BENZOTRIAZEPINES AS GASTRIN AND CHOLECYSTOKININ RECEPTOR LIGANDS

This application claims priority from U.K. patent application Nos. 0127262.4 and 0219051.0, the entire contents of which are hereby incorporated by reference.

This invention relates to gastrin and cholecystokinin (CCK) receptor ligands. (The receptor previously known as the CCK_B/gastrin receptor is now termed the CCK_2 receptor). The invention also relates to methods for preparing such ligands and to compounds which are useful intermediates in such methods. The invention further relates to pharmaceutical compositions comprising such ligands and methods for preparing such pharmaceutical compositions.

Gastrin and the cholecystokinins are structurally related neuropeptides which exist in gastrointestinal tissue and the central nervous system (Mutt V., *Gastrointestinal Hormones*, Glass G.B.J., ed., Raven Press, New York, p. 169; Nisson G., *ibid.*, p. 127).

Gastrin is one of the three primary stimulants of gastric acid secretion. Several forms of gastrin are found including 34-, 17- and 14-amino acid species with the minimum active fragment being the C-terminal tetrapeptide (TrpMetAspPhe-NH_2) which is reported in the literature to have full pharmacological activity (Tracy H.J. and Gregory R.A., *Nature* (London), 1964, **204**, 935). Much effort has been devoted to the synthesis of analogues of this tetrapeptide (and the N-protected derivative Boc-TrpMetAspPhe-NH_2) in an attempt to elucidate the relationship between structure and activity.

Natural cholecystokinin is a 33 amino acid peptide (CCK-33), the C-terminal 5 amino acids of which are identical to those of gastrin. Also found naturally is the C-terminal octapeptide (CCK-8) of CCK-33.

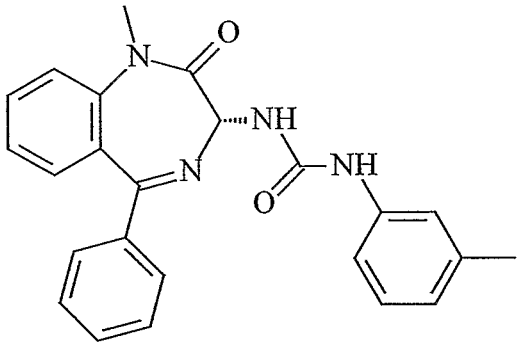
The cholecystokinins are reported to be important in the regulation of appetite. They stimulate intestinal mobility, gall bladder contraction, pancreatic enzyme secretion and are known to have a trophic action on the pancreas. They also inhibit gastric emptying and have various effects in the central nervous system.

Compounds which bind to cholecystokinin and/or gastrin receptors are important because of their potential pharmaceutical use as antagonists, inverse agonists or partial agonists of the natural peptides. Such compounds are described herein as ligands. The term ligand as used herein means either an antagonist, partial or full agonist, or an inverse agonist. Usually, the term ligand refers to an antagonist.

A number of gastrin ligands have been proposed for various therapeutic applications, including the prevention of gastrin-related disorders including gastrointestinal ulcers, dyspepsia, reflux oesophagitis (gastroesophageal reflux disease (GERD), both erosive and non-erosive) by reduction in gastric acid secretion and/or improving impaired motor activity at the lower oesophageal sphincter, Zollinger-Ellison syndrome, Barrett's oesophagus (specialized intestinal metaplasia of distal oesophagus), ECL cell hyperplasia, rebound hypersecretion (following cessation of anti-secretory therapy), ECL-derived gastric polyps most commonly found in patients with atrophic gastritis both with (pernicious anaemia) or without vitamin B12 deficiency, antral G cell hyperplasia and other conditions in which lower gastrin activity or lower acid secretion is desirable. The hormone has also been shown to have a trophic action on cells and so an antagonist may be expected to be useful in the treatment of cancers, particularly in the GI tract, more particularly in the stomach, oesophagus and colo-rectal areas. Tumours found in other organs such as the pancreas, lung (small cell lung carcinomas) and thyroid (thyroid medullary tumours) may also be treated.

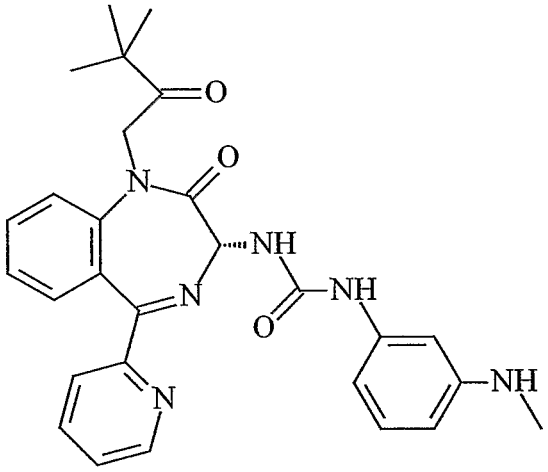
Other possible uses are in the potentiation of opiate (for example morphine) analgesia. Moreover, ligands for cholecystokinin receptors in the brain (so-called CCK_2 receptors) have been claimed to possess anxiolytic activity.

A known antagonist of the CCK_2 receptor is L-365,260 (M.G. Bock *et al.*, *J. Med Chem.*, 1989, *32*, 13-16), which is based on a benzodiazepine structure. In the rat stomach assay described hereinbelow, L-365,260 was shown to have an affinity of $pK_B = 7.61 \pm 0.12$ for the CCK_2 receptor (S.B. Kalindjian *et al.*, *J. Med. Chem.*, 1994, *37*, 3671-3).



L-365,260

More recently, another benzodiazepine, YF476, was developed as a potent CCK_2 antagonist (A. Nishida *et al.*, *Journal of Pharmacology and Experimental Therapeutics*, 1994, *269*, 725-731). In rat cortical membranes, YF476 was found to have an affinity pK_i of 10.17±0.03 for the CCK_2 receptor.



YF476

L-365,260 and YF476 are structurally closely related. Both compounds are 1,4-benzodiazepines. The carbon at position three of these 1,4-benzodiazepines is a chiral centre. In both cases, the optimal compounds have an *R*-configuration at this centre. Indeed, all 1,4-benzodiazepines that have found utility as gastrin antagonists have a chiral centre on the diazepine ring, and it has been found that better gastrin receptor antagonism is exhibited by one configuration relative to the other.

The requirement for a single enantiomer of the known 1,4-benzodiazepine gastrin ligands is undesirable. The synthesis of single enantiomers from achiral precursors, as in these

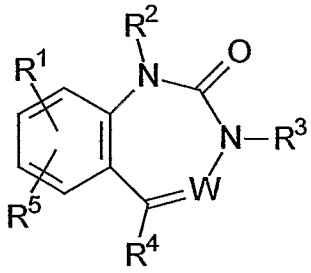
cases, is a costly and relatively complex procedure. This generally requires, for example, either a separation step, usually inefficient as one enantiomer is discarded, or the use of an often expensive chiral auxiliary during the synthesis, coupled with an increase in chemical steps. For these reasons, a drug candidate with no stereocentres on the seven-membered ring would offer a distinct advantage over chiral alternatives.

US 5,091,381 describes benzotriazepines which are said to bind to peripheral benzodiazepine receptors.

EP-A-0645378 describes a class of bicyclic compounds which are said to inhibit squalene synthetase.

It is an object of the present invention to provide potent and selective gastrin and CCK receptor ligands. It is a further object of the present invention to provide gastrin and CCK receptor ligands which have no chiral centre on the 7-membered ring and which can therefore be prepared using straightforward synthetic methods.

According to the present invention, there is provided the use of compounds of formula (I):



(I)

wherein:

W is N or N^+-O^-;

R^1 and R^5 are independently H, C_1 to C_6 alkyl, (C_1 to C_6 alkyl)oxy, thio, (C_1 to C_6 alkyl)thio, carboxy, carboxy(C_1 to C_6 alkyl), formyl, (C_1 to C_6 alkyl)carbonyl, (C_1 to C_6 alkyl)oxycarbonyl, (C_1 to C_6 alkyl)carbonyloxy, nitro, trihalomethyl, hydroxy, hydroxy(C_1 to C_6 alkyl), amino, (C_1 to C_6 alkyl)amino, di(C_1 to C_6 alkyl)amino, aminocarbonyl, halo, halo(C_1 to C_6 alkyl), aminosulfonyl, (C_1 to C_6 alkyl)sulfonylamino, (C_1 to C_6 alkyl)aminocarbonyl, di(C_1 to C_6 alkyl)aminocarbonyl, [*N*-Z](C_1 to C_6

alkyl)carbonylamino, formyloxy, formamido, (C_1 to C_6 alkyl)aminosulfonyl, di(C_1 to C_6 alkyl)aminosulfonyl, [*N*-Z](C_1 to C_6 alkyl)sulfonylamino or cyano; or R^1 and R^5 together form a methylenedioxy group;

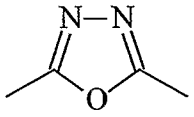
R^2 is H or an optionally substituted C_1 to C_{18} hydrocarbyl group wherein up to three C atoms may optionally be replaced by N, O and/or S atoms.

R^3 is $-(CR^{11}R^{12})_m-X-(CR^{13}R^{14})_p-R^9$;

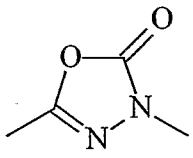
m is 0, 1, 2, 3 or 4;

p is 0, 1 or 2;

X is a bond, $-CR^{15}=CR^{16}-$, -C≡C-, C(O)NH, NHC(O), C(O)NMe, NMeC(O), C(O)O, NHC(O)NH, NHC(O)O, OC(O)NH, NH, O, CO, SO_2, SO_2NH, C(O)NHNH,



or



R^9 is H; C_1 to C_6 alkyl; or phenyl, naphthyl, pyridyl, benzimidazolyl, indazolyl, quinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, indolinyl, isoindolinyl, indolyl, isoindolyl or 2-pyridonyl, all optionally substituted with 1, 2 or 3 groups independently selected from

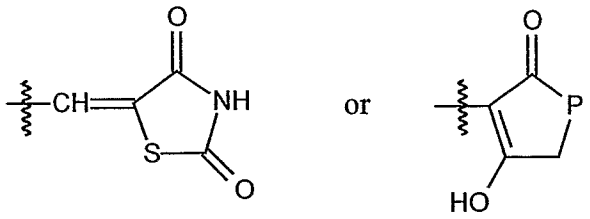
-L-Q

wherein:

L is a bond, or a group of the formula $-(CR^{17}R^{18})_v-Y-(CR^{17}R^{18})_w$, wherein v and w are independently 0, 1, 2 or 3, and Y is a bond, $-CR^{15}=CR^{16}-$, phenyl, furanyl, thiophenyl, pyrrolyl, thiazolyl, imidazolyl, oxazolyl, isoxazolyl, pyrazolyl, isoxazolonyl, piperazinyl, piperidinyl, morpholinyl, pyrrolidinyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, pyridyl or pyridazyl; and

Q is H, (C_1 to C_6 alkyl)oxy, [*N*-Z](C_1 to C_6 alkyl)oxy(C_1 to C_6 alkyl)amino, thio, (C_1 to C_6 alkyl)thio, carboxy(C_1 to C_6 alkyl)thio, carboxy, carboxy(C_1 to C_6 alkyl), carboxy(C_1 to C_6 alkenyl), [*N*-Z]carboxy(C_1 to C_6 alkyl)amino, carboxy(C_1 to C_6 alkyl)oxy, formyl, (C_1 to C_6 alkyl)carbonyl, (C_1 to C_6 alkyl)oxycarbonyl, (C_1 to C_6 alkyl)carbonyloxy, nitro, trihalomethyl, hydroxy, amino, [*N*-Z](C_1 to C_6 alkyl)amino, aminocarbonyl, (C_1 to C_6 alkyl)aminocarbonyl, di(C_1 to C_6 alkyl)aminocarbonyl, [*N*-Z](C_1 to C_6 alkyl)carbonylamino, C_5 to C_8 cycloalkyl, [*N*-Z](C_1 to C_6 alkyl)carbonyl(C_1 to C_6 alkyl)amino, halo, halo(C_1 to C_6 alkyl), sulfamoyl, [*N*-Z](C_1 to C_6 alkyl)sulfonylamino, (C_1 to C_6 alkyl)sulfonylaminocarbonyl, carboxy(C_1 to C_6 alkyl)sulfonyl, carboxy(C_1 to C_6

alkyl)sulfinyl, tetrazolyl, [*N*-Z]tetrazolylamino, cyano, amidino, amidinothio, SO_3H, formyloxy, formamido, C_3 to C_8 cycloalkyl, (C_1 to C_6 alkyl)sulphamoyl, di(C_1 to C_6 alkyl)sulphamoyl, (C_1 to C_6 alkyl)carbonylaminosulfonyl, 5-oxo-2,5-dihydro[1,2,4]oxadiazolyl, carboxy(C_1 to C_6 alkyl)carbonylamino, tetrazolyl(C_1 to C_6 alkyl)thio, [*N*-Z]tetrazolyl(C_1 to C_6 alkyl)amino, 5-oxo-2,5-dihydro[1,2,4]thiadiazolyl, 5-oxo-1,2-dihydro[1,2,4]triazolyl, [*N*-Z](C_1 to C_6 alkyl)amino(C_1 to C_6 alkyl)amino, or a group of the formula



wherein P is O, S or NR^{19};

Z is H, C_1 to C_6 alkyl, t-butoxycarbonyl, acetyl, benzoyl or benzyl;

R^4 is an optionally substituted C_1 to C_{18} hydrocarbyl group wherein up to three C atoms may optionally be replaced by N, O and/or S atoms;

R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{17}, R^{18} and R^{19} are independently H or C_1 to C_3 alkyl; and

R^{16} is H, C_1 to C_3 alkyl, or acetylamino;

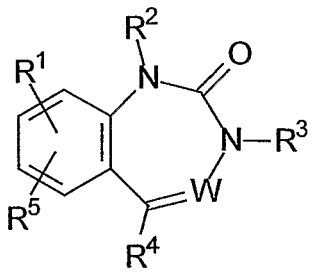
or a pharmaceutically acceptable salt thereof;

for the preparation of a medicament for the treatment of gastrin related disorders.

Preferably, W is N.

Typical gastrin related disorders are gastrointestinal ulcers, dyspepsia, reflux oesophagitis (gastroesophageal reflux disease (GERD), both erosive and non-erosive), Zollinger-Ellison syndrome, Barrett's oesophagus (specialized intestinal metaplasia of distal oesophagus), ECL cell hyperplasia, rebound hypersecretion (following cessation of anti-secretory therapy), ECL-derived gastric polyps, cancers of the GI tract, more particularly in the stomach, oesophagus and colo-rectal areas, as well as tumours found in other organs such as the pancreas, lung (small cell lung carcinomas) and thyroid (thyroid medullary tumours) and anxiety. The potentiation of opiate induced analgesia may also provide a role for the gastrin ligands of the present invention.

Further, the present invention provides compounds of formula (IIa)



(IIa)

wherein:

W is N or N^+-O^-;

R^1 and R^5 are independently H, C_1 to C_6 alkyl, (C_1 to C_6 alkyl)oxy, thio, (C_1 to C_6 alkyl)thio, carboxy, carboxy(C_1 to C_6 alkyl), formyl, (C_1 to C_6 alkyl)carbonyl, (C_1 to C_6 alkyl)oxycarbonyl, (C_1 to C_6 alkyl)carbonyloxy, nitro, trihalomethyl, hydroxy, hydroxy(C_1 to C_6 alkyl), amino, (C_1 to C_6 alkyl)amino, di(C_1 to C_6 alkyl)amino, aminocarbonyl, halo, halo(C_1 to C_6 alkyl), aminosulfonyl, (C_1 to C_6 alkyl)sulfonylamino, (C_1 to C_6 alkyl)aminocarbonyl, di(C_1 to C_6 alkyl)aminocarbonyl, [*N*-Z](C_1 to C_6 alkyl)carbonylamino, formyloxy, formamido, (C_1 to C_6 alkyl)aminosulfonyl, di(C_1 to C_6 alkyl)aminosulfonyl, [*N*-Z](C_1 to C_6 alkyl)sulfonylamino or cyano; or R^1 and R^5 together form a methylenedioxy group;

R^2 is -$(CH_2)_s$-C(O)-$(CH_2)_t$-R^8

s is 0, 1, 2 or 3;

t is 0, 1, 2 or 3;

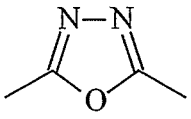
R^8 is selected from H, OH, C_1 to C_{12} alkyl, (C_1 to C_{12} alkyl)oxy, C_3 to C_{12} cycloalkyl, phenyl, naphthyl, pyridyl, pyrrolyl, imidazolyl, pyrazolyl, pyridazinyl, pyrimidinyl, triazolyl, furanyl, thienyl, furazanyl, oxazolyl, isoxazolyl, thiazolyl, thiazinyl, indolyl, indolinyl, isoindolyl, isoindolinyl, isoquinolinyl, quinolinyl, benzofuranyl, benzothienyl, piperazinyl, piperidinyl, pyrrolidinyl, pyrrolinyl, dihydropyranyl, tetrahydropyranyl, pyranyl, tetrahydrofuranyl, morpholinyl, thiazolidinyl, thiomorpholinyl or thioxanyl (all optionally substituted with 1, 2 or 3 groups independently selected from C_1 to C_6 alkyl, (C_1 to C_6 alkyl)oxy, thio, (C_1 to C_6 alkyl)thio, carboxy, carboxy(C_1 to C_6 alkyl), formyl, (C_1 to C_6 alkyl)carbonyl, (C_1 to C_6 alkyl)oxycarbonyl, (C_1 to C_6 alkyl)carbonyloxy, nitro, trihalomethyl, hydroxy, hydroxy(C_1 to C_6 alkyl), amino, (C_1 to C_6 alkyl)amino, di(C_1 to C_6 alkyl)amino, aminocarbonyl, halo, halo(C_1 to C_6 alkyl), aminosulfonyl, (C_1 to C_6 alkyl)sulfonylamino or cyano);

R^3 is -$(CR^{11}R^{12})_m$-X-$(CR^{13}R^{14})_p$-R^9;

m is 0, 1, 2, 3 or 4 (preferably 1 or 2);

p is 0, 1 or 2;

X is a bond, -CR^{15}=CR^{16}-, -C≡C-, C(O)NH, NHC(O), C(O)NMe, NMeC(O), C(O)O, NHC(O)NH, NHC(O)O, OC(O)NH, NH, O, CO, SO_2, SO_2NH, C(O)NHNH,



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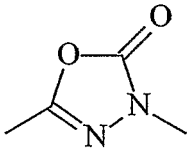


R^9 is H; C_1 to C_6 alkyl; or phenyl, naphthyl, pyridyl, benzimidazolyl, indazolyl, quinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, indolinyl, isoindolinyl, indolyl, isoindolyl or 2-pyridonyl, all optionally substituted with 1, 2 or 3 groups independently selected from

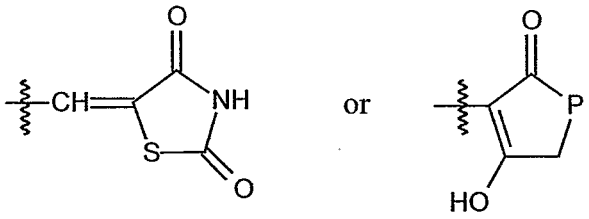
-L-Q

wherein:

L is a bond, or a group of the formula -$(CR^{17}R^{18})_v$-Y-$(CR^{17}R^{18})_w$, wherein v and w are independently 0, 1, 2 or 3, and Y is a bond, -CR^{15}=CR^{16}-, phenyl, furanyl, thiophenyl, pyrrolyl, thiazolyl, imidazolyl, oxazolyl, isoxazolyl, pyrazolyl, isoxazolonyl, piperazinyl, piperidinyl, morpholinyl, pyrrolidinyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, pyridyl or pyridazyl; and

Q is H, (C_1 to C_6 alkyl)oxy, [*N*-Z](C_1 to C_6 alkyl)oxy(C_1 to C_6 alkyl)amino, thio, (C_1 to C_6 alkyl)thio, carboxy(C_1 to C_6 alkyl)thio, carboxy, carboxy(C_1 to C_6 alkyl), carboxy(C_1 to C_6 alkenyl), [*N*-Z]carboxy(C_1 to C_6 alkyl)amino, carboxy(C_1 to C_6 alkyl)oxy, formyl, (C_1 to C_6 alkyl)carbonyl, (C_1 to C_6 alkyl)oxycarbonyl, (C_1 to C_6 alkyl)carbonyloxy, nitro, trihalomethyl, hydroxy, amino, [*N*-Z](C_1 to C_6 alkyl)amino, aminocarbonyl, (C_1 to C_6 alkyl)aminocarbonyl, di(C_1 to C_6 alkyl)aminocarbonyl, [*N*-Z](C_1 to C_6 alkyl)carbonylamino, C_5 to C_8 cycloalkyl, [*N*-Z](C_1 to C_6 alkyl)carbonyl(C_1 to C_6 alkyl)amino, halo, halo(C_1 to C_6 alkyl), sulfamoyl, [*N*-Z](C_1 to C_6 alkyl)sulfonylamino, (C_1 to C_6 alkyl)sulfonylaminocarbonyl, carboxy(C_1 to C_6 alkyl)sulfonyl, carboxy(C_1 to C_6 alkyl)sulfinyl, tetrazolyl, [*N*-Z]tetrazolylamino, cyano, amidino, amidinothio, SO_3H, formyloxy, formamido, C_3 to C_8 cycloalkyl, (C_1 to C_6 alkyl)sulphamoyl, di(C_1 to C_6 alkyl)sulphamoyl, (C_1 to C_6 alkyl)carbonylaminosulfonyl, 5-oxo-2,5-dihydro[1,2,4]oxadiazolyl, carboxy(C_1 to C_6 alkyl)carbonylamino, tetrazolyl(C_1 to C_6 alkyl)thio, [*N*-Z]tetrazolyl(C_1 to C_6 alkyl)amino, 5-oxo-2,5-dihydro[1,2,4]thiadiazolyl, 5-

oxo-1,2-dihydro[1,2,4]triazolyl, [*N*-Z](C_1 to C_6 alkyl)amino(C_1 to C_6 alkyl)amino, or a group of the formula



wherein P is O, S or NR^{19};

Z is H, C_1 to C_6 alkyl, t-butoxycarbonyl, acetyl, benzoyl or benzyl;

R^4 is an optionally substituted C_1 to C_{18} hydrocarbyl group wherein up to three C atoms may optionally be replaced by N, O and/or S atoms;

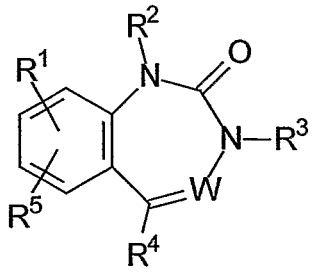
R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{17}, R^{18} and R^{19} are independently H or C_1 to C_3 alkyl; and

R^{16} is H, C_1 to C_3 alkyl, or acetylamino;

or a pharmaceutically acceptable salt thereof;

with the proviso that R^2 is not CH_2CO_2H or $C(O)CH_3$ when R^4 is phenyl.

Further, the present invention provides compounds of formula (IIb)



(IIb)

wherein:

W is N or N^+-O^-;

R^1 and R^5 are independently H, C_1 to C_6 alkyl, (C_1 to C_6 alkyl)oxy, thio, (C_1 to C_6 alkyl)thio, carboxy, carboxy(C_1 to C_6 alkyl), formyl, (C_1 to C_6 alkyl)carbonyl, (C_1 to C_6 alkyl)oxycarbonyl, (C_1 to C_6 alkyl)carbonyloxy, nitro, trihalomethyl, hydroxy, hydroxy(C_1 to C_6 alkyl), amino, (C_1 to C_6 alkyl)amino, di(C_1 to C_6 alkyl)amino, aminocarbonyl, halo, halo(C_1 to C_6 alkyl), aminosulfonyl, (C_1 to C_6 alkyl)sulfonylamino, (C_1 to C_6 alkyl)aminocarbonyl, di(C_1 to C_6 alkyl)aminocarbonyl, [*N*-Z](C_1 to C_6 alkyl)carbonylamino, formyloxy, formamido, (C_1 to C_6 alkyl)aminosulfonyl, di(C_1 to C_6 alkyl)aminosulfonyl, [*N*-Z](C_1 to C_6 alkyl)sulfonylamino or cyano; or R^1 and R^5 together form a methylenedioxy group;

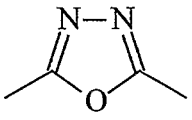
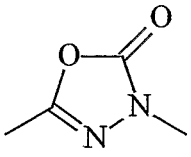
R^2 is H or an optionally substituted C_1 to C_{18} hydrocarbyl group wherein up to three C atoms may optionally be replaced by N, O and/or S atoms;

R^3 is $-(CR^{11}R^{12})_m-X-(CR^{13}R^{14})_p-R^9$;

m is 0, 1, 2, 3 or 4 (preferably 1 or 2);

p is 0, 1 or 2;

X is a bond, $-CR^{15}=CR^{16}-$, -C≡C-, C(O)NH, NHC(O), C(O)NMe, NMeC(O), C(O)O, NHC(O)NH, NHC(O)O, OC(O)NH, NH, O, CO, SO_2, SO_2NH, C(O)NHNH,

 or 

R^9 is H; C_1 to C_6 alkyl; or phenyl, naphthyl, pyridyl, benzimidazolyl, indazolyl, quinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, indolinyl, isoindolinyl, indolyl, isoindolyl or 2-pyridonyl, all optionally substituted with 1, 2 or 3 groups independently selected from

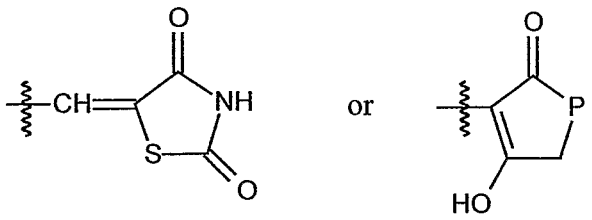
-L-Q

wherein:

L is a bond, or a group of the formula $-(CR^{17}R^{18})_v-Y-(CR^{17}R^{18})_w$, wherein v and w are independently 0, 1, 2 or 3, and Y is a bond, $-CR^{15}=CR^{16}-$, phenyl, furanyl, thiophenyl, pyrrolyl, thiazolyl, imidazolyl, oxazolyl, isoxazolyl, pyrazolyl, isoxazolonyl, piperazinyl, piperidinyl, morpholinyl, pyrrolidinyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, pyridyl or pyridazyl; and

Q is H, (C_1 to C_6 alkyl)oxy, [*N*-Z](C_1 to C_6 alkyl)oxy(C_1 to C_6 alkyl)amino, thio, (C_1 to C_6 alkyl)thio, carboxy(C_1 to C_6 alkyl)thio, carboxy, carboxy(C_1 to C_6 alkyl), carboxy(C_1 to C_6 alkenyl), [*N*-Z]carboxy(C_1 to C_6 alkyl)amino, carboxy(C_1 to C_6 alkyl)oxy, formyl, (C_1 to C_6 alkyl)carbonyl, (C_1 to C_6 alkyl)oxycarbonyl, (C_1 to C_6 alkyl)carbonyloxy, nitro, trihalomethyl, hydroxy, amino, [*N*-Z](C_1 to C_6 alkyl)amino, aminocarbonyl, (C_1 to C_6 alkyl)aminocarbonyl, di(C_1 to C_6 alkyl)aminocarbonyl, [*N*-Z](C_1 to C_6 alkyl)carbonylamino, C_5 to C_8 cycloalkyl, [*N*-Z](C_1 to C_6 alkyl)carbonyl(C_1 to C_6 alkyl)amino, halo, halo(C_1 to C_6 alkyl), sulfamoyl, [*N*-Z](C_1 to C_6 alkyl)sulfonylamino, (C_1 to C_6 alkyl)sulfonylaminocarbonyl, carboxy(C_1 to C_6 alkyl)sulfonyl, carboxy(C_1 to C_6 alkyl)sulfinyl, tetrazolyl, [*N*-Z]tetrazolylamino, cyano, amidino, amidinothio, SO_3H, formyloxy, formamido, C_3 to C_8 cycloalkyl, (C_1 to C_6 alkyl)sulphamoyl, di(C_1 to C_6 alkyl)sulphamoyl, (C_1 to C_6 alkyl)carbonylaminosulfonyl, 5-oxo-2,5-

dihydro[1,2,4]oxadiazolyl, carboxy(C_1 to C_6 alkyl)carbonylamino, tetrazolyl(C_1 to C_6 alkyl)thio, [*N*-Z]tetrazolyl(C_1 to C_6 alkyl)amino, 5-oxo-2,5-dihydro[1,2,4]thiadiazolyl, 5-oxo-1,2-dihydro[1,2,4]triazolyl, [*N*-Z](C_1 to C_6 alkyl)amino(C_1 to C_6 alkyl)amino, or a group of the formula



wherein P is O, S or NR^{19};

Z is H, C_1 to C_6 alkyl, t-butoxycarbonyl, acetyl, benzoyl or benzyl;

R^4 is of formula

$$-(CH_2)_q\text{-}T\text{-}R^{10}$$

wherein:

q is 0, 1, 2 or 3;

T is a bond, O, S, NH or N(C_1 to C_6 alkyl); and

R^{10} is C_1 to C_{12} alkyl, C_3 to C_{12} cycloalkyl, phenyl, naphthyl, pyridyl, pyrrolyl, imidazolyl, pyrazolyl, pyridazinyl, pyrimidinyl, triazolyl, furanyl, thienyl, furazanyl, oxazolyl, isoxazolyl, thiazolyl, thiazinyl, indolyl, indolinyl, isoindolyl, isoindolinyl, isoquinolinyl, quinolinyl, benzofuranyl, benzothienyl, piperazinyl, piperidinyl, pyrrolidinyl, pyrrolinyl, dihydropyranyl, tetrahydropyranyl, pyranyl, tetrahydrofuranyl, morpholinyl, thiazolidinyl, thiomorpholinyl or thioxanyl (all optionally substituted with 1, 2 or 3 groups independently selected from C_1 to C_6 alkyl, (C_1 to C_6 alkyl)oxy, C_3 to C_8 cycloalkyl, (C_3 to C_8 cycloalkyl)oxy, thio, (C_1 to C_6 alkyl)thio, carboxy, carboxy(C_1 to C_6 alkyl), formyl, (C_1 to C_6 alkyl)carbonyl, (C_1 to C_6 alkyl)oxycarbonyl, (C_1 to C_6 alkyl)carbonyloxy, nitro, trihalomethyl, hydroxy, hydroxy(C_1 to C_6 alkyl), amino, (C_1 to C_6 alkyl)amino, di(C_1 to C_6 alkyl)amino, aminocarbonyl, halo, halo(C_1 to C_6 alkyl), aminosulfonyl, (C_1 to C_6 alkyl)sulfonylamino or cyano);

R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{17}, R^{18} and R^{19} are independently H or C_1 to C_3 alkyl; and

R^{16} is H, C_1 to C_3 alkyl, or acetylamino;

or a pharmaceutically acceptable salt thereof;

with the proviso that R^{10} is not phenyl or substituted phenyl when q is 0 and T is a bond.

Preferably R^1 and R^5 are both H. However, it will be appreciated the benzo-fused ring system may have one or two substituents on the benzene ring as indicated hereinabove. The substituents may have subtle steric and/or electronic effects which modify the activity of the compound at the gastrin receptor. However, the presence or otherwise of certain substituents on the benzene ring is not crucial to the overall pharmacological activity of the present compounds.

Preferably, in the compound of formula (IIa) or (IIb), W is N.

Preferably, in the compound of formula (I) or (IIb) R^2 is of formula:

$$-(CH_2)_s-C(R^6R^7)_n-(CH_2)_t-R^8$$

wherein:

R^6 and R^7 are independently selected from H, C_1 to C_6 alkyl or OH; or R^6 and R^7 together represent an =O group;

n is 0 or 1;

s is 0, 1, 2 or 3;

t is 0, 1, 2 or 3; and

R^8 is selected from H, C_1 to C_{12} alkyl, (C_1 to C_{12} alkyl)oxy, C_3 to C_{12} cycloalkyl, phenyl, naphthyl, pyridyl, pyrrolyl, imidazolyl, pyrazolyl, pyridazinyl, pyrimidinyl, triazolyl, furanyl, thienyl, furazanyl, oxazolyl, isoxazolyl, thiazolyl, thiazinyl, indolyl, indolinyl, isoindolyl, isoindolinyl, isoquinolinyl, quinolinyl, benzofuranyl, benzothienyl, piperazinyl, piperidinyl, pyrrolidinyl, pyrrolinyl, dihydropyranyl, tetrahydropyranyl, pyranyl, tetrahydrofuranyl, morpholinyl, thiazolidinyl, thiomorpholinyl or thioxanyl (all optionally substituted with 1, 2 or 3 groups independently selected from C_1 to C_6 alkyl, (C_1 to C_6 alkyl)oxy, thio, (C_1 to C_6 alkyl)thio, carboxy, carboxy(C_1 to C_6 alkyl), formyl, (C_1 to C_6 alkyl)carbonyl, (C_1 to C_6 alkyl)oxycarbonyl, (C_1 to C_6 alkyl)carbonyloxy, nitro, trihalomethyl, hydroxy, hydroxy(C_1 to C_6 alkyl), amino, (C_1 to C_6 alkyl)amino, di(C_1 to C_6 alkyl)amino, aminocarbonyl, halo, halo(C_1 to C_6 alkyl), aminosulfonyl, (C_1 to C_6 alkyl)sulfonylamino or cyano).

A preferred group of compounds according to the present invention is where R^2 is of formula:

$$-(CH_2)C(O)R^8$$

wherein:

R^8 is a branched C_3 to C_{12} alkyl group (such as *tert*-butyl, *sec*-butyl, isopropyl, isobutyl or isovaleryl); or R^8 is a C_3 to C_{12} cycloalkyl (such as cyclopentyl, cyclohexyl, cycloheptyl or adamantyl) phenyl, pyridyl, pyrrolidinyl or piperidinyl group (all optionally substituted with 1, 2 or 3 C_{1-6} alkyl groups).

Preferably, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18} and R^{19} are all H.

A preferred group of compounds according to the present invention is where R^3 is of formula:

$$-(CH_2)-X-R^9$$

wherein:

X is C(O)NH or NHC(O), more preferably X is C(O)NH.

Preferably, R^9 is phenyl substituted with a carboxy, carboxy(C_1 to C_6 alkyl), tetrazolyl, tetrazolyl-*N*-(C_1 to C_6 alkyl)amino, carboxy(C_1 to C_6 alkyl)thio, carboxy(C_1 to C_6 alkyl)sulfonyl, (C_1 to C_6 alkyl)amino, or 5-oxo-2,5-dihydro[1,2,4]oxadiazolyl group; or R^9 is a *N*-[carboxy(C_1 to C_6 alkyl)]indolinyl or *N*-[carboxy(C_1 to C_6 alkyl)]indolyl group.

When R^9 is a substituted phenyl group, the substituent is preferably at the 3-position of the phenyl group.

Preferably, in compounds according to formula (I) or (IIa), R^4 is of formula:

$$-(CH_2)_q-T-R^{10}$$

wherein:

q is 0, 1, 2 or 3;

T is a bond, O, S, NH or N(C_1 to C_6 alkyl); and

R^{10} is C_1 to C_{12} alkyl, C_3 to C_{12} cycloalkyl, phenyl, naphthyl, pyridyl, pyrrolyl, imidazolyl, pyrazolyl, pyridazinyl, pyrimidinyl, triazolyl, furanyl, thienyl, furazanyl, oxazolyl, isoxazolyl, thiazolyl, thiazinyl, indolyl, indolinyl, isoindolyl, isoindolinyl, isoquinolinyl, quinolinyl, benzofuranyl, benzothienyl, piperazinyl, piperidinyl, pyrrolidinyl, pyrrolinyl, dihydropyranyl, tetrahydropyranyl, pyranyl, tetrahydrofuranyl, morpholinyl, thiazolidinyl, thiomorpholinyl or thioxanyl (all optionally substituted with 1, 2 or 3 groups independently selected from C_1 to C_6 alkyl, (C_1 to C_6 alkyl)oxy, C_3 to C_8 cycloalkyl, (C_3 to C_8 cycloalkyl)oxy, thio, (C_1 to C_6 alkyl)thio, carboxy, carboxy(C_1 to C_6 alkyl), formyl, (C_1 to C_6 alkyl)carbonyl, (C_1 to C_6 alkyl)oxycarbonyl, (C_1 to C_6 alkyl)carbonyloxy, nitro, trihalomethyl, hydroxy, hydroxy(C_1 to C_6 alkyl), amino, (C_1 to C_6 alkyl)amino, di(C_1 to C_6 alkyl)amino, aminocarbonyl, halo, halo(C_1 to C_6 alkyl), aminosulfonyl, (C_1 to C_6 alkyl)sulfonylamino or cyano).

