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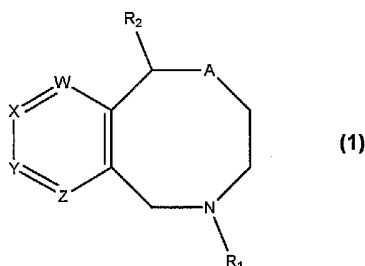
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(54) Title: BENZOXAZOCINES AND THEIR THERAPEUTIC USE AS MONOAMINE REUPTAKE INHIBITORS



(57) Abstract: Compounds having therapeutic utility are of general formula (1) wherein R₁ is H, C₁-C₆ alkyl optionally substituted with F or C₃-C₆ cycloalkyl or C₂-C₄ alkenyl; A is O, CH₂ or S(O)_n where n is 0-2; one of W, X, Y and Z is N, CH or CR₃ and the others are CH; R₂ is C₅-C₆ heteroaryl, C₅-C₁₀ cycloalkyl or cycloalkenyl optionally containing one or more heteroatoms selected from O, N and S(O)_n where n is 0-2, and optionally substituted with R₃; or a phenyl group optionally substituted in one or more positions with one or more substituents independently selected from halogen, CN, CF₃, C₁-C₆ alkyl and OR₁, or the phenyl group is fused to a five or six membered ring which may be carbocyclic, heterocyclic (containing 1-2 heteroatoms selected from O, N and S), aromatic or heteroaromatic (containing 1-2 heteroatoms selected from O and N); R₃ is selected from halogen; CF₃; CN; OR₅; SO₂N(R₅)₂; COR₅; CO₂R₅; CON(R₅)₂; NR₁COR₄; NR₁SO₂R₄; NR₁CO₂R₄; NR₁CON(R₅)₂; OC₁-C₆ alkyl substituted with R₃; C₁-C₆ alkyl optionally substituted with unsubstituted R₃; C₃-C₆ cycloalkyl optionally substituted with unsubstituted R₃; C₂-C₈ alkenyl optionally substituted with unsubstituted R₃; C₂-C₈ alkynyl optionally substituted with unsubstituted R₃; aryl optionally substituted with unsubstituted R₃; and five or six membered aromatic heterocycles containing 1-4 heteroatoms selected from N and O; R₄ is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, aryl and heteroaryl; and R₅ is H, C₁-C₆ alkyl; C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, aryl or heteroaryl and is the same as or different to another R₅; or a pharmaceutically acceptable salt thereof.

Field of the Invention

This invention relates to novel benzoxazocine compounds which inhibit monoamine reuptake. In particular, compounds of the present invention exhibit activity
 5 as analgesic agents and also as anti-emetics but also may find utility in a range of other therapeutic indications.

Background of the Invention

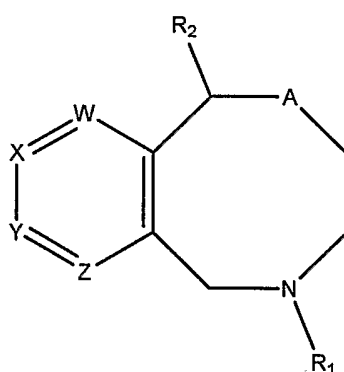
Nefopam, i.e. 5-methyl-1-phenyl-3,4,5,6-tetrahydro-1H-2,5-benzoxazocine hydrochloride, is a centrally acting non-narcotic analgesic.

10 WO03/092689 discloses that the single enantiomers of nefopam are useful for the treatment of pain and emesis.

WO2004/056788 discloses derivatives of nefopam. Its publication date is later than the priority dates now claimed.

Summary of the Invention

15 Novel compounds according to this invention are of general formula (1):



(1)

wherein R_1 is H, C_1 - C_6 alkyl optionally substituted with F or C_3 - C_6 cycloalkyl or C_2 - C_4 alkenyl;

20 A is O, CH_2 or $S(O)_n$ where n is 0-2;

one of W, X, Y and Z is N, CH or CR_3 and the others are CH;

R_2 is C_5 - C_6 heteroaryl, C_5 - C_{10} cycloalkyl or cycloalkenyl optionally containing one or more heteroatoms selected from O, N and $S(O)_n$ where n is 0-2, and optionally substituted with R_3 ; or a phenyl group optionally substituted in one or more positions with
 25 one or more substituents independently selected from halogen, CN, CF_3 , C_1 - C_6 alkyl and OR_1 , or the phenyl group is fused to a five or six membered ring which may be

carbocyclic, heterocyclic (containing 1-2 heteroatoms selected from O, N and S), aromatic or heteroaromatic (containing 1-2 heteroatoms selected from O and N);

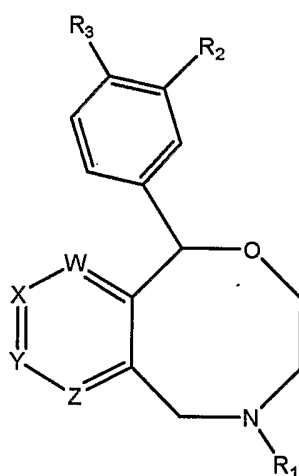
R_3 is selected from halogen; CF_3 ; CN; OR_5 ; $SO_2N(R_5)_2$; COR_5 ; CO_2R_5 ; $CON(R_5)_2$; NR_1COR_4 ; $NR_1SO_2R_4$; $NR_1CO_2R_4$; $NR_1CON(R_5)_2$; OC_1-C_6 alkyl substituted with R_3 ; C_1-C_6 alkyl optionally substituted with unsubstituted R_3 ; C_3-C_6 cycloalkyl optionally substituted with unsubstituted R_3 ; C_2-C_6 alkenyl optionally substituted with unsubstituted R_3 ; C_2-C_6 alkynyl optionally substituted with unsubstituted R_3 ; aryl optionally substituted with unsubstituted R_3 ; and five or six membered aromatic heterocycles containing 1-4 heteroatoms selected from N and O;

R_4 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, aryl and heteroaryl; and

R_5 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, aryl or heteroaryl and is the same as or different to another R_5 ;

or a pharmaceutically acceptable salt thereof.

Compounds disclosed in WO2004/056788 may be excluded, e.g. those of the general formula:



wherein

R_1 is H, C_1-C_6 alkyl, optionally substituted with F or C_3-C_6 cycloalkyl or C_2-C_6 alkenyl;

either R_2 and R_3 are the same or different and are H, a halogen, CN, CF_3 , C_1-C_6 alkyl or OR_1 , or R_2 and R_3 form a five or six membered ring which may be carbocyclic, heterocyclic (containing 1-2 heteroatoms taken from O, N or S), aromatic or heteroaromatic (containing 1-2 heteroatoms taken from O and N);

one of W , X , Y and Z is N, or CR_4 and the others are each CH;

R₄ is a halogen atom, CF₃, CN, OR₇, SO₂N(R₆)₂, COR₆, CO₂R₆, CON(R₆)₂, NR₁COR₅, NR₁SO₂R₅, NR₁CO₂R₅, NR₁CON(R₆)₂, OC₁-C₆ alkyl optionally substituted with R₄, C₁-C₆ alkyl optionally substituted with R₄, C₃-C₆ cycloalkyl optionally substituted with R₄, C₂-C₆ alkenyl optionally substituted with R₄, C₂-C₆ alkynyl optionally substituted with R₄, aryl optionally substituted with R₄, or a five or six membered aromatic heterocycle containing 1-4 heteroatoms selected from N and O, linked either through carbon or nitrogen;

R₅ is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, aryl or heteroaryl; each R₆ (which may be the same or different) is H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, aryl or heteroaryl; and

R₇ is aryl or heteroaryl;

or a pharmaceutically acceptable salt thereof.

Compounds of the invention have utility as therapeutic agents. Compositions containing them and their therapeutic uses are further aspects of the invention. Further, compounds of formula (1) wherein R₃ is a halogen atom such as Br are useful as intermediates.

Description of Preferred Embodiments

It will be appreciated that compounds according to the invention contain an asymmetrically substituted carbon atom. The presence of this asymmetric centre in a compound of formula (1) can give rise to stereoisomers, and in each case the invention is to be understood to extend to all such stereoisomers, including enantiomers and diastereomers, and mixtures including racemic and non-racemic mixtures thereof.

As used in this specification, the term "C₁-C₆ alkyl" refers to a straight or branched chain alkyl moiety having from one to six carbon atoms, including, for example, methyl, ethyl, propyl, isopropyl, butyl, *tert*-butyl, pentyl, hexyl and the like.

The term "C₅-C₆ heteroaryl" refers to an aryl system of five or six atoms, of which at least one atom is selected from O, N and S. This term includes, for example, pyridine, tetrahydropyran etc.

The term "C₂-C₆ alkenyl" refers to a straight or branched chain alkyl moiety having two to six carbon atoms and having in addition one double bond, of either E or Z stereochemistry where applicable. This term includes, for example, vinyl, 1-propenyl, 1- and 2-butenyl, 2-methyl-2-propenyl etc.

The term "C₂-C₆ alkynyl" refers to a straight or branched chain alkyl moiety having two to six carbon atoms and having in addition one triple bond. This term includes, for example, ethynyl, 1-propargyl, 1- and 2-butynyl etc.

The term "C₃-C₆ cycloalkyl" refers to a saturated alicyclic moiety having from three to six carbon atoms and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

5 The term "C₅-C₁₀ cycloalkenyl" refers to an unsaturated alicyclic moiety having from five to ten carbon atoms and at least one double bond and includes, for example, phenyl and the like.

The term "aryl" means an optionally substituted phenyl or naphthyl group.

10 The term "carbocyclic" refers to a saturated alicyclic moiety having five or six carbon atoms and includes, for example, benzofused cyclopentyl and cyclohexyl and the like.

The term "heterocyclic" refers to a saturated heterocyclic moiety having from five or six atoms but containing one or more heteroatom selected from N, O and S, and includes, for example, benzofused pyrrolidinyl, tetrahydrofuranyl, piperidinyl, dioxalane and the like.

15 The term "heteroaromatic" refers to aromatic ring systems of five or six atoms of which at least one atom is selected from O, N and S, and includes, for example, pyrrolyl, pyridinyl, diazoly, diazinyl, triazolyl, triazinyl, tetrazolyl, furanyl, oxazolyl, isoxazolyl or oxadiazolyl as well as benzofused furanyl, thiophenyl, pyridyl, indolyl, pyridazinyl, piperazinyl, pyrimidinyl and the like, e.g. benzofuranyl, quinolinyl, isoquinolinyl or
20 quinazolinyl. Such rings can be linked either through carbon or nitrogen.

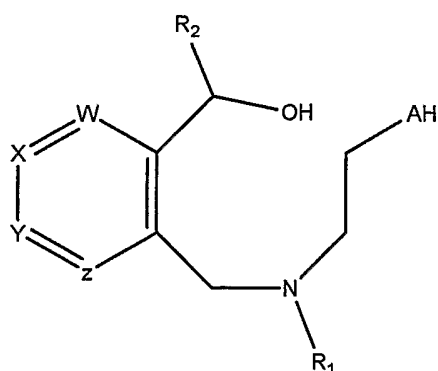
The term "halogen" means fluorine, chlorine, bromine or iodine.

Compounds of the general formula (1) may be prepared by any suitable method known in the art and/or by the processes described below. It will be appreciated that where a particular stereoisomer of formula (1) is required, the synthetic processes
25 described herein may be used with the appropriate homochiral starting material and/or isomers maybe resolved from mixtures using conventional separation techniques (eg. HPLC).

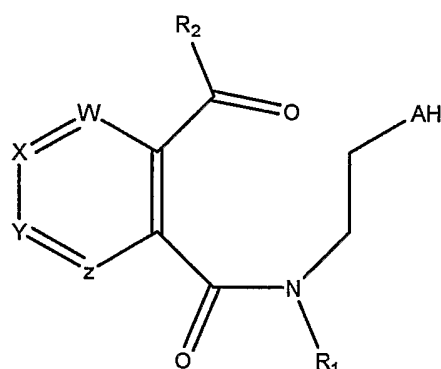
In the description and formulae below, variables such as R₁, R₂, R₃, R₄, R₅, A, W, X, Y and Z are as defined above, except where otherwise indicated. It will be
30 appreciated that functional groups, such as amino, hydroxyl or carboxyl groups, present in the various compounds described below, and which it is desired to retain, may need to be in protected form before any reaction is initiated. In such instances, removal of the protecting group may be the final step in a particular reaction. Suitable protecting groups for such functionality will be apparent to those skilled in the art. For specific details, see
35 "Protective Groups in Organic Synthesis", Wiley Interscience, T W Greene, PGM Wuts.

A process for preparing compounds of general formula (1), where W, X, Y or Z is N or C-Br and A is O or S(O)_n, comprises cyclisation with acid (for instance with p-toluenesulphonic acid) of a diol (2) which can in turn be obtained by reduction of ketone (3) with a suitable reducing agent.

5



(2)



(3)

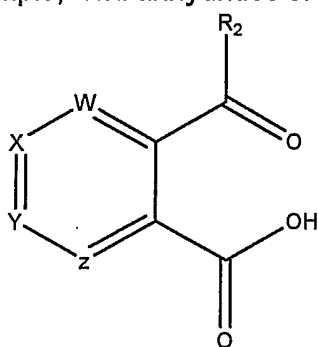
Reduction of a keto amide of general formula (3) can be carried out with reagents well known to those familiar in the art of synthetic organic chemistry. An example of a highly reactive reducing agent is lithium aluminium hydride, although reagents based on borane (e.g. borane.tetrahydrofuran complex) or modified sodium borohydride reduction (e.g. with a nickel or cobalt salt enhancer) may be equally effective.

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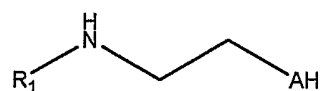
Equally, reduction of the ketone in (3), for example with sodium borohydride, followed by acid cyclisation, for example with p-toluenesulphonic acid, then ultimate reduction of the amide group, for example with borane, also leads to compounds of general formula (1).

15

Ketones (3) can be prepared by condensation of a carboxylic acid (4) or an active derivative thereof, with an amine (5). Active derivatives of acids of formula (4) include, for example, acid anhydrides or acid halides, such as acid chlorides.



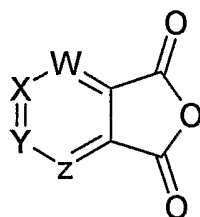
(4)



(5)

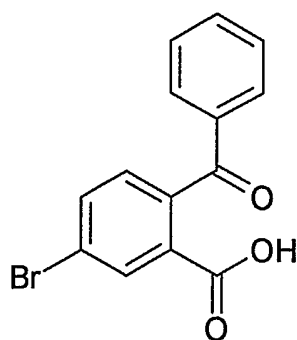
The coupling reaction may be performed using standard conditions for amidation reactions of this type. Thus, the reaction may be achieved in a solvent, for example an inert organic solvent such as an ether, e.g. a cyclic ether such as tetrahydrofuran, an amide, e.g. a substituted amide such as dimethylformamide, or a halogenated hydrocarbon such as dichloromethane at low temperature, e.g. -30°C to ambient temperature, such as -20°C to 0°C, optionally in the presence of a base, e.g. an organic base such as an amine, e.g. triethylamine or a cyclic amine such as *N*-methylmorpholine. Where an acid (4) is used directly, the reaction may additionally be performed in the presence of a condensing agent, for example a diimide such as *N,N*-dicyclohexylcarbodiimide, advantageously in the presence of a triazole such as 1-hydroxybenzotriazole. Alternatively, the acid may be reacted with a chloroformate, for example ethyl chloroformate, prior to reaction with the amine (5).

Acids (4) may be prepared by Friedel-Crafts acylation of R_2 with an anhydride (7). This reaction is carried out in an inert solvent (such as dichloromethane) in the presence of a Lewis acid catalyst (such as aluminium trichloride).

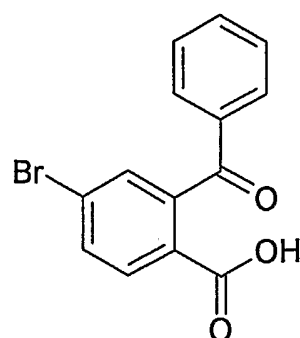


(7)

It is well recognised by those skilled in the art that such reactions may provide mixtures of products and in turn that these mixtures can often be separated by flash column chromatography. For example, where $Y = C-Br$, $W = X = Z = CH$ and R_2 is phenyl, Friedel-Crafts acylation under aluminium trichloride catalysis provides two isomeric bromides (4a) and (4b). These can be readily separated by column chromatography and independently progressed to compounds of general formula (1), wherein X or Y is C-Br, by the route described above.



(4a)



(4b)

Compounds of general formula (1) where one of W, X, Y and Z is C-hal such as C-Br represent flexible intermediates that may be used for the preparation of other compounds of general formula (1). For instance, such compounds can be smoothly converted into the corresponding nitrile ($R_3 = \text{CN}$) either by reaction with cuprous cyanide in a dipolar aprotic solvent such as *N*-methylpyrrolidinone (NMP) or under palladium-catalysed conditions.

The nitrile can be readily converted, by hydrolysis, into the primary amides ($R_3 = \text{CONH}_2$), esters and the corresponding carboxylic acids (CO_2R_5) or into the corresponding tetrazoles, by treatment with a suitable azide donor such as sodium azide or trimethylsilylazide.

In addition, compounds of general formula (1) where one of W, X, Y and Z is C-hal such as C-Br can be lithiated with *n*-, *sec*- or *tert*-butyllithium in an inert organic solvent such as an ether, e.g. a cyclic ether such as tetrahydrofuran, at very low temperature, e.g. -78°C . Treatment with either a carbon (e.g. carbon dioxide, *N,N*-dimethylformamide or paraformaldehyde), sulphur (e.g. SO_2Cl_2 , followed by amidation, such as with ammonia) or nitrogen (diphenylphosphoryl azide, followed by reduction, such as with REDAL) provides access, by subsequent derivatisation, to derivatives where R_3 is CO_2R_5 , $\text{CON}(\text{R}_5)$, CH_2OR_5 , $\text{SO}_2\text{N}(\text{R}_4)_2$, NR_1COR_4 , $\text{NR}_1\text{CO}_2\text{R}_5$ or $\text{NR}_1\text{CON}(\text{R}_5)_2$.

