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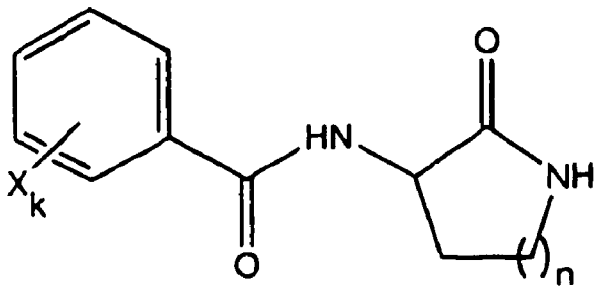


(I)

(57) Abstract: Disclosed herein are methods of preventing or treating inflammatory diseases using 3 - aminolactam compounds, each with aromatic "tail groups". Compounds as defined by formulae (I) and (I'), and the medical uses of the compounds, are described herein.

WO 2011/154696 A1

Anti-inflammatory agents

The invention relates to aryl substituted 3-aminolactam derivatives and their use in preventing or treating inflammatory diseases.

Inflammation is an important component of physiological host defence. Increasingly, however, it is clear that temporally or spatially inappropriate inflammatory responses play a part in a wide range of diseases, including those with an obvious leukocyte component (such as autoimmune diseases, asthma or atherosclerosis) but also in diseases that have not traditionally been considered to involve leukocytes (such as osteoporosis or Alzheimer's disease).

The chemokines are a large family of signalling molecules with homology to interleukin-8 which have been implicated in regulating leukocyte trafficking both in physiological and pathological conditions. With more than fifty ligands and twenty receptors involved in chemokine signalling, the system has the requisite information density to address leukocytes through the complex immune regulatory processes from the bone marrow, to the periphery, then back through secondary lymphoid organs. However, this complexity of the chemokine system has at first hindered pharmacological approaches to modulating inflammatory responses through chemokine receptor blockade. It has proved difficult to determine which chemokine receptor(s) should be inhibited to produce therapeutic benefit in a given inflammatory disease.

More recently, a family of agents which block signalling by a wide range of chemokines simultaneously has been described (see Reckless *et al.*, Biochem J. (1999) **340**: 803-811). The first such agent, a peptide termed "Peptide 3", was found to inhibit leukocyte migration induced by 5 different chemokines, while leaving migration in response to other chemoattractants (such as fMLP or TGF-beta) unaltered. This peptide, and its analogs such as NR58-3.14.3 (i.e. c(DCys-DGln-DIle-DTrp-DLys-DGln-DLys-DPro-DAsp-DLeu-DCys)-NH_2 [SEQ ID NO: 1]), are collectively termed "Broad Spectrum Chemokine Inhibitors" (BSCIs). Grainger *et al.* (2003, Biochem. Pharm. **65**: 1027-1034) have subsequently shown BSCIs to have potentially useful anti-inflammatory activity in a range of animal models of diseases. Interestingly, simultaneous blockade of multiple chemokines is not apparently

associated with acute or chronic toxicity, suggesting this approach may be a useful strategy for developing new anti-inflammatory medications with similar benefits to steroids but with reduced side-effects. This beneficial risk:benefit profile most likely results from the unexpected mechanism of action of these compounds (see International Patent Appl. No. PCT/GB2010/000354 in the name of Cambridge Enterprise Limited filed 28 February 2010, and International Patent Appl. No. PCT/GB2010/000342 in the name of Cambridge Enterprise Limited filed 26 February 2010).

However, peptides and peptoid derivatives such as NR58-3.14.3, may not be optimal for use in vivo. They are quite expensive to synthesise and have relatively unfavourable pharmacokinetic and pharmacodynamic properties. For example, NR58-3.14.3 is not orally bioavailable and is cleared from blood plasma with a half-life period of less than 30 minutes after intravenous injection.

Two parallel strategies have been adopted to identify novel preparations that retain the anti-inflammatory properties of peptide 3 and NR58-3.14.3, but have improved characteristics for use as pharmaceuticals. Firstly, a series of peptide analogs have been developed, some of which have longer plasma half-lives than NR58-3.14.3 and which are considerably cheaper to synthesise (see for example WO2009/017620). Secondly, a detailed structure: activity analysis of the peptides has been carried out to identify the key pharmacophores and design small non-peptidic structures which retain the beneficial properties of the original peptide.

This second approach yielded several structurally distinct series of compounds that retained the anti-inflammatory properties of the peptides, including 16-amino and 16-aminoalkyl derivatives of the alkaloid yohimbine, as well as a range of N-substituted 3-aminoglutarimides, identified from a small combinatorial library (see Fox *et al.*, 2002, J Med Chem **45**: 360-370; WO 99/12968 and WO 00/42071). All of these compounds are broad-spectrum chemokine inhibitors that retain selectivity over non-chemokine chemoattractants, and a number of them have been shown to block acute inflammation in vivo.

The most potent and selective of the above-mentioned aminoglutarimides was (S)-3-(undec-10-enoyl)-aminoglutarimide (NR58,4), which inhibited chemokine-induced

migration in vitro with an ED_{50} of 5nM. This compound was orders of magnitude more potent than 3-aminoglutarimides with more complex acyl side chains (such as benzoyl or tert-butyloxo (Boc) groups). As a result, subsequent studies of aminoglutarimide and aminolactam BSCIs have focussed almost exclusively on compounds with simple linear and branched alkyl side chains.

However, further studies revealed that the aminoglutarimide ring was susceptible to enzymatic ring opening in serum. Consequently, for some applications (for example, where the inflammation under treatment is chronic, such as in autoimmune diseases) these compounds may not have optimal properties, and a more stable compound with similar anti-inflammatory properties may be superior.

As an approach to identifying such stable analogs, various derivatives of (S)- 3-(undec-10-enoyl)-aminoglutarimide have been tested for their stability in serum. One derivative, the 6-deoxo analog (S)-3-(undec-10-enoyl)-tetrahydropyridin-2-one, is completely stable in human serum for at least 7 days at 37°C, but has considerably reduced potency compared with the parental molecule.

One such family of stable, broad spectrum chemokine inhibitors (BSCIs) are the 3-amino caprolactams, with a seven-membered monolactam ring (see, for example, WO2005/053702 and WO2006/016152). However, further useful anti-inflammatory compounds have also been generated from other 3-aminolactams with different ring size (see for example WO2006/134385). Other modifications to the lactam ring, including introduction of heteroatoms and bicyclolactam ring systems, also yield compounds with BSCI activity (see, for example, WO2006/018609 and WO2006/085096).

In general, these earlier studies have demonstrated that the BSCI activity is conferred on the molecule by the cyclic "head group" (a 3-amino lactam or imide) and defined, to an extent, the structural limitations for activity (for example, bulky substituents on the ring nitrogen are detrimental for activity, but variations in ring size have little impact). To be active as a BSCI, this "head group" must have an acyl "tail group" attached. Compounds with a 3-amino group, either free or N-alkyl substituted, bearing a positive charge at physiological pH are completely inactive as BSCIs. Previous

disclosures have shown that this "tail group" can be linked to the "head group" through simple amide, sulfonamide, urea or carbamate linkers.

While the structure of the "head" group and linker are critical for BSCI activity, it has been shown that a wide variety of "tail groups" can be selected with out affecting the primary pharmacology of the compound, at least in vitro. As a result, modification of the "tail group" has been extensively used to optimise the physical and pharmaceutical properties of the compounds. Changes in the structure of the "tail group" can, for example, change the primary route of metabolism or excretion, modify the pharmacokinetics or oral bioavailability, and thus act as the primary determinant of the ADME properties of a selected compound.

Although the universe of possible "tail groups" known to retain BSCI activity for suitable aminolactam "head groups" is very large, some "tail groups" have been described as preferred. In some cases, structural features of the "tail group" have been identified which increase the potency of BSCI activity of the aminolactam compound. The most obvious such example is the introduction of 2',2' disubstitution, with a tetrahedral sp3 arrangement at the 2' carbon centre in the tail group (the so-called "key carbon"), which confers a 10-fold increase in potency as a BSCI, at least in vitro, compared to a related compound lacking 2'2'-disubstitution. For example, 2'2'-dimethyldodecenanoyl-3-aminocaprolactam is 10-fold more potent as a BSCI in the MCP-1 induced THP-1 cell migration than assay than dodecanoyl-3-aminocaprolactam (as disclosed previously in WO2005/053702), or indeed any other related compound with a linear alkyl "tail group". The increased potency for branched alkyl "tail groups" is restricted to branching at the 2' position – 3'3'-dimethyldodecanoyl-3-aminocaprolactam is no more potent than the linear alkyl analogs.

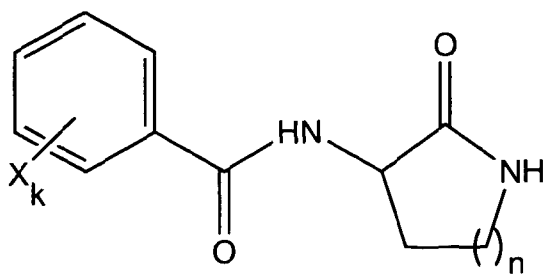
In other cases, structural features of the "tail group" have been identified which are associated with improved ADME properties. For example, the pivoyl "tail group" of 2'2'-dimethylpropanoyl-3-aminovalerolactam contributes to the unexpected, and particularly favourable, pharmaceutical properties of this molecule (as disclosed previously in WO2009/016390). In particular, the pivoyl group is resistant to

metabolism, and therefore contributes to the unusually prolonged biological half-life of this compound.

In marked contrast, other possible "tail groups" have generally been less preferred. For example, compounds with a planar (sp2) carbon centre at the 2' position (such as dodec-2',3'-enoyl-3-aminocaprolactam) have markedly lower potency as BSCIs than compounds with corresponding saturated alkyl "tail groups". Similarly, the data from the original library of glutarimides suggested that aromatic rings at the 2-position were also substantially less active (Fox *et al.*, 2002, J Med Chem **45**: 360-370). Taken together, these two findings have led to the reasonable assumption that aminolactams with aromatic "tail groups", such as benzoyl or substituted benzoyl, would not be useful as BSCIs. As a result, previous disclosures of compounds with BSCI activity have all excluded such aromatic "tail groups".

The present invention discloses a series of 3-aminolactam compounds with aromatic "tail groups", as well as pharmaceutical compositions comprising the compounds, and medical uses of the compounds and compositions such as for the treatment of inflammatory diseases. Surprisingly, all of the compounds as set out below have substantial BSCI activity (greater than either 2',3'-unsaturated acyl 3-aminolactams or benzoylaminoglutarimides).

In one aspect of the invention, there is provided according to the invention is a compound of general formula (**I**), or a pharmaceutically acceptable salt thereof, for use in the treatment of an inflammatory disorder:



(I)

wherein

n is an integer from 1 to 4;

k is an integer from 0 to 5, representing the number of groups substituting C_2, C_3, C_4, C_5 and/or C_6 of the benzyl ring; and

X are linear or branched groups substituting the benzyl ring independently selected from any one of the group consisting of: alkyl, haloalkyl, hydroxyalkyl, hydroxy, alkoxy, amino, aminoalkyl, aminodialkyl, carboxy, and halogen;

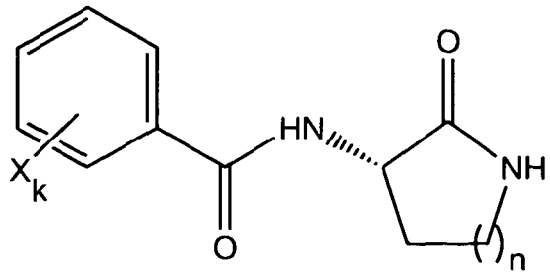
with the proviso that:

when on the benzyl ring C_2, C_5 and C_6 are unsubstituted, and C_4 is unsubstituted or is substituted with an hydroxy, alkoxy, amino, aminoalkyl, aminodialkyl, or halogen group, then C_3 is substituted with a halogen group; and

when on the benzyl ring C_2, C_5 and C_6 are unsubstituted, and C_3 is unsubstituted or is substituted with an alkyl, haloalkyl, hydroxyalkyl, hydroxy, alkoxy, amino, aminoalkyl, aminodialkyl or carboxy group, then C_4 is substituted with any one of the group consisting of: alkyl group, haloalkyl group, hydroxyalkyl group, and carboxy group.

The carbon atom at position 3 of the lactam ring is asymmetric and consequently, the compounds according to the present invention have at least two possible enantiomeric forms, that is, the "R" and "S" configurations. The present invention encompasses each of the two enantiomeric forms and all combinations of these forms, including the racemic "RS" mixtures. With a view to simplicity, when no specific configuration is shown in the structural formula, it should be understood that each of the two enantiomeric forms and their mixtures are represented.

Further provided is a compound of formula (**I'**), or a pharmaceutically acceptable salt thereof, for use in the treatment of an inflammatory disorder:

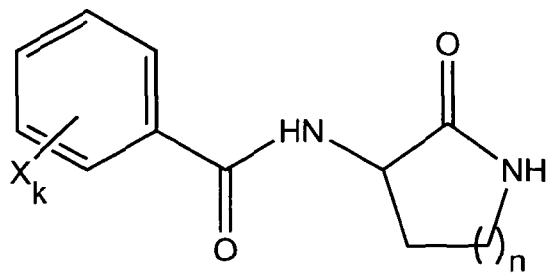


(I')

wherein n, k and X are defined as for general formula (**I**) compounds above.

Compounds (**I'**), having the (S)-configuration at the stereocentre, are 5-100 fold more potent as a BSCIs than the (R)-enantiomer of the same compound.

The invention also provides the use of a compound of general formula (**I**), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of an inflammatory disorder:



(I)

wherein

n is an integer from 1 to 4;

k is an integer from 0 to 5, representing the number of groups substituting C_2, C_3, C_4, C_5 and/or C_6 of the benzyl ring; and

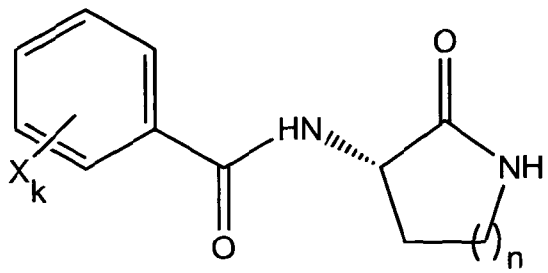
X are linear or branched groups substituting the benzyl ring independently selected from any one of the group consisting of: alkyl, haloalkyl, hydroxyalkyl, hydroxy, alkoxy, amino, aminoalkyl, aminodialkyl, carboxy, and halogen;

with the proviso that:

when on the benzyl ring C_2, C_5 and C_6 are unsubstituted, and C_4 is unsubstituted or is substituted with an hydroxy, alkoxy, amino, aminoalkyl, aminodialkyl, or halogen group, then C_3 is substituted with a halogen group; and

when on the benzyl ring C_2, C_5 and C_6 are unsubstituted, and C_3 is unsubstituted or is substituted with an alkyl, haloalkyl, hydroxyalkyl, hydroxy, alkoxy, amino, aminoalkyl, aminodialkyl or carboxy group, then C_4 is substituted with any one of the group consisting of: alkyl group, haloalkyl group, hydroxyalkyl group, and carboxy group.

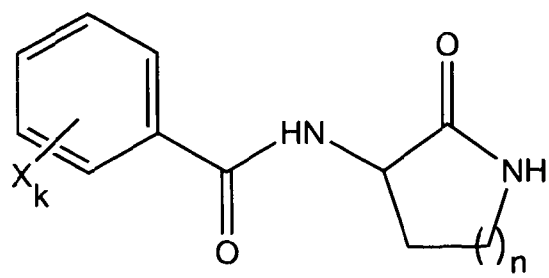
Additionally provided is the use of a compound of formula (**I'**), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of an inflammatory disorder:



(I')

wherein n, k and X are defined as for general formula (**I**) above.

Certain compounds have been found to be novel *per se*. Thus, in another aspect of the invention, there is provided a compound of general formula (**I**):



(I)

wherein

n is an integer from 1 to 4;

k is an integer from 1 to 5, representing the number of groups substituting C_2, C_3, C_4, C_5 and/or C_6 of the benzyl ring;

when n is 1 or 2, X are linear or branched groups independently selected from any one of the group consisting of: $C_{7\text{ or higher}}$ alkyl, haloalkyl with a $C_{7\text{ or higher}}$ alkyl group, hydroxyalkyl with a $C_{7\text{ or higher}}$ alkyl group, $C_{7\text{ or greater}}$ alkoxy, aminoalkyl with a $C_{4\text{ or higher}}$ alkyl group, aminodialkyl with two $C_{4\text{ or higher}}$ alkyl groups, and carboxy; and

when n is 3 or 4, X are linear or branched groups independently selected from any one of the group consisting of: alkyl, haloalkyl, hydroxyalkyl, hydroxy, alkoxy, amino, aminoalkyl, aminodialkyl, carboxy, and halogen;

with the proviso that:

when n is 3 or 4 and on the benzyl ring C_2, C_5 and C_6 are unsubstituted, and C_4 is unsubstituted or is substituted with an hydroxy, alkoxy, amino, aminoalkyl, aminodialkyl, or halogen group, then C_3 is substituted with a halogen group;

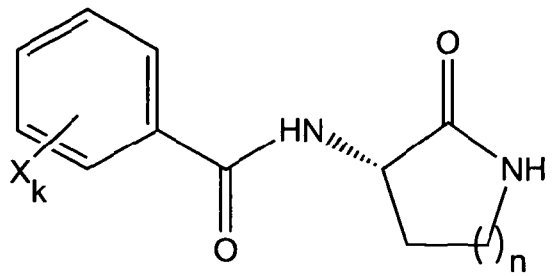
when n is 3 or 4 and on the benzyl ring C_2, C_5 and C_6 are unsubstituted, and C_3 is unsubstituted or is substituted with an alkyl, haloalkyl, hydroxyalkyl, hydroxy, alkoxy, amino, aminoalkyl, aminodialkyl or carboxy group, then C_4 is substituted with any one of the group consisting of: alkyl group, haloalkyl group, hydroxyalkyl group, and carboxy group; and

when n=3, X is other than 4'-methoxy, 3'-trifluoromethyl, or 3',4',5'-trimethoxy,

provided that the compound is none of the group consisting of: 3-(3'-trifluoromethylbenzoylamino)-caprolactam, 3-(4'-methylbenzoylamino)-caprolactam, 3-(2'-aminobenzoylamino)-caprolactam, 3-(3',4'-dimethoxybenzoylamino)-caprolactam, 3-(3',5'-di-*tert*-butyl -4'- hydroxybenzoylamino)-caprolactam, 3-(2',4'-dimethoxybenzoylamino)-caprolactam, 3-(3'-methoxybenzoylamino)-caprolactam, 3-(4'-trifluoromethylbenzoylamino)-caprolactam, 3-(2',3',4'-trimethoxybenzoylamino)-caprolactam, 3-(2',6'-difluoromethylbenzoylamino)-caprolactam, 3-(2'-

fluoromethylbenzoylamino)-caprolactam, 3-(2'-amino-3'-hydroxy-4'-methylbenzoylamino)-caprolactam, and 3-(3',5'-dimethylbenzoylamino)-caprolactam.

Also provided is a compound of formula (**I'**):



(**I'**)

wherein n, k and X are defined herein for general formula (**I**),

provided that the compound is none of the group consisting of: (S)-3-(3'-trifluoro-methylbenzoylamino)-caprolactam, (S)-3-(4'-methylbenzoylamino)-caprolactam, (S)-3-(4'-methoxybenzoylamino)-caprolactam, (S)-3-(2'-carboxybenzoylamino)-caprolactam, and (S)-3-(3', 4',5'-trimethoxybenzoylamino)-caprolactam.

WO2007/0038669 teaches diarylamine-containing compounds and their use as moduclators of c-kit receptors. Various intermediate compounds are used in the synthesis of the diarylamine-containing compounds. Any overlap of the intermediate compounds is hereby disclaimed from the present invention.

EP0462949 together with the related publication Angelucci *et al.*, 1993, J Medicinal Chemistry 36: 1512-1519 teach 7-membered 3-acylamino lactams as enhancers of learning and memory. Any overlap of specific compounds [such as (R)- and (S)-3-(3'-trifluoromethylbenzoylamino)-caprolactam, (S)-3-(4'-methoxybenzoylamino)-caprolactam, and (S)-3-(3', 4',5'-trimethoxybenzoylamino)-caprolactam] or generic compounds (notably where n=3 in compounds of generic formulae (**I**) and/or (**I'**) according to the present invention) mentioned in these documents is hereby disclaimed from the present invention.

JP03206042 discloses the preparation of 5,6,7,8-tetrahydo-4H-thiazolo[5,4-b]azepine derivatives with potassium channel activation activity, for use as antihypertensives.

Various intermediate compounds (notably where n=3 in compounds of generic formulae (**I**) and/or (**I'**) according to the present invention) are used in the synthesis of the derivatives. Any overlap of the intermediate compounds is hereby disclaimed from the present invention.

The prior art also discloses specific compounds, for example:

- 3-(4'-methylbenzoylamino)-caprolactam is disclosed in Uchikawa *et al.* (1996) Chemical & Pharmaceutical Bulletin **44**: 2070-2077;

- 3-(2'-aminobenzoylamino)-caprolactam is disclosed in Uchikawa *et al.* (1994) J Heterocyclic Chemistry **31**: 877-887;

- (S)-3-(2'-carboxybenzoylamino)-caprolactam is disclosed in Belyaev (1995) Tetrahedron Letters **36**: 439-440 ;

- 3-(3'-trifluoromethylbenzoylamino)-caprolactam (in both (S)- and (R)- forms) and (S)-3-(3', 4',5'-trimethoxybenzoylamino)-caprolactam are disclosed in EP462949A1; 3-(3'-trifluoromethylbenzoylamino)-caprolactam is also disclosed in EP351856A2;

- 3-(3',4'-dimethoxybenzoylamino)-caprolactam, 3-(3',5'-di-*tert*-butyl -4'-hydroxybenzoylamino)-caprolactam, 3-(2',4'-dimethoxybenzoylamino)-caprolactam, 3-(3'-methoxybenzoylamino)-caprolactam, 3-(4'-trifluoromethylbenzoylamino)-caprolactam, 3-(2',3',4'-trimethoxybenzoylamino)-caprolactam, 3-(2',6'-difluoromethylbenzoylamino)-caprolactam, and 3-(2'-fluoromethylbenzoylamino)-caprolactam are disclosed in JP03206042A;

- 3-(2'-amino-3'-hydroxy-4'-methylbenzoylamino)-caprolactam is disclosed in Kameda *et al.* (1968) Chemical & Pharmaceutical Bulletin **16**: 480-485; and

- 3-(3'5'-dimethylbenzoylamino)-caprolactam is disclosed in the Aurora Screening Library Catalogue published on 10 March 2010 (Order No. K07.167.701; CHEMCATS Acc. NO. 0015557046).