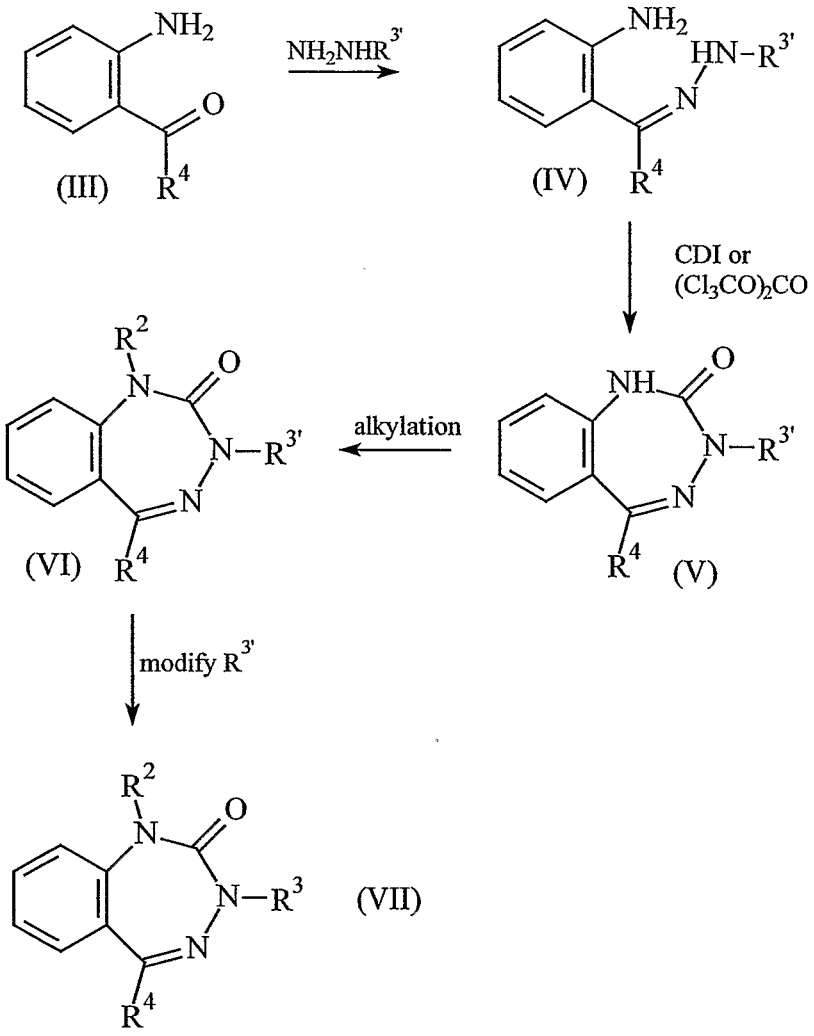
More preferably, in compounds according to formula (I) or (IIa), R^4 is selected from C_{1-12} alkyl (such as *tert*-butyl, *sec*-butyl, isopropyl, isobutyl or isovaleryl), C_{3-12} cycloalkyl (such as cyclopentyl, cyclohexyl, cycloheptyl or adamantyl), pyridyl or phenyl (all of which may be optionally substituted with 1, 2 or 3 groups selected from OMe, NMe_2, CF_3, Me, F, Cl, Br or I).

In all compounds of the present invention, preferably q is 0 and T is a bond. More preferably R^4 is C_3-C_{12} cycloalkyl, and more preferably, R^4 is cyclohexyl.

Certain compounds of the invention exist in various regioisomeric, enantiomeric, tautomeric and diastereomeric forms. It will be understood that the invention comprehends the different regioisomers, enantiomers, tautomers and diastereomers in isolation from each other as well as mixtures.

Compounds of the present invention wherein W is N may be prepared by the representative procedure shown in Reaction Scheme 1.

Reaction Scheme 1



Ketone (III) is reacted with $NH_2NHR^{3'}$ (wherein $R^{3'}$ represents either R^3 or a suitable precursor thereof) to form hydrazone (IV). The hydrazone (IV) is then cyclised using a bifunctional carbonyl reagent to form benzotriazepinone (V). Bifunctional carbonyl reagents are well known to the person skilled in the art and include, for example, carbonyldiimidazole (CDI), triphosgene, phosgene or cyanogen bromide. Alkylation under standard conditions followed by modification of $R^{3'}$ affords the desired benzotriazepinone (VII).

Compounds wherein W is N^+-O^- may be prepared by treating compound VII directly or an appropriately protected derivative of compound VI, with an oxidising agent such as

MCPBA. Such derivatives of compound VI yield the desired N-oxide following deprotection.

$R^{3'}$ groups which are suitable precursors of R^3 will depend on the particular nature of R^3. For example, when R^3 is $-(CH_2)_mC(O)NH-(CH_2)_p-R^9$, a suitable $R^{3'}$ group would be $-(CH_2)_mCO_2(C_{1-6}$ alkyl). In this case, the requisite R^3 groups may be readily accessed via an ester hydrolysis followed by a simple amide coupling reaction. The skilled person will be aware of many other suitable $R^{3'}$ groups, depending on the nature of R^3.

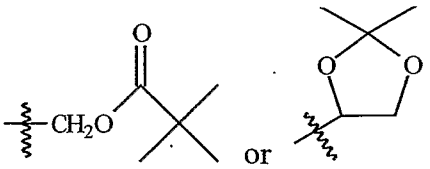
Alkylation may be performed by, for example, displacement of an alkyl halide in the presence of a base. Methods of alkylation will be readily apparent to the person skilled in the art.

Hence, the present invention also provides a method of making compounds according to formula (I), formula (IIa) or formula(IIb).

It is an important advantage of the synthesis described hereinabove that no chiral centres are generated in the benzotriazepinone ring system during the synthesis.

The invention also comprehends derivative compounds ("pro-drugs") which are degraded *in vivo* to yield the species of formula (IIa) or (IIb). Pro-drugs are usually (but not always) of lower potency at the target receptor than the species to which they are degraded. Pro-drugs are particularly useful when the desired species has chemical or physical properties which make its administration difficult or inefficient. For example, the desired species may be only poorly soluble, it may be poorly transported across the mucosal epithelium, or it may have an undesirably short plasma half-life. Further discussion of pro-drugs may be found in Stella, V. J. *et al.*, "Prodrugs", *Drug Delivery Systems*, 1985, pp. 112-176, and *Drugs*, 1985, **29**, pp. 455-473.

Pro-drug forms of the pharmacologically-active compounds of the invention will generally be compounds according to formula (II) having an acid group which is esterified or amidated. Included in such esterified acid groups are groups of the form $-COOR^a$, wherein R^a is C_1 to C_5 alkyl, phenyl, substituted phenyl, benzyl, substituted benzyl, or one of the following:



Amidated acid groups include groups of the formula $-CONR^bR^c$, wherein R^b is H, C_1 to C_5 alkyl, phenyl, substituted phenyl, benzyl, or substituted benzyl, and R^c is -OH or one of the groups just recited for R^b.

Compounds of formula (II) having an amino group may be derivatised with a ketone or an aldehyde such as formaldehyde to form a Mannich base. This will hydrolyse with first order kinetics in aqueous solution.

Another aspect of the present invention is a pharmaceutical composition comprising a compound of formula (II) substantially as described herein before with a pharmaceutically acceptable diluent or carrier.

Yet another aspect of the present invention is a method of making a pharmaceutical composition comprising a compound of formula (II) substantially as described herein before, comprising mixing said compound with a pharmaceutically acceptable diluent or carrier.

Pharmaceutically acceptable salts of the acidic or basic compounds of the invention can of course be made by conventional procedures, such as by reacting the free base or acid with at least a stoichiometric amount of the desired salt-forming acid or base.

Pharmaceutically acceptable salts of the acidic compounds of the invention include salts with inorganic cations such as sodium, potassium, calcium, magnesium, zinc, and ammonium, and salts with organic bases. Suitable organic bases include N-methyl-D-glucamine, arginine, benzathine, diolamine, olamine, procaine and tromethamine.

Pharmaceutically acceptable salts of the basic compounds of the invention include salts derived from organic or inorganic acids. Suitable anions include acetate, adipate, besylate, bromide, camsylate, chloride, citrate, edisylate, estolate, fumarate, gluceptate, gluconate,

glucuronate, hippurate, hyclate, hydrobromide, hydrochloride. iodide, isethionate, lactate, lactobionate, maleate, mesylate, methylbromide, methylsulfate, napsylate, nitrate, oleate, pamoate, phosphate, polygalacturonate, stearate, succinate, sulfate, sulfosalicylate, tannate, tartrate, terephthalate, tosylate and triethiodide.

It is anticipated that the compounds of the invention can be administered by oral or parenteral routes, including intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical administration, and inhalation.

For oral administration, the compounds of the invention will generally be provided in the form of tablets or capsules or as an aqueous solution or suspension.

Tablets for oral use may include the active ingredient mixed with pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavouring agents, colouring agents and preservatives. Suitable inert diluents include sodium and calcium carbonate, sodium and calcium phosphate and lactose. Corn starch and alginic acid are suitable disintegrating agents. Binding agents may include starch and gelatine. The lubricating agent, if present, will generally be magnesium stearate, stearic acid or talc. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate, to delay absorption in the gastrointestinal tract.

Capsules for oral use include hard gelatine capsules in which the active ingredient is mixed with a solid diluent and soft gelatine capsules wherein the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin or olive oil.

For intramuscular, intraperitoneal, subcutaneous and intravenous use, the compounds of the invention will generally be provided in sterile aqueous solutions or suspensions, buffered to an appropriate pH and isotonicity. Suitable aqueous vehicles include Ringer's solution and isotonic sodium chloride. Aqueous suspensions according to the invention may include suspending agents such as cellulose derivatives, sodium alginate, polyvinyl-pyrrolidone and gum tragacanth, and a wetting agent such as lecithin. Suitable preservatives for aqueous suspensions include ethyl and n-propyl p-hydroxybenzoate.

Effective doses of the compounds of the present invention may be ascertained be conventional methods. The specific dosage level required for any particular patient will depend on a number of factors, including severity of the condition being treated, the route of administration and the weight of the patient. In general, however, it is anticipated that the daily dose (whether administered as a single dose or as divided doses) will be in the range 0.001 to 5000 mg per day, more usually from 1 to 1000 mg per day, and most usually from 10 to 200 mg per day. Expressed as dosage per unit body weight, a typical dose will be expected to be between 0.01 μg/kg and 50 mg/kg, especially between 10 μg/kg and 10 mg/kg, eg. between 100 μg/kg and 2 mg/kg.

In a further aspect of the present invention there are provided pharmaceutical compositions comprising a compound according to formula (I) and a proton pump inhibitor. Compositions comprising a CCK_2/gastrin antagonist and a proton pump inhibitor are described in International patent application WO93/12817, incorporated herein by reference.

In one aspect of the present invention the proton pump inhibitor is

omeprazole which is 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-lH-benzimidazole;

BY308;

SK&F 95601 which is 2-[[(3-chloro-4-morpholino-2-pyridyl)methyl]sulfinyl]-5-methoxy-(lH)-benzimidazole;

SK & 96067 which is 3-butyryl-4-(2-methylphenylamino)-8-methoxyquinoline;

5-trifluoromethyl-2-[4-methoxy-3-methyl-2-pyridyl-methyl]-thio-[lH]-benzimidazole;

or pharmaceutically acceptable salts thereof.

These proton pump inhibitors are described and claimed in US Patents 4,472,409 and 4,255,431. These patents are incorporated herein by reference.

In a further aspect of the present invention, the proton pump inhibitor is

lansoprazole which is 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole;

pantoprazole which is 5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole;

perprazole;

rabeprazole which is 2-[[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]methylsulfinyl]-1H-benzimidazole;

[[4-(2,2,2-trifluoroethoxy)-3-methyl-2-pyridyl]- methyl]sulfenamide;

(Z)-5-methyl-2-[2-(1-naphthyl)ethenyl]-4- piperidinopyridine HCl;

2- (4-cyclohexyloxy-5-methylpyridin-2-yl) -3- (1- naphthyl) -1-propanol;

methyl 2-cyano-3-(ethylthio)-3-(methylthio)-2propenoate;

2-((4-methoxy-2-pyridyl)methylsulphinyl)-5-(1,1,2,2-tetrafluoroethoxy)-lH-benzimidazole sodium;

2-[[[4-(2,2,3,3,4,4,4-heptafluorobutoxy)-2-pyridyl]methyl)sulfinyl]-1H-thieno [3,4-d]imidazole;

2-[[[4-(2,2,2-trifluoroethoxy)-3-methyl-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole;

2-[[[4-(2,2,2-trifluoroethoxy)-3-methyl-2-pyridyl]methyl]sulfinyl]-lH-benzimidazole;

2-methyl-8-(phenylmethoxy)-imidazo(1,2-A)- pyridine-3-acetonitrile;

(2-((2-dimethylaminobenzyl)sulfinyl)-benzimidazole);

4-(N-allyl-N-methylamino)-1-ethyl-8-((5-fluoro-6-methoxy-2-benzimidazolyl) sulfinylmethyl)-1-ethyl 1,2,3,4-tetrahydroquinolone;

2-[[(2-dimethylaminophenyl)methyl]sulfinyl]-4,7-dimethoxy-lH-benz imidazole;

2-[(2-(2-pyridyl)phenyl)sulfinyl)-1H-benzimidazole;

(2-[(2-amino-4-methylbenzyl)sulfinyl]-5-methoxybenzo[d]imidazole;

(4(2-methylpyrrol-3-yl)-2-guanidisothiazole);

4-(4-(3-(imidazole)propoxy)phenyl)-2phenylthiazole;

(E)-2-(2-(4-(3-(dipropylamino)butoxy)phenyl)-ethenyl)benzoxazole;

(E)-2-(2-(4-(3-(dipropylamino)propoxy)phenyl)ethenyl)-benzothiazole;

Benzeneamine, 2-[[(5-methoxy-1H-benzimidazol-2-yl)sulfinyl]methyl)-4-methyl-;

Pumilacidin A;

2,3-dihydro-2-methoxycarbonylamino-1,2-benzisothiazol-3-one;

2-(2-ethylaminophenylmethylsulfinyl)-5,6-dimethoxybenzimidazole;

2-methyl-8-(phenylmethoxy)imidazo[1,2-a)pyridine-3-acetonitrile;

3-amino-2-methyl-8-phenylmethoxyimidazo[1,2-a)-pyrazine HC1;

2-[[(3-chloro-4-morpholino-2-pyridyl)methyl]-sulfinyl)-5-methoxy-(1H)-benzinidazole;

[3-butyryl-4-(2-methylphenylamino)-8-methoxy-quinoline);

2-indanyl 2-(2-pyridyl)-2-thiocarbamoylacetate HCl;

2,3-dihydro-2-(2-pyridinyl)-thiazolo (3,2-a) - benzimidazole;

3-cyanomethyl-2-methyl-8-(3-methyl-2-butenyloxy)- (1,2-a)imidazopyridine;

zinc L-carnosine;

or pharmaceutically acceptable salts thereof.

Rabeprazole is described in US patent 5,045,552. Lansoprazole is described in US patent 4,628,098. Pantoprazole is described in US patent 4,758,579. These patents are incorporated herein by reference.

Preferably, the proton pump inhibitor is selected from (RS)-rabeprazole, (RS)-omeprazole, lansoprazole, pantoprazole, (R)-omeprazole, (S)-omeprazole, perprazole, (R)-rabeprazole, (S)-rabeprazole, or the alkaline salts thereof. The alkaline salts may be, for example, the lithium, sodium, potassium, calcium or magnesium salts.

Compositions of this invention comprising a compound of formula (I) and a proton pump inhibitor may be administered as described above. Preferably the dose of each of the active ingredients in these compositions will be equal to or less than that which is approved or indicated in monotherapy with said active ingredient.

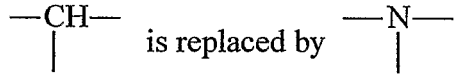
In another aspect of this invention, there is provided a kit comprising a compound of formula (I) and a proton pump inhibitor. The kit is useful as a combined preparation for simultaneous, separate or sequential use in the treatment of patients suffering from gastrointestinal disorders.

In yet a further aspect of the present invention there is provided a method of making a pharmaceutical composition comprising a compound of formula (I) substantially as

described herein before and a proton pump inhibitor, comprising mixing said compound and said proton pump inhibitor with a pharmaceutically acceptable carrier or diluent.

The term "hydrocarbyl" is used herein to refer to monovalent groups consisting of carbon and hydrogen. Hydrocarbyl groups thus include alkyl, alkenyl and alkynyl groups (in both straight and branched chain forms), cycloalkyl (including polycycloalkyl groups such as bicyclooctyl and adamantyl), cycloalkenyl and aryl groups, and combinations of the foregoing, such as alkylcycloalkyl, alkylpolycycloalkyl, alkylaryl, alkenylaryl, alkynylaryl, cycloalkylaryl and cycloalkenylaryl groups.

Where reference is made to a carbon atom of a hydrocarbyl group being replaced by a N, O or S atom, what is intended is that



or that $-CH_2-$ is replaced by –O– or –S–.

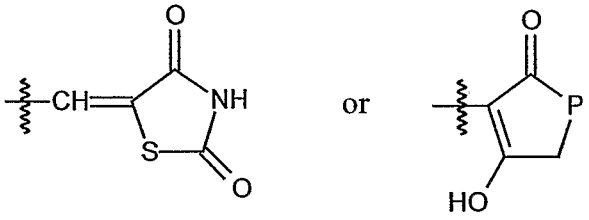
Where reference is made to an optionally substituted hydrocarbyl group, the hydrocarbyl group is substituted with 1, 2 or 3 groups independently selected from -L-Q

wherein:

L is a bond, or a group of the formula $-(CR^{17}R^{18})_v-Y-(CR^{17}R^{18})_w$, wherein v and w are independently 0, 1, 2 or 3, and Y is a bond, $-CR^{15}=CR^{16}-$, phenyl, furanyl, thiophenyl, pyrrolyl, thiazolyl, imidazolyl, oxazolyl, isoxazolyl, pyrazolyl, isoxazolonyl, piperazinyl, piperidinyl, morpholinyl, pyrrolidinyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, pyridyl or pyridazyl;

Q is H, (C_1 to C_6 alkyl)oxy, [*N*-Z](C_1 to C_6 alkyl)oxy(C_1 to C_6 alkyl)amino, thio, (C_1 to C_6 alkyl)thio, carboxy(C_1 to C_6 alkyl)thio, carboxy, carboxy(C_1 to C_6 alkyl), carboxy(C_1 to C_6 alkenyl), [*N*-Z]carboxy(C_1 to C_6 alkyl)amino, carboxy(C_1 to C_6 alkyl)oxy, formyl, (C_1 to C_6 alkyl)carbonyl, (C_1 to C_6 alkyl)oxycarbonyl, (C_1 to C_6 alkyl)carbonyloxy, nitro, trihalomethyl, hydroxy, amino, [*N*-Z](C_1 to C_6 alkyl)amino, aminocarbonyl, (C_1 to C_6 alkyl)aminocarbonyl, di(C_1 to C_6 alkyl)aminocarbonyl, [*N*-Z](C_1 to C_6 alkyl)carbonylamino, C_5 to C_8 cycloalkyl, [*N*-Z](C_1 to C_6 alkyl)carbonyl(C_1 to C_6 alkyl)amino, halo, halo(C_1 to C_6 alkyl), sulfamoyl, [*N*-Z](C_1 to C_6 alkyl)sulfonylamino, (C_1 to C_6 alkyl)sulfonylaminocarbonyl, carboxy(C_1 to C_6 alkyl)sulfonyl, carboxy(C_1 to C_6

alkyl)sulfinyl, tetrazolyl, [*N*-Z]tetrazolylamino, cyano, amidino, amidinothio, SO_3H, formyloxy, formamido, C_3 to C_8 cycloalkyl, (C_1 to C_6 alkyl)sulphamoyl, di(C_1 to C_6 alkyl)sulphamoyl, (C_1 to C_6 alkyl)carbonylaminosulfonyl, 5-oxo-2,5-dihydro[1,2,4]oxadiazolyl, carboxy(C_1 to C_6 alkyl)carbonylamino, tetrazolyl(C_1 to C_6 alkyl)thio, [*N*-Z]tetrazolyl(C_1 to C_6 alkyl)amino, 5-oxo-2,5-dihydro[1,2,4]thiadiazolyl, 5-oxo-1,2-dihydro[1,2,4]triazolyl, [*N*-Z](C_1 to C_6 alkyl)amino(C_1 to C_6 alkyl)amino, or a group of the formula



wherein P is O, S or NR^{19};

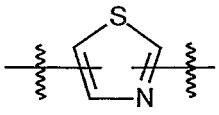
and

Z is H, C_1 to C_6 alkyl, t-butoxycarbonyl, acetyl, benzoyl or benzyl.

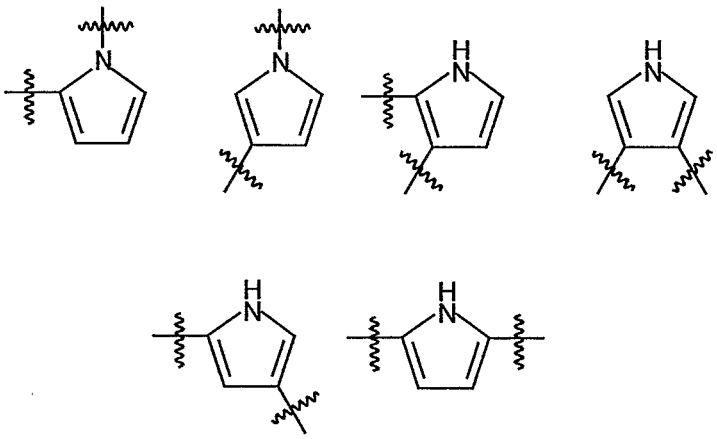
The term "alkyl" is used herein to refer to both straight and branched chain forms. Further, the alkyl chain may include multiple bonds. Hence, the term "alkyl" also encompasses alkenyl and alkynyl groups. Likewise, the term "cycloalkyl" also encompasses cycloalkenyl groups. Preferably, alkyl and cycloalkyl groups as used in the present invention do not contain multiple bonds. Where there are preferred alkenyl groups, these are specified as alkenyl groups. However, specific reference to alkenyl groups is not to be construed as any limitation on the definition of alkyl groups as described above.

Where reference is made to dialkyl groups [e.g. di(C_1 to C_6 alkyl)amino groups], it is understood that the two alkyl groups may be the same or different.

In the interests of simplicity, terms which are normally used to refer to monovalent groups (such as "alkyl" or "phenyl") are also used herein to refer to divalent bridging groups which are formed from the corresponding monovalent group by the loss of one hydrogen atom. Whether such a term refers to a monovalent group or to a divalent group will be clear from the context. For example, when L is $-(CR^{17}R^{18})_v-Y-(CR^{17}R^{18})_w-$, it is clear that Y must be a divalent group. Thus, when Y is defined as thiazolyl, for example, this refers to a divalent group having the structure

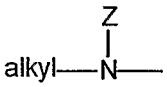


Where, as in this example, a divalent bridging group is formed from a cyclic moiety, the linking bonds may be on any suitable ring atom, subject to the normal rules of valency. Accordingly, by way of further example, the term pyrrolyl in the definition of Y includes all of the following groups:



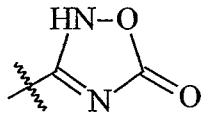
The term "halogen" or "halo" is used herein to refer to any of fluorine, chlorine, bromine and iodine. Most usually, however, halogen substituents in the compounds of the invention are chlorine and fluorine substituents. Groups such as halo(C_1 to C_6 alkyl) includes mono-, di- or tri-halo substituted C_1 to C_6 alkyl groups. Moreover, the halo substitution may be at any position in the alkyl chain.

The prefix [*N*-Z] refers to possible substitution of an amino group in the following compound or substituent name. For example, [*N*-Z]alkylamino refers to groups of the form



Similarly, [*N*-Z]tetrazolylamino, wherein Z is C_1 to C_6 alkyl, includes groups such as tetrazolyl[*N*-methyl]amino and tetrazolyl[*N*-ethyl]amino. Of course, when Z is H, no substitution is present.

In case there is any doubt, the group named as 5-oxo-2,5-dihydro[1,2,4]oxadiazolyl has the following formula



and comprehends tautomeric forms.

The invention is now further illustrated by means of the following Examples.

Experimental

All reactions were performed under an atmosphere of dry argon unless otherwise stated. Commercially available dichloromethane (DCM), tetrahydrofuran (THF) and *N,N*-dimethylformamide (DMF) were used. In reactions in which anilines were used, where necessary un-reacted aniline was removed either by chromatography or by stirring with excess methylisocyanate polystyrene HL resin (200-400 mesh, 2mmol/g) in DCM (R. J. Booth, *et. al., J. Am. Chem. Soc.,* (1997), **119**, 4882). Flash column chromatography was performed on Merck silica gel 60 (40-63μm) using the reported solvent systems. ^{1}H NMR spectra were recorded on a Bruker DRX-300 instrument at 300MHz and the chemical shifts (δ_H) were recorded relative to an internal standard. (2-Amino-phenyl)-cyclohexyl-methanone was prepared by a published method (M. S. Chambers, *et. al., Bioorg. Med. Chem. Lett.* (1993), **3**, 1919), and (2-amino-phenyl)-cyclopentyl-methanone and 1-(2-amino-phenyl)-3-methyl-butan-1-one were prepared by a modification of this method. 2-Bromo-1-cyclopentyl-ethanone and 2-bromo-1-cyclohexyl-ethanone were prepared by a published method (M. Gaudry, A. Marquet, *Org. Synth.*, (1976), **55**, 24), and 2-bromo-1-cyclopropyl-ethanone was prepared by a modification of this method. 2-Bromo-1-(1-methyl-cyclopentyl)-ethanone was prepared by a published method (T. S. Sorensen, *J. Am. Chem. Soc.*, (1969), **91**, 6398). Substituted anilines were either obtained commercially, synthesized by the literature method indicated where first mentioned or prepared in a number of steps and from the starting material as indicated, using standard chemical transformations.

Example 1. *3-{2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester.*

Step a. *{N'-[(2-Amino-phenyl)-cyclohexyl-methylene]-hydrazino}-acetic acid ethyl ester.* A mixture of (2-amino-phenyl)-cyclohexyl-methanone (20.3g, 0.1mol), ethyl hydrazinoacetate hydrochloride (23.25g, 0.15mol) and pyridine (12.1ml, 0.15mol) was heated at reflux in EtOH (400ml) for 72h. On cooling, un-reacted ethyl hydrazinoacetate hydrochloride crystallised from the solution and was removed by filtration. The filtrate was evaporated and the residue was partitioned between saturated $NaHCO_3$ (250ml) and EtOAc (250ml). The organic phase was washed with brine (250ml), dried over $MgSO_4$ then the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (EtOAc-hexane (1:4)) to afford {*N'*-[(2-amino-phenyl)-cyclohexyl-methylene]-hydrazino}-acetic acid ethyl ester as a pale yellow foam (21.2g, 71%) and un-reacted (2-amino-phenyl)-cyclohexyl-methanone (2.40g). ^{1}H NMR ($CDCl_3$) 7.17 (1H, dt), 6.98 (1H, dd), 6.80 (1H, dt), 6.73 (1H, dd), 5.32 (1H, t), 4.16 (2H, m), 3.95 (2H, br s), 3.89 (2H, m), 2.37 (1H, m), 1.80 (1H, m), 1.75-1.61 (4H, m), 1.33-1.19 (8H, m).

Step b. *(5-Cyclohexyl-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetic acid ethyl ester.* To a solution of the product of step a (23.39g, 77.0mmol) and triethylamine (26.8ml, 0.19mol) in DCM (300ml) at 0°C, a solution of triphosgene (11.4g, 39mmol) in DCM (100ml) was added drop-wise over 1h. The reaction mixture was stirred at this temperature for 1h, washed with H_2O (300ml), saturated $NaHCO_3$ (300ml) and brine (300ml). The organic phase was dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The crude product was re-crystallised from Et_2O-hexane (1:3) to afford the main product, (5-cyclohexyl-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetic acid ethyl ester (15.8g, 62%), as a yellow solid. Concentration of the mother liquors and re-crystallisation of the residue from EtOAc-hexane (1:9) yielded the minor product, (1-chlorocarbonyl-5-cyclohexyl-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetic acid ethyl ester (2.1g, 7.0%), as a pale yellow solid.

Major product: *(5-Cyclohexyl-2-oxo-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl)-acetic acid ethyl ester.* ^{1}H NMR ($CDCl_3$) 7.35 (2H, m), 7.12 (1H, t), 6.85 (2H, m), 4.32 (2H, s), 4.18 (2H, m), 2.68 (1H, m), 1.81-1.68 (5H, m), 1.49-1.22 (8H, m).

Minor product: *(1-Chlorocarbonyl-5-cyclohexyl-2-oxo-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl)-acetic acid ethyl ester.* ^{1}H NMR ($CDCl_3$) 7.65-7.49 (4H, m), 4.61-4.35 (2H, m), 4.15 (2H, m), 2.86 (1H, m), 2.00-1.22 (10H, m), 1.18 (3H, t).

Step c. *[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl]-acetic acid ethyl ester.* To an ice cooled solution of the major product of step b (3.29g, 10.0mml) in DMF (30ml) was added sodium hydride (60% dispersion in mineral oil, 480mg, 12.0mmol) in small portions. The mixture was stirred at room temperature for 30min then 1-bromo-3,3-dimethyl-butan-2-one (1.60ml, 12.0mmol) was added. The reaction mixture was stirred at room temperature for 2h, diluted with H_2O (200ml) and extracted with EtOAc (30ml × 3). The combined organic extracts were washed with brine (50ml), dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (EtOAc-DCM (1:9)) to afford the product as a yellow foam (3.59g, 84%). ^{1}H NMR ($CDCl_3$) 7.37 (2H, m), 7.17 (1H, dt), 6.93 (1H, d), 4.66 (2H, s), 4.35 (1H, m), 4.13 (3H, m), 2.74 (1H, m), 1.90-1.70 (6H, m), 1.31-1.16 (16H, m).

Step d. *[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl]-acetic acid.* A solution of the product of step c (3.57g, 8.20mmol), and 1.0M NaOH (8.70ml, 8.70mmol) in EtOH (30ml) was stirred at room temperature for 16h. The EtOH was evaporated under reduced pressure, the residue was diluted with H_2O (30ml) and acidified to pH 3 with 1N HCl. The mixture was extracted with DCM (30ml × 2), the combined extracts were dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure to afford the product as a pale yellow foam (3.10g, 95%). ^{1}H NMR ($CDCl_3$) 11.00 (1H, br s), 7.45 (2H, m), 7.25 (1H, m), 6.97 (1H, dd), 4.68 (2H, m), 4.25 (1H, d), 3.90 (1H, d), 2.80 (1H, m), 2.08-1.61 (6H, m), 1.44-1.18 (13H, m).

Step e. To a solution of the product of step d (1.60g, 4.00mmol), and 3-amino-benzoic acid methyl ester (600mg, 4.00mmol) in DMF (20ml) was added 1-hydroxybenzotriazole (HOBt) (810mg, 6.00mmol), 4-dimethylaminopyridine (DMAP) (50mg, 0.40mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (1.15g, 6.00mmol). The solution was maintained at room temperature for 16h, diluted with H_2O (100ml) and the reaction mixture was extracted with EtOAc (50ml × 2). The combined extracts were washed with 5% $KHSO_4$ (60ml), saturated $NaHCO_3$ (60ml)

and brine (60ml). The organic phase was dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The residue was triturated with Et_2O to afford the title compound as an off-white solid (1.51g, 71%). ^1H NMR ($CDCl_3$) 8.49 (1H, s), 7.92 (1H, m), 7.84 (1H, t), 7.74 (1H, dt), 7.48 (2H, m), 7.39-7.27 (2H, m), 7.03 (1H, d), 4.77 (1H, d), 4.60 (1H, d), 4.25 (2H, s), 3.91 (3H, s), 2.80 (1H, m), 2.05-1.73 (6H, m), 1.34-1.17 (13H, m). Found: C 67.56, H 6.83, N, 10.36%; $C_{30}H_{36}N_4O_5$ requires: C 67.56, H 6.81, N 10.52%.

Example 2. *3-{2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid.*

To a solution of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) (1.33g, 2.49mmol) in THF-H_2O (2:1 / 45ml) was added lithium hydroxide monohydrate (318mg, 7.58mmol) and the mixture was stirred at room temperature for 16h. The THF was evaporated under reduced pressure, the aqueous solution was diluted with H_2O (50ml) and acidified to pH 3 with 1N HCl. The reaction mixture was extracted with DCM (30ml × 2), the combined extracts were washed with brine (50ml), dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure to afford the product as an off-white solid (1.28g, 99%). ^1H NMR (DMSO-d_6) 12.89 (1H, br s), 9.99 (1H, s), 8.16 (1H, s), 7.70 (1H, dd), 7.60-7.36 (4H, m), 7.26-7.15 (2H, m), 4.78 (2H, d), 4.30 (1H, d), 3.98 (1H, d), 2.87 (1H, m), 1.80-1.50 (6H, m), 1.34-1.13 (13H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 60.39, H 7.31, N, 9.78%; $C_{29}H_{34}N_4O_5 \bullet C_7H_{17}NO_5$ requires: C 60.57, H 7.20, N 9.81%.

Example 3. *2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-*3H*-1,3,4-benzotriazepin-3-yl]-*N*-(3-methylamino-phenyl)-acetamide.*

Step a. *(3-Nitro-phenyl)-carbamic acid* tert*-butyl ester.* A solution of 3-nitrophenyl isocyanate (14.44g, 88.0mmol) in *tert*-butanol (80ml) was heated at reflux for 2h. After cooling the solvent was evaporated and the residue was dried under high vacuum, washed thoroughly with Et_2O to afford the product as a yellow solid (19.96g, 95%). ^1H NMR ($CDCl_3$) 8.30 (1H, s), 7.88 (1H, d), 7.71 (1H, d), 7.45 (1H, t), 6.68 (1H, br s), 1.55 (9H, s).

Step b. *Methyl-(3-nitro-phenyl)-carbamic acid* tert-*butyl ester.* To an ice-cooled solution of the product of step a (3.57g, 15.0mmol), in DMF (30ml) was added sodium hydride (60% dispersion in mineral oil, 720mg, 18.0mmol) in small portions. After stirring at room temperature for 1h, the reaction mixture was cooled externally with ice and iodomethane (1.4ml, 22.5mmol) was added. The reaction mixture was stirred at room temperature for 2h, H_2O (150ml) was added and extracted with EtOAc (50ml × 2). The combined extracts were washed with brine, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was purified by flash column chromatography (EtOAc-DCM (1:9)) to afford the product as a yellow foam (3.34g, 88%). ^{1}H NMR ($CDCl_3$) 8.16 (1H, t), 8.00 (1H, m), 7.63 (1H, m), 7.48 (1H, t), 3.34 (3H, s), 1.49 (9H, s).

Step c. *(3-Amino-phenyl)-methyl-carbamic acid* tert-*butyl ester.* A round bottom flask containing the product of step b (3.30g, 13.1mmol), 10% palladium on charcoal (300 mg) and THF-MeOH (1:1 / 50 ml) was evacuated and flushed with hydrogen three times. The mixture was stirred vigorously overnight under an atmosphere of hydrogen. The catalyst was removed by filtration through a pad of celite and the filtrate evaporated to afford the product as a white solid (2.90g, 99%). ^{1}H NMR ($CDCl_3$) 7.10 (1H, t), 6.62 (2H, m), 6.50 (1H, m), 3.66 (2H, br s), 3.22 (3H, s), 1.46 (9H, s).

Step d. *(3-{2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-methyl-carbamic acid* tert-*butyl ester* was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that (3-amino-phenyl)-methyl-carbamic acid *tert*-butyl ester (Example 3, step c) was used in place of 3-amino-benzoic acid methyl ester in step e. ^{1}H NMR ($CDCl_3$) 8.29 (1H, s), 7.44 (3H, m), 7.29-7.11 (4H, m), 7.03-6.94 (2H, m), 4.67 (2H, m), 4.23 (2H, m), 3.23 (3H, s), 2.79 (1H, m), 2.05-1.52 (6H, m), 1.45 (9H, s), 1.37-1.23 (13H, m).

Step e. A solution of the product of step d (270mg, 0.45mmol) in trifluoroacetic acid (3ml) was stirred at room temperature for 1h. The trifluoroacetic acid was evaporated under reduced pressure, the residue was partitioned between saturated $NaHCO_3$ (20ml) and EtOAc (20ml). The organic phase was separated and dried over $MgSO_4$. Filtration and evaporation of the solvent gave the crude product, which was purified by flash column

chromatography (EtOAc-DCM (1:9)) to afford the title compound, as a colourless foam (154mg, 68%). ^{1}H NMR ($CDCl_3$) 8.07 (1H, s), 7.48 (2H, m), 7.27 (1H, dt), 7.04 (2H, m), 6.91 (1H, t), 6.46(1H, dd), 6.31(1H, dd), 4.68 (2H, m), 4.35 (1H, d), 4.13 (1H, d), 3.72 (1H, br s), 2.80 (4H, m), 2.05-1.72 (6H, m), 1.27 (13H, m). Found: C 68.77, H 7.64, N 13.69%; $C_{29}H_{37}N_5O_3$ requires: C 69.16, H 7.40, N 13.91%.

