparation 150: 2-Bromo-1-(5-fluoronaphthalen-1-yl)propan-1-one



To a stirred solution of 1-(5-fluoronaphthalen-1-yl)propan-1-one (Preparation 183, 0.8g, 3.96mmol) in THF (30mL) was added PTAT (1.49g, 3.96mmol) and the reaction was stirred at rt for 72hr. The reaction mixture was filtered and the filtrate was concentrated *in vacuo* to afford the title compound. δ_H ($CDCl_3$): 2.00 (3H, d), 5.40 (1H, q), 7.23 (1H, d), 7.60 (2H, m), 7.98 (1H, d), 8.20 (1H, d), 8.40 (1H, d).

Preparation 151: 2-Bromo-3-(7-chloronaphthalen-1-yl)-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide

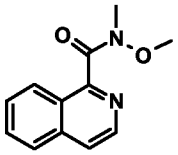
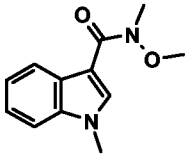
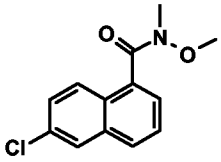
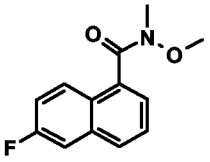
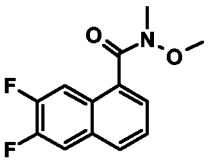
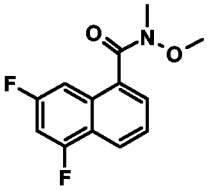


The title compound was prepared from 3-(7-chloronaphthalen-1-yl)-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide (Example 44) under similar conditions as described in Example 11. δ_H (DMSO): 3.90 (1H, m), 4.20 (3H, m), 7.71 (1H, d), 7.80 (3H, m), 8.05 (1H, s), 8.17 (1H, d), 8.26 (1H, d), 9.60 (1H, s).

Preparations 152 – 157:

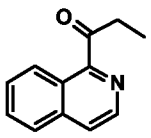
The following compounds were prepared by the indicated method.

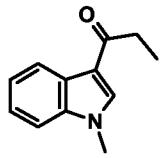
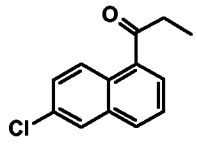
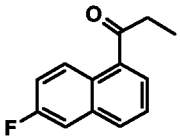
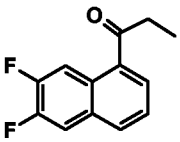
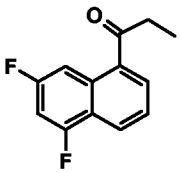
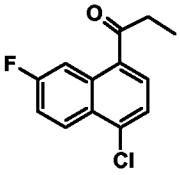
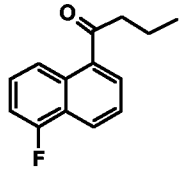
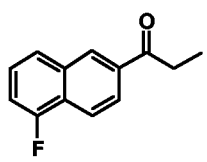
Prep	Structure	Name	Method	RT min	m/z (ES^+)

152		Isoquinoline-1-carboxylic acid methoxymethyl-amide	Prep 48	2.74	217.11 $[M+H]^+$
153		1-Methyl-1H-indole-3-carboxylic acidmethoxy-methylamide	Prep 48	2.97	219.09 $[M+H]^+$
154		6-Chloro-naphthalene-1-carboxylic acid methoxymethyl-amide	Prep 48	3.30	250.05 $[M+H)^+$
155		6-Fluoro-naphthalene-1-carboxylic acid methoxymethyl-amide	*via* acid chloride	3.03	234.09 $[M+H]^+$
156		6,7-Difluoro-naphthalene-1-carboxylic acid methoxymethyl-amide	*via* acid chloride	3.09	252.08 $[M+H]^+$
157		5,7-Difluoro-naphthalene-1-carboxylic acid methoxymethyl-amide	*via* acid chloride	3.17	252.10 $[M+H)^+$

Preparations 158 – 166:

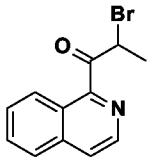
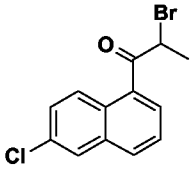
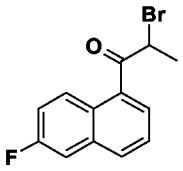
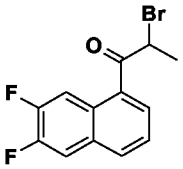
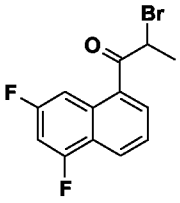
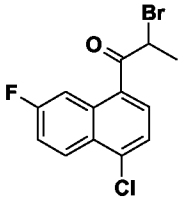
The following compounds were prepared by the indicated method.

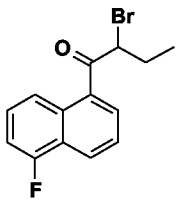
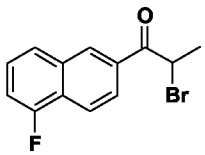
Prep	**Structure**	**Name**	**Method**	**^{1}H-NMR data**
158		1-Isoquinolin-1-ylpropan-1-one	Prep 28	δ_H (CD_3OD): 1.23 (3H, t), 3.29 (2H, q), 7.68 (1H, dd), 7.76 (1H, dd), 7.90-7.96 (2H, m), 8.51 (1H, dd), 8.70 (1H, d)

159		1-(1-Methyl-1H-indol-3-yl)-propan-1-one	Prep 28	δ_H (DMSO): 1.14 (3H, t), 2.86 (2H, q), 3.88 (3H, s), 7.24, 7.29 (2H, 2dd), 7.54 (1H, d), 8.22 (1H, d), 8.34 (1H, s)
160		1-(6-Chloro-naphthalen-1-yl)-propan-1-one	Prep 28	δ_H (DMSO): 1.16 (3H, t), 3.14 (2H, q), 7.63 (1H, dd), 7.67 (1H, dd), 8.11-8.16 (3H, m), 8.50 (1H, d)
161		1-(6-Fluoro-naphthalen-1-yl)-propan-1-one	Prep 28	δ_H (DMSO): 1.16 (3H, t), 3.14 (2H, q), 7.53 (1H, m), 7.66 (1H, dd), 7.83 (1H, dd), 8.07 (1H, d), 8.13 (1H, d), 8.54 (1H, dd)
162		1-(6,7-Difluoro-naphthalen-1-yl)-propan-1-one	Prep 28	δ_H (DMSO): 1.08 (3H, t), 3.09 (2H, q), 7.59 (1H, dd), 8.03 (1H, dd), 8.09 (1H, d), 8.14 (1H, d), 8.46 (1H, dd)
163		1-(5,7-Difluoro-naphthalen-1-yl)-propan-1-one	Prep 28	δ_H (DMSO): 1.16 (3H, t), 3.17 (2H, q), 7.59 (1H, m), 7.72 (1H, dd), 8.17 (1H, dd), 8.28 (1H, d), 8.31 (1H, d)
164		1-(4-Chloro-7-fluoro-naphthalen-1-yl)-propan-1-one	Prep 18	δ_H (DMSO): 1.16 (3H, t), 3.15 (2H, q), 7.69 (1H, m), 7.81 (1H, d), 8.19 (1H, d), 8.36-8.38 (2H, m)
165		1-(5-Fluoro-naphthalen-1-yl)-butan-1-one	Prep 183	δ_H (DMSO): 0.97 (3H, t), 1.70 (2H, m), 3.10 (2H, t), 7.43 (1H, dd), 7.62 (1H, m), 7.73 (1H, dd), 8.15 (1H, d), 8.24 (1H, d), 8.28 (1H, d)
166		1-(5-Fluoro-naphthalen-2-yl)-propan-1-one	Prep 183	δ_H ($CDCl_3$): 1.33 (3H, t), 3.17 (2H, q), 7.30 (1H, dd), 7.50 (1H, m), 7.78 (1H, d), 8.12 (1H, d), 8.19 (1H, d), 8.51 (1H, s)

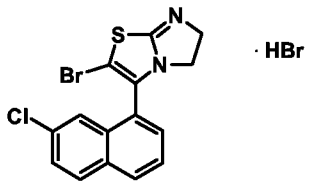
Preparations 167 – 175:

The following compounds were prepared by the indicated methods.

Prep	Structure	Name	Method	^{1}H-NMR data
167		2-Bromo-1-isoquinolin-1-yl-propan-1-one	Prep 11 Method A	δ_H (DMSO): 1.91 (3H, d), 6.23 (1H, q), 7.85 (1H, dd), 7.91 (1H, dd), 8.14 (1H, d), 8.20 (1H, d), 8.70 (2H, m)
168		2-Bromo-1-(1-methyl-1H-indol-3-yl)-propan-1-one	Prep 19	δ_H (DMSO): 1.80 (3H, d), 3.91 (3H, s), 5.56 (1H, q), 7.31 (2H, 2dd), 7.59 (1H, d), 8.22 (1H, d), 8.55 (1H, s)
169		2-Bromo-1-(6-chloro-naphthalen-1-yl)propan-1-one	Prep 19	δ_H (DMSO): 1.88 (3H, d), 5.91 (1H, q), 7.68-7.73 (2H, m), 8.18-8.23 (3H, m), 8.33 (1H, d)
170		2-Bromo-1-(6-fluoro-naphthalen-1-yl)propan-1-one	Prep 19	δ_H (DMSO): 1.89 (3H, d), 5.91 (1H, q), 7.59 (1H, m), 7.67 (1H, dd), 7.86 (1H, dd), 8.17-8.19 (2H, m), 8.38 (1H, dd)
171		2-Bromo-1-(6,7-difluoro-naphthalen-1-yl)propan-1-one	Prep 19	δ_H (DMSO): 1.89 (3H, d), 5.96 (1H, q), 7.72 (1H, dd), 8.17 (1H, dd), 8.24 (1H, d), 8.31-8.37 (2H, m)
172		2-Bromo-1-(5,7-difluoro-naphthalen-1-yl)propan-1-one	Prep 19	δ_H (DMSO): 1.89 (3H, d), 5.95 (1H, q), 7.63 (1H, m), 7.75 (1H, dd), 7.97 (1H, d), 8.33 (1H, d), 8.40 (1H, d)
173		2-Bromo-1-(4-chloro-7-fluoro-naphthalen-1-yl)propan-1-one	Prep 19	δ_H (DMSO): 1.88 (3H, d), 5.92 (1H, q), 7.75 (1H, dd), 7.88 (1H, d), 8.16 (1H, dd), 8.30 (1H, d), 8.42 (1H, dd)

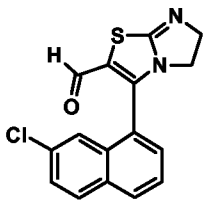
174		2-Bromo-1-(5-fluoro-naphthalen-1-yl)butan-1-one	Prep 19	δ_H (DMSO): 1.10 (3H, t), 2.07 (2H, m), 5.75 (1H, dd), 7.48 (1H, dd), 7.68 (1H, m), 7.76 (1H, dd), 8.13 (1H, d), 8.28 (1H, d), 8.34 (1H, d)
175		2-Bromo-1-(5-fluoro-naphthalen-2-yl)propan-1-one	Prep 19	δ_H ($CDCl_3$): 2.00 (3H, d), 5.47 (1H, q), 7.32 (1H, dd), 7.53 (1H, ddd), 7.81 (1H, d), 8.14 (1H, dd), 8.22 (1H, d), 8.60 (1H, s)

Preparation 176: 2-Bromo-3-(7-chloronaphthalen-1-yl)-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide



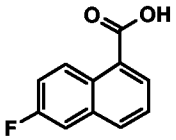
3-(7-Chloronaphthalen-1-yl)-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide (Example 51, 5.30g, 14.4 mmol) was distributed between saturated $NaHCO_3$ solution (200mL) and EtOAc (200mL). Separation of both layers was followed by further extraction of the aqueous layer with EtOAc (2 x 100mL). The combined extracts were washed with brine (100mL), dried ($MgSO_4$) and concentrated. The crystalline residue was dissolved in DCM, cooled to 0°C and treated with bromine (0.75mL, 14.6 mmol). After removal of the ice bath the thick suspension was stirred for 10hr at rt. The precipitate (the title compound) was collected and washed with iso-hexane/DCM : 1/1 before being dried *in vacuo*. δ_H (DMSO): 3.93 (1H, m), 4.21-4.26 (3H, m), 7.70 (1H, dd), 7.76 (1H, dd), 7.82 (1H, d), 8.03 (1H, d), 8.17 (1H, d), 8.26 (1H, d), 9.64 (1H, br s); m/z (ES^+) = 365.00, 366.98 $[M+H]^+$; RT = 2.64 min.

Preparation 177: 3-(7-Chloronaphthalen-1-yl)-5,6-dihydroimidazo[2,1-b]thiazole-2-carbaldehyde



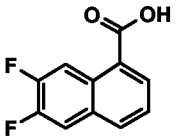
2-Bromo-3-(7-chloronaphthalen-1-yl)-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide (Preparation 176, 4.57g, 12.4 mmol) in THF (100mL) at 0°C. After 2hr DMF (5.6mL, 64.6mmol) was added and the mixture was stirred at rt for 12hr before being distributed between EtOAc (300mL) and saturated NH_4Cl solution (100mL). The organic layer was separated, washed (sat $NaHCO_3$ solution, then brine) and dried ($MgSO_4$), then concentration *in vacuo* gave the title compound. δ_H (DMSO): 3.57 (2H, m), 4.37 (2H, m), 7.59-7.66 (3H, m), 7.77 (1H, d), 7.96 (1H, d), 8.08 (1H, dd), 9.14 (1H, s); m/z (ES^+) = 315.00 $[M+H]^+$; RT = 2.49 min.

Preparation 178: 6-Fluoronaphthalene-1-carboxylic acid



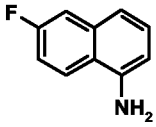
Anhydrous aluminium chloride (65g, 487mmol) was added carefully to a suspension of furan-2-carboxylic acid (25g, 260mmol) in fluorobenzene (250mL) at 0°C. After 1hr the ice bath was removed and the mixture was slowly heated to 75°C and kept at this temperature for a further 12hr. The mixture was added to a 2N HCl solution (1.5L) before extraction into ether (3 x 300mL). The combined ether layers were washed with water (250mL) and then extracted with saturated $NaHCO_3$ solution (3 x 250mL). The alkaline solution was made acidic with conc. HCl solution and re-extracted with EtOAc (3 x 250mL). Concentration *in vacuo* after drying ($MgSO_4$) gave a solid residue which was stirred in the presence of toluene (50mL) for 12hr. Filtration gave the title compound. δ_H (DMSO): 7.56 (1H, ddd), 7.66 (1H, dd), 7.84 (1H, dd), 8.16 (2H, m), 8.97 (1H, dd), 13.27 (1H, br s); m/z (ES^-) = 189.19 $[M-H]^+$; RT = 3.14 min.

Preparation 179: 6,7-Difluoronaphthalene-1-carboxylic acid



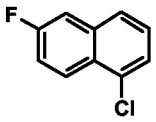
The title compound was prepared from 1,2-difluorobenzene using similar conditions as described in Preparation 178. δ_H (DMSO): 2.31 (3H, s), 7.66 (1H, dd), 8.13 (1H, dd), 8.21 (1H, d), 8.27 (1H, d), 8.91 (1H, dd), 13.70 (1H, br s).

Preparation 180: 6-Fluoronaphthalen-1-ylamine



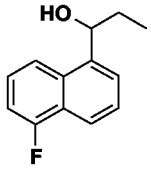
Sodium azide (10.2g, 157mmol) was added in small portions over a period of 5hr to a mixture of 6-fluoronaphthalene-1-carboxylic acid (Preparation 178, 20.0g, 105mmol) in $CHCl_3$ (400mL) and conc. H_2SO_4 (100mL) at 40°C. After separation of the $CHCl_3$ layer the aqueous layer was added onto ice (1kg). The resulting suspension was made alkaline with conc. NH_4OH solution under cooling and then extracted with Et_2O (3 x 250mL). Washing of the combined extracts (brine), drying ($MgSO_4$) and concentration *in vacuo* afforded the title compound. δ_H (DMSO): 5.82 (2H, br s), 6.66 (1H, d), 7.06 (1H, d), 7.23-7.27 (2H, m), 7.49 (1H, dd), 8.16 (1H, dd); m/z (ES^+) = 162.06 $[M+H]^+$; RT = 2.57 min.