In addition, compounds of general formula (1) where one or W, X, Y and Z is C-hal such as C-Br can undergo palladium-catalysed coupling reactions with carbon-based coupling partners. Thus, such compounds can be coupled to alkenes of the general type $\text{CH}_2=\text{CHR}_3$ under Heck conditions, to alkynes of the general type $\text{CH}=\text{CHR}_3$ under Sonogoshira conditions, or to metallocycles, e.g. where the metal is tin, under Stille coupling conditions. This gives access to compounds where R_3 is optionally

substituted C₂-C₆ alkenyl or C₂-C₆ alkynyl, or a five-membered aromatic heterocycle containing 1-4 heteroatoms selected from N (such as in pyrrole, diazoles, triazoles or tetrazoles) and O (such as in furan, oxazoles or oxadiazoles). Such coupling reactions ensure that chains and rings are linked through carbon.

5 In addition to the examples described above, additional compounds of formula (1) may be prepared by interconversion of other compounds of formula (1). Thus, for example, a compound wherein R₃ is alkyl may be prepared by hydrogenation (using palladium on carbon in a suitable solvent, such as an alcohol, e.g. ethanol) of a corresponding compound wherein R₃ is alkenyl.

10 Any mixtures of final products or intermediates obtained can be separated on the basis of the physico-chemical differences of the constituents, in known manner, into the pure final products or intermediates, for example by chromatography, distillation, fractional crystallization, or by formation of a salt if appropriate or possible under the circumstances.

15 The compounds according to the invention exhibit *in vitro* inhibiting activities with respect to monoamine (i.e. noradrenaline, serotonin and dopamine) reuptake. The activity and selectivity of the compounds may be determined by use of an appropriate monoamine reuptake assay.

This invention also relates to a method of treatment for patients (including man
20 and/or mammalian animals raised in the dairy, meat or fur industries or as pets) suffering from disorders or diseases which can be attributed to monoamine reuptake as previously described, and more specifically, a method of treatment involving the administration of the monoamine reuptake inhibitor of formula (1) as the active constituents.

Accordingly, the compounds of formula (1) can be used in the treatment of pain
25 and emesis. Pain and related conditions that can be treated include syndromes characterised by chronic pain and fatigue, fibromyalgia, chronic fatigue syndrome, complex regional pain syndrome, irritable bowel syndrome, myofacial pain and atypical chest pain. The compounds may also find utility in a range of other therapeutic indications such as depression, post-traumatic stress disorders, attention-deficit
30 disorders, obsessive-compulsive disorders, pre-menstrual syndrome, substance abuse and sexual dysfunction; a method of management (by which is meant treatment or prophylaxis) of disease or conditions mediated by monoamine reuptake in mammals, in particular in humans, which method comprises administering to the mammal an effective, amount of a compound of formula (1) above, or a pharmaceutically acceptable salt
35 thereof; and a compound of formula (1) for use in human or veterinary medicine,

particularly in the management (by which is meant treatment or prophylaxis) of diseases or conditions mediated by monoamine reuptake; and the use of a compound of formula (1) in the preparation of an agent for the management (by which is meant treatment or prophylaxis) of diseases or conditions mediated by monoamine reuptake.

5 The disease or conditions referred to above include pain, emesis, depression, post-traumatic stress disorders, attention-deficit disorders, obsessive-compulsive disorders, pre-menstrual syndrome, substance abuse and sexual dysfunction.

Compounds of formula (1) may be administered orally, topically, buccally, ocularly, rectally, vaginally, parenterally, intra-nasally, sublingually or by inhalation spray,
10 e.g. in dosage unit formulations containing non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle, sheep, dogs, cats etc, the compounds of the invention are effective in the
15 treatment of humans.

The pharmaceutical composition containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. The composition may be in immediate or controlled release form.

20 Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavouring agents, colouring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active
25 ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents,
30 for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in US4256108,
35 US4166452 and US4265874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules where in the active ingredient is mixed with an inert solid diluent, for example calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil. Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as a polyoxyethylene with partial esters derived from fatty acids and hexitol anhydrides, for example polyoxyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl or n-propyl p-hydroxybenzoate, one or more colouring agents, one or more flavouring agents, and one or more sweetening agents, such as sucrose or saccharin.

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

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified, for example sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally occurring phosphatides, for example soya bean, lecithin, and esters

or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

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

20 The compounds of formula (1) may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

25 For topical use, creams, ointments, jellies, solutions or suspensions, etc containing the compounds of Formula (1) are employed. For purposes of this specification, topical application includes mouth washes and gargles.

30 Dosage levels of the order of from about 0.05 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 2.5 mg to about 7 g per patient per day). For example, emesis may be effectively treated by the administration of from about 0.01 to 50 mg of the compound per kilogram of body weight per day (about 0.5 mg to about 3.5 g per patient per day).

35 The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans may vary from about 5 to about 95 percent of the total

composition. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient.

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

The following Examples illustrate the invention. They include compounds which are in the following Table.

Example	R1	R2	W,X,Y,Z
1	benzyl	phenyl	W=X=Y=Z=CH
13	methyl	(3-tosyloxy)phenyl	W=X=Z=CH Y=C-Br
20	methyl	(2-methyl-3-methoxy)phenyl	W=X=Z=CH Y=C-Br
21	methyl	(2-methyl-3-methoxy)phenyl	W=X=Z=CH Y=C-CN
22	methyl	(2-methyl-3-methoxy)phenyl	W=X=Z=CH Y=C-cyclopropyl
44	methyl	2-methylphenyl	W=Y=Z=CH X=C-Br
45	methyl	2-methylphenyl	W=Y=Z=CH X=C-CN
46	methyl	2-methylphenyl	W=Y=Z=CH X=C-cyclopropyl
47	methyl	2-methylphenyl	W=X=Z=CH Y=C-Br
48	methyl	2-methylphenyl	W=X=Z=CH Y=C-CN
49	methyl	2-methylphenyl	W=X=Z=CH Y=C-cyclopropyl
50	methyl	3-pyridyl	W=Y=Z=CH X=C-Br
51	methyl	3-pyridyl	W=X=Z=CH Y=C-Br
52	methyl	3-pyridyl	W=X=Z=CH Y=C-CN

10

All ^1H NMR recorded on a Bruker AC250. All chemical shifts (δ) have been rounded to 2 decimal places, and coupling constants (J) are measured in Hz and to the nearest 0.1 decimal place.

Example 1**5-Benzyl-1-phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine**

To a stirring solution of desmethylnepomam (96 mg, 0.41 mmol) in DMF (3 ml) were added sodium hydride (15 mg, 0.49 mmol) and then benzyl bromide (0.7 ml, 0.61 mmol). The resulting blue solution was heated at 65°C for 2 hours. The reaction was quenched by the addition of water and the organics were extracted into dichloromethane, dried (MgSO₄), filtered and concentrated *in vacuo* to provide the crude material. Purification by silica gel column chromatography (1→2%MeOH / DCM) furnished the target product (45 mg, 34%) as a brown oil.

δ_H (CDCl₃; 250MHz) 2.74-2.80 (1H, m, one of CH₂), 2.96-3.00 (1H, m, one of CH₂), 3.88-4.07 (4H, m, four of CH₂), 4.27-4.36 (1H, m, one of CH₂), 4.92 (1H, d, J12.7, one of ArCH₂NR₂), 5.82 (1H, s, CHOR), 7.05-7.07 (1H, m, aromatic H), 7.26-7.42 (11H, aromatic H), 7.56-7.60 (2H, m, aromatic H)

Example 2**5-Allyl-1-phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine**

Sodium hydride (24 mg, 1.01 mmol) was added to a solution of desmethylnepomam (200 mg, 0.84 mmol) at RT. The resulting mixture was stirred for 2 hours before allyl bromide (0.12 ml, 1.33 mmol) was added dropwise. The blue solution was heated at 65°C for a further two hours, then quenched with water. The aqueous mixture was extracted with dichloromethane and the combined extracts dried (MgSO₄), filtered and concentrated *in vacuo* to provide the target product (66 mg, 28%).

δ_H (CDCl₃; 250MHz) 2.90-3.13 (2H, m, two of CH₂), 3.64 (2H, d, J6.1, two of CH₂), 4.01 (1H, bd, J13.6, one of CH₂), 4.26 (1H, d, J12.1, one of ArCH₂NR₂), 4.38-4.49 (1H, m, one of CH₂), 5.01 (1H, d, J12.1, one of ArCH₂NR₂), 5.42-5.49 (2H, m, two terminal alkenic H), 5.77 (1H, s, CHOR), 6.27-6.37 (1H, m, alkenic H), 7.11-7.39 (8H, aromatic H), 7.51 (1H, bs, aromatic H).

Example 3**5-Cyclopropyl-1-phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine**

Sodium cyanoborohydride (106 mg, 1.69 mmol) was added to a stirring suspension of desmethylnepomam (100 mg, 0.42 mmol), acetic acid (0.24 ml, 4.22 mmol), (1-ethoxycyclopropyloxy)trimethylsilane (0.51 mL, 2.53 mmol) and 4A molecular sieves in methanol (1.5 ml). The resulting brown solution was heated at reflux temperature overnight. The reaction mixture was quenched by the addition of sodium bicarbonate solution and extracted into dichloromethane. The combined organic phases were dried (MgSO₄), filtered and concentrated *in vacuo*. The crude material was purified

by silica gel column chromatography (DCM→2%MeOH/DCM) to provide the target product (84 mg, 68%).

δ_{H} (CDCl₃; 250MHz) 0.56 (4H, bs, cyclopropyl CH₂CH₂), 1.90-1.94 (1H, m, cyclopropyl CH), 2.88 (1H, ddd, *J*14.3, 6.1, 2.7, one of CH₂CH₂), 3.00 (1H, ddd, *J*14.3, 7.3, 2.1, one of CH₂CH₂), 3.87 (1H, ddd, *J*12.5, 6.1, 2.1, one of CH₂CH₂), 3.96 (1H, d, *J*12.8, one of ArCH₂NR₂), 4.15 (1H, ddd, *J*12.5, 7.3, 2.7, one of CH₂CH₂), 4.86 (1H, d, one of ArCH₂NR₂), 5.84 (1H, s, CHOR), 6.99-7.00 (1H, m, aromatic H), 7.18-7.30 (8H, aromatic H).

Example 4

10 5-Propyl-1-phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine

5-Allyl-1-phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine (66 mg, 0.24 mmol) was dissolved in THF (4 ml) and 10% Pd/C (2 micro-spatulas) added. The reaction vessel was shaken under a hydrogen atmosphere for 3 hours. After this time, the mixture was filtered and the filtrate concentrated *in vacuo*. Purification of the crude mixture by silica gel column chromatography (DCM→5%MeOH/DCM) furnished the target product as a pale yellow oil (42 mg, 62%).

δ_{H} (CDCl₃; 250MHz) 1.03 (3H, t, *J*7.3, CH₃), 1.99-2.10 (2H, m, two of propyl CH₂CH₂), 2.96-3.22 (4H, m, two of propyl CH₂CH₂ and two of ring CH₂CH₂), 4.02-4.10 (1H, m, ArCH₂NR₂), 4.37-4.51 (2H, m, two of CH₂CH₂), 5.03-5.31 (1H, bs, one of ArCH₂NR₂), 5.77 (1H, CHOR), 7.15-7.18 (3H, m, aromatic H), 7.27-7.40 (5H, m, aromatic H), 7.63 (1H, bs, aromatic H).

Example 5

5-Methylcyclopropyl-1-phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine

Desmethylnefopam (110 mg, 0.43 mmol) was dissolved in anhydrous DMF (2 ml) under a nitrogen atmosphere and sodium hydride (as a 60% suspension in mineral oil, 21 mg, 0.52 mmol) was added. The resulting mixture was heated to 80°C. (Bromomethyl)cyclopropane (0.06 ml, 0.65 mmol) was added and the reaction mixture kept between 80 and 90°C. Once the starting material was shown to have been consumed by TLC, the reaction was quenched by the addition of water and brine. The aqueous mixture was extracted three times with ethyl acetate, and the combined organics were washed with brine, before being dried (MgSO₄), filtered and concentrated *in vacuo* to give a red/pink oil. Purification by silica gel column chromatography (DCM→1.5%MeOH/DCM) furnished the target product as a red oil (35 mg, 26%).

δ_{H} (CDCl₃; 250MHz) 0.08-0.20 (2H, m, two of cyclopropyl CH₂CH₂), 0.57-0.63 (2H, m, two of cyclopropyl CH₂CH₂), 0.99-1.04 (1H, m, cyclopropyl CH), 2.41 (1H, dd, *J*12.5, 7.0, one

of CH_2), 2.70 (1H, dd, $J_{12.5}$, 5.8, one of CH_2), 2.83-3.00 (2H, m, two of CH_2CH_2), 3.90 (1H, ddd, $J_{12.5}$, 5.8, 2.4, one of CH_2CH_2), 3.95 (1H, d, $J_{12.5}$, one of ArCH_2NR_2), 4.22 (1H, ddd, $J_{12.5}$, 7.6, 3.2, one of CH_2CH_2), 4.77 (1H, d, $J_{12.5}$, one of ArCH_2NR_2), 5.83 (1H, s, CHOR), 7.01 (1H, d, $J_{7.0}$, aromatic H), 7.16-7.33 (8H, m, aromatic H).

5 Example 6

5-Isopropyl-1-phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine

Desmethylnepom (116 mg, 0.45 mmol) was dissolved in acetone (3ml) over 4A molecular sieves (spatula tip). A drop of acetic acid was added and the resulting mixture was stirred at RT for one hour. After this time, sodium cyanoborohydride (114 mg, 1.82 mmol) was added and the mixture was stirred overnight at RT, after which time, TLC showed that starting material had been consumed. The reaction mixture was filtered and the collected solids washed with ethyl acetate. The filtrate was concentrated *in vacuo* to remove the acetone, providing a pale yellow residue. This was re-dissolved in dichloromethane and washed with a sat. aq. solution of sodium bicarbonate. The organic layer was separated, dried (MgSO_4), filtered and concentrated *in vacuo* to provide the crude product. Purification by silica gel column chromatography (DCM $\rightarrow$ 1% MeOH/DCM) furnished the desired compound (34 mg, 30%).

δ_{H} (CDCl_3 ; 250MHz) 1.13 (3H, d, $J_{6.7}$, one CH_3 of $\text{N}(\text{CH}_3)_2$), 1.25 (3H, d, $J_{6.4}$, one CH_3 of $\text{N}(\text{CH}_3)_2$), 1.73 (1H, dd, $J_{4.6}$, 1.5, CH), 2.77-3.11 (2H, m, two of CH_2CH_2), 3.71 (1H, d, $J_{12.8}$, one of ArCH_2NR_2), 3.87 (1H, ddd, $J_{12.2}$, 8.9, 1.8, one of CH_2CH_2), 4.11 (1H, ddd, $J_{12.2}$, 5.0, 2.3, one of CH_2CH_2), 4.34 (1H, d, $J_{12.8}$, one of ArCH_2NR_2), 5.90 (1H, s, CHOR), 7.02 (1H, d, $J_{7.3}$, aromatic H), 7.16-7.30 (8H, aromatic H).

Example 7

8-(4-Pyridyl)-5-methyl-1-(3-methoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine

8-Bromo-5-methyl-1-(3-methoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine, i.e. compound 21b in WO2004/056788 (117 mg, 0.32 mmol), pyridine-4-boronic acid (52 mg, 0.42 mmol), $\text{Pd}(\text{PPh}_3)_4$ (10 mol%) and KOH (2M solution in water, 0.48 ml) were suspended in DME (2 ml). The mixture was degassed and then purged with nitrogen before heating at reflux temperature under a nitrogen atmosphere for 17 hours. The mixture was allowed to cool to RT and diluted with ethyl acetate (20 ml) and washed with water (20 ml). The aqueous phase was extracted into ethyl acetate (2 x 20 ml) and the combined organic extracts were dried (MgSO_4), filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (EtOAc $\rightarrow$ 10% MeOH/EtOAc) furnished the target compound as a pale yellow oil (25 mg, 22%).

δ_{H} (CDCl₃; 250MHz) 2.50 (3H, s, NCH₃), 2.60 (1H, ddd, *J*14.2, 5.8, 2.6, one of CH₂CH₂), 2.86 (1H, ddd, *J*14.2, 8.3, 2.1, one of CH₂CH₂), 3.75 (1H, d, *J*12.8, one of ArCH₂NR₂), 3.78 (3H, s, OCH₃), 3.88 (1H, ddd, *J*12.5, 5.8, 2.1, one of CH₂CH₂), 4.22 (1H, ddd, *J*12.5, 8.3, 2.6, one of CH₂CH₂), 4.87 (1H, d, *J*12.8, one of ArCH₂NR₂), 5.81 (1H, s, CHOR), 6.79-6.91 (4H, m, aromatic H), 7.14 (1H, d, *J*7.6, aromatic H), 7.22-7.28 (1H, m, aromatic H), 7.44-7.62 (4H, m, aromatic H), 8.65 (1H, d, *J*5.8, aromatic H).

5-Pyrimidineboronic acid

^tBuLi (3.02 ml, 2M solution in hexane, 7.55 mmol) was added dropwise to a stirring solution of 5-bromopyrimidine (1 g, 6.29 mmol) and triisopropylborate (1.46 ml, 7.55 mmol) in anhydrous toluene (16 ml) and anhydrous THF (4 ml) at -70°C under a nitrogen atmosphere. The reaction mixture was stirred at -70°C for 30 mins and then removed from the cold bath. When the internal temp. reached -20°C, the reaction was quenched by the dropwise addition of 2M HCl (10 ml). The mixture was allowed to warm to RT and then separated. The aqueous phase was taken to pH 5.5 with 2M KOH and extracted into THF (3 x 25 ml). The combined organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo* to provide a colourless solid. The solid was slurried in acetonitrile (2 ml), collected by filtration and dried on the sinter to give the target boronic acid as a brilliant white solid (340 mg, 44%).

δ_{H} (MeOD; 250MHz) 8.98 (2H, s), 9.14 (1H, s).

Example 8

8-(5-Pyrimidine)-5-methyl-1-(3-methoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine

8-Bromo-5-methyl-1-(3-methoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine, i.e. compound 21b in WO2004/056788 (118 mg, 0.3 mmol), CsF (148 mg, 0.98 mmol), 5-pyrimidine boronic acid (52 mg, 0.42 mmol) and Pd(PPh₃)₄ (10 mol%) were suspended in DME (2 ml) and water (100 μ L). The mixture was degassed and purged with nitrogen then heated to reflux temperature for 17 hours. The reaction mixture was allowed to cool to RT before diluting with ethyl acetate (20 ml) and washing with water (20 ml). The aqueous phase was extracted with ethyl acetate (2 x 20 ml) and the combined organic extracts were dried (MgSO₄), filtered and evaporated to dryness to provide crude material. Purification by silica gel column chromatography (EtOAc→10% MeOH/EtOAc) furnished the target product as a pale yellow/brown solid (36 mg, 30%).