Example 4. *2-[1-(3,3-Dimethyl-2-oxo-butyl)-2-oxo-5-phenyl-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-*N*-(3-methylamino-phenyl)-acetamide.*

Step a. *[1-(3,3-Dimethyl-2-oxo-butyl)-2-oxo-5-phenyl-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid* was obtained using steps a-d of the method employed in the preparation of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d), except that 2-amino-benzophenone was used in step a instead of (2-amino-phenyl)-cyclohexyl-methanone. ^{1}H NMR ($CDCl_3$) 7.61 (2H, dd), 7.49-7.42 (4H, m), 7.17 (2H, m), 7.05 (1H, d), 4.76 (2H, br m), 4.28 (2H, br d), 1.25 (9H, s).

Step b. The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1, step e) except that [1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-5-phenyl-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 4, step a) and (3-amino-phenyl)-methyl-carbamic acid *tert*-butyl ester (Example 3, step c) were used in place of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d) and 3-amino-benzoic acid methyl ester respectively, followed by reaction of the product obtained, in place of (3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-methyl-carbamic acid *tert*-butyl ester (Example 3, step d), according to the method of Example 3, step e. ^{1}H NMR ($CDCl_3$) 8.01 (1H, s), 7.63 (2H, m), 7.55 (1H, m), 7.42 (3H, m), 7.25 (2H, m), 7.14 (1H, d), 7.00 (1H, t), 6.90 (1H, t), 6.40 (1H, dd), 6.29 (1H, dd), 4.76 (2H, m), 4.52 (1H, d), 4.34 (1H, d), 3.25 (1H, br s), 2.77 (3H, s), 1.26 (9H, s). Found: C 68.44, H 6.46, N 13.80%; $C_{29}H_{31}N_5O_3 \bullet 0.6H_2O$ requires: C 68.41, H 6.39, N 13.76%.

Example 5. *2-[1-(3,3-Dimethyl-2-oxo-butyl)-2-oxo-5-pyridin-2-yl-1,2-dihydro-3*H-*1,3,4-benzotriazepin-3-yl]*-N-*(3-methylamino-phenyl)-acetamide.*

Step a. *[1-(3,3-Dimethyl-2-oxo-butyl)-2-oxo-5-pyridin-2-yl-1,2-dihydro-3*H-*1,3,4-benzotriazepin-3-yl]-acetic acid* was prepared using steps a-d of the method employed in the preparation of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d), except that (2-amino-phenyl)-pyridin-2-yl-methanone (G. Semple, *et. al. Synth. Commun.*, (1996), **26**, 721) was used in step a instead of (2-amino-phenyl)-cyclohexyl-methanone. ^{1}H NMR (DMSO-d_6) 12.50 (1H, br s), 8.57 (1H, m), 7.94 (2H, m), 7.50 (2H, m), 7.16 (3H, m), 4.78 (2H, s), 4.25 (2H, br s), 1.15 (9H, s).

Step b. The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1, step e) except that [1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-5-pyridin-2-yl-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 5, step a) and (3-amino-phenyl)-methyl-carbamic acid *tert*-butyl ester (Example 3, step c) were used in place of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d) and 3-amino-benzoic acid methyl ester respectively, followed by reaction of the product obtained, in place of (3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-methyl-carbamic acid *tert*-butyl ester (Example 3, step d), according to the method of Example 3, step e. ^{1}H NMR ($CDCl_3$) 8.62 (1H, d), 8.10 (1H, d), 8.00 (1H, br s), 7.79 (1H, dt), 7.55 (1H, m), 7.29 (3H, m), 7.13 (1H, d), 7.01 (1H, t), 6.92 (1H, t), 6.48 (1H, dd), 6.30 (1H, dd), 4.68 (2H, br d), 4.45 (2H, br d), 2.80 (1H, br s), 2.78 (3H, s), 1.27 (9H, s). Found: C 67.18, H 6.28, N 16.63%; $C_{28}H_{30}N_6O_3$ requires: C 67.45, H 6.06, N 16.86%.

Example 6. N-*(3-Methylamino-phenyl)-2-[2-oxo-1-(2-oxo-2-pyrrolidin-1-yl-ethyl)-5-pyridin-2-yl-1,2-dihydro-3*H-*1,3,4-benzotriazepin-3-yl]-acetamide.*

Step a. *[2-Oxo-1-(2-oxo-2-pyrrolidin-1-yl-ethyl)-5-pyridin-2-yl-1,2-dihydro-3*H-*1,3,4-benzotriazepin-3-yl]-acetic acid* was obtained using steps a-d of the method

employed in the preparation of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d), except that (2-amino-phenyl)-pyridin-2-yl-methanone was used in step a instead of (2-amino-phenyl)-cyclohexyl-methanone and 2-bromo-1-pyrrolidin-1-yl-ethanone (prepared from pyrrolidine and bromoacetyl bromide) replaced 1-bromo-3,3-dimethyl-butan-2-one in step c.

Step b. The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1, step e) except that [2-oxo-1-(2-oxo-2-pyrrolidin-1-yl-ethyl)-5-pyridin-2-yl-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 6, step a) and (3-amino-phenyl)-methyl-carbamic acid *tert*-butyl ester (Example 3, step c) were used in place of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d) and 3-amino-benzoic acid methyl ester respectively, followed by reaction of the product obtained, in place of (3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-methyl-carbamic acid *tert*-butyl ester (Example 3, step d), according to the method of Example 3, step e. ^{1}H NMR ($CDCl_3$) 8.61 (1H, d), 8.07 (2H, m), 7.77 (1H, dt), 7.54 (2H, m), 7.36-7.24 (3H, m), 6.98 (1H, t), 6.88 (1H, s), 6.48 (1H, d), 6.28 (1H, d), 4.53-4.34 (4H, br m), 3.52-3.20 (5H, br m), 2.75 (3H, s), 1.97 (2H, m), 1.87 (2H, m). Found: C 65.44, H 6.00, N 18.79%; $C_{28}H_{29}N_7O_3$ requires: C 65.74, H 5.71, N 19.17%.

Example 7. N-*(3-Methylamino-phenyl)-2-[2-oxo-1-(2-oxo-2-*o*-tolyl-ethyl)-5-pyridin-2-yl-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]- acetamide.*

Step a. *[2-Oxo-1-(2-oxo-2-*o*-tolyl-ethyl)-5-pyridin-2-yl-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid* was obtained using steps a-d of the method employed in the preparation of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d), except (2-amino-phenyl)-pyridin-2-yl-methanone was used in step a instead of (2-amino-phenyl)-cyclohexyl-methanone and 2-bromo-1-*o*-tolyl-ethanone (H. Shinagawa, *et. al. Bioorg. Med. Chem.*, (1997), **5**, 601) replaced 1-bromo-3,3-dimethyl-butan-2-one in step c.

Step b. The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1, step e) except that [2-oxo-1-(2-oxo-2-*o*-tolyl-ethyl)-5-pyridin-2-yl-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 7, step a) and (3-amino-phenyl)-methyl-carbamic acid *tert*-butyl ester (Example 3, step c) were used in place of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d) and 3-amino-benzoic acid methyl ester respectively, followed by reaction of the product obtained, in place of (3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-methyl-carbamic acid *tert*-butyl ester (Example 3, step d), according to the method of Example 3, step e. ^{1}H NMR ($CDCl_3$) 8.64 (1H, d), 8.08 (1H, d), 8.03 (1H, s), 7.79 (1H, dt), 7.59 (2H, m), 7.39-7.26 (5H, m), 7.19 (2H, m), 7.01 (1H, t), 6.90 (1H, s), 6.47 (1H, dd), 6.30 (1H, dd), 4.98 (2H, s), 4.45 (2H, br m), 3.30 (1H, br s), 2.76 (3H, s), 2.47 (3H, s). Found: C 69.63, H 5.45, N 15.59%; $C_{31}H_{28}N_6O_3$ requires: C 69.91, H 5.30, N 15.78%.

Example 8. *1-[1-(3,3-Dimethyl-2-oxo-butyl)-2-oxo-5-pyridin-2-yl-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-ylmethyl]-3-(3-methylamino-phenyl)-urea.*

Step a. *(3-{3-[1-(3,3-Dimethyl-2-oxo-butyl)-2-oxo-5-pyridin-2-yl-1,2-dihydro-3H-1,3,4-benzotriazepin-3-ylmethyl]-ureido}-phenyl)-methyl-carbamic acid tert-butyl ester.* To an ice-cooled solution of [1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-5-pyridin-2-yl-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 5, step a) (390mg, 1.00mmol) and triethylamine (180µl, 1.30mmol) in acetone (3ml) was added ethyl chloroformate (120µl, 1.30mmol). The mixture was stirred for 20min, and a solution of sodium azide (100mg, 1.50mmol) in H_2O (3ml) was added. The reaction mixture was stirred at 0°C for 1h then poured into $PhCH_3$-H_2O (1:1 / 20ml). The organic phase was separated, dried over $MgSO_4$, filtered and the filtrate heated at reflux for 1h. After cooling to room temperature the solvent was evaporated under reduced pressure. The residue was dissolved in DCM (5ml) and (3-amino-phenyl)-methyl-carbamic acid tert-butyl ester (Example 3, step c) (220mg, 1.00mmol) was added. The solution was stirred at room temperature for 1h, diluted with DCM (15ml), washed with saturated $NaHCO_3$ (20ml) and dried over $MgSO_4$. Filtration and evaporation of the solvent gave the crude product which was purified by

flash column chromatography (EtOAc-DCM (1:1)) to afford the product as a colourless foam (166mg, 27%). ^{1}H NMR ($CDCl_3$) 8.51 (1H, d), 8.05 (1H, d), 7.85 (1H, d), 7.67 (1H, t), 7.39 (1H, m), 7.25 (2H, m), 7.13-7.05 (4H, m), 6.95 (1H, d), 6.84 (1H, d), 6.18 (1H, br t), 5.04 (1H, br s), 4.86 (1H, br s), 4.65 (1H, br s), 4.32 (1H, br s), 3.15 (3H, s), 1.49 (9H, s), 1.18 (9H, s).

Step b. The title compound was obtained by reaction of (3-{3-[1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-5-pyridin-2-yl-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-ylmethyl]-ureido}-phenyl)-methyl-carbamic acid *tert*-butyl ester (Example 8, step a), in place of (3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-methyl-carbamic acid *tert*-butyl ester (Example 3, step d), according to the method of Example 3, step e. ^{1}H NMR ($CDCl_3$) 8.56 (1H, d), 8.00 (1H, d), 7.71 (1H, dt), 7.43 (1H, m), 7.30-7.15 (4H, m), 7.02 (2H, m), 6.72 (1H, t), 6.52 (1H, dd), 6.29 (1H, dd), 6.09 (1H, br t), 4.97 (2H, br d), 4.70 (1H, br s), 4.44 (1H, br s), 3.90 (1H, br s), 2.76 (3H, s), 1.23 (9H, s). Found: C 65.55, H 6.27, N 19.00%; $C_{28}H_{31}N_7O_3$ requires: C 65.48, H 6.08, N 19.09%.

Example 9. *3-{2-[5-Cyclopentyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid.*

Step a. *[5-Cyclopentyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid* was obtained using steps a-d of the method employed in the preparation of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d), except that (2-amino-phenyl)-cyclopentyl-methanone was used in step a instead of (2-amino-phenyl)-cyclohexyl-methanone. ^{1}H NMR (DMSO-d_6) 12.30 (1H, br s), 7.51-7.10 (4H, m), 4.77 (2H, s), 4.05 (2H, m), 3.39 (1H, m), 1.74-1.56 (8H, m), 1.12 (9H, s).

Step b. The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1, step e) except that [5-cyclopentyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 9, step a) was used in place of [5-cyclohexyl-1-

(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d) followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR (DMSO-d_6) 12.89 (1H, br s), 9.98 (1H, s), 8.16 (1H, s), 7.71-7.14 (7H, m), 4.79 (2H, m), 4.22 (1H, m), 4.00 (1H, m), 3.42 (1H, m), 1.75-1.54 (8H, m), 1.32-1.19 (9H, s). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 57.08, H 7.45, N 9.60 %; $C_{28}H_{32}N_4O_5 \bullet C_7H_{17}NO_5 \bullet 2.0H_2O$ requires: C 57.13, H 7.26, N 9.52%.

Example 10. *2-[5-Cyclopentyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-[3-(2*H*-tetrazol-5-yl)-phenyl]-acetamide.*

Step a. *2,2-Dimethyl-propionic acid 5-(3-{2-[5-cyclopentyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-tetrazol-2-ylmethyl ester* was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), except that [5-cyclopentyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 9, step a) and 5-(3-amino-phenyl)-tetrazol-2-ylmethyl ester were used in place of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d) and 3-amino-benzoic acid methyl ester respectively in step e. ^{1}H NMR ($CDCl_3$) 8.00 (1H, s), 7.55-7.44 (3H, m), 7.27-7.22 (3H, m), 7.00 (2H, m), 6.29 (2H, s), 4.75 (1H, d), 4.65 (1H, d), 4.25 (1H, m), 4.11 (1H, m), 3.29 (1H, m), 2.00-1.30 (8H, m), 1.26-1.19 (18H, m).

Step b. 2,2-Dimethyl-propionic acid 5-(3-{2-[5-cyclopentyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-tetrazol-2-ylmethyl ester (Example 10, step a) (120mg, 0.22mmol) was stirred overnight in saturated methanolic ammonia solution (10ml) at room temperature. After concentration *in vacuo*, the residue was dissolved in H_2O-MeOH (10:1 / 22ml) and acidified to pH 3 by the addition of 5% $KHSO_4$ solution. The title compound was isolated as a light pink solid by filtration of the reaction mixture and dried *in vacuo* (81 mg, 68%). ^{1}H NMR ($CDCl_3$) 8.61

(1H, s), 7.50-7.44 (3H, m), 7.31-7.24 (2H, m), 7.14 (1H, m), 6.97 (2H, m), 4.95 (1H, d), 4.65 (1H, d), 4.17 (2H, m), 3.30 (1H, m), 1.80-1.58 (8H, m), 1.15 (9H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 54.46, H 7.13, N 16.28%; $C_{28}H_{32}N_8O_3 \bullet C_7H_{17}NO_5 \bullet 2.5H_2O$ requires: C 54.67, H 7.07, N 16.39%.

Example 11. *2-[5-Cyclopentyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]*-N-*(3-methylaminophenyl)-acetamide.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), except that [5-cyclopentyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 9, step a) and (3-amino-phenyl)-methyl-carbamic acid *tert*-butyl ester (Example 3, step c) were used in place of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d) and 3-amino-benzoic acid methyl ester respectively in step e, followed by reaction of the product obtained, in place of (3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-methyl-carbamic acid *tert*-butyl ester (Example 3, step d), according to the method of Example 3, step e. The product was characterised as the hydrochloride salt. ^{1}H NMR (DMSO-d_6) 9.89 (1H, br s), 7.84-7.40 (6H, m), 7.20 (1H, m), 6.66 (1H, m), 4.78 (2H, m), 3.98 (1H, m), 3.68 (1H, m), 3.35 (1H, m), 2.73 (3H, s), 1.85-1.33 (8H, m), 1.13 (9H, s).

Example 12. *3-{2-[1-(3,3-Dimethyl-2-oxo-butyl)-5-isobutyl-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid.*

Step a. *[1-(3,3-Dimethyl-2-oxo-butyl)-5-isobutyl-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid* was obtained using steps a-d of the method employed in the preparation of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d), except that 1-(2-amino-phenyl)-3-methyl-butan-1-one was used in step a instead of (2-amino-phenyl)-cyclohexyl-methanone. ^{1}H NMR ($CDCl_3$) 7.47-7.39 (2H, m), 7.24 (1H, m), 6.98 (1H, d), 4.60 (2H, br m), 4.10 (2H, br m), 2.60 (2H, br m), 1.93 (1H, m), 1.25 (9H, s), 0.95 (6H, br m).

Step b. The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), except that [1-(3,3-dimethyl-2-oxo-butyl)-5-isobutyl-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 12, step a) was used in place of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d) in step e, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR (DMSO-d_6) 13.0 (1H, br), 10.01 (1H, s), 8.17 (1H, t), 7.70 (1H, d), 7.60-7.49 (3H, m), 7.38 (1H, t), 7.24 (1H, t), 7.13 (1H, d), 4.74 (2H, br m), 4.35 (1H, br m), 4.02 (1H, br m), 2.85 (1H, br m), 2.35 (1H, br m), 1.74 (1H, m), 1.15 (9H, s), 0.85 (6H, br m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 56.58, H 7.55, N 9.54%; $C_{27}H_{32}N_4O_5 \bullet C_7H_{17}NO_5 \bullet 2.0H_2O$ requires C 56.42, H 7.38, N 9.68%.

Example 13. *2-[1-(3,3-Dimethyl-2-oxo-butyl)-5-isobutyl-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-N-(3-methylaminophenyl)-acetamide.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), except that [1-(3,3-dimethyl-2-oxo-butyl)-5-isobutyl-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 11, step a) and (3-amino-phenyl)-methyl-carbamic acid *tert*-butyl ester (Example 3, step c) were used in place of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d) and 3-amino-benzoic acid methyl ester respectively in step e, followed by reaction of the product obtained, in place of (3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-methyl-carbamic acid *tert*-butyl ester (Example 3, step d), according to the method of Example 3, step e. The compound was further characterised as the hydrochloride salt. ^{1}H NMR (DMSO-d_6) 10.03 (1H, br s), 7.56-7.46 (3H, m), 7.28-7.20 (3H, m), 7.13 (1H, d), 6.89 (1H, d), 4.73 (2H, br s), 4.10 (2H, br), 3.85 (1H, br m), 2.78 (3H, s), 2.30 (1H, br m), 1.74 (1H, m), 1.15 (9H, s), 0.86 (6H, br

m). Found: C 61.02, H 7.35, N 13.18%; $C_{27}H_{35}N_5O_3 \bullet H_2O \bullet HCl$ requires C 60.95, H 7.20, N 13.16%.

Example 14. *3-{2-[5-Cyclohexyl-1-methyl-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid.*

The title compound was obtained using the method employed in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that iodomethane was used in step c instead of 1-bromo-3,3-dimethyl-butan-2-one, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR (DMSO-d_6) 12.90 (1H, br s), 10.03 (1H, s), 8.16 (1H, s), 7.69 (1H, d), 7.60-7.50 (3H, m), 7.38 (1H, t), 7.31-7.22 (2H, m), 4.20 (2H, br d), 3.14 (3H, s), 2.85 (1H, m), 1.64-1.04 (10H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 56.92, H 7.12, N, 10.58%; $C_{24}H_{26}N_4O_4 \bullet C_7H_{17}NO_5 \bullet 1.4H_2O$ requires: C 56.82, H 7.05, N 10.69%.

Example 15. *3-{2-[5-Cyclohexyl-2-oxo-1-(2-oxo-2-*o*-tolyl-ethyl)-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid.*

The title compound was obtained using the method employed in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that 2-bromo-1-*o*-tolyl-ethanone was used in step c instead of 1-bromo-3,3-dimethyl-butan-2-one, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR (DMSO-d_6) 13.00 (1H, br s), 9.98 (1H, s), 8.15 (1H, s), 7.77 (1H, d), 7.70 (1H, dd), 7.60-7.51 (3H, m), 7.39 (2H, m), 7.26 (4H, m), 5.06 (2H, m), 4.32 (1H, d), 3.98 (1H, d), 2.85 (1H, m), 2.29 (3H, s), 1.65-1.54 (6H, m), 1.36-1.14 (4H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 60.58, H 6.86, N, 8.86%; $C_{32}H_{32}N_4O_5 \bullet C_7H_{17}NO_5 \bullet 1.4H_2O$ requires: C 60.45, H 6.76, N 9.04%.

Example 16. *3-{2-[5-Cyclohexyl-1-(3-methyl-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid.*

The title compound was obtained using the method employed in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that 1-bromo-3-methyl-butane was used in step c instead of 1-bromo-3,3-dimethyl-butan-2-one, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR (DMSO-d_6) 13.00 (1H, br s), 9.99 (1H, s), 8.14 (1H, s), 7.68 (1H, dd), 7.56 (3H, m), 7.40 (2H, m), 7.27 (1H, d), 4.33 (1H, d), 3.98 (2H, m), 3.60 (1H, m), 2.85 (1H, m), 1.65-1.06 (13H, m), 0.77 (6H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 59.05, H 7.81, N, 10.02%; $C_{28}H_{34}N_4O_4 \bullet C_7H_{17}NO_5 \bullet 1.3H_2O$ requires: C 59.23, H 7.62, N 9.87%.

Example 17. *3-{2-[1-(2-Adamantan-1-yl-2-oxo-ethyl)-5-cyclohexyl-2-oxo-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid.*

The title compound was obtained using the method employed in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that 1-adamantan-1-yl-2-bromo-ethanone was used in step c instead of 1-bromo-3,3-dimethyl-butan-2-one, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR ($CDCl_3$) 8.51 (1H, s), 8.04 (1H, d), 7.84 (1H, s), 7.80 (1H, d), 7.52-7.23 (4H, m), 7.03 (1H, d), 4.75 (1H, d), 4.59 (1H, d), 4.26 (2H, m), 2.80 (1H, m), 2.07-1.70 (21H, m), 1.27 (4H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 60.07, H 7.58, N, 8.37%; $C_{35}H_{40}N_4O_5 \bullet C_7H_{17}NO_5 \bullet 2.7H_2O$ requires: C 60.05, H 7.48, N 8.34%.

Example 18. *3-{2-[5-Cyclohexyl-1-(2-ethoxy-ethyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid.*

The title compound was obtained using the method employed in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that bromoethyl-ethyl ether was used in step c instead of 1-bromo-3,3-dimethyl-butan-2-one, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR ($CDCl_3$) 8.45 (1H, s), 7.97 (1H, dd), 7.80 (1H, d), 7.63 (1H, t), 7.57 (1H, dt), 7.48 (1H, d), 7.37 (3H, m), 4.44 (1H, d), 4.34 (1H, m), 4.16 (1H, d), 3.75 (1H, m), 3.55 (2H, m), 3.38 (2H, m), 2.81 (1H, m), 2.02-1.67 (6H, m), 1.28 (4H, m), 1.08 (3H, t). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 56.72, H 7.46, N, 9.69%; $C_{27}H_{32}N_4O_5 \bullet C_7H_{17}NO_5 \bullet 1.8H_2O$ requires: C 56.72, H 7.36, N 9.73%.

Example 19. *3-{2-[5-Cyclohexyl-2-oxo-1-(terahydro-pyran-2-ylmethyl)-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid.*

The title compound was obtained using the method employed in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that 2-bromomethyl-tetrahydro-pyran was used in step c instead of 1-bromo-3,3-dimethyl-butan-2-one, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR ($CDCl_3$) 8.45 (1H, d), 7.98 (1H, d), 7.79 (1H, d), 7.64-7.54 (2H, m), 7.49-7.33 (3H, m), 7.25 (1H, m), 4.47-4.12 (3H, m), 3.80 (1H, m), 3.55-3.30 (2H, m), 3.23 (1H, m), 2.82 (1H, m), 2.05-1.20 (16H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 57.71, H 7.53, N, 9.14%; $C_{29}H_{34}N_4O_5 \bullet C_7H_{17}NO_5 \bullet 2.1H_2O$ requires: C 57.54, H 7.40, N 9.32%.

Example 20. *3-{2-[5-Cyclohexyl-2-oxo-1-(2-oxo-2-pyrrolidin-1-yl-ethyl)-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid.*

The title compound was obtained using the method employed in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that 2-bromo-1-pyrrolidin-1-yl-ethanone was used in step c instead of 1-bromo-3,3-dimethyl-butan-2-one, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR ($CDCl_3$) 8.59 (1H, s), 8.02 (1H, d), 7.85 (1H, s), 7.75 (1H, d), 7.48 (2H, m), 7.33 (3H, m), 4.50 (1H, d), 4.35 (1H, d), 4.80 (2H, s), 3.53 (4H, m), 2.78 (1H, m), 2.05-1.70 (10H, m), 1.26 (4H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 56.43, H 7.30, N, 10.86%; $C_{29}H_{33}N_5O_5 \bullet C_7H_{17}NO_5 \bullet 2.3H_2O$ requires: C 56.34, H 7.16, N 10.95%.

Example 21. *3-{2-[5-Cyclohexyl-2-oxo-1-(2-oxo-propyl)-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid.*

Step a. *[5-Cyclohexyl-2-oxo-1-(2-oxo-propyl)-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid ethyl ester.* To a solution of (5-cyclohexyl-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetic acid ethyl ester (Example 1, major product of step b) (300mg, 1.00mmol in MeCN (5ml) were added K_2CO_3 (166mg, 1.20mmol), KI (20mg) and 1-chloro-propan-2-one (90µl, 1.10mmol). The reaction mixture was heated at reflux for 48h, then 1-chloro-propan-2-one (180µl, 2.20mmol) was added and heating continued for 16h. The reaction mixture was filtered and the filtrate was evaporated. The residue was partitioned between saturated $NaHCO_3$ (30ml) and EtOAc (30ml). The organic phase was dried ($MgSO_4$), filtered and the solvent was evaporated. The crude product was purified by flash column chromatography (EtOAc-DCM (1:19)) to afford the product as a colourless foam (297mg, 77%). ^{1}H NMR ($CDCl_3$) 7.40 (2H, m), 7.19 (1H, t), 6.98 (1H, d), 4.50-4.11 (6H, m), 2.73 (1H, m), 2.19 (3H, s), 1.98-1.60 (6H, m), 1.26 (7H, m).

Step b. The title compound was obtained using the method employed in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), except that [5-cyclohexyl-2-oxo-1-(2-oxo-propyl)-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid ethyl ester (Example 21, step a) was used in place of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid ethyl ester (Example 1, step c) in step d, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR ($CDCl_3$) 8.55 (1H, s), 7.99 (1H, d), 7.81 (2H, m), 7.54-7.31 (4H, m), 7.09 (1H, d), 4.66 (1H, d), 4.43 (1H, d), 4.27 (2H, m), 2.82 (1H, m), 2.21 (3H, s), 2.07-1.73 (6H, m), 1.24 (4H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 54.51, H 7.23, N, 9.88%; $C_{26}H_{28}N_4O_5 \bullet C_7H_{17}NO_5 \bullet 2.9H_2O$ requires: C 54.72, H 7.07, N 9.67%.

Example 22. *3-{2-[5-Cyclohexyl-1-(2-cyclopentyl-2-oxo-ethyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid.*

Step a. *[5-Cyclohexyl-1-(2-cyclopentyl-2-oxo-ethyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid* was obtained using steps a-d of the method employed in the preparation of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d) except that 2-bromo-cyclopentyl-ethanone was used in step c instead of 1-bromo-3,3-dimethyl-butan-2-one. ^{1}H NMR ($CDCl_3$) 11.00 (1H, br s), 7.45 (2H, m), 7.25 (1H, m), 7.01 (1H, d), 4.56 (2H, d), 4.23 and 3.95 (2H, 2xd), 2.97 (1H, m), 2.81 (1H, m), 2.03-1.58 (13H, m), 1.30 (5H, m).

Step b. The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that [5-cyclohexyl-1-(2-cyclopentyl-2-oxo-ethyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 22, step a) was used in place of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d) in step e, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-

(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR ($CDCl_3$) 8.52 (1H, s), 8.02 (1H, dd), 7.85 (1H, s), 7.81 (1H, d), 7.49 (2H, m), 7.41 (1H, t), 7.32 (1H, t), 7.08 (1H, d), 4.69 (1H, d), 4.46 (1H, d), 4.27 (2H, m), 2.96 (1H, m), 2.81 (1H, m), 2.05-1.61 (13H, m), 1.29 (5H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 58.44, H 7.42, N, 9.18%; $C_{30}H_{34}N_4O_5 \bullet C_7H_{17}NO_5 \bullet 1.9H_2O$ requires: C 58.43, H 7.27, N 9.21%.

Example 23. *2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-*N*-[3-(2*H*-tetrazol-5-yl)-phenyl]-acetamide.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that 2,2-dimethyl-propionic acid 5-(3-amino-phenyl)-tetrazol-2-ylmethyl ester was used in place of 3-amino-benzoic acid methyl ester in step e, followed by reaction of the product obtained, in place of 2,2-dimethyl-propionic acid 5-(3-{2-[5-cyclopentyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-tetrazol-2-ylmethyl ester (Example 10, step a), according to the method of Example 10, step b. ^{1}H NMR ($CDCl_3$) 8.86 (1H, s), 8.18 (1H, m), 7.79 (1H, m), 7.46-7.24 (6H, m), 6.97 (1H, m), 4.73 (1H, d), 4.63 (1H, d), 4.27 (1H, d), 4.22 (1H, d), 2.77 (1H, m), 1.97-1.68 (6H, m), 1.24-1.11 (13H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 55.36, H 7.36, N, 16.01%; $C_{29}H_{34}N_8O_3 \bullet C_7H_{17}NO_5 \bullet 2.5H_2O$ requires: C 55.23, H 7.21, N 16.10%.

Example 24. *2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-*N*-m-tolyl-acetamide.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that *m*-toluidine was used instead of 3-amino-benzoic acid methyl ester in step e. ^{1}H NMR ($CDCl_3$) 8.19 (1H, s), 7.48 (2H, m), 7.46 (2H, m), 7.28 (2H, m), 7.15 (1H, d), 6.87 (1H, m), 4.72 (1H, d), 4.65

(1H, d), 4.28 (1H, d), 4.20 (1H, d), 2.80 (1H, m), 2.30 (3H, s), 1.76-1.70 (6H, m), 1.29-1.19 (13H, m). Found: C 70.23, H 7.63, N 11.09 %; $C_{29}H_{36}N_4O_3 \bullet 0.5H_2O$ requires: C 69.99, H 7.49, N 11.26%.

Example 25. *2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-*N*-phenyl-acetamide.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that aniline was used instead of 3-amino-benzoic acid methyl ester in step e. ^{1}H NMR ($CDCl_3$) 8.20 (1H, s), 7.48-7.41 (5H, m), 7.38-7.27 (2H, m), 7.03 (2H, m), 4.70 (1H, d), 4.64 (1H, d), 4.32 (1H, d), 4.18 (1H, d), 2.78 (1H, m), 2.00-1.53 (6H, m), 1.32-1.23 (13H, m). Found: C 69.45, H 7.37, N 11.39 %; $C_{28}H_{34}N_4O_3 \bullet 0.5H_2O$ requires: C 69.54, H 7.29, N 11.58%.

Example 26. *2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-*N*-(3-methanesulfonylamino-phenyl)-acetamide.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that *N*-(3-amino-phenyl)-methanesulfonamide was used instead of 3-amino-benzoic acid methyl ester in step e. ^{1}H NMR ($CDCl_3$) 8.51 (1H, s), 7.61 (1H, s), 7.45 (2H, m), 7.29 (2H, m), 7.06 (4H, m), 4.75 (1H, d), 4.62 (1H, d), 4.26 (2H, m), 2.98 (3H, s), 2.79 (1H, m), 2.00-1.50 (6H, m), 1.32-1.23 (13H, m). Found: C 56.14, H 6.86, N 10.97 %; $C_{29}H_{37}N_5O_5S \bullet 3.0H_2O$ requires: C 56.02, H 6.97, N 11.26%.

Example 27. *2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-*N*-(3-pyrrolidin-1-yl-phenyl)-acetamide.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that 3-pyrrolidin-1-yl-

phenylamine (prepared in two steps from 3-nitro-aniline) was used instead of 3-amino-benzoic acid methyl ester in step e. ^{1}H NMR ($CDCl_3$) 8.01 (1H, s), 7.49 (2H, m), 7.24 (1H, m), 7.04 (2H, m), 6.72 (1H, s), 6.51 (1H, d), 6.26 (1H, d), 4.69 (2H, m), 4.42 (1H, d), 4.12 (1H, d), 3.25 (4H, m), 2.77 (1H, m), 2.00-1.69 (10H, m), 1.28-1.21 (13H, m). The compound was further characterised as the hydrochloride salt. Found: C 57.06, H 6.38, N 10.59 %; $C_{32}H_{41}N_5O_9$•HCl requires: C 56.82, H 6.26, N 10.36%.

Example 28. *4-{2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that 4-amino-benzoic acid methyl ester was used instead of 3-amino-benzoic acid methyl ester in step e. ^{1}H NMR ($CDCl_3$) 8.57 (1H, s), 7.98 (2H, d), 7.50 (4H, m), 7.24 (1H, m), 7.03 (1H, d), 4.69 (1H, d), 4.59 (1H, d), 4.22 (2H, m), 3.89 (3H, s), 2.79 (1H, m), 2.00-1.69 (6H, m), 1.28-1.21 (13H, m). Found: C 66.21, H 6.98, N 10.42%; $C_{30}H_{36}N_4O_5$•5.0H_2O requires: C 66.52, H 6.88, N 10.34%.

Example 29. *(3-{2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-acetic acid.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that (3-amino-phenyl)-acetic acid methyl ester was used instead of 3-amino-benzoic acid methyl ester in step e, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR ($CDCl_3$) 8.28 (1H, s), 7.48 (2H, m), 7.34-7.22 (4H, m), 7.00 (2H, m), 4.72 (1H, d), 4.64 (1H, d), 4.28 (1H, d), 4.15 (1H, d), 3.48 (2H, s), 2.70 (1H, m), 1.79-1.36 (6H, m), 1.22-1.05 (13H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 58.04, H 7.73, N 9.14%; $C_{30}H_{36}N_4O_5$•$C_7H_{17}NO_5$•2.0H_2O requires: C 58.18,

H, 7.52, N 9.17%.

Example 30. *2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]*-N-*(3-methoxy-phenyl)-acetamide.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that *m*-anisidine was used instead of 3-amino-benzoic acid methyl ester in step e. ^{1}H NMR ($CDCl_3$) 8.22 (1H, m), 7.45-7.30 (2H, m), 7.27 (1H, m), 7.20-7.12 (2H, m), 7.03 (1H, d), 6.84 (1H, d), 6.63 (1H, d), 4.73 (1H, d), 4.64 (1H, d), 4.28 (1H, d). 4.19 (1H, d), 3.79 (3H, s), 2.80 (1H, m), 1.76-1.55 (6H, m), 1.36-1.24 (13H, m). Found C 68.01, H 7.48, N 11.01; $C_{29}H_{36}N_4O_4 \bullet 0.5H_2O$ requires C 67.81, H, 7.26, N 10.91%

Example 31. *2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]*-N-p-*tolyl-acetamide.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that *p*-toluidine was used instead of 3-amino-benzoic acid methyl ester in step e. ^{1}H NMR ($CDCl_3$) 8.11 (1H, s), 7.47 (2H, m), 7.29-7.25 (2H, m), 7.08-7.00 (4H, m), 4.71 (1H, d), 4.64 (1H, d), 4.32 (1H, d), 4.16 (1H, d), 2.77 (1H, m), 2.29 (3H, s), 1.86-1.53 (6H, m), 1.33-1.21 (13H, m). Found C 71.49, H 7.54, N 11.25; $C_{29}H_{36}N_4O_3$ requires C 71.28, H, 7.43, N 11.47%

Example 32. *2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]*-N-*(4-methoxy-phenyl)-acetamide.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that *p*-anisidine was used instead of 3-amino-benzoic acid methyl ester in step e. ^{1}H NMR ($CDCl_3$) 8.11 (1H, m), 7.47 (2H, m), 7.32-7.24 (3H, m), 7.01 (1H, d), 6.82 (2H, m), 4.74 (1H, d), 4.60 (1H, d),

4.31 (1H, d), 4.16 (1H, d), 3.77 (3H, s), 2.78 (1H, m), 2.03-1.71 (6H, m), 1.36-1.13 (13H, m). Found C 67.74, H 7.53, N 10.67; $C_{29}H_{36}N_4O_4 \bullet 0.5H_2O$ requires C 67.81, H, 7.26, N 10.91%

Example 33. *2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-*N*-(3-dimethylamino-phenyl)-acetamide.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that *m-N,N*-dimethylaminoaniline was used instead of 3-amino-benzoic acid methyl ester in step e. ^{1}H NMR ($CDCl_3$) 8.08 (1H, s), 7.50 (2H, m), 7.28 (1H, m), 7.10 (2H, m), 6.88 (1H, m), 6.64 (1H, m), 6.45 (1H, m), 4.69 (1H, d), 4.67 (1H, d), 4.36 (1H, d), 4.14 (1H, d), 2.95 (6H, m), 2.74 (1H, m), 2.00-1.71 (6H, m), 1.36-1.17 (13H, m). The compound was further characterised as the hydrochloride salt. Found C 61.26, H 7.58, N 11.82; $C_{30}H_{39}N_5O_3 \bullet HCl \bullet 2.0H_2O$ requires C 61.05, H, 7.51, N 11.86%

Example 34. *(6-{2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-2,3-dihydro-indol-1-yl)-acetic acid.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that (6-amino-2,3-dihydro-indol-1-yl)-acetic acid methyl ester (prepared in two steps from 6-nitro-2,3-dihydro-1*H*-indole), was used instead of 3-amino-benzoic acid methyl ester in step e, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR (DMSO-d_6) 12.40 (1H, br s), 9.38 (1H, s), 7.53 (2H, m), 7.18 (2H, m), 6.86 (1H, d), 6.65 (1H, d), 6.54 (1H, s), 4.78 (2H, m), 4.25 (1H, d), 3.90 (1H, d), 3.78 (2H, s), 3.46 (2H, m), 2.84 (3H, m), 1.86-1.55 (6H, m), 1.25-1.17 (13H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found C 56.11, H 7.64, N 9.87; $C_{32}H_{39}N_5O_5 \bullet C_7H_{17}NO_5 \bullet 3.5H_2O$ requires C 56.30, H, 7.63, N 10.10%.