Preparation 181: 1-Chloro-6-fluoronaphthalene



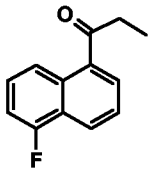
A solution of sodium nitrite (2.16g, 31.3mmol) in water (50mL) was added over 15min to a suspension of 6-fluoronaphthalen-1-ylamine (Preparation 180, 5.50g, 34.2mmol) in dilute HCl (100mL, 6M) at 0°C. The resulting mixture was stirred for 1hr in the cold and then added to a suspension of copper(I)chloride in dilute HCl (100mL, 6M). After 2hr of vigorous stirring water (1L) was added to the suspension which was extracted with ether (3 x 200mL). Drying of the combined extracts ($MgSO_4$) and subsequent concentration *in vacuo* gave a residue which was purified by flash-chromatography on silica gel (eluent: hexane / EtOAc : 6 / 1) to give the title compound. δ_H (DMSO): 7.33 (1H, dd), 7.38 (1H, ddd), 7.46 (1H, d), 7.63 (1H, dd), 7.72 (1H, d), 8.01 (1H, dd).

Preparation 182: 1-(5-Fluoronaphthalen-1-yl)propan-1-ol



n-Butyllithium (5.5mL, 2.5 M solution in hexane) was added slowly to a solution of 1-bromo-5-fluoronaphthalene (M.S. Newman et al, *J. Org. Chem.*, 1959, 24, 509-512) (2.40g, 10.7mmol) in THF (50mL) at -78°C. After stirring for 1hr propionaldehyde (2.5mL, 34.7mmol) was added to the green solution and the CO_2/IPA bath was removed. After stirring for a further 90min the mixture was added to sat. NH_4Cl solution (250mL). Extraction with EtOAc (3 x 100mL), drying of the combined extracts ($MgSO_4$) and subsequent concentration *in vacuo* gave a residue which was purified by flash-chromatography on silica gel (eluent: hexane / EtOAc : 4 / 1) to give the title compound. δ_H (DMSO): 0.93 (3H, t), 1.72 (2H, m), 5.24 (1H, m), 5.37 (1H, d), 7.33 (1H, dd), 7.53 (1H, m), 7.64 (1H, dd), 7.74 (1H, d), 7.98 (1H, d), 8.01 (1H, d).

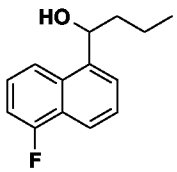
Preparation 183: 1-(5-Fluoronaphthalen-1-yl)propan-1-one



To a solution of 1-(5-fluoronaphthalen-1-yl)propan-1-ol (Preparation 182, 1.62g, 7.93mmol) in dry DCM (75mL) was added Dess-Martin periodinane (3.40g, 8.02mmol). After stirring for 2hr at rt alkaline sodium thiosulfate solution was added (8.0g Na_2SO_3 dissolved in 30mL saturated $NaHCO_3$ solution) and the emulsion was vigorously stirred for an additional 10min before further diluted with water (~100mL). Extraction with EtOAc (3 x 50mL), washing of the combined extracts with saturated sodium hydrogen carbonate (50mL) and brine (50mL). After drying ($MgSO_4$) and concentration *in vacuo* the residue was purified by flash-chromatography on silica gel (eluent: hexane / EtOAc : 4 / 1) to give the title compound. δ_H

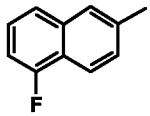
(DMSO): 1.17 (3H, t), 3.14 (2H, q), 7.43 (1H, dd), 7.61 (1H, m), 7.73 (1H, dd), 8.16 (1H, d), 8.26 (2H, m).

Preparation 184: 1-(5-Fluoronaphthalen-1-yl)butan-1-ol



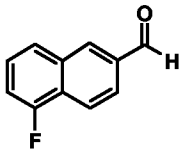
The title compound was prepared from 1-bromo-5-fluoronaphthalene and butyraldehyde under similar conditions as described in Preparation 182. δ_H (DMSO): 0.91 (3H, t), 1.44, 1.55 (4H, 2m), 5.30 (1H, m), 5.37 (1H, d), 7.33 (1H, dd), 7.54 (1H, m), 7.62 (1H, dd), 7.75 (1H, d), 7.98 (1H, d), 8.01 (1H, d).

Preparation 185: 1-Fluoro-6-methylnaphthalene



A solution of sodium nitrite (1.84g, 26.7mmol) in water (20mL) was added in portions under vigorous stirring to a suspension of 6-methylnaphthalen-1-ylamine (Preparation 79, 4.10g, 26.1mmol) in dilute HCl (40mL, 6M) at 0°C. After 2hr tetrafluoroboric acid (9.5mL, 48%) was added and the mixture was stirred for a further 30min in the cold. The precipitate was collected, washed with aqueous tetrafluoroboric acid (50mL, 20%) and water (50mL) and dried *in vacuo* at rt for 3 days. The powdered diazonium salt was heated to 160°C for 15min. After cooling to rt the residue was taken up in ether (300mL) and washed with $NaHCO_3$ solution and brine. Drying ($MgSO_4$) and concentration *in vacuo* gave a residue which was purified by flash-chromatography on silica gel (eluent: hexane / EtOAc : 9 / 1) to give the title compound. Diazonium salt: δ_H (DMSO): 2.62 (3H, s), 7.98-8.05 (2H, m), 8.22 (1H, s), 8.43 (1H, d), 8.83 (1H, d), 9.13 (1H, d); Title compound: δ_H (DMSO): 2.51 (3H, s), 7.25 (1H, dd), 7.45-7.50 (1H, m), 7.69 (1H, d), 7.79 (1H, s), 7.97 (1H, d).

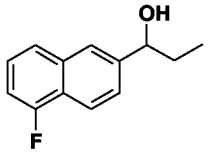
Preparation 186: 5-Fluoronaphthalene-2-carbaldehyde



A mixture of selenium dioxide (2.07g, 18.7mmol) and 1-fluoro-6-methylnaphthalene (Preparation 185, 734mg, 4.58mmol) in dioxane (20mL) was heated under reflux for 7 days. The mixture was diluted with EtOAc (200mL), filtered and washed with water (50mL) and brine (50mL). Drying ($MgSO_4$) and concentration *in vacuo* gave a residue which was purified by flash-chromatography on silica gel (eluent: hexane / EtOAc : 4 / 1) to give the title compound.

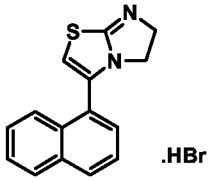
δ_H ($CDCl_3$): 7.27 (1H, dd), 7.46 (1H, ddd), 7.74 (1H, d), 7.93 (1H, dd), 8.13 (1H, d), 8.29 (1H, s), 10.11 (1H, s).

Preparation 187: 1-(5-Fluoronaphthalen-2-yl)propan-1-ol



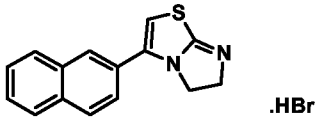
Ethyl magnesium chloride (0.8mL, 2 M solution in ether) was added to a solution of 5-fluoronaphthalene-2-carbaldehyde (Preparation 186, 117mg, 0.672mmol) in THF at -78°C. The CO_2/IPA bath was removed and the mixture was stirred for 12hr at rt before sat. NH_4Cl solution (50mL) was added. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 30mL). The combined organic layers were washed (brine), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash-chromatography on silica gel (eluent: hexane / EtOAc : 4 / 1) gave the title compound. δ_H ($CDCl_3$): 0.99 (3H, t), 1.91 (2H, dq), 4.82 (1H, t), 7.16 (1H, dd), 7.43 (1H, ddd), 7.56 (1H, dd), 7.65 (1H, d), 7.84 (1H, s), 8.13 (1H, d).

Example 1: 3-Naphthalen-1-yl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide



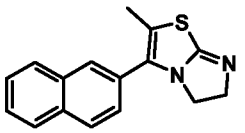
2-Bromo-1-naphthalen-1-yl-ethanone (Preparation 1, 0.643g, 2.58mmol) and 2-imidazolidinethione (0.264g, 2.58mmol) were dissolved in EtOH (15mL) and AcOH (7mL) and the reaction heated under reflux for 16hr. The reaction mixture was cooled to rt and the precipitate filtered, washed with Et_2O (2 x 20mL) and dried to afford the title compound. δ_H (DMSO): 4.06 (2H, m), 4.26 (2H, m), 7.03 (1H, s), 7.62 – 7.70 (4H, m), 7.98 (1H, m), 8.07 (1H, m), 8.14 (1H, m), 9.66 (1H, br s); m/z (ES^+) = 253 $[M+H]^+$; RT = 2.44 min.

Example 2: 3-Naphthalen-2-yl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide



2-Bromo-1-naphthalen-2-ylethanone (0.25g, 1mmol) and 2-imidazolidinethione (0.1g, 1mmol) were dissolved in EtOH (8mL) and AcOH (4mL) and the reaction heated under reflux for 4hr. The reaction mixture was then cooled to rt and the precipitate was filtered, washed with Et_2O (2 x 20mL) and dried *in vacuo* to afford the title compound. δ_H (DMSO): 4.06 (2H, m), 4.26 (2H, m), 7.03 (1H, s), 7.62 – 7.70 (4H, m), 7.98 (1H, m), 8.07 (1H, m), 8.14 (1H, m), 9.66 (1H, br s); m/z (ES^+) = 253 $[M+H]^+$; RT = 2.44 min.

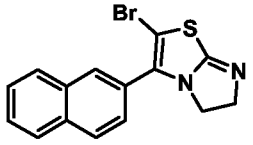
Example 3: 2-Methyl-3-naphthalen-2-yl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide



.HBr

2-Bromo-1-naphthalen-2-ylpropan-1-one (Preparation 3, 3.74g, 14.2mmol) and 2-imidazolidinethione (1.45g, 14.2mmol) were dissolved in AcOH (20mL) and EtOH (40mL) and heated to reflux for 16hr. The reaction mixture was cooled to rt and the precipitated solid was filtered, washed with Et_2O (2 x 40mL) and dried to afford the title compound. δ_H (DMSO): 2.31 (3H, s), 4.25 (2H, m), 4.37 (2H, m), 7.64 (3H, m), 8.04 (2H, m), 8.11 – 8.15 (2H, m), 9.60 (1H, br s); m/z (ES^+) = 267.1 $[M+H]^+$; RT = 2.42min.

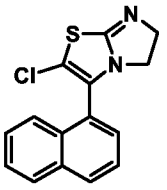
Example 4: 2-Bromo-3-naphthalen-2-yl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide



.HBr

3-Naphthalen-2-yl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide (Example 2, 1g, 3.0mmol) was partitioned between saturated Na_2CO_3 solution (30mL) and DCM (3 x 30mL). The combined organic fractions were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in DCM (10mL) and cooled to 0°C. Bromine (154µL, 3.0mmol) was added and the reaction stirred at 0°C for 30min then warmed to rt and stirred for 1hr. The reaction mixture was diluted with Et_2O (30mL) and the solid filtered and washed with Et_2O (2 x 30mL) to afford the title compound. δ_H (DMSO): 4.25 (2H, m), 4.38 (2H, m), 7.66 (3H, m), 8.04 (1H, d), 8.08 (1H, d), 8.14 (1H, d), 8.21 (1H, s), 9.62 (1H, br s); m/z (ES^+) = 331 $[M+H]^+$; RT = 2.86min.

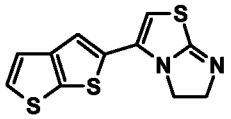
Example 5: 2-Chloro-3-naphthalen-1-yl-5,6-dihydroimidazo[2,1-b]thiazole hydrochloride



.HCl

3-Naphthalen-1-yl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide (Example 1, 1g, 3.0mmol) was partitioned between saturated $NaHCO_3$ solution (40mL) and DCM (2 x 50mL). The combined organic fractions were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in acetone (70mL) and cooled to 0°C. Benzyltrimethylammonium tetrachloroiodate (1.28g, 3.1mmol) was added portionwise over 5min and the reaction stirred at 0°C for 1hr, then rt for 2hr. The reaction mixture was filtered and washed with MeCN:Et_2O (1:2, 2 x 25mL), then Et_2O (2 x 25mL). The solid was triturated with hot ^{i}PrOH to afford the title compound. δ_H (DMSO): 3.91 (1H, m), 4.19 (3H, m), 7.71 (4H, m), 7.91 (1H, m), 8.10 (1H, m), 8.20 (1H, m), 10.42 (1H, br s); m/z (ES^+) = 286 $[M+H]^+$; RT = 2.56min.

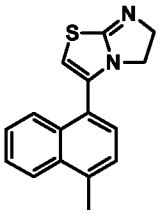
Example 6: 3-Thieno[2,3-b]thiophen-2-yl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide



.HBr

2-Bromo-1-thieno[2,3-b]thiophen-2-ylethanone (Preparation 6, 420mg, 1.61mmol) and 2-imidazolidinethione (164mg, 1.61mmol) were heated to reflux in AcOH (5mL) and EtOH (10mL) for 48hr. The reaction mixture was cooled to rt and the precipitated solid was filtered and washed with Et_2O to afford the title compound. δ_H (DMSO): 4.34 (2H, m), 4.64 (2H, m), 7.05 (1H, s), 7.38 (1H, d), 7.72 (1H, d), 7.75 (1H, s), 9.75 (1H, br s); m/z (ES^+) = 265 $[M+H]^+$; RT = 2.54min.

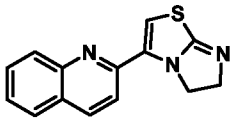
Example 7: 3-(4-Methylnaphthalen-1-yl)-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide



.HBr

A stirred solution of 2-bromo-1-(4-methylnaphthalen-1-yl)ethanone (Preparation 7, 0.54g, 1.9mmol) and imidazolidine-2-thione (0.2g, 1.9mmol) in EtOH (10mL) was heated to reflux and AcOH (5mL) was added. The reaction was stirred at reflux for 24hr then cooled to 0°C. The solid was collected by filtration to afford the title compound. δ_H (DMSO): 2.73 (3H, s), 4.01 (2H, m), 4.24 (2H, m), 6.94 (1H, s), 7.51 (1H, d), 7.57 (1H, d), 7.67 (2H, m), 7.97 (1H, d), 8.16 (1H, d), 9.59 (1H, br s); m/z (ES^+) = 267 $[M+H]^+$; RT = 2.90min.

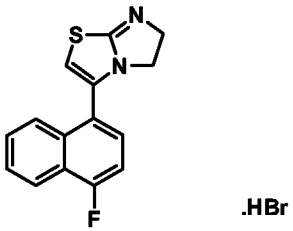
Example 8: 2-(5,6-Dihydroimidazo[2,1-b]thiazol-3-yl)quinoline hydrobromide



.HBr

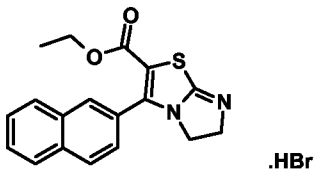
To a solution of 2-bromo-1-quinolin-2-ylethanone (Preparation 11, 98mg, 0.392mmol) in a mixture of EtOH and AcOH (2:1, 15mL) was added imidazolidine-2-thione (42mg, 0.411mmol) and the resulting suspension heated under reflux for 12hr. On cooling in an ice bath a precipitate formed spontaneously, which was collected and washed with EtOAc to give the title compound. δ_H (DMSO): 4.39 (2H, dd), 5.07 (2H, dd), 7.72 (1H, m), 7.83 (1H, s), 7.88 (1H, m), 8.08 (2H, m), 8.16 (1H, d), 8.55 (1H, d), 9.69 (1H, br s); m/z (ES^+) = 254.09 $[M+H]^+$; RT = 2.64 min.