However, none of the above prior art compounds have been shown to have BSCI activity, or to be useful for the treatment of inflammatory diseases. As a result, compounds disclosed in the prior art documents mentioned herein in no way teach or suggest our unexpected finding that the class of aryl-substituted aminolactams and analogs as defined herein have useful BSCI activity, and the prior art compounds are hereby disclaimed.

In another aspect of the invention, there is provided a pharmaceutical composition comprising, as active ingredient, a compound *per se* as defined above, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient and/or carrier.

By pharmaceutically acceptable salt is meant in particular the addition salts of inorganic acids such as hydrochloride, hydrobromide, hydroiodide, sulphate, phosphate, diphosphate and nitrate or of organic acids such as acetate, maleate, fumarate, tartrate, succinate, citrate, lactate, methanesulphonate, p-toluenesulphonate, palmoate and stearate. Also within the scope of the present invention, when they can be used, are the salts formed from bases such as sodium or potassium hydroxide. For other examples of pharmaceutically acceptable salts, reference can be made to "Salt selection for basic drugs" (1986) Int. J. Pharm. **33**: 201-217.

The pharmaceutical composition can be in the form of a solid, for example powders, granules, tablets, gelatin capsules, liposomes or suppositories. Appropriate solid supports can be, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidine and wax. Other appropriate pharmaceutically acceptable excipients and/or carriers will be known to those skilled in the art.

The pharmaceutical compositions according to the invention can also be presented in liquid form, for example, solutions, emulsions, suspensions or syrups. Appropriate liquid supports can be, for example, water, organic solvents such as glycerol or glycols, as well as their mixtures, in varying proportions, in water.

Exemplar compounds according to general formula (**I**) and formula (**I'**) for medical uses according to the invention may be selected from the group consisting of:

(S)-3-(4'-methylbenzoylamino)-caprolactam, and
(S)-3-(3',5'-dimethylbenzoylamino)-caprolactam,

and pharmaceutically acceptable salts thereof.

Exemplar *per se* compounds of the invention according to general formula (**I'**), and/or exemplar compounds according to general formula (**I**) and formula (**I'**) for medical uses according to the invention, may be selected from the group consisting of:

(*S*)-3-Fluoro-N-(2-oxopiperidin-3-yl)benzamide,
(*S*)-2-Fluoro-N-(2-oxopiperidin-3-yl)benzamide,
(*S*)-4-Fluoro-N-(2-oxopiperidin-3-yl)benzamide,
(*S*)-N-(2-Oxopiperidin-3-yl)-4-(trifluoromethyl)benzamide,
(*S*)-N-(2-Oxopiperidin-3-yl)-3-(trifluoromethyl)benzamide,
(*S*)-N-(2-Oxopiperidin-3-yl)-2-(trifluoromethyl)benzamide,
(*S*)-2,3-difluoro-N-(2-oxopiperidin-3-yl)benzamide,
(*S*)-2,4-difluoro-N-(2-oxopiperidin-3-yl)benzamide,
(*S*)-2,5-difluoro-N-(2-oxopiperidin-3-yl)benzamide,
(*S*)-2,6-difluoro-N-(2-oxopiperidin-3-yl)benzamide,
(*S*)-3,4-difluoro-N-(2-oxopiperidin-3-yl)benzamide,
(*S*)-3,5-difluoro-N-(2-oxopiperidin-3-yl)benzamide,
(S)-3-(3'-Butylbenzoylamino)-azepan-2-one,
(S)-3-(4'-Ethylbenzoylamino)-tetrahydropyridin-2-one,
(S)-3-(4'-Butylbenzoylamino)-tetrahydropyridin-2-one,
(S)-3-(4'-tert-Butylbenzoylamino)-tetrahydropyridin-2-one, and
(S)-3-(4'-Hexylbenzoylamino)-tetrahydropyridin-2-one,

and pharmaceutically acceptable salts thereof.

The compound (*S*)-4-Fluoro-N-(2-oxopiperidin-3-yl)benzamide is also known as (S)-3-(4'-fluorobenzoylamino)-tetrahydropyridin-2-one (see Example 3 below).

Exemplar *per se* compounds of the invention according to general formula (**I**) or (**I'**), and/or exemplar compounds according to general formula (**I**) and formula (**I'**) for medical uses according to the invention, may be selected from the group consisting of:

(S)-3-(4'-Ethylbenzoylamino)-azepan-2-one,
(S)-3-(4'-Butylbenzoylamino)-azepan-2-one,
(S)-3-(4'-*tert*-Butylbenzoylamino)-azepan-2-one,
(S)-3-(4'-Hexylbenzoylamino)-azepan-2-one,
(S)-3-(4'-Octylbenzoylamino)-azepan-2-one, and
(S)-3-(4'-Octylbenzoylamino)-tetrahydropyridin-2-one,

and pharmaceutically acceptable salts thereof.

Exemplar compounds according to general formula (**I**) for medical uses according to the invention, may be selected from the group consisting of:

(R)-3-(4'-Butylbenzoylamino)-tetrahydropyridin-2-one,
(R)-3-(4'-*tert*-Butylbenzoylamino)-tetrahydropyridin-2-one, and
(R)-3-(4'-Hexylbenzoylamino)-tetrahydropyridin-2-one,

and pharmaceutically acceptable salts thereof.

Exemplar *per se* compounds of the invention according to general formula (**I**), and/or exemplar compounds according to general formula (**I**) for medical uses according to the invention, may be (R)-3-(4'-Octylbenzoylamino)-tetrahydropyridin-2-one or a pharmaceutically acceptable salt thereof.

The compounds (R)-3-(4'-Butylbenzoylamino)-tetrahydropyridin-2-one, (R)-3-(4'-*tert*-Butylbenzoylamino)-tetrahydropyridin-2-one, (R)-3-(4'-Hexylbenzoylamino)-tetrahydropyridin-2-one, and (R)-3-(4'-Octylbenzoylamino)-tetrahydropyridin-2-one, and pharmaceutical salts of each, are a further aspect of the invention.

According to the invention, inflammatory disorders (which term is used herein interchangeably with "inflammatory disease") intended to be prevented or treated by the compounds of formula (**I**) or (**I'**), or pharmaceutically acceptable salts thereof or

pharmaceutical compositions or medicaments containing them as active ingredients, include notably:

- autoimmune diseases, for example such as multiple sclerosis, rheumatoid arthritis, lupus, irritable bowel syndrome, Crohn's disease;
- vascular disorders including stroke, coronary artery diseases, myocardial infarction, unstable angina pectoris, atherosclerosis or vasculitis, e. g., Behçet's syndrome, giant cell arteritis, polymyalgia rheumatica, Wegener's granulomatosis, Churg-Strauss syndrome vasculitis, Henoch-Schönlein purpura and Kawasaki disease;
- asthma, and related respiratory disorders such as allergic rhinitis and COPD;
- organ transplant rejection and/or delayed graft or organ function, e.g. in renal transplant patients;
- psoriasis;
- skin wounds and other fibrotic disorders including hypertrophic scarring (keloid formation), adhesion formations following general or gynaecological surgery, lung fibrosis, liver fibrosis (including alcoholic liver disease) or kidney fibrosis, whether idiopathic or as a consequence of an underlying disease such as diabetes (diabetic nephropathy); or
- allergies.

The inflammatory disorder may be selected from the group consisting of autoimmune diseases, asthma, rheumatoid arthritis, a disorder characterised by an elevated TNF-α level, psoriasis, allergies, multiple sclerosis, fibrosis (including diabetic nephropathy), and formation of adhesions.

The above clinical indications fall under the general definition of inflammatory disorders or disorders characterized by elevated TNFα levels.

In one aspect of the invention, merely in order to circumvent any potentially conflicting prior art (for example as noted above), the term inflammatory disorder may exclude cognitive disorders such as Alzheimer's disease and/or memory loss.

Compounds of formula **(I)** or **(I')** are particularly useful for local delivery, and also for the preparation of medicaments for local delivery, including creams and ointments for topical delivery, powders, aerosols or emulsions for inhaled delivery, and solutions or emulsions for injection. Pharmaceutical compositions containing one or more excipients suitable for such local delivery are therefore envisaged, and subsequently claimed.

Also provided according to the invention is a method of treatment, amelioration or prophylaxis of the symptoms of an inflammatory disease (including an adverse inflammatory reaction to any agent) by the administration to a patient of an anti-inflammatory amount of a compound, pharmaceutical composition or medicament as defined herein.

Administration of a compound, composition or medicament according to the invention can be carried out by topical, oral, parenteral route, by intramuscular injection, etc.

The administration dose envisaged for a compound, composition or medicament according to the invention is comprised between 0.1 mg and 10 g depending on the formulation and route of administration used.

The invention further encompasses a library consisting of elements all of which have structures according to the formula **(I)** or **(I')**, and hence which all have anti-inflammatory activity, useful for screening compounds for novel or improved properties in a particular assay of anti-inflammatory activity.

The invention includes compounds, compositions and uses thereof as defined, wherein the compound is in hydrated or solvated form. Unless specified otherwise, compounds of the invention include tautomers, resolved enantiomers, resolved diastereomers, racemic mixtures, solvates, metabolites, salts and prodrugs thereof, including pharmaceutically acceptable salts and prodrugs.

In any of the compounds described above, n may be 2. Alternatively, n may be 3.

X may be haloalkyl, for example trifluoromethyl.

An exemplar group of compounds *per se* and/or for medical use according to any aspect of the invention is selected from among compounds according to formula (**I**) or (**I'**) where X is halogen or haloakyl and where k is between 1 and 3. For example, X may be fluoro or fluoroalkyl (such as trifluoromethyl) and k may be between 1 and 3.

Where permissible according to the formulae herein, the benzyl ring may be monosubstituted with a group X as defined above (i.e. k = 1). For example, the benzyl ring may be monosubstituted with an alkyl group (such as other than para-methyl or other than C_{1-6} alkyl), haloalkyl (such as trifluoromethyl, for example para-trifluoromethyl [i.e. 4'-trifluoromethyl], ortho-trifluoromethyl [i.e. 2'-triflouromethyl] or meta-trifluoromethyl [i.e. 3'-trifluoromethyl]). The benzyl ring may be monosubstituted with an haloalkyl other than a C_{1-6} haloalkyl. The benzyl ring may be monosubstituted with halogen. The benzyl ring may be monosubstituted with ortho-carboxy [i.e. 2'-carboxy].

The single substitution group X may in particular be located in the meta (i.e. 3'-) position on the benzyl ring.

In one aspect, the above features for k=1 apply when n=2.

Where permissible according to the formulae herein, n may be 3 and the benzyl ring may be monosubstituted with a group X as defined above (i.e. k = 1). For example, the benzyl ring may be monosubstituted with an alkyl group other than a C_{1-6} alkyl.

According to the invention, the compounds of general formula (**I**) or (**I'**) can be prepared using the processes described hereafter.

DEFINITIONS

The term "about" refers to an interval around the considered value. As used in this patent application, "about X" means an interval from X minus 10% of X to X plus 10% of X, and preferably an interval from X minus 5% of X to X plus 5% of X.

The use of a numerical range in this description is intended unambiguously to include within the scope of the invention all individual integers within the range and all the

combinations of upper and lower limit numbers within the broadest scope of the given range. Hence, for example, the range of 0.1mg to 10g specified in respect of (*inter alia*) a dose of a compound or composition of the invention to be used is intended to include all doses between 0.1mg and 10g and all sub-ranges of each combination of upper and lower numbers, whether exemplified explicitly or not.

As used herein, the term "comprising" is to be read as meaning or encompassing both comprising and consisting of. Consequently, where the invention relates to a "pharmaceutical composition comprising as active ingredient" a compound, this terminology is intended to cover both compositions in which other active ingredients may be present and also compositions which consist only of one active ingredient as defined.

The term "alkyl" or "alkyl group" as used herein refers to a saturated linear or branched- chain monovalent hydrocarbon radical, for example of one to twenty carbon atoms, one to twelve carbon atoms, one to six carbon atoms, one to four carbon atoms, or as otherwise specified herein. Examples of alkyl groups include, but are not limited to, methyl (Me, $-CH_3$), ethyl (Et, $-CH_2CH_3$), 1-propyl (n-Pr, n-propyl, $-CH_2CH_2CH_3$), 2-propyl (i-Pr, i-propyl, $-CH(CH_3)_2$), 1-butyl (n-Bu, n- butyl, $-CH_2CH_2CH_2CH_3$), 2-methyl-1-propyl (i-Bu, i-butyl, $-CH_2CH(CH_3)_2$), 2-butyl (s- Bu, s-butyl, $-CH(CH_3)CH_2CH_3$), 2-methyl-2-propyl (t-Bu, t-butyl, $-C(CH_3)_3$), 1-pentyl (n- pentyl, $-CH_2CH_2CH_2CH_2CH_3$), 2-pentyl ($-CH(CH_3)CH_2CH_2CH_3$), 3-pentyl ($-CH(CH_2CH_3)_2$)$_5$ 2-methyl-2-butyl ($-C(CHs)_2CH_2CH_3$), 3-methyl-2-butyl ($-CH(CH_3)CH(CH_3)_2$), 3-methyl-l -butyl ($-CH_2CH_2CH(CH_3)2$), 2-methyl-l -butyl ($-CH_2CH(CH_3)CH_2CH_3$), 1-hexyl ($-CH_2CH_2CH_2CH_2CH_2CH_3$), 2-hexyl ($-CH(CH_3)CH_2CH_2CH_2CH_3$), 3-hexyl ($-CH(CH_2CH_3)(CH_2CH_2CH_3)$), 2-methyl-2-pentyl ($-C(CHs)_2CH_2CH_2CH_3$), 3-methyl-2-pentyl ($-CH(CH_3)CH(CH_3)CH_2CH_3$), 4-methyl-2- pentyl ($-CH(CH_3)CH_2CH(CH_3)_2$), 3-methyl-3-pentyl ($-C(CH_3)(CH_2CH_3)_2$), 2-methyl-3- pentyl ($-CH(CH_2CH_3)CH(CH_3)_2$), 2,3-dimethyl-2-butyl ($-C(CH_3)_2CH(CH_3)_2$), 3,3- dimethyl-2-butyl ($-CH(CH_3)C(CH_3)_3$, 1-heptyl, and 1-octyl.

The term "haloalkyl" or "haloalkyl group" as used herein refers to an alkyl group (as defined above) except that one or more or all of the hydrogens of the alkyl group is replaced by a halogen, which replacement can be at any site on the alkyl, including the

end. Examples include, but are not limited to, CH_2F, CHF_2, CF_3, $CH_2CH_2F_5$ CH_2CHF_2, CH_2CF_3, $CHFCF_3$, CF_2CF_3, CH_2Cl, $CHCl_2$, CCl_3, CH_2CH_2Cl, CH_2CHCl_2, CH_2CCl_3, $CHClCCl_3$, and CCl_2CCl_3.

The term "halogen" (which may be abbreviated to "halo") or "halogen group" as used herein includes fluorine (F), bromine (Br), chlorine (Cl), and iodine (I).

The term "hydroxy" or "hydroxy group" denotes the group "-OH".

The term "hydroxyalkyl" or "hydroxyalkyl group" as used herein refers to an alkyl group (as defined above) except wherein one or more or all of the hydrogens of the alkyl group is replaced by an hydroxy group, which replacement can be at any site on the alkyl, including the end.

The term "alkoxy" or "alkoxy group" denotes an alkyl group as defined above attached via a divalent oxygen atom to the rest of the molecule. Examples include but are not limited to methoxy ($-OCH_3$), ethoxy, propoxy, isopropoxy, n-butoxy, *sec*-butoxy, *tert*-butoxy, pentoxy, isopentoxy, neopentoxy, hexoxy, and 3-methylpentoxy.

The term "amino" or "amino group" denotes the group "$-NH_2$".

The term "aminoalkyl" or "aminoalkyl group" refers to an amino group in which one of the hydrogen atoms has been replaced by an alkyl group as defined above.

The term "aminodialkyl" or "aminodialkyl group" refers to an amino group in which both of the hydrogen atoms have been replaced by an alkyl group as defined above. The alkyl groups attached to the nitrogen atom may be different or the same.

The term "carboxy" or "carboxy group" denotes the group "–C(O)OH".

The term "benzyl ring" (also known as a "phenyl group") refers to a 6 carbon aryl group in compounds of general formulae (**I**) or (**I'**) shown above. For the purposes of the general formulae of the present invention, numbering to locate the carbon atoms C_2-C_6 within the benzyl ring is in a clockwise direction from C_1 which is linked to the 3-aminolactam group. However, numbering of ring carbons with respect to one or more substituent groups on the benzyl ring for specific compounds follows the IUPAC rule that the second substituent in a clockwise or counter clockwise direction is

afforded the lower possible location number. Where two or more substituents are present in a specific compound, the IUPAC rule is that they are listed in alphabetical order. Location numbers on the ring are assigned according to the IUPAC rule to the substituents so that they have the lowest possible number (starting from C_1 which is linked to the 3-aminolactam group), counting in either a clockwise or counter-clockwise direction.

As would be understood by a person skilled in the art, where there are fewer than 5 groups substituting the benzyl ring in compounds of general formulae (**I**) or (**I'**), i.e., where k=0, 1 2, 3 or 4, the or each unsubstituted position is occupied by a hydrogen atom.

Unless otherwise defined, all the technical and scientific terms used here have the same meaning as that usually understood by an ordinary specialist in the field to which this invention belongs. Similarly, all the publications, patent applications, all the patents and all other references mentioned here are incorporated by way of reference (where legally permissible).

Preparation of the compounds of general formula (I) or (I')

All the compounds of general formula **(I)** or **(I')** can be prepared easily according to general methods known to the person skilled in the art.

Typically, such compounds are made by coupling the "tail group" in the form of a suitably activated acid (such as an acid chloride) with the appropriate 3-aminolactam. Methods for the preparation of 3-aminolactams with 5,6,7 and 8 membered rings, encompassing all the compounds claimed herein, have been extensively described in the literature. For example, we have provided suitable methods for the preparation of 6-membered aminolactams from ornithine (see WO2009/016390) and 7-membered aminolactams from lysine (see WO2005/053702), as well as methods for 5- and 8-membered aminolactams (see WO2006/134385). We have described in particular detail various synthesis routes to the 6-membered aminolactam, including processes suitable for scaling up the manufacture to Kg quantities (WO2009/016390). Various other methods for the synthesis of 3-aminolactams of various ring sizes have also been described in the literature (see for example Pellegata *et al.*, 1978, Synthesis 614-616

and Boyle *et al.*, 1979, J Org Chem **44**:4841-4847), and any suitable method for the preparation of the aminolactam "head group" may be employed in accordance with the method of the present invention.

In the second step, the 3-aminolactam product is reacted with an appropriate acid chloride, for example as previously described for 7-ring aminolactams (Fox *et al.*, 2005, J Med Chem **48**: 867-74). This reaction may be carried out, for example, in chloroform or dichloromethane. The most preferred reaction solvent is dichloromethane, and is preferably carried out in the presence of a base, for example Na_2CO_3. The above reaction may be carried out at ambient temperature (about 25 °C) or more generally at a temperature between 20 and 50 °C. The two reactions may be carried out independently, with separation and purification of the 3-aminolactam between the reactions, or alternatively, the reactions may be performed in a single vessel without purification of the 3-aminolactam prior to its derivatisation with acid chloride.

As noted previously (see WO2009/016390) care must be exercised during the acylation reaction when preparing an enantiomerically pure compound, according to formula (**I'**) by acylating an enantiomeriocally pure 3-aminolactam. In particular, the base, such as sodium carbonate, must be added slowly continually monitoring the pH of the reaction vessel to ensure that the pH of the reaction remains below pH 9.0 throughout. Excess basicity, for example due to rapid or excessive addition of sodium carbonate, increases the racemisation of the 3-aminolactam and yields enantiomerically impure product.

The following examples are presented in order to illustrate the above procedures and should in no way be considered to limit the scope of the invention.

FIGURES

Fig. 1 shows the chemical structure of various examples of compounds according to the inventions and reference examples; and

Fig. 2 . is a graph showing the results of a murine sub-lethal endotoxemia test. In the graph, column A shows data from a control group (1% CMC 10ml/kg p.o.), and

column B shows data from a group treated with 1mg/kg p.o. (*S*)-4-Fluoro-N-(2-oxopiperidin-3-yl)benzamide (a compound according to one embodiment of the present invention – see also Example 3 below) The y-axis shows levels of TNF-α in pg/ml.

EXAMPLES

In the following further examples, ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker Avance DRX 400 MHz fourier transform machine and ^{19}F-NMR spectra were recorded on a Bruker Avance DRX 300. Chemical shifts are given in ppm and coupling constants, *J*, are given in Hz to the nearest 0.5. IR spectra were recorded on an Avatar 320. HRMS data was gained via an Esquire 2000. $[\alpha]_D$ values were recorded on an optical activity AA 1000 polarimeter set at 598 nm (Sodium D line). The samples were made using spectroscopic grade MeOH.

Reference Example 1: **3-(Benzoylamino)tetrahydropyridin-2-one**:

3-aminotetrahydropyridin-2-one hydrochloride (10 mmol) and K_2CO_3 (30 mmol) were added to water (20 mL) and stirred. A solution of benzoyl chloride (10 mmol) in CH_2Cl_2 (10 mL) was added and the reaction was stirred overnight at room temperature in an inert atmosphere (using dinitrogen). The reaction was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers where then dried (Na_2SO_4) and reduced *in vacuo* to give a crude product which was recrystallised from CH_2Cl_2 / petroleum ether (bp 40-60 °C) to give the product (1.62 g, 74%):

ν_{max}/cm^{-1} 3250 (N-H, amide), 1664, 1633, 1538 (secondary CONH, lactam), 1605, 1578, 1486 (aromatic ring), 766, 715, 704, 690 (monosubstituted benzene ring).