δ_{H} (CDCl₃; 250MHz) 2.53 (3H, s, NCH₃), 2.68 (1H, ddd, *J*14.2, 5.8, 2.6, one of CH₂CH₂), 2.88 (1H, ddd, *J*14.2, 8.2, 2.2, one of CH₂CH₂), 3.79 (1H, d, *J*12.8, one of ArCH₂NR₂), 3.79 (3H, s, OCH₃), 3.89 (1H, ddd, *J*12.8, 5.8, 2.2, one of CH₂CH₂), 4.24 (1H, ddd, *J*12.8,

8.2, 2.6, one of CH_2CH_2), 4.89 (1H, d, $J_{12.8}$, one of ArCH_2NR_2), 5.82 (1H, s, CHOR), 6.79-6.91 (3H, m, aromatic H), 7.17-7.29 (2H, m, aromatic H), 7.40-7.43 (2H, m, aromatic H), 8.95 (s, 2H, pyrimidine H), 9.20 (1H, s, pyrimidine H).

Example 9

5-Methyl-1-(3-methoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine

8-Bromo-5-methyl-1-(3-methoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine, i.e. compound 21b in WO2004/056788 (206 mg, 0.57mmol), was suspended in toluene (3 ml) and degassed under vacuum, then purged with nitrogen. Palladium tetrakis (33 mg) was added to the mixture, which was then subjected to the degassing/nitrogen purge sequence again. A degassed solution of sodium carbonate (2M, 12 ml) and boronic ester (117 mg, 0.57 mmol) were added and the whole mixture was then degassed, purged with nitrogen and heated to 80°C overnight. The reaction mixture was allowed to cool, diluted with water (10 ml) and the resulting mixture extracted into ethyl acetate (3 x 50 ml). The combined organic phases were dried (MgSO₄), filtered and concentrated *in vacuo* to provide the crude product. Purification by silica gel column chromatography [EtOAc] was carried out twice to give a mixture of products.

Mass spec analysis suggested the debrominated species had been formed. m/z (ES^+) 284 (MH^+). δ_{H} (CDCl_3 ; 250MHz) 2.51 (3H, s, $N\text{-CH}_3$), 2.68 (1H, ddd, $J_{14.2}$, 5.2, 2.9, one of CH_2CH_2), 2.88 (1H, ddd, $J_{14.2}$, 9.0, 2.6, one of CH_2CH_2), 3.78 (3H, s, OCH_3), 3.81 (1H, d, $J_{12.8}$, one of ArCH_2NR_2), 3.88 (1H, ddd, $J_{12.8}$, 5.2, 2.6, one of CH_2CH_2), 4.23 (1H, ddd, $J_{12.8}$, 9.0, 2.9, one of CH_2CH_2), 4.86 (1H, d, $J_{12.8}$, one of ArCH_2NR_2), 5.76 (1H, s, CHOR), 6.78-6.86 (3H, m, aromatic H), 7.03-7.05 (1H, m, aromatic H), 7.20-7.27 (4H, m, aromatic H).

Example 10

5-Methyl-1-(3-methoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine-8-carboxamide

8-Cyano-5-methyl-1-(3-methoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine, i.e. compound 21b in WO2004/056788 (73 mg, 0.24 mmol), was heated to reflux temperature in $t\text{BuOH}$ (3 mL) with KOH (20 mg, 0.36 mmol) for 90 mins. At the end of this time, the reaction mixture was allowed to cool to RT. The mixture was then washed with brine (20 ml) and extracted into dichloromethane (3 x 20 ml). The combined organic extracts were dried (MgSO₄) and concentrated *in vacuo* to provide the crude amide as a yellow solid. The solid was slurried in ethyl acetate, collected by

suction filtration, washed with heptane and dried on the sinter to provide amide (24 mg, 31%).

δ (MeOD; 250MHz) 2.44 (3H, s, NCH₃), 2.51-2.60 (1H, m (poorly resolved ddd), one of CH₂CH₂), 2.72-2.81 (1H, m (poorly resolved ddd), one of CH₂CH₂), 3.75 (4H, s, OCH₃ and one of ArCH₂), 3.84-3.90 (1H, m (poorly resolved ddd), one of CH₂CH₂), 4.17-4.27 (1H, m (poorly resolved ddd), one of CH₂CH₂), 5.01 (1H, d, J12.5, one of ArCH₂), 5.83 (1H, s, CHOR), 6.80-6.83 (3H, m, aromatic H), 7.14-7.21 (2H, m, aromatic H), 7.70-7.76 (2H, m, aromatic H).

MS (ESI⁻) 325 ([M-H]⁻); (ESI⁺) 349 ([M+Na]⁺)

10 **2-Benzoyl-4-fluorobenzoic acid and 2-Benzoyl-5-fluorobenzoic acid**

3-Fluorophthalic anhydride (5 g, 33 mmol) was suspended in benzene (17.7 ml) at RT under nitrogen. Aluminium chloride (8.8 g, 66 mmol) was added in portions, turning the mixture orange in colour. The reaction was heated at reflux temperature for 4 hours before cooling to RT. The yellow slurry was added carefully to 10% HCl (100 ml),
15 producing a white precipitate. The aqueous mixture was extracted into ethyl acetate (3 x 100 mL) and the combined organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo* to provide a mixture of the keto-acids 2-benzoyl-4-fluorobenzoic acid and 2-benzoyl-5-fluorobenzoic acid as colourless crystals (8 g, quantitative yield).

δ_H (MeOD; 250MHz) 7.17-7.25 (3H, m, ArH), 7.31-7.42 (2H, m, ArH), 7.48 (2H, d, J8.0, ArH), 7.69 (1H, d, J8.0, ArH).

2-Benzoyl-6-fluoro-N-(2-hydroxyethyl)-N-methylbenzamide and 2-Benzoyl-3-fluoro-N-(2-hydroxyethyl)-N-methylbenzamide

A crude mixture of 2-benzoyl-6-fluorobenzoic acid and 2-benzoyl-3-fluorobenzoic acid (7 g, 28 mmol) was suspended in dichloromethane (70 ml) at RT. A few drops of
25 DMF, followed by oxalyl chloride (3 ml, 34 mmol) were added dropwise and the resulting mixture was stirred until gas evolution had ceased, and the suspended solid had dissolved. The mixture was concentrated *in vacuo* and co-evaporated with dichloromethane (2 x 40 mL) to provide the crude acid chloride. (2-methylamino)-ethanol (2.24 ml, 28 mmol) and triethylamine (3.9 ml, 28 mmol) were dissolved in
30 dichloromethane (50 ml) and cooled in an ice bath. The acid chloride was dissolved in dichloromethane (50 ml) and added dropwise to the cooled solution of amine. The mixture was allowed to warm to RT and stirred for 4.5 hours, after which point the reaction was quenched by the addition of sat. aq ammonium chloride solution (200 ml). The organics were extracted into dichloromethane (3 x 100 ml), and the combined
35 extracts were dried (MgSO₄), filtered and concentrated *in vacuo*. Purification was

achieved by gravity silica gel column chromatography (50% EtOAc/heptane to 100% EtOAc) with pre-absorption of the crude amide onto silica.

2-Benzoyl-6-fluoro-*N*-(2-hydroxyethyl)-*N*-methylbenzamide (490 mg) was obtained as a 3:4 mixture of two rotamers:

5 δ_H (CDCl₃; 250MHz) 3.04 (3H, s, CH₃, major rotamer), 3.10 (3H, s, CH₃, minor rotamer), 3.33-3.40 (2H, two of CH₂CH₂, major rotamer), 3.52-3.64 (2H, two of CH₂CH₂, minor rotamer), 3.78-3.96 (4H, two of CH₂CH₂ for major and minor rotamer), 7.22-7.27 (4H, m, ArH both rotamers), 7.28-7.42 (6H, m, ArH both rotamers), 7.55-7.61 (2H, ArH both rotamers), 7.75-7.83 (4H, m, ArH both rotamers).

10 2-Benzoyl-3-fluoro-*N*-(2-hydroxyethyl)-*N*-methylbenzamide (2.74 g) was obtained as two rotamers:

δ_H (CDCl₃; 250MHz) 3.03 (3H, s, CH₃, one rotamer), 3.05 (3H, s, CH₃, one rotamer), 3.55-3.59 (4H, m, two of CH₂CH₂ for each rotamer), 3.75-3.79 (4H, m, two of CH₂CH₂ for each rotamer), 7.16-7.27 (4H, m, ArH both rotamers), 7.44-7.63 (4H, m, ArH both rotamers), 7.84 (2H, d, J7.9, ArH both rotamers).

2-[[3-Fluoro-2-(hydroxyphenyl-methyl)-benzyl]-methylamino]-ethanol

2-Benzoyl-3-fluoro-*N*-(2-hydroxyethyl)-*N*-methylbenzamide (2.58 g, 8.57 mmol) was dissolved in anhydrous THF (25ml) at RT under a nitrogen atmosphere. Borane-dimethylsulfide complex (2.0M in THF, 18.8 ml, 37.7 mmol) was added dropwise and the resulting mixture was stirred at RT overnight. The reaction was carefully quenched by the addition of HCl (10%, 36ml). The mixture was then heated to reflux temperature for approx. 1 hour before cooling to ambient temperature. The THF was removed *in vacuo* and the remaining solution was partitioned between MTBE (40 ml) and water (60 ml). The aqueous phase was separated, basified with 2M NaOH(aq) and extracted into ethyl acetate (4 x 50 ml). The combined organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo* to give 2-[[3-fluoro-2-(hydroxyphenyl-methyl)-benzyl]-methylamino]-ethanol as a viscous oil which later crystallised.

25 δ_H (CDCl₃; 250MHz) 2.17 (3H, s, CH₃), 2.35-2.42 (1H, m, one of CH₂CH₂), 2.52-2.62 (1H, m, one of CH₂CH₂), 2.88 (1H, d, J12.5, one of ArCH₂NR₂), 3.42 (1H, d, J12.5, one of ArCH₂NR₂), 3.62-3.65 (2H, m, two of CH₂CH₂), 6.38 (1H, s, CHOH), 6.96 (1H, d, J7.3, ArH), 7.10-7.37 (7H, m, ArH).

Example 11

10-Fluoro-5-methyl-1-phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine

35 Crude 2-[[3-fluoro-2-(hydroxyphenylmethyl)benzyl]methylamino]ethanol (234 mg, 0.81 mmol) was heated to reflux temperature with *p*TSA (231 mg, 1.21 mmol) in toluene

(4 ml). The reaction was kept open to allow the toluene/water to evaporate. After approx. 1.5 hours, a gummy residue remained in the reaction flask. It was allowed to cool to RT at which point, sat. aq sodium bicarbonate solution and ethyl acetate were added to solubilise the residue. The aqueous phase was repeatedly extracted with ethyl acetate, and the combined extracts were dried (MgSO₄), filtered and evaporated to dryness to provide the crude cyclised product. Purification by gravity silica gel column chromatography [EtOAc] furnished the target compound, (90 g, 25%).

δ_H (CDCl₃; 250MHz) 2.47 (3H, s, CH₃), 2.59 (1H, ddd, *J*13.9, 5.6, 3.3, one of CH₂CH₂), 2.78 (1H, ddd, *J*13.9, 8.5, 2.6, one of CH₂CH₂), 3.58 (1H, d, *J*12.4, one of ArCH₂NR₂), 3.83 (1H, ddd, *J*12.3, 5.6, 2.6, one of CH₂CH₂), 4.30 (1H, ddd, *J*12.3, 8.5, 3.3, one of CH₂CH₂), 5.09 (1H, d, *J*12.4, one of ArCH₂NR₂), 5.94 (1H, d, *J*1.9, CHOR), 6.89-6.96 (1H, m, ArH), 7.04 (1H, d, *J*7.6, ArH), 7.19-7.32 (6H, m, ArH)

2-[[2-Fluoro-6-(hydroxyphenylmethyl)benzyl]methylamino]ethanol

2-Benzoyl-6-fluoro-N-(2-hydroxyethyl)-N-methylbenzamide (440 mg, 1.46 mmol) was dissolved in dry THF (4 ml) under nitrogen. Borane-dimethylsulfide (2.0M solution in THF, 3.2 ml, 6.43 mmol) was added dropwise and the resulting mixture was stirred overnight at RT. The reaction was quenched by the addition of 2M HCl (6ml) and heated at reflux temperature for 1 hour. The acidic mixture was then cooled and partitioned between MTBE (30 ml) and water (30 ml). The aqueous phase was separated and extracted with ethyl acetate (4 x 30 ml). The combined extracts were dried (MgSO₄), filtered and concentrated *in vacuo* to give the crude amine. Purification by gravity silica gel column chromatography [EtOAc] furnished 2-[[2-fluoro-6-(hydroxyphenylmethyl)benzyl]methylamino]ethanol (19 mg, 5%).

δ_H (250MHz; CDCl₃) 2.72 (3H, s, NCH₃), 2.54-2.73 (2H, m, two of CH₂CH₂), 3.36 (1H, dd, *J*12.8, 2.1, one of ArCH₂NR₂), 3.63-3.72 (3H, two of CH₂CH₂ and one of ArCH₂NR₂), 5.91 (1H, s, CHOH), 6.97-7.07 (2H, m, aromatic H), 7.22-7.40 (6H, m, aromatic H).

Example 12

7-Fluoro-5-methyl-1-phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine

Crude 2-[[2-fluoro-6-(hydroxyphenyl-methyl)benzyl]methylamino]ethanol (20 mg, 0.069 mmol) was dissolved in toluene and *p*TSA (20 mg, 0.1 mmol) added. The mixture was heated to 120°C in an open vessel to allow evaporation of the solvent. After 30 mins, a gummy residue remained in the reaction vessel. The vessel was allowed to cool and the residue dissolved in ethyl acetate (5 ml) and sat. aq. sodium bicarbonate solution (10 ml). The aqueous phase was washed with ethyl acetate and the combined

organic extracts dried (MgSO_4), filtered and concentrated *in vacuo* to provide the product as a crude light brown oil (10 mg, 53%).

δ_{H} (CDCl_3 , 250MHz) 2.50 (3H, s, NCH_3), 2.68 (1H, ddd, J 13.9, 6.3, 2.8, one of CH_2CH_2), 2.84 (1H, ddd, J 13.9, 7.8, 2.1, one of CH_2CH_2), 3.90 (1H, ddd, J 12.5, 6.3, 2.1, one of CH_2CH_2), 4.05 (1H, d, J 13.4, one of ArCH_2), 4.21 (1H, ddd, J 12.5, 7.8, 2.8, one of CH_2CH_2), 4.71 (1H, dd, J 13.4, 3.4, one of ArCH_2), 5.81 (1H, s, CHOR), 6.82 (1H, d, J 7.6, aromatic H), 7.37 (1H, t, J 8.5, aromatic H), 7.10-7.23 (2H, m, aromatic H), 7.25-7.35 (3H, m, aromatic H), 7.37-7.45 (1H, m, aromatic H).

Purity measured at 50%.

10 TBS-protected 3-bromophenol

To a solution of 3-bromophenol (100 g, 0.6 mol) in dichloromethane (600 ml) was added imidazole (100 g, 1.46 mol) at 0°C. After 10 min, TBDMS-Cl (96 g, 0.64 mol) was added, and the mixture was stirred at RT overnight. The mixture was then diluted with MTBE (1L) and filtered. The filtrate was washed with sat. ammonium chloride (4 x 200 ml), sat. bicarb. (200 ml) and brine (200 ml), before being dried (MgSO_4), filtered and concentrated *in vacuo* to give the product as a yellow oil (156.6 g) that was used without further purification.

δ_{H} (CDCl_3 ; 250MHz) 7.10-6.77 (4H, m, aromatics), 0.99 (9H, s, $\text{C}(\text{CH}_3)_3$), 0.21 (6H, s, 2 x CH_3).

20 4-Bromo-2-(3-*t*-butyldimethylsilyloxy-benzoyl)-benzoic acid and 5-Bromo-2-(3-*t*-butyldimethylsilyloxy-benzoyl)-benzoic acid

A solution of TBS-protected 3-bromophenol (156.6 g, 0.54 mol) in anhydrous THF (160 ml) was added dropwise to a stirring suspension of magnesium turnings (13 g, 0.54 mol) in dry THF (240 ml). The Grignard formation initiated following the addition of 1 ml of solution. The resulting mixture was left stirring until the reflux had stopped, and then this was added in a single portion to a stirred solution of 4-bromophthalic anhydride (122.4 g, 0.54 mol) in anhydrous THF (240 ml). The reaction mixture was heated at reflux temperature overnight. After cooling to RT, the reaction was quenched by the addition of sat. aq. solution of ammonium chloride (250 ml) and the organics were extracted into ethyl acetate (3 x 250 ml). The combined organic extracts were dried (MgSO_4), filtered and concentrated *in vacuo* to provide the crude acid as a brown oil (226.6 g). The crude material was carried through to the next step without further purification.

δ_{H} (CDCl_3 ; 250MHz) 8.07-6.75 (7H, m, aromatics), 0.99-0.94 (9H, m, $\text{C}(\text{CH}_3)_3$), 0.20-0.13 (6H, m, 2 x CH_3).

5-Bromo-*N*-(2-hydroxyethyl)-*N*-methyl-2-(3-^tbutyldimethylsilyloxy-benzoyl)-benzamide

To a solution of a mixture of 4-bromo-2-(3-^tbutyldimethylsilyloxy-benzoyl)-benzoic acid and 5-bromo-2-(3-^tbutyldimethylsilyloxy-benzoyl)-benzoic acid (226.6 g, 0.52 mol) in anhydrous dichloromethane (900 ml), under an atmosphere of nitrogen, was added anhydrous *N,N*-dimethylformamide (1 ml) followed by the slow addition of oxalyl chloride (50.8 ml, 0.57 mol), and the reaction stirred at RT overnight. The dichloromethane was then removed *in vacuo*. Dichloromethane (2 x 500 ml) was added to the crude oil and evaporated *in vacuo*. The crude acid chloride was dissolved in dichloromethane (900 ml), cooled to 0°C (ice bath) and triethylamine (81 ml, 0.57 mol) added dropwise. *N*-methylethanolamine (42.8 g, 0.57 mol) was then added dropwise and the mixture left to warm to RT overnight under an atmosphere of nitrogen. The mixture was then quenched with brine (800 ml) and the layers separated. The aqueous layer was then separated and washed with dichloromethane (800 ml), and the combined organics were dried (MgSO₄), filtered and concentrated *in vacuo* to yield the mixture of regioisomers (255.5 g) as a dark brown oil.