Example 9: 3-(4-Fluoronaphthalen-1-yl)-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide



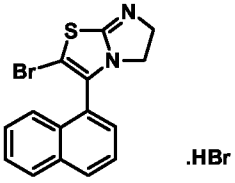
2-Bromo-1-(4-fluoronaphthalen-1-yl)ethanone (Preparation 12, 0.60g, 2.25mmol) and 2-imidazolidinethione (0.23g, 2.25mmol) were heated to reflux in AcOH (7mL) and EtOH (14mL) for 16hr. The reaction mixture was cooled to rt and the precipitated solid was filtered and washed with Et_2O to afford the title compound. δ_H (DMSO): 4.06 (2H, m), 4.27 (2H, m), 7.04 (1H, s), 7.52 (1H, m), 7.75 (3H, m), 8.05 (1H, m), 8.19 (1H, m), 9.68 (1H, br s); m/z (ES^+) = 271 $[M+H]^+$; RT = 1.77min.

Example 10: 3-Naphthalen-2-yl-5,6-dihydroimidazo[2,1-b]thiazole-2-carboxylic acid ethyl ester hydrobromide



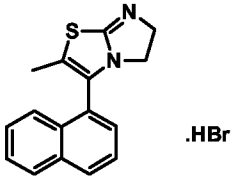
2-Bromo-3-naphthalen-2-yl-3-oxopropionic acid ethyl ester (Preparation 14, 5.58g, 17.4mmol) and 2-imidazolidinethione (1.78g, 17.4mmol) were heated to reflux in AcOH (25mL) and EtOH (50mL) for 16hr. The solvent was removed *in vacuo* and the residue dissolved in MeCN (80mL) and Et_2O (5mL). The precipitated solid was filtered and washed with Et_2O (2 x 40mL) to afford the title compound. δ_H (DMSO): 1.03 (3H, t), 4.12 (2H, q), 4.29 (4H, m), 7.66 (3H, m), 8.04 (2H, d), 8.08 (1H, d), 8.24 (1H, s), 10.10 (1H, br s); m/z (ES^+) = 325 $[M+H]^+$; RT = 2.69min.

Example 11: 2-Bromo-3-naphthalen-1-yl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide



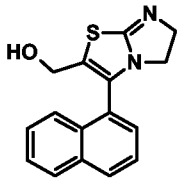
3-Naphthalen-1-yl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide (Example 1, 5g, 15.0mmol) was partitioned between saturated $NaHCO_3$ solution (70mL) and DCM (2 x 75mL). The combined organic fractions were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in DCM (50mL) and cooled to 0°C. A solution of bromine (0.77mL, 15.0mmol) in DCM (7mL) was added dropwise, the reaction warmed to rt and stirred for 3hr. The reaction mixture was diluted with Et_2O (50mL) and the precipitate was filtered, washed with MeCN:Et_2O (2:1, 3 x 50mL) and then Et_2O (2 x 30mL) to afford the title compound. δ_H (DMSO): 3.90 (1H, m), 4.17 (3H, m), 7.66 (2H, m), 7.72 (2H, m), 7.89 (1H, m), 8.10 (1H, m), 8.20 (1H, d), 9.66 (1H, br s); m/z (ES^+) = 331 $[M+H]^+$; RT = 2.44min.

Example 12: 2-Methyl-3-naphthalen-1-yl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide



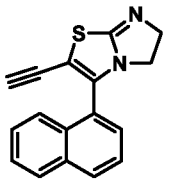
2-Bromo-1-naphthalen-1-ylpropanone (Preparation 16, 4.28g, 16.3mmol) and imidazolidine-2-thione (1.64g, 16.3mmol) were dissolved in EtOH (15mL) and AcOH (7.5mL) and the reaction heated to reflux for 4hr. The reaction mixture was cooled overnight and the precipitate collected by filtration, washed with acetonitrile (20mL) and Et_2O (2 x 20mL) then dried to afford the title compound. δ_H (DMSO): 2.05 (3H, s), 3.82 (1H, m), 4.07 (1H, m), 4.28 (2H, m), 7.65 – 7.70 (4H, m), 7.81 (1H, m), 8.05 (1H, m), 8.18 (1H, m), 9.58 (1H, br s); m/z (ES^+) = 266.99 $[M+H]^+$; RT = 2.62 min.

Example 13: 3-Naphthalen-1-yl-5,6-dihydroimidazo[2,1-b]thiazol-2-yl methanol



3-Naphthalen-1-yl-5,6-dihydroimidazo[2,1-b]thiazole-2-carbaldehyde (Preparation 17, 281mg, 1.0mmol) was suspended in MeOH (10mL) under an argon atmosphere and cooled to 0°C. Sodium borohydride (57mg, 1.5mmol) was added and the reaction stirred at 0°C for 2hr, then rt for 16hr. Water (40mL) was added and the precipitate was filtered, washed with water (2 x 20mL) and dried under vacuum at 40°C to afford the title compound. δ_H (DMSO): 3.32 (2H, s), 3.98 (4H, m), 5.19 (1H, br s), 7.59 (4H, m), 7.85 (1H, m), 8.04 (2H, m); m/z (ES^+) = 283 $[M+H]^+$; RT = 2.26min.

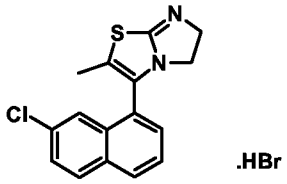
Example 14: 2-Ethynyl-3-naphthalen-1-yl-5,6-dihydroimidazo[2,1-b]thiazole



N-Butyllithium (0.256mL, 0.64mmol) was added to diisopropylamine (89.4 µL, 0.64mmol) in THF at 0°C. After 10min the solution was cooled to -78°C and trimethylsilyldiazomethane (0.51mL, 1.02mmol, 2M in THF) was added. After 1hr 3-naphthalen-1-yl-5,6-dihydroimidazo[2,1-b]thiazole-2-carbaldehyde (Preparation 17, 150mg, 0.535mmol) in THF (10mL) was added dropwise and the reaction allowed to warm to rt. After heating under reflux for 3hr the solution was allowed to cool and partitioned between DCM (3 x 25mL) and water (20mL). The organic layer was separated, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified on silica gel by elution with acetone:hexane

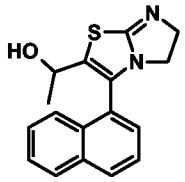
(1:1) to afford the title compound. δ_H ($CDCl_3$) 7.85 (3H, m), 7.42 (4H, m), 4.10 (2H, m), 3.40 (2H, m), 2.90 (1H, s); m/z (ES^+) = 277.01 $[M-H]^+$; RT = 2.45min.

Example 15: 3-(7-Chloronaphthalen-1-yl)-2-methyl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide



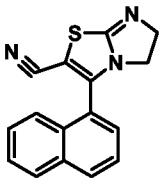
To a solution of 2-bromo-1-(7-chloronaphthalen-1-yl)propan-1-one (Preparation 19, 1.45g, 4.87mmol) in a mixture of EtOH and AcOH (1:1, 100mL) was added imidazolidine-2-thione (580mg, 5.68mmol) and the resulting suspension heated under reflux for 12hr. The solvent was removed *in vacuo* and the residue distributed between dilute NaOH solution (300mL) and EtOAc (100mL). Separation of both layers was followed by further extraction of the aqueous layer with EtOAc (2 x 100mL). The combined extracts were washed with brine (100mL), dried ($MgSO_4$) and concentrated. Purification by flash-chromatography on silica gel (eluent DCM:MeOH, 10:1) gave the free base of the title compound. The free base was taken up in MeOH (150mL) and treated with hydrobromic acid (30% in acetic acid, 1.0mL). After removal of the solvent the residue was stirred in a mixture of EtOAc and acetonitrile (10:1, 50mL) until the title compound crystallised out and was collected by filtration. δ_H (DMSO): 2.06 (3H, s), 3.89 (1H, ddd), 4.06-4.27 (3H, m), 7.69 (1H, dd), 7.72-7.78 (2H, m), 7.94 (1H, s), 8.16 (1H, d), 8.23 (1H, dd), 9.55 (1H, br s); m/z (ES^+) = 300.96 $[M+H]^+$; RT = 2.56 min.

Example 16: 1-(3-Naphthalen-1-yl-5,6-dihydroimidazo[2,1-b]thiazol-2-yl)ethanol



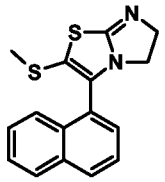
3-Naphthalen-1-yl-5,6-dihydroimidazo[2,1-b]thiazole-2-carbaldehyde (Preparation 17, 200mg, 0.71mmol) was dissolved in THF (25mL) under an argon atmosphere and cooled to 0°C. Methylmagnesium bromide (3.0M in Et_2O, 0.71mL, 2.14mmol) was added and the reaction stirred at 0°C for 1hr, then rt for 16hr. The reaction was quenched with water (40mL) and extracted into EtOAc (3 x 40mL). The combined organic fractions were dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound. δ_H ($CDCl_3$): 1.24, 1.35 (3H, 2d), 2.52 (1H, br s), 3.30 (2H, m), 4.03 (2H, m), 4.49 (1H, m), 7.27 – 7.53 (4H, m), 7.73 – 7.90 (3H, m); m/z (ES^+) = 297 $[M+H]^+$; RT = 2.26min.

Example 17: 3-Naphthalen-1-yl-5,6-dihydroimidazo[2,1-b]thiazole-2-carbonitrile



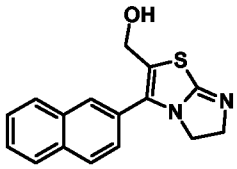
3-Naphthalen-1-yl-5,6-dihydroimidazo[2,1-b]thiazole-2-carbaldehyde (Preparation 17, 300mg, 1.07mmol) and hydroxylamine hydrochloride (97mg, 1.39mmol) were dissolved in formic acid (10mL) and heated to 100°C for 16hr. The reaction mixture was diluted with Et_2O (50mL) and the solid filtered and washed with Et_2O (2 x 30mL). The solid was purified by chromatography on silica gel eluting with MeOH:DCM (3:97) to afford the title compound. δ_H ($CDCl_3$): 3.50 (1H, m), 3.61 (1H, m), 4.28 (2H, m), 7.62 (4H, m), 7.79 (1H, d), 7.97 (1H, d), 8.04 (1H, d); m/z (ES^+) = 278 $[M+H]^+$; RT = 2.31min.

Example 18: 2-Methylsulfanyl-3-naphthalen-1-yl-5,6-dihydroimidazo[2,1-b]thiazole



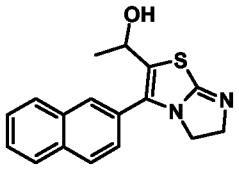
2-Bromo-3-naphthalen-1-yl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide (Example 11, 0.5g, 1.21mmol) was suspended in THF (20mL) under an argon atmosphere and cooled to 0°C. Ethylmagnesium chloride (2.0M in Et_2O, 1.8mL, 3.64mmol) was added dropwise over 5min and the reaction stirred at 0°C for 2hr. Dimethyl disulphide (0.22mL, 2.43mmol) was added and the reaction mixture stirred at rt for 16hr. The reaction was quenched with saturated NH_4Cl solution (40mL) then extracted into EtOAc (3 x 30mL). The combined organic fractions were dried ($MgSO_4$), concentrated *in vacuo* and purified by chromatography on silica gel eluting with MeOH:DCM (1:19) to afford the title compound. δ_H ($CDCl_3$): 2.18 (3H, s), 3.41 (2H, m), 4.10 (2H, m), 7.45 (1H, d), 7.55 (3H, m), 7.83 (1H, m), 7.95 (2H, m); m/z (ES^+) = 299 $[M+H]^+$; RT = 2.45min.

Example 19: (3-Naphthalen-2-yl-5,6-dihydroimidazo[2,1-b]thiazol-2-yl)methanol



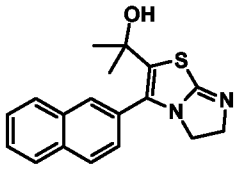
3-Naphthalen-2-yl-5,6-dihydroimidazo[2,1-b]thiazole-2-carbaldehyde (Preparation 20, 0.5g, 1.78mmol) was suspended in MeOH (20mL) under an argon atmosphere and cooled to 0°C. Sodium borohydride (0.10g, 2.68mmol) was added and the reaction stirred at 0°C for 0.5hr, then warmed to rt for 2hr. Water (40mL) was added and the precipitate was filtered and washed with water (2 x 20mL), and Et_2O (2 x 20mL) and dried to afford the title compound. δ_H (DMSO): 3.70 (2H, m), 4.01 (2H, m), 4.28 (2H, d), 5.34 (1H, m), 7.58 (3H, m), 7.98 (3H, m), 8.03 (1H, m); m/z (ES^+) = 283 $[M+H]^+$; RT = 2.27min.

Example 20: 1-(3-Naphthalen-2-yl-5,6-dihydroimidazo[2,1-b]thiazol-2-yl)ethanol



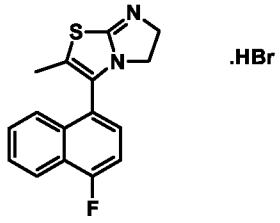
3-Naphthalen-2-yl-5,6-dihydroimidazo[2,1-b]thiazole-2-carbaldehyde (Preparation 20, 200mg, 0.71mmol) was dissolved in THF (25mL) under an argon atmosphere and cooled to 0°C. Methylmagnesium bromide (3.0M in Et_2O, 0.71mL, 2.14mmol) was added dropwise and the reaction maintained at 0°C for 1hr, then stirred at rt for 16hr. Water (40mL) was added and the reaction mixture extracted into EtOAc (3 x 30mL). The combined organic fractions were dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound. δ_H ($CDCl_3$): 1.46 (3H, d), 3.40 (1H, br s), 3.66 (2H, m), 4.14 (2H, m), 4.86 (1H, m), 7.47 (1H, d), 7.56 (2H, m), 7.90 (4H, m); m/z (ES^+) = 297 $[M+H]^+$; RT = 2.40min.

Example 21: 2-(3-Naphthalen-2-yl-5,6-dihydroimidazo[2,1-b]thiazol-2-yl)propan-2-ol



3-Naphthalen-2-yl-5,6-dihydroimidazo[2,1-b]thiazole-2-carboxylic acid ethyl ester hydrobromide (Example 10, 1g, 2.5mmol) was partitioned between saturated $NaHCO_3$ solution (40mL) and DCM (3 x 30mL). The combined organic fractions were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in THF (20mL) under an argon atmosphere and cooled to 0°C. Methylmagnesium bromide (3.0M in Et_2O, 2.5mL, 7.4mmol) was added dropwise and the reaction stirred at 0°C for 1hr, then rt for 16hr. Water (40mL) was added and the reaction mixture was extracted into EtOAc (3 x 30mL). The combined organic fractions were dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound. δ_H ($CDCl_3$): 1.37 (6H, s), 3.43 (2H, m), 4.06 (2H, m), 7.44 (1H, dd), 7.56 (2H, m), 7.89 (4H, m); m/z (ES^+) = 311 $[M+H]^+$; RT = 2.45min.

Example 22: 3-(4-Fluoronaphthalen-1-yl)-2-methyl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide

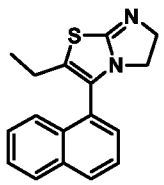


.HBr

2-Bromo-1-(4-fluoronaphthalen-1-yl)propan-1-one (Preparation 22, 4.59g, 16.3mmol) and 2-imidazolidinethione (1.67g, 16.3mmol) were heated to reflux in AcOH (20mL) and EtOH (40mL) for 24hr. The solvent was removed *in vacuo* and the residue dissolved in MeCN

(10mL), followed by addition of Et_2O (80mL). The precipitated solid was filtered and washed with Et_2O (2 x 30mL) to afford the title compound. δ_H (DMSO): 2.05 (3H, s), 3.85 (1H, m), 4.09 (1H, m), 4.20 (2H, m), 7.54 (1H, m), 7.71 (1H, m), 7.75 (2H, m), 7.88 (1H, m), 8.20 (1H, m), 9.56 (1H, br s); m/z (ES^+) = 285 $[M+H]^+$; RT = 2.56min.