^{1}H NMR: δ_H (400MHz, $CDCl_3$) 7.80 (2H, br d, *J* 7.0, *ortho*-H), 7.47-7.40 (1H, m, *para*-H), 7.42-7.39 (1H, m, C_6H_5-CON*H*), 7.40-7.31 (2H, m, *meta*-H), 6.78 (1H, br s, CON*H*-CH_2), 4.41 (1H, dt, *J* 11.5, 5.5, CH-CO), 3.36-3.23 (2H, m, C*H*$_2$NH), 2.59 (1H,

dq, *J* 13.0, 4.5, NHCH-C*H*$_2$), 1.94-1.81 (2H, m, lactam CH_2), 1.64 (1H, tt, *J* 12.5, 8.0, NHCH-C*H*$_2$).

^{13}C NMR: δ_C (100MHz, $CDCl_3$) 171.9 (lactam C=O), 167.4 (aryl C=O), 134.0 (*ipso*-C), 131.4 (*ortho*-C), 128.3 (*meta*-C), 127.0 (*para*-C), 50.8 (*C*H-CO), 41.5 (CH_2NH), 27.0 (lactam CH_2), 20.9 (lactam CH_2).

HRMS (+ESI) $C_{12}H_{14}N_2O_2 + Na^+$: calcd 241.0947; found 241.0950.

Reference Example 2: **3-(Benzoylamino)azepan-2-one**:

3-aminoazepan-2-one hydrochloride (10 mmol) and K_2CO_3 (30 mmol) were added to water (20 mL) and stirred. A solution of benzoyl chloride (10 mmol) in CH_2Cl_2 (10 mL) was added and the reaction was stirred overnight at room temperature in an inert atmosphere (using dinitrogen). The reaction was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers where then dried (Na_2SO_4) and reduced *in vacuo* to give a crude product which was recrystallised from CH_2Cl_2 / petroleum ether (bp 40-60 °C) to give the product (1.59 g, 68%):

ν_{max}/cm^{-1} 3244, 3202 (N-H, amide), 1660, 1642, 1536 (secondary CONH, lactam), 1601, 1578, 1536 (aromatic ring), 771, 707 (monosubstituted benzene ring).

^{1}H NMR: δ_H (400MHz, $CDCl_3$) 7.86-7.80 (2H, m, *ortho*-H), 7.65 (1H, d, *J* 4.0, C_6H_5-CON*H*), 7.52-7.45 (1H, m, *para*-H), 7.46-7.39 (2H, m, *meta*-H), 6.11 (1H, br s, CON*H*-CH_2), 4.72 (1H, ddd, *J* 11.0, 5.5, 1.5, CH-CO), 3.49-3.39 (2H, m, C*H*$_2$NH), 2.25 (1H, br d, *J* 13.5, lactam CH_2), 2.08-1.98 (1H, m, lactam CH_2), 1.94-1.82 (2H, m, lactam CH_2), 1.62-1.49 (1H, m, lactam CH_2), 1.49-1.36 (1H, m, lactam CH_2).

^{13}C NMR: δ_C (100MHz, $CDCl_3$) 175.9 (lactam C=O), 166.4 (aryl C=O), 134.3 (*ipso*-C), 131.7 (*ortho*-C), 128.7 (*meta*-C), 127.2 (*para*-C), 52.7 (*C*H-CO), 42.3 (CH_2-NH), 31.7 (lactam *C*H_2), 29.0 (lactam *C*H_2), 28.1 (lactam *C*H_2).

HRMS (+ESI) $C_{12}H_{14}N_2O_2 + H^+$: calcd 233.1285; found 233.1283.

Reference Example 3: **3-(4'-Methylbenzoylamino)tetrahydropyridin-2-one:**

3-aminotetrahydropyridin-2-one hydrochloride (10 mmol), K_2CO_3 (30 mmol) and 4-methylbenzoyl chloride (10 mmol) were reacted according to the above procedure to give the product (1.62 g, 78%):

ν_{max}/cm^{-1} 3306, 3203 (N-H, amide), 1669, 1649 (secondary CONH, lactam), 1612, 1489 (aromatic ring), 842, 810 (*para*-disubstituted benzene ring).

^1H NMR: δ_H (400MHz, $CDCl_3$) 7.69 (2H, br d, *J* 8.0, *ortho*-H), 7.20 (2H, br d, *J* 8.0, *meta*-H), 7.13 (1H, br d, *J* 4.0, CON*H*-CH_2), 6.03 (1H, br s, C_7H_7-CON*H*), 4.41 (1H, dt, *J* 11.0, 5.5, CH-CO), 3.41-3.30 (2H, m, C*H*$_2$NH), 2.72 (1H, dq, *J* 13.0, 4.5, lactam CH_2), 2.36 (3H, s, CH_3), 2.05-1.90 (2H, m, lactam CH_2), 1.68-1.54 (1H, m, lactam CH_2).

^{13}C NMR: δ_C (100MHz, $CDCl_3$) 172.3 (lactam C=O), 167.7 (aryl C=O), 142.1 (*ipso*-C), 131.2 (*para*-C), 129.3 (aromatic-CH), 127.3 (aromatic-CH), 51.1 (*C*H-CO), 41.8 (CH_2-NH), 27.4 (lactam CH_2), 21.7 (CH_3), 21.2 (lactam CH_2).

HRMS (+ESI) $C_{13}H_{16}N_2O_2 + Na^+$: calcd 255.1104; found 255.1104.

Reference Example 4: **3-(4'-Methylbenzoylamino)azepan-2-one** :

3-aminoazepan-2-one hydrochloride (10 mmol), K_2CO_3 (30 mmol) and 4-methylbenzoyl chloride (10 mmol) were reacted according to the above procedure to give the product (1.63 g, 74%):

ν_{max}/cm^{-1} 3265, 3219 (N-H, amide), 1663, 1647 (secondary CONH, lactam), 1607, 1570, 1505 (aromatic ring), 838, 823 (*para*-disubstituted benzene ring).

^1H NMR: δ_H (400MHz, $CDCl_3$) 7.72 (2H, br d, *J* 8.0, *ortho*-H), 7.58 (1H, br d, *J* 4.50, CON*H*-CH_2), 7.21 (2H, d, *J* 8.0, *meta*-H), 5.98 (1H, br s, C_7H_7-CON*H*), 4.69 (1H, ddd, *J* 11.0, 5.5, 2.0, CH-CO), 3.40-3.321 (2H, m, C*H*$_2$NH), 2.37 (3H, s, CH_3), 2.23

(1H, br d, lactam CH_2), 2.08-1.99 (1H, m, lactam CH_2), 1.96-1.83 (2H, m, lactam CH_2), 1.60-1.51 (2H, m, lactam CH_2).

^{13}C NMR: δ_C (100MHz, $CDCl_3$) 176.1 (lactam C=O), 166.3 (aryl C=O), 142.0 (*ipso*-C), 131.5 (*para*-C), 129.3 (aromatic-CH), 127.2 (aromatic-CH), 52.6 (*C*H-CO), 42.2 (CH_2-NH), 31.7 (lactam CH_2), 29.0 (lactam CH_2), 28.1 (lactam CH_2), 21.6 (CH_3).

HRMS (+ESI) $C_{14}H_{18}N_2O_2 + H^+$: calcd 247.1441; found 247.1453.

Reference Example 5: **3-(4'-Chlorobenzoylamino)tetrahydropyridin-2-one**:

3-aminotetrahydropyridin-2-one hydrochloride (10 mmol), K_2CO_3 (30 mmol) and 4-chlorobenzoyl chloride (10 mmol) were reacted according to the above procedure to give the product (0.87 g, 39%):

ν_{max}/cm^{-1} 3295, 3202 (N-H, amide), 1668, 1648, 1629 (secondary CONH, lactam), 1594, 1486 (aromatic ring), 859, 845, 808, (*para*-disubstituted benzene ring), 750, 656 (C-Cl).

^1H NMR: δ_H (400MHz, $CDCl_3$) 7.74 (2H, br d, *J* 8.5, *ortho*-H), 7.38 (2H, br d, *J* 8.5, *meta*-H), 7.14 (1H, br d, *J* 3.0, C_6H_4Cl-CON*H*), 5.83 (1H, br s, CON*H*-CH_2), 4.40 (1H, dt, *J* 11.0, 5.5, CH-CO), 3.44-3.33 (2H, m, CH_2NH), 2.73 (1H, dq, *J* 13.0, 4.5, NHCH-CH_2), 2.05-1.93 (2H, m, lactam CH_2), 1.66-1.56 (1H, m, lactam CH_2).

^{13}C NMR: δ_C (100MHz, $CDCl_3$) 180.2 (lactam C=O), 171.8 (aryl C=O), 138.1 (*ipso*-C), 132.7 (C-Cl), 129.1 (aromatic-CH), 128.5 (aromatic-CH), 51.4 (*C*H-CO), 42.0 (CH_2-NH), 27.2 (lactam CH_2), 21.2 (lactam CH_2).

HRMS (+ESI) $C_{12}H_{13}ClN_2O_2 + Na^+$: calcd 275.0558; found 275.0559.

Reference Example 6: **3-(4'-Chlorobenzoylamino)azepan-2-one**:

3-aminoazepan-2-one hydrochloride (10 mmol), K_2CO_3 (30 mmol) and 4-chlorobenzoyl chloride (10 mmol) were reacted according to the above procedure to give the product (1.79 g, 75%):

ν_{max}/cm^{-1} 3243, 3200 (N-H, amide), 1662, 1643 (secondary CONH, lactam), 1595, 1484 (aromatic ring), 856, 841, 819 (*para*-disubstituted benzene ring), 776, 732 (C-Cl).

^1H NMR: δ_H (400MHz, $CDCl_3$) 7.76 (2H, br d, *J* 8.5, *ortho*-H), 7.59 (1H, br d, *J* 4.0, C_6H_4Cl-CON*H*), 7.39 (2H, br d, *J* 8.5, *meta*-H), 6.00 (1H, br s, CON*H*-CH_2), 4.67 (1H, ddd, *J* 11.0, 5.5, 1.5, CH-CO), 3.39-3.22 (2H, m, C*H*$_2$NH), 2.22 (1H, br d, *J* 14.0, lactam CH_2), 2.09-2.00 (1H, m, lactam CH_2), 1.96-1.82 (2H, m, lactam CH_2), 1.60-1.36 (2H, m, lactam CH_2).

^{13}C NMR: δ_C (100MHz, $CDCl_3$) 175.9 (lactam C=O), 165.3 (aryl C=O), 137.9 (*ipso*-C), 132.7 (C-Cl), 128.9 (aromatic-CH), 128.7 (aromatic-CH), 52.8 (*C*H-CO), 42.3 (CH_2-NH), 31.7 (lactam CH_2), 29.0 (lactam CH_2), 28.1 (lactam CH_2).

HRMS (+ESI) $C_{13}H_{15}ClN_2O_2 + H^+$: calcd 267.0895; found 267.0890.

Reference Example 7: **3-(4'-Methoxybenzoylamino)tetrahydropyridin-2-one:**

3-aminotetrahydropyridin-2-one hydrochloride (10 mmol), K_2CO_3 (30 mmol) and 4-methoxybenzoyl chloride (10 mmol) were reacted according to the above procedure to give the product (2.18 g, 98%):

ν_{max}/cm^{-1} 3305, 3212 (N-H, amide), 2854 (O-CH_3), 1693, 1627 (secondary CONH, lactam), 1605, 1576, 1505 (aromatic ring), 837 (*para*-disubstituted benzene ring).

^1H NMR: δ_H (400MHz, $CDCl_3$) 7.76 (2H, br d, *J* 9.0, *ortho*-H), 7.19 (1H, br d, *J* 5.0, C_7H_7O-CON*H*), 6.87 (2H, br d, *J* 9.0, *meta*-H), 6.31 (1H, br s, CON*H*-CH_2), 4.39 (1H, dt, *J* 11.5, 5.5, CH-CO), 3.81 (3H, s, OCH_3), 3.39-3.28 (2H, m, C*H*$_2$NH), 2.64 (1H, dq,

J 13.0, 4.5, NHCH-C*H*$_2$), 2.01-1.88 (2H, m, lactam CH_2), 1.68-1.55 (1H, m, lactam CH_2).

^{13}C NMR: δ_C (100MHz, $CDCl_3$) 172.4 (lactam C=O), 167.3 (aryl C=O), 162.4 (*C*-OCH_3), 129.1 (aromatic-CH), 126.6 (*ipso*-C), 113.8 (aromatic-CH), 55.6 (OCH_3), 51.1 (*C*H-CO), 41.9 (CH_2-NH), 27.4 (lactam CH_2), 21.3 (lactam CH_2).

HRMS (+ESI) $C_{13}H_{16}N_2O_3 + Na^+$: calcd 271.1053; found 271.1057.

Reference Example 8: **3-(4'-Methoxybenzoylamino)azepan-2-one**:

3-aminoazepan-2-one hydrochloride (10 mmol), K_2CO_3 (30 mmol) and 4-methoxybenzoyl chloride (10 mmol) were reacted according to the above procedure to give the product (1.54 g, 65%):

ν_{max}/cm^{-1} 3270, 3205 (N-H, amide), 2839 (O-CH_3), 1642 (secondary CONH, lactam), 1602, 1577, 1504 (aromatic ring), 854, 822 (*para*-disubstituted benzene ring).

^{1}H NMR: δ_H (400MHz, $CDCl_3$) 7.79 (2H, br d, *J* 9.0, *ortho*-H), 7.52 (1H, br d, *J* 5.0, C_7H_7O-CON*H*), 6.91 (2H, br d, *J* 9.0, *meta*-H), 5.94 (1H, br s, CON*H*-CH_2), 4.69 (1H, ddd, *J* 11.0, 5.5, 1.5, CH-CO), 3.83 (3H, s, OCH_3), 3.40-3.21 (2H, m, C*H*$_2$NH), 2.22 (1H, br d, *J* 12.5, lactam CH_2), 2.08-1.97 (1H, m, lactam CH_2), 1.95-1.82 (2H, m, lactam CH_2), 1.60-1.36 (2H, m, lactam CH_2).

^{13}C NMR: δ_C (100MHz, $CDCl_3$) 176.2 (lactam C=O), 165.9 (aryl C=O), 162.1 (*C*-OCH_3), 129.1 (aromatic-CH), 126.7 (*ipso*-C), 113.8 (aromatic-CH), 55.5 (OCH_3), 52.7 (*C*H-CO), 42.3 (CH_2-NH), 31.9 (lactam CH_2), 29.1 (lactam CH_2), 28.1 (lactam CH_2).

HRMS (+ESI) $C_{14}H_{18}N_2O_3 + Na^+$: calcd 285.1210; found 285.1215.

Reference Example 9: **3-(4'-Fluorobenzoylamino)tetrahydropyridin-2-one**:

3-aminotetrahydropyridin-2-one hydrochloride (10 mmol), K_2CO_3 (30 mmol) and 4-fluorobenzoyl chloride (10 mmol) were reacted according to the above procedure (except that $CHCl_3$ was used instead of CH_2Cl_2) to give the product (1.41 g, 54%):

ν_{max}/cm^{-1} 3216, 3075 (N-H, amide), 1650, 1555 (secondary CONH, lactam), 1595, 1491 (aromatic ring), 809, 844 (*para*-disubstituted benzene ring), 1105, 1158, 1226, 1328, 756 (C-F).

^1H NMR: δ_H (400MHz, $CDCl_3$) 7.76 (2H, br dd, *J* 9.0, 5.5, *ortho*-H), 7.21 (1H, br s, C_6H_4F-CON*H*), 7.02 (2H, br t, *J* 8.5, *meta*-H), 6.08 (1H, br s, CON*H*-CH_2), 4.35 (1H, dt, *J* 11.5, 5.5, CH-CO), 3.40-3.26 (2H, m, C*H*$_2$NH), 2.62 (1H, dq, *J* 13.0, 4.5, NHCH-C*H*$_2$), 2.00-1.86 (2H, m, lactam CH_2), 1.66-1.52 (1H, m, lactam CH_2).

^{13}C NMR: δ_C (100MHz, $CDCl_3$) 172.2 (lactam C=O), 166.6 (aryl C=O), 164.9 (d, *J* 252.0, C-F), 130.4 (d, *J* 3.0, *ipso*-C), 129.7 (d, *J* 9.0, *ortho*-C), 115.6 (d, *J* 22.0, *meta*-C), 51.1 (*C*H-CO), 41.9 (CH_2-NH), 27.3 (lactam CH_2), 21.3 (lactam CH_2).

HRMS (+ESI) $C_{12}H_{13}FN_2O_2 + H^+$: calcd 237.1034; found 237.1034.

Reference Example 10: **3-(4'-Fluorobenzoylamino)azepan-2-one**:

3-aminoazepan-2-one hydrochloride (10 mmol), K_2CO_3 (30 mmol) and 4-fluorobenzoyl chloride (10 mmol) were reacted according to the above procedure (except that $CHCl_3$ was used instead of CH_2Cl_2) to give the product (0.86 g, 45%):

ν_{max}/cm^{-1} 3205, 3056 (N-H, amide), 1544 (secondary CONH, lactam), 1599, 1501 (aromatic ring), 821, 858 (*para*-disubstituted benzene ring), 1164, 1222, 1291, 765, 696 (C-F).

^1H NMR: δ_H (400MHz, $CDCl_3$) 7.84 (2H, br dd, *J* 9.0, 5.5, *ortho*-H), 7.57 (1H, br s, C_6H_4F-CON*H*), 7.09 (2H, br t, *J* 8.5, *meta*-H), 5.94 (1H, br s, CON*H*-CH_2), 4.67 (1H, ddd, *J* 11.5, 5.5, 1.5, CH-CO), 3.40-3.22 (2H, m, C*H*$_2$NH), 2.26-2.19 (1H, m, lactam

CH_2), 2.09-2.00 (1H, m, lactam CH_2), 1.96-1.83 (2H, m, lactam CH_2), 1.60-1.36 (2H, m, lactam CH_2).

^{13}C NMR: δ_C (100MHz, d_6-DMSO) 174.3 (lactam C=O), 164.1 (aryl C=O), 163.9 (C-F,d *J* 247), 130.7 (*ipso*-C), 129.8 (*ortho*-C, d, *J* 7), 115.2 (*meta*-C, d, *J* 22), 52.0 (*C*H-CO), 40.6 (CH_2-NH), 30.6 (lactam CH_2), 28.9 (lactam CH_2), 27.7 (lactam CH_2).

HRMS (+ESI) $C_{13}H_{15}FN_2O_2 + H^+$: calcd 251.1190; found 251.1192.

Reference Example 11: 3-(Pyridin-3'-carbonylamino)tetrahydropyridin-2-one:

Oxalyl chloride (20 mmol) was added to a solution of nicotinic acid (10 mmol) in DCM (40 mL), along with one drop of catalytic DMF. The reaction mixture was stirred for 16 h and then the solvent was removed under high vacuum. The resulting crystals were dissolved in DCM (10 mL). In a separate flask, 3-aminotetrahydropyridin-2-one hydrochloride (10 mmol) and K_2CO_3 (30 mmol) were added to water (30 mL) and stirred, giving a solution to which the acid chloride solution was added. The reaction was worked-up as above to give the product (0.10 g, 5%):

ν_{max}/cm^{-1} 3257 (N-H, amide), 1642, 1541 (secondary CONH, lactam, NH), 1591, 1479 (aromatic pyridine ring).

^1H NMR: δ_H (400MHz, $CDCl_3$) 9.03 (1H, d, *J* 2.0, 2'-aryl CH), 8.71 (1H, dd, *J* 5.0, 1.5, 6'-aryl CH), 8.12 (1H, dt, *J* 8.0, 2.0, 4'-aryl CH), 7.36 (1H, dd, *J* 8.0, 5.0, 5'-aryl CH), 7.27 (1H, br d, *J* 2.0, C_5H_4N-CON*H*), 5.91 (1H, br s, CON*H*-CH_2), 4.45 (1H, dt, *J* 11.0, 5.5, CH-CO), 3.44-3.32 (2H, m, CH_2NH), 2.72 (1H, dt, *J* 14.5, 4.5, NHCH-CH_2), 2.06-1.93 (2H, m, lactam CH_2), 1.70-1.54 (1H, m, lactam CH_2).

^{13}C NMR: δ_C (100MHz, $CDCl_3$) 171.8 (lactam C=O), 166.0 (aryl C=O), 152.5 (aryl N-CH), 148.6 (aryl N-CH), 135.3 (*ortho*-C(-CH)), 133.4 (*ipso*-C), 123.6 (*meta*-C), 51.2 (*C*H-CO), 42.0 (CH_2-NH), 27.3 (lactam CH_2), 21.3 (lactam CH_2).

HRMS (+ESI) $C_{11}H_{13}N_3O_2 + H^+$: calcd 220.1081; found 220.1085.

Reference Example 12: **3-(Pyridin-3'-carbonylamino)azepan-2-one**:

Oxalyl chloride (1.69 mL, 20 mmol) was added to a solution of nicotinic acid (1.23 g, 10 mmol) in DCM (40 mL), along with one drop of catalytic DMF. The reaction mixture was stirred for 16 h and then the solvent was removed under high vacuum. The resulting crystals were dissolved in DCM (10 mL). In a separate flask, 3-aminoazepan-2-one hydrochloride (10 mmol) and K_2CO_3 (30 mmol) were added to water (30 mL) and stirred, giving a solution to which the acid chloride solution was added. The reaction was worked-up as above to give the product (0.66 g, 42%):

ν_{max}/cm^{-1} 3200 (N-H, amide), 1642, 1548 (secondary CONH, lactam), 1590, 1476 (aromatic pyridine ring).

^1H NMR: δ_H (400MHz, $CDCl_3$) 9.06 (1H, d, *J* 2.0, 2'-aryl CH), 8.72 (1H, dd, *J* 5.0, 1.5, 6'-aryl CH), 8.11 (1H, dt, *J* 8.0, 2.0, 4'-aryl CH), 7.72-7.62 (1H, m, C_5H_4N-CON*H*), 7.37 (1H, dd, 8.0, 5.0, 5'-aryl CH), 5.99 (1H, br s, CON*H*-CH_2), 4.70 (1H, ddd, *J* 11.0, 5.5, 1.5, CH-CO), 3.40-3.23 (2H, m, CH_2NH), 2.24 (1H, br d, *J* 14.5, lactam CH_2), 2.11-2.02 (1H, m, lactam CH_2), 1.97-1.83 (2H, m, lactam CH_2), 1.63-1.38 (2H, m, lactam CH_2).