Example 35. *2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-*N*-(4-fluoro-phenyl)-acetamide.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that 4-fluoroaniline was used instead of 3-amino-benzoic acid methyl ester in step e. ^{1}H NMR ($CDCl_3$) 8.31 (1H, s), 7.48-7.28 (5H, m), 6.96 (3H, m), 4.75 (1H, d), 4.55 (1H, d), 4.21 (2H, m), 2.74 (1H, m), 1.90-1.65 (6H, m), 1.34-1.15 (13H, m). Found C 66.98, H 7.09, N 10.88; $C_{28}H_{33}FN_4O_3 \bullet 0.5H_2O$ requires C 67.04, H, 6.82, N 11.16%.

Example 36. *2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-*N*-{4-[methyl-(2*H*-tetrazol-5-yl)-amino]-phenyl}-acetamide.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that 2,2-dimethyl-propionic acid 5-[(3-amino-phenyl)-methyl-amino]-tetrazol-2-ylmethyl ester (J. L. Castro *et al. J. Med. Chem.* (1996), **39**, 842) was used in place of 3-amino-benzoic acid methyl ester in step e, followed by reaction of the product obtained, in place of 2,2-dimethyl-propionic acid 5-(3-{2-[5-cyclopentyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-tetrazol-2-ylmethyl ester (Example 10, step a), according to the method of Example 10, step b. ^{1}H NMR (DMSO-d_6) 9.84 (1H, s), 7.55-7.05 (8H, m), 4.78 (2H, m), 3.96 (1H, m), 3.55 (1H, m), 3.39 (3H, s), 2.86 (1H, m), 1.85-1.65 (6H, m), 1.33-1.10 (13H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found C 57.86, H 7.31, N 18.31; $C_{30}H_{37}N_9O_3 \bullet C_7H_{17}NO_5$ requires C 57.94, H, 7.10, N 18.26%.

Example 37. N-*(3-Cyano-phenyl)-2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetamide.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-

cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that 3-aminobenzonitrile was used instead of 3-amino-benzoic acid methyl ester in step e. ^{1}H NMR ($CDCl_3$) 8.76 (1H, s), 7.83 (2H, m), 7.50-7.29 (5H, m), 7.02 (1H, m), 4.81 (1H, d), 4.48 (1H, d), 4.28 (1H, d), 4.14 (1H, d), 2.79 (1H, m), 1.91-1.65 (6H, m), 1.36-1.17 (13H, m). Found C 66.32, H 6.89, N 13.39; $C_{29}H_{33}N_5O_3 \bullet 1.5H_2O$ requires C 66.14, H, 6.89, N 13.29%.

Example 38. *(3-{2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenylsulfanyl)-acetic acid.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that (3-amino-phenylsulfanyl)-acetic acid ethyl ester (S. Hagishita *et al. Bioorg. Med. Chem.* (1997), **5**, 1433) was used instead of 3-amino-benzoic acid methyl ester in step e, followed by reaction of the product obtained, in place of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid ethyl ester (Example 1, step c), according to the method of Example 1, step d. ^{1}H NMR (DMSO-d_6) 12.60 (1H, br s), 9.81 (1H, s), 7.50 (3H, m), 7.27-7.21 (4H, m), 6.97 (1H, m), 4.78 (2H, m), 4.27 (1H, d), 3.96 (1H, d), 3.72 (2H, s), 2.86 (1H, m), 1.83-1.65 (6H, m), 1.29-1.17 (13H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found C 54.50, H 7.36, N 8.44; $C_{30}H_{36}N_4O_5S \bullet C_7H_{17}NO_5 \bullet 3.0H_2O$ requires C 54.59, H, 7.30, N 8.60%.

Example 39. *5-{2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-isophthalic acid.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that 5-amino-isophthalic acid dimethyl ester was used instead of 3-amino-benzoic acid methyl ester in step e, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR

(DMSO-d_6) 10.19 (1H, s), 8.33 (2H, s), 8.13 (1H, s), 7.53 (1H, d), 7.48 (1H, t), 7.23 (1H, t), 7.16 (1H, d), 4.80 (2H, br), 4.30 (1H, br), 4.00 (1H, br), 2.85 (1H, m), 1.90-1.50 (6H, m), 1.45-1.13 (13H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 54.69, H 7.11, N 8.70%; $C_{30}H_{34}N_4O_7 \bullet C_7H_{17}NO_5 \bullet 3.0H_2O$ requires C 54.74, H 7.08, N 8.63%.

Example 40. *2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]*-N-*(3-methanesulfonylaminocarbonyl-phenyl)-acetamide.*

Methanesulfonamide (96mg, 1.00mmol) was added to a solution of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid (Example 2) (409mg, 0.80mmol), EDC (207mg, 1.08mmol) and DMAP (122mg, 1.00mmol) in DCM (20ml) at room temperature. After stirring for 17h, the mixture was washed with 5% $KHSO_4$ (50ml), brine (50ml) and dried ($MgSO_4$). Filtration and evaporation of the solvent gave the crude product which was purified by flash column chromatography (MeOH-DCM (1:10) to afford the title compound as a white crystalline solid (392mg, 83%). ^{1}H NMR (DMSO-d_6) 9.99 (1H, s), 8.02 (1H, s), 7.63-7.36 (5H, m), 7.23 (1H, t), 7.13 (1H, d), 4.73 (2H, dd), 4.29 and 4.25 (2H, d × 2), 3.24 (3H, s), 2.87 (1H, m), 1.80-1.48 (6H, m), 1.30-1.09 (13H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 53.93, H 7.07, N, 10.17%; $C_{30}H_{37}N_5O_6S \bullet C_7H_{17}NO_5 \bullet 2.0H_2O$ requires: C 53.74, H 7.07, N 10.16%.

Example 41. *2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]*-N-*(3-propylamino-phenyl)-acetamide.*

Step a. *(3-{2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-propyl-carbamic acid tert-butyl ester* was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that (3-amino-phenyl)-propyl-carbamic acid *tert*-butyl ester (obtained using steps b and c of the method employed in the preparation of (3-amino-phenyl)-methyl-carbamic acid *tert*-butyl ester (Example 3, step c) except that 1-

bromopropane was used in step b instead of iodomethane), was used instead of 3-amino-benzoic acid methyl ester in step e.

Step b. 4.0M HCl in dioxan (5ml, 20.0mmol) was added to a solution of (3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-propyl-carbamic acid *tert*-butyl ester (Example 41, step a) (524mg,0.83mmol) in dioxan (15ml) at room temperature. The mixture was stirred for 2h during which time a white precipitate formed. The solvent was evaporated, and the solid obtained was washed with Et_2O, isolated by filtration and dried, to afford the hydrochloride salt of the title compound (430mg, 91%). ^{1}H NMR ($CDCl_3$) 8.39 (1H, s), 7.61-7.27 (7H, m), 7.01 (1H, d), 4.69 (2H, br s), 4.60 (1H, d), 4.29 (2H, dd), 3.21 (2H, br s), 2.80 (1H, br s), 2.01-1.45 (6H, m), 1.43-1.19 (15H, m), 0.95 (3H, t). Found: C 63.68, H 7.65, N, 11.98%; $C_{31}H_{41}N_5O_3 \bullet HCl \bullet H_2O$ requires: C 63.52, H 7.57, N 11.95%.

Example 42. *2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-*N*-[3-(2-ethoxy-ethylamino)-phenyl)-acetamide.*

The title compound was obtained as the hydrochloride salt by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), except that (3-amino-phenyl)-2-ethoxyethyl-carbamic acid *tert*-butyl ester (obtained using the method employed in the preparation of (3-amino-phenyl)-methyl-carbamic acid tert-butyl ester (Example 3, step c) except that 2-bromoethyl-ethyl ether was used in step b instead of iodomethane) was used instead of 3-amino-benzoic acid methyl ester in step e, followed by reaction of the product obtained, in place of (3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-propyl-carbamic acid *tert*-butyl ester (Example 41, step a) according to the method of Example 41 step b. ^{1}H NMR ($CDCl_3$) 8.45 (1H, s), 7.61 (1H, s), 7.56-7.47 (2H, m), 7.36 (4H, m), 7.03 (1H, d), 4.70 (2H, dd), 4.26 (2H, dd), 3.73 (2H, br s), 3.51 (4H, m), 2.82 (1H, br s), 2.05-1.65 (6H, m), 1.30-1.17 (16H, m). Found: C 63.90 H 7.66, N, 11.58%; $C_{32}H_{43}N_5O_4 \bullet HCl \bullet 0.25H_2O$ requires: C 63.77, H 7.44, N 11.62%.

Example 43. *5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-3-(2-oxo-2-*m*-tolyl-ethyl)-1,3-dihydro-3*H*-1,3,4-benzotriazepin-2-one.*

Step a. *2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-*N*-methoxy-*N*-methyl-acetamide* was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that *N,O*-dimethylhydroxylamine hydrochloride and triethylamine were used instead of 3-amino-benzoic acid methyl ester in step e. ^{1}H NMR ($CDCl_3$) 7.86 (2H, m), 7.17 (1H, m), 6.94 (1H, d), 4.70-4.14 (3H, m), 4.09 (1H, m), 3.68 (3H, s), 3.17 (3H, s), 2.72 (1H, m), 1.93-1.55 (6H, m), 1.43-1.22 (13H, m).

Step b. A 1.0M solution of *m*-tolylmagnesium chloride in THF (0.6ml, 0.6mmol) was added drop-wise to a solution of 2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-*N*-methoxy-*N*-methyl-acetamide (Example 43, step a) (220mg, 0.5mmol) in Et_2O (10ml) at –78 °C. The reaction mixture was allowed to warm to room temperature and stirred overnight. After solvent concentration, the reaction mixture was extracted with Et_2O, washed with saturated NH_4Cl solution, brine and dried ($MgSO_4$). Flash column chromatography (EtOAc-hexane (1:4)) afforded the title compound as a white solid (36 mg, 15%). ^{1}H NMR ($CDCl_3$) 7.69 (2H, m), 7.39-7.31 (4H, m), 7.26 (1H, m), 6.95 (1H, dd), 5.20 (1H, m), 4.68 (3H, m), 2.79 (1H, m), 2.30 (3H, s), 1.80-1.62 (6H, m), 1.31-1.24 (13H, m). Found C 73.14, H 7.82, N 8.51; $C_{29}H_{35}N_3O_3$ requires C 73.54, H 7.45, N 8.87%

Example 44. *3-{5-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-ylmethyl]-[1,3,4]oxadiazol-2-yl}-benzoic acid.*

Step a. *3-(*N*'-{2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetyl}-hydrazinocarbonyl)-benzoic acid methyl ester* was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that 3-hydrazinocarbonyl-benzoic acid methyl ester

(prepared in two steps from isophthalic acid dimethyl ester) was used instead of 3-amino-benzoic acid methyl ester in step e.

Step b. *3-{5-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3H-1,3,4-benzotriazepin-3-ylmethyl]-[1,3,4]oxadiazol-2-yl}-benzoic acid methyl ester.* A solution of the 3-(*N'*-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetyl}-hydrazinocarbonyl)-benzoic acid methyl ester (Example 44, step a) (94mg, 0.16mmol), triphenylphosphine (64mg, 0.24mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (75mg, 0.49mmol) in CCl_4-MeCN (1:1 / 2ml) was stirred at room temperature for 5h. A further quantity of triphenylphosphine (43mg, 0.16mmol) was added after 3h. The solvent was evaporated under reduced pressure and the residue purified by flash column chromatography (EtOAc-hexane (1:1)) to afford the product as a off-white solid (52mg, 57%). ^{1}H NMR ($CDCl_3$) 8.62 (1H, s), 8.19 (2H, m), 7.56 (1H, t), 7.39-7.35 (2H, m), 7.19 (1H, t), 6.97 (1H, d), 5.05 (1H, br d), 4.85 (1H, br d), 4.68 (2H, s), 3.96 (3H, s), 2.70 (1H, m), 1.80-1.60 (6H, br), 1.25 (13H, m).

Step c. The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid (Example 2) except that 3-{5-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-ylmethyl]-[1,3,4]oxadiazol-2-yl}-benzoic acid methyl ester (Example 44, step b) was used in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1). ^{1}H NMR ($CDCl_3$) 8.69 (1H, s), 8.27 (2H, m), 7.61 (1H, t), 7.42-7.38 (2H, m), 7.20 (1H, t), 6.98 (1H, d), 5.10 (1H, br d), 4.90 (1H, br d), 4.70 (2H, s), 2.73 (1H, m), 1.90-1.60 (6H, m), 1.30-1.25 (13H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 56.75, H 7.08, N, 10.61%; $C_{30}H_{33}N_5O_5 \bullet C_7H_{17}NO_5 \bullet 2.5H_2O$ requires: C 56.69, H 7.07, N 10.72%.

Example 45. *3-({2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl]-acetylamino}-methyl)-benzoic acid.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that 3-aminomethyl-benzoic acid methyl ester was used instead of 3-amino-benzoic acid methyl ester in step e, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR ($CDCl_3$) 8.02 (1H, d), 7.94 (1H, s), 7.51 (1H, d), 7.45-7.35 (2H, m), 7.21 (1H, dd), 7.14 (1H, d), 6.93 (1H, d), 6.75 (1H, br t), 4.66-4.53 (3H, m), 4.38-4.19 (3H, m), 2.64 (1H, br m), 1.88-1.49 (6H, m), 1.31-1.20 (13H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 58.33, H 7.64, N 8.95%; $C_{30}H_{36}N_4O_5 \bullet C_7H_{17}NO_5 \bullet 2.0H_2O$ requires C 58.18, H 7.52, N 9.17%.

Example 46. *[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid* N'-m-*tolyl-hydrazide.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that *meta*-tolyl-hydrazine was used instead of 3-amino-benzoic acid methyl ester in step e. ^{1}H NMR ($CDCl_3$) 8.12 (1H, d), 7.43-7.41 (2H, m), 7.25 (1H, t), 7.09 (1H, m), 6.99 (1H, d), 6.70 (1H, d), 6.65-6.31 (2H, m), 6.01 (1H, d), 4.71 (1H, d), 4.63 (1H, d), 4.24 (2H, s), 2.80 (1H, m), 2.29 (3H, s), 2.10-1.60 (6H, m), 1.35-1.24 (13H, m). Found: C 68.00, H 7.69, N 13.66%; $C_{29}H_{37}N_5O_3 \bullet 0.5H_2O$ requires C 67.94, H 7.47, N 13.66%.

Example 47. *5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-3-(5-oxo-4-*m-*tolyl-4,5-dihydro-[1,3,4]oxadiazol-2-ylmethyl)-1,3-dihydro-3*H*-1,3,4-benzotriazepin-2-one.*

A solution of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid *N'-m*-tolyl-hydrazide (Example 46) (300mg, 0.60mmol), 1,1'-carbonyldiimidzole (483mg, 2.98mmol) and triethylamine (181mg, 1.79mmol) in THF (6ml) was stirred at room temperature for 19h, then heated at reflux for 6h. The solvent was evaporated under reduced pressure and the residue was purified by flash column

chromatography (EtOAc-hexane (2:3-7:3)) to afford the title compound as an off-white solid (83mg, 26%). ^{1}H NMR ($CDCl_3$) 7.63-7.60 (2H, m), 7.41-7.37 (2H, m), 7.32 (1H, m), 7.20 (1H, t), 7.05 (1H, d), 6.96 (1H, d), 4.75 (1H, br d), 4.68 (2H, d), 4.55 (1H, br d), 2.75 (1H, m), 2.38 (3H, s), 1.95-1.60 (6H, m), 1.35-1.20 (13H, m). Found: C 67.93, H 6.78, N 13.23%; $C_{30}H_{35}N_5O_4$ requires C 68.03, H 6.66, N 13.22%.

Example 48. *2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-N-(3-hydroxymethyl-phenyl)-acetamide.*

Step a. Carbonic acid 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzyl ester methyl ester was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that carbonic acid 3-amino-benzyl ester methyl ester was used instead of 3-amino-benzoic acid methyl ester in step e. ^{1}H NMR ($CDCl_3$) 8.30 (1H, s), 7.51-7.39 (4H, m), 7.31-7.24 (2H, m), 5.11 (2H, s), 4.72 (1H, d), 4.64 (1H, d), 4.23 (1H, d), 4.14 (1H, d), 3.80 (3H, s), 2.89 (1H, m), 1.76-1.67 (6H, m), 1.29-1.24 (13H, m).

Step b. Carbonic acid 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzyl ester methyl ester (Example 48, step a) was dissolved in THF-MeOH (1:1 / 40 ml) and 1% K_2CO_3 solution (30ml) was added. The mixture was stirred at room temperature for 2h. After concentration of the organic solvents, a precipitate formed, which was collected by filtration and dried *in vacuo* to afford the title compound as a yellow solid (790 mg, 89%). ^{1}H NMR ($CDCl_3$) 8.31 (1H, s), 7.51-7.45 (3H, m), 7.31-7.28 (3H, m), 7.26-7.10 (2H, m), 4.70 (1H, d), 4.67 (2H, s), 4.64 (1H, d), 4.26 (1H, d), 4.22 (1H, d), 2.89 (1H, m), 1.85-1.55 (6H, m), 1.30-1.24 (13H, m). Found: C 67.70, H 7.40, N 10.79 %; $C_{29}H_{36}N_4O_4 \bullet 0.5H_2O$ requires: C 67.81, H 7.26, N 10.91%.

Example 49. *N-(3-Carbamimidoylsulfanylmethyl-phenyl)-2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl]-acetamide.*

Step a. *N*-(3-Chloromethyl-phenyl)-2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl]-acetamide. 2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl]-N-(3-hydroxymethyl-phenyl)-acetamide (Example 48) (750mg, 1.49mmol) and triphenylphosphine polystyrene resin (1.20mmol/g; 2.50g, 3.00mmol) (P. Hodge, G. Richardson, *J. C. S. Chem. Commun.*, (1983), 622) were heated at reflux in CCl_4 (30ml) for 3h. After filtration and evaporation of the solvent the product was obtained as a pale pink solid (220 mg, 29%). ^{1}H NMR ($CDCl_3$) 8.36 (1H, s), 7.50-7.28 (4H, m), 7.10-7.01 (4H, m), 4.75 (1H, d), 4.60 (1H, d), 4.54 (2H, s), 4.25 (1H, d), 4.22 (1H, d), 2.79 (1H, m), 2.05-1.62 (6H, m), 1.30-1.22 (13H, m).

Step b. *N*-(3-Chloromethyl-phenyl)-2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl]-acetamide (Example 49, step a) (52mg, 0.10mmol) was reacted with thiourea (7.6mg, 0.10mmol) and NaI (2 mg) in refluxing acetone (10ml) for 3h. After cooling, the solvents were concentrated in vacuo, affording the title compound as a yellow solid after trituration with Et_2O (18 mg, 30%). ^{1}H NMR (DMSO-d_6) 9.89 (1H, br s), 8.99 (3H, br s), 7.75-7.46 (3H, m), 7.29-7.04 (5H, m), 4.77 (2H, m), 4.40 (2H, m), 4.38 (1H, m), 3.93 (1H, m), 2.86 (1H, m), 1.73-1.64 (6H, m), 1.21-1.08 (13H, m).

Example 50. *(3-{2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzenesulfonyl)-acetic acid ethyl ester.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that (3-amino-benzenesulfonyl)-acetic acid ethyl ester (prepared in one step from (3-amino-phenylsulfanyl)-acetic acid ethyl ester) was used instead of 3-amino-benzoic acid methyl ester in step e, followed by reaction of the product obtained, in place of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid ethyl ester (Example 1, step c), according to the method of Example 1, step d. ^{1}H NMR (DMSO-d_6) 13.08 (1H, br s), 10.26 (1H, s), 8.16 (1H, s), 7.77-7.45 (5H, m), 7.26-7.15 (2H, m), 4.80 (2H, m), 4.39 (2H, s), 4.38 (1H, d), 3.98 (1H, d), 2.86 (1H, m), 1.65-1.34 (6H, m),

1.25-1.13 (13H, m). The compound was further characterised as the N-methyl-D-glucamine salt. Found: C 53.55, H 6.90, N 8.48 %; $C_{30}H_{36}N_4O_7S \bullet C_7H_{17}NO_5 \bullet 2.0H_2O$ requires: C 53.67, H 6.94, N 8.46%.

Example 51. *[tert-Butoxycarbonyl-(3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-amino]-acetic acid.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that [(3-amino-phenyl)-*tert*-butoxycarbonyl-amino]-acetic acid methyl ester (prepared in three steps from 1-isocyanato-3-nitro-benzene) was used instead of 3-amino-benzoic acid methyl ester in step e, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR (DMSO-d_6) 12.60 (1H, br s), 9.81 (1H, s), 7.52-7.47 (3H, m), 7.23-7.17 (4H, m), 6.89 (1H, d), 4.78 (2H, m), 4.25 (1H, d), 4.14 (2H, s), 3.92 (1H, d), 2.86 (1H, m), 1.86-1.51 (6H, m), 1.36-1.13 (22H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 55.18, H 7.90, N 9.20 %; $C_{35}H_{45}N_5O_7 \bullet C_7H_{17}NO_5 \bullet 4.0H_2O$ requires: C 55.12, H 7.71, N 9.18%.

Example 52. *(3-{2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenylamino)-acetic acid.*

[*tert*-Butoxycarbonyl-(3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-amino]-acetic acid (Example 51) (137mg, 0.21mmol) was stirred in trifluoroacetic acid for 2h at room temperature. After concentration, the resulting gum was dissolved in DCM, washed with saturated $NaHCO_3$ and then with 1N HCl. The organic phase was dried over $MgSO_4$, filtered and the solvent was evaporated to afford the title compound as a yellow solid (85 mg, 73%). ^{1}H NMR (DMSO-d_6) 9.47 (1H, s), 7.55-7.27 (2H, m), 7.23-7.15 (2H, m), 6.97 (1H, t), 6.92-6.68 (2H, m), 6.25(1H, m), 5.80 (2H, br s), 4.78 (2H, m), 4.25 (1H, d), 3.95 (1H, d), 3.72 (2H, s), 2.80 (1H, m), 1.86-1.51 (6H, m), 1.26-1.09 (13H, m). The compound was

further characterised as the N-methyl-D-glucamine salt. Found: C 57.66, H 7.45, N 9.07 %; $C_{30}H_{36}N_4O_6 \bullet C_7H_{17}NO_5 \bullet 1.5H_2O$ requires: C 57.65, H 7.32, N 9.09%.

Example 53. *(3-{2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenoxy)-acetic acid.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that (3-amino-phenoxy)-acetic acid methyl ester was used instead of 3-amino-benzoic acid methyl ester in step e, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR (DMSO-d_6) 13.00 (1H, br s), 9.75 (1H, s), 7.50 (2H, m), 7.26-7.13 (4H, m), 7.04 (1H, d), 6.55 (1H, d), 4.78 (2H, s), 4.58 (2H, s), 4.27 (1H, d), 3.97 (1H, d), 2.85 (1H, m), 1.90-1.20 (10H, m), 1.13 (9H, s). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 57.66, H 7.45, N 9.07%; $C_{30}H_{36}N_4O_6 \bullet C_7H_{17}NO_5 \bullet 1.5H_2O$ requires: C 57.65, H 7.32, N 9.09%.

Example 54. *3-{2-[5-Adamantan-1-yl-1-(3,3-dimethyl-2-oxo-butyl)2-oxo-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid.*

The title compound was obtained using the method employed in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that adamantan-1-yl-(2-amino-phenyl)-methanone (A. Cappelli, *et. al.*, *J. Med. Chem.*, (1999), **42**, 1556) was used in step a instead of (2-amino-phenyl)-cyclohexyl-methanone, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR (DMSO-d_6) 13.0 (1H, br s), 9.89 (1H, s), 8.14 (1H, s), 7.67 (1H, m), 7.59 (2H, d), 7.42 (2H, m), 7.21 (2H, m), 4.79 (2H, m), 4.29 (1H, d), 3.93 (1H, d), 2.04-1.66 (15H, m), 1.13 (9H, s). The compound was further

characterised as the *N*-methyl-D-glucamine salt. Found: C 59.82, H 7.66, N 8.67%; $C_{33}H_{38}N_4O_5 \bullet C_7H_{17}NO_5 \bullet 2.0H_2O$ requires C 59.91, H 7.41, N 8.73%.

Example 55. *3-{2-[5-Cycloheptyl-1-(3,3-dimethyl-2-oxo-butyl)2-oxo-1,2-dihydro-3*H-*1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid.*

The title compound was obtained using the method employed in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that (2-amino-phenyl)-cycloheptyl-methanone (prepared according to the method of A. Cappelli, *et. al., J. Med. Chem.,* (1999), **42**, 1556) was used in step a instead of (2-amino-phenyl)-cyclohexyl-methanone, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR ($CDCl_3$) 8.49 (1H, s), 8.04 (1H, m), 7.87 (1H, m), 7.81 (1H, m), 7.50-7.26 (4H, m), 7.04 (1H, d), 4.78 (1H, d), 4.60 (1H, d), 4.27 (2H, s), 3.00 (1H, m), 2.05-1.44 (12H, m), 1.25 (9H, s). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 57.03, H 7.58, N 8.77 %; $C_{30}H_{36}N_4O_5 \bullet C_7H_{17}NO_5 \bullet 3.5H_2O$ requires: C 56.84, H 7.61, N 8.95%.

Example 56. *(3-{2-[5-Cyclohexy-1-(2-cyclopentyl-2-oxo-ethyl)-2-oxo-1,2-dihydro-3*H-*1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-acetic acid.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), except that [5-cyclohexyl-1-(2-cyclopentyl-2-oxo-ethyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 22, step a) and (3-amino-phenyl)-acetic acid methyl ester were used in place of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d) and 3-amino-benzoic acid methyl ester respectively in step e, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR

($CDCl_3$) 9.20 (1H, br s), 8.29 (1H, s), 7.46 (2H, m), 7.36-7.19 (4H, m), 7.06 (1H, d), 6.99 (1H, d), 4.66 (1H, d), 4.46 (1H, d), 4.32 (1H, d), 4.17 (1H, d), 3.58 (2H, s), 2.93 (1H, m), 2.78 (1H, m), 1.99-1.51 (13H, m), 1.27 (5H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 58.65, H 7.44, N 9.06%; $C_{31}H_{36}N_4O_5 \bullet C_7H_{17}NO_5 \bullet 2.1H_2O$ requires: C 58.70, H 7.41, N 9.01%.

Example 57. *2-[5-Cyclohexyl-1-(2-cyclopentyl-2-oxo-ethyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-*N*-(3-methylaminophenyl)-acetamide.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that [5-cyclohexyl-1-(2-cyclopentyl-2-oxo-ethyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 22, step a) and (3-amino-phenyl)-methyl-carbamic acid *tert*-butyl ester (Example 3, step c) were used in place of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d) and 3-amino-benzoic acid methyl ester respectively in step e, followed by reaction of the product obtained, in place of (3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-methyl-carbamic acid *tert*-butyl ester (Example 3, step d), according to the method of Example 3, step e. ^{1}H NMR ($CDCl_3$) 8.07 (1H, s), 7.47 (2H, m), 7.27 (1H, m), 7.04 (2H, m), 6.92 (1H, t), 6.44 (1H, dd), 6.31 (1H, dd), 4.64 (1H, d), 4.48 (1H, d), 4.36 (1H, d), 4.13 (1H, d), 3.71 (1H, br s), 2.95 (1H, m), 2.80 (4H, m), 2.05-1.56 (13H, m), 1.27 (5H, m). The compound was further characterised as the hydrochloride salt. Found: C 64.90, H 7.02, N 12.57%; $C_{30}H_{37}N_4O_3 \bullet HCl$ requires: C 65.26, H 6.94, N 12.68%.

Example 58. *(3-{2-[5-Cyclohexyl-1-(2-cyclopentyl-2-oxo-ethyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenylsulfanyl)-acetic acid.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that [5-cyclohexyl-1-(2-

cyclopentyl-2-oxo-ethyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 22, step a) and (3-amino-phenylsulfanyl)-acetic acid ethyl ester were used instead of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d) and 3-amino-benzoic acid methyl ester respectively in step e, followed by reaction of the product obtained, in place of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid ethyl ester (Example 1, step c), according to the method of Example 1, step d. ^{1}H NMR ($CDCl_3$) 8.41 (1H, s), 7.45 (2H, m), 7.31-7.17 (4H, m), 7.08 (2H, m), 6.12 (1H, br s), 4.66 (1H, d), 4.21 (1H, d), 4.23 (1H, d), 4.19 (1H, d), 3.65 (2H, s), 2.96 (1H, m), 2.79 (1H, m), 1.82-1.62 (13H, m), 1.29 (5H, m). The compound was further characterised as the N-methyl-D-glucamine salt. Found: C 52.82, H 7.43, N 8.12 %; $C_{31}H_{36}N_4O_5S\bullet C_7H_{17}NO_5\bullet 5.0H_2O$ requires: C 52.95, H 7.36, N 8.04%.

Example 59. *2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]*-N-*[3-(5-oxo-2,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenyl]-acetamide.*

A solution of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d) (200mg, 0.5mmol), EDC (140mg, 0.74mmol), HOBT (100mg, 0.74mmol) and DMAP (20mg) in DMF (10ml) was stirred at room temperature for 2h. Thereafter, a solution of 3-(3-amino-phenyl)-2*H*-[1,2,4]oxadiazol-5-one trifluoroacetic acid salt (WO 93/19063) (170mg, 0.58mmol) and triethylamine (120µl, 1.00mmol) in DMF (2ml) was added and the reaction mixture was stirred for 16h. The mixture was diluted with EtOAc (20ml), and the organic layer washed with aqueous 5% $KHSO_4$, brine and dried over $MgSO_4$. Filtration and evaporation of the solvent afforded an oil which was purified by flash column chromatography (acetone-DCM (1:6)) to give the title compound as an orange foam (62 mg, 22%). ^{1}H NMR ($CDCl_3$) 8.83 (1H, s), 7.90 (1H, m), 7.53-7.25 (7H, m), 7.02 (1H, d), 4.76 (1H, d), 4.57 (1H, d), 4.22 (1H, d), 4.20 (1H, d), 2.80 (1H, m), 1.95-1.55 (6H, m), 1.28-1.20 (13H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 55.99, H 7.15, N 12.14 %; $C_{30}H_{34}N_6O_5\bullet C_7H_{17}NO_5\bullet 2.0H_2O$ requires: C 56.26, H 7.01, N 12.41%.

Example 60. *3-(3-{2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-acrylic acid.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that 3-(3-amino-phenyl)-acrylic acid methyl ester was used instead of 3-amino-benzoic acid methyl ester in step e, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR ($CDCl_3$) 8.43 (1H, s), 7.75-7.45 (5H, m), 7.35-7.23 (3H, m), 7.04 (1H, d), 6.42 (1H, d), 4.76 (1H, d), 4.61 (1H, d), 4.27 (2H, m), 2.79 (1H, m), 2.01-1.65 (6H, m), 1.28-1.23 (13H, m). Found: C 60.70, H 7.50, N 9.60 %; $C_{31}H_{36}N_4O_5 \bullet C_7H_{17}NO_5 \bullet 0.5H_2O$ requires: C 60.49, H 7.26, N 9.35%.

Example 61. *3-(3-{2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-propionic acid.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that 3-(3-amino-phenyl)-propionic acid methyl ester (D. F. Biggs, *et. al., J. Med. Chem.* (1976), **19**, 472) was used instead of 3-amino-benzoic acid methyl ester in step e, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR ($CDCl_3$) 9.05 (1H, br s), 8.35 (1H, s), 7.45 (2H, m), 7.31-7.18 (4H, m), 7.03 (1H, d), 6.92 (1H, d), 4.73 (1H, d), 4.63 (1H, d), 4.27 (1H, d), 4.20 (1H, d), 2.91 (2H, m), 2.79 (1H, m), 2.63 (2H, m), 1.90-1.35 (6H, m), 1.29-1.21 (13H, m). The compound was further characterised as the N-methyl-D-glucamine salt. Found: C 57.25, H 7.81, N 9.02 %; $C_{31}H_{38}N_4O_5 \bullet C_7H_{17}NO_5 \bullet 3.0H_2O$ requires: C 57.34, H 7.72, N 8.80%.

Example 62. N-*(3,5-Bis-hydroxymethyl-phenyl)-2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl]-acetamide.*

The title compound was prepared by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that carbonic acid 3-amino-5-methoxycarbonyloxymethyl-benzyl ester methyl ester was used instead of 3-amino-benzoic acid methyl ester in step e, followed by reaction of the product obtained, in place carbonic acid 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzyl ester methyl ester (Example 48, step a), according to the method of Example 48, step b. ^{1}H NMR ($CDCl_3$) 8.37 (1H, s), 7.47 (2H, m), 7.30 (3H, m), 7.09 (1H, s), 7.02 (1H, d), 4.78-4.58 (6H, m), 4.23 (2H, m), 2.79 (1H, m), 2.04-1.44 (8H, m), 1.26 (13H, m). Found: C 64.88, H 7.45, N 10.15%; $C_{30}H_{38}N_4O_5 \bullet 1.2H_2O$ requires: C 64.75, H 7.32, N 10.07%.

Example 63. *2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]*-N*-pyridin-2-yl-acetamide.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that 2-aminopyridine was used instead of 3-amino-benzoic acid methyl ester in step e. ^{1}H NMR ($CDCl_3$) 8.83 (1H, s), 8.20-8.14 (2H, m), 7.62 (1H, t), 7.46-7.40 (2H, m), 7.25 (1H, m), 6.98-6.93 (2H, m), 4.70 (1H, d), 4.66 (1H, d), 4.30 (1H, d), 4.20 (1H, m), 2.78 (1H, m), 2.03-1.60 (6H, m), 1.38-1.22 (13H, m). The compound was further characterised as the hydrochloride salt. Found: C 61.20, H 6.90, N 13.04%; $C_{27}H_{33}N_5O_3 \bullet HCl \bullet H_2O$ requires: C 61.18, H 6.85, N 13.21%.

Example 64. *2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]*-N*-pyridin-3-yl-acetamide.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-

yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that 3-aminopyridine was used instead of 3-amino-benzoic acid methyl ester in step e. ^{1}H NMR ($CDCl_3$) 8.52 (1H, br s), 8.36 (1H, d), 8.31-8.24 (2H, m), 7.48-7.44 (2H, m), 7.31-7.22 (2H, m), 7.02 (1H, d), 4.79 (1H, d), 4.56 (1H, d), 4.23 (2H, s), 2.80 (1H, br m), 2.01 (1H, br m), 1.87-1.62 (5H, m), 1.33-1.23 (13H, m). The compound was further characterised as the hydrochloride salt. Found: C 60.81, H 7.01, N 12.93%; $C_{27}H_{33}N_5O_3 \bullet HCl \bullet H_2O$ requires: C 61.18, H 6.85, N 13.21%.

Example 65. *[Acetyl-(3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-amino]-acetic acid.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that [acetyl-(3-amino-phenyl)-amino]-acetic acid methyl ester (prepared in three steps from 3-nitroaniline) was used instead of 3-amino-benzoic acid methyl ester in step e, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR (DMSO-d_6) 13.00 (1H, br s), 10.01 (1H, s), 7.50 (4H, m), 7.33 (1H, t), 7.23 (1H, m), 7.16 (1H, d), 7.03 (1H, d), 4.79 (2H, s), 4.28 (1H, d), 4.17 (2H, s), 3.96 (1H, d), 2.86 (1H, m), 2.01 (1H, br m), 1.90-1.10 (10H, m), 1.76 (3H, s), 1.16 (9H, s). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 55.77, H 7.44, N 9.81%; $C_{32}H_{39}N_5O_6 \bullet C_7H_{17}NO_5 \bullet 3.0H_2O$ requires: C 55.83, H 7.49, N 10.02%.