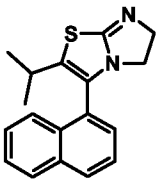
Example 23: 2-Ethyl-3-naphthalen-1-yl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide



.HBr

2-Bromo-1-naphthalen-1-ylbutan-1-one (Preparation 24, 0.82g, 3.0mmol) and 2-imidazolidinethione (0.30g, 3.0mmol) was dissolved in AcOH (10mL) and EtOH (20mL) and heated to reflux for 8hr, then stirred at rt for 72hr. The solvent was removed *in vacuo* and the residue partitioned between saturated $NaHCO_3$ solution (40mL) and EtOAc (2 x 40mL). The combined organic fractions were dried ($MgSO_4$), concentrated *in vacuo* and purified by chromatography on silica gel eluting with MeOH:DCM (2:23). The residue was dissolved in EtOAc (20mL) and 30% HBr in AcOH (1mL) was added. The solvent was removed *in vacuo* to afford the title compound. δ_H (DMSO): 1.04 (3H, t), 2.33 – 2.47 (2H, m), 3.83 (1H, m), 4.06 (1H, m), 4.21 (2H, m), 7.67 (4H, m), 7.83 (1H, m), 8.09 (1H, m), 8.17 (1H, m), 9.68 (1H, br s); m/z (ES^+) = 281 $[M+H]^+$; RT = 2.52min.

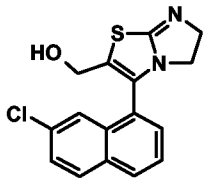
Example 24: 2-Isopropyl-3-naphthalen-1-yl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide



.HBr

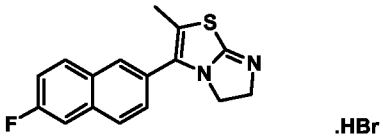
2-Bromo-3-methyl-1-naphthalen-1-ylbutan-1-one (Preparation 26, 0.39g, 1.3mmol) and 2-imidazolidinethione (0.14g, 1.3mmol) were dissolved in AcOH (5mL) and EtOH (10mL) and heated to reflux for 16hr. The solvent was removed *in vacuo* and the residue partitioned between saturated $NaHCO_3$ solution (40mL) and EtOAc (3 x 30mL). The combined organic fractions were dried ($MgSO_4$), concentrated *in vacuo* and purified by chromatography on silica gel eluting with MeOH:DCM (2:23). The residue was dissolved in MeCN (20mL) followed by addition of 30% HBr in AcOH (0.5mL). The solvent was removed *in vacuo* and the residue dissolved in MeCN (5mL) and added to Et_2O (25mL). The solid was filtered and dried to afford the title compound. δ_H (DMSO): 1.10 (3H, d), 1.15 (3H, d), 2.69 (1H, m), 3.80 (1H, m), 4.01 (1H, m), 4.20 (2H, m), 7.68 (4H, m), 7.84 (1H, m), 8.09 (1H, m), 8.17 (1H, m), 9.74 (1H, br s); m/z (ES^+) = 295 $[M+H]^+$; RT = 2.62min.

Example 25: [3-(7-Chloronaphthalen-1-yl)-5,6-dihydroimidazo[2,1-b]thiazol-2-yl]-methanol



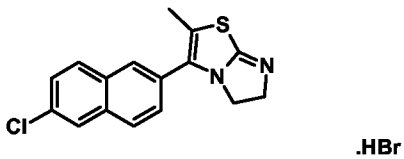
To a solution of 3-(7-chloronaphthalen-1-yl)-5,6-dihydroimidazo[2,1-b]thiazole-2-carbaldehyde (Preparation 177, 1.14g, 3.62mmol) in ethanol / water : 5 / 1 (60mL) was added sodium borohydride (300mg, 7.92mmol). After stirring for 12hr the solution was acidified with dilute HCl solution and further diluted with water (100mL). After concentration in vacuo the residue was twice codestillated with methanol (~50mL) before being distributed between EtOAc (200mL) and sat. $NaHCO_3$ solution (200mL). The organic layer was separated and the aqueous layer was further extracted with EtOAc (2 x 100mL). The combined extracts were washed (brine), dried ($MgSO_4$) and concentrated. Purification of the residue by flash-chromatography (eluent : DCM / methanol : 8/2) gave the title compound. δ_H (DMSO): 3.35 (1H, m), 3.47 (1H, m), 3.95-4.05 (3H, m), 5.40 (1H, br s), 7.64-7.69 (3H, m), 7.86 (1H, d), 8.11-8.15 (2H, m); m/z (ES^+) = 317.05 $[M+H]^+$; RT = 2.50 min.

Example 26: 3-(6-Fluoronaphthalen-2-yl)-2-methyl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide



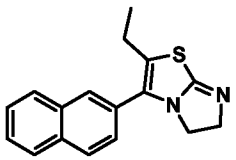
A stirred solution of 2-bromo-1-(6-fluoronaphthalen-2-yl)propan-1-one (Preparation 32, 0.86g, 4.1mmol) and imidazolidine-2-thione (0.42g, 4.1mmol) in EtOH (20mL) was heated to reflux and AcOH (10mL) was added. The reaction was stirred under reflux for 24hr and then cooled to rt. Acetonitrile (20mL) was added and a solid precipitated. The precipitate was collected by filtration to afford the title compound. δ_H (DMSO): 2.31 (3H, s), 4.24 (2H, m), 4.35 (2H, m), 7.56 (1H, td), 7.69 (1H, d), 7.85 (1H, dd), 8.10 (1H, d) 8.15 (1H, m), 8.19 (1H, s), 9.50 (1H, br s); m/z (ES^+) = 285 $[M+H]^+$; RT = 2.56min.

Example 27: 3-(6-Chloronaphthalen-2-yl)-2-methyl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide



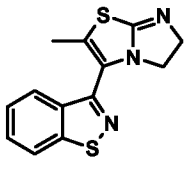
A stirred solution of 2-bromo-1-(6-chloronaphthalen-2-yl)propan-1-one (Preparation 36, 1.27g, 4.3mmol) and imidazolidine-2-thione (0.43g, 4.3mmol) in EtOH (20mL) was heated to reflux and AcOH (10mL) added. The reaction was stirred at reflux for 24hr. The reaction was cooled to rt and the resulting precipitate was collected by filtration to afford the title compound. δ_H (DMSO): 2.31 (3H, s), 4.25 (2H, m), 4.35 (2H, m), 7.65 (1H, dd), 7.77 (1H, dd), 8.11 (2H, m), 8.18 (2H, s), 9.52 (1H, br s); m/z (ES^+) = 301 $[M+H]^+$; RT = 2.74min.

Example 28: 2-Ethyl-3-naphthalen-2-yl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide



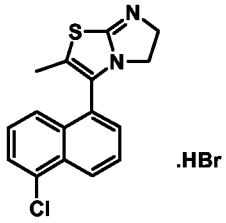
A stirred solution of 2-bromo-1-naphthalen-2-ylbutan-1-one (Preparation 38, 0.87g, 3.5mmol) and imidazolidine-2-thione (0.36g, 3.5mmol) in EtOH (10mL) was heated to reflux and AcOH (5mL) added. The reaction was stirred at reflux for 48hr and then cooled to rt. The solvent was removed *in vacuo*, EtOAc and acetonitrile were added and a solid precipitated out. The solvent was removed *in vacuo* to give a solid which was triturated with Et_2O and then collected by filtration to afford the title compound. δ_H (DMSO): 1.17 (3H, t), 2.69 (2H, q), 4.24 (2H, m), 4.31 (2H, m), 7.64 (3H, m), 8.04 (2H, m), 8.11 (2H, m), 9.70 (1H, br s); m/z (ES^+) = 281 $[M+H]^+$; RT = 2.64min.

Example 29: 3-(2-Methyl-5,6-dihydroimidazo[2,1-b]thiazol-3-yl)benzo[d]isothiazole hydrobromide



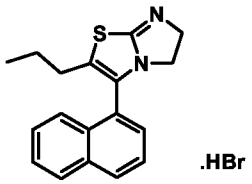
A stirred solution of 1-benzo[d]isothiazol-3-yl-2-bromopropan-1-one (Preparation 43, 0.4g, 1.8mmol) and imidazolidine-2-thione (0.18g, 1.8mmol) in EtOH (10mL) was heated to reflux and AcOH (5mL) was added. The reaction was heated under reflux for 48hr, cooled to rt and the solvent removed *in vacuo*. EtOAc was added to the residue and precipitation was observed. The solid was collected by filtration to afford the title compound. δ_H (DMSO): 2.28 (3H, s), 4.24 (4H, m), 7.64 (1H, t), 7.74 (1H, t), 8.12 (1H, d), 8.39 (1H, d), 9.57 (1H, br s); m/z (ES^+) = 274 $[M+H]^+$; RT = 2.12 min.

Example 30: 3-(5-Chloronaphthalen-1-yl)-2-methyl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide



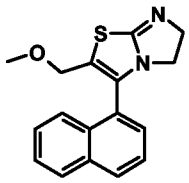
2-Bromo-1-(5-chloronaphthalen-1-yl)propan-1-one (Preparation 71, 118mg, 0.4mmol) and 2-imidazolidinethione (41mg, 0.4mmol) were heated to reflux in EtOH (10mL) and AcOH (5mL) for 24hr. The reaction mixture was cooled to rt and concentrated *in vacuo*. EtOAc (20mL) was added to the residue and the resulting precipitate was filtered affording the title compound. δ_H (DMSO): 2.05 (3H, s), 3.84 (1H, m), 4.07 (1H, m), 4.19 (2H, t), 7.62 (1H, t), 7.85 (4H, m), 8.43 (1H, d), 9.52 (1H, br s); RT = 2.56min; m/z (ES^+) = 301 $[M+H]^+$.

Example 31: 3-Naphthalen-1-yl-2-propyl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide



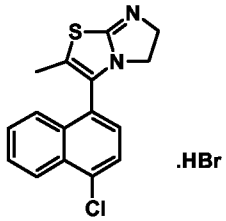
2-Bromo-1-naphthalen-1-ylpentan-1-one (Preparation 71, 1.57g, 5.4mmol) and 2-imidazolidinethione (0.55g, 5.4mmol) were heated to reflux in EtOH (20mL) and AcOH (10mL) for 16hr. The reaction mixture was cooled to rt and concentrated *in vacuo*. EtOAc (20mL) was added and the resulting precipitate was triturated with Et_2O and filtered, washed with Et_2O (2 x 20mL) and dried under vacuum affording the title compound. δ_H (DMSO): 0.73 (3H, t), 1.44 (2H, m), 2.31 (1H, m), 2.43 (1H, m), 3.82 (1H, m), 4.05 (1H, m), 4.21 (2H, t), 7.67 (4H, m), 7.84 (1H, m), 8.08 (1H, m), 8.16 (1H, m), 9.71 (1H, br s); m/z (ES^+) = 295 $[M+H]^+$; RT = 2.69min.

Example 32: 2-Methoxymethyl-3-naphthalen-1-yl-5,6-dihydroimidazo[2,1-b]thiazole



3-Benzyloxy-2-bromo-1-naphthalen-1-ylpropan-1-one (Preparation 65, 1.44g, 3.9mmol) and 2-imidazolidinethione (0.40g, 3.9mmol) were heated to reflux in AcOH (10mL) and MeOH (20mL) for 48hr. The solvent was removed *in vacuo* and the residue partitioned between saturated $NaHCO_3$ solution (100mL) and EtOAc (3 x 100mL). The combined organic fractions were dried ($MgSO_4$), concentrated *in vacuo* and chromatographed on silica gel eluting with MeOH:DCM 1:49 to 3:97 affording the title compound. δ_H ($CDCl_3$): 3.45 (2H, m), 4.09 (2H, s), 4.18 (2H, m), 5.34 (3H, s), 7.47 (1H, m), 7.57 (3H, m), 7.95 (3H, m); m/z (ES^+) = 297 $[M+H]^+$; RT = 2.47min.

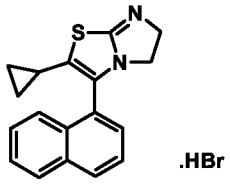
Example 33: 3-(4-Chloronaphthalen-1-yl)-2-methyl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide



2-Bromo-1-(4-chloronaphthalen-1-yl)propan-1-one (Preparation 72, 6.05g, 20.3mmol) and 2-imidazolidinethione (2.08g, 20.3mmol) were heated to reflux in EtOH (100mL) and AcOH (50mL) for 24hr. The reaction mixture was cooled to rt and concentrated *in vacuo*. Et_2O (100mL) was added to the residue and this was stirred at rt for 30min. The solid was filtered and washed with Et_2O (2 x 40mL) and dried under vacuum affording the title compound. δ_H

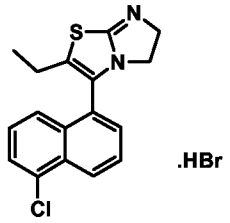
(DMSO): 2.06 (3H, s), 3.86 (1H, m), 4.09 (1H, m), 4.20 (2H, t), 7.69 (1H, d), 7.76 (1H, m), 7.83 (1H, m), 7.91 (2H, d), 8.34 (1H, d), 9.53 (1H, br s); m/z (ES^+) = 301 $[M+H]^+$; RT = 2.61min.

Example 34: 2-Cyclopropyl-3-naphthalen-1-yl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide



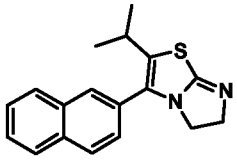
2-Bromo-2-cyclopropyl-1-naphthalen-1-ylethanone (Preparation 73, 282mg, 0.98mmol) and 2-imidazolidinethione (100mg, 0.98mmol) were heated to reflux in EtOH (10mL) and AcOH (5mL) for 16hr. The reaction mixture was cooled to rt and concentrated *in vacuo*. The residue was partitioned between saturated $NaHCO_3$ solution (30mL) and EtOAc (3 x 30mL). The combined organic fractions were dried ($MgSO_4$), concentrated *in vacuo* and chromatographed on silica gel eluting with MeOH:DCM 7:93. The product was acidified with HBr (30% in AcOH) and the residue crystallised from MeCN and acetone affording the title compound. δ_H (DMSO): 0.51 (2H, m), 0.75 (2H, m), 1.69 (1H, m), 3.83 (1H, m), 4.09 (1H, m), 4.19 (2H, t), 7.65 (2H, m), 7.71 (2H, m), 7.89 (1H, m), 8.09 (1H, m), 8.17 (1H, d), 9.69 (1H, br s); m/z (ES^+) = 293 $[M+H]^+$; RT = 2.45min.

Example 35: 3-(5-Chloronaphthalen-1-yl)-2-ethyl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide



2-Bromo-1-(5-chloronaphthalen-1-yl)butan-1-one (Preparation 74, 0.43g, 1.38mmol) and 2-imidazolidinethione (0.14g, 1.38mmol) were heated to reflux in EtOH (10mL) and AcOH (5mL) for 16hr. The reaction was cooled to rt and concentrated *in vacuo*. The residue was triturated with acetone (20mL) and EtOAc (30mL), and the filtered solid washed with EtOAc (20mL), Et_2O (2 x 20mL) and dried under vacuum affording the title compound. δ_H (DMSO): 1.03 (3H, t), 2.39 (2H, m), 3.82 (1H, m), 4.05 (1H, m), 4.20 (2H, t), 7.63 (1H, m), 7.84 (4H, m), 8.43 (1H, d), 9.66 (1H, br s); m/z (ES^+) = 315 $[M+H]^+$; RT = 2.79min.

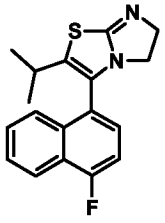
Example 36: 2-Isopropyl-3-naphthalen-2-yl-5,6-dihydroimidazo[2,1-b]thiazole



2-Bromo-3-methyl-1-naphthalen-2-ylbutan-1-one (Preparation 75, 0.70g, 2.4mmol) and 2-imidazolidinethione (0.24g, 2.4mmol) were heated to reflux in EtOH (10mL) and AcOH

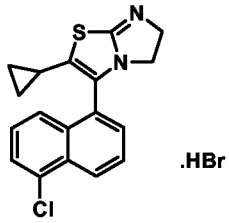
(5mL) for 16hr. The reaction mixture was cooled to rt and concentrated *in vacuo*. The residue was partitioned between saturated $NaHCO_3$ solution (50mL) and EtOAc (3 x 20mL). The combined organic fractions were dried ($MgSO_4$), concentrated *in vacuo* and chromatographed on silica gel eluting with MeOH:DCM 7:93 affording the title compound. δ_H ($CDCl_3$): 1.20 (6H, d), 3.04 (1H, m), 3.65 (2H, t), 4.15 (2H, t), 7.42 (1H, m), 7.56 (2H, m), 7.79 (1H, s), 7.90 (3H, m); m/z (ES^+) = 295 $[M+H]^+$; RT = 2.62min.