^{13}C NMR: δ_C (100MHz, $CDCl_3$) 175.7 (lactam C=O), 164.6 (aryl C=O), 152.4 (aryl N-CH), 148.5 (aryl N-CH), 135.1 (*ortho*-C(-CH)), 130.0 (*ipso*-C), 123.5 (*meta*-C), 52.8 (*C*H-CO), 42.2 (CH_2-NH), 31.6 (lactam CH_2), 28.9 (lactam CH_2), 28.1 (lactam CH_2).

HRMS (+ESI) $C_{12}H_{15}N_3O_2 + H^+$: calcd 234.1237; found 234.1239.

Reference Example 13: **3-(3',5'-Dimethylbenzoylamino)tetrahydropyridin-2-one**:

3-aminotetrahydropyridin-2-one hydrochloride (10 mmol), K_2CO_3 (30 mmol) and 3,5-dimethylbenzoyl chloride (10 mmol) were reacted according to the above procedure (except that $CHCl_3$ was used instead of CH_2Cl_2) to give the product (2.06 g, 94%):

ν_{max}/cm^{-1} 3212 (N-H, amide), 1675, 1627, 1534 (secondary CONH, lactam), 1598, 1491 (aromatic ring), 890, 865, 817 (*meta*-trisubstituted benzene ring).

^1H NMR: δ_H (400MHz, $CDCl_3$) 7.39 (2H, s, *ortho*-H), 7.15 (1H, br d, *J* 4.5, C_8H_9-CON*H*), 7.09 (1H, s, *para*-H), 6.25 (1H, br s, CON*H*-CH_2), 4.41 (1H, dt, *J* 11.5, 5.5, CH-CO), 3.43-3.29 (2H, m, C*H*$_2$NH), 2.69 (1H, dq, *J* 13.0, 4.5, NHCH-C*H*$_2$), 2.31 (6H, s, CH_3), 2.03-1.89 (2H, m, lactam CH_2), 1.66-1.53 (1H, m, lactam CH_2).

^{13}C NMR: δ_C (100MHz, $CDCl_3$) 172.2 (lactam C=O), 168.0 (aryl C=O), 138.2 (*ipso*-C), 134.3 (*meta*-C), 133.5 (aromatic CH), 125.1 (aromatic CH), 51.2 (*C*H-CO), 41.9 (CH_2-NH), 27.2 (lactam CH_2), 21.4 (CH_3), 21.2 (lactam CH_2).

HRMS (+ESI) $C_{14}H_{18}N_2O_2 + H^+$: calcd 247.1441; found 247.1455.

Reference Example 14: **3-(3',5'-Dimethylbenzoylamino)azepan-2-one**:

3-aminoazepan-2-one hydrochloride (10 mmol), K_2CO_3 (30 mmol) and 3,5-dimethylbenzoyl chloride (10 mmol) were reacted according to the above procedure (except that $CHCl_3$ was used instead of CH_2Cl_2) to give the product (2.26 g, 96%):

ν_{max}/cm^{-1} 3319 (N-H, amide), 1682, 1635 (secondary CONH, lactam), 1600, 1498 (aromatic ring), 888, 866, 828 (*meta*-trisubstituted benzene ring).

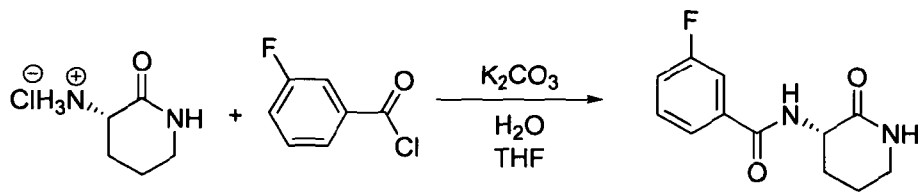
^1H NMR: δ_H (400MHz, $CDCl_3$) 7.57 (1H, br d, *J* 5.0, C_8H_9-CON*H*), 7.42 (2H, s, *ortho*-H), 7.10 (1H, s, *para*-H), 6.09 (1H, br s, CON*H*-CH_2), 4.69 (1H, ddd, *J* 11.0, 6.0, 1.5, CH-CO), 3.40-3.20 (2H, m, C*H*$_2$NH), 2.33 (6H, s, CH_3), 2.21 (1H, br d, *J* 12.5, lactam CH_2), 2.08-1.98 (1H, m, lactam CH_2), 1.97-1.82 (2H, m, lactam CH_2), 1.59-1.35 (2H, m, lactam CH_2).

^{13}C NMR: δ_C (100MHz, $CDCl_3$) 176.0 (lactam C=O), 166.8 (aryl C=O), 138.3 (*ipso*-C), 134.3 (*meta*-C), 133.3 (aromatic CH), 124.9 (aromatic CH), 52.6 (*C*H-CO), 42.3 (CH_2-NH), 31.8 (lactam CH_2), 29.0 (lactam CH_2), 28.1 (lactam CH_2), 21.4 (CH_3).

HRMS (+ESI) $C_{15}H_{20}N_2O_2 + H^+$: calcd 261.1598; found 261.1602.

In the examples below, the general procedure for the synthesis of 3-acylamino-2-oxopiperidines was: potassium carbonate (3 mmol) and (*S*)-3-amino-2-oxopiperidine hydrochloride (1.5 mmol) were dissolved in water (5 ml) and the solution was cooled to 0 °C, and a solution of substituted benzoyl chloride (1 mmol) in tetrahydrofuran (5 mL) was added. The mixture was stirred for 16 hours, and then the reaction was extracted with dichloromethane or chloroform. The combined organic layers were dried over sodium sulfate and reduced in vacuo to give a solid. This solid was redissolved in a minimum amount of dichloromethane and crystallised by addition of petroleum ether 40-60 °C. The solid product was isolated by filtration and dried over potassium pentoxide.

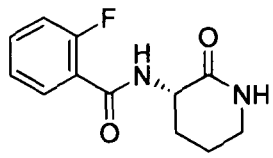
Example 1: (S)-3-Fluoro-N-(2-oxopiperidin-3-yl)benzamide



0.147 g off-white coarse powder (41 %). mp 164-166 °C. $[\alpha]^{24}_D$ -5.50 (c 0.1, MeOH); ν_{max}/cm^{-1} 1669, 1644 (*C*=O, amide), 1552 (N-H, amide), 1303 (*C*-F). Anal. ($C_{12}H_{13}FN_2O_2$) C, H, N: calcd C 61.01, H 5.55, N 11.86; found C 60.65, H 5.50, N 11.78. ^{1}H-NMR δ_H. 7.52 (2H, tt, *J* 8 and 2 , Ar*H*4 and Ar*H*6), 7.38 (1H, td, *J* 8 and 5.5, Ar*H*2), 7.21-7.14 (2H, m, N*H*CH and Ar*H*3), 5.9 (1H, s, N*H*CH_2), 4.41 (1H, dt, *J* 11.5 and 6 , C*H*NH), 3.42-3.28 (2H, m, CH_2NH), 2.72 (1H, dq, *J* 13 and 5 , CH_2CH), 2.04-1.95 (2H, m, CH_2CH_2NH), 1.62 (1H, dq, *J* 16 and 5 , CH_2CH). ^{13}C-NMR δ_C

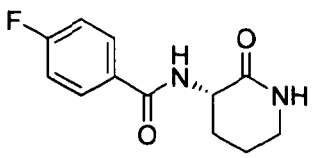
171.6 (CHCONH), 166.3 (*C*ONHCH), 162.8 (d, *J* 247, ArC3), 136.4 (*C*CO), 130.17 (d, *J* 12, ArC5), 122.6 (ArC6), 118.6 (d, *J* 21, ArC2), 114.6 (d, *J* 21, ArC4), 51.2 (*C*HNH), 41.8 ($C H_2$NH), 27.0 ($C H_2$CHNH), 21.0 ($C H_2CH_2$NH). ^{19}F-NMR δ_F -111.9. HRMS (+ESI) $C_{12}H_{13}FN_2O_2Na$: calcd 259.0853; found 259.0859.

Example 2: (S)-2-Fluoro-N-(2-oxopiperidin-3-yl)benzamide



0.222 g white fluffy powder (63 %). mp 166-168 °C. $[\alpha]^{24}_D$ -10.00 (c 0.1, MeOH). ν_{max}/cm^{-1} 1647, 1613 (C=O, amide), 1512 (N-H, amide), 1277 (C-F). Anal. ($C_{12}H_{13}FN_2O_2$) C, H, N: calcd C 61.01, H 5.55, N 11.86; found C 60.78, H 5.54, N 11.69. ^{1}H-NMR δ_H. 8.05 (1H, td, *J* 8 and 2 , Ar*H*6), 7.62 (1H, dd, *J* 6 and 4, N*H*CH), 7.45 (1H, dddd, *J* 8,7, 5 and 2, Ar*H*4), 7.21 (1H, td, *J* 7.5 and 1, Ar*H*5), 7.13 (1H, ddd, *J* 12, 9 and 1, Ar*H*3), 6.01 (1H, s, N*H*CH_2), 4.53 (1H, dt, *J* 11 and 6, C*H*NH), 3.45 (2H, td, *J* 6 and 3, CH_2NH), 2.72 (1H, dq, *J* 13 and 6, CH_2CH), 2.02-1.95 (2H, m, CH_2CH_2NH), 1.72-1.59 (1H, m, CH_2CH). ^{13}C-NMR δ_C 171.3 (CH*C*ONH), 163.4 (*C*ONHCH), 160.9 (d, *J* 248.5, ArC2), 130.17 (d, *J* 12, ArC5), 133.4 (d, *J* 9, ArC4), 131.9 (ArC6), 120.9 (d, *J* 9, *C*CO), 116.1 (d, *J* 21, ArC3), 51.3 (*C*HNH), 41.9 ($C H_2$NH), 27.2 ($C H_2$CHNH), 21.1 ($C H_2CH_2$NH). ^{19}F-NMR δ_F -112.4. HRMS (+ESI) $C_{12}H_{13}FN_2O_2Na$: calcd 259.0853; found 259.0858.

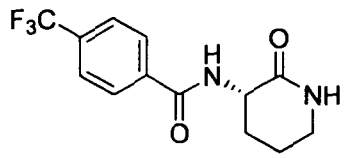
Example 3: (*S*)-4-Fluoro-N-(2-oxopiperidin-3-yl)benzamide



0.145 g cream coloured fine crystals (41 %)mp 133-135 °C; $[\alpha]^{24}_D$ -7.90 (c 0.1, MeOH); ν_{max}/cm^{-1} 1650, 1636 (C=O, amide), 1557 (N-H, amide), 1327 (C-F) Anal.

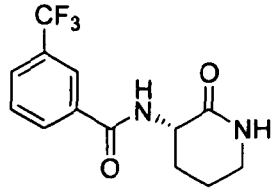
($C_{12}H_{13}FN_2O_2$) C, H, N: calcd C 61.01, H 5.55, N 11.86; found C 60.71, H 5.38, N 11.44 (1/3 H_2O). ^{1}H-NMR δ_H 7.98 (2H, q, *J* 5, Ar*H*3 and Ar*H*5), 7.41 (1H, d, *J* 6, N*H*CH), 7.20 (2H, tt, *J* 9,2, Ar*H*2 and Ar*H*6), 6.31 (1H, s, N*H*CH_2), 4.52 (1H, dt, *J* 11 and 6, C*H*NH), 3.52 (2H, td, *J* 6 and 2, CH_2NH), 2.84 (1H, dq, *J* 13 and 4, CH_2CH), 2.19-2.10 (2H, m, CH_2CH_2NH), 1.81 (1H, dq, *J* 12 and 8, CH_2CH). ^{13}C-NMR δ_C 171.7 (CH*C*ONH), 166.6 (*C*ONHCH), 164.9 (d, *J* 251.5, ArC4), 130.3 (d, *J* 4, *C*CO), 129.5 (d, *J* 9, ArC2/6), 115.5 (ArC3/5), 51.2 (*C*HNH), 41.8 (*C*H_2NH), 27.1 (*C*H_2CHNH), 21.0 (*C*H_2CH_2NH). HRMS (+ESI) $C_{12}H_{13}FN_2O_2Na$: calcd 259.0853; found 259.0852.

Example 4: (*S*)-N-(2-Oxopiperidin-3-yl)-4-(trifluoromethyl)benzamide



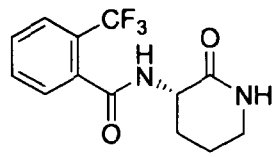
0.376 g white fine powder (87 %). mp 212-214 °C; $[\alpha]^{24}_D$ -6.35 (c 0.1, MeOH); ν_{max}/cm^{-1} 1650, 1636 (C=O, amide), 1557 (N-H, amide), 1327 (C-F). Anal. ($C_{13}H_{13}F_3N_2O_2$) C, H, N: calcd C 54.55, H 4.58, N 9.79; found C 53.99, H 4.68, N 9.59. ^{1}H-NMR δ_H ^{1}H-NMR δ_H. 7.51 (2H, d, *J* 8, Ar*H*2 and Ar*H*6), 7.22 (2H, d, *J* 8.5, Ar*H*3 and Ar*H*5), 7.15 (1H, s, N*H*CH), 5.70 (1H, s, N*H*CH_2), 4.00 (1H, dt, *J* 11.5 and 6, C*H*NH), 2.98 (2H, td, *J* 6 and 2, CH_2NH), 2.25 (1H, dq, *J* 13 and 4, CH_2CH), 1.62-1.53 (2H, m, CH_2CH_2NH), 1.28 (1H, dq, *J* 12 and 8, CH_2CH). ^{13}C-NMR δ_C 171.8 (CH*C*ONH), 166.3 (*C*ONHCH), 137.3 (ArC1), 133.3 (q, *J* 31, ArC4), 127.6 (ArC2/6), 125.5.9 (q, *J* 4, ArC3/5), 123.7 (q, *J* 271, *C*F_3), 51.2 (*C*HNH), 41.9 (*C*H_2NH), 27.0 (*C*H_2CHNH), 21.1 (*C*H_2CH_2NH). ^{19}F-NMR δ_F -62.9. HRMS (+ESI) $C_{13}H_{13}F_3N_2O_2Na$: calcd 309.0821; found 309.0822.

Example 5: (*S*)-N-(2-Oxopiperidin-3-yl)-3-(trifluoromethyl)benzamide



0.251 g cream fine powder (59 %). mp 148-150 °C; $[\alpha]^{24}_D$ -10.20 (c 0.1, MeOH); ν_{max}/cm^{-1} 1671, 1648 (C=O, amide), 1554 (N-H, amide), 1327 (C-F). Anal. ($C_{13}H_{13}F_3N_2O_2$) C, H, N: calcd C 54.55, H 4.58, N 9.79; found C 53.90, H 4.56, N 9.60. ^{1}H-NMR δ_H 7.80 (1H, s, Ar*H*2), 7.73 (1H, d, *J* 7, Ar*H*4), 7.60 (1H, d, *J* 6, N*H*CH), 7.43 (1H, d, *J* 7, Ar*H*6), 7.23 (1H, d, *J* 8, Ar*H*5), 6.52 (1H, s, N*H*CH_2), 4.23 (1H, dt, *J* 11 and 6, C*H*NH), 3.17-3.06 (2H, m, CH_2NH), 2.30 (1H, dq, *J* 13 and 6, CH_2CH), 1.74-1.65 (2H, m, CH_2CH_2NH), 1.62-1.42 (1H, m, CH_2CH). ^{13}C-NMR δ_C 171.6 (CH*C*ONH), 166.1 (*C*ONHCH), 134.9 (ArC1), 131.1 (q, *J* 34, ArC3), 130.3 (ArC5), 129.1 (ArC6), 128.2 (q, *J* 4, ArC2), 124.3 (q, *J* 4, ArC4), 123.7 (q, *J* 271, *C*F_3), 51.2 (*C*HNH), 41.8 (*C*H_2NH), 27.1 (*C*H_2CHNH), 21.1 (*C*H_2CH_2NH).^{19}F-NMR δ_F -62.7. HRMS (+ESI) $C_{13}H_{13}F_3N_2O_2Na$: calcd 309.0821; found 309.0820.

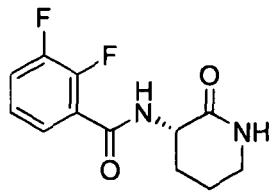
Example 6: (*S*)-N-(2-Oxopiperidin-3-yl)-2-(trifluoromethyl)benzamide



0.262 g white fluffy powder (61 %). mp 155-156 °C; $[\alpha]^{24}_D$ -18.20 (c 0.1, MeOH); ν_{max}/cm^{-1} 1674, 1654 (C=O, amide), 1543 (N-H, amide), 1312 (C-F). Anal. ($C_{13}H_{13}F_3N_2O_2$) C, H, N: calcd C 54.55, H 4.58, N 9.79; found C 54.25, H 4.51, N 9.70. ^{1}H-NMR δ_H 7.64 (1H, d, *J* 7, Ar*H*6), 7.54 (1H, d, *J* 6, Ar*H*3), 7.22-7.15 (2H, m, Ar*H*4 and Ar*H*5), 6.78 (1H, d, *J* 5, N*H*CH), 6.08 (1H, N*H*CH_2), 4.42 (1H, dt, *J* 11 and 6, C*H*NH), 3.35 (2H, td, *J* 6 and 2, CH_2NH), 2.73 (1H, dq, *J* 13 and 6, CH_2CH), 1.99-1.91 (2H, m, CH_2CH_2NH), 1.59 (1H, dq, *J* 12 and 8, CH_2CH). ^{13}C-NMR δ_C 171.0 (CH*C*ONH), 167.8 (*C*ONHCH), 135.5 (ArC1), 131.9 (ArC4), 129.9 (ArC5), 128.6 (ArC6), 127.4 (q, *J* 31, ArC2), 126.4 (q, *J* 4, ArC3), 123.6 (q, *J* 270, *C*F_3), 51.3

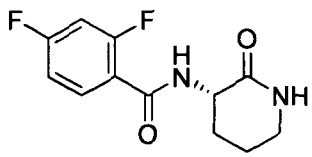
(*C*HNH), 41.8 (*C*H_2NH), 26.5 (*C*H_2CHNH), 20.9 (*C*H_2CH_2NH). ^{19}F-NMR δ_F -58.7. HRMS (+ESI) $C_{13}H_{13}F_3N_2O_2Na$: calcd 309.0821; found 309.0818.

Example 7: (*S*)-2,3-difluoro-N-(2-oxopiperidin-3-yl)benzamide



0.234 g white needle crystals (61 %). mp 160-162 °C; $[\alpha]^{24}_D$ -5.65 (c 0.1, MeOH); ν_{max}/cm^{-1} 1686, 1648 (C=O, amide), 1536 (N-H, amide), 1320 (C-F). Anal. ($C_{12}H_{12}F_2N_2O_2$) C, H, N: calcd C 56.99, H 4.76, N 11.02; found C 56.26, H 4.69, N 10.84. ^{1}H-NMR δ_H. 7.76 (1H, ddt, *J* 8, 6 and 2, Ar*H*6), 7.51 (1H, q, *J* 3, N*H*CH), 7.28 (1H, dddd, *J* 9.5, 8, 7.5, 2, Ar*H*4), 7.15 (1H, tdd, *J* 8, 5, 1.5, Ar*H*5), 6.18 (1H, s, N*H*CH_2), 4.47 (1H, dt, *J* 12 and 4, C*H*NH), 3.38 (2H, td, *J* 6 and 2, CH_2NH), 2.69 (1H, dq, *J* 12.5 and 3.5, CH_2CH), 2.02-1.93 (2H, m, CH_2CH_2NH), 1.73-1.59 (1H, m, CH_2CH). ^{13}C-NMR δ_C 171.2 (CH*C*ONH), 162.5 (*C*CONH), 132.8 (dd, *J* 250 and 15, ArC3), 149.1 (dd, *J* 251 and 14, ArC2), 126.2 (t, *J* 3, ArC5), 124.4 (t, *J* 4, ArC6), 123.3 (d, *J* 9, *C*CONH), 120.3 (d, *J* 17, ArC4), 51.4 (*C*HNH), 41.8 (*C*H_2NH), 27.1 (*C*H_2CHNH), 21.1 (*C*H_2CH_2NH). HRMS (+ESI) $C_{12}H_{12}F_2N_2O_2Na$: calcd 277.0759; found 277.0769.

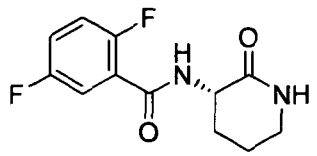
Example 8: (*S*)-2,4-difluoro-N-(2-oxopiperidin-3-yl)benzamide



0.236 g off-white crystals (62 %). mp 140-141 °C; $[\alpha]^{24}_D$ -2.00 (c 0.1, MeOH); ν_{max}/cm^{-1} 1682, 1638 (C=O, amide), 1526 (N-H, amide), 1289 (C-F). Anal. ($C_{12}H_{12}F_2N_2O_2.1/6\ H_2O$) C, H, N: calcd C 56.03, H 4.83, N 10.89; found C 56.40, H 4.69, N 10.93. ^{1}H-NMR δ_H. 8.07 (1H, td, *J* 9 and 7, Ar*H*6), 7.54 (1H, q, *J* 5, N*H*CH),

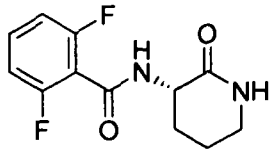
6.95 (1H, tdd, *J* 8, 2.5, 1, Ar*H*5), 6.84 (1H, dq, *J* 8.5, 2, Ar*H*3), 6.43 (1H, s, N*H*CH_2), 4.45 (1H, dt, *J* 11 and 6, C*H*NH), 3.36 (2H, td, *J* 6.5 and 2.5, CH_2NH), 2.66 (1H, dq, *J* 12.5 and 5.5, CH_2CH), 2.00-1.91 (2H, m, C$H_2$$CH_2$NH), 1.73-1.59 (1H, m, C$H_2$CH). ^{13}C-NMR δ_C 171.4 (CH*C*ONH), 162.5 (C*C*ONH), 164.9 (dd, *J* 255 and 12, ArC2), 161.2 (dd, *J* 253 and 12, ArC4), 133.6 (dd, *J* 10 and 4, ArC6), 117.4 (dd, *J* 12 and 4, *C*CONH), 112.2 (dd, *J* 21 and 3, ArC5), 104.3 (t, *J* 27, ArC3), 51.3 (*C*HNH), 41.8 (*C*H_2NH), 27.2 (*C*H_2CHNH), 21.1 (*C*$H_2$$CH_2$NH). HRMS (+ESI) $C_{12}H_{12}F_2N_2O_2Na$: calcd 277.0759; found 277.0761.