100 g of the above brown oil was purified by silica gel column chromatography (3:1 EtOAc: Heptane). This afforded 14 g of 5-bromo-*N*-(2-hydroxyethyl)-*N*-methyl-2-(3-^tbutyldimethylsilyloxy-benzoyl)-benzamide.

20 δ_H (CDCl₃; 250MHz) 7.59-7.25 (7H, m, aromatics), 3.91-3.57 (4H, m, CH₂-CH₂), 3.11 and 2.99 (3H, 2 x s, NCH₃), 0.98 (9H, s, C(CH₃)₃), 0.21 (6H, s, 2 x CH₃).

5-Bromo-*N*-(2-hydroxyethyl)-*N*-methyl-2-(3-tosyloxy-benzoyl)-benzamide

TBAF (10.1 ml, 1M solution in THF, 10.14 mmol) was added to a stirred solution of 5-bromo-*N*-(2-hydroxyethyl)-*N*-methyl-2-(3-^tbutyldimethylsilyloxy-benzoyl)-benzamide (5g, 10.14 mmol) in THF (60 ml) at RT. A solution of tosyl chloride (1.9 g, 10.14 mmol) in THF (60 ml) was then added dropwise and the mixture heated to reflux temperature for 3 h. A further 10mmol of triethylamine followed by 7 mmol of TsCl were added over a further hour to drive the reaction to completion. After cooling to RT the mixture was diluted with ethyl acetate (100 ml), washed with water (2 x 100 ml), dried (MgSO₄), filtered and concentrated *in vacuo* to give 7 g of an orange oil. Purification by silica gel column chromatography [2:1 EtOAc:Heptane] afforded the title compound (3.14 g, 58%) as a pale yellow oil.

30 δ_H (CDCl₃; 250MHz) 7.74-7.20 (11H, m, aromatics), 3.86-3.53 (4H, m, CH₂CH₂), 3.07 and 2.97 (3H, 2 x s, NCH₃), 2.47 (3H, s, Ar-CH₃).

2-({5-Bromo-2-[hydroxyl-(3-tosyloxy-phenyl)-methyl]-benzyl}-methylamino)-ethanol

Borane dimethylsulfide complex (2.0M in THF, 12.94 ml, 25.88 mmol) was added dropwise to a solution of 5-bromo-*N*-(2-hydroxyethyl)-*N*-methyl-2-(3-tosyloxy-benzoyl)-benzamide (3.14 g, 5.88 mmol) in anhydrous THF (20 ml) at 0°C. The reaction mixture was left to stir at RT overnight. The crude mixture was then quenched carefully by addition of an aqueous 6M HCl solution (20 ml) and then heated to reflux temperature for 2h. After cooling to RT, the THF was removed *in vacuo*. Water (10 ml) was added and the mixture was then basified to pH 10 by addition of an aqueous solution of sodium hydroxide solution (50 %), and then extracted with ethyl acetate (2 x 20 mL). The combined organic layers were then dried (MgSO₄), filtered and concentrated *in vacuo* to give a white oil/solid (3.17 g). Purification by silica gel column chromatography [5:1, EtOAc:Heptane] afforded the title compound (0.74g, 24%) as a colourless oil.

δ_H (CDCl₃; 250MHz) 7.67-6.83 (11H, m, aromatics), 5.72 (1H, s, CHOH), 3.73-3.67 (2H, m, CH₂), 3.39-3.27 (2H, m, CH₂), 2.63-2.53 (2H, m, CH₂), 2.44 (3H, s, Ar-CH₃), 2.22 (3H, s, NCH₃).

Example 13**8-Bromo-5-methyl-1-(3-tosyloxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine**

2-({5-Bromo-2-[hydroxyl-(3-tosyloxyphenyl)methyl]benzyl}methylamino)ethanol (0.74 g, 1.43 mmol) was heated to reflux temperature under Dean-Stark conditions with *p*TSA (0.41 g, 2.14 mmol) in toluene (20 ml) for 2 h. The reaction mixture was allowed to cool and then diluted with ethyl acetate (10 ml). The mixture was washed with sat. aq. sodium bicarbonate solution (2 x 10 ml). The combined organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo* to provide 0.65 g of product that was used without further purification.

δ_H (CDCl₃; 250MHz) 7.67-6.72 (11H, m, aromatics), 5.67 (1H, s, CH-O), 4.55 (1H, d, *J* 13, ArCH_AH_BN), 4.11 (1H, ddd, *J* 13, 8 and 2.5, CH_AH_BCH₂), 3.83 (1H, ddd, *J* 13, 8 and 2.5, CH_AH_BCH₂), 3.60 (1H, d, *J* 13, ArCH_AH_BN), 2.79-2.59 (2H, m, CH₂CH₂), 2.48 and 2.46 (6H, 2 x s, 2 x CH₃).

Example 14**8-Bromo-5-methyl-1-(3-hydroxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine**

Potassium hydroxide (0.30 g, 5.33 mmol) was added to a stirred solution of 8-bromo-5-methyl-1-(3-tosyloxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine (0.65 g, 1.3 mmol) in MeOH (5 ml) and DMF (5 ml) and the mixture heated at 60 °C for 3h.

After cooling to RT, the crude mixture was poured into water (10 ml) and the mixture extracted with dichloromethane (2 x 10 ml). The aqueous layer was then acidified to pH 9 and extracted with dichloromethane (2 x 10 ml). The combined organics were dried (MgSO₄), filtered and concentrated *in vacuo* to give 0.42 g of a yellow oil. Purification by silica gel column chromatography (5% MeOH/DCM) afforded the title compound (0.20 g, 44%) as a white solid.

δ_H (CDCl₃; 250MHz) 7.34-6.67 (7H, m, aromatics), 5.60 (1H, s, CH-O), 5.17 (1H, d, *J* 13, ArCH_AH_BN), 4.20 (1H, ddd, *J* 13, 8 and 2.5, CH_AH_BCH₂), 3.80 (1H, ddd, *J* 13, 8 and 2.5, CH_AH_BCH₂), 3.53 (1H, d, *J* 13, ArCH_AH_BN), 2.75-2.56 (2H, m, CH₂CH₂), 2.36 (3H, s, NCH₃).

Example 15

8-Cyano-5-methyl-1-(3-hydroxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine

8-Bromo-5-methyl-1-(3-hydroxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine (100 mg, 0.29 mmol), Zn (1 mg, 0.02 mmol), Zn(OAc)₂ (7 mg, 0.034 mmol), Zn(CN)₂ (25 mg, 0.22 mmol), Pd₂(dba)₃ (37 mg, 0.04 mmol) and 1,1'-bis(diphenylphosphino)ferrocene (18 mg, 0.034 mmol) were heated to 140°C in DMF (3 ml) and H₂O (30 μ l) for 4h. The black reaction mixture was allowed to cool to RT and diluted with water (20 ml). The resulting brown precipitate was collected by filtration and washed with water then brine. The filtrate was extracted with ethyl acetate (2 x 60 ml). The combined organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo* to provide the crude product as a brown oil. Purification by gravity silica gel column chromatography [dichloromethane] furnished the desired product (25 mg, 29%) as a yellow oil.

δ_H (CDCl₃; 250MHz) 7.45-6.70 (7H, m, aromatics), 5.65 (1H, s, CHO), 5.03 (1H, d, *J* 13, ArCH_AH_B-N), 4.26-4.18 (1H, m, CH_AH_BCH₂), 3.81-3.75 (1H, m, CH_AH_BCH₂), 3.61 (1H, d, *J* 13, ArCH_AH_B-N), 2.70-2.53 (2H, m, CH₂CH₂), 2.41 (3H, s, NCH₃).

Example 16

8-Cyclopropyl-5-methyl-1-(3-hydroxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine

8-Bromo-5-methyl-1-(3-hydroxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine (100 mg, 0.29 mmol), cyclopropylboronic acid (33 mg, 0.36 mmol), K₃PO₄ (217 mg, 1.01 mmol), Pd(OAc)₂ (4 mg, 0.015 mmol) and P(cyclohexane)₃ (9 mg, 0.029 mmol) were heated to 100°C in toluene (2.5 mL) and H₂O (125 μ l) for 4 hours. After cooling to RT, water (2.5 ml) was added and the mixture extracted with ethyl acetate (2 x 5 ml), washed with brine, dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by

gravity silica gel column chromatography [dichloromethane] furnished the desired product (40 mg, 44%) as a colourless oil.

δ_{H} (CDCl₃; 250MHz) 7.27-6.69 (7H, m, aromatics), 5.61(1H, s, CHO), 5.04 (1H, d, *J* 13, ArCH_AH_B-N) 4.23-4.15 (1H, m, CH_AH_BCH₂), 3.83-3.78 (1H, m, CH_AH_BCH₂), 3.66 (1H, d, *J* 13, ArCH_AH_B-N), 2.78-2.58 (2H, m, CH₂CH₂), 2.41 (3H, s, NCH₃), 1.84-1.78 (1H, m, CHCH₂), 0.95-0.90 (2H, m, CH₂CH₂), 0.64-0.62 (2H, m, CH₂CH₂).

Example 17

8-Bromo-5-methyl-1-(3-allyloxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine

8-Bromo-5-methyl-1-(3-hydroxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine (50 mg, 0.14 mmol), allyl alcohol (33 mg, 0.57 mmol), Pd(OAc)₂ (1 mg, 0.0035 mmol), triphenylphosphine (2 mg, 0.0075 mmol), Ti(O^{*i*}Pr)₄ (10 mg, 0.035 mmol), molecular sieves (4 Å, 28 mg) were heated at 50°C in benzene (1 ml) overnight. After cooling to RT, the black reaction mixture poured into water (5 ml), extracted with MTBE (2 x 5 ml). The combined organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo* to provide the crude product as a brown oil. Purification by gravity silica gel column chromatography [dichloromethane] furnished the desired product (16 mg, 30%) as a pale yellow oil.

δ_{H} (CDCl₃; 250MHz) 7.38-7.19 (3H, m, aromatics), 6.90-6.80 (4H, m, aromatics), 6.09-5.96 (1H, m, CH=CH₂), 5.71 (1H, s, CHO), 5.42-5.25 (2H, m, CH=CH₂), 4.76 (1H, d, *J* 13, ArCH_AH_B-N), 4.51 (2H, d, *J* 5, OCH₂), 4.21-4.12 (1H, m, CH_AH_BCH₂), 3.88-3.80 (1H, m, CH_AH_BCH₂), 3.63 (1H, d, *J* 13, ArCH_AH_B-N), 2.87-2.77 (1H, m, CH₂CH_AH_B), 2.69-2.60 (1H, m, CH₂CH_AH_B) 2.47 (3H, s, NCH₃).

Example 18

8-Cyano-5-methyl-1-(3-allyloxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine

8-Cyano-5-methyl-1-(3-hydroxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine (50 mg, 0.17 mmol), allyl alcohol (49 mg, 0.68 mmol), Pd(OAc)₂ (1 mg, 0.0035 mmol), triphenylphosphine (2 mg, 0.0075 mmol), Ti(O^{*i*}Pr)₄ (20 mg, 0.07 mmol), molecular sieves (4 Å, 40 mg) were heated at 50°C in benzene (2 ml) overnight. After cooling to RT, the black reaction mixture poured into water (5 ml) and extracted with MTBE (2 x 5 ml). The combined organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo* to provide the crude product as a brown oil. Purification by gravity silica gel column chromatography [dichloromethane] furnished the desired product (4 mg, 7%) as a pale yellow oil.

δ_{H} (CDCl₃; 250MHz) 7.65-6.81 (7H, m, aromatics), 6.08-5.97 (1H, m, CH=CH₂), 5.74 (1H, s, CHO), 5.42-5.25 (2H, m, CH=CH₂), 4.98 (1H, d, *J* 13, ArCH_AH_B-N), 4.51 (2H, d, *J* 5,

OCH₂), 4.31-4.23 (1H, m, CH_AH_BCH₂), 3.90-3.82 (1H, m, CH_AH_BCH₂), 3.74 (1H, d, *J* 13, ArCH_AH_B-N), 2.81-2.70 (2H, m, CH₂CH₂), 2.51 (3H, s, NCH₃).

Example 19

8-Cyclopropyl-5-methyl-1-(3-allyloxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-

5 oxazocine

8-Cyclopropyl-5-methyl-1-(3-hydroxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine (90 mg, 0.29 mmol), allyl alcohol (0.1 ml, 1.16 mmol), Pd(OAc)₂ (1 mg, 0.0035 mmol), triphenylphosphine (3 mg, 0.011 mmol), Ti(O^{*i*}Pr)₄ (0.03 mL, 0.07 mmol), molecular sieves (4 Å, 64 mg) were heated at 50°C in benzene (3 ml) overnight. After
10 cooling to RT, the black reaction mixture was poured into water (5 ml), extracted with MTBE (2 x 5 ml). The combined organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo* to provide the crude product as a brown oil. Purification by gravity silica gel column chromatography [dichloromethane] furnished the desired product (3 mg, 3%) as a pale yellow oil.

15 δ_{H} (CDCl₃; 250MHz) 7.24-6.76 (7H, m, aromatics), 6.04-5.97 (1H, m, CH=CH₂), 5.41 (1H, s, CHO), 5.41-5.24 (2H, m, CH=CH₂), 4.70 (1H, d, *J* 13, ArCH_AH_B-N), 4.49 (2H, d, *J* 5, OCH₂), 4.19-4.11 (1H, m, CH_AH_BCH₂), 3.88-3.82 (1H, m, CH_AH_BCH₂), 3.71 (1H, d, *J* 13, ArCH_AH_B-N), 2.92-2.82 (1H, m, CH₂CH_AH_B), 2.69-2.66 (1H, m, CH₂CH_AH_B), 2.49 (3H, s, NCH₃), 1.89-1.83 (1H, m, CHCH₂), 0.98-0.90 (2H, m, CHCH₂), 0.71-0.65 (2H, m,
20 CHCH₂).

The following Examples were prepared in a similar manner.

The substituted 'bromophenyl' starting materials, used for the Grignard formation, were either sourced commercially or generated synthetically via known organic chemistry, e.g. as in the following example where a nitro group was converted to a
25 bromo via the intermediate amine.

2-Methoxy-6-aminotoluene

2-methyl-3-nitroanisole (20 g, 0.12 mol) was suspended in methanol (200 ml) at RT under nitrogen. Pd/C (5%, 2 g) was added and the system was shaken under an atmosphere of hydrogen overnight, until TLC indicated one product. The reaction
30 mixture was filtered through celite, and the celite washed with methanol (3 x 100 ml) and the filtrate concentrated *in vacuo*. This afforded 18 g of a red oil that was used without further purification.

δ_{H} (CDCl₃; 250MHz) 7.01 (1H, t, *J* 8, aromatics), 6.38 (2H, d, *J* 8, aromatics), 3.83 (3H, s, OCH₃), 2.08 (3H, s, CH₃).

2-Methoxy-4-bromotoluene

Crude 2-methoxy-6-amino-toluene (max. 120 mmol) was suspended in HBr (48%, 48 ml) and water (120 ml) and cooled to 0°C in an ice bath. Sodium nitrite (9.2 g) in water (24 ml) was added dropwise to the cold mixture, which turned yellow then
5 brown. After 10 min, excess nitrite was destroyed by addition of urea (0.08 g) and the mixture was rapidly filtered into cold (0°C) acetone (480 ml) to give a bright yellow solution. CuBr (99.999%, 18.89, 131 mmol) was then added portionwise and the resulting mixture stirred at 0°C for 3h. Gas evolution was observed. The mixture was allowed to warm to ambient temperature, and then concentrated *in vacuo*.
10 Dichloromethane was then added and the mixture washed with sat. aq. sodium bicarbonate solution. The organic layer was separated, dried over magnesium sulphate and concentrated *in vacuo* to give the product (23.1 g, 96%) as a red oil.

δ_H (CDCl₃; 250MHz) 7.18-6.77 (3H, m, aromatics), 3.83 (3H, s, OCH₃), 2.32 (3H, s, CH₃).

5-Bromo-2-(3-methoxy-2-methylbenzoyl)-benzoic acid and 4-Bromo-2-(3-methoxy-2-methylbenzoyl)-benzoic acid

2-methoxy-4-bromo-toluene (23.1 g, 115 mmol) in dry THF (35 ml) was added dropwise to a stirred suspension of magnesium turnings (2.77 g, 115 mmol) and a crystal of iodine in dry THF (40 ml) under a nitrogen atmosphere. Upon addition, the reaction mixture reached reflux. After cooling to RT, this Grignard solution was added dropwise to a
20 stirred solution of 4-bromophthalic anhydride (26.1 g, 115 mmol) in dry THF (45 ml) and the resulting mixture heated to reflux temperature overnight. After cooling, the reaction was quenched with sat. aq. ammonium chloride solution, and extracted with ethyl acetate. The organics were dried (MgSO₄), filtered and concentrated *in vacuo* to give the crude mixture of keto-acids (34 g) as a brown solid. This material was carried
25 straight on to the subsequent step.

5-Bromo-N-(2-hydroxyethyl)-N-methyl-2-(3-methoxy-2-methyl-benzoyl)-benzamide

A crude mixture of 5-bromo-2-(3-methoxy-2-methylbenzoyl)-benzoic acid and 4-bromo-2-(3-methoxy-2-methylbenzoyl)-benzoic acid (34 g, 98.5 mmol) was dissolved in dichloromethane (200 ml) at RT. DMF (1 ml) followed by oxalyl chloride (9.67 ml, 13.98
30 g, 108.35 mmol) were added dropwise and the reaction stirred at RT overnight. The reaction mixture was then concentrated *in vacuo* and co-evaporated with dichloromethane (2 x 200 ml) to provide the crude acid chloride. This was dissolved in dichloromethane (200 ml), cooled to 0°C, and triethylamine (15.35 ml, 11.22 g, 108.35 mmol) was added dropwise, followed by N-methylethanolamine and the mixture left to
35 warm to RT overnight. The reaction was then quenched with brine and extracted with

dichloromethane. The combined organic extracts were dried (MgSO_4), filtered and concentrated *in vacuo* to give the crude amide as a mixture of regioisomers. The 5-bromo-*N*-(2-hydroxyethyl)-*N*-methyl-2-(3-methoxy-2-methyl-benzoyl)-benzamide (10 g, 25 %) was separated by silica gel column chromatography [4:1 EtOAc/heptane].