Example 37: 3-(4-Fluoronaphthalen-1-yl)-2-isopropyl-5,6-dihydroimidazo[2,1-b]thiazole



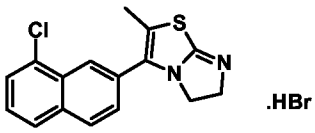
2-Bromo-1-(4-fluoronaphthalen-1-yl)-3-methylbutan-1-one (Preparation 76, 0.59g, 1.9mmol) and 2-imidazolidinethione (0.22g, 2.1mmol) were heated to reflux in EtOH (10mL) and AcOH (5mL) for 24hr. The reaction mixture was cooled to rt and concentrated *in vacuo*. The residue was partitioned between saturated $NaHCO_3$ solution (50mL) and EtOAc (3 x 20mL). The combined organic fractions were dried ($MgSO_4$), concentrated *in vacuo* and chromatographed on silica gel eluting with MeOH:DCM 1:9 affording the title compound. δ_H ($CDCl_3$): 1.07 (3H, d), 1.18 (3H, d), 2.69 (1H, m), 3.47 (2H, m), 4.16 (2H, m), 7.22 (1H, m), 7.38 (1H, m), 7.65 (2H, m), 7.81 (1H, m), 8.21 (1H, m); m/z (ES^+) = 313 $[M+H]^+$; RT = 2.87min.

Example 38: 3-(5-Chloronaphthalen-1-yl)-2-cyclopropyl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide



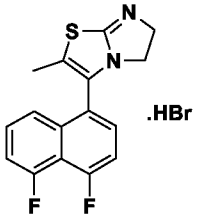
2-Bromo-1-(5-chloronaphthalen-1-yl)-2-cyclopropylethanone (Preparation 77, 140mg, 0.43mmol) and 2-imidazolidinethione (44mg, 0.43mmol) were heated to reflux in EtOH (6mL) and AcOH (3mL) for 24hr. The reaction mixture was cooled to rt and concentrated *in vacuo*. The residue was triturated with Et_2O (20mL), filtered and washed with Et_2O (2 x 10mL) affording the title compound. δ_H (DMSO): 0.51 (2H, m), 0.75 (2H, m), 1.68 (1H, m), 3.83 (1H, m), 4.08 (1H, m), 4.17 (2H, m), 7.64 (1H, t), 7.88 (4H, m), 8.43 (1H, d), 9.65 (1H, br s); m/z (ES^+) = 327 $[M+H]^+$; RT = 2.74min.

Example 39: 3-(8-Chloronaphthalen-2-yl)-2-methyl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide



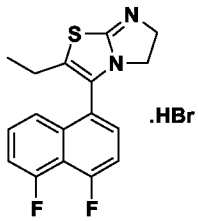
2-Bromo-1-(8-chloronaphthalen-2-yl)propan-1-one (Preparation 78, 222mg, 0.75mmol) and 2-imidazolidinethione (76mg, 0.75mmol) were heated to reflux in EtOH (10mL) and AcOH (5mL) for 16hr. The reaction mixture was cooled to rt and concentrated *in vacuo*. EtOAc (20mL) was added to the residue and this was filtered, washed with cold EtOAc (2 x 10mL), Et_2O (2 x 10mL) and dried under vacuum affording the title compound. δ_H (DMSO): 2.32 (3H, s), 4.25 (2H, m), 4.33 (2H, m), 7.65 (1H, t), 7.77 (1H, m), 7.83 (1H, d), 8.07 (1H, d), 8.24 (1H, d), 8.29 (1H, s), 9.55 (1H, br s); m/z (ES^+) = 301 $[M+H]^+$; RT = 2.77min.

Example 40: 3-(4,5-Difluoronaphthalen-1-yl)-2-methyl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide



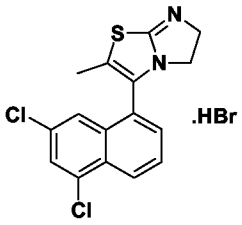
2-Bromo-1-(4,5-difluoronaphthalen-1-yl)propan-1-one (Preparation 93, 1.17g, 3.91mmol) and 2-imidazolidinethione (0.399g, 3.91mmol) were dissolved in an ethanol (10mL)/ acetic acid (5mL) mixture and the reaction heated under reflux for 16hr. The reaction mixture was cooled to rt and the solvent evaporated *in vacuo*. Trituration with acetonitrile yielded the title compound. δ_H (DMSO): 2.02 (3H, s), 3.80 (1H, q), 4.10 (1H, q), 4.2 (2H, m), 7.60-7.80 (5H, m); m/z (ES^+) = 303.07 $[M+H]^+$; RT = 2.45min.

Example 41: 3-(4,5-Difluoronaphthalen-1-yl)-2-ethyl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide



The title compound was prepared from 2-bromo-1-(4,5-difluoronaphthalen-1-yl)butan-1-one (Preparation 95, 1.1g, 3.41mmol) under similar conditions as described in Example 12. δ_H (DMSO): 1.00 (3H, t), 2.40 (2H, m), 3.80 (1H, q), 4.10 (1H, q), 4.20 (2H, m), 7.50-7.80 (5H, m), 9.60 (1H, br); m/z (ES^+) = 317.17 $[M+H]^+$; RT = 2.7min.

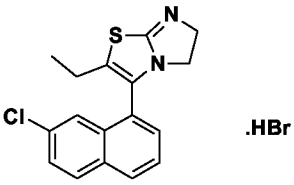
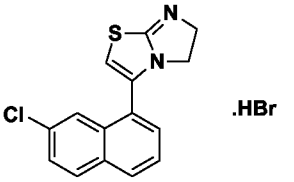
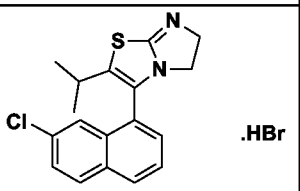
Example 42: 3-(5,7-Dichloronaphthalen-1-yl)-2-methyl-5,6-dihydroimidazo[2,1-b]th iazole hydrobromide

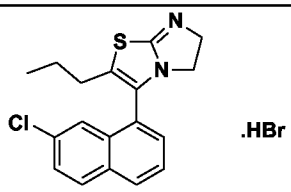
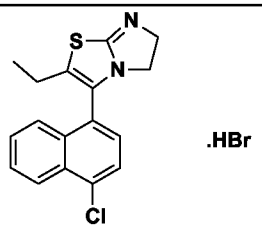
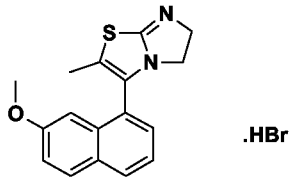
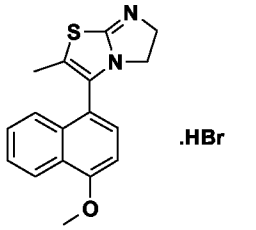
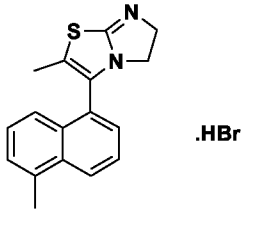


The title compound was prepared from 2-bromo-1-(5,7-dichloronaphthalen-1-yl)-propan-1-one (Preparation 99, 0.945g, 2.84mmol) and 2-imidazolidinethione under similar conditions as described in Example 12. δ_H (DMSO): 2.05 (3H, s), 3.85 (1H, q), 4.10 (1H, q), 4.20 (2H, t), 7.90 (3H, m), 8.00 (1H, d), 8.40 (1H, d), 9.50 (1H, br); m/z (ES^+) = 336.97 $[M+H]^+$; RT = 2.92 min.

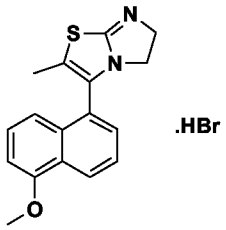
Examples 43 – 50:

The procedure described in Example 1 was used to prepare the compounds of Examples 43 – 50.

Ex	Structure	Name	LCMS	^{1}H NMR data
43		3-(7-Chloronaphthalen-1-yl)-2-ethyl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide	m/z (ES^+) = 315.04 $[M+H]^+$; RT = 2.79 min	δ_H (DMSO): 1.05 (3H, t), 2.31-2.44 (2H, m), 3.82-3.89 (1H, m), 4.09-4.16 (1H, m), 4.21-4.26 (2H, m), 7.67 (1H, d), 7.71-7.79 (2H, m), 7.97 (1H, s), 8.16 (1H, d), 8.23 (1H, d), 9.80 (1H, br s)
44		3-(7-Chloronaphthalen-1-yl)-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide	m/z (ES^+) = 286.99 $[M+H]^+$; RT = 2.56 min	δ_H (DMSO): 4.09-4.14 (2H, m), 4.27-4.32 (2H, m), 7.09 (1H, s), 7.67-7.73 (2H, m), 7.79 (1H, d), 8.11-8.16 (2H, m), 8.21 (1H, d), 9.67 (1H, br s)
45		3-(7-Chloronaphthalen-1-yl)-2-isopropyl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide	m/z (ES^+) = 329.03 $[M+H]^+$; RT = 2.92min	δ_H ($CDCl_3$): 1.22 (3H, d), 1.24 (3H, d), 2.77-2.82 (1H, m), 3.89, 4.19, 4.40, 4.52 (4H, 4m), 7.58-7.68 (4H, m), 7.96 (1H, d), 8.06 (1H, d), 10.81 (1H, br s)

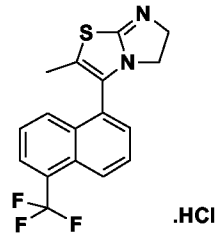
46		3-(7-Chloronaphthalen-1-yl)-2-propyl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide	m/z (ES^+) = 329.02 $[M+H]^+$; RT = 2.86 min	δ_H ($CDCl_3$): 0.89 (3H, t), 1.57-1.62 (2H, m), 2.38-2.48 (2H, m), 3.92, 4.27, 4.39, 4.53 (4H, 4m), 7.57-7.71 (4H, m), 7.95 (1H, d), 8.05 (1H, d), 10.72 (1H, br s)
47		3-(4-Chloronaphthalen-1-yl)-2-ethyl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide	m/z (ES^+) = 315.12 $[M+H]^+$; RT = 2.77 min	δ_H (DMSO): 1.06 (3H, t), 2.36-2.49 (2H, m), 3.83-3.88 (1H, m), 4.06-4.11 (1H, m), 4.20-4.24 (2H, m), 7.70 (1H, d), 7.77-7.80 (1H, m) 7.83-7.87 (1H, m), 7.91-7.95 (2H, m), 8.36 (1H, d), 9.66 (1H, br s)
48		3-(7-Methoxynaphthalen-1-yl)-2-methyl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide	m/z (ES^+) = 297.09 $[M+H]^+$; RT = 2.69 min	δ_H (DMSO): 2.09 (3H, s), 3.89 (3H, s), 3.92 (1H, m), 4.17-4.23 (3H, m), 7.05 (1H, d), 7.32 (1H, m), 7.53 (1H, m), 7.65 (1H, d), 8.02 (1H, d), 8.09 (1H, d), 9.59 (1H, s)
49		3-(4-Methoxynaphthalen-1-yl)-2-methyl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide	m/z (ES^+) = 297.07 $[M+H]^+$; RT = 2.80 min	δ_H (DMSO): 2.06 (3H, s), 3.83-3.90 (1H, m), 4.06 (3H, s), 4.10-4.13 (1H, m), 4.20-4.25 (2H, m), 7.16 (1H, d), 7.62-7.66 (3H, m), 7.76 (1H, d), 8.29 (1H, d), 9.68 (1H, br s)
50		2-Methyl-3-(5-methyl-naphthalen-1-yl)-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide	m/z (ES^+) = 281.01 $[M+H]^+$; RT = 2.76 min	δ_H (DMSO): 2.07 (3H, s), 2.74 (3H, s), 3.84-3.88 (1H, m), 4.06 (1H, m), 4.25 (2H, m), 7.50 (2H, m), 7.67-7.76 (3H, m), 8.28 (1H, d), 9.62 (1H, br s)

Example 51: 3-(5-Methoxynaphthalen-1-yl)-2-methyl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide



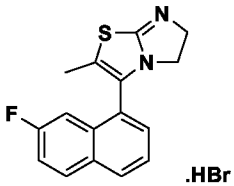
The title compound was prepared from 2-bromo-1-(5-methoxynaphthalen-1-yl)propan-1-one (Preparation 121) under similar conditions as described in Example 1. δ_H (DMSO): 2.1 (3H, s), 3.80 (1H, m), 4.05 (1H, m), 4.20 (2H, m), 7.08 (1H, d), 7.36 (1H, d), 7.57 (1H, m), 7.64 (2H, m), 8.40 (1H, m), 9.50 (1H, s); m/z (ES^+) = 297.08 $[M+H]^+$; RT = 2.70 min.

Example 52: 2-Methyl-3-(5-trifluoromethylnaphthalen-1-yl)-5,6-dihydro-imidazo[2,1-b]thiazole hydrochloride



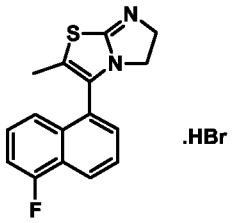
2-Bromo-1-(5-trifluoromethylnaphthalen-1-yl)propan-1-one (Preparation 130, 2.625g, 7.93mmol) and 2-imidazolidinethione (0.810g, 7.93mmol) were dissolved in ethanol (40mL)/ acetic acid (20mL) mixture and the reaction heated under reflux for 16hr. The reaction mixture was cooled to rt and the solvent evaporated *in vacuo*. The organics were basified with sat. $NaHCO_3$, extracted with DCM (3 x 50mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash-chromatography on silica gel (eluent: DCM/MeOH, 4/1) gave the free base which was acidified with cold ethereal 2M HCl (excess) to afford the title compound upon evaporation *in vacuo*. δ_H (DMSO): 2.10 (3H, s), 3.90 (1H, q), 4.10 (1H, q), 4.22 (2H, m), 7.80 (1H, t), 7.90 (1H, d), 7.95 (1H, t), 8.15 (1H, d), 8.20 (1H, d), 8.30 (1H, d), 11.00 (1H, br); m/z (ES^+) = 335.97 $[M+H]^+$; RT = 2.82 min.