Example 66. N-*(3-{2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-succinamic acid.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that *N*-(3-amino-phenyl)-succinamic acid methyl ester (prepared in three steps from 3-nitroaniline) was used instead of 3-amino-benzoic acid methyl ester in step e, followed by reaction of the product

obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR (DMSO-d_6) 12.00 (1H, br s), 9.91 (1H, s), 9.75 (1H, s), 7.88 (1H, s), 7.50 (2H, m), 7.25-7.13 (5H, m), 4.78 (2H, s), 4.25 (1H, d), 3.96 (1H, d), 2.86 (1H, m), 2.48 (4H, s), 1.98-1.17 (10H, m), 1.13 (9H, s). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 55.74, H 7.69, N 9.91%; $C_{32}H_{39}N_5O_6 \bullet C_7H_{17}NO_5 \bullet 3.0H_2O$ requires: C 55.84, ·H 7.49, N 10.02%.

Example 67. *2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-*N*-[3-(1*H*-tetrazol-5-ylmethyl)-phenyl]-acetamide.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that 3-(1*H*-tetrazol-5-yl-methyl)-aniline was used instead of 3-amino-benzoic acid methyl ester in step e. ^{1}H NMR ($CDCl_3$) 8.61 (1H, s), 7.44 (4H, m), 7.27 (4H, m), 6.98 (2H, m), 4.70 (2H, q), 4.25 (2H, d), 2.80 (1H, m), 2.04 (1H, br m), 1.84 (1H, br d), 1.67 (6H, m), 1.28 (2H, m), 1.19 (9H, s). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found C 56.69, H 7.43, N 16.08, $C_{30}H_{36}N_8O_3 \bullet C_7H_{17}NO_5 \bullet 1.9H_2O$ requires C 56.57, H 7.43, N 16.77%.

Example 68. *3-{2-[5-Cyclohexyl-1-(2-morpholin-4-yl-2-oxo-ethyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid.*

Step a. *(1-*tert*-Butoxycarbonylmethyl-5-cyclohexyl-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetic acid ethyl ester* was obtained by the method used in the preparation of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid ethyl ester (Example 1, step c) except that *tert*-butyl-bromoacetate was used in place of 1-bromo-3,3-dimethyl-butan-2-one. ^{1}H NMR ($CDCl_3$) 7.40 (2H, m), 7.18 (1H, dt), 7.10 (1H, d), 4.51-4.10 (6H, m), 2.72 (1H, m), 1.66 (6H, m), 1.45 (9H, s), 1.23 (7H, m).

Step b. *(5-Cyclohexyl-3-ethoxycarbonylmethyl-2-oxo-2,3-dihydro-3*H*-1,3,4-benzotriazepin-1-yl)-acetic acid.* (1-*tert*-Butoxycarbonylmethyl-5-cyclohexyl-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetic acid ethyl ester (Example 68, step a) (860mg, 1.94mmol) was dissolved in trifluoroacetic acid (5ml) and the solution was stirred at room temperature for 2h. The trifluoroacetic acid was evaporated, the residue was dissolved in DCM (20ml) and washed with H_2O (20ml × 2). The organic phase was separated and dried over $MgSO_4$. Filtration and evaporation of the solvent afford the product (630mg, 84%). ^{1}H NMR ($CDCl_3$) 9.50 (1H, br s), 7.43 (2H, m), 7.25 (1H, m), 7.14 (1H, d), 4.40 (4H, m), 4.15 (2H, m), 2.73 (1H, m), 1.75 (6H, m), 1.24 (7H, m).

Step c. *[5-Cyclohexyl-1-(2-morpholin-3-yl-2-oxo-ethyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid ethyl ester* was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1, step e) except that (5-cyclohexyl-3-ethoxycarbonylmethyl-2-oxo-2,3-dihydro-3*H*-1,3,4-benzotriazepin-1-yl)-acetic acid (Example 68, step b) and morpholine were used instead of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d) and 3-amino-benzoic acid methyl ester respectively. ^{1}H NMR ($CDCl_3$) 7.40 (2H, m), 7.18 (2H, m), 4.51 (2H, br d), 4.26 (2H, br d), 4.14 (2H, m), 3.69-3.50 (8H, m), 2.74 (1H, m), 1.74 (6H, m), 1.24 (7H, m).

Step d. The title compound was obtained using steps d and e of the method employed in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that [5-cyclohexyl-1-(2-morpholin-3-yl-2-oxo-ethyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid ethyl ester (Example 68, step c) was used in step d instead of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid ethyl ester (Example 1, step c), followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR ($CDCl_3$) 8.60 (1H, s), 8.09 (1H, dd), 7.90 (1H, t), 7.78 (1H, d), 7.52 (2H, m), 7.42-7.29 (2H, m), 7.20 (1H, d), 4.64 (1H, d), 4.41 (1H, d), 4.26 (2H, m), 3.70 (6H, br s), 3.50 (2H, br s), 2.80 (1H, m),

2.05-1.71 (6H, m), 1.25 (4H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 55.33, H 7.19, N 10.70%; $C_{29}H_{33}N_5O_6 \bullet C_7H_{17}NO_5 \bullet 2.2H_2O$ requires: C 55.22, H 7.01, N 10.73%.

Example 69. *(3-{2-[5-(4-*tert*-Butyl-cyclohexyl)-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-acetic acid.*

The title compound was obtained using the method employed in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that (2-amino-phenyl)-(4-*tert*-butyl-cyclohexyl)-methanone (prepared from 1-bromo-4-*tert*-butyl-cyclohexane (A. L. J. Beckwith, *et. al., J. Chem. Soc. Perkin Trans. II*, (1983), 661) and 2-aminobenzonitrile) was used in step a instead of (2-amino-phenyl)-cyclohexyl-methanone, and (3-amino-phenyl)-acetic acid methyl ester replaced 3-amino-benzoic acid methyl ester in step e, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR ($CDCl_3$) 8.28 (1H, s), 7.50-7.44 (2H, m), 7.33-7.21 (4H, m), 7.03-6.98 (2H, m), 4.76 (1H, d), 4.60 (1H, d), 4.31 (1H, d), 4.17 (1H, d), 3.61 (2H, s), 2.71 (1H, m), 2.11-1.66 (5H, m), 1.34-1.24 (10H, m), 1.21-1.02 (3H, br m), 0.86 (9H, s). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 58.81, H 8.24, N 8.49%; $C_{34}H_{44}N_4O_5 \bullet C_7H_{17}NO_5 \bullet 3.0H_2O$ requires C 58.76, H 8.06, N 8.36%.

Example 70. *(6-{2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-indol-1-yl)-acetic acid.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that (6-amino-indol-1-yl)-acetic acid ethyl ester (prepared in two steps from 6-nitroindole) was used instead of 3-amino-benzoic acid methyl ester in step e, followed by reaction of the product obtained, in place of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid ethyl ester (Example 1, step c), according to the method of

Example 1, step d. ^{1}H NMR ($CDCl_3$) 8.33 (1H, s), 7.92 (1H, s), 7.45 (3H, m), 7.28 (1H, m), 7.02 (2H, m), 6.58 (1H, dd), 6.47 (1H, t), 4.84 (2H, s), 4.68 (2H, m), 4.40 (1H, d), 4.18 (1H, d), 2.78 (1H, m), 2.02-1.15 (19H, m). The compound was further characterised as the N-methyl-D-glucamine salt. Found: C 58.25, H 7.41, N 10.61%; $C_{32}H_{37}N_5O_5 \bullet C_7H_{17}NO_5 \bullet 2.0H_2O$ requires: C 58.38, H 7.28, N 10.47%.

Example 71. *(3-{2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzylsulfanyl)-acetic acid.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that (3-amino-benzyl-sulfanyl)-acetic acid methyl ester (prepared in two steps from 3-bromomethyl nitrobenzene) was used instead of 3-amino-benzoic acid methyl ester in step e, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR ($CDCl_3$) 8.37 (1H, s), 7.51-7.45 (2H, m), 7.31-7.20 (4H, m), 7.01 (1H, d), 6.80 (1H, br s), 4.79 (1H, d), 4.60 (1H, d), 4.31 (1H, d), 4.17 (1H, d), 3.78 (2H, s), 3.10 (2H, s), 2.79 (1H, m), 1.99-1.71 (6H, m), 1.29-1.19 (13H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 52.84, H 7.53, N, 8.10%; $C_{31}H_{38}N_4O_5S \bullet C_7H_{17}NO_5 \bullet 5.0H_2O$ requires: C 52.82, H 7.58, N 8.10%.

Example 72. *2-{5-Cyclohexyl-1-[2-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl}-*N*-(3-methylamino-phenyl)-acetamide.*

Step a. *{5-Cyclohexyl-1-[2-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl}-acetic acid ethyl ester* was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1, step e) except that (5-cyclohexyl-3-ethoxycarbonylmethyl-2-oxo-2,3-dihydro-3*H*-1,3,4-benzotriazepin-1-yl)-acetic acid (Example 68, step b) and 1-methylpiperazine were used instead of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-

benzotriazepin-3-yl]-acetic acid (Example 1, step d) and 3-amino-benzoic acid methyl ester respectively. ^{1}H NMR ($CDCl_3$) 7.40 (2H, m), 7.19 (2H, m), 4.48 (2H, br d), 4.25-4.10 (4H, m), 3.59 (4H, br m), 2.77 (1H, m), 2.60 (4H, m), 2.41 (3H, s), 1.72 (6H, m), 1.24 (7H, m).

Step b. *{5-Cyclohexyl-1-[2-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetic acid* was obtained by the method used in the preparation of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d) except that {5-cyclohexyl-1-[2-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl}-acetic acid ethyl ester (Example 72, step a) was used in place of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid ethyl ester (Example 1, step c). ^{1}H NMR ($CDCl_3$) 9.30 (1H, br s), 7.42 (2H, m), 7.21 (2H, m), 4.45 (2H, br s), 4.08-3.78 (6H, br m), 2.92 (4H, m), 2.76 (1H, m), 2.62 (3H, s), 1.98-1.44 (6H, m), 1.23 (4H, m).

Step c. The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1, step e) except that {5-cyclohexyl-1-[2-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetic acid (Example 72, step b) and (3-amino-phenyl)-methyl-carbamic acid *tert*-butyl ester (Example 3, step c) were used instead of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d) and 3-amino-benzoic acid methyl ester respectively, followed by reaction of the product obtained, in place of (3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-methyl-carbamic acid *tert*-butyl ester (Example 3, step d), according to the method of Example 3, step e. ^{1}H NMR ($CDCl_3$) 8.12 (1H, s), 7.46 (2H, m), 7.27 (2H, m), 7.03 (1H, t), 6.91 (1H, t), 6.46 (1H, dd), 6.30 (1H, dd), 4.52 (2H, m), 4.37 (1H, d), 4.14 (1H, d), 3.62 (2H, m), 3.49 (2H, m), 2.79 (5H, m), 2.40 (4H, m), 2.30 (3H, s), 2.00-1.75 (6H, m), 1.26 (4H, m). The compound was further characterised as the di-hydrochloride salt. Found: C 53.60, H 7.08, N, 14.50%; $C_{30}H_{39}N_7O_3 \bullet 2.0HCl \bullet 3.0H_2O$ requires: C 53.54, H 7.05, N 14.57%.

Examples 73/74

3-{2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl]-acetylamino}-5-methylamino-benzoic acid methyl ester was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that with 3-amino-5-[methyl-(2,2,2-trifluoro-acetyl)-amino]-benzoic acid methyl ester (prepared in four steps from 3-amino-5-nitrobenzoic acid) was used in place of 3-amino-benzoic acid methyl ester in step e, and following reaction of the product according to the method of Example 2, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), two compounds were isolated by chromatography.

Example 73. *3-{2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H-*1,3,4-benzotriazepin-3-yl]-acetylamino}-5-methylamino-benzoic acid.*

^{1}H NMR ($CDCl_3$) 8.30 (1H, s), 7.52-7.46 (3H, m), 7.35-7.29 (1H, m), 7.05-6.92 (3H, m), 4.77 (1H, d, 17.7), 4.68 (1H, d, 17.7), 4.36-4.12 (2H, m), 2.88-2.76 (4H, m), 1.88-1.69 (5H, m), 1.31-1.23 (14H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 56.60, H 7.65, N 10.44%; $C_{30}H_{37}N_5O_5 \bullet C_7H_{17}NO_5 \bullet 3.5H_2O$ requires: C 56.40, H 7.55, N 10.67%.

Example 74. *3-{2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H-*1,3,4-benzotriazepin-3-yl]-acetylamino}-5-methylamino-benzoic acid methyl ester.*

^{1}H NMR ($CDCl_3$) 8.31 (1H, s), 7.61-7.41 (3H, m), 7.33-7.27 (1H, m), 7.04-6.92 (3H, m), 4.77-4.61 (2H, m), 4.33 (1H, d, 13.2), 4.19 (1H, d, 13.2), 3.88 (4H, br s), 2.86-2.76 (4H, m), 2.05-1.73 (5H, m), 1.31-1.19 (14H, m). Found: C 65.98, H 7.25, N 12.20%; $C_{31}H_{39}N_5O_5$ requires: C 66.29, H 7.00, N 12.47%.

Example 75. *2-(3{2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H-*1,3,4-benzotriazepin-3-yl]-acetylamino}-phenylamino)-propionic acid.*

The title compound was obtained as the hydrochloride salt by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that 2-[(3-amino-phenyl)-*tert*-butoxycarbonyl-amino]-propionic acid methyl ester (prepared in two steps from 3-nitro-*N*-*tert*-butoxycarbonylaniline) was used instead of 3-amino-benzoic acid methyl ester in step e, followed by reaction of the product obtained, in place of (3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-propyl-carbamic acid *tert*-butyl ester (Example 41, step a) according to the method of Example 41, step b. ^{1}NMR (DMSO-d_6) 9.53 (1H,s), 7.50 (2H, m), 7.25 (2H, m), 6.98 (2H, m), 6.73 (1H, d), 6.30 (1H, d), 5.00 (3H, br s), 4.79 (2H, s), 4.25 (1H, m), 3.91 (2H, m), 2.86 (1H, m), 2.00-1.00 (10H, m), 1.33 (3H, d), 1.13 (9H, s). Found: C 60.48, H 6.77, N 11.18%; $C_{31}H_{39}N_5O_5 \bullet HCl \bullet H_2O$ requires: C 60.43, H 6.87, N 11.37%.

Example 76. *(R)-1-(3-{2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxobutyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-pyrrolidine-2-carboxylic acid.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that (*R*)-1-(3-amino-phenyl)-pyrrolidine-2-carboxylic acid methyl ester (prepared in three steps from 3-nitro-iodobenzene and *L*-proline) was used instead of 3-amino-benzoic acid methyl ester in step e, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR (DMSO-d_6) 12.40 (1H, br s), 9.48 (1H, s), 7.50 (2H, m), 7.24 (2H, m), 7.01 (1H, t), 6.78 (1H, d), 6.68 (1H, s), 6.13 (1H, d), 4.78 (2H, s), 4.20 (1H, d), 4.06 (1H, d), 3.90 (1H, d), 3.21 (2H, m), 2.90 (1H, m), 2.20-1.20 (14H, m), 1.13 (9H, s). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 60.09, H 7.50, N 10.41%. $C_{33}H_{41}N_5O_5 \bullet C_7H_{17}NO_5 \bullet H_2O$ requires: C 59.98, H 7.55, N 10.49%.

Example 77. *2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-N-[3-(1*H*-imidazol-4-yl)-phenyl]-acetamide.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that 4-(3-amino-phenyl)-imidazole-1-carboxylic acid *tert*-butyl ester (prepared in three steps from 2-bromo-3'-nitroacetophenone) was used in place of 3-amino-benzoic acid methyl ester in step e, followed by reaction of the product obtained, in place of (3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-methyl-carbamic acid *tert*-butyl ester (Example 3, step d), according to the method of Example 3, step e. ^{1}H NMR ($CDCl_3$) 8.35 (1H, s), 7.82 (1H, s), 7.68 (1H, s), 7.51-7.46 (3H, m), 7.33-7.19 (5H, m), 7.04 (1H, d, 8.1), 4.78 (1H, d, 17.1), 4.66 (1H, d, 17.1), 4.35 (1H, d, 16.5), 4.22 (1H, d, 16.5), 2.80 (1H, m), 2.05-1.62 (5H, m), 1.31-1.18 (14H, m). Found C 62.46, H 7.01, N 14.35%; $C_{31}H_{36}N_6O_3 \bullet 3.0H_2O$ requires C 62.61, H 7.12, N 14.13%.

Example 78. *3-{2-[5-Cyclohexyl-1(-2-hydroxy-3,3-dimethyl-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-5-methylamino-benzoic acid methyl ester.*

Sodium borohydride (5mg, 0.13mmol) was added to an ice-cooled solution of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-5-methylamino-benzoic acid methyl ester (Example 74) (64mg, 0.11mmol) in MeOH (2ml). The reaction mixture was stirred at 0-5°C for 40mins, then at room temperature for 2h. Saturated NH_4Cl solution (10ml) was added and the product was extracted with $CHCl_3$ (15ml). The organic phase was dried ($MgSO_4$), filtered and the filtrate was evaporated to afford the title compound (60mg, 97%). ^{1}H NMR ($CDCl_3$) 8.10-8.79 (1H, m), 7.55 (2H, m), 7.36 (2H, m), 7.24 (1H, m), 6.95 (1H, s), 6.70 (1H, m), 4.46 (1H, m), 4.29-4.04 (2H, m), 3.89 (4H, m), 3.82-3.60 (1H. m), 3.43-3.23 (1H, m), 2.81 (4H, m), 2.15-1.66 (7H, m), 1.33-1.24 (3H, m), 0.97 and 0.93 (9H, s × 2). Found C 63.17, H 7.59, N 11.85%; $C_{31}H_{41}N_5O_5 \bullet 1.5H_2O$ requires C 63.03, H 7.51, N 11.86%.

Example 79. *3-{2-[5-Cyclohexyl-1-(2-cyclohexyl-2-oxo-ethyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid.*

Step a. *[5-Cyclohexyl-1-(2-cyclohexyl-2-oxo-ethyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid* was obtained using steps a-d of the method employed in the preparation of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d) except that 2-bromo-cyclohexyl-ethanone was used in step c instead of 1-bromo-3,3-dimethyl-butan-2-one. ^{1}H NMR ($CDCl_3$) 7.45 (2H, m), 7.23 (1H, m), 7.01 (1H, d), 4.56 (2H, d), 4.25 (1H, d), 3.89 (1H, d), 2.82 (1H, m), 2.47 (1H, m), 2.08-1.61 (11H, m), 1.46-1.19 (9H, m).

Step b. The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that [5-cyclohexyl-1-(2-cyclohexyl-2-oxo-ethyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 79, step a) was used in place of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d) in step e, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR ($CDCl_3$) 8.52 (1H, s), 8.03 (1H, d), 7.82 (2H, m), 7.49 (2H, m), 7.41 (1H, t), 7.32 (1H, t), 7.06 (1H, d), 4.69 (1H, d), 4.47 (1H, d), 4.27 (2H, m), 2.81 (1H, m) 2.48 (1H, m), 2.05-1.69 (11H, m), 1.48-1.23 (9H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 57.41, H 7.60, N 9.02%; $C_{31}H_{36}N_4O_5 \bullet C_7H_{17}NO_5 \bullet 2.9H_2O$ requires: C 57.59, H 7.48, N 8.84%.

Example 80. *(3-{2-[5-Cyclohexyl-1-(2-cyclohexyl-2-oxo-ethyl)-2-oxo-1,2-dihydro-*3H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-acetic acid.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), except that [5-cyclohexyl-1-(2-cyclohexyl-2-oxo-ethyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 79, step a) and (3-amino-phenyl)-acetic acid methyl ester were used in place of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d) and 3-amino-benzoic acid methyl ester respectively in

step e, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR ($CDCl_3$) 8.27 (1H, s), 7.47 (2H, m), 7.27 (4H, m), 7.04 (1H, d), 6.99 (1H, d), 4.64 (1H, d), 4.46 (1H, d), 4.31 (1H, d), 4.17 (1H, d), 3.60 (2H, s), 2.78 (1H, m) 2.46 (1H, m), 2.04-1.66 (11H, m), 1.44-1.23 (9H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 56.73, H 7.67, N 8.65%; $C_{32}H_{38}N_4O_5 \bullet C_7H_{17}NO_5 \bullet 3.9H_2O$ requires: C 56.87, H 7.68, N 8.50%.

Example 81. *(3-{2-[1-(2-Cyclopentyl-2-oxo-ethyl)-2-oxo-5-pyridin-2-yl-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-phenyl)-acetic acid.*

Step a. *[1-(2-Cyclopentyl-2-oxo-ethyl)-2-oxo-5-pyridin-2-yl-1,2-dihydro-3*H*-1,3,4-benzotriazapin-3-yl]-acetic acid* was obtained using steps a-d of the method employed in the preparation of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d) except that (2-amino-phenyl)-pyridin-2-yl-methanone was used in step a instead of (2-amino-phenyl)-cyclohexyl-methanone and 2-bromo-1-cyclopentyl-ethanone replaced 1-bromo-3,3-dimethyl-butan-2-one in step c.

Step b. The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that [1-(2-cyclopentyl-2-oxo-ethyl)-2-oxo-5-pyridin-2-yl-1,2-dihydro-3*H*-1,3,4-benzotriazapin-3-yl]-acetic acid and (3-amino-phenyl)-acetic acid methyl ester were used in place of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d) and 3-amino-benzoic acid methyl ester respectively in step e, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR (DMSO-d_6) 12.20 (1H, br s), 9.99 (1H, s), 8.57 (1H, d), 7.91 (2H, m), 7.43 (4H, m), 7.20 (4H, m), 6.91 (1H, d), 4.66 (2H, br s), 4.40 (2H, br m), 3.50 (2H, s), 3.00 (1H, m), 1.75-1.47 (8H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt.

Found: C 56.91, H 6.61, N 10.65%; $C_{30}H_{29}N_5O_5 \bullet C_7H_{17}NO_5 \bullet 2.5H_2O$ requires: C 56.99, H 6.59, N 10.78%.

Example 82. *[3-(2-{5-Cyclohexyl-1-[2-(1-methyl-cyclopentyl)-2-oxo-ethyl]-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl}-acetylamino)-phenyl]-acetic acid.*

Step a. *{5-Cyclohexyl-1-[2-(1-methyl-cyclopentyl)-2-oxo-ethyl]-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl}-acetic acid* was obtained using a-d of the method employed in the preparation of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d) except that 2-bromo-1-(1-methyl-cyclopentyl)-ethanone was used in step c instead of 1-bromo-3,3-dimethyl-butan-2-one. ^{1}H NMR ($CDCl_3$) 11.00 91H, br s), 7.45 (2H, m), 7.25 (1H, m), 6.99 (1H, d), 4.67 (2H, m), 4.24 (1H, d), 3.86 (1H, d), 2.83 (1H, m), 2.17-1.22 (21H, m).

Step b. The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that {5-cyclohexyl-1-[2-(1-methyl-cyclopentyl)-2-oxo-ethyl]-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl}-acetic acid (Example 82, step a) and (3-amino-phenyl)-acetic acid methyl ester were used in place of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d) and 3-amino-benzoic acid methyl ester respectively in step e, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR ($CDCl_3$) 8.27 (1H, s), 7.46 (2H, m), 7.35-7.20 (4H, m), 7.03 (1H, d), 6.99 (1H, d), 4.75 (1H, d), 4.58 (1H, d), 4.30 (1H, d), 4.18 (1H, d), 3.61 (2H, s), 2.78 (1H, m), 2.15-1.23 (21H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 56.76, H 7.92, N 8.59%; $C_{32}H_{38}N_4O_5 \bullet C_7H_{17}NO_5 \bullet 4.0H_2O$ requires: C 56.69, H 7.69, N 8.48%.

Example 83. *3-({2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetyl}-methyl-amino)-benzoic acid.*

Step a. *3-({2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl]-acetyl}-methyl-amino)-benzoic acid methyl ester.* Methyl trifluoromethane sulfonate (329mg, 2.0mmol) was added drop-wise to an ice-cooled solution of 1,1'-carbonyldiimidazole (162mg, 1.0mml) in nitromethane (2ml). The solution was stirred at this temperature for 5 min, then added to a suspension of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d) (400mg, 1.0mmol) in nitromethane (2ml). The resulting mixture was stirred for 10 min at room temperature, then a solution of 3-methylamino-benzoic acid methyl ester (165mg, 1.0mmol) in nitromethane (2ml) was added. The mixture was stirred at room temperature for 19h, diluted with H_2O (30ml) and extracted with EtOAc (15ml × 3). The combined extracts were washed with H_2O (15ml × 2), and dried ($MgSO_4$). Filtration and evaporation of the solvent gave the crude product which was purified by flash column chromatography (EtOAc-hexane (4:1)) to give the product as an off-white solid (330mg, 60%). ^{1}H NMR ($CDCl_3$) 7.95 (1H, d), 7.85 (1H, s), 7.40-7.34 (4H, m), 7.14 (1H, t), 6.88 (1H, d), 4.65 (2H, br d), 4.25 (1H, br), 3.98 (1H, br), 3.94 (3H, s), 3.25 (3H, s), 2.75 (1H, br m), 2.00-1.60 (5H, m), 1.35-1.20 (14H, m).

Step b. The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid (Example 2) except that 3-({2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetyl}-methyl-amino)-benzoic acid methyl ester (Example 83, step a) was used in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1). ^{1}H NMR (DMSO-d_6) 13.10 (1H, br), 7.85 (1H, m), 7.79 (1H, s), 7.51-7.41 (4H, m), 7.21 (1H, t), 7.11 (1H, d), 4.71 (2H, d), 4.15 (1H, br), 3.70 (1H, br), 3.12 (3H, s), 2.83 (1H, m), 1.85-1.00 (19H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 57.48, H 7.61, N 9.25%; $C_{30}H_{36}N_4O_5 \bullet C_7H_{17}NO_5 \bullet 2.5H_2O$ requires C 57.50, H 7.56, N 9.06%.

Example 84. *2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl]-N-(3-hydroxy-phenyl)-acetamide.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that 3-aminophenol was used instead of 3-amino-benzoic acid methyl ester in step e. ^{1}H NMR ($CDCl_3$) 8.31 (1H, s), 7.68 (1H, s), 7.30 (2H, m), 7.26 (1H, m), 7.08 (2H, m), 6.60 (1H, m), 6.57 (1H, m), 6.41 (1H, m), 4.72 (1H, d), 4.65 (1H, d), 4.32 (1H, d), 4.22 (1H, d), 2.77 (1H, m), 1.98-1.69 (6H, m), 1.27-1.24 (13H, m). Found: C 67.78, H 7.28, N11.27%; $C_{28}H_{34}N_4O_4 \bullet 0.4H_2O$ requires: C 67.56, H 7.04, N 11.25%.

Example 85. N-*(3-Amino-phenyl)-2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H-*1,3,4-benzotriazepin-3-yl]-acetamide.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that (3-amino-phenyl)-carbamic acid *tert*-butyl ester was used in place of 3-amino-benzoic acid methyl ester in step e, followed by reaction of the product obtained, in place of (3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-methyl-carbamic acid *tert*-butyl ester (Example 3, step d), according to the method of Example 3, step e. ^{1}H NMR ($CDCl_3$) 11.28 (1H, br s), 8.85 (1H, s), 7.69 (1H, s), 7.57-7.27 (6H, m), 7.04 (1H, m), 4.76 (1H, d), 4.63 (1H, d), 4.21 (2H, m), 2.80 (1H, m), 2.18-1.35 (6H, m), 1.32-1.22 (13H, m). The product was further characterised as the hydrochloride salt. Found: C 59.71, H 7.33, N, 12.48%; $C_{28}H_{35}N_5O_3 \bullet HCl \bullet 2.0H_2O$ requires: C 59.83, H 7.17, N 12.46%.

Example 86. *2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H-*1,3,4-benzotriazepin-3-yl]-*N-*[3-(1*H*-tetrazol-5-ylmethylsulfanyl)-phenyl]-acetamide.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that 3-(1*H*-tetrazol-5-ylmethylsulfanyl)-aniline was used instead of 3-amino-benzoic acid methyl ester in step e. ^{1}H NMR ($CDCl_3$) 8.82 (1H, s), 7.72 (1H, br s), 7.40 (3H, m), 7.27 (1H, m), 7.15 (1H, t),

6.96 (3H, m), 4.70 (2H, q), 4.41 (2H, s), 4.24 (2H, s), 2.82 (1H, m), 2.1-1.6 (6H, m), 1.28 (4H, m), 1.22 (9H, s).

Example 87. *2-{5-Cyclohexyl-1-[2-(1-methyl-cyclopentyl)-2-oxo-ethyl]-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl}-*N*-[3-(5-oxo-2,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenyl]-acetamide.*

The title compound was obtained by the method used in the preparation of 2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-*N*-[3-(5-oxo-2,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenyl]-acetamide (Example 59) except that {5-cyclohexyl-1-[2-(1-methyl-cyclopentyl)-2-oxo-ethyl]-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl}-acetic acid (Example 82, step a) was used in place of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d). ^{1}H NMR ($CDCl_3$) 11.00 (1H, br s), 8.84 (1H, s), 7.91 (1H, s), 7.58 (2H, m), 7.44 (3H, m), 7.28 (1H, t), 7.04 (1H, d), 4.81 (1H, d), 4.55 (1H, d), 4.21 (2H, s), 2.80 (1H, m), 2.09-1.24 (21H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 56.28, H 6.94, N 11.95%; $C_{32}H_{36}N_6O_5 \bullet C_7H_{17}NO_5 \bullet 2.8H_2O$ requires: C 56.45, H 7.11, N 11.82%.

Example 88. *3-(2-{5-Cyclohexyl-1-[2-(1-methyl-cyclopentyl)-2-oxo-ethyl]-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl}-acetylamino)-benzoic acid.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that {5-cyclohexyl-1-[2-(1-methyl-cyclopentyl)-2-oxo-ethyl]-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl}-acetic acid (Example 82, step a) was used in place of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d) in step e, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR ($CDCl_3$) 8.51 (1H, s), 8.03 (1H, d), 7.87 (1H, s), 7.81 (1H, d), 7.53-7.27 (4H, m), 7.05 (1H, d), 4.78 (1H, d), 4.57 (1H, d), 4.26 (2H, m), 2.81 (1H, m), 2.16-1.23 (21H, m). The

compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 57.94, H 7.53, N 8.71%; $C_{31}H_{36}N_4O_5 \bullet C_7H_{17}NO_5 \bullet 2.8H_2O$ requires: C 57.80 H 7.47, N 8.87%.

Example 89. *2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-*N*-[3-(1*H*-imidazol-1-yl)-phenyl]-acetamide.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that 3-imidazol-1-yl-phenylamine (prepared in two steps from 1-fluoro-nitrobenzene and imidazole) was used instead of 3-amino-benzoic acid methyl ester in step e. ^{1}H NMR ($CDCl_3$) 8.57 (1H, s), 7.86 (1H, s), 7.71 (1H, t, 1.8), 7.52-7.28 (6H, m), 7.19 (1H, s), 7.11-7.08 (1H, m), 7.04-7.01 (1H, m), 4.84 (1H, d, 17.7), 4.58 (1H, d, 17.7), 4.24-4.23 (2H, m), 2.83-2.77 (1H, m), 2.05-1.67 (6H, m), 1.38-1.19 (13H, m). Found: C 68.06, H 6.75, N 15.09%; $C_{31}H_{36}N_6O_3 \bullet 0.4H_2O$ requires: C 67.87, H 6.78, N 15.32%.

Example 90. N-*(3*H*-Benzimidazol-5-yl)-2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetamide.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that 6-amino-benzimidazole-1-carboxylic acid *tert*-butyl ester (prepared in two steps from 5(6)-nitro-benzimidazole) was used in place of 3-amino-benzoic acid methyl ester in step e, followed by reaction of the product obtained, in place of (3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-methyl-carbamic acid *tert*-butyl ester (Example 3, step d), according to the method of Example 3, step e. ^{1}H NMR ($CDCl_3$) 8.44 (1H, s), 8.24 (1H, br s), 7.98 (1H, s), 7.60-7.47 (3H, m), 7.32-7.27 (1H, m), 7.04 (1H, d, 8.1), 6.84 (1H, br s), 4.77 (1H, d, 18), 4.67 (1H, d, 18), 4.40 (1H, d, 16.5), 4.25 (1H, d, 16.5), 2.84-2.76 (1H, m), 2.05-1.65 (6H, m), 1.45-1.24 (13H, m). Found C 65.40, H 6.89, N 15.79%; $C_{29}H_{34}N_6O_3 \bullet H_2O$ requires C 65.39, H 6.81, N 15.78%.

Example 91. *3-{2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H-*1,3,4-benzotriazepin-3-yl]-acetylamino}-5-methyl-benzoic acid.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that 3-amino-5-methyl-benzoic acid methyl ester (prepared in three steps from 4-bromo-3-methylbenzoic acid) was used instead of 3-amino-benzoic acid methyl ester in step e, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR ($CDCl_3$) 8.44 (1H, s), 7.87 (1H, s), 7.62 (2H, m), 7.53-7.47 (2H, m), 7.34-7.28 (1H, m), 7.05 (1H, d, 8.1), 4.81-4.58 (2H, m), 4.26-4.19 (2H, m), 2.84-2.80 (1H, m), 2.39 (3H, s), 2.05-173 (6H, m), 1.41-1.19 (13H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found C 58.77, H 7.70, N 9.33%; $C_{30}H_{36}N_4O_5 \bullet C_7H_{17}NO_5 \bullet 1.5H_2O$ requires C 58.87, H 7.48, N 9.28%.

Example 92. N-*[3-(Acetyl-methyl-amino)-5-methylamino-phenyl]-2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H-*1,3,4-benzotriazepin-3-yl]-acetamide.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that *N*-(3-amino-5-methylamino-phenyl)-*N*-methyl-acetamide (prepared in four steps from 3,5-difluoronitrobenzene) was used instead of 3-amino-benzoic acid methyl ester in step e. ^{1}H NMR ($CDCl_3$) 8.29 (1H, s), 7.51-7.43 (2H, m), 7.30-7.24 (1H, m), 7.03 (1H, d, 8.4), 6.92 (1H, s), 6.39 (1H, s), 6.10 (1H, s), 4.79 (1H, d, 18), 4.62 (1H, d, 18), 4.29 (1H, d, 16.5), 4.21 (1H, d, 16.5), 3.21 (3H, s), 2.83-2.75 (4H, m), 2.04-1.67 (9H, m), 1.33-1.17 (13H, m).

Example 93. *3-[2-(1-Carboxymethyl-5-cyclohexyl-2-oxo-1,2-dihydro-3*H-*1,3,4-benzotriazepin-3-yl)-acetylamino]-benzoic acid.*

Step a. *(1-*tert*-Butoxycarbonylmethyl-5-cyclohexyl-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetic acid* was obtained by the method used in the preparation of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d) except that (1-*tert*-butoxycarbonylmethyl-5-cyclohexyl-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetic acid ethyl ester (Example 68, step a) was used in place of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid ethyl ester (Example 1, step c). ^{1}H NMR ($CDCl_3$) 7.45 (2H, m), 7.27 (1H. m), 7.14 (1H, d), 4.41-3.93 (4H, br m), 2.80 (1H, m), 2.02-1.45 (6H, m), 1.46 (9H, m), 1.21 (4H, m).

Step b. 3-[2-(1-*tert*-Butoxycarbonylmethyl-5-cyclohexyl-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetylamino]-benzoic acid methyl ester was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1, step e) except that (1-tert-butoxycarbonylmethyl-5-cyclohexyl-2-oxo-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl)-acetic acid was used instead of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d). ^{1}H NMR ($CDCl_3$) 8.51 (1H, s), 7.89 (1H, d), 7.80 (1H, t), 7.74 (1H, d), 7.50 (2H, m), 7.35 (2H, m), 7.18 (1H, d), 4.43-4.09 (4H, m), 3.91 (3H, s), 2.80 (1H, m), 2.05-1.60 (6H, m), 1.43 (9H, s), 1.24 (4H, m).

Step c. The title compound was obtained by the method used in the preparation of (5-cyclohexyl-3-ethoxycarbonylmethyl-2-oxo-2,3-dihydro-3H-1,3,4-benzotriazepin-1-yl)-acetic acid (Example 68, step b) except that 3-[2-(1-tert-butoxycarbonylmethyl-5-cyclohexyl-2-oxo-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl)-acetylamino]-benzoic acid methyl ester (Example 93, step b) was used instead of (1-tert-butoxycarbonylmethyl-5-cyclohexyl-2-oxo-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl)-acetic acid ethyl ester (Example 68, step a), followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR ($CDCl_3$) 9.15 (2H, br s), 8.84 (1H, s), 8.03 (1H, d), 7.73 (1H, s), 7.67 (1H, d), 7.48 (2H, m), 7.30 (2H, m), 7.14 (1H, d), 4.62 (1H, d), 4.29 (3H, m), 2.81 (1H, m), 2.07-1.74 (6H, m), 1.27 (4H, m). The compound was further characterised as the bis(N-

methyl-D-glucamine) salt. Found: C 50.94, H 7.29, N 8.05%; $C_{25}H_{26}N_4O_6 \bullet C_{14}H_{34}N_2O_{10} \bullet 3.0H_2O \bullet 1.2C_4H_8O_2$ requires: C 51.05 H 7.41, N 8.16%.