- 5 δ_{H} (CDCl_3 ; 250MHz) 7.55-6.91 (6H, m, aromatics), 3.98-3.69 (7H, m, OCH_3 and CH_2CH_2), 3.15 and 2.99 (3H, 2 x s, NCH_3), 2.20 and 2.17 (3H, 2 x s, CH_3).

2-({5-Bromo-2-[hydroxyl-(3-methoxy-2-methylphenyl)methyl]benzyl}methylamino)-ethanol

- Borane-dimethyl sulphide complex (2.0 M, 55 ml, 0.11 mol) was added dropwise to a stirring solution of 5-bromo-*N*-(2-hydroxyethyl)-*N*-methyl-2-(3-methoxy-2-methyl-benzoyl)-benzamide (10 g, 0.025 mol) in anhydrous THF (80 ml) at RT under nitrogen, and allowed to stir overnight. The reaction was quenched by the careful addition of 6M HCl (80 ml), and the resulting mixture was heated to reflux temperature for 2 hours. After cooling to RT, the THF was removed *in vacuo* and the mixture partitioned between water (40 ml) and MTBE (80 ml). The aqueous phase was separated, basified with aq. 2M NaOH, and extracted into ethyl acetate (3 x 90 ml). The combined organic extracts were dried (MgSO_4), filtered and concentrated *in vacuo* to provide the desired amine as a viscous oil, which slowly crystallised (6.2 g, 63 %). The material was used in the next step without further purification.

- 20 δ_{H} (CDCl_3 ; 250MHz) 7.41-7.25 (4H, m, aromatics), 6.89 (1H, d, J 8, aromatics), 6.61 (1H, d, J 8, aromatics), 6.10 (1H, s, CHOH), 4.33 (1H, d, J 13, $\text{CH}_\text{A}\text{H}_\text{B}\text{N}$), 3.84 (3H, s, OCH_3), 3.84-3.62 (2H, m, CH_2), 3.26 (1H, d, J 13, $\text{CH}_\text{A}\text{H}_\text{B}\text{N}$), 2.77-2.73 (2H, m, CH_2), 2.33 (3H, s, NCH_3), 1.83 (3H, s, CH_3).

Example 20

- 25 **8-Bromo-5-methyl-1-(2-methyl-3-methoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine**

- 2-({5-bromo-2-[hydroxyl-(3-methoxy-2-methylphenyl)-methyl]-benzyl}-methylamino)-ethanol (5 g, 12.6 mmol) was heated to reflux temperature in toluene (250 ml) with *p*TSA (3.65 g, 18.95 mmol) under Dean-Stark conditions for 4 hours. The reaction mixture was allowed to cool to RT, diluted with ethyl acetate (200 ml) and washed with a sat. aq. solution of sodium bicarbonate (300 ml). The aqueous layer was extracted with ethyl acetate (3 x 200 ml) and the combined organic extracts were dried over magnesium sulfate, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography [DCM] gave the target product as a pale straw coloured oil (2.8 g, 59 %).

δ_H (CDCl₃; 250MHz) 7.42-6.70 (6H, m, aromatics), 5.97 (1H, s, CHO), 4.69 (1H, d, *J* 13, CH_AH_BN), 4.14-4.05 (1H, m, CH_AH_B), 3.89-3.73 (5H, m, CH_AH_B, OCH₃, and CH_AH_BN), 2.92-2.82 (1H, m, CH_AH_B), 2.69-2.59 (1H, m, CH_AH_B), 2.45 (3H, s, CH₃N), 2.15 (3H, s, CH₃).

5 Example 21

8-Cyano-5-methyl-1-(2-methyl-3-methoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine

8-Bromo-5-methyl-1-(2-methyl-3-methoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine (250 mg, 0.66 mmol), Zn (4 mg, 0.04 mmol), Zn(OAc)₂ (14 mg, 0.07 mmol), Zn(CN)₂ (50 mg, 0.44 mmol), 1,1'-bis(diphenylphosphino)ferrocene (36 mg, 0.07 mmol) and Pd₂(dba)₃ (74 mg, 0.08 mmol) were heated to 140 °C in degassed DMF (3 ml) and H₂O (30 μl) overnight. The mixture was allowed to cool to RT and water (10 ml) was added, producing a brown precipitate. The precipitate was collected by filtration and washed with water and brine. The filtrate was then extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo* to provide 100 mg of the crude product. Purification by gravity silica gel column chromatography [DCM] furnished the target product as a yellow oil (70 mg, 33 %).

δ_H (CDCl₃; 250MHz) 7.60 (1H, d, *J* 1.5, aromatics), 7.48 (1H, dd, *J* 1.5 and 8, aromatics), 7.12-7.01 (2H, m, aromatics), 6.82 (1H, d, *J* 8, aromatics), 6.46 (1H, d, *J* 8, aromatics), 5.97 (1H, s, CHO), 5.02 (1H, d, *J* 13, CH_AH_BN), 4.30-4.24 (1H, m, CH_AH_BCH₂), 3.96-3.80 (2H, m, CH_AH_BN and CH_AH_BCH₂), 3.82 (3H, s, OCH₃), 2.96-2.85 (1H, m, CH₂CH_AH_B), 2.76-2.65 (1H, m, CH₂CH_AH_B), 2.53 (3H, s, NCH₃), 2.20 (3H, s, CH₃).

Example 22

25 8-Cyclopropyl-5-methyl-1-(2-methyl-3-methoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine

8-Bromo-5-methyl-1-(2-methyl-3-methoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine (295 mg, 0.71 mmol), cyclopropylboronic acid (89 mg, 0.96 mmol), P(cyclohexane)₃ (24 mg, 0.08 mmol), K₃PO₄ (586 mg, 2.73 mmol) and Pd(OAc)₂ (10.4 mg, 0.04 mmol) were heated at 100 °C in toluene (7 ml) and water (336 μl) overnight. The reaction mixture was allowed to cool and then diluted with ethyl acetate (30 ml). The organic mixture was washed with water (30 ml) and the aqueous phase extracted into ethyl acetate (3 x 20 ml). The combined organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo* to provide 0.29 g of the crude product. Purification by silica gel gravity column chromatography [DCM] furnished the target product (100 mg, 38%) as a yellow oil/solid.

δ_H (CDCl₃; 250MHz) 7.11 (1H, t, *J* 8, aromatics), 6.97 (1H, d, *J* 1.5, aromatics), 6.88-6.71 (4H, m, aromatics), 5.98 (1H, s, CH_O), 4.63 (1H, d, *J* 13, CH_AH_BN), 4.18-4.06 (1H, m, CH_AH_BCH₂), 3.89-3.82 (5H, m, CH_AH_BN, CH_AH_BCH₂ and OCH₃), 2.98-2.88 (1H, m, CH₂CH_AH_B), 2.72-2.64 (1H, m, CH₂CH_AH_B), 2.50 (3H, s, NCH₃), 2.16 (3H, s, CH₃), 1.91-1.84 (1H, m, CH₂CH₂), 0.99-0.91 (2H, m, CH₂CH₂), 0.73-0.66 (2H, m, CH₂CH₂).

Example 23

8-Bromo-5-methyl-1-(3-methoxy-4-methyl)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine

2-({5-bromo-2-[hydroxyl-(3-methoxy-4-methyl)phenyl]-methyl}-benzyl)-methylamino-ethanol (879 mg, 2.23 mmol) was heated to reflux temperature in toluene (9ml) with *p*TSA (635 mg, 3.34 mmol) under Dean-Stark conditions for 3 hours. The reaction mixture was allowed to cool to RT, diluted with ethyl acetate (50 ml) and washed with a saturated solution of sodium bicarbonate (60 ml). The aqueous layer was extracted into ethyl acetate (3 x 50 ml) and the combined organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by gravity silica gel column chromatography [EtOAc] gave the target product as a pale straw coloured oil (23 g, 28%). A second impure batch of product was obtained from the column.

δ_H (CDCl₃; 250MHz) 2.18 (3H, s, CH₃), 2.48 (3H, s, NCH₃), 2.66 (1H, ddd, *J*14.2, 5.6, 2.7, one of CH₂CH₂), 2.84 (1H, ddd, *J*14.2, 8.2, 2.1, one of CH₂CH₂), 3.67 (1H, d, *J*12.8, one of ArCH₂NR₂), 3.80 (3H, s, OCH₃), 3.86 (1H, ddd, *J*12.7, 5.6, 2.1, one of CH₂CH₂), 4.18 (1H, ddd, *J*12.8, 8.2, 2.7, one of CH₂CH₂), 4.80 (1H, d, *J*12.8, one of ArCH₂NR₂), 5.71 (1H, s, CH_OR), 6.68 (1H, dd, *J*7.6, 1.2, one of ArH), 6.76 (1H, bs, one of ArH), 6.89 (1H, d, *J* 8.2, ArH), 7.06 (1H, d, *J*7.6, one of ArH), 7.32 (1H, dd, *J*8.2, 1.8, one of ArH), 7.39 (1H, d, *J*1.8, one of ArH).

Example 24

8-Cyano-5-methyl-1-(3-methoxy-4-methyl)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine

8-Bromo-5-methyl-1-(3-methoxy-4-methyl)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine (154 mg, 0.41 mmol), Zn (2 mg, 0.03 mmol), Zn(OAc)₂ (10 mg, 0.05 mmol), Zn(CN)₂ (29 mg, 0.25 mmol), 1,1'-bis(diphenylphosphino)ferrocene (30 mg, 0.05 mmol) and Pd₂(dba)₃ (55 mg, 0.06 mmol) were heated to 140°C in DMF (3 ml) and H₂O (30 μ l) overnight. The mixture was allowed to cool to RT and water (30 ml) was added, producing a brown precipitate. The precipitate was collected by filtration and washed with water and ethyl acetate. The filtrate was then washed with brine (2 x 40 ml) and the combined aqueous phases were extracted with ethyl acetate (3 x 20 ml). The combined

organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo* to provide the crude product. Purification by silica gel gravity column chromatography [EtOAc] furnished the target product as a brown oil (75 mg, 57%).

5 δ_{H} (CDCl₃; 250MHz) 2.17 (3H, s, CH₃), 2.46 (3H, s, NCH₃), 2.65 (1H, ddd, *J*14.3, 5.1, 3.0, one of CH₂CH₂), 2.78 (1H, ddd, *J*14.3, 8.6, 2.5, one of CH₂CH₂), 3.71 (1H, d, *J*13.0, one of ArCH₂NR₂), 3.79 (3H, s, OCH₃), 3.84 (1H, ddd, *J*12.8, 5.1, 2.5, one of CH₂CH₂), 4.26 (1H, ddd, *J*12.8, 8.6, 3.0, one of CH₂CH₂), 4.99 (1H, d, *J*13.0, one of ArCH₂NR₂), 5.73 (1H, CHOR), 6.63 (1H, d, *J*1.5, ArH), 6.72 (1H, s, ArH), 7.06 (1H, d, *J*7.6, ArH), 7.14 (1H, d, *J*8.2, ArH), 7.47 (1H, dd, *J*8.2, 1.8, ArH), 7.53 (1H, d, *J*1.5, ArH).

10 Example 25

5-Methyl-1-(3-methoxy-4-methyl)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine-8-carboxamide

8-Cyano-5-methyl-1-(3-methoxy-4-methyl)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine (1.1 g, 3.56 mmol) was heated to reflux temperature in *t*BuOH (24 ml) with
15 potassium hydroxide (0.29 mg, 5.34 mmol) for 2 h. At the end of this time, the reaction mixture was allowed to cool to RT. The mixture was then washed with brine (50 ml) and extracted into dichloromethane (3 x 50 ml). The combined organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo* to provide the crude amide as a light brown solid. Purification by silica gel column chromatography [1% MeOH in DCM to 12%
20 MeOH in DCM] afforded the title compound (385 mg, 32%).

δ (CDCl₃; 250MHz) 2.16 (3H, s, CH₃), 2.47 (3H, s, NCH₃), 2.52-2.62 (1H, m (poorly resolved ddd), one of CH₂CH₂), 2.75-2.88 (1H, m (poorly resolved ddd), one of CH₂CH₂), 3.77 (4H, s, OCH₃ and one of ArCH₂), 3.81-3.92 (1H, m (poorly resolved ddd), one of CH₂CH₂), 4.15-4.28 (1H, m (poorly resolved ddd), one of CH₂CH₂), 4.89 (1H, d, *J*12.8,
25 one of ArCH₂), 5.77 (1H, s, CHOR), 6.76-6.75 (3H, m, aromatic H), 7.03-7.12 (2H, m, aromatic H), 7.59-7.68 (2H, m, aromatic H).

Example 26

8-Cyclopropyl-5-methyl-1-(3-methoxy-4-methyl)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine

30 8-Bromo-5-methyl-1-(3-methoxy-4-methyl)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine (154 mg, 0.41 mmol), cyclopropylboronic acid (46 mg, 0.53 mmol), P(cyclohexane)₃ (11 mg, 0.041 mmol), K₃PO₄ (304 mg, 1.43 mmol) and Pd(OAc)₂ (5 mg, 0.02 mmol) were heated at 100°C in toluene (3 ml) and water (150 μ l) for 3 hours
15 mins. The reaction mixture was allowed to cool and then diluted with ethyl acetate (30ml). The organic mixture was washed with water (30 ml) and the aqueous phase
35

extracted into ethyl acetate (3 x 20 ml). The combined organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo* to provide the crude product. Purification by silica gel gravity column chromatography [EtOAc] furnished the target product and recovered starting material.

- 5 δ_H (CDCl₃; 250MHz) 0.64-0.71 (2H, m, two of cyclopropyl CH₂CH₂), 0.89-0.97 (2H, m, two of cyclopropyl CH₂CH₂), 1.80-1.89 (1H, m, cyclopropyl CH), 2.16 (3H, s, CH₃), 2.48 (3H, s, NCH₃), 2.63 (1H, ddd, *J*14.2, 5.6, 2.6, one of CH₂CH₂), 2.85 (1H, ddd, *J*14.2, 8.4, 2.3, one of CH₂CH₂), 3.70 (1H, d, *J*12.7, one of ArCH₂NR₂), 3.78 (3H, s, OCH₃), 3.84 (1H, ddd, *J*12.5, 5.6, 2.3, one of CH₂CH₂), 4.17 (1H, ddd, *J*12.5, 8.4, 2.6, one of CH₂CH₂), 4.70 (1H, d, *J*12.7, one of ArCH₂NR₂), 5.73 (1H, s, CHOR), 6.69 (1H, dd, *J*7.6, 1.2, one of ArH), 6.79 (1H, s, ArH), 6.86 (2H, d, *J*1.2, ArH), 6.94 (1H, s, ArH), 7.03 (1H, d, *J*7.6, ArH).

Example 27

- 15 **9-Bromo-5-methyl-1-(3,4-methylenedioxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine**

- 2-[[2-(Benzo-[1,3]-dioxol-yl-hydroxymethyl)-4-bromobenzyl]-methylamino]-ethanol (148 mg, 0.38 mmol) was heated to reflux temperature with *p*TSA (107 mg, 0.56 mmol) in toluene (3 ml) under Dean-stark conditions for 3 hours. The mixture was then cooled, diluted with ethyl acetate and washed with sat. aq. sodium bicarbonate solution.
- 20 The organic phase was dried (MgSO₄), filtered and concentrated *in vacuo* to provide the crude product. Purification by silica gel gravity column chromatography [3%MeOH/EtOAc to 10%MeOH/EtOAc] furnished product (89 mg, 62%).
- δ_H (CDCl₃; 250MHz) 2.43 (3H, s, CH₃), 2.60 (1H, ddd, *J*14.2, 5.3, 2.9, one of CH₂CH₂), 2.78 (1H, ddd, *J*14.2, 8.7, 2.4, one of CH₂CH₂), 3.61 (1H, d, *J*12.7, one of ArCH₂N), 3.81 (1H, ddd, *J*12.5, 5.3, 2.4, one of CH₂CH₂), 4.20 (1H, ddd, *J*12.5, 8.7, 2.9, one of CH₂CH₂), 4.84 (1H, d, *J*12.7, one of ArCH₂N), 5.61 (1H, s, CHOR), 5.93 (2H, s, ROCH₂OR), 6.71-6.75 (3H, m, ArH), 7.07-7.14 (2H, m, ArH), 7.36 (1H, dd, *J*8.0, 4.0, ArH).

Example 28

- 30 **9-Cyano-5-methyl-1-(3,4-methylenedioxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine**

- A solution of 9-bromo-5-methyl-1-(3,4-methylenedioxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine (89 mg, 0.23 mmol), Zn (1 mg, 0.012 mmol), Zn(CN)₂ (16 mg, 0.138 mmol), Zn(OAc)₂ (2 mg, 0.011 mmol), 1,1'-bis(diphenylphosphino)ferrocene (18 mg, 0.05 mmol) and Pd₂(dba)₃ (11 mg, 0.06 mmol) in DMF (2 ml) and H₂O (20 μ l) was

degassed under vacuum for 15 minutes and then heated at 140°C overnight. The mixture was then allowed to cool and water added. The organics were extracted into ethyl acetate and then washed with brine to remove the DMF. The combined organic washings were dried (MgSO₄), filtered and concentrated *in vacuo* to provide the crude product. Purification by silica gel column chromatography [EtOAc] furnished product (21 mg, 27%).

δ_H (CDCl₃; 250MHz) 2.45 (3H, s, NCH₃), 2.63 (1H, ddd, *J*14.3, 5.2, 2.8, one of CH₂CH₂), 2.76 (1H, ddd, *J*14.3, 8.4, 2.4, one of CH₂CH₂), 3.70 (1H, d, *J*12.8, one of ArCH₂NR₂), 3.81 (1H, ddd, *J*12.6, 5.2, 2.4, one of CH₂CH₂), 4.20 (1H, ddd, *J*12.6, 8.4, 2.8, one of CH₂CH₂), 4.90 (1H, d, *J*12.8, one of ArCH₂NR₂), 5.69 (1H, s, CHOR), 5.94 (2H, s, ROCH₂OR), 6.69-6.78 (3H, m, ArH), 7.27-7.33 (2H, m, ArH), 7.51 (1H, dd, *J*7.9, 1.5, ArH).