Example 53: 3-(7-Fluoronaphthalen-1-yl)-2-methyl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide



The title compound was prepared from 2-bromo-1-(7-fluoronaphthalen-1-yl)-propan-1-one (Preparation 133) and 2-imidazolidinethione under similar conditions as described in Example 1. δ_H (DMSO): 2.05 (3H, s), 3.90 (1H, q), 4.10 (1H, q), 4.20 (2H, t), 7.55-7.75 (4H, m), 8.05 (2H, m), 9.50 (1H, br); m/z (ES^+) = 285.05 $[M+H]^+$; RT = 2.55 min

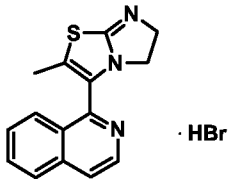
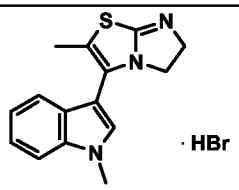
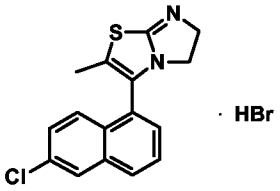
Example 54: 3-(5-Fluoronaphthalen-1-yl)-2-methyl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide

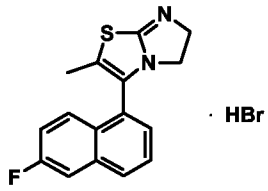
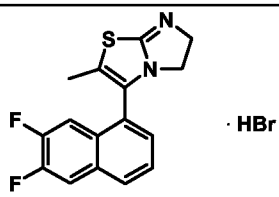
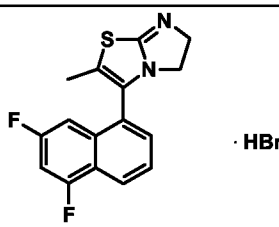
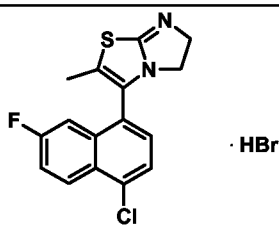
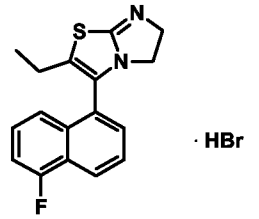
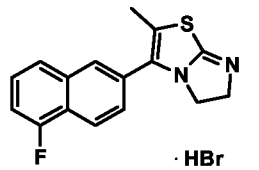


2-Bromo-1-(5-fluoronaphthalen-1-yl)propan-1-one (Preparation 150, 1.1g, 3.96mmol) and imidazolidine-2-thione (404mg, 3.96mmol) were dissolved in EtOH (15mL) and AcOH (7.5mL) and the reaction heated to reflux for 16hr. The reaction mixture was cooled overnight and the precipitate collected by filtration, washed with acetonitrile (20mL) to afford the title compound. δ_H (DMSO): 2.10 (3H, s), 3.85 (1H, m), 4.10 (1H, m), 4.20 (2H, m), 7.50 (1H, m), 7.70 (2H, m), 7.80 (2H, m), 8.25 (1H, m), 9.58 (1H, br s); m/z (ES^+) = 284.95 $[M+H]^+$; RT = 2.59min.

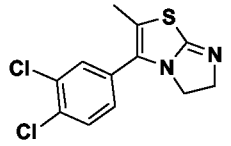
Examples 55 – 63:

The procedure described in Example 1 was used to prepare the compounds of Examples 55 – 63.

Ex	Structure	Name	LCMS	^{1}H NMR data
55		1-(2-Methyl-5,6-dihydro-imidazo[2,1-b]thiazol-3-yl)-isoquinoline hydrobromide	m/z (ES^+) =268.00 $[M+H]^+$; RT = 2.14 min	δ_H (DMSO): 2.13 (3H, s), 4.01 (1H, m), 4.19-4.35 (2H, m) 4.43 (1H, m), 7.82 (1H, dd), 7.93 (1H, dd), 8.06 (1H, d), 8.11 (1H, d), 8.18 (1H, d), 8.72 (1H, d), 9.63 (1H, br s)
56		1-Methyl-3-(2-methyl-5,6-dihydroimidazo[2,1-b]thiazol-3-yl)-1H-indole hydrobromide	m/z (ES^+) =270.01 $[M+H]^+$; RT = 2.37 min	δ_H (DMSO): 2.24, 4.26 (6H, 2s), 7.20 (1H, dd), 7.31 (1H, dd), 7.59 (2H, 2d), 7.82 (1H, s), 9.60 (1H, br s)
57		3-(6-Chloronaphthalen-1-yl)-2-methyl-5,6-dihydro-imidazo[2,1-b]thiazole hydrobromide	m/z (ES^+) =301.04 $[M+H]^+$; RT = 2.72 min	δ_H (DMSO): 2.07 (3H, s), 3.87 (1H, m), 4.11-4.25 (3H, 2m), 7.64 (1H, dd), 7.73-7.79 (2H, m), 7.89 (1H, d), 8.18 (1H, d), 8.26 (1H, d), 9.60 (1H, br s)

58		3-(6-Fluoronaphthalen-1-yl)-2-methyl-5,6-dihydro-imidazo[2,1-b]thiazole hydrobromide	m/z (ES^+) =285.07 $[M+H]^+$; RT = 2.42 min	δ_H (DMSO): 2.07 (3H, s), 3.87 (1H, m), 4.11-4.25 (3H, 2m), 7.56 (1H, m), 7.68 (1H, d), 7.75 (1H, dd), 7.91-7.96 (2H, m), 8.18 (1H, d), 9.61 (1H, br s)
59		3-(6,7-Difluoronaphthalen-1-yl)-2-methyl-5,6-dihydro-imidazo[2,1-b]thiazole hydrobromide	m/z (ES^+) =3.03.03 $[M+H]^+$; RT = 2.56 min	δ_H (DMSO): 2.06 (3H, s), 3.87 (1H, m), 4.09 (1H, m), 4.20-4.25 (2H, m), 7.72-7.77 (2H, m) 7.93 (1H, dd), 8.19-8.24 (2H, m), 9.59 (1H, br s)
60		3-(5,7-Difluoronaphthalen-1-yl)-2-methyl-5,6-dihydro-imidazo[2,1-b]thiazole hydrobromide	m/z (ES^+) =303.08 $[M+H]^+$; RT = 2.39 min	δ_H (DMSO): 2.07 (3H, s), 3.88 (1H, m), 4.10 (1H, m), 4.20-4.25 (2H, m), 7.57 (1H, d) 7.67 (1H, m), 7.79 (1H, dd), 7.86 (1H, d), 8.30 (1H, d), 9.57 (1H, br s)
61		3-(4-Chloro-7-fluoro-naphthalen-1-yl)-2-methyl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide	m/z (ES^+) =319.09 $[M+H]^+$; RT = 2.81 min	δ_H (DMSO): 2.07 (3H, s), 3.88 (1H, m), 4.10 (1H, m), 4.20-4.24 (2H, m), 7.75-7.78 (3H, m), 7.90 (1H, d), 8.43 (1H, dd), 9.58 (1H, br s)
62		2-Ethyl-3-(5-fluoro-naphthalen-1-yl)-5,6-dihydro-imidazo[2,1-b]thiazole hydrobromide	m/z (ES^+) =299.51 $[M+H]^+$; RT = 2.57 min	δ_H (DMSO): 1.06 (3H, t), 2.44 (2H, m), 3.86, 4.08, (2H, 2 m), 4.25 (2H, m), 7.51 (1H, dd), 7.63-7.68 (2H, m), 7.71 (2H, m), 8.31 (1H, m), 9.71 (1H, br s)
63		3-(5-Fluoronaphthalen-2-yl)-2-methyl-5,6-dihydro-imidazo[2,1-b]thiazole hydrobromide	m/z (ES^+) =284.98 $[M+H]^+$; RT = 2.62 min	δ_H (DMSO): 2.34 (3H, t), 4.26, 4.37 (4H, 2m), 7.52 (1H, dd), 7.66 (1H, m), 7.77 (1H, dd), 7.94 (1H, d), 8.23-8.27 (2H, m), 9.58 (1H, br s)

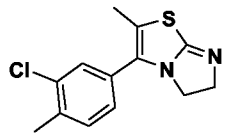
Example 64: 3-(3,4-Dichlorophenyl)-2-methyl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide



.HBr

To a solution of 2-bromo-1-(3,4-dichlorophenyl)propan-1-one (Preparation 44, 1.50g, 5.10mmol) in EtOH (10.0mL) and acetic acid (5.0mL) was added imidazolidine-2-thione (530mg, 5.10mmol). The mixture was stirred at 110°C under an inert atmosphere for 16hr. The solvent was removed under reduced pressure and the resulting solid triturated with Et_2O (2 x 10mL) then acetonitrile (1 x 5mL) to afford the title compound. δ_H (DMSO): 9.50 (1H, br s), 7.90 (2H, m), 7.55 (1H, d), 4.30-4.20 (4H, m), 2.25 (3H, s); m/z (ES^+) = 284.92 $[M-H]^+$; RT = 2.36 min.

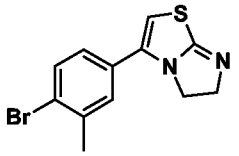
Example 65: 3-(3-Chloro-4-methylphenyl)-2-methyl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide



.HBr

Prepared from 2-bromo-1-(4-chloro-3-methylphenyl)propan-1-one and imidazolidine-2-thione according to the method of Example 64. δ_H (DMSO): 9.50 (1H, br s), 7.60 (1H, d), 7.55 (1H, s), 7.40 (1H, t), 4.30- 4.20 (4H, m), 2.40 (3H, s), 2.20 (3H, s); m/z (ES^+) = 265.01 $[M-H]^+$; RT = 2.65 min.

Example 66: 3-(4-Bromo-3-methylphenyl)-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide



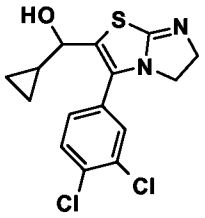
.HBr

Imidazolidine-2-thione (0.2788g, 2.73mmol) was added to a solution of 2-bromo-1-(4-bromo-3-methylphenyl)ethanone (Preparation 47, 790mg, 2.73mmol) in EtOH(10mL) / acetic acid (3mL). The mixture was stirred at 110°C under an inert atmosphere for 16hr. The solvent was removed *in vacuo* and the resultant solid was washed with EtOH and Et_2O to yield the title compound. δ_H (MeOH): 7.68 (1H, d), 7.60 (1H, s), 7.40 (1H, d), 6.98 (1H, s), 4.60-4.40 (4H, m), 2.42 (3H, s); m/z (ES^+) = 296.01 $[M-H]^+$; RT = 2.31 min.

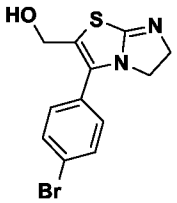
Examples 67 to 70:

The following compounds were made using procedures analogous to those described above:

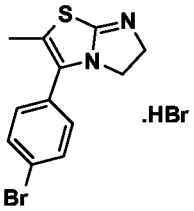
Example 67: Cyclopropyl[3-(3,4-dichlorophenyl)-5,6-dihydroimidazo[2,1-b]thiazol-2-yl]methanol



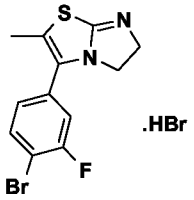
Example 68: [3-(4-Bromophenyl)-5,6-dihydroimidazo[2,1-b]thiazol-2-yl]methanol



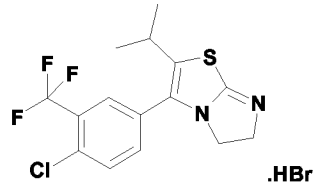
Example 69: 3-(4-Bromophenyl)-2-methyl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide



Example 70: 3-(4-Bromo-3-fluorophenyl)-2-methyl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide

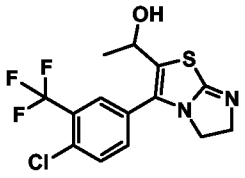


Example 71: 3-(4-Chloro-3-trifluoromethylphenyl)-2-isopropyl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide



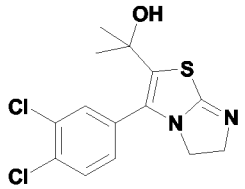
The title compound was prepared from 2-bromo-1-(4-chloro-3-trifluoromethylphenyl)-3-methylbutan-1-one (Preparation 146, 3.6g, 10.48mmol) and 2-imidazolidinethione under similar conditions as described in Example 1. δ_H (DMSO): 1.20 (6H, m), 3.00 (1H, m), 4.20 (4H, br s), 7.90 (1H, d), 8.00 (1H, d), 8.05 (1H, s), 9.70 (1H, br s); m/z (ES^+) = 346.98 $[M+H]^+$; RT = 2.74 min.

Example 72: 1-[3-(4-Chloro-3-trifluoromethylphenyl)-5,6-dihydroimidazo[2,1-b]thiazol-2-yl]ethanol



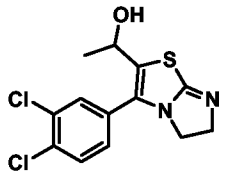
The title compound was prepared from 3-(4-chloro-3-trifluoromethylphenyl)-5,6-dihydroimidazo[2,1-b]thiazole-2-carbaldehyde (Preparation 144, 0.50g, 1.503mmol) under similar conditions as described in Example 64. δ_H (DMSO): 1.25 (3H, m), 3.50 (1H, m), 3.65 (1H, m), 4.00 (2H, m), 4.55 (1H, m), 5.40 (1H, m), 7.80 (1H, d), 7.85 (1H, d), 7.95 (1H, s); m/z (ES^+) = 348.93 $[M+H]^+$; RT = 2.40min.

Example 73: 2-[3-(3,4-Dichlorophenyl)-5,6-dihydroimidazo[2,1-b]thiazol-2-yl]-propan-2-ol



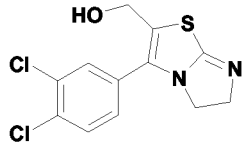
A solution of 3-(3,4-dichlorophenyl)-5,6-dihydroimidazo[2,1-b]thiazole-2-carboxylic acid methyl ester (Preparation 140, 1.50g, 3.67mmol) in THF (30.0mL) was cooled at 0°C under inert atmosphere and methylmagnesium bromide 2.0 M solution in diethyl ether (7.30mL, 14.67mmol) was added over 5min. The mixture was stirred for 1hr before removing the ice bath and stirred for further 16hr. Saturated ammonium chloride (50mL) was added slowly, stirred vigorously for 15min then the obtained suspension filtered. The resulting solid was washed with water (2 x 5.0mL) and dried under *vacuo* to afford the title compound. δ_H (DMSO): 1.25 (6H, s), 4.00 (2H, m), 4.15 (2H, m), 6.25 (1H, s), 7.55 (1H, d), 7.90 (2H, m); m/z (ES^+) = 328.94 $[M+H]^+$; RT = 2.34 min.

Example 74: 1-[3-(3,4-Dichlorophenyl)-5,6-dihydroimidazo[2,1-b]thiazol-2-yl]ethanol



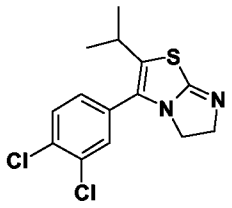
A solution of 3-(3,4-dichlorophenyl)-5,6-dihydroimidazo[2,1-b]thiazole-2-carbaldehyde (Preparation 138, 0.50g, 1.67mmol) in THF (20.0mL) was cooled at 0°C under inert atmosphere and methylmagnesium bromide 3.0 M solution in diethyl ether (1.67mL, 5.01mmol) was added over 5min. The mixture was stirred for 1hr before removing the ice bath and stirred for further 16hr. Water (40mL) was then added, stirred vigorously for 15min then the aqueous layer extracted with EtOAc (3 x 50mL), the organic layer dried ($MgSO_4$) and concentrated *in vacuo*. The yellow solid obtained was triturated with DCM (2 x 2.0mL) and residual solvent removed *in vacuo* to the title compound. δ_H (DMSO): 1.25 (3H, d), 3.70-3.50 (2H, m), 4.00 (2H, m), 4.55 (1H, m), 5.40 (1H, m), 7.50 (1H, d), 7.80 (2H, m); m/z (ES^+) = 314.91 $[M+H]^+$; RT = 2.39 min.

Example 75: [3-(3,4-Dichlorophenyl)-5,6-dihydroimidazo[2,1-b]thiazol-2-yl]methanol



To a suspension of 3-(3,4-dichlorophenyl)-5,6-dihydroimidazo[2,1-b]thiazole-2-carbaldehyde (Preparation 138, 0.50g, 1.672mmol) in methanol (10.0mL) at 0°C, was added sodium borohydride in one portion (95.0mg, 2.51mmol). The above mixture was stirred at 0°C under an inert atmosphere for 2hr before removing the cooling bath and then stirred for 16hr. Water (40mL) was then added, stirred vigorously for 1hr then the obtained suspension filtered. The resulting solid was washed with Et_2O (2 x 10mL) and dried *under vacuo* to afford the title compound. δ_H (DMSO): 3.65 (2H, m), 4.00 (2H, m), 4.20 (2H, m), 5.40 (1H, m), 7.50 (1H, d), 7.80 (2H, m); m/z (ES^+) = 300.94 $[M+H]^+$; RT = 2.29 min.