Example 94. *(6-{2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzimidazol-1-yl)-acetic acid.*

The of title compound was obtained as the hydrochloride salt by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that (5-amino-benzimidazol-1-yl)-acetic acid *tert*-butyl ester (prepared in two steps from 5(6)-nitro-benzimidazole) was used instead of 3-amino-benzoic acid methyl ester in step e, followed by reaction of the product obtained, in place of (1-*tert*-butoxycarbonylmethyl-5-cyclohexyl-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetic acid ethyl ester (Example 68, step a) according to the method of Example 68, step b. ^{1}H NMR (DMSO-d_6) 10.27-10.23 (1H, br s), 9.23 and 9.10 (1H, s), 8.19 (1H, s), 7.77-7.73 (1H, m), 7.55-7.40 (3H, m), 7.26-7.15 (2H, m), 5.40 and 5.32 (2H, m), 4.79 (2H, s), 4.41 (1H, br d, 15), 3.99 (1H, br d, 15), 2.87 (1H, m), 1.83-1.65 (6H, m), 1.30-1.06 (13H, m). Found: C 61.13, H 6.08, N 13.77%; $C_{31}H_{36}N_6O_5 \bullet HCl$ requires: C 61.13, H 6.12, N 13.77%.

Example 95. *3-[2-(1-tert-Butoxycarbonylmethyl-5-cyclohexyl-2-oxo-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl)-acetylamino]-benzoic acid.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid (Example 2) except that 3-[2-(1-*tert*-butoxycarbonylmethyl-5-cyclohexyl-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetylamino]-benzoic acid methyl ester (Example 93, step b) was used in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1). ^{1}H NMR ($CDCl_3$) 8.53 (1H, s), 8.02 (1H, d), 7.81 (2H, m), 7.50 (2H, m), 7.37 (2H, m), 7.18 (1H, d), 4.45-4.12 (4H, m), 2.81 (1H, m), 2.05-1.65 (6H, m), 1.44 (9H, s), 1.27 (4H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 56.81, H 7.01, N 8.72%; $C_{29}H_{34}N_4O_6 \bullet C_7H_{17}NO_5 \bullet 1.5H_2O \bullet 0.3C_4H_8O_2$ requires: C 57.04, H 7.26, N 8.94%.

Example 96. *[(3-{2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-methyl-amino]-acetic acid.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that [(3-amino-phenyl)-methyl-amino]-acetic acid methyl ester (prepared in three steps from sarcosine and 3-nitro-iodobenzene) was used instead of 3-amino-benzoic acid methyl ester in step e, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR (DMSO-d_6) 12.40 (1H, br s), 9.47 (1H, s), 7.50 (2H, m), 7.20 (2H, m), 7.02 (1H, t), 6.80 (2H, m), 6.33 (1H, m), 4.78 (2H, s), 4.25-3.75 (2H, m), 4.00 (2H, s) 2.91 (3H, s), 2.90 (1H, m), 2.00-1.16 (10H, m), 1.13 (9H, s). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 58.95, H 7.81, N 10.76%. $C_{31}H_{39}N_6O_5 \bullet C_7H_{17}NO_5 \bullet H_2O$ requires: C 58.90, H 7.55, N 10.85%.

Example 97. *[4-(3-{2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-imidazol-1-yl]-acetic acid.*

The of title compound was obtained as the hydrochloride salt by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that [4-(3-amino-phenyl)-imidazol-1-yl]-acetic acid *tert*-butyl ester (prepared in three steps from 2-bromo-3′-nitro-acetophenone) was used instead of 3-amino-benzoic acid methyl ester in step e, followed by reaction of the product obtained, in place of (1-*tert*-butoxycarbonylmethyl-5-cyclohexyl-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetic acid ethyl ester (Example 68, step a) according to the method of Example 68, step b. ^{1}H NMR (DMSO-d_6/D_2O) 10.02 (1H, s), 8.89 and 8.79 (1H, s), 8.04 (1H, s), 7.95 and 7.91 (1H, s), 7.53-7.34 (5H, m), 7.26-7.12 (2H, m), 5.14 and 5.08 (2H, s), 4.76-4.74 (2H, m), 4.31 (1H, m), 4.01-3.96 (1H, m), 2.87-2.84 (1H, m), 1.82-1.64 (6H, m), 1.32-1.04 (13H,

m). Found: C 59.97, H 6.48, N 12.22%; $C_{33}H_{38}N_6O_5 \bullet 1.6HCl \bullet 0.5C_4H_8O_2$ requires: C 59.96, H 6.27, N 11.99%.

Example 98. *3-[2-(Carbamoylmethyl-5-cyclohexyl-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetylamino]-benzoic acid.*

Step a. *(1-Carbamoylmethyl-5-cyclohexyl-2-oxo-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl)-acetic acid ethyl ester.* To a solution of (5-cyclohexyl-3-ethoxycarbonylmethyl-2-oxo-2,3-dihydro-3H-1,3,4-benzotriazepin-1-yl)-acetic acid (Example 68, step b) (200mg, 0.52mmol) in DMF-THF (1:1 / 10ml) were added EDC (150mg, 0.77mmol), HOBt (100mg, 0.77mmol) and DMAP (20mg). The solution was stirred at room temperature for 1h, and then ammonia was bubbled into the reaction mixture for 5min. The reaction mixture was stirred at room temperature for 16h, H_2O (30ml) was added and the mixture was extracted with EtOAc (20ml × 2). The extracts were washed with brine, dried ($MgSO_4$) and the solvent was evaporated. The residue was purified by flash column chromatography (DCM-EtOAc (1:1)) to afford the product (141mg, 71%). ^{1}H NMR (300MHz, $CDCl_3$) 7.41 (2H, m), 7.22 (2H, m), 6.61 (1H, br s), 5.66 (1H, br s), 4.31-4.11 (6H, m), 2.75 (1H, m), 1.75 (6H, m), 1.23 (7H, m).

Step b. The title compound was obtained using steps d and e of the method employed in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1, step e) except that (1-carbamoylmethyl-5-cyclohexyl-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetic acid ethyl ester (Example 98, step a) was used in step d instead of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid ethyl ester (Example 1, step c), followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR (DMSO-d_6) 12.88 (1H, br s), 11.12 (1H, s), 9.97 (1H, s), 8.19 (1H, s), 7.80 (1H, d), 7.61 (1H, d), 7.55 (1H, m), 7.45 (1H, m), 7.25 (1H, dd), 5.60 (1H, m), 4.27 (2H, m), 3.80 (2H, m), 2.15 (1H, m), 1.67-0.87 (9H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C

55.13, H 6.93, N 11.11%; $C_{25}H_{27}N_5O_5 \bullet C_7H_{17}NO_5 \bullet 1.3H_2O \bullet 0.7C_4H_8O_2$ requires: C 55.16, H 6.94, N 11.09%.

Example 99. *(6-{2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl]-acetylamino}-indazol-1-yl)-acetic acid.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that (6-amino-indazol-1-yl)-acetic acid methyl ester (prepared in two steps from 6-nitro-indazole) was used instead of 3-amino-benzoic acid methyl ester in step e, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR (DMSO-d_6) 13.0 (1H, br s), 9.97 (1H, s), 7.95-7.94 (2H, m), 7.66-7.46 (3H, m), 7.27-7.03 (3H, m), 5.11 (2H, s), 4.80-4.79 (2H, m), 4.34 (1H, m), 4.03 (1H, m), 2.88-2.84 (1H, m), 1.90-1.65 (6H, m), 1.34-1.08 (13H, m).

Example 100. *(3-{2-[5-Cyclohexyl-1-(2-cyclohexyl-2-oxo-ethyl)-2-oxo-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenylsulfanyl)-acetic acid.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that [5-cyclohexyl-1-(2-cyclohexyl-2-oxo-ethyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 79, step a) and (3-amino-phenylsulfanyl)-acetic acid ethyl ester were used instead of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d) and 3-amino-benzoic acid methyl ester respectively in step e, followed by reaction of the product obtained, in place of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid ethyl ester (Example 1, step c), according to the method of Example 1, step d. ^{1}H NMR ($CDCl_3$) 8.44 (1H, s), 7.45 (3H, m), 7.38 (1H, d), 7.24 (2H, m), 7.11 (1H, d), 7.05 (1H, d), 6.70 (1H, br s), 4.70 (1H, d), 4.44 (1H, d), 4.21 (2H, m), 3.66 (2H, s), 2.80 (1H, m), 2.47 (1H, m), 2.18-1.66 (11H, m), 1.44-1.22 (9H, m). The compound was further

characterised as the *N*-methyl-D-glucamine salt. Found: C 56.91, H 6.96, N 8.36%; $C_{32}H_{38}N_4O_5S \bullet C_7H_{17}NO_5 \bullet 2.0H_2O$ requires: C 56.99, H 7.24, N 8.52%.

Example 101. *2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-*N*-(2-methylamino-phenyl)-acetamide.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that *N*-methyl-benzene-1,2-diamine (prepared in two steps from 2-fluoro-nitrobenzene) was used instead of 3-amino-benzoic acid methyl ester in step e. ^{1}H NMR ($CDCl_3$) 8.26 (1H, s), 7.48-7.41 (2H, m), 7.35-7.32 (1H, m), 7.26-7.20 (1H, m), 7.17-7.11 (1H, m), 7.00 (1H, d,), 6.74-6.68 (2H, m), 4.78 (1H, d), 4.60 (1H, d), 4.20-4.19 (3H, m), 2.84-2.76 (4H, m), 2.07-1.71 (6H, m), 1.44-1.02 (13H, m). Found: C 66.60, H 7.02, N 13.15%; $C_{29}H_{37}N_5O_3 \bullet 0.3CH_2Cl_2$ requires: C 66.51, H 7.16, N 13.24%.

Example 102. *3-{2-[1-(3,3-Dimethyl-2-oxo-butyl)-5-(4-methyl-cyclohexyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid.*

The title compound was obtained using the method employed in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that (2-amino-phenyl)-(4-methyl-cyclohexyl)-methanone (prepared from 4-methyl-cyclohexanol by bromination using phosphorus pentabromide (A. L. J. Beckwith et al.: *J. Chem. Soc. Perkin Trans. II*, 1983, 661) and reaction of the corresponding Grignard reagent with 2-aminobenzonitrile (J. A. Robl, *Synthesis*, 1991, 56-58)) was used in step a instead of (2-amino-phenyl)-cyclohexyl-methanone, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR ($CDCl_3$) 8.51 (1H, br s), 8.02 (1H, d), 7.85-7.79 (2H, m), 7.53-7.29 (4H, m), 7.03 (1H, d), 4.78 (1H, d), 4.60 (1H, d), 4.30 (1H, d), 4.22 (1H, d), 2.75 (1H, m), 2.00 (1H, br m), 1.90-1.65 (4H, br m), 1.50-1.20 (11H, m), 1.10-0.85 (5H, m). The

compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 59.10, H 7.20, N 9.07%; $C_{30}H_{36}N_4O_5 \bullet C_7H_{17}NO_5 \bullet H_2O$ requires C 59.58, H 7.43, N 9.39%.

Example 103. *(3-{2-[1-(3,3-Dimethyl-2-oxo-butyl)-5-(4-methyl-cyclohexyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-acetic acid.*

The title compound was obtained using the method employed in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that (2-amino-phenyl)-(4-methyl-cyclohexyl)-methanone was used in step a instead of (2-amino-phenyl)-cyclohexyl-methanone, and (3-amino-phenyl)-acetic acid methyl ester replaced 3-amino-benzoic acid methyl ester in step e, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR ($CDCl_3$) 8.27 (1H, br), 7.47-7.44 (2H, m), 7.33-7.23 (4H, m), 7.03-6.98 (2H, m), 4.75 (1H, d), 4.61 (1H, d), 4.31 (1H, d), 4.17 (1H, d), 3.60 (2H, s), 2.70 (1H, m), 2.00 (1H, br), 1.85-1.65 (4H, m), 1.45-1.25 (2H, m), 1.23 (9H, s), 1.05-0.80 (5H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 59.28, H 7.36, N 8.90%; $C_{31}H_{38}N_4O_5 \bullet C_7H_{17}NO_5 \bullet 1.5H_2O$ requires C 59.36, H 7.60, N 9.11%.

Example 104. N-*(3,5-Bis-methylamino-phenyl)-2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetamide.*

The title compound was obtained as the tri-hydrochloride salt by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that (3-amino-5-methylamino-phenyl)-methyl-carbamic acid *tert*-butyl ester (prepared in four steps from 3,5-difluoro-nitrobenzene) was used instead of 3-amino-benzoic acid methyl ester in step e, followed by reaction of the product obtained, in place of (3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-propyl-carbamic acid *tert*-butyl ester (Example 41, step a) according to the method of Example 41, step b. ^{1}H NMR (DMSO-d_6) 9.83 (1H, br s),

7.55-7.45 (2H, m), 7.26-7.14 (2H, m), 6.79 (2H, br s), 6.26 (1H, s), 4.77 (2H, s), 4.31-4.26 (1H, m), 3.96-3.91 (1H, m), 3.65 (4H, br s), 2.86 (1H, m), 2.72 (6H, m), 1.84-1.64 (6H, m), 1.34-1.10 (13H, m). Found: C 55.92, H 6.79, N 12.84%; $C_{30}H_{40}N_6O_3 \bullet 3.0HCl$ requires: C 56.11, H 6.75, N 13.09%.

Example 105. *2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]*-N-*(4-methoxy-3-methylamino-phenyl)-acetamide.*

The title compound was obtained as the hydrochloride salt by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that (5-amino-2-methoxy-phenyl)-methyl-carbamic acid *tert*-butyl ester (prepared in two steps from 2-methoxy-5-nitrophenylisocyanate) was used instead of 3-amino-benzoic acid methyl ester in step e, followed by reaction of the product obtained, in place of (3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-propyl-carbamic acid *tert*-butyl ester (Example 41, step a) according to the method of Example 41, step b. ^{1}H NMR ($CDCl_3$) 11.00-10.00 (1H, br s), 8.16-8.12 (1H, m), 7.61-7.27 (5H, m), 7.02-6.89 (2H, m), 4.74-4.68 (2H, m), 4.37 (1H, d, 16.8), 4.18 (1H, d), 3.90 (3H, s), 2.99 (3H, s), 2.84 (1H, m), 2.05-1.70 (6H, m), 1.36-1.12 (13H, m). Found: C 61.98, H 7.12, N 11.65%; $C_{30}H_{39}N_5O_4 \bullet 1.4HCl$ requires: C 61.66, H 6.97, N 11.99%.

Example 106. *2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]*-N-*(6-hydroxymethyl-pyridin-2-yl)-acetamide.*

The title compound was obtained by the method used in the preparation 3-({2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetyl}-methyl-amino)-benzoic acid methyl ester (Example 83, step a), except that (6-amino-pyridin-2-yl)-methanol (prepared from 6-amino-pyridine-2-carboxylic acid methyl ester (T. R. Kelly *et al.*: *J. Org. Chem.*, (1996), **61**, 4633) by reaction with lithium aluminium hydride) was used instead of 3-amino-benzoic acid methyl ester. ^{1}H NMR ($CDCl_3$) 7.38-7.33 (3H, m), 7.16 (1H, t), 6.93 (1H, d), 6.59 (1H, d), 6.39 (1H, d), 5.04 (2H, s), 4.67 (2H, s), 4.45 (1H, br), 4.40 (2H, br), 4.30 (1H, br), 2.70 (1H, m), 1.90-1.55 (7H,

m), 1.40-1.15 (12H, m). Found: C 66.28, H 7.03, N 13.60%; $C_{28}H_{35}N_5O_4$ requires C 66.51, H 6.98, N 13.85%.

Example 107. *2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-*N*-[3-(2-methyl-thiazol-4-yl)-phenyl]-acetamide.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that 3-(2-methyl-thiazol-4-yl)-phenylamine (prepared in two steps from 2-bromo-3'-nitroacetophenone) was used instead of 3-amino-benzoic acid methyl ester in step e. ^{1}H NMR ($CDCl_3$) 8.38 (1H, br s), 7.85 (1H, d), 7.62-7.59 (1H, m), 7.50-7.46 (3H, m), 7.35-7.27 (3H, m), 7.04-7.01 (1H, m), 4.77 (1H, d), 4.67 (1H, d), 4.35 (1H, d), 4.22 (1H, d), 2.84-2.78 (4H, m), 2.05-1.71 (6H, m), 1.31-1.22 (13H, m). Found: C 66.74, H 6.49, N 12.05%; $C_{32}H_{37}N_5O_3S\bullet 0.3H_2O$ requires: C 66.62, H 6.57, N 12.14%.

Example 108. *4-(3-{2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-thiazole-2-carboxylic acid.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that 4-(3-amino-phenyl)-thiazole-2-carboxylic acid ethyl ester (prepared in two steps from 2-bromo-3'-nitroacetophenone) was used instead of 3-amino-benzoic acid methyl ester in step e, followed by reaction of the product obtained, in place of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid ethyl ester (Example 1, step c), according to the method of Example 1, step d. ^{1}H NMR ($CDCl_3$) 8.49 (1H, br s), 8.09-8.07 (1H, m), 7.89 (1H, s), 7.63-7.61 (1H, m), 7.56-7.46 (3H, m), 7.40-7.28 (2H, m), 7.05 (1H, d, 7.8), 4.82 (1H, d), 4.62 (1H, d), 4.33-4.20 (2H, m), 2.81-2.77 (1H, m), 2.05-1.69 (6H, m), 1.44-1.16 (13H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 56.05, H 6.47, N 9.82%; $C_{32}H_{35}N_5O_5S\bullet C_7H_{17}NO_5\bullet 2.0H_2O$ requires: C 56.24, H 6.78, N 10.09%.

Example 109. *(3-{2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-2-oxo-2*H*-pyridin-1-yl)-acetic acid.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that (3-amino-2-oxo-2*H*-pyridin-1-yl)-acetic acid ethyl ester (prepared in two steps from 3-nitro-1*H*-pyridin-2-one) was used in place of 3-amino-benzoic acid methyl ester in step e, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR ($CDCl_3$) 9.04(1H, s), 8.50 (1H, dd), 7.48-7.41 (2H, m), 7.25 (1H, m), 6.99-6.96 (2H, m), 6.37 (1H, t), 4.70-4.60 (4H, m), 4.46 (1H, d), 4.15 (1H, d), 2.75 (1H, m), 2.00-1.65 (6H, m), 1.40-1.23 (14H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 55.03, H 6.91, N 10.29%; $C_{29}H_{35}N_5O_6 \bullet C_7H_{17}NO_5 \bullet 2.5H_2O$ requires C 54.74, H 7.27, N 10.64%.

Example 110. *(3-{2-[5-Cyclohexyl-1-(4-hydroxy-3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-acetic acid.*

The title compound was obtained using the method employed in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that benzoic acid 4-bromo-2,2-dimethyl-3-oxo-butyl ester (prepared in four steps from 2,2-dimethyl-3-oxo-butyric acid ethyl ester) was used in step c instead 1-bromo-3,3-dimethyl-butan-2-one, and (3-amino-phenyl)-acetic acid methyl ester replaced 3-amino-benzoic acid methyl ester in step e, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR (DMSO-d_6) 12.20 (1H, br s), 9.75 (1H, s), 7.55-7.11 (7H, m), 6.90 (1H, d), 4.90 (1H, br s), 4.79 (2H, s), 4.30-3.90 (2H, m), 3.48 (4H, s), 2.82 (1H, m), 2.00-1.10 (10H, m) 1.05 (6H, s). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 56.88, H 7.22, N 8.66%. $C_{30}H_{36}N_4O_6 \bullet C_7H_{17}NO_5 \bullet 2.0H_2O$ requires: C 56.98, H 7.36, N 8.98%.

Example 111. *2-[5-Cyclohexyl-1-(2-cyclohexyl-2-oxo-ethyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-*N*-[3-(5-oxo-2,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenyl]-acetamide.*

The title compound was obtained by the method used in the preparation of 2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-*N*-[3-(5-oxo-2,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenyl]-acetamide (Example 59) except that [5-cyclohexyl-1-(2-cyclohexyl-2-oxo-ethyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 79, step a) was used in place of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d). ^{1}H NMR ($CDCl_3$) 10.9 (1H, br s), 8.82 (1H, s), 7.85 (1H, s), 7.60 (2H, m), 7.45 (3H, m), 7.28 (1H, t), 7.04 (1H, d),), 4.73 (1H, d), 4.45 (1H, d), 4.20 (2H, s), 2.80 (1H, m), 2.47 (1H, m), 2.01-1.64 (11H, m), 1.47-1.17 (9H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 56.12, H 6.88, N 11.10%; $C_{32}H_{36}N_6O_5 \bullet C_7H_{17}NO_5 \bullet 2.8H_2O \bullet 0.4C_4H_8O_2$ requires: C 56.34, H 7.20, N 11.33%.

Example 112. *3-{2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-8-methyl-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid.*

The title compound was obtained using the method employed in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that (2-amino-4-methyl-phenyl)-cyclohexyl-methanone was used in step a instead of (2-amino-phenyl)-cyclohexyl-methanone, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR ($CDCl_3$) 8.54 (1H, s), 8.05 (1H, d), 7.82 (1H, s), 7.79 (1H, d), 7.40 (2H, m), 7.11 (1H, d), 6.82 (1H, s), 4.65 (2H, q), 4.25 (2H, q), 2.78 (1H, m), 2.41 (3H, s), 2.00 (1H, br m), 1.75 (4H, m), 1.31 (5H, m), 1.24 (9H, s). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found C 58.49, H 7.20, N 8.34; $C_{30}H_{36}N_4O_5 \bullet C_7H_{17}NO_5 \bullet 1.3H_2O \bullet 0.6C_4H_8O_2$ requires C 58.85, H 7.57, N 8.71%.

Example 113. *3-{2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-6-fluoro-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid.*

The title compound was obtained using the method employed in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that (2-amino-6-fluoro-phenyl)-cyclohexyl-methanone was used in step a instead of (2-amino-phenyl)-cyclohexyl-methanone, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR ($CDCl_3$) 8.60 (1H, s), 8.07 (1H, d), 7.98 (1H, s), 7.82 (1H, d), 7.42 (2H, m), 7.02 (1H, t), 6.81 (1H, d), 4.81 (1H, d), 4.56 (1H, d), 4.25 (2H, q), 2.91 (1H, m), 2.10 (1H, br m), 1.9-1.6 (4H, m), 1.28 (5H, m), 1.29 (9H, s). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found C 56.33, H 7.07, N 8.60; $C_{29}H_{33}FN_4O_5 \bullet C_7H_{17}NO_5 \bullet 1.9H_2O \bullet 0.5C_4H_8O_2$ requires C 56.34, H 7.19, N 8.64%.

Example 114. *3-{2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-6-methyl-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid.*

The title compound was obtained using the method employed in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that (2-amino-6-methyl-phenyl)-cyclohexyl-methanone was used in step a instead of (2-amino-phenyl)-cyclohexyl-methanone, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR ($CDCl_3$) 8.41 (1H, s), 8.11 (1H, d), 7.82 (1H, d), 7.75 (1H, s), 7.39 (2H, m), 7.17 (1H, d), 6.86 (1H, d), 4.76 (1H, d), 4.57 (1H, d), 4.37 (1H, d), 4.21 (1H, d), 2.66 (1H, m), 2.40 (3H, s), 2.00 (1H, br m), 1.75 (5H, m), 1.27 (4H, m), 1.26 (9H, s). The compound was further characterised as the *N*-methyl-D-glucamine. Found C 57.70, H 7.27, N 8.30; $C_{30}H_{36}N_4O_5 \bullet C_7H_{17}NO_5 \bullet 2.5\ H_2O \bullet 0.6C_4H_8O_2$ requires C 57.85, H 7.62, N 8.65%.

Example 115. *2-[5-Cyclohexyl-2-oxo-1-(pyrrolidine-1-carbonyl)1,2-dihyhdro-3*H-*1,3,4-benzotriazepin-3-yl]*-N-m-*tolyl-acetamide.*

Step a. *[5-Cyclohexyl-2-oxo-1-(pyrrolidine-1-carbonyl)-1,2-dihydro-3*H-*1,3,4-benzotriazepin-3-yl]-acetic acid ethyl ester.* A mixture of (1-chlorocarbonyl-5-cyclohexyl-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetic acid ethyl ester (Example 1, minor product of step b) (391mg, 1.0mmol), and pyrrolidine (156mg, 2.2mmol) in DCM (5ml) was stirred at room temperature for 30min. The solution was washed with dilute HCl, dried ($MgSO_4$), and the solvent evaporated under reduced pressure to afford the product as a white solid (417mg, 98%). ^{1}H NMR ($CDCl_3$) 8.12 (1H, d), 7.50 (1H, t), 7.39-7.31 (2H, m), 4.31 (2H, s), 4.16 (2H, q), 3.45 (4H, m), 2.81 (1H, m), 1.92-1.27 (14H, m), 1.22 (3H, t).

Step b. *[5-Cyclohexyl-2-oxo-1-(pyrrolidine-1-carbonyl)-1,2-dihydro-3*H-*1,3,4-benzotriazepin-3-yl]-acetic acid* was obtained by the method used in the preparation of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d) except that [5-cyclohexyl-2-oxo-1-(pyrrolidine-1-carbonyl)-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid ethyl ester (Example 115, step a) was used in place of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid ethyl ester (Example 1, step c). ^{1}H NMR ($CDCl_3$) 8.11 (1H, d), 7.50 (1H, t), 7.42-7.33 (2H, m), 4.26 (2H, s), 3.42 (4H, m), 2.85 (1H, m), 1.91-1.19 (10H, m).

Step c. The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1, step e) except that [5-cyclohexyl-2-oxo-1-(pyrrolidine-1-carbonyl)-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 115, step b) and *m*-toluidine were used instead of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d) and 3-amino-benzoic acid methyl ester respectively. ^{1}H NMR ($CDCl_3$) 8.12 (1H, d), 8.10 (1H, br s), 7.59 (1H, t), 7.43 (2H, m), 7.16 (2H, m), 7.07 (1H, d), 6.88 (1H, d), 4.34 (2H, s), 3.45-3.35 (4H, m), 2.88 (1H, m), 2.31 (3H, s), 2.00-1.31

(14H, m). Found: C 68.00, H 6.73, N 14.07%; $C_{28}H_{33}N_5O_3 \bullet 0.5H_2O$ requires: C 67.72, H 6.90, N 14.10%.

Example 116. *(7-{2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-3,4-dihydro-1*H*-isoquinolin-2-yl)-acetic acid.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that (7-amino-3,4-dihydro-1*H*-isoquinolin-2-yl)-acetic acid ethyl ester was used instead of 3-amino-benzoic acid methyl ester in step e, followed by reaction of the product obtained, in place of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid ethyl ester (Example 1, step c), according to the method of Example 1, step d. ^{1}H NMR (DMSO-d_6) 9.90 (1H, brs), 7.54-7.42 (3H, m), 7.28-7.11 (4H, m), 4.78 (2H, m), 4.33 (2H, m), 4.09 (2H, m), 3.39 (3H, m), 3.00 (3H, m), 1.65-1.21 (6H, m), 1.12-1.04 (13H, m). The product was further characterised as the hydrochloride salt. Found: C 47.05, H 5.34, N, 7.72%; $C_{33}H_{41}N_5O_5 \bullet HCl \bullet 3.4CH_2Cl_2$ requires: C 47.14, H 5.48, N 7.55%.

Example 117. *(5-{2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-indol-1-yl)-acetic acid.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that (5-amino-indol-1-yl)-acetic acid ethyl ester (prepared in two steps from 5-nitroindole) was used instead of 3-amino-benzoic acid methyl ester in step e, followed by reaction of the product obtained, in place of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl]-acetic acid ethyl ester (Example 1, step c), according to the method of Example 1, step d. ^{1}H NMR ($CDCl_3$) 8.21 (1H, s), 7.70 (1H, s), 7.47 (2H, m), 7.27 (1H, m), 7.05 (4H, m), 6.47 (1H, d), 4.79 (2H, s), 4.68 (2H, m), 4.39 (1H, d), 4.20 (1H, d), 2.78 (1H, m), 2.18-1.07 (19H, m). The compound was further characterised as the N-methyl-D-

glucamine salt. Found: C 58.02, H 7.08, N 9.62%; $C_{32}H_{37}N_5O_5 \bullet C_7H_{17}NO_5 \bullet 1.9H_2O \bullet 0.6C_4H_8O_2$ requires: C 58.23, H 7.39, N 9.84%.

Example 118. *(5-{2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl]-acetylamino}-indazol-1-yl)-acetic acid.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that (5-amino-indazol-1-yl)-acetic acid methyl ester (prepared in two steps from 5-nitro-indazole) was used in place of 3-amino-benzoic acid methyl ester in step e, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR ($CDCl_3$) 8.43 (1H, s), 8.05 (1H, s), 7.52-7.45 (2H, m), 7.32-7.23 (3H, m), 7.04 (1H, d, 8.1), 5.12 (2H, s), 4.82 (1H, d, 17.4), 4.61 (1H, d, 17.4), 4.27-4.26 (2H, m), 2.79 (1H, m), 2.05-1.72 (6H, m), 1.48-1.19 (13H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 56.75, H 6.90, N 11.81%; $C_{31}H_{36}N_6O_5 \bullet C_7H_{17}NO_5 \bullet 2.3H_2O$ requires: C 56.46, H 7.17, N 12.13%.

Example 119. *(3-{2-[5-Cyclohexyl1-1-(2-cyclopropyl-2-oxo-ethyl)-2-oxo-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-acetic acid.*

Step a. *[5-Cyclohexyl-1-(2-cyclopropyl-2-oxo-ethyl)-2-oxo-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl]-acetic acid* was obtained using steps a-d of the method employed in the preparation of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d) except that 2-bromo-1-cyclopropyl-ethanone was used in step c instead of 1-bromo-3,3-dimethyl-butan-2-one. ^{1}H NMR ($CDCl_3$) 10.80 (1H, br s), 7.46 (2H, m), 7.27 (1H, m), 7.04 (1H, d), 4.66 (2H, m), 4.28 (1H, d), 3.93 (1H, d), 2.85 (1H, m), 1.99-0.92 (15H, m).

Step b. The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-

benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1, step e) except that [5-cyclohexyl-1-(2-cyclopropyl-2-oxo-ethyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 119, step a) and (3-amino-phenyl)-acetic acid methyl ester were used in place of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d) and 3-amino-benzoic acid methyl ester respectively, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR ($CDCl_3$) 10.80 (1H, br s), 8.30 (1H, s), 7.46 (2H, m), 7.26 (4H, m), 7.08 (1H, d), 6.98 (1H, d), 4.78 (1H, d), 4.57 (1H, d), 4.32 (1H, d), 4.18 (1H, d), 3.59 (2H, s), 2.78 (1H, m), 2.17-1.68 (7H, m), 1.24 (4H, m), 1.08 (2H, m), 0.93 (2H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 58.57, H 7.22, N 8.57%; $C_{29}H_{32}N_4O_5 \bullet C_7H_{17}NO_5 \bullet 1.2H_2O \bullet 0.9C_4H_8O_2$ requires: C 58.52, H 7.27, N 8.62%.

Example 120. *[3-(2-{5-Cyclohexyl-1-(2-cyclopropyl-2-oxo-ethyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenylsulfanyl)-acetic acid.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except [5-cyclohexyl-1-(2-cyclopropyl-2-oxo-ethyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 119, step a) and (3-amino-phenylsulfanyl)-acetic acid ethyl ester were used instead of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d) and 3-amino-benzoic acid methyl ester respectively in step e, followed by reaction of the product obtained, in place of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid ethyl ester (Example 1, step c), according to the method of Example 1, step d. ^{1}H NMR ($CDCl_3$) 8.90 (1H, br s), 8.44 (1H, s), 7.49 (3H, m), 7.29 (2H, m), 7.19 (1H, t), 7.08 (2H, t), 4.81 (1H, d), 4.56 (1H, d), 4.22 (2H, m), 3.65 (2H, s), 2.79 (1H, m), 2.01-1.68 (7H, m), 1.26 (4H, m), 1.09 (2H, m), 0.93 (2H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 55.42, H 6.74, N 8.42%; $C_{29}H_{32}N_4O_5S \bullet C_7H_{17}NO_5 \bullet 1.8H_2O \bullet 0.4C_4H_8O_2$ requires: C 55.65, H 6.93, N 8.63%.

Example 121. *2-[5-Cyclohexyl-1-(2-cyclopentyl-2-oxo-ethyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]*-N-*[3-(5-oxo-2,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenyl]-acetamide.*

The title compound was obtained by the method used in the preparation of 2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-*N*-[3-(5-oxo-2,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenyl]-acetamide (Example 59) except that [5-cyclohexyl-1-(2-cyclopentyl-2-oxo-ethyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 22, step a) was used in place of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d). ^{1}H NMR ($CDCl_3$) 10.80 (1H, br s), 8.85 (1H, s), 7.85 (1H, s), 7.59 (2H, m), 7.43 (3H, m), 7.28 (1H, t), 7.05 (1H, d),), 4.73 (1H, d), 4.45 (1H, d), 4.22 (2H, s), 2.93 (1H, m), 2.80 (1H, m), 2.18-1.59 (13H, m), 1.28 (5H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 57.52, H 6.80, N 12.01%; $C_{31}H_{34}N_6O_5 \bullet C_7H_{17}NO_5 \bullet 1.7H_2O$ requires: C 57.25, H 6.89, N 12.30%.

Example 122. *2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]*-N-*[3-(5-methyl-[1,3,4]oxadiazol-2-yl)-phenyl]-acetamide.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that 3-(5-methyl-[1,3,4]oxadiazol-2-yl)-phenylamine (prepared in three steps from 3-nitrobenzoic acid) was used instead of 3-amino-benzoic acid methyl ester in step e. ^{1}H NMR ($CDCl_3$) 8.57 (1H, s), 8.04 (1H, s), 7.78-7.70 (2H, m), 7.50-7.30 (4H, m), 7.02 (1H, m), 4.80-4.56 (2H, m), 4.25 (2H, s), 2.81 (1H, m), 2.61 (3H, s), 2.00-1.27 (10H, m), 1.24 (9H, s). Found: C 66.70, H 6.71, N 14.98%; $C_{31}H_{36}N_6O_4$ requires: C 66.89, H 6.52, N 15.10%.

Example 123. *2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]*-N-*(3-morpholin-4-yl-phenyl)-acetamide.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-

yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that 3-morpholin-4-yl-phenylamine (prepared in two steps from 3-fluoro-1-nitrobenzene) was used instead of 3-amino-benzoic acid methyl ester in step e. ^{1}H NMR ($CDCl_3$) 8.22 (1H, br s), 7.50-7.44 (2H, m), 7.29-7.12 (3H, m), 7.03 (1H, d, 8.1), 6.75 (1H, d, 8.1), 6.63-6.60 (1H, m), 4.77 (1H, d, 17.7), 4.65 (1H, d, 17.7), 4.34 (1H, d, 16.8), 4.19 (1H, d, 16.8), 3.84 (4H, t, 4.8), 3.15 (4H, t, 4.8), 2.82-2.75 (1H, m), 2.05-1.74 (6H, m), 1.36-1.24 (13H, m). Found: C 68.18, H 7.42, N 12.29%; $C_{32}H_{41}N_5O_4 \bullet 0.3H_2O$ requires: C 68.10, H 7.42, N 12.41%.

Example 124. *2-[5-Cyclohexyl-1-(2-cyclopentyl-2-oxo-ethyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-*N*-{3-[methyl-(2*H*-tetrazol-5-yl)-amino]-phenyl}-acetamide.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), except that [5-cyclohexyl-1-(2-cyclopentyl-2-oxo-ethyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 22, step a) and 2,2-dimethyl-propionic acid 5-[(3-amino-phenyl)-methyl-amino]-tetrazol-2-ylmethyl ester were used in place of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d) and 3-amino-benzoic acid methyl ester respectively in step e, followed by reaction of the product obtained, in place of 2,2-dimethyl-propionic acid 5-(3-{2-[5-cyclopentyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-tetrazol-2-ylmethyl ester (Example 10, step a), according to the method of Example 10, step b. ^{1}H NMR (DMSO-d_6) 9.85 (1H, s), 7.56-7.48 (3H, m), 7.30-7.20 (3H, m), 7.15 (1H, d), 7.06 (1H, d), 7.00 (1H, br m), 6.65 (1H, br m), 4.65 (2H, br m), 4.25 (1H, br d), 3.95 (1H, br d), 3.40 (3H, s), 3.05-2.85 (2H, m), 1.90-1.40 (9H, m), 1.40-0.95 (9H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 56.42, H 7.05, N 16.27%; $C_{31}H_{37}N_9O_3 \bullet C_7H_{17}NO_5 \bullet 1.5CH_3CO_2H$ requires C 56.67, H 6.96, N 16.12%.