Example 29

9-Cyclopropyl-5-methyl-1-(3,4-methylenedioxy)phenyl-1,3,4,6-tetrahydro-5H-benz[*f*]-2,5-oxazocine

A mixture of 9-bromo-5-methyl-1-(3,4-methylenedioxy)phenyl-1,3,4,6-tetrahydro-5H-benz[*f*]-2,5-oxazocine (280 mg, 0.75 mmol), cyclopropylboronic acid (84 mg, 0.97 mmol), K₃PO₄ (555 mg, 2.61 mmol), Pd(OAc)₂ (8.4 mg, 0.04 mmol) and P(cyclohexane)₃ (21 mg, 0.075 mmol) in toluene (5 ml) and H₂O (250 μ l) was heated at 100°C for 3 hours, during which time it turned black. After cooling, water (12 ml) was added and the organics were extracted into ethyl acetate. The combined organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo* to provide the crude product. Purification (repeated) by silica gel column chromatography [EtOAc] furnished product (56 mg, 22%).

δ_H (CDCl₃; 250MHz) 0.58-0.63 (2H, m, two of cyclopropyl CH₂CH₂), 0.86-0.94 (2H, m, two of cyclopropyl CH₂CH₂), 1.75-1.84 (1H, m, cyclopropyl CH), 2.44 (3H, s, CH₃), 2.55-2.63 (1H, m, one of CH₂CH₂), 2.75-2.84 (1H, m, one of CH₂CH₂), 3.62 (1H, d, *J*12.5, one of ArCH₂NR₂), 3.81 (1H, ddd, *J*12.5, 5.6, 2.4, one of CH₂CH₂), 4.14-4.22 (1H, m, one of CH₂CH₂), 4.79 (1H, d, *J*12.5, one of ArCH₂NR₂), 6.63 (1H, s, CHOR), 5.91 (2H, s, ROCH₂OR), 6.74 and 6.75 (4H, 2 x s, ArH), 6.87 (1H, dd, *J*7.6, 1.9, ArH), 7.10 (1H, d, *J*7.9).

Example 30

8-Bromo-5-methyl-1-(3,4-methylenedioxy)phenyl-1,3,4,6-tetrahydro-5H-benz[*f*]-2,5-oxazocine

2-[[2-(Benzo-[1,3]-dioxol-5-yl-hydroxymethyl)-5-bromobenzyl]-methylamino]-

ethanol (715 mg, 1.82 mmol) and *p*TSA (519 mg, 2.73 mmol) were heated to reflux temperature in toluene (8 ml) under Dean-Stark conditions for 2 hours. Once cooled to RT, the reaction mixture was diluted with ethyl acetate and washed with sat. aq. sodium bicarbonate solution. The organic phases were dried (MgSO₄), filtered and concentrated
5 *in vacuo* to provide the crude product. Purification by silica gel column chromatography [100% EtOAc to 5%MeOH/EtOAc] yielded 214 mg, (31%).

δ_{H} (CDCl₃; 250MHz) 2.45 (3H, s, CH₃), 2.61 (1H, ddd, *J*14.1, 5.8, 2.8, one of CH₂CH₂), 2.79 (1H, ddd, *J*14.1, 8.2, 2.2, one of CH₂CH₂), 3.58 (1H, d, *J*12.8, one of ArCH₂NR₂), 3.81 (1H, ddd, *J*12.5, 5.8, 2.2, one of CH₂CH₂), 4.78 (1H, ddd, *J*12.5, 8.2, 2.8, one of
10 CH₂CH₂), 4.80 (1H, d, *J*12.8, one of ArCH₂NR₂), 5.64 (1H, s, CHOR), 5.91 (2H, s, ROCH₂OR), 6.70-6.77 (3H, m, ArH), 6.87 (1H, d, *J*8.3, ArH), 7.29-7.37 (2H, m, ArH).

Example 31

8-Cyano-5-methyl-1-(3,4-methylenedioxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine

15 8-Bromo-5-methyl-1-(3,4-methylenedioxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine (99 mg, 0.26 mmol), Zn (1 mg, 0.015 mmol), Zn(OAc)₂ (6 mg, 0.033 mmol), Zn(CN)₂ (18 mg, 0.156 mmol), 1,1'-bis(diphenylphosphino)ferrocene (18 mg, 0.054 mmol) and Pd₂(dba)₃ (33 mg, 0.036 mmol) were degassed and then heated at 140°C overnight. The reaction mixture was cooled and water added. The organics were
20 extracted three times with ethyl acetate, and the combined organic extracts were washed with brine, dried (MgSO₄), filtered and concentrated *in vacuo* to provide the crude target as a black oil. Purification by silica gel column chromatography [EtOAc] furnished product 21 mg, (25%).

δ_{H} (CDCl₃; 250MHz) 2.46 (3H, s, CH₃), 2.63 (1H, ddd, *J*14.3, 5.4, 3.1, one of CH₂CH₂), 2.75 (1H, ddd, *J*14.3, 8.3, 2.6, one of CH₂CH₂), 3.64 (1H, d, *J*12.8, one of ArCH₂NR₂), 3.81 (1H, ddd, *J*12.7, 5.4, 2.6, one of CH₂CH₂), 4.24 (1H, ddd, *J*12.7, 8.3, 3.1, one of
25 CH₂CH₂), 4.97 (1H, d, *J*12.8, one of ArCH₂NR₂), 5.68 (1H, CHOR), 5.93 (2H, s, ROCH₂OR), 6.69-6.78 (3H, m, ArH), 7.12 (1H, d, *J*7.9, ArH), 7.45- 7.52 (2H, m, ArH).

Example 32

8-Cyclopropyl-5-methyl-1-(3,4-methylenedioxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine

8-Bromo-5-methyl-1-(3,4-methylenedioxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine (90 mg, 0.24 mmol), cyclopropylboronic acid (26.8 mg, 0.312 mmol), K₃PO₄ (178 mg, 0.84 mmol), Pd(OAc)₂ (3 mg, 0.012 mmol) and P(cyclohexane)₃ (7 mg,
35 0.024 mmol) were heated to 100°C in toluene (2 ml) and water (100 μ l) for 3 hours. The

reaction mixture was cooled, diluted with water and extracted with ethyl acetate. The combined organic extracts were dried (MgSO_4), filtered and concentrated *in vacuo* to provide the crude product. Purification was by silica gel column chromatography [100 %EtOAc to 5%MeOH/EtOAc] furnished 8-cyclopropyl-(3,4-methylenedioxy)-nefopam 49 mg, (61%).

δ_{H} (CDCl_3 ; 250MHz) 0.67-0.72 (2H, m, two of cyclopropyl CH_2CH_2), 0.91-0.99 (2H, m, two of cyclopropyl CH_2CH_2), 2.48 (3H, s, CH_3), 2.61 (1H, ddd, J 14.2, 5.7, 2.6, one of CH_2CH_2), 2.83 (1H, ddd, J 14.2, 8.4, 2.5, one of CH_2CH_2), 3.64 (1H, d, J 12.8, one of ArCH_2NR_2), 3.83 (1H, ddd, J 12.5, 5.7, 2.5, one of CH_2CH_2), 4.42 (1H, ddd, J 12.5, 8.4, 2.6, one of CH_2CH_2), 4.74 (1H, d, J 12.8, one of ArCH_2NR_2), 5.67 (1H, s, CHOH), 5.91 (2H, s, ROCH_2OR), 6.75 (3H, s, ArH), 6.88-6.9 (3H, m, ArH)

Example 33

8-Bromo-5-methyl-1-(3-ethoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine

2-({5-Bromo-2-[hydroxyl-(3-ethoxy-phenyl)-methyl]-benzyl}-methylamino)-ethanol (1.06 g, 2.69 mmol) was heated to reflux temperature under Dean-Stark conditions with $p\text{TSA}$ (0.78 g, 4.03 mmol) in toluene (40 ml) for 2.5 h. The reaction mixture was allowed to cool and then diluted with ethyl acetate (20 ml). The mixture was washed with sat. aq sodium bicarbonate solution (2 x 20 ml) and the combined organic extracts were dried (MgSO_4), filtered and concentrated *in vacuo* to provide 0.94 g of crude product. Purification by silica gel gravity column chromatography [EtOAc] gave the product (0.60 g, 59%) as a colourless oil.

δ_{H} (CDCl_3 ; 250MHz) 7.37-6.87 (7H, m, aromatics), 5.71 (1H, s, CH-O), 4.77 (1H, d, J 13, $\text{ArCH}_A\text{H}_B\text{N}$), 4.14 (1H, ddd, J 13, 8 and 2.5, $\text{CH}_A\text{H}_B\text{CH}_2$), 4.00 (2H, q, J 7, CH_2CH_3), 3.84 (1H, ddd, J 13, 8 and 2.5, $\text{CH}_A\text{H}_B\text{CH}_2$), 3.62 (1H, d, J 13, $\text{ArCH}_A\text{H}_B\text{N}$), 2.85-2.79 (1H, m, $\text{CH}_A\text{H}_B\text{CH}_2$), 2.68-2.60 (1H, m, $\text{CH}_A\text{H}_B\text{CH}_2$), 2.46 (3H, s, NCH_3), 1.39 (3H, t, J 7, CH_2CH_3).

Example 34

8-Cyano-5-methyl-1-(3-ethoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine

8-Bromo-5-methyl-1-(3-ethoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine (250 mg, 0.65 mmol), Zn (3 mg, 0.05 mmol), $\text{Zn}(\text{OAc})_2$ (15 mg, 0.077 mmol), $\text{Zn}(\text{CN})_2$ (46 mg, 0.4 mmol), $\text{Pd}_2(\text{dba})_3$ (93 mg, 0.1 mmol) and 1,1'-bis(diphenylphosphino)ferrocene (43 mg, 0.077 mmol) were heated to 140°C in DMF (5 ml) and H_2O (100 μl) for 4h. The black reaction mixture was allowed to cool to RT and diluted with water. The resulting brown precipitate was collected by filtration and washed with water then brine. The filtrate was extracted with ethyl acetate (2 x 60ml). The

combined organic extracts were dried (MgSO_4), filtered and concentrated *in vacuo* to provide the crude product as a brown oil. Purification by silica gel gravity column chromatography [DCM] gave clean product (56 mg, 27%).

δ_{H} (CDCl_3 ; 250MHz) 7.50-6.78 (7H, m, aromatics), 5.72 (1H, s, CHO), 4.96 (1H, d, J 13, $\text{ArCH}_A\text{H}_B\text{-N}$), 4.39-4.19 (1H, m, $\text{CH}_A\text{H}_B\text{CH}_2$), 3.98 (2H, q, J 7, CH_2CH_3), 3.85-3.79 (1H, m, $\text{CH}_A\text{H}_B\text{CH}_2$), 3.67 (1H, d, J 13, $\text{ArCH}_A\text{H}_B\text{-N}$), 2.82-2.58 (2H, m, CH_2CH_2), 2.43 (3H, s, NCH_3), 1.38 (3H, t, J 7, CH_2CH_3).

Example 35

8-Cyclopropyl-5-methyl-1-(3-ethoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine

8-Bromo-5-methyl-1-(3-ethoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine (100 mg, 0.26 mmol), cyclopropylboronic acid (29 mg, 0.33 mmol), K_3PO_4 (193 mg, 0.91 mmol), $\text{Pd}(\text{OAc})_2$ (3 mg, 0.013 mmol) and $\text{P}(\text{cyclohexane})_3$ (8 mg, 0.026 mmol) were heated to 100°C in toluene (2 ml) and H_2O (100 μl) for 4 hours. After cooling to RT, water (2 ml) was added and the mixture extracted with ethyl acetate, washed with brine, dried (MgSO_4), filtered and concentrated *in vacuo*. Purification by silica gel gravity column chromatography [DCM] furnished clean product (20 mg, 23%) as a colourless oil.

δ_{H} (CDCl_3 ; 250MHz) 7.26-6.76 (7H, m, aromatics), 5.71 (1H, s, CHO), 4.75 (1H, d, J 12.5, $\text{ArCH}_A\text{H}_B\text{-N}$) 4.22-4.12 (1H, m, $\text{CH}_A\text{H}_B\text{CH}_2$), 3.99 (2H, q, J 7, CH_2CH_3), 3.88-3.79 (1H, m, $\text{CH}_A\text{H}_B\text{CH}_2$), 3.81 (1H, d, J 12.5, $\text{ArCH}_A\text{H}_B\text{-N}$), 2.90-2.61 (2H, m, CH_2CH_2), 2.50 (3H, s, NCH_3), 1.89-1.82 (1H, m, CHCH_2), 1.39 (3H, t, J 7, CH_2CH_3), 0.96-0.92 (2H, m, CH_2CH_2), 0.70-0.67 (2H, m, CH_2CH_2).

Example 36

9-Bromo-5-methyl-1-(3-ethoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine 2-({4-Bromo-2-[hydroxyl-(3-ethoxy-phenyl)-methyl]-benzyl}-methylamino)-ethanol (1.20 g, 3.04 mmol) was heated to reflux temperature under Dean-Stark conditions with $p\text{TSA}$ (0.88 g, 4.57 mmol) in toluene (50 ml) for 4 h. The reaction mixture was allowed to cool and then diluted with ethyl acetate (25 ml). The mixture was washed with sat. aq sodium bicarbonate solution (2 x 25 ml), and the combined organic extracts were dried (MgSO_4), filtered and concentrated *in vacuo* to provide 1.4 g of crude product. Purification by silica gel gravity column chromatography [EtOAc] gave product (0.59 g, 51%) as a colourless oil.

δ_{H} (CDCl_3 ; 250MHz) 7.37-6.76 (7H, m, aromatics), 5.67 (1H, s, CH-O), 4.79 (1H, d, J 13, $\text{ArCH}_A\text{H}_B\text{N}$), 4.16 (1H, ddd, J 13, 8 and 2.5, $\text{CH}_A\text{H}_B\text{CH}_2$), 4.01 (2H, q, J 7, CH_2CH_3), 3.81 (1H, ddd, J 13, 8 and 2.5, $\text{CH}_A\text{H}_B\text{CH}_2$), 3.63 (1H, d, J 13, $\text{ArCH}_A\text{H}_B\text{N}$), 2.84-2.78 (1H, m,

$\text{CH}_\text{A}\text{H}_\text{B}\text{CH}_2$), 2.66-2.63 (1H, m, $\text{CH}_\text{A}\text{H}_\text{B}\text{CH}_2$), 2.44 (3H, s, NCH_3), 1.40 (3H, t, J 7, CH_2CH_3).

Example 37

9-Cyano-5-methyl-1-(3-ethoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine

- 5 9-Bromo-5-methyl-1-(3-ethoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine (150 mg, 0.39 mmol), Zn (2 mg, 0.03 mmol), $\text{Zn}(\text{OAc})_2$ (9 mg, 0.046 mmol), $\text{Zn}(\text{CN})_2$ (28 mg, 0.24 mmol), $\text{Pd}_2(\text{dba})_3$ (56 mg, 0.06 mmol) and 1,1'-bis(diphenylphosphino)ferrocene (25 mg, 0.046 mmol) were heated to 140°C in DMF (3 ml) and H_2O (30 μl) overnight. The black reaction mixture was allowed to cool to RT and
- 10 diluted with water. The resulting brown precipitate was collected by filtration and washed with water then brine. The filtrate was extracted with ethyl acetate (2 x 80 ml), and the combined organic extracts dried (MgSO_4), filtered and concentrated *in vacuo* to provide the crude product. Purification by silica gel gravity column chromatography [DCM] gave clean product (12 mg, 10%).
- 15 $\delta_\text{H}(\text{CDCl}_3; 250\text{MHz})$ 7.53-6.80 (7H, m, aromatics), 5.75 (1H, s, CHO), 4.87 (1H, d, J 13, $\text{ArCH}_\text{A}\text{H}_\text{B}\text{N}$), 4.29-4.14 (1H, m, $\text{CH}_\text{A}\text{H}_\text{B}\text{CH}_2$), 4.01 (2H, q, J 7, CH_2CH_3), 3.88-3.78 (1H, m, $\text{CH}_\text{A}\text{H}_\text{B}\text{CH}_2$), 3.73 (1H, d, J 13, $\text{ArCH}_\text{A}\text{H}_\text{B}\text{N}$), 2.82-2.71 (1H, m, $\text{CH}_\text{A}\text{H}_\text{B}-\text{CH}_2$), 2.68-2.59 (1H, m, $\text{CH}_\text{A}\text{H}_\text{B}\text{CH}_2$), 2.46 (3H, s, $\text{N}-\text{CH}_3$), 1.39 (3H, t, J 7, CH_2CH_3).

Example 38

- 20 9-Cyclopropyl-5-methyl-1-(3-ethoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine

- 9-Bromo-5-methyl-1-(3-ethoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine (140 mg, 0.36 mmol), cyclopropylboronic acid (41 mg, 0.45 mmol), K_3PO_4 (269 mg, 1.26 mmol), $\text{Pd}(\text{OAc})_2$ (5 mg, 0.02 mmol) and $\text{P}(\text{cyclohexane})_3$ (11 mg, 0.04 mmol)
- 25 were heated to 100°C in toluene (3 ml) and H_2O (150 μl) for 4 hours. After cooling to RT, water (2 ml) was added and the mixture extracted with ethyl acetate, washed with brine, dried (MgSO_4), filtered and concentrated *in vacuo*. Purification by silica gel gravity column chromatography [DCM] gave product (61 mg, 50%) as a colourless oil.
- 30 $\delta_\text{H}(\text{CDCl}_3; 250\text{MHz})$ 7.25-6.76 (7H, m, aromatics), 5.69 (1H, s, CHO), 4.79 (1H, d, J 13, $\text{ArCH}_\text{A}\text{H}_\text{B}\text{N}$), 4.23-4.16 (1H, m, $\text{CH}_\text{A}\text{H}_\text{B}\text{CH}_2$), 4.01 (2H, q, J 7, CH_2CH_3), 3.89-3.81 (1H, m, $\text{CH}_\text{A}\text{H}_\text{B}\text{CH}_2$), 3.70 (1H, d, J 13, $\text{ArCH}_\text{A}\text{H}_\text{B}\text{N}$), 2.88-2.78 (1H, m, $\text{CH}_\text{A}\text{H}_\text{B}-\text{CH}_2$), 2.68-2.60 (1H, m, $\text{CH}_\text{A}\text{H}_\text{B}\text{CH}_2$), 2.48 (3H, s, $\text{N}-\text{CH}_3$), 1.83-1.72 (1H, m, CHCH_2), 1.39 (3H, t, J 7, CH_2CH_3), 0.92-0.88 (2H, m, CH_2CH_2), 0.62-0.58 (2H, m, CH_2CH_2).