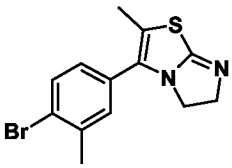
Example 76: 3-(3,4-Dichlorophenyl)-2-isopropyl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide



.HBr

The title compound was prepared from 2-bromo-1-(3,4-dichlorophenyl)-3-methylbutan-1-one (Preparation 91, 1.6g, 5.16mmol) and 2-imidazolidinethione under similar conditions as described in Example 12. δ_H (d_4MeOH): 1.25 (6H, d), 3.10 (1H, m), 4.30 (4H, m), 7.40 (1H, d), 7.80 (2H, m); m/z (ES^+) = 314.97 $[M+H]^+$; RT = 2.72min.

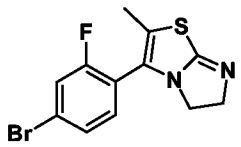
Example 77: 3-(4-Bromo-3-methylphenyl)-2-methyl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide



.HBr

The title compound was prepared from 2-bromo-1-(4-bromo-3-methylphenyl)propan-1-one (Preparation 89, 2g, 0.65mmol) and 2-imidazolidinethione under similar conditions as described in Example 12. δ_H (d_4MeOH): 2.25 (3H, s), 2.50 (3H, s), 4.30 (4H, m), 7.20 (1H, d), 7.40 (1H, s), 7.80 (1H, d); m/z (ES^+) = 310.9 $[M+H]^+$; RT = 2.42min.

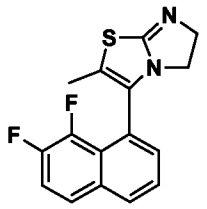
Example 78: 3-(4-Bromo-2-fluorophenyl)-2-methyl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide



.HBr

The title compound was prepared from 2-bromo-1-(4-bromo-2-fluorophenyl)propan-1-one (Preparation 87, 3.1g, 100mmol) and 2-imidazolidinethione under similar conditions as described in Example 12. δ_H ($CDCl_3$): 2.21 (3H, s), 4.30-4.65 (4H, m), 7.50 (3H, m); m/z (ES^+) = 314.88 $[M+H]^+$; RT = 2.36min.

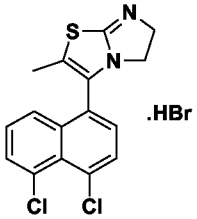
Example 79: 2-Methyl-3-(7,8-difluoronaphthalen-1-yl)-5,6-dihydroimidazo[2,1-b]thiazole hydrochloride



.HCl

The title compound was prepared from 2-bromo-1-(7,8-difluoronaphthalene-1-yl)-propan-1-one (Preparation 84) under similar conditions as described in Example 64. δ_H ($CDCl_3$): 1.81 (3H, s), 3.35 (2H, m), 4.15 (2H, m), 7.39 (2H, m), 7.43 (1H, t), 7.61 (1H, m), 7.85 (1H, d); m/z$^+$(ES^+) = 302.94 $[M+H]^+$; RT=2.54 min.

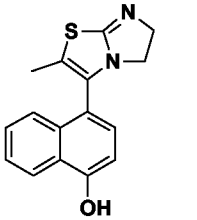
Example 80: 3-(4,5-Dichloronaphthalen-1-yl)-2-methyl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide



.HBr

The title compound was prepared from 2-bromo-1-(4,5-dichloronaphthalen-1-yl)propan-1-one (Preparation 97, 0.73g, 2.2mmol) under similar conditions as described in Example 12. δ_H (DMSO): 2.00 (3H, s), 3.80 (1H, q), 4.10 (1H, q), 4.25 (2H, m), 7.60 (1H, t), 7.70 (1H, d), 7.90 (3H, m), 9.60 (1H, br); (ES^+) = 336.93 $[M+H]^+$; RT = 2.77min.

Example 81: 3-(4-Hydroxynaphthalen-1-yl)-2-methyl-5,6-dihydroimidazo[2,1-b]thiazole

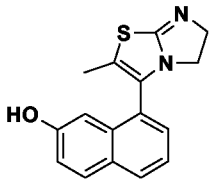


.HBr

To a solution of 3-(4-methoxynaphthalen-1-yl)-2-methyl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide (Example 49, 0.207g, 0.549mmol) in DCM (10mL) at 0°C was added BBr_3 (1.0M, 1.64mL) over a period of 2min. After stirring for 16hr at rt the reaction was

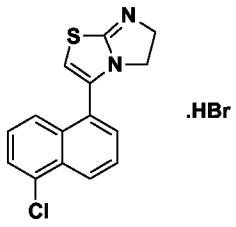
partitioned between saturated sodium bicarbonate solution (100mL) and EtOAc. The combined extracts were dried ($MgSO_4$) and concentrated to give an oil, which was dissolved in methanol and treated with HBr in acetic acid. The solvent was evaporated and the title compound was obtained via addition of EtOAc to precipitate the title compound which was collected by filtration. δ_H ($CDCl_3$): 2.13 (3H, s), 3.31 (1H, br s), 3.91-3.97 (1H, m), 4.09-4.15 (1H, m), 4.27-4.31 (2H, m), 6.96 (1H, d), 7.44 (1H, d), 7.51-7.63 (3H, m), 8.34 (1H, d); m/z (ES^+) = 283.09 $[M+H]^+$; RT = 2.49 min.

Example 82: 3-(7-Hydroxynaphthalen-1-yl)-2-methyl-5,6-dihydroimidazo[2,1-b]thiazole



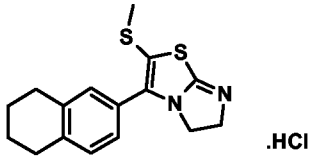
The title compound was prepared from 3-(7-methoxynaphthalen-1-yl)-2-methyl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide (Example 48) according to the procedure of Example 81. δ_H (DMSO): 1.88 (3H, s), 3.38-3.43 (2H, m), 3.90-4.03 (2H, m), 7.13-7.16 (2H, m), 7.34-7.38 (1H, m), 7.43-7.45 (1H, d), 7.87-7.92 (2H, m), 9.94 (1H, br s); m/z (ES^+) = 283.03 $[M+H]^+$; RT = 2.43 min.

Example 83: 3-(5-Chloronaphthalen-1-yl)-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide



The title compound was prepared from 2-bromo-1-(5-chloro-naphthalen-1-yl)ethanone (Preparation 124) under similar conditions as described in Example 1. δ_H (DMSO): 4.04 (2H, m), 4.30 (2H, m), 7.64 (1H, m), 7.84 (3H, m), 8.03 (1H, d), 8.40 (1H, d), 9.61 (1H, s); m/z (ES^+) = 287.14 $[M+H]^+$; RT = 2.67 min.

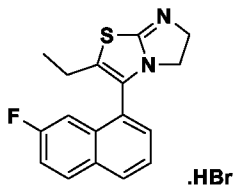
Example 84: 2-Methylsulfanyl-3-(5,6,7,8-tetrahydronaphthalen-2-yl)-5,6-dihydro-imidazo[2,1-b]thiazole hydrochloride



The title compound was prepared from 2-bromo-3-(5,6,7,8-tetrahydronaphthalen-2-yl)-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide (Preparation 127) and dimethyl disulphide under similar conditions as described in Example 18. δ_H (DMSO): 1.79 (4H, m), 2.40 (3H, s),

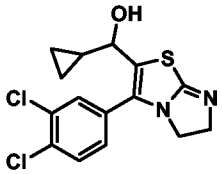
2.81 (4H, m), 4.18-4.33 (4H, m), 7.27 (3H, m), 10.20 (1H, br); m/z (ES^+) = 303.04 $[M+H]^+$; RT = 2.79 min.

Example 85: 2-Ethyl-3-(7-fluoronaphthalen-1-yl)-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide



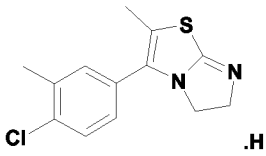
The title compound was prepared 2-bromo-1-(7-fluoronaphthalen-1-yl)butan-1-one and 2-imidazolidinethione (Preparation 135) under similar conditions as described in Example 1. δ_H (DMSO): 1.05 (3H, t), 2.30-2.50 (2H, m), 3.85 (1H, q), 4.05 (1H, q), 4.22 (2H, t), 7.55-7.75(4H, m), 8.20-8.25 (2H, m), 9.60 (1H, br); m/z (ES^+) = 300.1 $[M+H]^+$; RT = 2.62 min.

Example 86: Cyclopropyl[3-(3,4-dichlorophenyl)-5,6-dihydroimidazo[2,1-b]thiazol-2-yl]-methanol



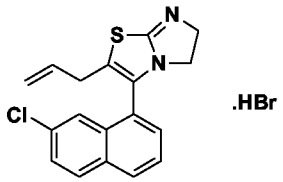
A solution of 3-(3,4-dichlorophenyl)-5,6-dihydroimidazo[2,1-b]thiazole-2-carbaldehyde (Preparation 138, 0.80g, 2.67mmol) in THF (30.0mL) was cooled at 0°C under inert atmosphere and cyclopropylmagnesium bromide 0.5 M solution in THF (16.0mL, 8.01mmol) was added over 10min. The mixture was stirred for 1hr before removing the ice bath and stirred for further 16hr. Water (40mL) was then added, stirred vigorously for 15min then the aqueous layer extracted with EtOAc (3 x 50mL), the organic layer dried ($MgSO_4$) and concentrated *in vacuo*. The yellow solid obtained was triturated with DCM (2 x 2.0mL) and residual solvent removed *in vacuo* to afford the title compound. δ_H (DMSO): 0.10 (1H, m), 0.45-0.30 (3H, m), 1.00 (1H, m), 3.50 (1H, q), 3.75 (1H, q), 4.00 (3H, m), 5.40 (1H, m), 7.50 (1H, d), 7.75 (1H, d), 7.80 (1H, s); m/z (ES^+) = 340.90 $[M+H]^+$; RT = 2.56 min.

Example 87: 3-(4-Chloro-3-methylphenyl)-2-methyl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide



The title compound was prepared from 2-bromo-1-(4-chloro-3-methylphenyl)propan-1-one (Preparation 149, 5.15g, 19.71mmol) and 2-imidazolidinethione under similar conditions as described in Example 1. δ_H (DMSO): 2.21 (3H, s), 2.41 (1H, s), 4.20-4.35 (4H, m), 7.40 (1H, d), 7.55 (1H, s), 7.65 (1H, d), 9.45 (1H, br s); m/z (ES^+) = 264.99 $[M+H]^+$; RT = 2.39 min.

Example 88: 2-Allyl-3-(7-chloronaphthalen-1-yl)-5, 6-dihydroimidazo[2, 1-b]thiazole hydrobromide



To a solution of 2-bromo-3-(7-chloronaphthalen-1-yl)-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide (Preparation 151, 3.42g) in THF (150mL) under an inert atmosphere at 0°C was added ethyl magnesium bromide solution (40% in ether, 7.65mL) and stirred for 20min. Allyl bromide (6.6mL) was added dropwise, stirred at 0°C for 20min and allowed to warm to rt and stirred for 16hr. Saturated ammonium chloride (40mL) was added and the reaction mixture extracted into EtOAc (3 x 300mL). The combined organic fractions were dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (DCM:MeOH, 96:4) gave the desired product which was converted to the hydrobromide salt by treating a MeOH solution with 30% HBr in acetic acid and then filtration to afford the title compound. δ_H (DMSO): 3.18 (2H, m), 3.85 (1H, m), 4.10 (1H, m), 4.22 (2H, m), 5.80 (1H, m), 7.70 (3H, m), 8.01 (1H, s), 8.18 (1H, d), 8.25 (1H, d), 9.68 (1H, s); m/z (ES^+) = 327.05 $[M+H]^+$; RT = 2.97 min.

The biological activity of the compounds of the invention may be tested in the following assay systems:

1. [^{3}H]Nisoxetine Binding to Noradrenaline Transporter Sites in Human Recombinant Membrane preparation

Membrane:

Membranes from a MDCK stable recombinant cell line expressing the human Noradrenaline Transporter sites was used to investigate the effects of compounds of the invention on binding of [^{3}H]nisoxetine.

Binding assay:

In displacement experiments, membranes were incubated with [^{3}H]nisoxetine at a single concentration of 1.0nM and buffer (total binding) or test compound (10^{-6} M or a range of concentrations) or desipramine (1μM; non-specific binding) for 90min at 4°C.

Alternatively membranes were incubated with [^{3}H]nisoxetine at a single concentration of 1.0nM and buffer (total binding) or test compound (11 concentrations) or nisoxetine (2μM, non-specific binding) for 4hr at 4°C.

Membrane bound radioactivity was recovered by filtration. Filters were rapidly washed with ice-cold buffer and radioactivity determined by liquid scintillation counting.

2. [^{3}H]Noradrenaline incorporation into rat hypothalamus synaptosomes Preparation of Synaptosomes

[^{3}H]-Noradrenaline incorporation assay:

Rat hypothalamic synaptosomes prepared according to standard procedures were incubated with test compound (a range of concentrations) or protriptyline for 20min at 37°C.

Synaptosomal incorporation was recovered by filtration. Filters were rapidly washed with ice-cold buffer and radioactivity determined by liquid scintillation counting.

3. [^{3}H]Imipramine Binding to 5-HT Transporter Sites in Human Recombinant Membrane preparation

Membrane:

Membranes from a HEK-293 stable recombinant cell line expressing the human Serotonin Transporter sites was used to investigate the effects of compounds of the invention on binding of [^{3}H]Imipramine.

Binding assay:

In displacement experiments, membranes were incubated with [^{3}H]imipramine at a single concentration of 2.0nM and buffer (total binding) or test compound (10^{-6} M or a range of concentrations) or imipramine (10μM; non-specific binding) for 30min at 22°C.

Alternatively binding was characterised using [^{3}H]paroxetine. In these displacement experiments membranes were incubated with [^{3}H]paroxetine at a single concentration of 0.5nM and buffer (total binding) or test compound (11 concentrations) or paroxetine (2μM, non-specific binding) for 4hr at 4°C.

Membrane bound radioactivity was recovered by filtration. Filters were rapidly washed with ice-cold buffer and radioactivity determined by liquid scintillation counting.

4. [^{3}H]serotonin incorporation into rat brain synaptosomes

Preparation of Synaptosomes

[^{3}H]-Serotonin incorporation assay:

Rat brain synaptosomes were incubated with test compound (a range of concentrations) or imipramine for 15min at 37°C.

Synaptosomal incorporation was recovered by filtration. Filters were rapidly washed with ice-cold buffer and radioactivity determined by liquid scintillation counting.

5. $5HT_{1A}$ Binding Assay and [^{35}S]GTPγS Binding Assay in Human Recombinant Membrane preparation

Membrane:

Membranes from a HEK-293 stable recombinant cell line or a CHO-K1 stable recombinant cell line expressing the human Serotonin 1A receptor were used to investigate the effects of compounds of the invention on binding of [^{3}H]8-OH-DPAT and the binding of [^{35}S]GTPγS.

Binding assay:

In displacement experiments, membranes were incubated with [^{3}H]8-OH-DPAT at a single concentration of 0.5nM and buffer (total binding) or test compound (10^{-6} M or a range of concentrations) or 8-OH-DPAT (10μM; non-specific binding) for 60min at 22°C.

Alternatively membranes were incubated with [^{3}H]8-OH-DPAT at a single concentration of 1nM and buffer (total binding) or test compound (11 concentrations) or 5-HT (2μM; non-specific binding) for 60min at 30°C.

Membrane bound radioactivity was recovered by filtration. Filters were rapidly washed with ice-cold buffer and radioactivity determined by liquid scintillation counting.

Functional [^{35}S]-GTPγS Binding Assay:

In [^{35}S]GTPγS binding assay, membranes were incubated with test compound (a range of concentrations) for 16min at rt. Following this pre-incubation 150pM of [^{35}S]GTPγS was

added to the membrane and incubated for a further 45min at 30°C. 5-HT and buspirone concentration effect curves were run alongside test compounds.

Membrane bound radioactivity was recovered by filtration. Filters were rapidly washed with ice-cold buffer and radioactivity determined by liquid scintillation counting.