Example 125. *2-[5-Cyclohexyl-1-(2-cyclopentyl-2-oxo-ethyl)-2-oxo-1,2-dihydro-*3H*-1,3,4-benzotriazepin-3-yl]-N-[3-(2*H*-tetrazol-5-yl)-phenyl]-acetamide.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), except that [5-cyclohexyl-1-(2-cyclopentyl-2-oxo-ethyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 22, step a) and 2,2-dimethyl-propionic acid 5-(3-amino-phenyl)-tetrazol-2-ylmethyl ester were used in place of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d) and 3-amino-benzoic acid methyl ester respectively in step e, followed by reaction of the product obtained, in place of 2,2-dimethyl-propionic acid 5-(3-{2-[5-cyclopentyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-tetrazol-2-ylmethyl ester (Example 10, step a), according to the method of Example 10, step b. ^{1}H NMR (d_6-DMSO) 10.11 (1H, s), 8.36 (1H, s), 7.68-7.46 (5H, m), 7.22 (1H, m), 7.16 (1H, d), 6.95 (1H, br), 6.65 (1H, br), 4.64 (2H, m br), 4.35 (1H, m br), 4.00 (1H, m br), 3.00-2.80 (2H, m), 1.95-1.45 (9H, m), 1.40-1.00 (9H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 56.11, H 7.00, N 14.82%; $C_{30}H_{34}N_8O_3 \bullet C_7H_{17}NO_5 \bullet 0.8CH_3CO_2H \bullet 2.2CH_3OH$ requires C 56.43, H 7.31, N 14.52%.

Example 126. *(6-{2-[5-Cyclohexyl-1-(2-cyclopentyl-2-oxo-ethyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-indol-1-yl)-acetic acid.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), except that [5-cyclohexyl-1-(2-cyclopentyl-2-oxo-ethyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 22, step a) and (6-amino-indol-1-yl)-acetic acid ethyl ester were used in place of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d) and 3-amino-benzoic acid methyl ester respectively in step e, followed by reaction of the product obtained, in place of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid ethyl ester (Example 1, step c), according to the method of Example 1, step d. ^{1}H NMR (DMSO-d_6) 9.65 (1H, s), 7.67 (1H, s), 7.58-7.47 (2H, m), 7.39 (1H, d), 7.28-7.15 (3H, m), 6.97 (1H, d), 6.31 (1H, d), 4.75-4.55 (4H, m), 4.30 (1H, br d), 3.95 (1H, br d), 3.00-2.88 (2H, m), 1.98-1.40 (14H, m), 1.35-1.10 (4H, m). The compound was further characterised

as the *N*-methyl-D-glucamine salt. Found: C 58.53, H 6.80, N 10.01%; $C_{33}H_{37}N_5O_5 \bullet C_7H_{17}NO_5 \bullet 2.0H_2O$ requires C 58.95, H 7.17, N 10.31%.

Example 127. *(4-{2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H-*1,3,4-benzotriazepin-3-yl]-acetylamino}-indol-1-yl)-acetic acid.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that (4-amino-indol-1-yl)-acetic acid ethyl ester (prepared in two steps from 4-nitroindole) was used instead of 3-amino-benzoic acid methyl ester in step e, followed by reaction of the product obtained, in place of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl]-acetic acid ethyl ester (Example 1, step c), according to the method of Example 1, step d. ^{1}H NMR ($CDCl_3$) 8.47 (1H, s), 7.84 (1H, d), 7.47 (2H, m), 7.27 (1H, m), 7.15 (1H, t), 7.05 (1H, d), 6.96 (1H, d), 6.87 (1H, t), 5.69 (1H, d), 4.75 (4H, m), 4.57 (1H, d), 4.25 (1H, d), 2.79 (1H, m), 1.99-1.09 (19H, m). The compound was further characterised as the N-methyl-D-glucamine salt. Found: C 58.46, H 7.08, N 9.78%; $C_{32}H_{37}N_5O_5 \bullet C_7H_{17}NO_5 \bullet 1.6H_2O \bullet 0.5C_4H_8O_2$ requires: C 58.64, H 7.35, N 10.01%.

Example 128. *3-(3-{2-[5-Cyclohexyl-1-(2-cyclopentyl-2-oxo-ethyl)-2-oxo-1,2-dihydro-3*H-*1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-propionic acid.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), except that [5-cyclohexyl-1-(2-cyclopentyl-2-oxo-ethyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 22, step a) and 3-(3-amino-phenyl)-propionic acid methyl ester were used in place of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d) and 3-amino-benzoic acid methyl ester respectively in step e, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR ($CDCl_3$) 8.28 (1H, s), 7.47 (2H, m), 7.32-7.16 (4H, m), 7.07 (1H, d),

6.92 (1H, d), 4.67 (1H, d), 4.45 (1H, d), 4.32 (1H, d), 4.18 (1H, d), 2.95 (3H, m), 2.80 (1H, m), 2.66 (2H, m), 1.84-1.57 (14H, m), 1.30 (4H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 59.30, H 7.18, N 8.70%; $C_{32}H_{38}N_4O_5 \bullet C_7H_{17}NO_5 \bullet 1.8H_2O$ requires: C 59.63, H 7.51, N 8.91%.

Example 129. *2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-*3H-*1,3,4-benzotriazepin-3-yl]-*N-*[3-(4-methyl-piperazin-1-yl)-phenyl]-acetamide.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), except that 3-(4-methyl-piperazin-1-yl)-phenylamine (prepared in two steps from 3-fluoro-1-nitrobenzene) was used instead of 3-amino-benzoic acid methyl ester in step e. ^{1}H NMR ($CDCl_3$) 8.17 (1H, br s), 7.50-7.44 (2H, m), 7.29-7.27 (1H, m), 7.16-7.09 (2H, m), 7.04 (1H, d, 8.1), 6.78-6.75 (1H, m), 6.64-6.61 (1H, m), 4.76-4.60 (2H, m), 4.36-4.12 (2H, m), 3.21-3.18 (4H, m), 2.82-2.74 (1H, m), 2.57-2.54 (4H, m), 2.35 (3H, s), 2.04-1.60 (6H, m), 1.45-1.23 (13H, m). Found: C 68.32, H 7.55, N 14.16%; $C_{33}H_{44}N_6O_3 \bullet 0.5H_2O$ requires: C 68.19, H 7.79, N 14.46%.

Example 130. *(4-{2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H-*1,3,4-benzotriazepin-3-yl]-acetylamino}-indazol-1-yl)-acetic acid.*

Step a. *(4-{2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H-*1,3,4-benzotriazepin-3-yl]-acetylamino}-indazol-1-yl)-acetic acid* tert-*butyl ester* was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that (4-amino-indazol-1-yl)-acetic acid *tert*-butyl ester (prepared in two steps from 4-nitro-indazole) was used in place of 3-amino-benzoic acid methyl ester in step e.

Step b. *(4-{2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H-*1,3,4-benzotriazepin-3-yl]-acetylamino}-indazol-1-yl)-acetic acid* tert-*butyl ester* (Example 130, step a) (522mg, 0.82mmol) was dissolved in trifluoroacetic acid (5ml) and the

solution was stirred at room temperature for 2h. The solvent was evaporated, and the solid obtained was washed with Et_2O, isolated by filtration and dried to afford the trifluoroacetate salt of the title compound (430mg, 91%). ^{1}H NMR ($CDCl_3$) 8.98 (1H, s), 8.00-7.86 (3H, br m), 7.57-7.29 (5H, m), 7.10-7.05 (2H, m), 5.21 (2H, s), 4.77-4.62 (2H, m), 4.47-4.30 (2H, m), 2.80-2.76 (1H, m), 2.02-1.61 (6H, m), 1.30-1.16 (13H, m). Found: C 57.90, H 5.54, N 12.51%; $C_{31}H_{36}N_6O_5 \bullet CF_3CO_2H$ requires: C 57.72, H 5.43, N 12.24%.

Example 131. *2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-*N*-[1-(1*H*-tetrazol-5-ylmethyl)-1*H*-indol-6-yl]-acetamide.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), except that 2,2-dimethyl-propionic acid 5-(6-amino-indol-1-ylmethyl)-tetrazol-1-ylmethyl ester (prepared in four steps from 6-nitro-indole) was used in place of 3-amino-benzoic acid methyl ester in step e, followed by reaction of the product obtained, in place of 2,2-dimethyl-propionic acid 5-(3-{2-[5-cyclopentyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-tetrazol-2-ylmethyl ester (Example 10, step a), according to the method of Example 10, step b. ^{1}H NMR ($CDCl_3$) 8.66 (1H, s), 7.87 (1H, s), 7.38 (3H, m), 7.24 (1H, m), 7.14 (1H, d), 6.93 (1H, d), 6.66 (1H, d), 6.45 (1H, d), 5.39 (2H, s), 4.60 (2H, q), 4.13 (2H, q), 2.78 (1H, m), 2.00 (1H, m), 1.70 (5H, m), 1.25 (4H, m), 1.15 (9H, s).

Example 132. *(3-{2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-6-methyl-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-acetic acid.*

The title compound was obtained using the method employed in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that (2-amino-6-methyl-phenyl)-cyclohexyl-methanone was used in step a instead of (2-amino-phenyl)-cyclohexyl-methanone, and (3-amino-phenyl)-acetic acid methyl ester replaced 3-amino-benzoic acid methyl ester in step e, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-

yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR ($CDCl_3$) 8.22 (1H, s), 7.31 (4H, m), 7.10 (1H, d), 7.00 (1H, d), 6.84 (1H, d), 4.73 (1H, d), 4.56 (1H, d), 4.34 (1H, d), 4.16 (1H, d), 3.61 (2H, s), 2.63 (1H, m), 2.35 (3H, s), 2.00 (1H, br m), 1.75 (5H, m), 1.24 (13H, m).

Example 133. *[3-(2-{5-Cyclohexyl-1-[2-(1-methyl-cyclohexyl)-2-oxo-ethyl]-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl}-acetylamino)-phenyl]-acetic acid.*

Step a. *{5-Cyclohexyl-1-[2-(1-methyl-cyclohexyl)-2-oxo-ethyl]-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl}-acetic acid* was obtained using steps a-d of the method employed in the preparation of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d) except that 2-bromo-1-(1-methyl-cyclohexyl)-ethanone (prepared from 1-methyl-cyclohexane-carboxylic acid in two steps) was used in step c instead of 1-bromo-3,3-dimethyl-butan-2-one. ^{1}H NMR ($CDCl_3$) 10.80 (1H, br s), 7.45 (2H, m), 7.24 (1H, t), 6.96 (1H, d), 4.67 (2H, m), 4.22 (1H, d), 3.90 (1H, d), 2.82 (1H, m), 2.01-1.17 (23H, m).

Step b. The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), except that {5-cyclohexyl-1-[2-(1-methyl-cyclohexyl)-2-oxo-ethyl]-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl}-acetic acid (Example 133, step a) and (3-amino-phenyl)-acetic acid methyl ester were used in place of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d) and 3-amino-benzoic acid methyl ester respectively in step e, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR ($CDCl_3$) 8.28 (1H, s), 7.47 (2H, m), 7.37-7.20 (4H, m), 7.00 (2H, t), 4.66 (2H, m), 4.25 (2H, m), 3.60 (2H, s), 2.78 (1H, m), 2.18-1.23 (20H, m), 1.19 (3H, s). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 60.87, H 7.66, N 8.38%; $C_{33}H_{40}N_4O_5 \bullet C_7H_{17}NO_5 \bullet 0.9H_2O \bullet 0.6C_4H_8O_2$ requires: C 60.84, H 7.66, N 8.37%.

Example 134. *[3-(2-{5-Cyclohexyl-1-[2-(1-methyl-cyclohexyl)-2-oxo-ethyl]-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl}-acetylamino)-phenylsulfanyl]-acetic acid.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), except that {5-cyclohexyl-1-[2-(1-methyl-cyclohexyl)-2-oxo-ethyl]-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl}-acetic acid (Example 133, step a) and (3-amino-phenylsulfanyl)-acetic acid ethyl ester were used instead of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d) and 3-amino-benzoic acid methyl ester respectively in step e, followed by reaction of the product obtained, in place of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid ethyl ester (Example 1, step c), according to the method of Example 1, step d. ^{1}H NMR ($CDCl_3$) 8.40 (1H, s), 7.48 (3H, m), 7.31 (2H, m), 7.20 (1H, t), 7.10 (1H, d), 7.02 (1H, d), 4.76 (1H, d), 4.58 (1H, d), 4.23 (2H, m), 3.67 (2H, s), 2.79 (1H, m), 1.99-1.25 (20H, m), 1.19 (3H, s). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 58.41, H 7.21, N 8.18%; $C_{33}H_{40}N_4O_5S \bullet C_7H_{17}NO_5 \bullet 1.4H_2O$ requires: C 58.17, H 7.31, N 8.48%.

Example 135. *5-{2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-1*H*-indole-2-carboxylic acid ethyl ester.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that 5-amino-1H-indole-2-carboxylic acid ethyl ester was used instead of 3-amino-benzoic acid methyl ester in step e. ^{1}H NMR ($CDCl_3$) 8.75 (1H, s), 8.24 (1H, s), 7.90 (1H, s), 7.48-7.19 (6H, m), 7.04 (1H, d), 4.68 (1H, d), 4.45 (1H, d), 4.41-4.25 (4H, m), 2.79 (1H, m), 2.05-1.39 (6H, m), 1.28-1.23 (16H, m). Found: C 67.04, H 6.98, N 11.19 %; $C_{33}H_{39}N_5O_5 \bullet 0.4CH_3CO_2C_2H_5$ requires: C 66.93, H 6.85, N 11.28 %.

Example 136. *2-[5-Cyclohexyl-1-(2-cyclopentyl-2-oxo-ethyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-*N*-[3-(2-methyl-thiazol-4-yl)-phenyl]-acetamide.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), except that [5-cyclohexyl-1-(2-cyclopentyl-2-oxo-ethyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 22, step a) and 3-(2-methyl-thiazol-4-yl)-phenylamine were used in place of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d) and 3-amino-benzoic acid methyl ester respectively in step e. ^{1}H NMR ($CDCl_3$) 8.39 (1H, s), 7.84 (1H, t), 7.61 (1H, d), 7.47 (3H, t), 7.30 (3H, m), 7.08 (1H, d), 4.57 (2H, m), 4.26 (2H, m), 2.95 (1H, m), 2.82 (1H, m), 2.77 (3H, s), 1.82-1.26 (18H, m). Found: C 67.52, H 6.42, N 11.83%; $C_{33}H_{37}N_5O_3S\bullet 0.2H_2O$ requires: C 67.44, H 6.42, N 11.92%.

Example 137. *4-(3-{2-[5-Cyclohexyl-1-(2-cyclopentyl-2-oxo-ethyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-thiazole-2-carboxylic acid.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), except that [5-cyclohexyl-1-(2-cyclopentyl-2-oxo-ethyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 22, step a) and 4-(3-amino-phenyl)-thiazole-2-carboxylic acid ethyl ester were used in place of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d) and 3-amino-benzoic acid methyl ester respectively in step e, followed by reaction of the product obtained, in place of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid ethyl ester (Example 1, step c), according to the method of Example 1, step d. ^{1}H NMR ($CDCl_3$) 8.51 (1H, s), 8.05 (1H, s), 7.88 (1H, s), 7.63 (1H, d), 7.49 (3H, m), 7.40-7.27 (2H, m), 7.07 (1H, d), 4.70 (1H, d), 4.45 (1H, d), 4.27 (2H, m), 2.95 (1H, m), 2.81 (1H, m), 2.06-1.56 (14H, m), 1.28 (4H, m). The compound was further characterised the *N*-methyl-D-glucamine salt. Found: C 57.65, H 6.41, N 9.83%; $C_{33}H_{35}N_5O_5S\bullet C_7H_{17}NO_5\bullet 1.5H_2O$ requires: C 57.51, H 6.63, N 10.06%.

Example 138. *(3-{2-[1-(3,3-Dimethyl-2-oxo-butyl)-2-oxo-5-pyridin-2-yl-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenylsulfanyl)-acetic acid.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), except that [1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-5-pyridin-2-yl-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 5, step a) and (3-amino-phenylsulfanyl)-acetic acid ethyl ester were used instead of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d) and 3-amino-benzoic acid methyl ester respectively in step e, followed by reaction of the product obtained, in place of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid ethyl ester (Example 1, step c), according to the method of Example 1, step d. ^{1}H NMR ($CDCl_3$) 8.63 (1H, m), 8.36 (1H, m), 8.02 (1H, m), 7.81 (1H, t), 7.36 (2H, m), 7.23 (3H, m), 7.11 (4H, m), 5.05 (1H, br s), 4.72 (2H, m), 4.36 (2H, m), 3.61 (2H, s), 1.27 (9H, s).

Example 139. *(3-{2-[1-(3,3-Dimethyl-2-oxo-butyl)-2-oxo-5-phenyl-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenylsulfanyl)-acetic acid.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that [1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-5-phenyl-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 4, step a) and (3-amino-phenylsulfanyl)-acetic acid ethyl ester were used instead of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d) and 3-amino-benzoic acid methyl ester respectively in step e, followed by reaction of the product obtained, in place of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid ethyl ester (Example 1, step c), according to the method of Example 1, step d. ^{1}H NMR ($CDCl_3$) 8.60 (1H, br s), 8.40 (1H, s), 7.63-7.40 (7H, m), 7.25-7.14 (6H, m), 4.76 (2H, m), 4.43 (2H, s), 3.58 (2H, s), 1.25 (9H, s). The compound was further

characterised as the *N*-methyl-D-glucamine salt. Found: C 50.02, H 6.04, N 7.59%; $C_{30}H_{30}N_5O_5S \bullet C_7H_{17}NO_5 \bullet 1.8C_4H_8O_2 \bullet 2.2CH_2Cl_2$ requires: C 50.06, H 5.96, N 7.55%.

Example 140. *2-(3-{2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H-*1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-oxazole-4-carboxylic acid methyl ester.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), except that 2-(3-amino-phenyl)-oxazole-4-carboxylic acid methyl ester (prepared in three steps from serine methyl ester and 3-nitrobenzoic acid) was used instead of 3-amino-benzoic acid methyl ester in step e. ^{1}H NMR ($CDCl_3$) 8.51 (1H, br s), 8.28 (1H, s), 8.00 (1H, t, 1.8), 7.86-7.83 (1H, m), 7.76-7.73 (1H, m), 7.54-7.34 (4H, m), 7.05 (1H, d, 1.8), 4.81 (1H, d, 17.7), 4.64 (1H, d, 17.7), 4.26-4.25 (2H, m), 3.96 (3H, s), 2.83-2.77 (1H, m), 2.05-1.70 (6H, m), 1.38-1.18 (13H, m). Found: C 64.43, H 6.10, N 11.25%; $C_{33}H_{37}N_6O_5 \bullet 0.8H_2O$ requires: C 64.56, H 6.33, N 11.41%.

Example 141. *2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H-*1,3,4-benzotriazepin-3-yl]-*N-*[3-(1-methyl-1*H*-imidazol-4-yl)-phenyl]-acetamide.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), except that 3-(1-methyl-1*H*-imidazol-4-yl)-phenylamine (prepared in three steps from 2-bromo-3′-nitroacetophenone) was used instead of 3-amino-benzoic acid methyl ester in step e. ^{1}H NMR ($CDCl_3$) 8.25 (1H, br s), 7.85 (1H, t, 1.8), 7.54-7.44 (4H, m), 7.30-7.24 (2H, m), 7.19 (2H, m), 7.04 (1H, d, 7.8), 4.71-4.68 (2H, m), 4.37 (1H, d, 16.2), 4.21 (1H, d, 16.2), 3.72 (3H, s), 2.79 (1H, m), 2.05-1.72 (6H, m), 1.32-1.24 (13H, m). Found: C 68.00, H 6.90, N 14.55%; $C_{32}H_{38}N_6O_3 \bullet 0.7H_2O$ requires: C 67.77, H 7.00, N 14.82%.

Example 142. *(4-{2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H-*1,3,4-benzotriazepin-3-yl]-acetylamino}-indazol-2-yl)-acetic acid.*

The title compound was obtained as the trifluoroacetate salt by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), except that (4-amino-indazol-2-yl)-acetic acid *tert*-butyl ester (prepared in two steps from 4-nitro-indazole) was used instead of 3-amino-benzoic acid methyl ester in step e, followed by reaction of the product obtained, in place of (4-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-indazol-1-yl)-acetic acid *tert*-butyl ester (Example 130, step a), according to the method of Example 130, step b. ^{1}H NMR ($CDCl_3$) 10.04-9.95 (2H, br s), 9.06 (1H, s), 8.13 (1H, s), 7.53-7.20 (6H, m), 7.06 (1H, d, 6), 5.26 (2H, s), 4.80 (1H, d, 18), 4.63 (1H, d, 18), 4.29 (2H, s), 2.81-2.78 (1H, m), 2.07-1.67 (6H, m), 1.37-1.19 (13H, m). Found: C 56.82, H 5.42, N 11.88%; $C_{31}H_{36}N_6O_5 \bullet CF_3CO_2H \bullet 0.7H_2O$ requires: C 56.72, H 5.53, N 12.03%.

Example 143. *2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]*-N-*{3-[methyl-(2-methylamino-ethyl)-amino]-phenyl}-acetamide.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), except that {2-[(3-amino-phenyl)-methyl-amino]-ethyl}-methyl-carbamic acid *tert*-butyl ester (prepared in three steps from 3-fluoro-1-nitrobenzene and *N,N'*-dimethylethylenediamine) was used instead of 3-amino-benzoic acid methyl ester in step e, followed by reaction of the product obtained, in place of (3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-methyl-carbamic acid *tert*-butyl ester (Example 3, step d), according to the method of Example 3, step e. ^{1}H NMR ($CDCl_3$) 8.09 (1H, s), 7.50-7.45 (2H, m), 7.29-7.24 (1H, m), 7.12-7.01 (3H, m), 6.53-6.46 (2H, m), 4.69-4.67 (2H, m), 4.38 (1H, d, 13.8), 4.17 (1H, d, 13.8), 3.50-3.44 (2H, m), 2.93 (3H, s), 2.86-2.74 (3H, m), 2.49 (3H, s), 2.04-1.58 (7H, m), 1.31-1.19 (13H, m). Found: C 65.52, H 7.53, N 14.12%; $C_{32}H_{44}N_6O_5 \bullet 0.4CH_2Cl_2$ requires: C 65.58, H 7.61, N 14.17%.

Example 144. *2-(3-{2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-oxazole-4-carboxylic acid.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid (Example 2) except that 2-(3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-oxazole-4-carboxylic acid methyl ester (Example 140) was used instead of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1). ^{1}H NMR ($CDCl_3$) 8.58 (1H, m), 8.36 (1H, s), 8.08 (1H, t, 1.2), 7.83-7.81 (1H, m), 7.76-7.73 (1H, m), 7.54-7.32 (4H, m), 7.05 (1H, d, 8.1), 4.83 (1H, d, 17.4), 4.63 (1H, d, 17.4), 4.26 (2H, s), 2.84-2.78 (1H, m), 2.06-1.73 (6H, m), 1.36-1.18 (13H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 57.95, H 6.68, N 10.18%; $C_{32}H_{35}N_6O_5 \bullet C_7H_{17}NO_5 \bullet 1.6H_2O$ requires: C 57.85, H 6.87, N 10.38%.

Example 145. *5-(3-{2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-furan-2-carboxylic acid.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), except that 5-(3-amino-phenyl)-furan-2-carboxylic acid methyl ester (prepared in two steps from 5-(3-nitrophenyl)-2-furoic acid) was used in place of 3-amino-benzoic acid methyl ester in step e, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR ($CDCl_3$) 8.34 (1H, br s), 7.63-7.50 (5H, m), 7.40-7.27 (3H, m), 7.05 (1H, d), 6.77 (1H, m), 4.79 (1H, d), 4.65 (1H, d), 4.39 (1H, d), 2.81 (1H, m), 2.05-1.72 (6H, m), 1.36-1.23 (13H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 59.03, H 6.69, N 8.48%; $C_{33}H_{36}N_4O_6 \bullet C_7H_{17}NO_5 \bullet 1.7H_2O$ requires: C 59.34, H 7.01, N 8.65%.

Example 146. *3'-{2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-biphenyl-4-carboxylic acid.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), except that 3'-amino-biphenyl-4-carboxylic acid methyl ester (prepared by catalytic hydrogenation of 3'-nitro-biphenyl-4-carboxylic acid methyl ester (Y. Matsushita, *et. al.*, *Syn. Comm.*, (1994), **24**, 3307)) was used in place of 3-amino-benzoic acid methyl ester in step e, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR (DMSO-d_6) 12.9 (1H, br s), 9.90 (1H, s), 8.02 (2H, d), 7.88 (1H, s), 7.71 (2H, d), 7.57-7.38 (5H, m), 7.26-7.16 (2H, m), 4.80-4.79 (2H, m), 4.37-4.31 (1H, m), 4.01 (1H, m), 2.87 (1H, m), 1.75-1.65 (6H, m), 1.34-1.13 (13H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 61.82, H 7.05, N 8.19%; $C_{35}H_{38}N_4O_5 \bullet C_7H_{17}NO_5 \bullet 1.7H_2O$ requires: C 61.51, H 7.17, N 8.54%.

Example 147. *2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-*N*-[3-(2,4-dioxo-thiazolidin-5-ylidenemethyl)-phenyl]-acetamide.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that 5-(3-amino-benzylidene)-thiazolidine-2,4-dione (prepared in two steps from 3-nitro-benzaldehyde) was used in place of 3-amino-benzoic acid methyl ester in step e. ^{1}H NMR (DMSO-d_6) 9.84 (1H, br s), 7.62-7.45 (4H, m), 7.33-7.15 (4H, m), 4.80-4.76 (2H, m), 4.32-4.30 (1H, br m), 4.03-3.94 (1H, br m), 2.87 (1H, m), 1.86-1.53 (6H, m), 1.34-1.10 (13H, m). Found: C 61.16, H 5.89, N 11.08%; $C_{32}H_{44}N_6O_5S \bullet 1.4H_2O$ requires: C 61.34, H 6.07, N 11.18%.

Example 148. *2-(3-{2-[5-Cyclohexyl-1-(2-cyclopentyl-2-oxo-ethyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-oxazole-4-carboxylic acid.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), except that [5-cyclohexyl-1-(2-

cyclopentyl-2-oxo-ethyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 22, step a) and 2-(3-amino-phenyl)-oxazole-4-carboxylic acid methyl ester were used in place of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d) and 3-amino-benzoic acid methyl ester respectively in step e, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR ($CDCl_3$) 8.60 (1H, s), 8.35 (1H, s), 8.08 (1H, s), 7.83-7.81 (1H, m), 7.74-7.72 (1H, m), 7.61-7.32 (4H, m), 7.09 (1H, d), 4.73 (1H, d), 4.49 (1H, d), 4.26 (2H, s), 3.01-2.91 (1H, m), 2.81 (1H, m), 2.13-1.58 (14H, m), 1.31-1.25 (4H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 57.97, H 6.50, N 9.95%; $C_{33}H_{35}N_5O_6 \bullet C_7H_{17}NO_5 \bullet 1.8H_2O$ requires: C 58.20, H 6.79, N 10.18%.

Example 149. *5-(3-{2-[5-Cyclohexyl-1-(2-cyclopentyl-2-oxo-ethyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-furan-2-carboxylic acid.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), except that [5-cyclohexyl-1-(2-cyclopentyl-2-oxo-ethyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 22, step a) and 5-(3-amino-phenyl)-furan-2-carboxylic acid methyl ester were used in place of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d) and 3-amino-benzoic acid methyl ester respectively in step e, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR ($CDCl_3$) 8.35 (1H, s), 7.63-7.50 (5H, m), 7.41-7.32 (3H, m), 7.11 (1H, d), 6.80 (1H, d), 4.71 (1H, d), 4.51 (1H, d), 4.45 (1H, d), 4.24 (1H, d), 3.01-2.91 (1H, m), 2.85-2.79 (1H, m), 2.06-1.60 (14H, m), 1.31-1.30 (4H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 60.14, H 6.70, N 8.49%; $C_{34}H_{36}N_4O_6 \bullet C_7H_{17}NO_5 \bullet 1.5H_2O$ requires: C 60.16, H 6.89, N 8.56%.

Example 150. *2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-*3H-*1,3,4-benzotriazepin-3-yl]-*N-*[3-(2-methylamino-thiazol-4-yl)-phenyl]-acetamide.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), except that [4-(3-amino-phenyl)-thiazol-2-yl]-methyl-amine (prepared in two steps from 2-bromo-3′-nitroacetophenone) was used in place of 3-amino-benzoic acid methyl ester in step e. ^{1}H NMR ($CDCl_3$) 8.28 (1H, s), 7.77 (1H, s), 7.55-7.25 (7H, m), 7.04 (1H, d), 6.71 (1H, s), 5.12 (1H, d), 4.77 (1H, d), 4.67 (1H,d), 4.36 (1H, d), 4.22 (1H, d), 3.04 (3H, d), 2.79 (1H, m), 2.05-1.73 (6H, m), 1.45-1.19 (13H, m). Found: C 64.64, H 6.57, N 14.05%; $C_{32}H_{38}N_6O_3S \bullet 0.5H_2O$ requires: C 64.57, H 6.59 N 14.12%.

Example 151. *3′-{2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H-*1,3,4-benzotriazepin-3-yl]-acetylamino}-biphenyl-3-carboxylic acid.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), except that 3'-amino-biphenyl-3-carboxylic acid ethyl ester (prepared in two steps from 3-nitrophenylboronic acid) was used instead of 3-amino-benzoic acid methyl ester in step e, followed by reaction of the product obtained, in place of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid ethyl ester (Example 1, step c), according to the method of Example 1, step d. ^{1}H NMR ($CDCl_3$) 8.40 (1H, s), 8.29 (1H, t), 8.12-8.08 (1H, m), 7.85-7.81 (1H, m), 7.64-7.61 (1H, m), 7.57-7.47 (4H, m), 7.41-7.27 (3H, m), 7.06 (1H, d), 4.80 (1H, d), 4.65 (1H, d), 4.39 (1H, d), 4.25 (1H, d), 2.84-2.77 (1H, m), 2.02-1.70 (6H, m), 1.44-1.16 (13H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 61.19, H 7.07, N 8.48%; $C_{35}H_{38}N_4O_5 \bullet C_7H_{17}NO_5 \bullet 1.9H_2O$ requires: C 61.21, H 7.19, N 8.50%.

Example 152. *(3-{2-[1-(2-*tert*-Butyl-allyl)-5-cyclohexyl-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-acetic acid.*

The title compound was obtained by using the method employed in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3H-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that 2-bromomethyl-3,3-dimethyl-but-1-ene (E. Lee, *et al.*, *J. Org. Chem.* (1994), **59**, 1444) was used instead of 1-bromo-3,3-dimethyl-butan-2-one in step c, and (3-amino-phenyl)-acetic acid methyl ester replaced 3-amino-benzoic acid methyl ester in step e, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR (DMSO-d_6) 12.10 (1H, br s), 9.79 (1H, s), 7.58-7.34 (5H, m), 7 21 (2H, m), 6.90 (1H, d), 4.79 (1H, s), 4.68 (2H, m), 4.32 (2H, br t), 3.95 (1H, d), 3.48 (2H, s), 2.80 (1H, m), 2.00-1.10 (10H, m), 1.04 (9H, s). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 58.80, H 7.60, N 8.73%; $C_{31}H_{38}N_4O_4 \bullet C_7H_{17}NO_5 \bullet 3.0H_2O$ requires: 58.52, H 7.88, N 8.97%.

Example 153. *5-(3-{2-[1-(2-tert-Butyl-allyl)-5-cyclohexyl-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino]-phenyl)-furan-2-carboxylic acid.*

The title compound was obtained by the method employed in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that 2-bromomethyl-3,3-dimethyl-but-1-ene was used instead of 1-bromo-3,3-dimethyl-butan-2-one in step c, and 5-(3-amino-phenyl)-furan-2-carboxylic acid methyl ester replaced 3-amino-benzoic acid methyl ester in step e, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR (DMSO-d_6) 13.00 (1H, br s), 10.01 (1H, s), 7.59-7.34 (7H, m), 7.25 (2H, m), 7.03 (1H, d), 4.80 (1H, s), 4.68 (1H, s), 4.60-4.04 (2H, br m), 4.30 (2H, br m), 2.90 (1H, m), 2.00-1.20 (10H, m), 1.04 (9H, s). The compound was further characterised as the *N*-Methyl-D-glucamine salt. Found: C 58.88, H 7.03, N 8.13%; $C_{34}H_{38}N_4O_6 \bullet C_7H_{17}NO_5 \bullet 3.0H_2O$ requires: C 59.19, H 7.39, N 8.41%.

Example 154. *3'-{2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-biphenyl-2-carboxylic acid.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), except that 3'-amino-biphenyl-2-carboxylic acid methyl ester (prepared in two steps from 3-nitrophenylboronic acid) was used instead of 3-amino-benzoic acid methyl ester in step e, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR ($CDCl_3$) 8.52 (1H, s), 7.91 (1H, d), 7.63-7.20 (9H, m), 7.11 (1H, d), 7.03 (1H, d), 4.82 (1H, d), 4.61 (1H, d), 4.30 (1H, d), 4.16 (1H, d), 2.82-2.75 (1H, m), 2.05-1.57 (6H, m), 1.44-1.00 (13H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 61.11, H 6.88, N 8.29%; $C_{35}H_{38}N_4O_5 \bullet C_7H_{17}NO_5 \bullet 1.8H_2O$ requires: C 61.40, H 7.18, N 8.53%.

Example 155. *2-Acetylamino-3-(3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-acrylic acid.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), except that 2-acetylamino-3-(3-amino-phenyl)-acrylic acid methyl ester (prepared in three steps from 3-nitro-benzaldehyde and *N*-acetyl-glycine) was used instead of 3-amino-benzoic acid methyl ester in step e, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR ($CDCl_3$) 8.43 (1H, s), 7.99 (1H, s), 7.61-7.00 (9H, m), 4.80 (1H, d), 4.61 (1H, d), 4.22-4.16 (2H, m), 2.79 (1H, m), 2.19-1.65 (9H, m), 1.44-1.19 (13H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 56.61, H 6.99, N 9.44%; $C_{33}H_{39}N_5O_6 \bullet C_7H_{17}NO_5 \bullet 3.2H_2O$ requires: C 56.22, H 7.36, N 9.83%.

Example 156. *3-{2-[1-(*tert*-Butylcarbamoyl-methyl)-5-cyclohexyl-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid.*

Step a. *[1-(*tert*-Butylcarbamoyl-methyl)-5-cyclohexyl-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid ethyl ester* was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1, step e), except that (5-cyclohexyl-3-ethoxycarbonylmethyl-2-oxo-2,3-dihydro-3*H*-1,3,4-benzotriazepin-1-yl)-acetic acid (Example 68, step b) and *tert*-butylamine were used instead of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d) and 3-amino-benzoic acid methyl ester respectively. ^{1}H NMR ($CDCl_3$) 7.40 (2H, m), 7.22 (2H, m), 6.63 (1H, s), 4.27-4.09 (6H, m), 2.75 (1H, m), 2.00-1.55 (6H, m), 1.30-1.20 (16H, m).

Step b. The title compound was obtained using steps d and e of the method employed in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), except that [1-(*tert*-butylcarbamoyl-methyl)-5-cyclohexyl-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid ethyl ester (Example 156, step a) was used in step d instead of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid ethyl ester (Example 1, step c), followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR ($CDCl_3$) 8.59 (1H, s), 7.95 (1H, d), 7.78-7.75 (2H, m), 7.54-7.45 (2H, m), 7.40-7.28 (3H, m), 6.49 (1H, s), 4.35-4.09 (4H, m), 2.81 (1H, m br), 2.05 (1H, br), 1.88 (1H, br), 1.80-1.60 (4H, m), 1.35-1.20 (13H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 55.95, H 7.01, N 10.29%; $C_{29}H_{35}N_5O_5 \bullet C_7H_{17}NO_5 \bullet 0.7CH_2Cl_2$ requires C 55.92, H 6.83, N 10.66%.

Example 157. *5-(3-{2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-thiophene-2-carboxylic acid.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), except that 5-(3-amino-phenyl)-thiophene-2-carboxylic acid methyl ester (prepared in three steps from 5-bromo-2-thiophenecarboxylic acid) was used instead of 3-amino-benzoic acid methyl ester in step e, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR ($CDCl_3$) 8.47 (1H, s), 7.85 (1H, d), 7.62-7.47 (4H, m), 7.37-7.27 (4H, m), 7.06 (1H, d), 4.81 (1H, d), 4.64 (1H, d), 4.36 (1H, d), 4.25 (1H, d), 2.84-2.78 (1H, m), 2.07-1.70 (6H, m), 1.30-1.19 (13H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 58.29, H 6.63, N 8.22%; $C_{33}H_{36}N_4O_5S \bullet C_7H_{17}NO_5 \bullet 1.7H_2O$ requires: C 58.10, H 6.88, N 8.46%.