Example 9: (*S*)-2,5-difluoro-N-(2-oxopiperidin-3-yl)benzamide



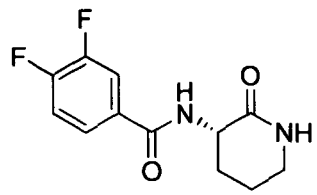
0.252 g off-white crystals (66 %). mp 140-142 °C; $[\alpha]^{24}_D$ +0.85 (c 0.1, MeOH); ν_{max}/cm^{-1} 1681, 1635 (C=O, amide), 1519 (N-H, amide), 1328 (C-F). Anal. ($C_{12}H_{12}F_2N_2O_2$.1/6 H_2O) C, H, N: calcd C 56.03, H 4.83, N 10.89; found C 55.47, H 4.72, N 10.67. ^{1}H-NMR δ_H. 8.07 (1H, dt, *J* 11 and 8.5, Ar*H*6), 7.54 (1H, dd, *J* 11, 5, N*H*CH), 6.68-6.54 (2H, m, Ar*H*3 and Ar*H*4), 6.43 (1H, s, N*H*CH_2), 4.45 (1H, dt, *J* 11 and 6, C*H*NH), 3.36 (2H, td, *J* 6.5 and 2.5, CH_2NH), 2.66 (1H, dq, *J* 12.5 and 5.5, CH_2CH), 1.99-1.90 (2H, m, C$H_2$$CH_2$NH), 1.64 (1H, dq, *J* 11 and 8 CH_2CH). ^{13}C-NMR δ_C 171.3 (CH*C*ONH), 162.2 (C*C*ONH), 158.6 (d, *J* 258, ArC5), 156.7 (d, *J* 258, ArC2), 133.6 (dd, *J* 10 and 4, ArC6), 122.4 (dd, *J* 8 and 6, *C*CONH), 120.0 (dd, *J* 24 and 8, ArC3), 118.0 (dd, *J* 26 and 4, ArC4), 117.5 (dd, *J* 28 and 7, ArC6), 51.4 (*C*HNH), 41.8 (*C*H_2NH), 27.1 (*C*H_2CHNH), 21.1 (*C*$H_2$$CH_2$NH). HRMS (+ESI) $C_{12}H_{12}F_2N_2O_2Na$: calcd 277.0759; found 277.0766.

Example 10: (*S*)-2,6-difluoro-N-(2-oxopiperidin-3-yl)benzamide



0.209 g white fine powder (55 %). mp 190-194 °C; $[\alpha]^{24}_D$ -7.20 (c 0.1, MeOH); ν_{max}/cm^{-1} 1672, 1638 (C=O, amide), 1492 (N-H, amide), 1329 (C-F). Anal. ($C_{12}H_{12}F_2N_2O_2$) C, H, N: calcd C 56.99, H 4.76, N 11.02; found C 55.93, H 4.68, N 10.83 (1/6 H_2O). ^{1}H-NMR δ_H. 7.30 (1H, tt, *J* 9 and 6, Ar*H*4), 7.06 (1H, d, *J* 3.5, N*H*CH), 6.89 (2H, t, *J* 3.5, Ar*H*3 and Ar*H*5), 6.23 (1H, s, N*H*CH_2), 4.43 (1H, dt, *J* 11 and 5, C*H*NH), 3.37-3.32 (2H, m, CH_2NH), 2.75 (1H, dq, *J* 14.5 and 4.5, CH_2CH), 1.99-1.90 (2H, m, CH_2CH_2NH), 1.68-1.54 (1H, m, CH_2CH). ^{13}C-NMR δ_C 171.1 (CH*C*ONH), 160.5 (C*C*ONH), 160.1 (dd, *J* 250 and 7.5, ArC2 and ArC6), 131.7 (t, *J* 11, ArC4), 114.1 (t, *J* 20, *C*CONH), 111.9 (dd, *J* 20 and 5, ArC3 and ArC5), 51.3 (*C*HNH), 41.7 (*C*H_2NH), 26.8 (*C*H_2CHNH), 20.9 (*C*H_2CH_2NH). ^{19}F-NMR δ_F -112.5. HRMS (+ESI) $C_{12}H_{12}F_2N_2O_2Na$: calcd 277.0759; found 277.0760.

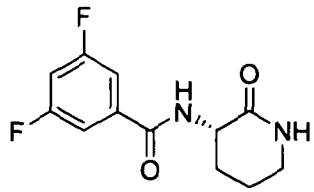
Example 11: (*S*)-3,4-difluoro-N-(2-oxopiperidin-3-yl)benzamide



0.226 g off-white fine powder (59%). mp 202-204 °C; $[\alpha]^{24}_D$ -7.50 (c 0.1, MeOH); ν_{max}/cm^{-1} 1691, 1652 (C=O, amide), 1487 (N-H, amide), 1285 (C-F). Anal. ($C_{12}H_{12}F_2N_2O_2$) C, H, N: calcd C 56.99, H 4.76, N 11.02; found C 56.06, H 4.68, N 10.88 (1/6 H_2O). ^{1}H-NMR δ_H. 7.66 (1H, qd, *J* 7 and 2, Ar*H*2), 7.56-7.50 (1H, m, Ar*H*5), 7.24-7.14 (2H, m, Ar*H*6 and N*H*CH), 5.90 (1H, s, N*H*CH_2), 4.38 (1H, dt, *J* 11.5 and 5, C*H*NH), 3.39 (2H, td, *J* 7 and 3, CH_2NH), 2.69 (1H, dq, *J* 14 and 5, CH_2CH), 2.03-1.94 (2H, m, CH_2CH_2NH), 1.68-1.54 (1H, m, CH_2CH). ^{13}C-NMR δ_C 171.5 (CH*C*ONH), 165.4 (C*C*ONH), 152.5 (dd, *J* 253 and 12, ArC3), 150.2 (dd, *J* 249 and 12, ArC4), 131.2 (t, *J* 4.5, *C*CONH), 123.5 (q, *J* 3.5, ArC6), 117.4 (d, *J* 18, ArC5),

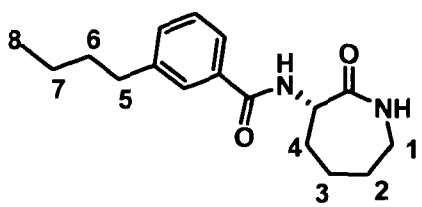
116.9 (d, *J* 18, ArC2), 51.2 (*C*HNH), 41.8 (*C*H_2NH), 26.9 (*C*H_2CHNH), 21.1 (*C*$H_2$$CH_2$NH). HRMS (+ESI) $C_{12}H_{12}F_2N_2O_2Na$: calcd 277.0759; found 277.0751.

Example 12: (*S*)-3,5-difluoro-N-(2-oxopiperidin-3-yl)benzamide



0.234 g white fine powder (61 %). mp 198-199 °C; $[\alpha]^{24}_D$ -9.50 (c 0.1, MeOH); ν_{max}/cm^{-1} 1674, 1641 (C=O, amide), 1565 (N-H, amide), 1333 (C-F). Anal. ($C_{12}H_{12}F_2N_2O_2$) C, H, N: calcd C 56.99, H 4.76, N 11.02; found C 56.20, H 4.69, N 10.93. ^{1}H-NMR δ_H. 7.31 (2H, dd, *J* 8 and 2.5, Ar*H*2 and Ar*H*6), 7.26 (1H, d, *J* 5, N*H*CH), 6.9 (1H, tt, *J* 9 and 2, Ar*H*4), 6.01 (1H, s, N*H*CH_2), 4.39 (1H, dt, *J* 12 and 5.5, C*H*NH), 3.41-3.36 (2H, m, C*H*$_2$NH), 2.68 (1H, dq, *J* 12 and 5, C*H*$_2$CH), 2.03-1.94 (2H, m, C*H*$_2$$CH_2$NH), 1.69-1.55 (1H, m, C*H*$_2$CH). ^{13}C-NMR δ_C 171.3 (CH*C*ONH), 165.2 (C*C*ONH), 162.9 (dd, *J* 251.5 and 12, ArC3 and ArC5), 137.5 (t, *J* 9, *C*CONH), 110.4 (dd, *J* 20 and 7, ArC2 and ArC6), 107.0 (t, *J* 20, ArC4), 51.3 (*C*HNH), 41.8 (*C*H_2NH), 26.9 (*C*H_2CHNH), 20.9 (*C*$H_2$$CH_2$NH). ^{19}F-NMR δ_F -108.2. HRMS (+ESI) $C_{12}H_{12}F_2N_2O_2Na$: calcd 277.0759; found 277.0750.

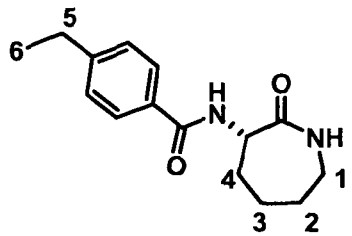
Example 13: (S)-3-(3'-Butylbenzoylamino)-azepan-2-one



(*S*)-3-Amino-azepan-2-one hydrochloride (0.72 g, 4.39 mmoles) was dissolved in H_2O (20 mL) and cooled to 0°C. 3-Butylbenzoyl chloride in dichloromethane was added and triethylamine (1.3 mL, 9 mmoles) and the reaction was stirred over night. H_2O (20 mL) was added and the reaction was extracted with dichloromethane (3 × 20 mL), the

organic layer was washed with a pH 2 buffer (3 × 15 mL), dried over Na_2SO_4 and reduced *in vacuo*. The product was purified by silica column chromatography (petroleum ether:ethyl acetate 75:25 to 0:100) to give the product as a white solid δ_H (400 MHz, $CDCl_3$) 7.71-7.62 (m, 3H, Ar & N*H*CH), 7.35-7.29 (m, 2H, Ar), 7.06 (br.t, 1H, *J* 6, N*H*CH_2), 4.72 (dd, 1H, *J* 11, 6, NHC*H*), 3.37-3.32 (m, 2H, NHC*H*$_2$), 2.65 (t, 2H, *J* 8, $CH_3CH_2CH_2CH_2$), 2.22 (br.d, 1H, *J* 13.5, NHCHC*H*$_2$), 2.03 (br.d, 1H, *J* 14, NHCHCH_2C*H*$_2$), 1.95-1.81 (m, 2H, NHCHCH_2C*H*$_2$C*H*$_2$), 1.61 (quintet, 2H, *J* 7, $CH_3CH_2CH_2$), 1.57-1.48 (m, 1H. NHCHC*H*$_2$), 1.46-1.25 (m, 3H, NHCHCH_2CH_2C*H*$_2$ and CH_3CH_2) and 0.92 (t, 3H, *J* 7.5, H8); δ_C (100 MHz, $CDCl_3$) 176.0 (*C*=O), 166.6 (*C*=O), 143.4 (Ar quat, *C*-^{n}Bu), 134.2 (Ar quat, *C*-C=O), 128.4 (CH, Ar), 127.2 (CH, Ar), 126.8 (CH, Ar), 124.0 (CH, Ar), 52.6 (*C*H-NH), 42.1 (*C*H_2-NH), 35.6 (*C*H_2), 33.5 (*C*H_2), 31.6 (*C*H_2), 28.9 (*C*H_2), 28.0 (*C*H_2), 22.3 (*C*H_2) and 13.9 (*C*H_3).

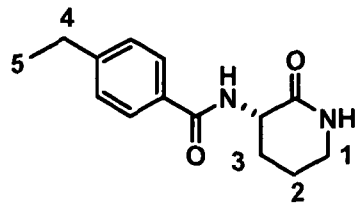
Example 14: (S)-3-(4'-Ethylbenzoylamino)-azepan-2-one



(*S*)-3-amino-azepan-2-one hydrochloride (1.65 g, 10 mmoles) was dissolved in H_2O (20 mL) and cooled to 0°C. 4-Ethylbenzoyl chloride in dichloromethane was added and triethylamine (4.2 mL, 30 mmoles) and the reaction was stirred over night. H_2O (20 mL) was added and the reaction was extracted with dichloromethane (3 × 20 mL), the organic layer was washed with a pH 2 buffer (3 × 15 mL), dried over Na_2SO_4 and reduced *in vacuo*. The product was purified by recrystallisation from chloroform and cold petroleum ether to give the product as a white solid 0.94 g (36 %); *mp* 218-219 ° C; δ_H (400 MHz, $CDCl_3$) 7.66 (d, 2H, *J* 8, C*H*-C-Et), 7.62 (d, 1H, *J* 5.5, N*H*-CH), 7.24 (d, 2H, *J* 8, C*H*-C-CO), 6.55 (br.t, 1H, *J* 6, N*H*-C1), 4.70 (dd, 1H, *J* 11, 5.5, C*H*-C4), 3.37-3.32 (m, 2H, H1), 2.67 (q, 2H, *J* 7.5, H5), 2.21 (br.d, 1H, *J* 13, H4 equatorial), 2.02 (dt, 1H, *J* 14, 4, H3 equatorial), 1,95-1.82 (m, 2H, H2 equatorial & H3 axial), 1.53 (br.q, 1H, *J* 12.5, H4 axial), 1.40 (br.q, 1H, *J* 13, H2 axial) and 1.22 (t, 3H, *J* 7.5, H6); δ_C (100 MHz, $CDCl_3$) 175.9 (*C*=O), 166.2 (*C*=O), 148.2 (*C*-Et), 131.6 (*C*-C=O), 128.0, 127.2 (*C*H phenyl), 52.6 (*C*H-NH), 42.2 (C1), 28.9 (C5), 28.8, 28.0 (C2, C3)

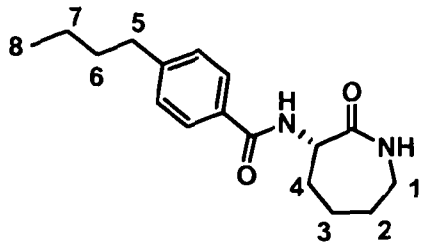
and 15.4 (C6); υ_{max}/cm^{-1}: 3200 (NH indole), 2956 (C-H), 1642 (amide C=O) and 1543 (aromatic); ESI *m/z* 100 %, 542.9 (M_2Na^+), 70%, 283.1 (MNa^+) and 10 %, 261.2 (MH^+); HR ESI *m/z* ($C_{15}H_{20}N_2O_2Na$ requires 283.1417) found 283.1414; $[\alpha]^{23}_D$ (c = 0.49, $CHCl_3$) +70.48.

Example 15: (S)-3-(4'-Ethylbenzoylamino)-tetrahydropyridin-2-one



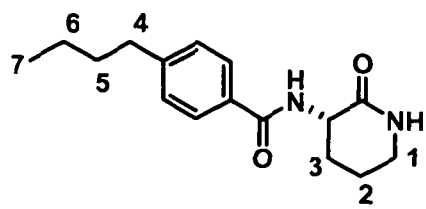
(*S*)-3-amino-tetrahydropyridin-2-one (20 mmoles) was dissolved in H_2O (100 mL) and cooled to 0°C. 4-Ethylbenzoyl chloride (16 mmoles) in dichloromethane was added and triethylamine (6.7 mL, 48 mmoles) and the reaction was stirred over night. The reaction was extracted with dichloromethane (3 × 30 mL), the organic layer was washed with a pH 2 buffer (3 × 20 mL), dried over Na_2SO_4 and reduced *in vacuo*. The product was purified by silica column chromatography (petroleum ether:ethyl acetate 50:50:0 to 0:80:20) to give the product as a white solid 1.46 g (37 %); *mp* 112-113 ° C; δ_H (400 MHz, $CDCl_3$) 7.71 (d, 2H, *J* 8.5, C*H*-C-Et), 7.55 (d, 1H, *J* 5.5, N*H*-CH), 7.19 (d, 2H, *J* 8.5, C*H*-C-CO), 6.69 (br.s, 1H, N*H*-C1), 4.39 (dt, 1H, *J* 11, 5.5, C*H*-C3), 3.35-3.28 (m, 2H, H1), 2.67 (q, 2H, *J* 7.5, H4), 2.63-2.56 (m, 1H, H3 equatorial), 1.94-1.87 (m, 2H, H2), 1.68 (tt, 1H, *J* 12.5, 8, H3 axial), and 1.20 (t, 3H, *J* 7.5, H5); δ_C (100 MHz, $CDCl_3$) 172.2 (*C*=O), 167.5 (*C*=O), 148.2 (*C*-Et), 131.5 (*C*-C=O), 127.9, 127.2 (*C*H phenyl), 50.9 (*C*H-NH), 41.7 (C1), 28.8 (C4), 27.2 (C3), 21.1 (C2) and 15.3 (C5); υ_{max}/cm^{-1}: 3334, 3245 (NH), 2932 (C-H), 1656, 1634 (C=O) and 1528 (aromatic); ESI *m/z* 100 %, 514.9 (M_2Na^+) and 35%, 269.1 (MNa^+); HR ESI *m/z* ($C_{14}H_{18}N_2O_2Na$ requires 269.1260) found 269.1261; $[\alpha]^{23}_D$ (c = 0.491, $CHCl_3$) +103.95.

Example 16: (S)-3-(4'-Butylbenzoylamino)-azepan-2-one



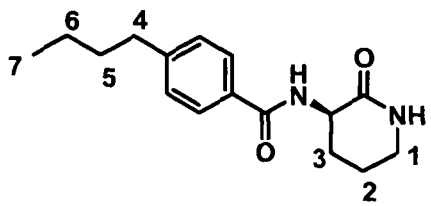
(*S*)-3-amino-azepan-2-one hydrochloride (1.65 g, 10 mmoles) was dissolved in H_2O (20 mL) and cooled to 0°C. 4-Butylbenzoyl chloride (8 mmoles) in dichloromethane was added and triethylamine (4.2 mL, 30 mmoles) and the reaction was stirred over night. H_2O (20 mL) was added and the reaction was extracted with dichloromethane (3 × 20 mL), the organic layer was washed with a pH 2 buffer (3 × 15 mL), dried over Na_2SO_4 and reduced *in vacuo*. The product was purified by silica column chromatography (petroleum ether:ethyl acetate 75:25 to 0:100) to give the product as a white solid 0.42 g (18 %); *mp* 183-184 ° C; δ_H (400 MHz, $CDCl_3$) 7.73 (d, 2H, *J* 8, Ar), 7.63 (d, 1H, *J* 5.5, N*H*CH), 7.21 (d, 2H, *J* 8, Ar), 6.80 (br.t, 1H, *J* 6, N*H*CH_2), 4.69 (dd, 1H, *J* 10.5, 5.5, NHC*H*), 3.35-3.20 (m, 2H, C*H*$_2$NH), 2.61 (t, 2H, *J* 7.5, H5), 2.19 (br.d, 1H, *J* 13.5, H4 equatorial), 2.00 (br.d, 1H, *J* 12.5, H3 equatorial), 1.93-1.80 (m, 2H, H2 equatorial & H3 axial), 1.70-1.46 (m, 3H, H6 and H4 axial), 1.38 (br.q, 1H, *J* 13, H2 axial), 1.31 (sextet, H2, *J* 7, H7) and 0.89 (t, 3H, *J* 7.5, H8); δ_C (100 MHz, $CDCl_3$) 176.0 (*C*=O), 166.3 (*C*=O), 146.7 (*C*-^{n}Bu), 131.6 (*C*-C=O), 128.5, 127.1 (*C*H phenyl), 52.5 (*C*H-NH), 42.2 (C1), 35.5 (C5), 33.4 (C4), 31.6 (C6), 28.9, 28.0 (C2, C3), 22.3 (C7) and 13.9 (C6); υ_{max}/cm^{-1}: 3359, 3207 (NH), 2951 (C-H), 1671, 1650 (C=O) and 1543 (aromatic); ESI *m/z* 100 %, 311.2 (MNa^+) and 22 %, 289.2 (MH^+); HR ESI *m/z* ($C_{17}H_{24}N_2O_2Na$ requires 311.1730) found 311.1732; $[\alpha]^{25}_D$ (c = 0.515, $CHCl_3$) +64.88.

Example 17: (S)-3-(4'-Butylbenzoylamino)-tetrahydropyridin-2-one



(*S*)-3-amino-tetrahydropyridin-2-one (20 mmoles) was dissolved in H_2O (20 mL) and cooled to 0°C. The 4-butylbenzoyl chloride in dichloromethane was added and triethylamine (4.2 mL, 30 mmoles) and the reaction was stirred over night. H_2O (20 mL) was added and the reaction was extracted with dichloromethane (3 × 20 mL), the organic layer was washed with a pH 2 buffer (3 × 15 mL), dried over Na_2SO_4 and reduced *in vacuo*. The product was purified by silica column chromatography (petroleum ether:ethyl acetate:methanol 50:50:0 to 0:80:20) to give the product as a white solid 0.45 g (16 %); δ_H (400 MHz, $CDCl_3$) 7.70 (d, 2H, *J* 8, C*H*-C-^{n}Bu), 7.36 (d, 1H, *J* 6, N*H*- *mp* 117-118 ° C; CH), 7.17 (d, 2H, *J* 8, C*H*-C-CO), 6.67 (br.s, 1H, N*H*-C1), 4.69 (dt, 1H, *J* 12, 6, C*H*-C4), 3.36-3.29 (m, 2H, H1), 2.60 (t, 3H, *J* 7.5, H4 & H3), 1.93-1.86 (m, 2H, H2), 1.67-1.54 (m, 1H, H3), 1.55 (quintet, 2H, *J* 7.5, H5), 1.30 (sextet, 2H, *J* 7, H7.5, H6) and 0.89 (t, 3H, *J* 7.5, H7); δ_C (100 MHz, $CDCl_3$) 172.2 (*C*=O lactam), 167.5 (*C*=O amide), 146.9 (*C*-^{n}Bu), 131.5 (*C*-C=O), 128.5 (*C*H phenyl), 127.2 (*C*H phenyl), 50.8 (*C*H-NH), 41.7 (C1), 35.5 (C4), 33.3 (C5), 27.2 (C3), 22.3 (C6), 21.1 (C2) and 13.9 (C7); ESI *m/z* 100 %, 297.2 (MNa^+) and 26 %, 275.2 (MH^+); HR ESI *m/z* ($C_{16}H_{22}N_2O_2Na$ requires 297.1573) found 297.1573; $[\alpha]^{24}_D$ (c = 0.523, $CHCl_3$) +98.73.