Example 39**8-Bromo-5-methyl-1-(3-trifluoromethoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine**

2-({5-bromo-2-[hydroxyl-(3-trifluoromethoxy-phenyl)-methyl]-benzyl}-
5 methylamino)-ethanol (635 mg, 1.47 mmol) was heated to reflux under Dean-Stark conditions with *p*TSA (420 mg, 2.21 mmol) in toluene (6 ml) for 2 hours. The reaction mixture was allowed to cool to RT and then diluted with ethyl acetate (30 ml). The mixture was washed with sat. aq. sodium bicarbonate solution (50 ml) and was extracted into ethyl acetate. The combined organic extracts were dried (MgSO₄), filtered and
10 concentrated *in vacuo* to provide the crude cyclised product. Purification by silica gel gravity column chromatography [EtOAc] furnished the target product (116 mg, 19%).
 δ_{H} (CDCl₃; 250MHz) 2.47 (3H, s, CH₃), 2.67 (1H, ddd, *J*14.3, 6.1, 2.5, one of CH₂CH₂), 2.84 (1H, ddd, *J*14.3, 7.8, 2.2, one of CH₂CH₂), 3.67 (1H, d, *J*12.8, one of ArCH₂NR₂), 3.86 (1H, ddd, *J*12.8, 6.1, 2.2, one of CH₂CH₂), 4.13 (1H, ddd, *J*12.8, 7.8, 2.5, one of
15 CH₂CH₂), 4.61 (1H, d, *J*12.8, one of ArCH₂NR₂), 5.79 (1H, s, CHOR), 6.85 (1H, d, *J*8.2, ArH), 7.11-7.19 (3H, m, ArH), 7.31-7.36 (3H, m, ArH).

Example 40**8-Cyano-5-methyl-1-(3-trifluoromethoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine**

20 8-Bromo-5-methyl-1-(3-trifluoromethoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine (116 mg, 0.28 mmol), Zn (1 mg, 0.02mmol), Zn(OAc)₂ (7 mg, 0.038 mmol), Zn(CN)₂ (20 mg, 0.17 mmol), Pd₂(dba)₃ (40 mg, 0.04 mmol) and 1,1'-bis-(diphenylphosphine)ferrocene (20 mg, 0.036 mmol) were heated to 140°C in DMF (3 ml) and H₂O (30 μ l) overnight. The black reaction mixture was allowed to cool and diluted
25 with water. The resulting brown precipitate was collected by filtration and washed with ethyl acetate. The filtrate was washed with brine (2 x 60 ml) and the combined aqueous phases were then washed with ethyl acetate (2 x 80 ml). The combined organic extracts were dried (MgSO₄) and concentrated *in vacuo* to provide the crude product. Purification by silica gel gravity column chromatography [1:1 ethyl acetate/heptane) furnished the
30 desired product (9 mg, 9%).
 δ_{H} (CDCl₃; 250MHz) 2.50 (3H,s, CH₃), 2.61-2.87 (2H, m, two of CH₂CH₂), 3.76 (1H, d, *J*13.1, one of ArCH₂NR₂), 3.87 (1H, ddd, *J*12.7, 5.4, 2.5, one of CH₂CH₂), 4.25 (1H, ddd, *J*12.7, 8.4, 3.1, one of CH₂CH₂), 4.86 (1H, d, *J*13.1, one of ArCH₂NR₂), 5.82 (1H, s, CHOR), 7.11-7.16 (4H, m, ArH), 7.33-7.39 (1H, m, ArH), 7.52 (1H, dd, *J*7.9, 1.8, ArH),
35 7.57 (1H, bs, ArH).

Example 41**8-Cyclopropyl-5-methyl-1-(3-trifluoromethoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine**

8-Bromo-5-methyl-1-(3-trifluoromethoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine (160 mg, 0.39 mmol), cyclopropylboronic acid (43 mg, 0.5 mmol), K₃PO₄ (288 mg, 1.36 mmol), Pd(OAc)₂ (4 mg, 0.019 mmol) and P(cyclohexane)₃ (11 mg, 0.039 mmol) were heated to 100°C in toluene (2 ml) and H₂O (100 µl) for 4 hours. The reaction mixture, now black in colour, was allowed to cool to RT. Water (50 ml) was added and the mixture extracted into ethyl acetate (3 x 80 ml). The combined organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo* to provide the crude cyclopropyl analogue. Purification by silica gel column chromatography [1:1 EtOAc/heptane, then 100% EtOAc] furnished 8-cyclopropyl-(*m*-trifluoromethoxy)-nefopam.

δ_H (CDCl₃; 250MHz) 0.67-0.74 (2H, m, two of cyclopropyl CH₂CH₂), 0.89-1.00 (2H, m, two of cyclopropyl CH₂CH₂), 1.82-1.93 (1H, m, cyclopropyl CH), 2.51 (3H, s, CH₃), 2.68 (1H, ddd, *J*14.2, 5.7, 2.5, one of CH₂CH₂), 2.89 (1H, ddd, *J*14.2, 8.2, 2.0, one of CH₂CH₂), 3.74 (1H, d, *J*12.8, one of ArCH₂NR₂), 3.87 (1H, ddd, *J*12.7, 5.7, 2.0, one of CH₂CH₂), 4.13 (1H, ddd, *J*12.7, 8.2, 2.5, one of CH₂CH₂), 4.58 (1H, d, *J*12.5, one of ArCH₂NR₂), 5.81 (1H, s, CHOR), 6.84-6.97 (3H, m, ArH), 7.09-7.20 (3H, m, ArH), 7.29-7.37 (1H, m, ArH).

Example 42**9-Bromo-5-methyl-1-(3-trifluoromethoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine**

Crude 2-({4-bromo-2-[hydroxyl-(3-trifluoromethoxy-phenyl)-methyl]-benzyl}-methylamino)-ethanol (1.159 g, 2.69 mmol) was heated to reflux with *p*TSA (768 mg, 4.04 mmol) in xylene (12ml) with Dean-Stark for 4 hours, 45 mins. The reaction mixture was allowed to cool and then washed with a saturated solution of sodium bicarbonate (100 ml). The organics were extracted into ethyl acetate (2 x 100 ml) and the combined organic extracts dried (MgSO₄), filtered and concentrated *in vacuo* to provide the crude product as a 2:1 mixture with starting material. Purification by silica gel column chromatography provided the target product (189 mg, 17%).

δ_H (CDCl₃; 250MHz) 2.44 (3H, s, CH₃), 2.64 (1H, ddd, *J*15.0, 5.0, 2.5, one of CH₂CH₂), 2.81 (1H, ddd, *J*15.0, 7.5, 2.5, one of CH₂CH₂), 3.67 (1H, d, *J*12.5, one of ArCH₂NR₂), 3.84 (1H, ddd, *J*12.5, 5.0, 2.5, one of CH₂CH₂), 4.14 (1H, ddd, *J*12.5, 5.0, 2.5, one of

CH_2CH_2), 4.65 (1H, d, $J_{12.5}$, one of ArCH_2NR_2), 5.75 (1H, s, CHOR), 7.09-7.19 (5H, m, ArH), 7.34 (1H, d, $J_{8.0}$, one of ArH), 7.40 (1H, dd, $J_{8.0}$, 1.9, one of ArH).

Example 43

5 9-Cyclopropyl-5-methyl-1-(3-trifluoromethoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine

9-Bromo-5-methyl-1-(3-trifluoromethoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine (95 mg, 0.28 mmol), K_3PO_4 (205 mg, 0.97 mmol), cyclopropylboronic acid (31 mg, 0.36 mmol), $\text{P}(\text{cyclohexane})_3$ (8 mg, 0.028 mmol) and $\text{Pd}(\text{OAc})_2$ (3 mg, 0.014 mmol) were heated at 100°C in toluene (2ml) and water (100 μl). The reaction mixture turned
10 black in colour after about 20 mins. At the end of 3 hours, the mixture was allowed to cool to RT, and water (30 ml) was added. The organics were extracted into ethyl acetate (2 x 30 ml) and the combined extracts dried (MgSO_4), filtered and concentrated *in vacuo*. Purification by silica gel gravity column chromatography [EtOAc] furnished product.

δ_{H} (CDCl_3 ; 250MHz) 0.58-0.63 (2H, m, two of cyclopropyl CH_2CH_2), 0.90-0.94 (2H, m, two of CH_2CH_2), 1.73-1.79 (1H, m, cyclopropyl CH), 2.45 (3H, s, CH_3), 2.68 (1H, ddd, $J_{15.0}$, 5.0, 2.5, one of CH_2CH_2), 2.87 (1H, ddd, $J_{15.0}$, 7.5, 2.5, one of CH_2CH_2), 3.75 (1H, d, $J_{12.5}$, one of ArCH_2NR_2), 3.88 (1H, ddd, $J_{12.5}$, 5.0, 2.5, one of CH_2CH_2), 4.19 (1H, ddd, $J_{12.5}$, 7.5, 2.5, one of CH_2CH_2), 4.67 (1H, $J_{12.5}$, one of ArCH_2NR_2), 5.75 (1H, s, CHOR), 6.72 (1H, d, $J_{2.5}$, one of ArH), 6.93 (1H, dd, $J_{7.5}$, 2.5, ArH), 7.10-7.19 (4H, m, ArH), 7.29-7.38 (1H, ArH)
20

Example 44

9-Bromo-5-methyl-1-(2-methyl)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine

2-[(4-bromo-2-(hydroxyl-*o*-tolyl)methyl)-benzyl]-methylamino]-ethanol (790 mg, 2.18 mmol) was dissolved in toluene (8 ml) at RT. $p\text{TSA}$ (623 mg, 3.27 mmol) was added
25 and the resulting mixture was heated to reflux temperature under Dean-Stark conditions for 1.5 hours. Once cooled to RT, the mixture was diluted with ethyl acetate and washed with sat. aq. solution of sodium bicarbonate. The organic extracts were dried (MgSO_4), filtered and concentrated *in vacuo* to provide the crude material as an oil. Purification by silica gel gravity column chromatography [20% EtOAc /heptane to 30% EtOAc] furnished
30 the product (357 mg, 55% corrected yield)

δ_{H} (CDCl_3 ; 250MHz) 2.31 (3H, s, ArCH_3), 2.44 (3H, s, NCH_3), 2.63 (1H, ddd, $J_{14.4}$, 5.3, 2.4, one of CH_2CH_2), 2.86 (1H, ddd, $J_{14.4}$, 8.9, 2.1, one of CH_2CH_2), 3.76 (1H, d, $J_{13.0}$, one of ArCH_2NR_2), 3.85 (1H, ddd, $J_{12.7}$, 5.3, 2.1, one of CH_2CH_2), 4.12 (1H, ddd, $J_{12.7}$, 8.9, 2.4, one of CH_2CH_2), 4.68 (1H, d, $J_{13.0}$, one of ArCH_2NR_2), 5.95 (1H, s, CHOR),
35 7.02-7.22 (6H, m, ArH), 7.38 (1H, dd, $J_{8.2}$, 2.1, ArH).

Example 45**9-Cyano-5-methyl-1-(2-methyl)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine**

9-Bromo-5-methyl-1-(2-methyl)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine (156 mg, 0.45 mmol), Zn dust (2 mg, 0.03 mmol), Zn(CN)₂ (32 mg, 0.27 mmol), Zn(OAc)₂ (10 mg, 0.054 mmol), 1,1'-bis(diphenylphosphino)ferrocene (30 mg, 0.054 mmol) and Pd₂(dba)₃ (55 mg, 0.06 mmol) were heated to 140°C in DMF (3 ml) and water (30 µl) under a nitrogen atmosphere over-night. After cooling, water was added and the resulting black/brown precipitate was collected by suction filtration and washed well with ethyl acetate. The filtrate was washed with brine and extracted into ethyl acetate. The combined organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo* to provide the crude material as a very dark brown oil. Purification by silica gel gravity column chromatography [EtOAc] furnished the product (79 mg, 60%).

δ_H (CDCl₃; 250MHz) 2.28 (3H, s, ArCH₃), 2.45 (3H, s, ArCH₃), 2.65 (1H, ddd, *J*14.4, 5.5, 2.4, one of CH₂CH₂), 2.85 (3H, ddd, *J*14.4, 8.9, 2.1, one of CH₂CH₂), 3.82-3.90 (2H, m, one of CH₂CH₂ and one of ArCH₂NR₂), 4.07-4.17 (1H, m, one of CH₂CH₂), 4.74 (1H, d, *J*12.8, one of ArCH₂NR₂), 6.02 (1H, s, CHOR), 7.05 (1H, d, *J*6.7, ArH), 7.14-7.27 (4H, m, ArH), 7.34 (1H, d, *J*7.9, ArH), 7.54 (1H, dd, *J*7.9, 1.7, ArH).

Example 46**9-Cyclopropyl-5-methyl-1-(2-methyl)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine**

9-Bromo-5-methyl-1-(2-methyl)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine (188 mg, 0.55 mmol) was dissolved in toluene (4 ml) and water (200 µl) at RT. Cyclopropylboronic acid (61 mg, 0.71 mmol), K₃PO₄ (409 mg, 1.93 mmol), Pd(OAc)₂ (6 mg, 0.03 mmol) and P(cyclohexane)₃ (15.4 mg, 0.055 mmol) were added. The mixture was heated to 100°C for a total of 3 hours, during which time the reaction mixture became black. After cooling to RT, the mixture was diluted with water and extracted into ethyl acetate. The organic phases were dried (MgSO₄), filtered and concentrated *in vacuo* to provide the crude product. Purification by silica gel gravity column chromatography [EtOAc] furnished the product (129 g, 81%).

δ_H (CDCl₃; 250MHz) 0.54-0.60 (2H, m, two of cyclopropyl CH₂CH₂), 0.86-0.89 (2H, m, two of cyclopropyl CH₂CH₂), 1.69-1.80 (1H, m, cyclopropyl CH), 2.34 (3H, s, ArCH₃), 2.45 (3H, s, ArCH₃), 2.62 (1H, ddd, *J*14.3, 5.5, 2.4, one of CH₂CH₂), 2.87 (1H, ddd, *J*14.3, 8.5, 2.1, one of CH₂CH₂), 3.75 (1H, d, *J*13.0, one of ArCH₂NR₂), 3.85 (1H, ddd, *J*12.7, 5.5, 2.1, one of CH₂CH₂), 4.11 (1H, ddd, *J*12.7, 8.5, 2.4, one of CH₂CH₂), 4.64 (1H, d, *J*13.0,

one of ArCH₂NR₂), 5.96 (1H, s, CHOR), 6.62 (1H, d, J1.8, ArH), 6.89 (1H, dd, J7.9, 1.8, ArH), 7.05-7.20 (5H, ArH).

Example 47

8-Bromo-5-methyl-1-(2-methyl)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine

5 2[(5-bromo-2-(hydroxyl-o-tolylmethyl)-benzyl)methylamino]-ethanol (777 mg, 2.16 mmol) was dissolved in toluene (8 ml) at RT. pTSA (616 mg, 3.24 mmol) was added, and the resulting mixture heated at reflux temperature under Dean-Stark conditions for 4 hours. The reaction was allowed to cool to RT and then diluted with ethyl acetate, and washed with sat. aq. sodium bicarbonate solution. The organic washings were dried
10 (MgSO₄), filtered and concentrated *in vacuo* to provide the impure product. Purification by silica gel gravity column chromatography [1:1 EtOAc/heptane to 100% EtOAc] gave the desired product (504 mg, 64%).

δ_H (CDCl₃; 250MHz) 2.29 (3H, s, ArCH₃), 2.46 (3H, s, NCH₃), 2.66 (1H, ddd, J14.4, 5.6, 2.4, one of CH₂CH₂), 2.89 (1H, ddd, J14.4, 8.5, 2.1, one of CH₂CH₂), 3.77 (1H, d, J13.1,
15 one of ArCH₂NR₂), 3.86 (1H, ddd, J12.7, 5.6, 2.1, one of CH₂CH₂), 4.09 (1H, ddd, J12.7, 8.5, 2.4, one of CH₂CH₂), 4.64 (1H, d, J13.1, one of ArCH₂NR₂), 5.97 (1H, s, CHOR), 6.74 (1H, d, J8.2, ArH), 7.07-7.20 (4H, m, ArH), 7.29 (1H, dd, J8.6, 2.1, ArH), 7.41 (1H, d, J2.1, ArH).

Example 48

8-Cyano-5-methyl-1-(2-methyl)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine

20 8-Bromo-5-methyl-1-(2-methyl)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine (207 mg, 0.60 mmol), Zn (2 mg, 0.03 mmol), Zn(OAc)₂ (13 mg, 0.071 mmol), Zn(CN)₂ (42 mg, 0.36 mmol), 1,1'-bis(diphenylphosphino)ferrocene (40 mg, 0.072 mmol) and Pd₂(dba)₃ (75 mg, 0.082 mmol) were heated to 140°C in DMF (5 ml) and H₂O (50 μ l)
25 overnight. The black reaction mixture was cooled and water added, producing a brown precipitate. The precipitate was washed with ethyl acetate and the filtrate washed with brine to remove the DMF. The organic phase was dried (MgSO₄), filtered and concentrated *in vacuo* to provide the crude product. Purification by silica gel gravity column chromatography [EtOAc] furnished the desired product (39 g, 22%).

30 δ_H (CDCl₃; 250MHz) 2.33 (3H, s, ArCH₃), 2.46 (3H, s, NCH₃), 2.64 (1H, ddd, J14.9, 5.1, 2.6, one of CH₂CH₂), 2.77 (1H, ddd, J14.9, 8.9, 2.4, one of CH₂CH₂), 3.78 (1H, d, J13.1, one of ArCH₂NR₂), 3.86 (1H, ddd, J12.7, 5.1, 2.4, one of CH₂CH₂), 4.18 (1H, ddd, J12.7, 8.9, 2.6, one of CH₂CH₂), 4.89 (1H, d, J13.1, one of ArCH₂NR₂), 5.99 (1H, s, CHOR), 6.91-6.98 (2H, m, ArH), 7.12-7.22 (3H, ArH), 7.46 (1H, dd, J7.9, 1.8, ArH), 7.55 (1H, d,
35 J1.5, ArH).