Representative compounds of the invention exhibit displacements of >50% when measured at a concentration of 1 micromolar.

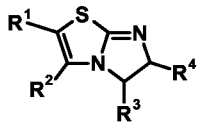
Examples 1-88 all exhibit 5-HT_{1A} agonism and noradrenaline reuptake inhibition or 5-HT_{1A} agonism, noradrenaline reuptake inhibition and 5-HT reuptake inhibition in these assay systems.

The biological activity of the compounds of the invention may also be tested in *in vivo* models known to those skilled in the art. Thus, for example, representative compounds of the invention following acute oral dosing of lean male Sprague Dawley rats or female Wistar rats significantly reduced food intake for up to 24hr compared to controls to a greater degree than sibutramine. Sub-chronic oral administration of representative compounds significantly attenuated weight gain in a diet-induced obese mouse model over 21 days and sub-chronic oral dosing once daily to high-fat fed male Sprague Dawley rats for 21 days reduced weight gain and to a greater extent than sibutramine.

Representative compounds have also demonstrated effects including decrease in fat pad masses and/or decrease in plasma levels of leptin, glucose, insulin or triglycerides as compared to vehicle-treated controls after sub-chronic oral dosing in rats. Also, in contrast to sibutramine, representative compounds of the invention showed no increases in heart rate or mean arterial blood pressure in conscious, telemeterised normotensive rats at doses significantly higher than those which give efficacy.

WHAT IS CLAIMED IS:

1. A compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof,

wherein R^1 is hydrogen, halo, C_{1-6} alkyl optionally substituted by one or more halo atoms or hydroxy groups, C_{3-6} cycloalkyl optionally substituted by one or more halo atoms or hydroxy groups, C_{1-2} alkylC_{3-6} cycloalkyl optionally substituted by one or more halo atoms or hydroxy groups, C_{1-6} alkoxycarbonyl, cyano, -C=N-OR^7, C_{2-6} alkenyl optionally substituted by one or more halo atoms or hydroxy groups in which hydroxy is not directly attached to either carbon of the double bond, C_{2-6} alkynyl optionally substituted by one or more halo atoms or hydroxy groups in which hydroxy is not directly attached to either carbon of the triple bond, $(CH_2)_mNR^5R^6$, C_{1-3}alkoxy, C_{1-3} alkylthio, C_{1-3} alkoxyC_{1-3} alkyl or C_{1-3} alkylthioC_{1-3} alkyl;

R^2 is an 8- to 10-membered bicyclic aromatic group optionally containing up to 3 heteroatoms selected from N and S, or phenyl, provided that R^2 is not benzo[b]thiophene;

R^2 may be optionally substituted by one or more groups selected from halo, cyano, hydroxy, NR^5R^6, $CONR^5R^6$, or $COOR^7$, or C_{1-3} alkyl, C_{2-3} alkenyl, C_{1-3} alkynyl, C_{3-6} cycloalkyl, C_{1-3} alkoxy, C_{1-3} hydroxyalkyl, C_{2-3} alkoxyalkyl or C_{1-3} alkyl$S(O)_n$ any of which may be optionally substituted by one or more halo atoms; or when R^2 is phenyl two substituents on phenyl may join to form a fused C_{5-6} carbocyclic ring;

R^3 and R^4 are independently hydrogen or C_{1-3} alkyl;

R^5 and R^6 are independently hydrogen or C_{1-3} alkyl, or together with the nitrogen to which they are attached form a 5- or 6-membered heterocyclyl group;

R^7 is hydrogen or C_{1-3} alkyl;

m is 1, 2 or 3; and

n is 0, 1 or 2;

provided that the compound is not:

a) 3-naphthalen-1-yl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide,

b) 3-naphthalen-2-yl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide,

c) 3-(3-chloro-4-propoxyphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

d) 3-(4-chlorophenyl)-2-ethyl-5,6-dihydroimidazo[2,1-b]thiazole,

e) 3-(4-chlorophenyl)-2-methyl-5,6-dihydroimidazo[2,1-b]thiazole,

f) 3-(3,4-dichlorophenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

g) 3-(2-hydroxy-5-methylphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

h) 3-(4-aminophenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

i) 3-(2-chlorophenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

j) 3-(3-chlorophenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

k) 3-(4-chlorophenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

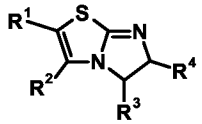
l) 3-(2,4-dichlorophenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

m) 3-(2,5-dichlorophenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

n) 3-(4-bromophenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

o) 3-(2,4-difluorophenyl)-5,6-dihydroimidazo[2,1-b]thiazole,
p) 3-(2-methylphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,
q) 3-(3-methylphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,
r) 3-(4-methylphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,
s) 3-(2,4-dimethylphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,
t) 3-(3,4-dimethylphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,
u) 3-(4-cyanophenyl)-5,6-dihydroimidazo[2,1-b]thiazole,
v) 3-(4-carboxyphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,
w) 3-(2-methoxyphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,
x) 3-(3-methoxyphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,
y) 3-(4-methoxyphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,
z) 3-(2-hydroxyphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,
aa) 3-(3-hydroxyphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,
ab) 3-(4-hydroxyphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,
ac) 3-(3,4-dihydroxyphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,
ad) 3-(2-hydroxy-4-methoxyphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,
ae) 3-(3-hydroxy-4-methoxyphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,
af) 3-(4-hydroxy-3-methoxyphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,
ag) 3-(4-hydroxy-3-chlorophenyl)-5,6-dihydroimidazo[2,1-b]thiazole,
ah) 3-(4-hydroxy-3-methylphenyl)-5,6-dihydroimidazo[2,1-b]thiazole, or
ai) 3-(3,4-dichlorophenyl)-2-phenyl-5,6-dihydroimidazo[2,1-b]thiazole.

2. A compound of formula (Ia):



(Ia)

or a pharmaceutically acceptable salt thereof,

wherein R^1 is hydrogen, halo, C_{1-6} alkyl optionally substituted by one or more halo atoms or hydroxy groups, C_{3-6} cycloalkyl optionally substituted by one or more halo atoms or hydroxy groups, C_{1-2} alkylC_{3-6} cycloalkyl optionally substituted by one or more halo atoms or hydroxy groups, C_{1-6} alkoxycarbonyl, cyano, -C=N-OR^7, C_{2-6} alkenyl optionally substituted by one or more halo atoms or hydroxy groups in which hydroxy is not directly attached to either carbon of the double bond, C_{2-6} alkynyl optionally substituted by one or more halo atoms or hydroxy groups in which hydroxy is not directly attached to either carbon of the triple bond, $(CH_2)_mNR^5R^6$, C_{1-3}alkoxy, C_{1-3} alkylthio, C_{1-3} alkoxyC_{1-3} alkyl or C_{1-3} alkylthioC_{1-3} alkyl;

R^2 is an 8- to 10-membered bicyclic aromatic group optionally containing up to 3 heteroatoms selected from N and S, provided that R^2 is not benzo[b]thiophene;

R^2 may be optionally substituted by one or more groups selected from halo, cyano, hydroxy, NR^5R^6, $CONR^5R^6$, or $COOR^7$, or C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} hydroxyalkyl, C_{2-3} alkoxyalkyl or C_{1-3} alkyl$S(O)_n$ any of which may be optionally substituted by one or more halo atoms;

R^3 and R^4 are independently hydrogen or C_{1-3} alkyl;

R^5 and R^6 are independently hydrogen or C_{1-3} alkyl, or together with the nitrogen to which they are attached form a 5- or 6-membered heterocyclyl group;

R^7 is hydrogen or C_{1-3} alkyl;

m is 1, 2 or 3; and

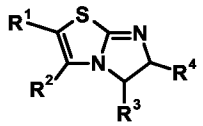
n is 0, 1 or 2;

provided that the compound is not:

a) 3-naphthalen-1-yl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide, or

b) 3-naphthalen-2-yl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide.

3. A compound of formula (Ib):



(Ib)

or a pharmaceutically acceptable salt thereof, wherein

R^1 is hydrogen, halo, C_{1-6} alkyl optionally substituted by one or more halo atoms or hydroxy groups, C_{3-6} cycloalkyl optionally substituted by one or more halo atoms or hydroxy groups, C_{1-2} alkylC_{3-6} cycloalkyl optionally substituted by one or more halo atoms or hydroxy groups, C_{1-6} alkoxycarbonyl, cyano, -C=N-OR^7, C_{2-6} alkenyl optionally substituted by one or more halo atoms or hydroxy groups in which hydroxyl is not directly attached to either carbon of the double bond, C_{2-6} alkynyl optionally substituted by one or more halo atoms or hydroxy groups in which hydroxyl is not directly attached to either carbon of the triple bond, $(CH_2)_mNR^5R^6$, C_{1-3}alkoxy, C_{1-3} alkylthio, C_{1-3} alkoxyC_{1-3} alkyl or C_{1-3} alkylthioC_{1-3} alkyl;

R^2 is phenyl substituted by one or more groups selected from halo, cyano, hydroxy, NR^5R^6, $CONR^5R^6$, or $COOR^7$, or C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, C_{3-6} cycloalkyl, C_{1-3} alkoxy, C_{1-3} hydroxyalkyl, C_{2-3} alkoxyalkyl or C_{1-3} alkyl$S(O)_n$ any of which may be optionally substituted by one or more halo atoms;

R^3 and R^4 are independently hydrogen or C_{1-3} alkyl;

R^5 and R^6 are independently hydrogen or C_{1-3} alkyl, or together with the nitrogen to which they are attached form a 5- or 6-membered heterocyclyl group;

R^7 is hydrogen or C_{1-3} alkyl;

m is 1, 2 or 3; and

n is 0, 1 or 2;

provided that the compound is not:

c) 3-(3-chloro-4-propoxyphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

d) 3-(4-chlorophenyl)-2-ethyl-5,6-dihydroimidazo[2,1-b]thiazole,

e) 3-(4-chlorophenyl)-2-methyl-5,6-dihydroimidazo[2,1-b]thiazole,

f) 3-(3,4-dichlorophenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

g) 3-(2-hydroxy-5-methylphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

h) 3-(4-aminophenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

i) 3-(2-chlorophenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

j) 3-(3-chlorophenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

k) 3-(4-chlorophenyl)-5,6-dihydroimidazo[2,1-b]thiazole,

l) 3-(2,4-dichlorophenyl)-5,6-dihydroimidazo[2,1-b]thiazole,
m) 3-(2,5-dichlorophenyl)-5,6-dihydroimidazo[2,1-b]thiazole,
n) 3-(4-bromophenyl)-5,6-dihydroimidazo[2,1-b]thiazole,
o) 3-(2,4-difluorophenyl)-5,6-dihydroimidazo[2,1-b]thiazole,
p) 3-(2-methylphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,
q) 3-(3-methylphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,
r) 3-(4-methylphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,
s) 3-(2,4-dimethylphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,
t) 3-(3,4-dimethylphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,
u) 3-(4-cyanophenyl)-5,6-dihydroimidazo[2,1-b]thiazole,
v) 3-(4-carboxyphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,
w) 3-(2-methoxyphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,
x) 3-(3-methoxyphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,
y) 3-(4-methoxyphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,
z) 3-(2-hydroxyphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,
aa) 3-(3-hydroxyphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,
ab) 3-(4-hydroxyphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,
ac) 3-(3,4-dihydroxyphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,
ad) 3-(2-hydroxy-4-methoxyphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,
ae) 3-(3-hydroxy-4-methoxyphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,
af) 3-(4-hydroxy-3-methoxyphenyl)-5,6-dihydroimidazo[2,1-b]thiazole,
ag) 3-(4-hydroxy-3-chlorophenyl)-5,6-dihydroimidazo[2,1-b]thiazole,
ah) 3-(4-hydroxy-3-methylphenyl)-5,6-dihydroimidazo[2,1-b]thiazole, or
ai) 3-(3,4-dichlorophenyl)-2-phenyl-5,6-dihydroimidazo[2,1-b]thiazole.

4. A compound according to any one of claims 1 to 3 wherein R^1 is hydrogen, C_{1-6} alkyl optionally substituted by one or more halo atoms or hydroxy groups, C_{3-6} cycloalkyl optionally substituted by one or more halo atoms or hydroxy groups, or C_{1-2} alkylC_{3-6} cycloalkyl optionally substituted by one or more halo atoms or hydroxy groups.

5. A compound according to claim 4 wherein R^1 is C_{1-6} alkyl.

6. A compound according to claim 1, 2, 4 or 5 wherein R^2 is naphthalenyl, thienothiophenyl, indolyl, quinolinyl, isoquinolinyl or benzoisothiazolyl, or a pharmaceutically acceptable salt thereof.

7. A compound according to claim 6 wherein R^2 is naphthalen-1-yl, naphthalen-2-yl, thieno[2,3-b]thiophen-2-yl, quinolin-2-yl, isoquinolinyl or benzoisothiaxol-3-yl.

8. A compound according to claim 7 wherein R^2 is naphthalen-1-yl.

9. A compound according to any one of claims 1, 2 or 4 to 8 wherein R^2 is substituted by one or two substituents selected from halo and C_{1-3} alkyl.

10. A compound according to any one of claims 1 or 3 to 5 wherein R^2 is phenyl substituted in the 3-, 4- and/or 5-positions by one or two substituents selected from halo and C_{1-3} alkyl optionally substituted by one or more halo atoms.

11. A compound according to any one of the preceding claims wherei R^3 and R^4 are both hydrogen.

12. A compound of formula (I) as defined in any one of Examples 3 to 88, as the free base or a pharmaceutically acceptable salt thereof.

13. A pharmaceutical composition comprising a compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

14. A method for the treatment of a disease or condition in which Noradrenaline and optionally also Serotonin reuptake plays a role comprising a step of administering to a subject in need thereof an effective amount of a compound according to any one of claims 1 to 12, including the compounds of provisos a), b) and f) to ai), or a pharmaceutically acceptable salt thereof.

15. A method for the treatment of a disease or condition in which Noradrenaline and optionally also Serotonin reuptake plays a role and in which 5-HT_{1A} agonism is desirable comprising a step of administering to a subject in need thereof an effective amount of a compound according to any one of claims 1 to 12, including the compounds of provisos a), b) and f) to ai), or a pharmaceutically acceptable salt thereof.

16. A method for the regulation of food intake and/or satiety comprising a step of administering to a subject in need thereof an effective amount of a compound according to any one of claims 1 to 12, including the compounds of provisos a), b) and f) to ai), or a pharmaceutically acceptable salt thereof.

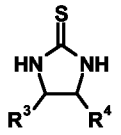
17. A method for the treatment of obesity comprising a step of administering to a subject in need thereof an effective amount of a compound according to any one of claims 1 to 12, including the compounds of provisos a), b) and f) to ai), or a pharmaceutically acceptable salt thereof.

18. A method for the treatment of a metabolic disease selected from Type II diabetes, metabolic syndrome (syndrome X), impaired glucose tolerance, dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL levels and hypertension, comprising a step of administering to a subject in need thereof an effective amount of a compound according to any one of claims 1 to 12, including the compounds of provisos a), b) and f) to ai), or a pharmaceutically acceptable salt thereof.

19. A method for reducing the potential for cardiovascular side effects in the treatment of a disease or condition as defined in any one of claims 13 to 18 comprising a step of administering

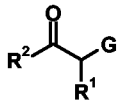
to a subject in need thereof an effective amount of a compound according to any one of claims 1 to 3, including the compounds of provisos a), b) and f) to ai), or a pharmaceutically acceptable salt thereof.

20. A process for the production of a compound of formula (I) which comprises the step of reacting a compound of formula (III):



III

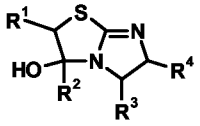
with a compound of formula (IV):



IV

wherein R^1 to R^4 are as defined in claim 1 and G is hydrogen or a leaving group.

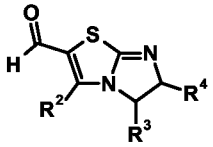
21. A compound of formula (II):



II

wherein R^1, R^2, R^3 and R^4 are as defined in claim 1.

22. A compound of formula (X):



X

wherein R^2, R^3 and R^4 are as defined in claim 1.