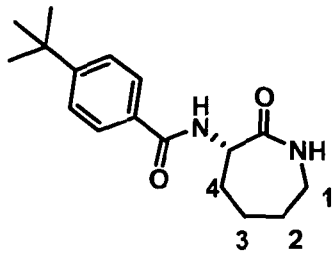
Example 18: (R)-3-(4'-Butylbenzoylamino)-tetrahydropyridin-2-one



(*R*)-3-amino-tetrahydropyridin-2-one (10 mmoles) was dissolved in H_2O (30 mL) and cooled to 0°C. 4-Butylbenzoyl chloride (8.5 mmoles) in dichloromethane was added and triethylamine (4.2 mL, 30 mmoles) and the reaction was stirred over night. The reaction was extracted with dichloromethane (3 × 15 mL), the organic layer was washed with a pH 2 buffer (3 × 15 mL), dried over Na_2SO_4 and reduced *in vacuo*. The product was purified by silica column chromatography (petroleum ether:ethyl acetate:methanol 50:50:0 to 0:80:20) to give the product as a white solid 1.10 g (40 %); *mp* 116-117 ° C; δ_H (400 MHz, $CDCl_3$) 7.72 (d, 2H, *J* 8, C*H*-C-^{n}Bu), 7.25 (d, 1H, *J*

5.5, N*H*-CH), 7.20 (d, 2H, *J* 8, C*H*-C-CO), 6.41 (br.s, 1H, N*H*-C1), 4.41 (dt, 1H, *J* 11.5, 5.5, C*H*-C4), 3.37-3.32 (m, 2H, H1), 2.66 (ddt, 1H, *J* 13, 6, 4.5, H3 equatorial), 2.62 (t, 3H, *J* 8, H4), 1.98-1.90 (m, 2H, H2), 1.67-1.53 (m, 3H, H3 axial & H5), 1.32 (quintet, 2H, *J* 7.5, H6) and 0.90 (t, 3H, *J* 7, H7); δ_C (100 MHz, $CDCl_3$) 172.1 (*C*=O lactam), 167.6 (*C*=O amide), 147.0 (*C*-^{n}Bu), 131.5 (*C*-C=O), 128.5 (*C*H phenyl), 127.2 (*C*H phenyl), 51.0 (*C*H-NH), 41.7 (C1), 35.5 (C4), 33.3 (C5), 27.2 (C3), 22.3 (C6), 21.1 (C2) and 13.9 (C7); υ_{max}/cm^{-1}: 3319, 3245 (NH), 2949 (C-H), 1651, 1634 (C=O) and 1521 (aromatic); ESI *m/z* 100 %, 297.1 (MNa^+); HR ESI *m/z* ($C_{16}H_{22}N_2O_2Na$ requires 297.1573) found 297.1574; $[\alpha]^{25}_D$ (c = 0.493, $CHCl_3$) -89.45.

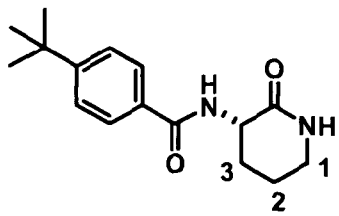
Example 19: (S)-3-(4'-*tert*-Butylbenzoylamino)-azepan-2-one



(*S*)-3-amino-azepan-2-one hydrochloride (2.04 g, 12.44 mmoles) was dissolved in H_2O (20 mL) and cooled to 0°C. The 4-^{t}Butylbenzoyl chloride in dichloromethane was added and triethylamine (4.2 mL, 30 mmoles) and the reaction was stirred over night. H_2O (20 mL) was added and the reaction was extracted with dichloromethane (3 × 20 mL), the organic layer was washed with a pH 2 buffer (3 × 20 mL), dried over Na_2SO_4 and reduced *in vacuo*. The product was purified by recrystallisation from chloroform and cold petroleum ether and washed with boiling ethyl acetate to give the product as a white solid 1.44 g (50 %); *mp* 204-205 ° C; δ_H (400 MHz, $CDCl_3$) 7.76 (d, 2H, *J* 8.5, C*H*-C-^{t}Bu), 7.66 (d, 1H, *J* 6, N*H*-CH), 7.42 (d, 2H, *J* 8.5, C*H*-C-CO), 6.00 (br.s, 1H, N*H*-C1), 4.67 (ddd, 1H, *J* 11, 6, 1.5, C*H*-C4), 3.34-3.19 (m, 2H, H1), 2.18 (br.d, 1H, *J* 13, H4 equatorial), 2.00 (br.d, 1H, *J* 12.5, H3 equatorial), 1.92-1.78 (m, 2H, H2 equatorial & H3 axial), 1.51 (q, 1H, *J* 13, H4 axial), 1.33 (br.q, 1H, *J* 11, H2 axial), and 1.29 (s, 3H, C(C*H*$_3$)$_3$); δ_C (100 MHz, $CDCl_3$) 176.0 (*C*=O), 166.2 (*C*=O), 155.0 (*C*-C(CH$_3$)$_3$), 131.4 (*C*-C=O), 127.9, 125.4 (*C*H phenyl), 52.5 (*C*H-NH), 42.1 (C1), 34.9 (*C*(CH$_3$)$_3$), 31.6 (C4), 31.2 (C(*C*H$_3$)$_3$) and 28.9, 28.0 (C2, C3); ESI *m/z* 100 %,

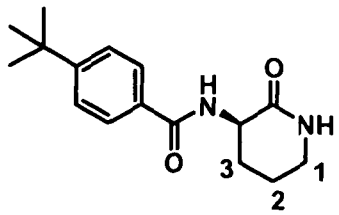
598.8 (M_2Na^+) and 32 %, 289.2 (MH^+); HR ESI *m/z* ($C_{17}H_{24}N_2O_2Na$ requires 311.1730) found 311.1736; υ_{max}/cm^{-1}: 3210 (NH indole), 2906 (C-H), 1640 (C=O) and 1566 (aromatic); $[\alpha]^{23}_D$ (c = 0.523, $CHCl_3$) +63.77.

Example 20: (S)-3-(4'-*tert*-Butylbenzoylamino)-tetrahydropyridin-2-one



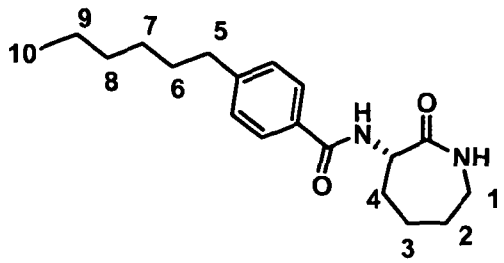
(*S*)-3-amino-tetrahydropyridin-2-one (33 mmoles) was dissolved in H_2O (100 mL) and cooled to 0°C. 4-^{t}Butylbenzoyl chloride (20 mmoles) in dichloromethane was added and triethylamine (6.3 mL, 45 mmoles) and the reaction was stirred over night. The reaction was extracted with dichloromethane (3 × 20 mL), the organic layer was washed with a pH 2 buffer (3 × 20 mL), dried over Na_2SO_4 and reduced *in vacuo*. The product was purified by silica column chromatography (petroleum ether:ethyl acetate:methanol 50:50:0 to 0:80:20) to give the product as a white solid 3.13 g (53 %) *mp* 195-196 °C; δ_H (400 MHz, $CDCl_3$) 7.24 (d, 2H, *J* 8.5, C*H*-C-^{t}Bu), 7.49 (d, 1H, *J* 6, N*H*-CH), 7.36 (d, 2H, *J* 8.5, C*H*-C-CO), 6.94 (br.s, 1H, N*H*-C1), 4.62 (dt, 1H, *J* 11, 6, 1.5, C*H*-C4), 3.31-3.26 (m, 2H, H1), 2.52 (ddt, 1H, *J* 13, 6, 4.5, H3 equatorial), 1.90-183 (m, 2H, H2), 1.63 (tt, 1H, *J* 12.5, 8.5, H3 axial) and 1.27 (s, 9H, C(C*H*$_3$)$_3$); δ_C (100 MHz, $CDCl_3$) 172.3 (*C*=O), 167.4 (*C*=O), 154.9 (*C*-C(CH_3)$_3$), 131.2 (*C*-C=O), 127.0, 126.7, 125.3 (*C*H phenyl), 50.8 (*C*H-NH), 41.6 (C1), 34.9 (*C*(CH_3)$_3$), 31.2 (C(*C*H$_3$)$_3$), 27.2 (C3) and 21.1 (C2); ESI *m/z* 100 %, 297.2 (MNa^+) and 38 %, 275.2 (MH^+); υ_{max}/cm^{-1}: 3251 (NH), 2959 (C-H), 1683, 1648 (C=O) and 1558 (aromatic); HR ESI *m/z* ($C_{16}H_{23}N_2O_2$ requires 275.1754) found 275.1752; $[\alpha]^{23}_D$ (c = 0.515, $CHCl_3$) +82.52.

Example 21: (R)-3-(4'-*tert*-Butylbenzoylamino)-tetrahydropyridin-2-one



(*R*)-3-amino-tetrahydropyridin-2-one (15 mmoles) was dissolved in H_2O (100 mL) and cooled to 0°C. 4-^{t}Butylbenzoyl chloride (10 mmoles) in dichloromethane was added and triethylamine (4.2 mL, 30 mmoles) and the reaction was stirred over night. The reaction was extracted with dichloromethane (3 × 20 mL), the organic layer was washed with a pH 2 buffer (3 × 20 mL), dried over Na_2SO_4 and reduced *in vacuo*. The product was purified by silica column chromatography (petroleum ether:ethyl acetate:methanol 50:50:0 to 0:80:20) to give the product as a white solid 1.03 g (38 %) *mp* 193-194 °C; δ_H (400 MHz, $CDCl_3$) 7.72 (d, 2H, *J* 8.5, C*H*-C-^{t}Bu), 7.49 (d, 1H, *J* 6, N*H*-CH), 7.36 (d, 2H, *J* 8.5, C*H*-C-CO), 6.93 (br.s, 1H, N*H*-C1), 4.39 (dt, 1H, *J* 11.5, 6, C*H*-C4), 3.31-3.26 (m, 2H, H1), 2.52 (ddt, 1H, *J* 12.5, 5.5, 4.5, H3 equatorial), 1.90-1.87 (m, 2H, H2), 1.63 (tt, 1H, *J* 12.5, 8.5, H3) and 1.27 (s, 9H, C(C*H*$_3$)$_3$); δ_C (100 MHz, $CDCl_3$) 172.3 (*C*=O), 167.4 (*C*=O), 154.9 (*C*-C(CH_3)$_3$), 131.2 (*C*-C=O), 127.0, 125.3 (*C*H phenyl), 50.8 (*C*H-NH), 41.6 (C1), 34.9 (*C*(CH_3)$_3$), 31.2 (C(*C*H_3)$_3$), 27.2 (C3) and 21.1 (C2); υ_{max}/cm^{-1}: 3247 (NH), 2958 (C-H), 1682, 1647 (C=O) and 1544 (aromatic); ESI *m/z* 19 %, 297.2 (MNa^+) and 13 %, 275.2 (MH^+); HR ESI *m/z* ($C_{16}H_{23}N_2O_2$ requires 297.1573) found 275.1750; $[\alpha]^{23}_D$ (c = 0.512, $CHCl_3$) -84.08.

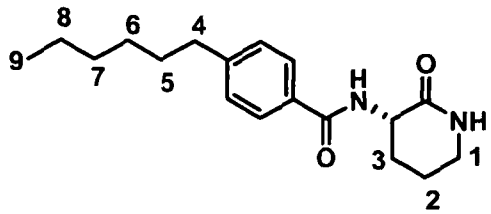
Example 22: (S)-3-(4'-Hexylbenzoylamino)-azepan-2-one



(*S*)-3-amino-azepan-2-one hydrochloride (0.95 g, 5.79 mmoles) was dissolved in H_2O (15 mL) and cooled to 0°C. 4-Hexylbenzoyl chloride (1.2 mL, 5 mmoles) in

dichloromethane was added and triethylamine (2.1 mL, 15 mmoles) and the reaction was stirred over night. H_2O (20 mL) was added and the reaction was extracted with dichloromethane (3 × 20 mL), the organic layer was washed with a pH 2 buffer (3 × 15 mL), dried over Na_2SO_4 and reduced *in vacuo*. The product was purified by silica column chromatography (petroleum ether:ethyl acetate 50:50:0 to 0:80:20) to give the product as a white solid 0.76 g (48 %); *mp* 167-168 ° C; δ_H (400 MHz, $CDCl_3$) 7.74 (d, 2H, *J* 8, C*H*-C-Hex), 7.61 (d, 1H, *J* 6, N*H*-CH), 7.21 (d, 2H, *J* 8, C*H*-C-CO), 6.54 (br.t, 1H, *J* 6, N*H*-C1), 4.69 (ddd, 1H, *J* 11, 6, 1.5, C*H*-C4), 3.37-3.22 (m, 2H, H1), 2.62 (t, 2H, *J* 7.5, H5), 2.21 (d, 1H, *J* 13, H4 equatorial), 2.03 (dt, 1H, *J* 14, 3.5, H3 equatorial), 1.95-1.82 (m, 2H, H2 equatorial & H3 axial), 1.64-1.49 (m, 3H, H4 axial & H6), 1.41 (q, 1H, *J* 13, H2 axial) 1.33-1.23 (m, 6H, H7, H8 & H9) and 0.86 (t, 3H, *J* 7, H10); δ_C (100 MHz, $CDCl_3$) 175.9 (*C*=O lactam), 166.3 (*C*=O amide), 147.0 (*C*-Hex), 131.6 (*C*-C=O), 128.5 (*C*H phenyl), 127.1 (*C*H phenyl), 52.6 (*C*H-NH), 42.2 (C1), 35.8 (C5), 31.7 (C4), 31.2 (C6), 29.0, 28.9, 28.0, (C2, C3, C7, and C8), 22.6 (C9) and 14.1 (C10); υ_{max}/cm^{-1}: 3244 (NH), 2956 (C-H), 1658, 1644 (C=O) and 1543 (aromatic); ESI *m/z* 43 %, 317.2 (MH^+), 6% 339.2 (MNa^+) and 6 %, 654.7 (M_2Na^+); HR ESI *m/z* ($C_{19}H_{28}N_2O_2Na$ requires 339.2043) found 339.2050; $[\alpha]^{25}_D$ (c = 0.507, $CHCl_3$) +60.06.

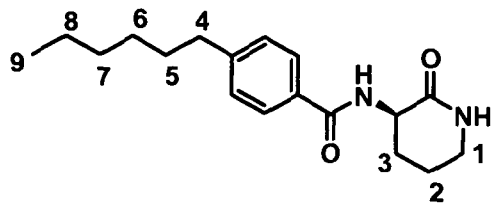
Example 23: (S)-3-(4'-Hexylbenzoylamino)-tetrahydropyridin-2-one



(*S*)-3-amino-tetrahydropyridin-2-one (10 mmoles) was dissolved in H_2O (35 mL) and cooled to 0°C. 4-Hexylbenzoyl chloride (1.2 mL, 5 mmoles) in dichloromethane was added and triethylamine (2.1 mL, 15 mmoles) and the reaction was stirred over night. The reaction was extracted with dichloromethane (3 × 15 mL), the organic layer was washed with a pH 2 buffer (3 × 15 mL), dried over Na_2SO_4 and reduced *in vacuo*. The product was purified by silica column chromatography (petroleum ether:ethyl acetate 50:50:0 to 0:80:20) to give the product as a white solid 0.95 g (63 %); *mp* 118-119 ° C;

δ_H (400 MHz, $CDCl_3$) 7.70 (d, 2H, *J* 8, C*H*-C-Hex), 7.38 (d, 1H, *J* 6, N*H*-CH), 7.17 (d, 2H, *J* 8, C*H*-C-CO), 6.81 (br.s, 1H, N*H*-C1), 4.39 (dt, 1H, *J* 11.5, 6, C*H*-C3), 3.33-3.26 (m, 2H, H1), 2.58 (t, 2H, *J* 7.5, H4), 2.57-2.52 (m, 1H, H3 equatorial obscured by H4), 1.92-1.84 (m, 2H, H2), 1.67-1.52 (m, 3H, H3 axial & H5), 1.29-1.23 (m, 6H, H6, H7 & H8) and 0.84 (t, 3H, *J* 7.5, H9);); δ_C (100 MHz, $CDCl_3$) 172.3 (*C*=O lactam), 167.5 (*C*=O amide), 146.9 (*C*-Hex), 131.5 (*C*-C=O), 128.4 (*C*H phenyl), 127.2 (*C*H phenyl), 50.8 (*C*H-NH), 41.6 (C1), 35.8 (C4), 31.7 (C3), 31.2 (C5), 28.9 (C6), 27.2, (C7), 22.6 (C8), 21.1 (C2) and 14.1 (C9); υ_{max}/cm^{-1}: 3338, 3247 (NH), 2921 (C-H), 1656, 1637 (C=O) and 1562 (aromatic); ESI *m/z* 100 %, 325.2 (MNa^+) and 37% 303.2 (MH^+); HR ESI *m/z* ($C_{18}H_{26}N_2O_2Na$ requires 325.1886) found 325.1883; $[\alpha]^{23}_D$ (c = 0.511, $CHCl_3$) +79.55.

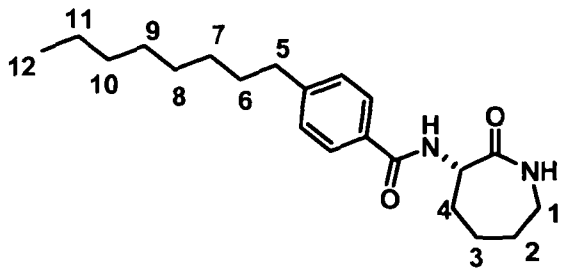
Example 24: (R)-3-(4'-Hexylbenzoylamino)-tetrahydropyridin-2-one



(*R*)-3-amino-tetrahydropyridin-2-one (10 mmoles) was dissolved in H_2O (20 mL) and cooled to 0°C. 4-Hexylbenzoyl chloride (1.2 mL, 5 mmoles) in dichloromethane was added and triethylamine (2.1 mL, 15 mmoles) and the reaction was stirred over night. The reaction was extracted with dichloromethane (3 × 15 mL), the organic layer was washed with a pH 2 buffer (3 × 15 mL), dried over Na_2SO_4 and reduced *in vacuo*. The product was purified by silica column chromatography (petroleum ether:ethyl acetate 50:50:0 to 0:80:20) to give the product as a white solid 0.53 g (35 %); *mp* 117-118 ° C; δ_H (400 MHz, $CDCl_3$) 7.71 (d, 2H, *J* 8, C*H*-C-Hex), 7.28 (d, 1H, *J* 5, N*H*-CH), 7.19 (d, 2H, *J* 8, C*H*-C-CO), 6.52 (br.s, 1H, N*H*-C1), 4.41 (dt, 1H, *J* 11.5, 5.5, C*H*-C3), 3.35-3.31 (m, 2H, H1), 2.67-2.60 (m, 1H, H3 equatorial), 2.61 (t, 2H, *J* 7.5, H4), 2.00-1.89 (m, 2H, H2), 1.67-1.54 (m, 3H, H3 equatorial & H5), 1.32-1.23 (m, 6H, H6, H7 & H8) and 0.85 (t, 3H, *J* 7, H9);); δ_C (100 MHz, $CDCl_3$) 172.1 (*C*=O lactam), 167.6 (*C*=O amide), 147.0 (*C*-Hex), 131.5 (*C*-C=O), 128.5 (*C*H phenyl), 127.2 (*C*H phenyl), 50.9 (*C*H-NH), 41.7 (C1), 35.8 (C4), 31.7 (C3), 31.2 (C5), 28.9 (C6), 27.2, (C7), 22.6 (C8),

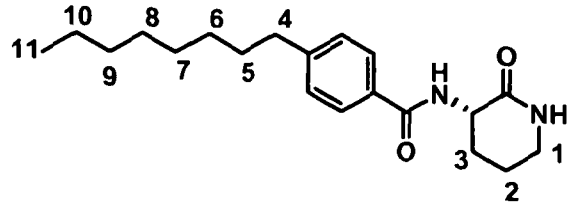
21.1 (C2) and 14.1 (C9); υ_{max}/cm^{-1}: 3328, 3240 (NH), 2954 (C-H), 1651, 1635 (C=O) and 1533 (aromatic); ESI *m/z* 100 %, 325.2 (MNa^+) and 33% 303.2 (MH^+); HR ESI *m/z* ($C_{18}H_{26}N_2O_2Na$ requires 325.1886) found 325.1888; $[\alpha]^{25}_D$ (c = 0.496, $CHCl_3$) -81.17.

Example 25: (S)-3-(4'-Octylbenzoylamino)-azepan-2-one



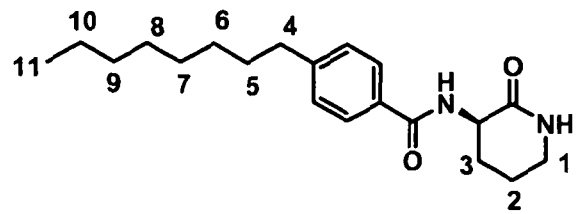
(*S*)-3-amino-azepan-2-one hydrochloride (0.91 g, 5.55 mmoles) was dissolved in H_2O (15 mL) and cooled to 0°C. The 4-octylbenzoyl chloride in dichloromethane was added and triethylamine (0.84 mL, 6 mmoles) and the reaction was stirred over night. H_2O (20 mL) was added and the reaction was extracted with dichloromethane (3 × 20 mL), the organic layer was washed with a pH 2 buffer (3 × 15 mL), dried over Na_2SO_4 and reduced *in vacuo*. The product was purified by silica column chromatography (petroleum ether:ethyl acetate 50:50:0 to 0:80:20) to give the product as a white solid 0.087 g (4 %); *mp* 159-160 ° C; δ_H (400 MHz, $CDCl_3$) 7.73 (d, 2H, *J* 8, C*H*-C-Oct), 7.64 (d, 1H, *J* 5.5, N*H*-CH), 7.20 (d, 2H, *J* 8, C*H*-C-CO), 6.94 (br.t, 1H, *J* 6, N*H*-C1), 4.68 (dd, 1H, *J* 11, 6, C*H*-C4), 3.35-3.20 (m, 2H, H1), 2.60 (t, 2H, *J* 7.5, H5), 2.19 (d, 1H, *J* 13, H4 equatorial), 2.00 (br.d, 1H, H3 equatorial), 1.92-1.79 (m, 3H, H2 & H3 axial), 1.62-1.46 (m, 3H, H4 axial & H6), 1.38 (q, 1H, *J* 11.5, H2 axial) 1.30-1.19 (m, 10H, H7, H8, H9, H10 & H11) and 0.84 (t, 3H, *J* 7.5, H12); δ_C (100 MHz, $CDCl_3$) 176.0 (*C*=O lactam), 166.3 (*C*=O amide), 146.9 (*C*-Oct), 131.6 (*C*-C=O), 128.5 (*C*H phenyl), 127.1 (*C*H phenyl), 52.5 (*C*H-NH), 42.1 (C1), 35.8 (C5), 31.9 (C4), 31.6 (C6), 31.2 (C7), 29.4, 29.3, 28.9, 28.0, (C2, C3, C8, C9 and C10), 22.7 (C11) and 14.1 (C12); υ_{max}/cm^{-1}: 3204 (NH indole), 2923 (C-H), 1637 (amide C=O) and 1544 (aromatic); ESI *m/z* 100 %, 345.2 (MH^+) and 9 %, 710.8 (M_2Na^+); HR ESI *m/z* ($C_{21}H_{32}N_2O_2Na$ requires 367.2356) found 367.2361; $[\alpha]^{25}_D$ (c = 0.124, $CDCl_3$) +68.01.