Example 49**8-Cyclopropyl-5-methyl-1-(2-methyl)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine**

8-Bromo-5-methyl-1-(2-methyl)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine (205 mg, 0.60 mmol) was dissolved in toluene (4 ml) and H₂O (200 μ l) at RT. Cyclopropylboronic acid (67 mg, 0.77 mmol), K₃PO₄ (446 mg, 2.1 mmol), Pd (OAc)₂ (7 mg, 0.03 mmol) and P(cyclohexane)₃ (17 mg, 0.06 mmol) were added and the resulting mixture heated at 100°C for 3 hours. The mixture was then allowed to cool to RT before partitioning the mixture between water and ethyl acetate. The organic phases were dried (MgSO₄), filtered and concentrated *in vacuo* to yield the crude product. Purification by silica gel gravity column chromatography [EtOAc] provided the desired target (117 g, 64%).

δ_{H} (CDCl₃; 250MHz) 0.67-0.74 (2H, m, two of CH₂CH₂), 0.92-1.0 (2H, m, two of CH₂CH₂), 1.83-1.93 (1H, m, cyclopropyl CH), 2.28 (3H, s, ArCH₃), 2.48 (3H, s, NCH₃), 2.66 (1H, ddd, *J*14.4, 5.6, 2.3, one of CH₂CH₂), 2.95 (1H, ddd, *J*14.4, 8.5, 2.1, one of CH₂CH₂), 3.81 (1H, d, *J*12.8, one of ArCH₂), 3.87 (1H, ddd, *J*12.8, 5.6, 2.1, one of CH₂CH₂), 4.08 (1H, ddd, *J*12.8, 8.5, 2.3, one of CH₂CH₂), 4.56 (1H, d, *J*12.8, one of ArCH₂NR₂), 5.98 (1H, s, CHOR), 6.73 (1H, d, *J*7.9, ArH), 6.85 (1H, dd, *J*7.9, 1.8, ArH), 6.97 (1H, d, *J*1.8, ArH), 7.14-7.18 (4H, m, ArH).

Example 50**9-Bromo-5-methyl-1-(3-pyridyl)-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine**

2-[[4-Bromo-2-(hydroxypyridin-3-yl-methyl)-benzyl]-methylamino]-ethanol (100 mg, 0.29 mmol) was dissolved in xylene (2 mL) at RT. *p*TSA (434 mg, 2.28 mmol) was added, and the resulting mixture was heated at 120°C in an open vessel until all solvent and water had evaporated. The reaction vessel was removed from the heat and allowed to cool. Ethyl acetate (20 ml) and a sat. aq. solution of sodium bicarbonate (20 ml) were added to partition the gummy mixture. The organic phase was separated, and the aqueous phase was extracted into ethyl acetate (2 x 20 ml). Combined extracts were dried (MgSO₄), filtered and concentrated *in vacuo* to give the cyclised product as a pale brown oil. Purification by silica gel column chromatography with a stepped gradient, [100%EtOAc to 3%/5%/10% MeOH/EtOAc], furnished product (23 mg, 24%).

δ_{H} (CDCl₃, 250MHz) 2.46 (3H, s, NCH₃), 2.66 (1H, ddd, *J*14.4, 5.5, 2.8, one of CH₂CH₂), 2.83 (1H, ddd, *J*14.4, 8.2, 2.1, one of CH₂CH₂), 3.67 (1H, d, *J*13.1, one of ArCH₂NR₂), 3.86 (1H, ddd, *J*12.7, 5.5, 2.1, one of CH₂CH₂), 4.19 (1H, ddd, *J*12.7, 8.2, 2.8, one of CH₂CH₂), 4.73 (1H, d, *J*13.1, one of ArCH₂NR₂), 5.77 (1H, s, CHOR), 7.11-7.14 (2H, m,

aromatic H), 7.24-7.29 (1H, m, aromatic H), 7.39 (1H, dd, *J*7.9, 1.8, aromatic H), 7.56 (1H, d, *J*7.9, aromatic H), 8.53-8.57 (2H, m, aromatic H).

Example 51

8-Bromo-5-methyl-1-(3-pyridyl)-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine

5 2-[[5-Bromo-2-(hydroxypyridin-3-yl-methyl)-benzyl]-methylamino]-ethanol (84 mg, 0.24 mmol) was dissolved in xylene (2 ml). *p*TSA (364 mg, 1.9 mmol) was added and the mixture was heated to reflux temperature in an open vessel to allow evaporation of the solvent and water. When the mixture had concentrated down to a dark gum, the vessel was removed from the heat and allowed to cool. The residue was partitioned between
10 ethyl acetate (20 ml) and sat. aq. sodium bicarbonate solution (20 ml). The aqueous phase was extracted further with ethyl acetate (2 x 20 ml), and the combined organic extracts dried (magnesium sulphate), filtered and evaporated to dryness to give crude product. Purification was by silica gel column chromatography [Ethyl acetate] to provide the target compound as an oil/solid.

15 δ_{H} (CDCl₃; 250MHz) 2.46 (3H, s, CH₃), 2.58 (1H, ddd, *J*14.3, 6.1, 2.6, one of CH₂CH₂), 2.83 (1H, ddd, *J*14.3, 7.9, 2.1, one of CH₂CH₂), 3.63 (1H, d, *J*13.1, one of ArCH₂NR₂), 3.86 (1H, ddd, *J*12.6, 6.1, 2.1, one of CH₂CH₂), 4.16 (1H, ddd, *J*12.6, 7.9, 2.6, one of CH₂CH₂), 4.68 (1H, d, *J*13.1, one of ArCH₂NR₂), 5.80 (1H, s, CHOR), 6.84 (1H, d, *J*8.3, aromatic H), 7.21-7.27 (2H, m, aromatic H), 7.32-7.40 (2H, m, aromatic H), 7.55 (1H, dd, *J*7.8, 1.6, aromatic H), 8.52 (1H, dd, *J*4.6, 1.6, aromatic H), 8.54 (1H, d, *J*8.6, aromatic H).
20

Example 52

8-Cyano-5-methyl-1-(3-pyridyl)-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine

8-Bromo-5-methyl-1-(3-pyridyl)-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine (50
25 mg, 0.15 mmol), Zn (1 mg, 0.01 mmol), Zn(OAc)₂ (4 mg, 0.02 mmol), Zn(CN)₂ (13 mg, 0.11 mmol), Pd₂(dba)₃ (18 mg 0.02 mmol), and 1,1'-bis(diphenylphosphine)ferrocene (9 mg 0.02 mmol) were heated to 140 °C in DMF (2 ml) and H₂O (20 μ l) overnight. The black reaction mixture was allowed to cool and diluted with water (20 ml). The resulting brown precipitate was collected by filtration and washed with water then brine. The
30 filtrate was extracted with ethyl acetate (2 x 50 ml). The combined organic extracts were dried (magnesium sulphate), filtered and concentrated in vacuo to provide the crude product as a brown oil. Purification was by silica gel column chromatography [dichloromethane] to furnish the desired product (10 mg, 24%) as a yellow oil.

35 δ_{H} (CDCl₃; 250MHz) 2.47 (3H, s, CH₃), 2.58-2.84 (2H, m, CH₂CH₂), 3.68 (1H, d, *J*13.1, one of ArCH₂NR₂), 3.82-3.90 (1H, m, one of CH₂CH₂), 4.19-4.29 (1H, m, one of

CH₂CH₂), 4.88 (1H, d, J13.1, one of ArCH₂NR₂), 5.84 (1H, s, CHOR), 7.11 (1H, d, J8.3, aromatic H), 7.22-7.30 (2H, m, aromatic H), 7.49-7.55 (3H, m, aromatic H), 8.52 (1H, dd, J4.6, 1.6 aromatic H), 8.55 (1H, d, J8.6, aromatic H).

Biological Assay

- 5 The assay was carried out according to the method described by Perovic *et al* (1995), *Arzneim-Forsch. Drug Res.*, 45: 1145.

Assay for Inhibition of Noradrenaline Reuptake Activity

- Synaptosomes (100 µg) are incubated for 20 min at 37°C with 0.1 µCi [³H]norepinephrine in the absence (control) or presence of the test compound or the
10 reference compound in a buffer containing 118 mM NaCl, 5 mM KCl, 2.5 mM MgSO₄, 1.2 mM NaH₂PO₄, 25 mM NaHCO₃, 11 mM glucose, 10 µM EGTA and 50 µM ascorbic acid (pH 7.4). Basal control activity is determined by incubating the same mixture for 20 min at 0°C in the presence of 10 µM protriptyline to block the uptake. Following incubation, the samples are filtered rapidly under vacuum through glass fiber filters (GF/B, Packard)
15 and rinsed twice with ice-cold incubation buffer using a 96-sample cell harvester (Unifilter, Packard) to eliminate free [³H]norepinephrine. The filters are dried and the retained radioactivity is measured in a scintillation counter (Topcount, Packard) using a scintillation cocktail (Microscint 0, Packard).

- The results are expressed as a percent inhibition of the control uptake of
20 [³H]norepinephrine. The standard inhibitory reference compound is protriptyline, which is tested in each experiment at several concentrations to obtain an inhibition curve from which its IC₅₀ value is calculated.

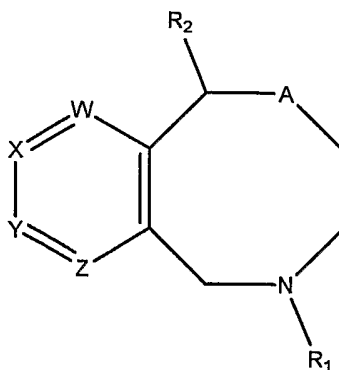
Assay for Inhibition of Serotonin Reuptake Activity

- Synaptosomes (100 µg) are incubated for 15 min at 37°C with 0.1 µCi
25 [³H]serotonin in the absence (control) or presence of the test compound or the reference compound in a buffer containing 118 mM NaCl, 5 mM KCl, 2.5 mM MgSO₄, 1.2 mM NaH₂PO₄, 25 mM NaHCO₃, 11 mM glucose, 10 µM EGTA and 50 µM ascorbic acid (pH 7.4). Basal control activity is determined by incubating the same mixture for 15 min at 4°C in the presence of 10 µM imipramine to block the uptake. Following incubation, the
30 samples are filtered rapidly under vacuum through glass fiber filters (GF/B, Packard) and rinsed twice with ice-cold incubation buffer using a 96-sample cell harvester (Unifilter, Packard) to eliminate free [³H]serotonin. The filters are dried and the retained radioactivity is measured in a scintillation counter (Topcount, Packard) using a scintillation cocktail (Microscint 0, Packard).

The results are expressed as a percent inhibition of the control uptake of [³H]serotonin. The standard inhibitory reference compound is imipramine, which is tested in each experiment at several concentrations to obtain an inhibition curve from which its IC₅₀ value is calculated.

Claims

1. A compound of general formula (1)



(1)

wherein R_1 is H, C_1 - C_6 alkyl optionally substituted with F or C_3 - C_6 cycloalkyl or C_2 - C_4 alkenyl;

A is O, CH_2 or $S(O)_n$ where n is 0-2;

one of W, X, Y and Z is N, CH or CR_3 and the others are CH;

R_2 is C_5 - C_6 heteroaryl, C_5 - C_{10} cycloalkyl or cycloalkenyl optionally containing one or more heteroatoms selected from O, N and $S(O)_n$ where n is 0-2, and optionally substituted with R_3 ; or a phenyl group optionally substituted in one or more positions with one or more substituents independently selected from halogen, CN, CF_3 , C_1 - C_6 alkyl and OR_1 , or the phenyl group is fused to a five or six membered ring which may be carbocyclic, heterocyclic (containing 1-2 heteroatoms selected from O, N and S), aromatic or heteroaromatic (containing 1-2 heteroatoms selected from O and N);

R_3 is selected from halogen; CF_3 ; CN; OR_5 ; $SO_2N(R_5)_2$; COR_5 ; CO_2R_5 ; $CON(R_5)_2$; NR_1COR_4 ; $NR_1SO_2R_4$; $NR_1CO_2R_4$; $NR_1CON(R_5)_2$; OC_1 - C_6 alkyl substituted with R_3 ; C_1 - C_6 alkyl optionally substituted with unsubstituted R_3 ; C_3 - C_6 cycloalkyl optionally substituted with unsubstituted R_3 ; C_2 - C_6 alkenyl optionally substituted with unsubstituted R_3 ; C_2 - C_6 alkynyl optionally substituted with unsubstituted R_3 ; aryl optionally substituted with unsubstituted R_3 ; and five or six membered aromatic heterocycles containing 1-4 heteroatoms selected from N and O;

R_4 is C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl, aryl and heteroaryl; and

R_5 is H, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl, aryl or heteroaryl and is the same as or different to another R_5 ;

or a pharmaceutically acceptable salt thereof.

2. A compound of claim 1, wherein R₂ is optionally substituted heteroaryl, cycloalkyl or cycloalkenyl.
3. A compound of claim 1, wherein R₂ is optionally substituted phenyl.
4. A compound of claim 1, selected from:
 - 5-benzyl-1-phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine;
 - 5-allyl-1-phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine;
 - 5-cyclopropyl-1-phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine;
 - 5-propyl-1-phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine;
 - 5-methylcyclopropyl-1-phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine;
 - 5-isopropyl-1-phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine;
 - 8-(4-pyridyl)-5-methyl-1-(3-methoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine;
 - 8-(5-pyrimidine)-5-methyl-1-(3-methoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine;
 - 5-methyl-1-(3-methoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine;
 - 5-methyl-1-(3-methoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine-8-carboxamide;
 - 10-fluoro-5-methyl-1-phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine;
 - 7-fluoro-5-methyl-1-phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine;
 - 8-bromo-5-methyl-1-(3-tosyloxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine;
 - 8-bromo-5-methyl-1-(3-hydroxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine;
 - 8-cyano-5-methyl-1-(3-hydroxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine;
 - 8-cyclopropyl-5-methyl-1-(3-hydroxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine;
 - 8-bromo-5-methyl-1-(3-allyloxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine;
 - 8-cyano-5-methyl-1-(3-allyloxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine;
 - 8-cyclopropyl-5-methyl-1-(3-allyloxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine;
 - 8-bromo-5-methyl-1-(2-methyl-3-methoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine;

- 8-cyano-5-methyl-1-(2-methyl-3-methoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine;
- 8-cyclopropyl-5-methyl-1-(2-methyl-3-methoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine;
- 5 8-bromo-5-methyl-1-(3-methoxy-4-methyl)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine;
- 8-cyano-5-methyl-1-(3-methoxy-4-methyl)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine;
- 10 5-methyl-1-(3-methoxy-4-methyl)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine-8-carboxamide;
- 8-cyclopropyl-5-methyl-1-(3-methoxy-4-methyl)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine;
- 9-bromo-5-methyl-1-(3,4-methylenedioxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine;
- 15 9-cyano-5-methyl-1-(3,4-methylenedioxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine;
- 9-cyclopropyl-5-methyl-1-(3,4-methylenedioxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine;
- 8-bromo-5-methyl-1-(3,4-methylenedioxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine;
- 20 8-cyano-5-methyl-1-(3,4-methylenedioxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine;
- 8-cyclopropyl-5-methyl-1-(3,4-methylenedioxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine;
- 25 8-bromo-5-methyl-1-(3-ethoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine;
- 8-cyano-5-methyl-1-(3-ethoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine;
- 8-cyclopropyl-5-methyl-1-(3-ethoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine;
- 30 9-bromo-5-methyl-1-(3-ethoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine;
- 9-cyano-5-methyl-1-(3-ethoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine;

- 9-cyclopropyl-5-methyl-1-(3-ethoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine;
- 8-bromo-5-methyl-1-(3-trifluoromethoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine;
- 5 8-cyano-5-methyl-1-(3-trifluoromethoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine;
- 8-cyclopropyl-5-methyl-1-(3-trifluoromethoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine;
- 9-bromo-5-methyl-1-(3-trifluoromethoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine;
- 10 9-cyclopropyl-5-methyl-1-(3-trifluoromethoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine;
- 9-bromo-5-methyl-1-(2-methyl)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine;
- 15 9-cyano-5-methyl-1-(2-methyl)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine;
- 9-cyclopropyl-5-methyl-1-(2-methyl)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine;
- 8-bromo-5-methyl-1-(2-methyl)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine;
- 20 8-cyano-5-methyl-1-(2-methyl)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine;
- 8-cyclopropyl-5-methyl-1-(2-methyl)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine;
- 25 9-bromo-5-methyl-1-(3-pyridyl)-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine;
- 8-bromo-5-methyl-1-(3-pyridyl)-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine; and
- 8-cyano-5-methyl-1-(3-pyridyl)-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine
5. A compound of any preceding claim, in the form of a single (+) or (-) enantiomer.
6. A pharmaceutical composition for use in therapy, comprising a compound of any preceding claim, and a pharmaceutically acceptable diluent or carrier.
- 30 7. Use of a compound of any of claims 1 to 5, for the manufacture of a medicament for the treatment or prevention of a condition associated with monoamine re-uptake.
8. Use according to claim 7, wherein the condition is selected from depression, post-traumatic stress disorders, attention-deficit disorders, obsessive-compulsive

disorders, pre-menstrual syndrome, substance abuse, micturition disorders and sexual dysfunction.

9. Use according to claim 7, where the condition is acute, chronic or neuropathic pain, dysmenorrhoea or migraine headache.

5 10. Use according to claim 9, wherein the subject of treatment is also treated with an opiate.

11. Use according to claim 9, wherein the subject of treatment is also treated with an analgesia inducer selected from acetaminophen, non-steroidal anti-inflammatory drugs, narcotic analgesics, local anesthetics, NMDA antagonists, neuroleptic agents, anti-convulsants, anti-spasmodics, anti-depressants and muscle relaxants.

12. Use according to claim 7, wherein the condition is emesis.

13. Use according to claim 12, wherein the emesis is acute, delayed, post-operative, last-phase or anticipatory emesis.

14. Use according to claim 12 or claim 13, wherein the emesis is induced by
15 chemotherapy, radiation, toxins, pregnancy, vestibular disorder, motion, post-operative sickness, surgery, gastrointestinal obstruction, reduced gastrointestinal motility, visceral pain, migraine or an opioid analgesic.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB2005/001519

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D267/22 C07D413/04 A61K31/395

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	claim 1; examples 5,7	1-14
X	US 3 978 085 A (EBERLIN ET AL) 31 August 1976 (1976-08-31) claim 1; table 1	1,3
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB2005/001519

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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