Example 26: (S)-3-(4'-Octylbenzoylamino)-tetrahydropyridin-2-one



(*S*)-3-amino-tetrahydropyridin-2-one (10 mmoles) was dissolved in H_2O (35 mL) and cooled to 0°C. 4-Octylbenzoyl chloride (2 mmoles) in dichloromethane was added and triethylamine (0.85 mL, 6 mmoles) and the reaction was stirred over night. The reaction was extracted with dichloromethane (3 × 10 mL), the organic layer was washed with a pH 2 buffer (3 × 10 mL), dried over Na_2SO_4 and reduced *in vacuo*. The product was purified by silica column chromatography (petroleum ether:ethyl acetate 50:50:0 to 0:80:20) to give the product as a white solid 0.55 g (83 %); *mp* 122-123 ° C; δ_H (400 MHz, $CDCl_3$) 7.71 (d, 2H, *J* 8, C*H*-C-Oct), 7.26 (d, 1H, *J* 5.5, N*H*-CH), 7.19 (d, 2H, *J* 8, C*H*-C-CO), 6.47 (br.s, 1H, N*H*-C1), 4.41 (dt, 1H, *J* 11.5, 5.5, C*H*-C3), 3.33-3.27 (m, 2H, H1), 2.84-2.58 (m, 1H, *J* 13, H3 equatorial obscured by H4), 2.60 (t, 2H, *J* 7.5, H4), 1.97-1.90 (m, 2H, H2), 1.67-1.54 (m, 3H, H3 axial & H5), 1.29-1.23 (m, 10H, H6, H7, H8, H9 & H10) and 0.86 (t, 3H, *J* 7, H11); δ_C (100 MHz, $CDCl_3$) 172.1 (*C*=O lactam), 167.6 (*C*=O amide), 147.0 (*C*-Oct), 131.5 (*C*-C=O), 128.5 (*C*H phenyl), 127.2 (*C*H phenyl), 50.9 (*C*H-NH), 41.7 (C1), 35.8 (C4), 31.9 (C5), 31.2 (C3), 29.4 (C6), 29.3 (C7, C8), 27.2 (C9), 22.3 (C10), 21.1 (C2) and 14.1 (C11); υ_{max}/cm^{-1}: 3240 (NH), 2921 (C-H), 1653, 1615 (C=O) and 1563 (aromatic); ESI *m/z* 100 %, 353.2 (MNa^+) and 47 %, 331.2 (MH^+); HR ESI *m/z* ($C_{20}H_{30}N_2O_2Na$ requires 353.2199) found 353.2198; $[\alpha]^{23}_D$ (c = 0.509, $CHCl_3$) +75.74.

Example 27: (R)-3-(4'-Octylbenzoylamino)-tetrahydropyridin-2-one



(*R*)-3-amino-tetrahydropyridin-2-one (5 mmoles) was dissolved in H_2O (25 mL) and cooled to 0°C. 4-Octylbenzoyl chloride (2 mmoles) in dichloromethane was added and triethylamine (0.85 mL, 6 mmoles) and the reaction was stirred over night. The reaction was extracted with dichloromethane (3 × 10 mL), the organic layer was washed with a pH 2 buffer (3 × 10 mL), dried over Na_2SO_4 and reduced *in vacuo*. The product was purified by silica column chromatography (petroleum ether:ethyl acetate 50:50:0 to 0:80:20) to give the product as a white solid 0.16 g (25 %); *mp* 122-123 ° C; δ_H (400 MHz, $CDCl_3$) 7.71 (d, 2H, *J* 8.5, C*H*-C-Oct), 7.23 (d, 1H, *J* 6.5, N*H*-CH), 7.20 (d, 2H, *J* 8.5, C*H*-C-CO), 6.34 (br.s, 1H, N*H*-C1), 4.41 (dt, 1H, *J* 11.5, 5.5, C*H*-C3), 3.37-3.33 (m, 2H, H1), 2.68 (ddt, 1H, *J* 13, 5.5, 4.5, H3 equatorial), 2.61 (t, 2H, *J* 7.5, H4), 1.98-1.91 (m, 2H, H2), 1.67-1.55 (m, 3H, H3 axial & H5), 1.31-1.22 (m, 10H, H6, H7, H8, H9 & H10) and 0.86 (t, 3H, *J* 7, H11); δ_C (100 MHz, $CDCl_3$) 172.1 (*C*=O lactam), 167.6 (*C*=O amide), 147.0 (*C*-Oct), 131.5 (*C*-C=O), 128.5 (*C*H phenyl), 127.2 (*C*H phenyl), 51.0 (*C*H-NH), 41.7 (C1), 35.8 (C4), 31.9 (C5), 31.2 (C3), 29.4 (C6), 29.3 (C7, C8), 27.2 (C9), 22.7 (C10), 21.1 (C2) and 14.1 (C11); ESI *m/z* 39 %, 353.2 (MNa^+), 19 %, 331.2 (MH^+) and 14 %, 682.7 (M_2Na^+); HR ESI *m/z* ($C_{20}H_{30}N_2O_2H^+$ requires 331.2380) found 331.2381; υ_{max}/cm^{-1}: 3250 (NH), 2955 (C-H), 1653 (C=O) and 1540 (aromatic); $[\alpha]^{23}_D$ (c = 0.485, $CHCl_3$) -77.80.

Pharmacological study of the products of the invention

A. Inhibition of MCP-1 induced leukocyte migration

Assay principle

The biological activity of the compounds of the current invention may be demonstrated using any of a broad range of functional assays of leukocyte migration in vitro, including but not limited to Boyden chamber and related transwell migration assays, under-agarose migration assays and direct visualisation chambers such as the Dunn Chamber.

For example, to demonstrate the inhibition of leukocyte migration in response to chemokines (but not other chemoattractants) the 96-well format micro transwell assay system from Neuroprobe (Gaithersburg, MD, USA) has been used. In principle, this assay consists of two chambers separated by a porous membrane. The chemoattractant is placed in the lower compartment and the cells are placed in the upper compartment. After incubation for a period at 37°C the cells move towards the chemoattractant, and the number of cells in the lower compartment is proportional to the chemoattractant activity (relative to a series of controls).

This assay can be used with a range of different leukocyte populations. For example, freshly prepared human peripheral blood leukocytes may used. Alternatively, leukocyte subsets may be prepared, including polymorphonuclear cells or lymphocytes or monocytes using methods well known to those skilled in the art such as density gradient centrifugation or magnetic bead separations. Alternatively, immortal cell lines which have been extensively validated as models of human peripheral blood leukocytes may be used, including, but not limited to THP-1 cells as a model of monocytes or Jurkat cells as model of naïve T cells.

Although a range of conditions for the assay are acceptible to demonstrate the inhibition of chemokine-induced leukocyte migration, a specific example is hereby provided.

Materials

The transwell migration systems are manufactured by Neuroprobe, Gaithersburg, MD, USA.

The plates used are ChemoTx plates (Neuroprobe 101-8) and 30 μl clear plates (Neuroprobe MP30).

Geys' Balanced Salt Solution is purchased from Sigma (Sigma G-9779).

Fatty acid-free BSA is purchased from Sigma (Sigma A-8806).

MTT, i.e. 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, is purchased from Sigma (Sigma M-5655).

RPMI-1640 without phenol red is purchased from Sigma (Sigma R-8755).

The THP-1 cell line (European Cell culture Collection) were used as the leukocyte cell population.

Test protocol

The following procedure is used for testing the invention compounds for MCP-1 induced leukocyte migration:

First, the cell suspension to be placed in the upper compartment is prepared. The THP-1 cells are pelleted by centrifugation (770 x g; 4 mins) and washed with Geys Balanced Salt Solution with 1mg/ml BSA (GBSS + BSA). This wash is then repeated, and the cells repelleted before being resuspended in a small volume of GBSS + BSA for counting, for example using a standard haemocytometer.

The volume of GBSS + BSA is then adjusted depending on the number of cells present so that the cells are at final density of 4.45×10^6 cells per ml of GBSS + BSA. This ensures that there are 100,000 THP-1 cells in each 25µl of the solution that will be placed in the upper chamber of the plate.

To test a single compound for its ability to inhibit MCP-1 induced migration, it is necessary to prepare two lots of cells. The suspension of THP-1 cells at 4.45×10^6 cells/ml is divided into two pots. To one pot the inhibitor under test is added at an appropriate final concentration, in an appropriate vehicle (for example at 1µM in not more than 1% DMSO). To the second pot an equal volume of GBSS + BSA plus vehicle as appropriate (e.g. not more than 1% DMSO) is added to act as a control.

Next, the chemoattractant solution to be placed in the lower compartment is prepared. MCP-1 is diluted in GBSS + BSA to give a final concentration of 25 ng/ml. This is divided into two pots, as for the cell suspension. To one pot, the test compound is added to the same final concentration as was added to the cell suspension, while to the

other pot an equal volume of GBSS + BSA plus vehicle as appropriate (e,g. not more than 1% DMSO) is added.

Note that the volume of liquid that needs to be added to make the addition of the text compound needs to be taken into account, when establishing the final concentration of MCP-1 in the solution for the lower compartment and the final concentration of cells in the upper compartment.

Once the chemoattractant solutions for the lower wells and cell solutions for the upper chambers have been prepared, the migration chamber should be assembled. Place 29 µl of the appropriate chemoattractant solution into the lower well of the chamber. Assays should be performed with at least triplicate determinations of each condition. Once all the lower chambers have been filled, apply the prous membrane to the chamber in accordance with the manufacturer's instructions. Finally, apply 25 µl of the appropriate cell solution to each upper chamber. A plastic lid is placed over the entire apparatus to prevent evaporation.

The assembled chamber is incubated at 37 °C, 5% CO_2, for 2 hours. A suspension of cells in GBSS + BSA is also incubated under identical conditions in a tube: these cells will be used to construct a standard curve for determining the number of cells that have migrated to the lower chamber under each condition.

At the end of the incubation, the liquid cell suspension is gently removed from the upper chamber, and 20µl of ice-cold 20mM EDTA in PBS is added to the upper chamber, and the apparatus is incubated at 4°C for 15 mins. This procedure causes any cells adhering to the underside of the membrane to fall into the lower chamber.

After this incubation the filter is carefully flushed with GBSS + BSA to wash off the EDTA, and then the filter is removed.

The number of cells migrated into the lower chamber under each condition can then be determined by a number of methods, including direct counting, labelling with fluorescent or radioactive markers or through the use of a vital dye. Typically, we utilise the vital dye MTT. 3 µl of stock MTT solution are added to each well, and then the plate is incubated at 37 °C for 1-2 hours during which time dehydrogenase

enzymes within the cells convert the soluble MTT to an insoluble blue formazan product that can be quantified spectrophotometrically.

In parallel, an 8-point standard curve is set up. Starting with the number of cells added to each upper chamber (100,000) and going down in 2-fold serial dilutions in GBSS + BSA, the cells are added to a plate in 25 µl, with 3 µl of MTT stock solution added. The standard curve plate is incubated along side the migration plate.

At the end of this incubation, the liquid is carefully removed from the lower chambers, taking care not to disturb the precipitated formazan product. After allowing to air dry briefly, 20µl of DMSO is added to each lower chamber to solubilise the blue dye, and absorbance at 595nm is determined using a 96-well plate reader. The absorbance of each well is then interpolated to the standard curve to estimate the number of cells in each lower chamber.

The MCP-1 stimulated migration is determined by subtracting the average number of cells that reached the lower compartment in wells where no MCP-1 was added from the average number of cells that reached the lower compartment where MCP-1 was present at 25ng/ml.

The impact of the test substance is calculated by comparing the MCP-1-induced migration which occurred in the presence or absence of various concentrations of the test substance. Typically, the inhibition of migration is expressed as a percentage of the total MCP-1 induced migration which was blocked by the presence of the compound. For most compounds, a dose-response graph is constructed by determining the inhibition of MCP-1 induced migration which occurs at a range of different compound concentrations (typically ranging from 1nM to 1µM or higher in the case of poorly active compounds). The inhibitory activity of each compound is then expressed as the concentration of compound required to reduce the MCP-1-induced migration by 50% (the ED_{50} concentration).

Results

The compounds of reference examples 1 to 14 were tested and were shown to have an ED_{50} of 100 nM or less in this test.

B. *In vivo* assay

The anti-inflammatory efficacy of an exemplary compound according to the present invention was tested using the murine sub-lethal endotoxemia model. This model has been widely used to demonstrate the anti-inflammatory effect of compounds *in vivo* – Fox *et al.*, 2009, J Med Chem. 52(11): 3591-3595.

Briefly, the method is as follows: Female CD1 mice (28-30g, ~7 weeks of age) were dosed with their respective treatment in sterile filtered 1% CMC by oral gavage in a dose volume of 10ml/kg one hour prior to an endotoxin (LPS) challenge. The endotoxin challenge was injected by the intraperitoneal route containing 675,000 Endotoxin Units of LPS (*E. coli* strain 0111:B4 (Code L4130)) in endotoxin free PBS. Mice were left for two hours and then exsanguinated under terminal anaesthesia and blood was taken. Serum was prepared from this terminal bleed and aliquoted and stored at -20°C. Serum TNF-α levels were measured by ELISA per manufacturers instructions (R and D Systems).

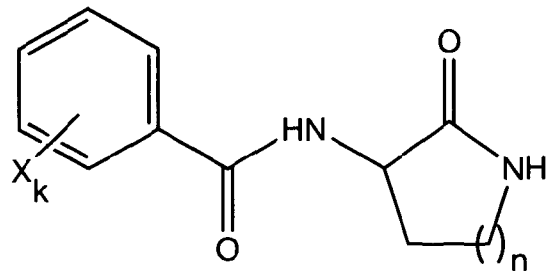
Eight animals were treated in each group, and the data for the animal with the highest and lowest TNF- α level in each group were eliminated, and the mean and standard error reported for the remaining six animals. Data for untreated animals were taken from an historical control experiment.

A single dose of (S)-4-Fluoro-N-(2-oxopiperidin-3-yl)benzamide (also known as (S)-3-(4'-fluorobenzoylamino)-tetrahydropyridin-2-one; see Example 3 above) administered by oral gavage, inhibited endotoxin-stimulated TNF-alpha levels by 50% (see Fig. 2, column B).

This experiment demonstrates that the compounds according to the invention have anti-inflammatory activity *in vivo*.

Claims

1. A compound of general formula (I), or a pharmaceutically acceptable salt thereof, for use in the treatment of an inflammatory disorder:



(I)

wherein

n is an integer from 1 to 4;

k is an integer from 0 to 5, representing the number of groups substituting C_2, C_3, C_4, C_5 and/or C_6 of the benzyl ring; and

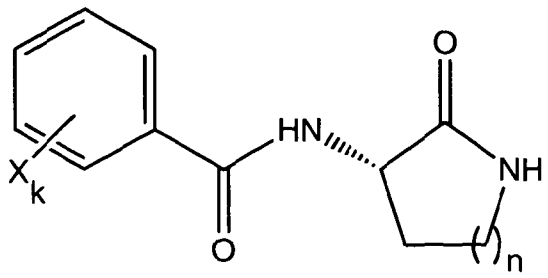
X are linear or branched groups substituting the benzyl ring independently selected from any one of the group consisting of: alkyl, haloalkyl, hydroxyalkyl, hydroxy, alkoxy, amino, aminoalkyl, aminodialkyl, carboxy, and halogen;

with the proviso that:

when on the benzyl ring C_2, C_5 and C_6 are unsubstituted, and C_4 is unsubstituted or is substituted with an hydroxy, alkoxy, amino, aminoalkyl, aminodialkyl, or halogen group, then C_3 is substituted with a halogen group; and

when on the benzyl ring C_2, C_5 and C_6 are unsubstituted, and C_3 is unsubstituted or is substituted with an alkyl, haloalkyl, hydroxyalkyl, hydroxy, alkoxy, amino, aminoalkyl, aminodialkyl or carboxy group, then C_4 is substituted with any one of the group consisting of: alkyl group, haloalkyl group, hydroxyalkyl group, and carboxy group.

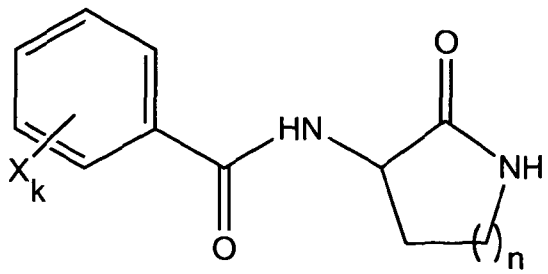
2. A compound of formula (I'), or a pharmaceutically acceptable salt thereof, for use in the treatment of an inflammatory disorder:



(I')

wherein n, k and X are defined as in claim 1.

3. Use of a compound of general formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of an inflammatory disorder:



(I)

wherein

n is an integer from 1 to 4;

k is an integer from 0 to 5, representing the number of groups substituting C_2, C_3, C_4, C_5 and/or C_6 of the benzyl ring; and

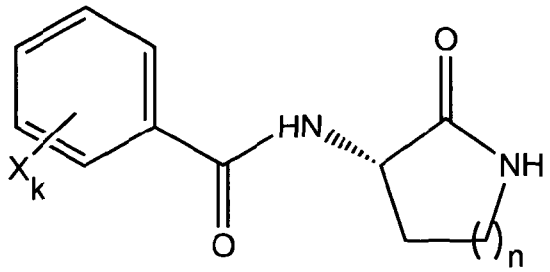
X are linear or branched groups substituting the benzyl ring independently selected from any one of the group consisting of: alkyl, haloalkyl, hydroxyalkyl, hydroxy, alkoxy, amino, aminoalkyl, aminodialkyl, carboxy, and halogen;

with the proviso that:

when on the benzyl ring C_2, C_5 and C_6 are unsubstituted, and C_4 is unsubstituted or is substituted with an hydroxy, alkoxy, amino, aminoalkyl, aminodialkyl, or halogen group, then C_3 is substituted with a halogen group; and

when on the benzyl ring C_2, C_5 and C_6 are unsubstituted, and C_3 is unsubstituted or is substituted with an alkyl, haloalkyl, hydroxyalkyl, hydroxy, alkoxy, amino, aminoalkyl, aminodialkyl or carboxy group, then C_4 is substituted with any one of the group consisting of: alkyl group, haloalkyl group, hydroxyalkyl group and carboxy group.

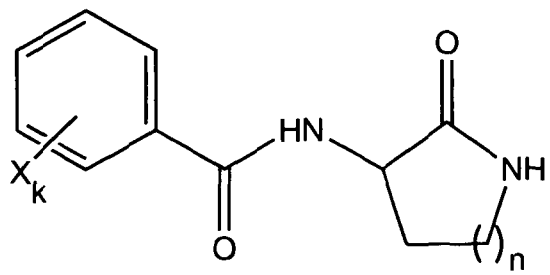
4. Use of a compound of formula (**I'**), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of an inflammatory disorder:



(I')

wherein n, k and X are defined as in claim 3.

5. A compound of general formula (**I**):



(I)

wherein

n is an integer from 1 to 4;

k is an integer from 1 to 5, representing the number of groups substituting C_2, C_3, C_4, C_5 and/or C_6 of the benzyl ring;

when n is 1 or 2, X are linear or branched groups independently selected from any one of the group consisting of: $C_{7\text{ or higher}}$ alkyl, haloalkyl with a $C_{7\text{ or higher}}$ alkyl group, hydroxyalkyl with a $C_{7\text{ or higher}}$ alkyl group, $C_{7\text{ or greater}}$ alkoxy, aminoalkyl with a $C_{4\text{ or higher}}$ alkyl group, aminodialkyl with two $C_{4\text{ or higher}}$ alkyl groups, and carboxy;

when n is 3 or 4, X are linear or branched groups independently selected from any one of the group consisting of: alkyl, haloalkyl, hydroxyalkyl, hydroxy, alkoxy, amino, aminoalkyl, aminodialkyl, carboxy, and halogen;

with the proviso that:

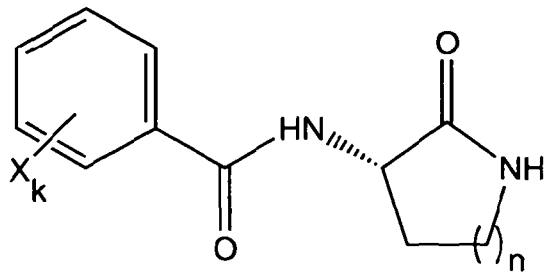
when n is 3 or 4 and on the benzyl ring C_2, C_5 and C_6 are unsubstituted, and C_4 is unsubstituted or is substituted with an hydroxy, alkoxy, amino, aminoalkyl, aminodialkyl, or halogen group, then C_3 is substituted with a halogen group;

when n is 3 or 4 and on the benzyl ring C_2, C_5 and C_6 are unsubstituted, and C_3 is unsubstituted or is substituted with an alkyl, haloalkyl, hydroxyalkyl, hydroxy, alkoxy, amino, aminoalkyl, aminodialkyl or carboxy group, then C_4 is substituted with any one of the group consisting of: alkyl group, haloalkyl group, hydroxyalkyl group, and carboxy group; and

when n=3, X is other than 4'-methoxy, 3'-trifluoromethyl, or 3',4',5'-trimethoxy,

provided that the compound is none of the group consisting of: 3-(3'-trifluoromethylbenzoylamino)-caprolactam, 3-(4'-methylbenzoylamino)-caprolactam, 3-(2'-aminobenzoylamino)-caprolactam, 3-(3',4'-dimethoxybenzoylamino)-caprolactam, 3-(3',5'-di-*tert*-butyl -4'- hydroxybenzoylamino)-caprolactam, 3-(2',4'-dimethoxybenzoylamino)-caprolactam, 3-(3'-methoxybenzoylamino)-caprolactam, 3-(4'-trifluoromethylbenzoylamino)-caprolactam, 3-(2',3',4'-trimethoxybenzoylamino)-caprolactam, 3-(2',6'-difluoromethylbenzoylamino)-caprolactam, 3-(2'-fluoromethylbenzoylamino)-caprolactam, 3-(2'-amino-3'-hydroxy-4'-methylbenzoylamino)-caprolactam, and 3-(3',5'-dimethylbenzoylamino)-caprolactam.

6. A compound of formula (**I'**):



(**I'**)

wherein n, k and X are defined as in either of claim 1 or claim 5,

provided that the compound is compound is none of the group consisting of: (S)-3-(4'-methoxybenzoylamino)-caprolactam, (S)-3-(4'-methylbenzoylamino)-caprolactam, (S)-3-(3'-trifluoromethylbenzoylamino)-caprolactam, (S)-3-(2'-carboxybenzoyl-amino)-caprolactam, and (S)-3-(3', 4',5'-trimethoxybenzoylamino)-caprolactam.

7. A pharmaceutical composition comprising, as active ingredient, a compound as defined in either of claims 5 or 6, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient and/or carrier.

8. The compound, use or composition according to any preceding claim, wherein n=2.

9. The compound, use or composition according to any preceding claim, wherein n=3.

10. The compound, use or composition according to any preceding claim, wherein X is haloalkyl, for example trifluoromethyl.

11. The compound according to claims 1 or 2, or the use according to claims 3 or 4, wherein the compound is selected from the group consisting of:

(S)-3-(4'-methylbenzoylamino)-caprolactam, and
(S)-3-(3',5'-dimethylbenzoylamino)-caprolactam,

and pharmaceutically acceptable salts thereof.

12. The compound according to any of claims 1, 2 or 6, or the use according to claims 3 or 4, wherein the compound is selected from the group consisting of:

(*S*)-3-Fluoro-N-(2-oxopiperidin-3-yl)benzamide,
(*S*)-2-Fluoro-N-(2-oxopiperidin-3-yl)benzamide,
(*S*)-4-Fluoro-N-(2-oxopiperidin-3-yl)benzamide,
(*S*)-N-(2-Oxopiperidin-3-yl)-4-(trifluoromethyl)benzamide,
(*S*)-N-(2-Oxopiperidin-3-yl)-3-(trifluoromethyl)benzamide,
(*S*)-N-(2-Oxopiperidin-3-yl)-2-(trifluoromethyl)benzamide,
(*S*)-2,3-difluoro-N-(2-oxopiperidin-3-yl)benzamide,
(*S*)-2,4-difluoro-N-(2-oxopiperidin-3-yl)benzamide,
(*S*)-2,5-difluoro-N-(2-oxopiperidin-3-yl)benzamide,
(*S*)-2,6-difluoro-N-(2-oxopiperidin-3-yl)benzamide,
(*S*)-3,4-difluoro-N-(2-oxopiperidin-3-yl)benzamide,
(*S*)-3,5-difluoro-N-(2-oxopiperidin-3-yl)benzamide,
(S)-3-(3'-Butylbenzoylamino)-azepan-2-one,
(S)-3-(4'-Ethylbenzoylamino)-tetrahydropyridin-2-one,
(S)-3-(4'-Butylbenzoylamino)-tetrahydropyridin-2-one,
(S)-3-(4'-tert-Butylbenzoylamino)-tetrahydropyridin-2-one, and
(S)-3-(4'-Hexylbenzoylamino)-tetrahydropyridin-2-one,

and pharmaceutically acceptable salts thereof.

13. The compound according to any of claims 1, 2, 5 or 6, or the use according to claims 3 or 4, wherein the compound is selected from the group consisting of:

(S)-3-(4'-Ethylbenzoylamino)-azepan-2-one,
(S)-3-(4'-Butylbenzoylamino)-azepan-2-one,
(S)-3-(4'-*tert*-Butylbenzoylamino)-azepan-2-one,
(S)-3-(4'-Hexylbenzoylamino)-azepan-2-one,
(S)-3-(4'-Octylbenzoylamino)-azepan-2-one, and
(S)-3-(4'-Octylbenzoylamino)-tetrahydropyridin-2-one,

and pharmaceutically acceptable salts thereof.

14. The compound according to claim 1, or the use according to claim 3, wherein the compound is selected from the group consisting of:

(R)-3-(4'-Butylbenzoylamino)-tetrahydropyridin-2-one,
(R)-3-(4'-*tert*-Butylbenzoylamino)-tetrahydropyridin-2-one, and
(R)-3-(4'-Hexylbenzoylamino)-tetrahydropyridin-2-one,

and pharmaceutically acceptable salts thereof.

15. The compound according to either of claim 1 or claim 5, or the use according to claim 3, wherein the compound is (R)-3-(4'-Octylbenzoylamino)-tetrahydropyridin-2-one or a pharmaceutically acceptable salt thereof.

16. The compound according to either of claims 1 or 2 or the use according to either of claims 3 or 4, wherein the inflammatory disorder is selected from the group consisting of autoimmune diseases, asthma, rheumatoid arthritis, a disorder characterised by an elevated TNF-α level, psoriasis, allergies, multiple sclerosis, fibrosis (including diabetic nephropathy), and formation of adhesions.

17. The compound or use according to claim 16, wherein the inflammatory disorder is formation of adhesions.

18. The compound or use according to claim 16 or claim 17, wherein the compound is administered locally.

19. A method of treatment, amelioration or prophylaxis of the symptoms of an inflammatory disease (including an adverse inflammatory reaction to any agent) by the administration to a patient of an anti-inflammatory amount of a compound, pharmaceutical composition or medicament as defined in any preceding claim.

20. A library consisting of elements all of which have structures according to the formula (**I**) or (**I'**) as defined in any of claims 1to 18, and hence which all have anti-inflammatory activity, useful for screening compounds for novel or improved properties in a particular assay of anti-inflammatory activity.

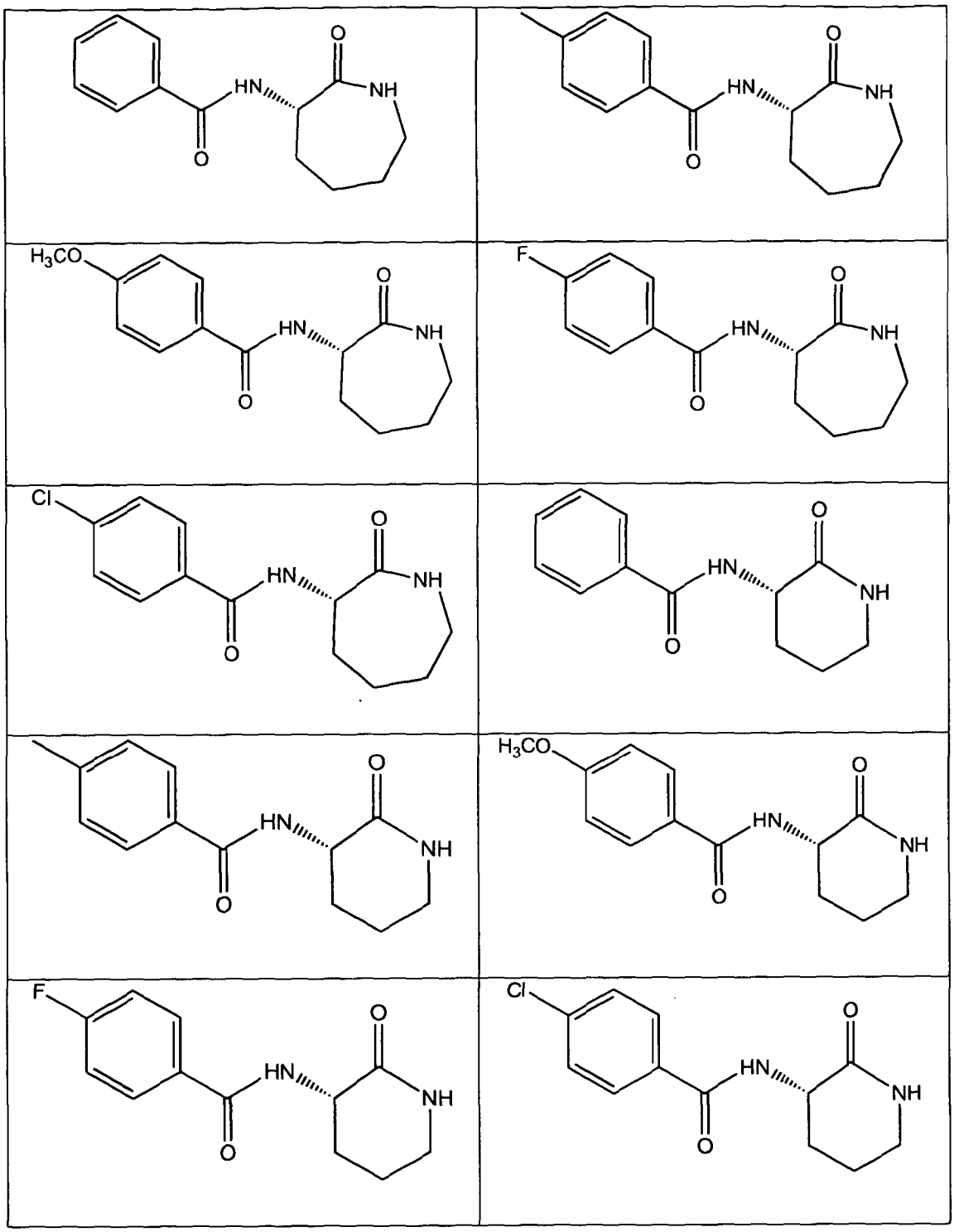


Fig. 1

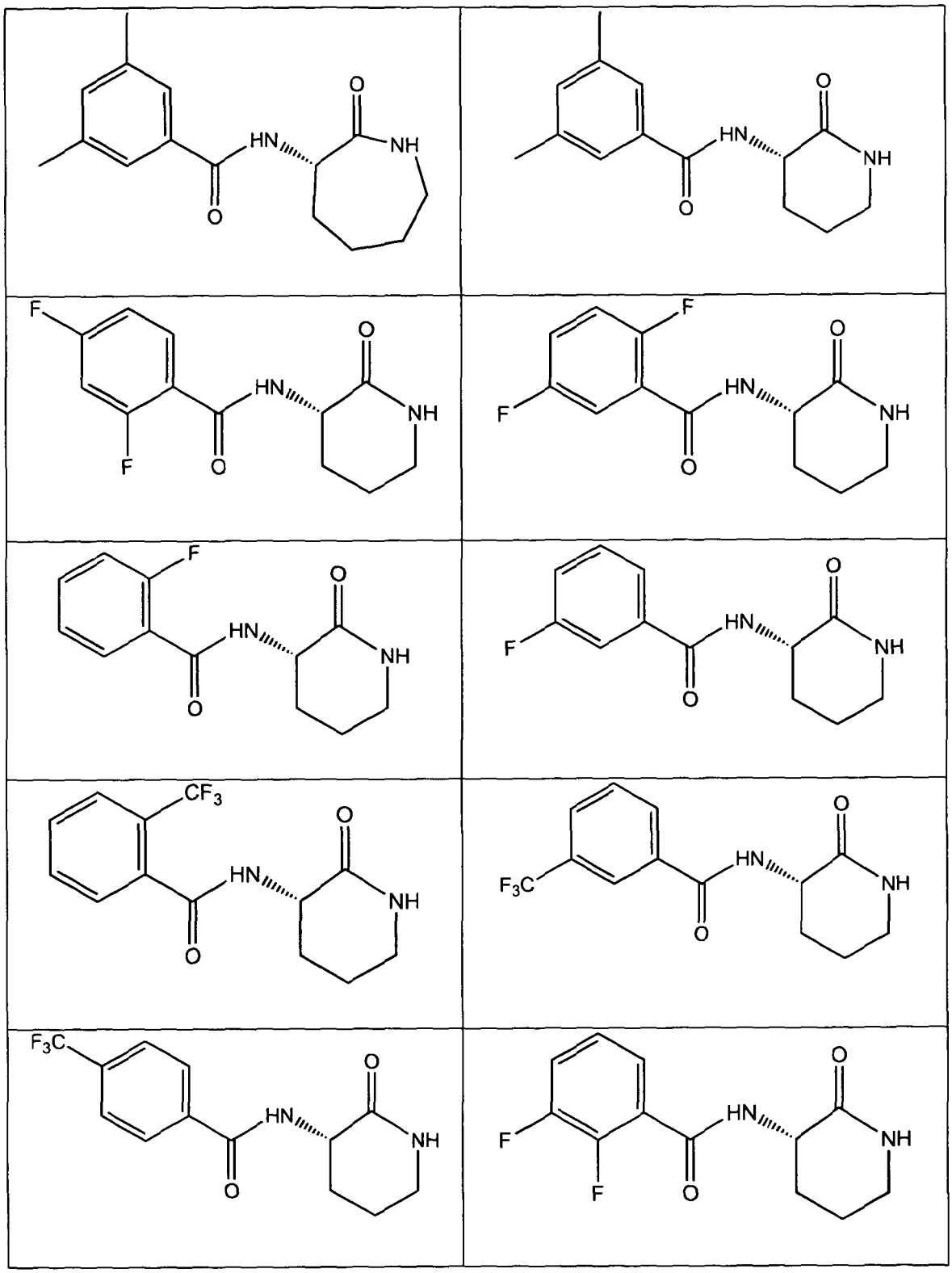


Fig. 1 (cont.)

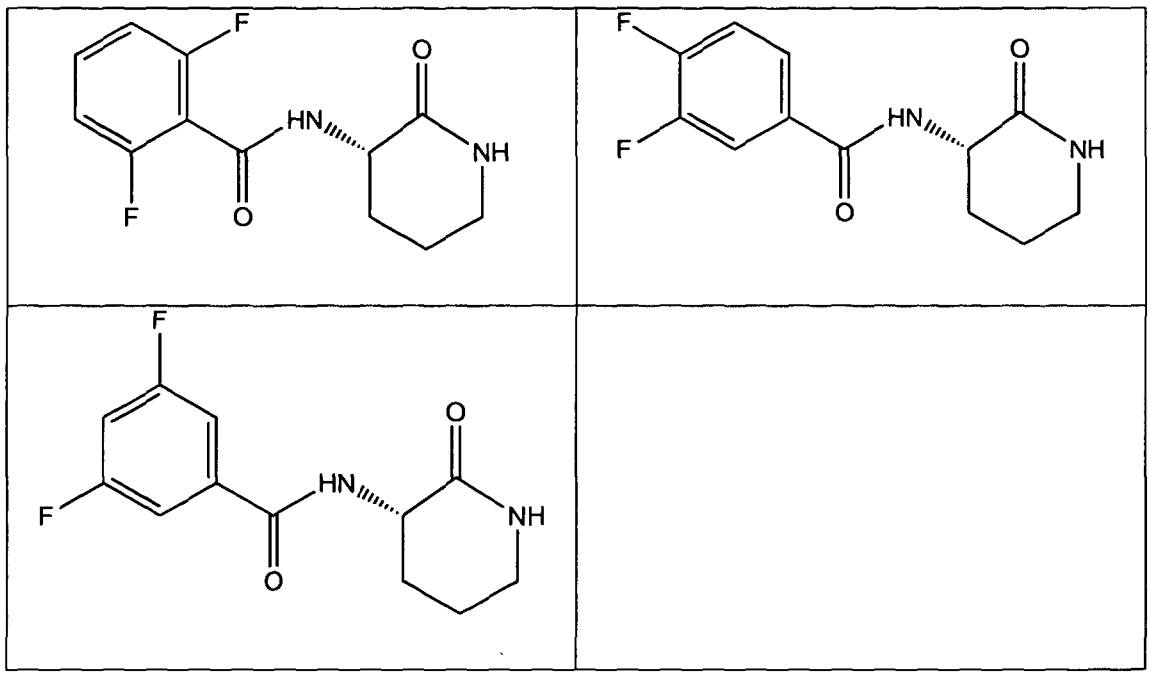


Fig. 1 (cont.)

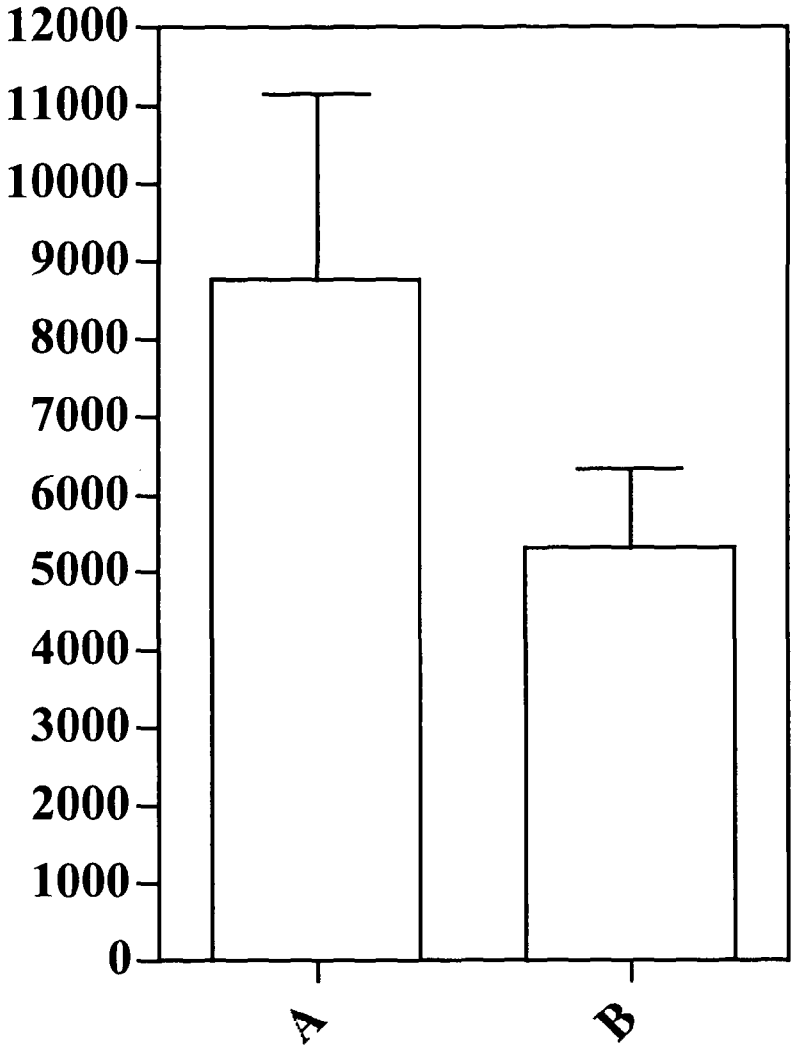

12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
A
B

Fig. 2

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2011/000863

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D211/56 C07D223/12 C07D401/12 A61K31/4523 A61K31/45
A61K31/55 A61P29/00 A61P37/00 A61P17/06
ADD.
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)
C07D

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, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2005/053702 A2 (UNIV CAMBRIDGE TECH [GB]; GRAINGER DAVID JOHN [GB]; FOX DAVID JOHN [GB]) 16 June 2005 (2005-06-16) cited in the application Claims, pages 1 and 10 and examples	1-20
A	WO 2006/016152 A1 (UNIV CAMBRIDGE TECH [GB]; GRAINGER DAVID JOHN [GB]; FOX DAVID JOHN [GB]) 16 February 2006 (2006-02-16) cited in the application Claims, pages 1 and 9 and examples	1-20
A	WO 2006/134385 A2 (UNIV CAMBRIDGE TECH [GB]; GRAINGER DAVID JOHN [GB]; FOX DAVID JOHN [GB]) 21 December 2006 (2006-12-21) cited in the application Claims, pages 1 and 9 and examples	1-20

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family 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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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 August 2011	16/08/2011

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Lécaillon, Jennifer

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INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2011/000863

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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A	FOX D J ET AL: "Highly potent, orally available anti-inflammatory broad-spectrum chemokine inhibitors", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 52, no. 11, 11 June 2009 (2009-06-11) , pages 3591-3595, XP002579389, ISSN: 0022-2623, DOI: DOI:10.1021/JM900133W [retrieved on 2009-05-08] the whole document	1-20
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A	Compounds 13-16 and 21	1-5,8,9, 11-19

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INTERNATIONAL SEARCH REPORT

International application No
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A	Compounds 2d, 2e, 2f, 2i, 10a, 10b and 15a	1-4,6-8, 10-19

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A	Compound 3 and page 440 last paragraph	1-4,6-8, 10-19

X	PAQUET A ET AL: "Synthesis of conjugates of 3-hydroxy- and 3-phenoxybenzoic acid", JOURNAL OF ENVIRONMENTAL SCIENCES AND HEALTH B: PESTICIDES, TAYLOR AND FRANCIS GROUP, XX, vol. B28, no. 2, 1 January 1993 (1993-01-01), pages 171-191, XP009150354, ISSN: 0360-1234	6,8,20
A	Compounds 22, 23 and 25	1-5,7, 9-19

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International application No
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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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A	Footnote ** page 1350 (preparation of 3-Benzoylamino-L-piperidin-2-one)	1-5,7-19
A	UCHIKAWA O ET AL: "IN VIVO BIOLOGICAL ACTIVITY OF ANTIOXIDATIVE AMINOTHIAZOLE DERIVATIVES", CHEMICAL AND PHARMACEUTICAL BULLETIN, PHARMACEUTICAL SOCIETY OF JAPAN, TOKYO, JP, vol. 44, no. 11, 1 January 1996 (1996-01-01), pages 2070-2077, XP001247776, ISSN: 0009-2363 cited in the application Compounds 4a, 5a, 5c and 6a	1-20
A	EP 0 462 949 A1 (SIGMA TAU IND FARMACEUTI [IT]) 27 December 1991 (1991-12-27) cited in the application Examples 8, 9, 10 and 15	1-20
A	KAMEDA ET AL.: "Synthesis of Actinomycin Related Compounds I", CHEMICAL AND PHARMACEUTICAL BULLETIN, vol. 16, no. 3, 1968, pages 480-485, XP002655823, cited in the application Table II 4th entry	1-20

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International application No
PCT/GB2011/000863

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