Example 158. *[2-(3-{2-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl)-pyrrol-1-yl]-acetic acid.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), except that [2-(3-amino-phenyl)-pyrrol-1-yl]-acetic acid methyl ester (prepared in four steps from 1-(*tert*-butoxycarbonyl)-pyrrole-2-boronic acid and 1-bromo-3-nitrobenzene) was used instead of 3-amino-benzoic acid methyl ester in step e, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR ($CDCl_3$) 8.46 (1H, s), 7.47-7.43 (3H, m), 7.32-7.23 (3h, m), 7.09-7.00 (2H, m), 6.77-6.75 (1H, m), 6.27-6.21 (2H, m), 4.79-4.56 (4H, m), 4.31 (1H, d), 4.21 (1H, d), 2.81-2.75 (1H, m), 2.05-1.71 (6H, m), 1.36-1.19 (13H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 59.36, H 7.02, N 9.65%; $C_{34}H_{39}N_5O_5 \bullet C_7H_{17}NO_5 \bullet 2.2H_2O$ requires: C 59.12, H 7.31, N 10.09%.

Example 159. *4-(3-{2-[5-Cyclohexyl-1-(2-cyclopentyl-2-oxo-ethyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-phenyl-butyric acid.*

The title compound was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), except that [5-cyclohexyl-1-(2-cyclopentyl-2-oxo-ethyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 22, step a) and 4-(3-amino-phenyl)-butyric acid methyl ester (J. P. Weichert, *et. al., J. Med. Chem.* (1995), **38**, 636) were used in place of [5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetic acid (Example 1, step d) and 3-amino-benzoic acid methyl ester respectively in step e, followed by reaction of the product obtained, in place of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1), according to the method of Example 2. ^{1}H NMR (DMSO-d_6) 12.00 (1H, br s), 9.67 (1H, s), 7.50 (2H, m), 7.32-7.15 (5H, m), 6.84 (1H, d), 4.63 (2H, m), 4.25 (1H, br d), 3.99 (1H, br d), 3.00 (1H, m), 2.88 (1H, m), 2.52 (2H, t), 2.19 (2H, t), 2.00-1.00 (20H, m). The compound was further characterised as the *N*-methyl-D-glucamine salt. Found: C 59.52, H 7.41, N 8.62%; $C_{33}H_{40}N_4O_5 \bullet C_7H_{17}NO_5 \bullet 2.0H_2O$ requires: C 59.76, H 7.65, N 8.71%.

Example 160. *2-(5-Cyclohexyl-1-methyl-2-oxo–4-oxy-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-*N*-phenyl-acetamide.*

Step a. *2-(5-Cyclohexyl-1-methyl-2-oxo -1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-*N*-phenyl-acetamide* was obtained by the method used in the preparation of 3-{2-[5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-ox0-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl]-acetylamino}-benzoic acid methyl ester (Example 1) except that iodomethane was used in step c instead of 1-bromo-3,3-dimethyl-butane-2-one, and aniline was used in step e instead of 3-amino-benzoic acid methyl ester. ^{1}H NMR ($CDCl_3$) 8.25 (1H, s), 7.55 (1H, t), 7.44 (1H, d), 7.32-7.21 (6H, m), 7.06 (1H, t), 4.47 (1H, d), 4.14 (1H, d), 3.29 (3H, s), 2.76 (1H, m), 2.00-1.00 (10H, m).

Step b. To a solution of the product of step a (390mg, 1.00mmol) in DCM (10ml) was added 3-chloroperoxybenzoic acid (1.23 g of 70%, 5.00mmol) and the solution stirred at room temperature for 16hr. After dilution with DCM (50ml) the solution was washed with 5% Na_2CO_3 (2 x 50ml), then brine (50ml). The organic phase was dried over $MgSO_4$, and the solvent evaporated under reduced pressure. The residue was purified by flash column chromatography (EtOAc-DCM (1:9) to afford the product as a white solid (94mg, 23%) ^1H NMR ($CDCl_3$) 8.17 (1H br.s), 7.51 (2H, d), 7.39-7.22 (6H, m), 7.06 (1H, m), 4.60 (1H, d), 4.23 (1H, d), 3.39 (3H, s), 3.15 (1H, m), 2.00-1.00 (10H, m). Found: C 67.73, H 6.46, N 13.71%; $C_{23}H_{26}N_4O_3$ requires: C 67.96, H 6.45, N 13.78%

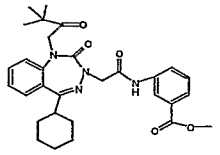
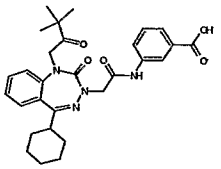
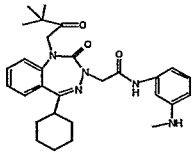
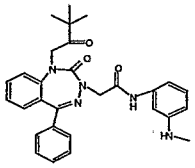
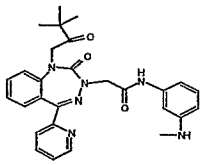
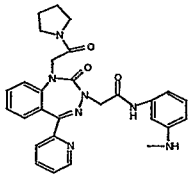
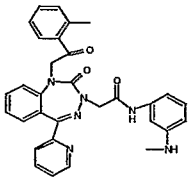
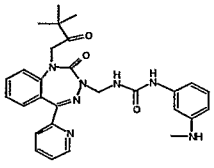
Gastrin (CCK_2) Antagonist Activity

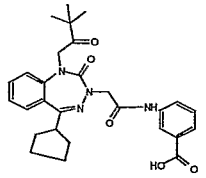
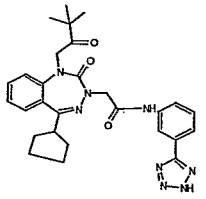
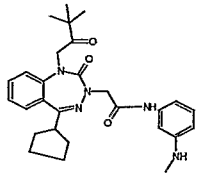
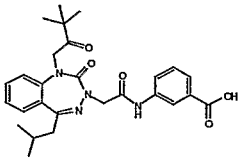
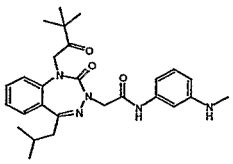
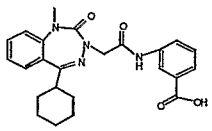
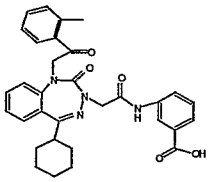
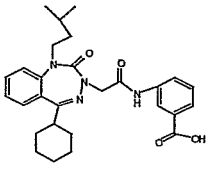
The compounds of the examples were tested for gastrin (CCK_2) antagonist activity in an immature rat stomach assay. The procedure was as follows:

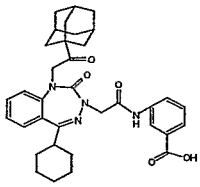
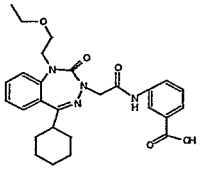
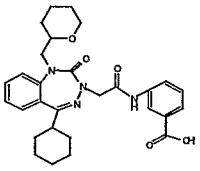
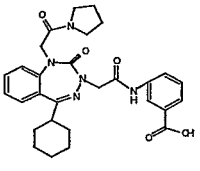
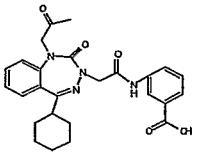
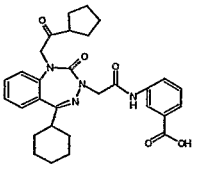
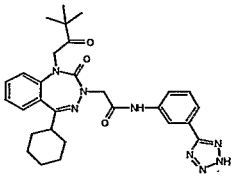
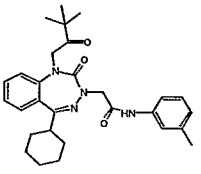
The oesophagus of immature rats (33-50 g, ca. 21 days old) was ligated at the level of the cardiac sphincter and the duodenal sphincter was cannulated. The stomach was excised and flushed with ca. 1 ml of unbuffered physiological saline solution. The fundus was punctured and cannulated. A further 4-5 ml of unbuffered solution was flushed through the stomach to ensure the preparation was not leaking. The stomach was lowered into a jacketed organ bath containing 40 ml of buffered solution containing 3 x 10^{-8} M 5-methylfurmethide, maintained at 37° and gassed vigorously with 95% O_2 / 5% CO_2. The stomach was continuously perfused at a rate of 1 ml min^{-1} with unbuffered solution gassed with 100% O_2 with the perfusate passing over an internally referenced pH-electrode fixed 12 cm above the stomach.

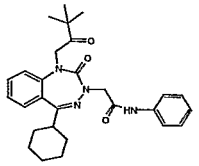
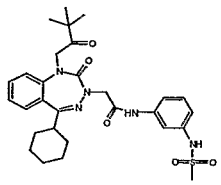
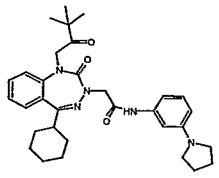
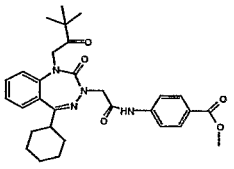
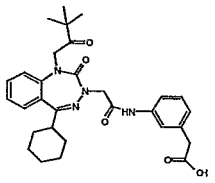
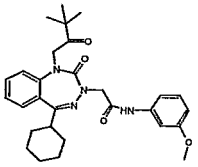
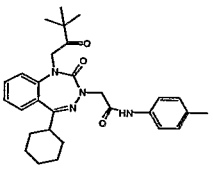
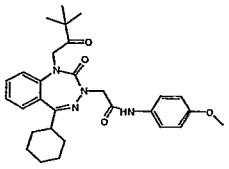
After 120 min of stabilisation the drugs were added directly to the serosal solution in the organ bath and after a further 60 min cumulative pentagastrin dose-response curves were started. Changes in acid secretion were monitored and the curves analysed according to Black *et al.*, *Br. J. Pharmacol.*, 1985, **86**, 581.

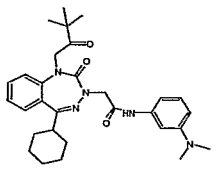
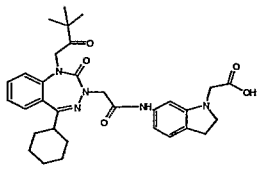
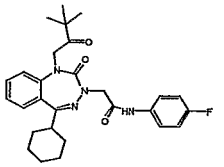
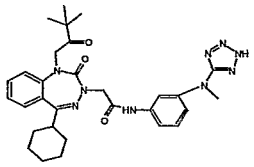
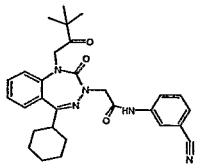
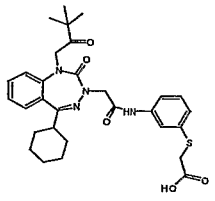
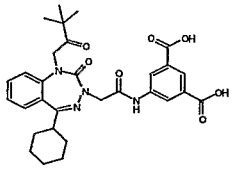
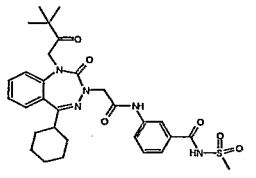
The results obtained at gastrin (CCK_2) receptors are set out in the following Table.

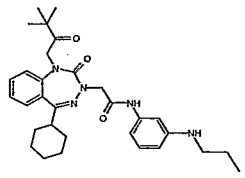
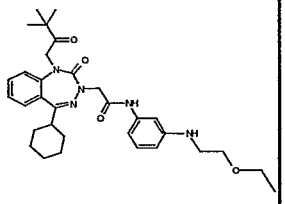
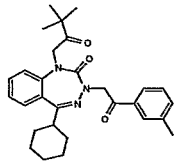
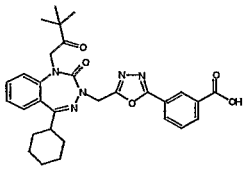
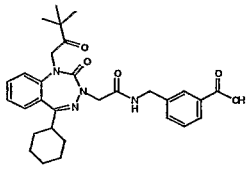
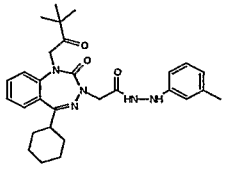
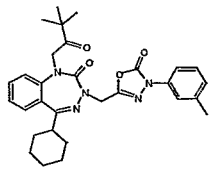
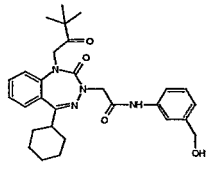
Example No		pKB rat stomach
1		8.55±0.32
2		9.18±0.31
3		8.1±0.13
4		6.88±0.29
5		6.62±0.27
6		5.98±0.27
7		7.30±0.26
8		6.58±0.24

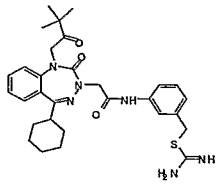
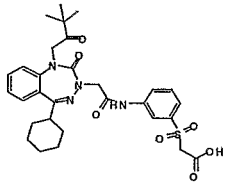
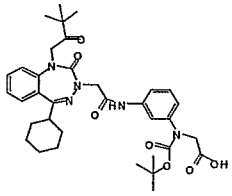
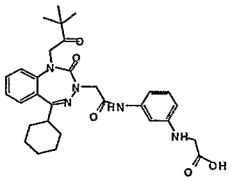
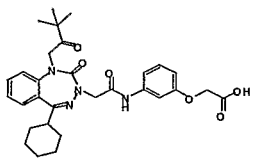
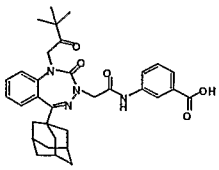
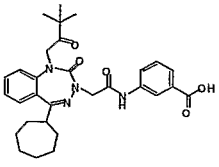
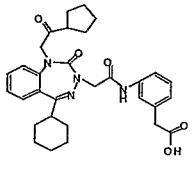
9		7.12±0.26
10		7.05±0.18
11		7.35±0.17
12		
13		7.29±0.28
14		
15		8.02±0.27
16		7.37±0.38

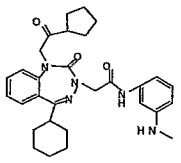
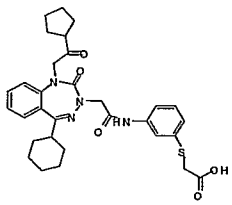
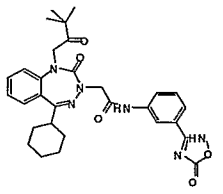
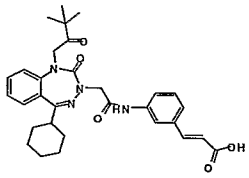
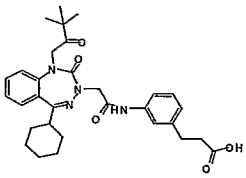
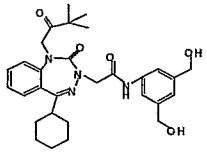
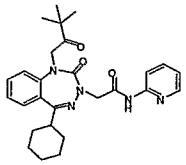
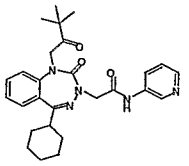
17		6.94±0.18
18		
19		
20		7.23±0.41
21		
22		8.73±0.44
23		7.95±0.26
24		

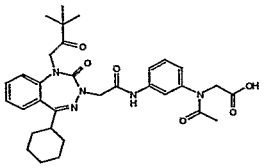
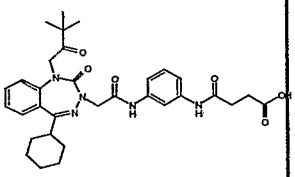
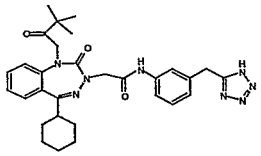
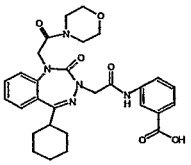
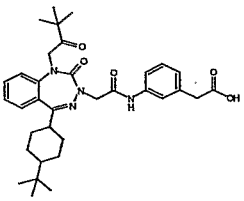
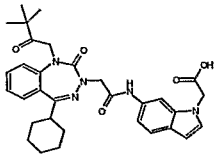
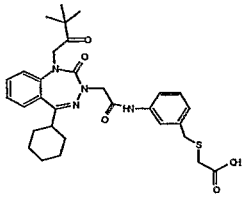
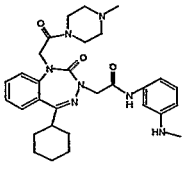
25		
26		6.34±0.31
27		6.84±0.26
28		
29		7.21±0.25
30		
31		
32		7.11±0.29

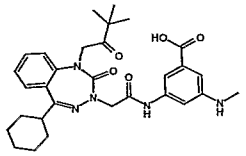
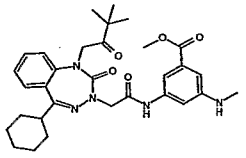
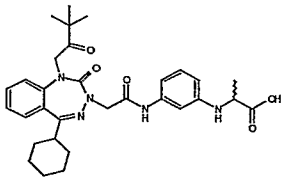
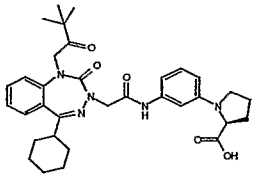
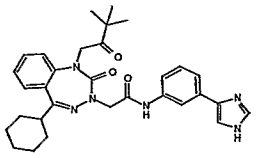
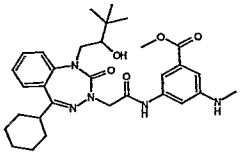
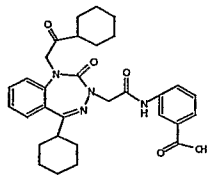
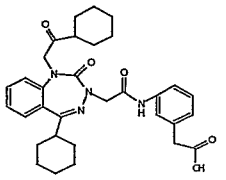
33		7.04±0.28
34		7.80±0.30
35		
36		7.64±0.45
37		
38		8.18±0.36
39		8.12±0.18
40		7.64±0.40

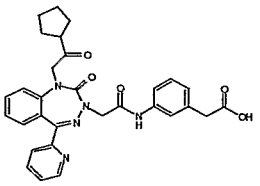
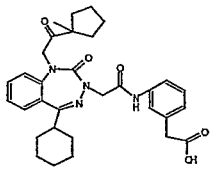
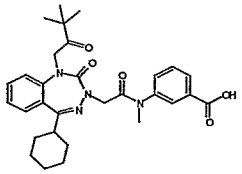
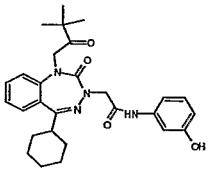
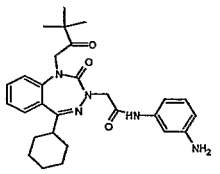
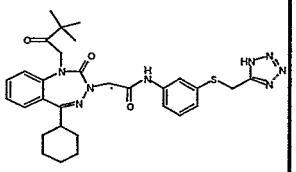
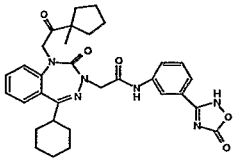
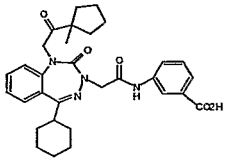
41		
42		6.98±0.40
43		
44		
45		7.03±0.30
46		6.76±0.36
47		
48		7.77±0.28

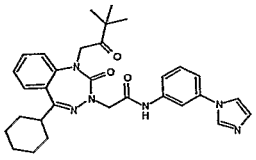
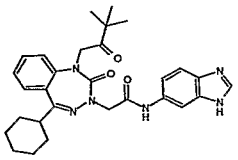
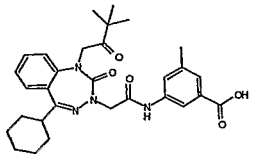
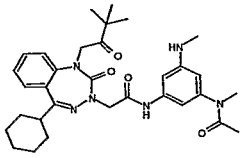
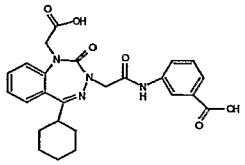
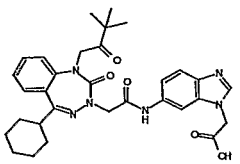
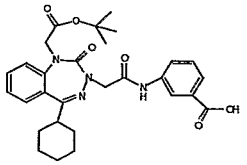
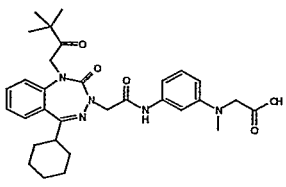
49		7.00±0.27
50		7.96±0.34
51		
52		7.49±0.24
53		7.68±0.34
54		7.77±0.43
55		9.16±0.28
56		9.13±0.22

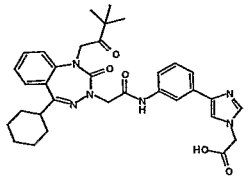
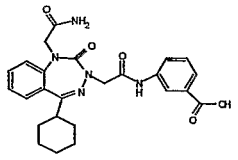
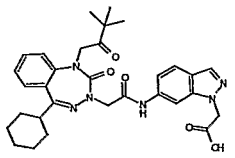
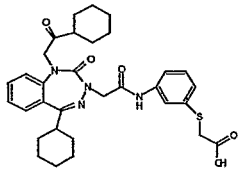
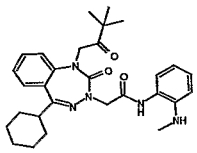
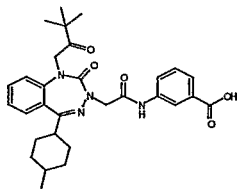
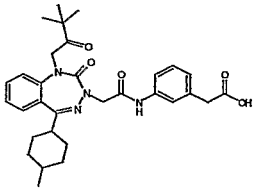
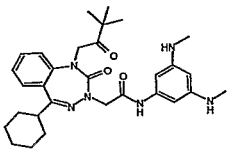
57		8.93±0.47
58		8.83±0.18
59		8.02±0.37
60		8.46±0.28
61		8.35±0.22
62		
63		6.18±0.29
64		

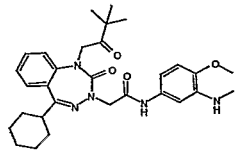
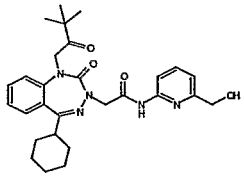
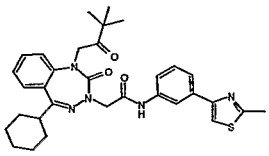
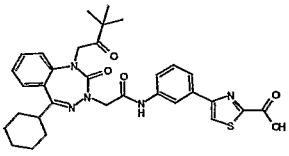
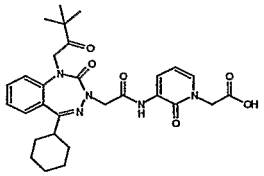
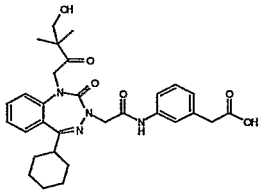
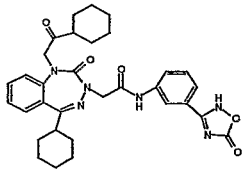
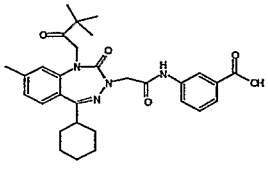
65		7.28±0.25
66		7.13±0.26
67		7.11±0.21
68		7.09±0.28
69		
70		9.07±0.23
71		8.42±0.24
72		6.58±0.16

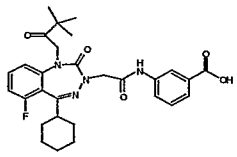
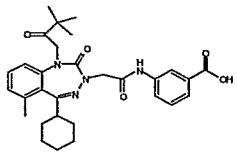
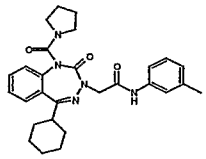
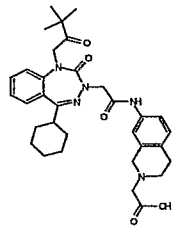
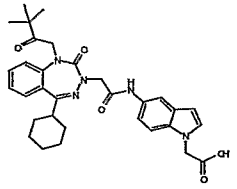
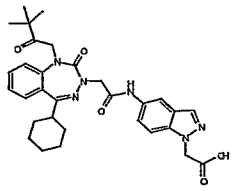
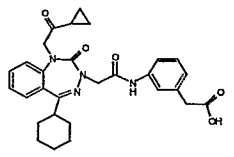
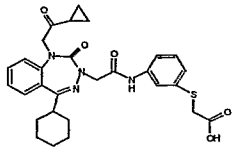
73		7.17±0.27
74		6.43±0.17
75		6.68±0.30
76		6.96±0.16
77		
78		6.49±0.33
79		8.60±0.40
80		8.47±0.36

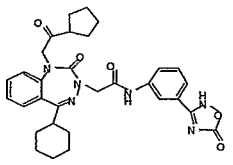
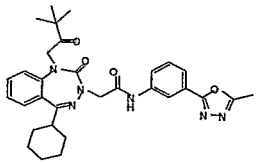
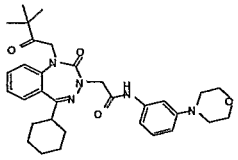
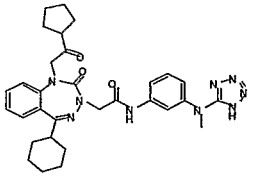
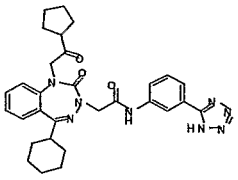
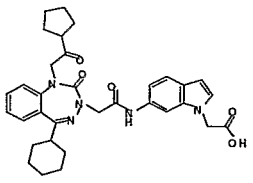
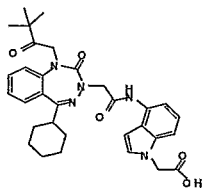
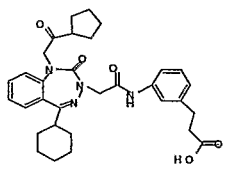
81		7.14±0.35
82		8.02±0.27
83		
84		7.56±0.32
85		7.44±0.30
86		8.47±0.31
87		8.50±0.28
88		7.93±0.30

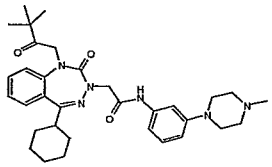
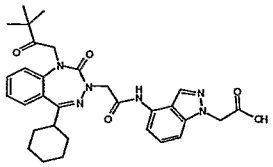
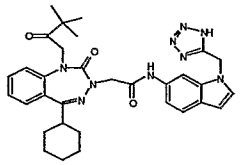
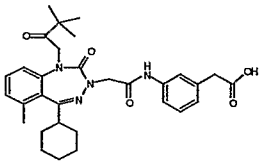
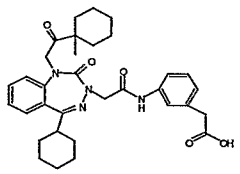
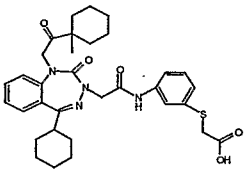
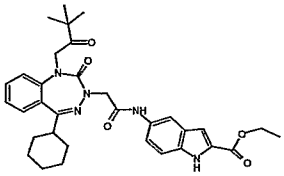
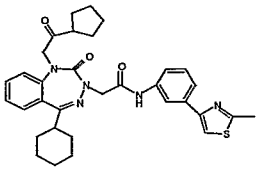
89		6.06±0.19
90		
91		7.39±0.34
92		
93		
94		6.81±0.41
95		8.40±0.25
96		8.14±0.31

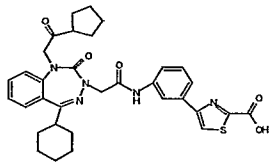
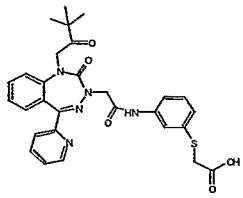
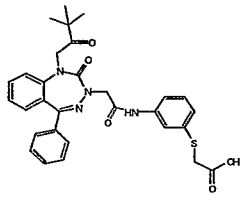
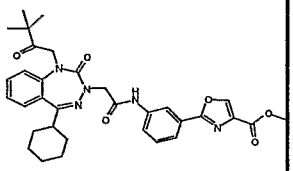
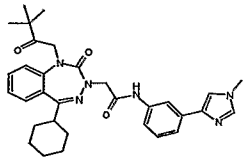
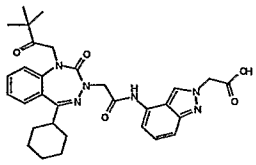
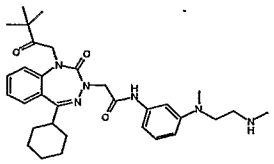
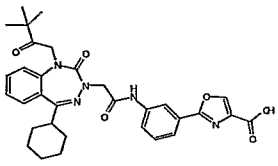
97		7.59±0.30
98		
99		7.85±0.20
100		9.24±0.34
101		6.89±0.21
102		9.11±0.36
103		8.40±0.28
104		7.35±0.18

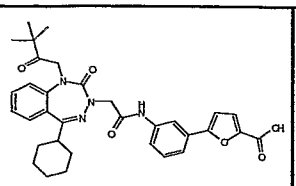
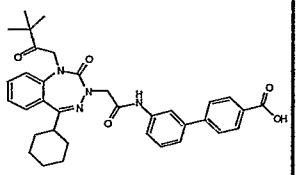
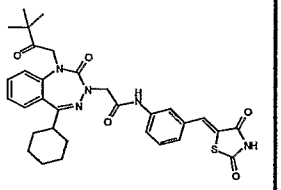
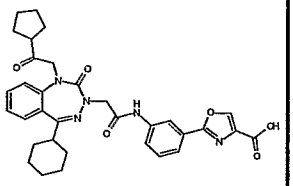
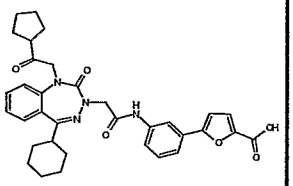
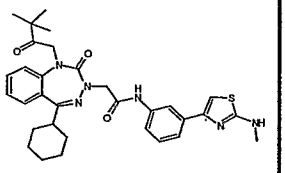
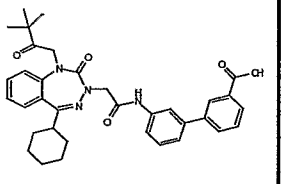
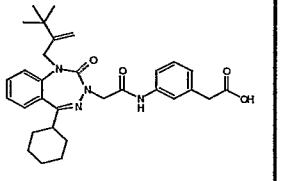
105		7.56±0.26
106		6.89±0.26
107		8.48±0.32
108		7.43±0.11
109		
110		7.03±0.24
111		8.66±0.33
112		7.39±0.48

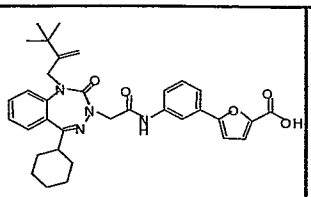
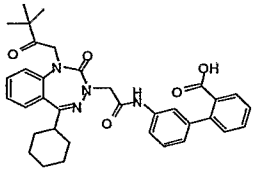
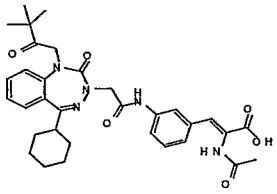
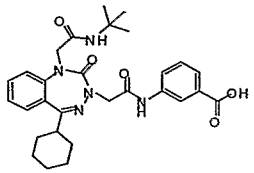
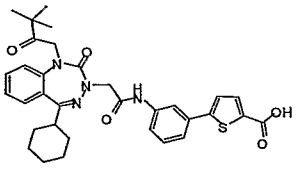
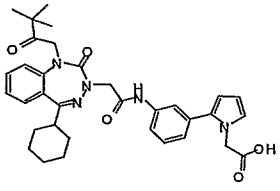
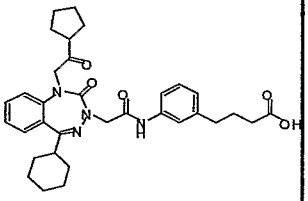
113		8.22±0.29
114		7.45±0.43
115		
116		
117		7.56±0.17
118		
119		7.61±0.33
120		7.43±0.44

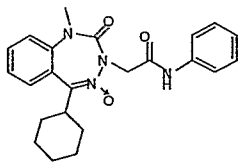
121		9.53±0.22
122		
123		7.74±0.36
124		8.67±0.39
125		8.36±0.34
126		10.24±0.39
127		8.68±0.19
128		8.91±0.20

129		
130		7.35±0.27
131		8.79±0.23
132		7.18±0.36
133		7.85±0.22
134		7.76±0.28
135		
136		8.22±0.47

137		8.54±0.42
138		
139		
140		8.95±0.41
141		
142		7.81±0.29
143		6.93±0.40
144		8.38±0.44

145		8.47±0.26
146		8.15±0.30
147		8.08±0.35
148		8.41±0.47
149		8.96±0.48
150		8.89±0.42
151		7.94±0.33
152		7.30±0.50

153		
154		8.49±0.2
155		7.15±0.2
156		
157		8.11±0.2
158		8.37±0.3
159		8.90±0.3

160		

A number of compounds were tested at human gastrin (CCK_2) receptors which have been cloned into an NIH3T3 cell line as follows:

Step a: Subcloning of IMAGE clone encoding the human CCK_2R into a mammalian expression vector

I.M.A.G.E. (Integrated Molecular Analysis of Genomes and their Expression) clone number 3504160 (Lennon et al. Genomics **33**, 151-152 (1996)) was purchased from the HGMP (Human Genome Mapping Project, Cambridge). The cDNA encoding the mRNA for the human CCK_2R, corresponding to accession number BC000740, was present in vector pOTB7 in host cell DH10B. The cells, initially streaked on to LB-Agar plates containing 20μg/ml chloramphenicol, were then grown in LB containing 20μg/ml chloramphenicol with shaking at 37°C according to standard techniques (Current Protocols in Molecular Biology, Wiley). DNA was prepared using the QIAGEN® EndoFree™ plasmid Maxi kit (Qiagen Ltd.) according to the manufacturer's protocol. The DNA was then amplified by PCR (polymerase chain reaction) from the start codon to the stop codon using primers containing restriction sites, *Eco* R1 and *Xba* I respectively, to facilitate uni-directional cloning. The start codon primer also contained a Kozak consensus site (Kozak M, *Nucleic Acids Res.* 1984 Jan 25;12(2):857-72) for optimal initiation of translation. Primers 1 and 2 (see Table 1) were synthesised to HPLC grade by Invitrogen. The PCR was performed in 20mM Tris-HCl (pH 8.4), 50mM KCl containing 2mM $MgCl_2$, 0.2mM dNTP (Invitrogen) and 0.1μM of each primer. A hot start PCR was used: the samples were denatured for 2min at 95°C, cooled to 75°C, then 1U *Taq* Polymerase (Invitrogen) was added and the reactions were cycled 30 times at 95°C for 1min, 60°C for 30sec and 72°C for 3min. The samples were cooled to 4°C, after a final extension at 72°C for 5min.

The PCR product was purified using the QIAGEN® MinElute™ PCR purification kit, according to the manufacturer's instructions. The PCR product and a mammalian expression vector were digested using both *Eco* RI (Promega Corp.) and *Xba* I (Promega Corp.) in 1x Buffer H (90mM Tris-HCl, 10mM $MgCl_2$, 50mM NaCl, pH 7.5) (Promega Corp.) and 0.1μg/ml BSA. The digested DNA bands of the correct size, analysed by ethidium bromide stained agarose/TBE gels, were excised and purified using QIAGEN® MinElute™ gel extraction kit, according to the manufacturer's instructions. The PCR product was then ligated into the vector using the Lightning™ DNA Ligation kit (Bioline) and transformed into *Escherichia coli*, strain XL1-Blue cells (Stratagene) according to the manufacturer's instructions.

Colonies were selected and screened using restriction digestion of DNA prepared from small-scale cultures (5ml) using QIAGEN® plasmid Mini-prep columns. One positive clone was cultured on a larger scale (100ml) using standard techniques (Current Protocols in Molecular Biology, Wiley) and DNA was prepared using QIAGEN® plasmid Maxi-prep columns. The DNA was then custom sequenced by MWG Biotech AG using primers 3, 4 and 5 (**Table A**). The sequence contained the correct sequence of primers 1 and 2 and the sequence of the coding region exactly matched that of accession number BC000740.

Step b: Generation of Stable Cell Line

NIH3T3 cells from (ECACC) were cultured in Dulbecco's modified Eagle's medium (DMEM) (Invitrogen), containing 2mM Glutamax I (Invitrogen), 10% heat inactivated newborn calf serum (Invitrogen). Cells (4×10^5) were seeded into 35mm x 10 mm dishes (Corning) and transfected using the Transfast™ reagent (Promega Corp.) according to the manufacturers instructions using 10μg of the $hCCK_2R$ plasmid DNA at a ratio of 1:1 (DNA:Transfast™ reagent). Untransfected cells and cells transfected with vector only were also prepared as controls. After 48 h the cells were trypsinised using standard techniques (Culture of Animal Cells, A Manual of Basic Techniques 4th Ed, R. Ian Freshney) and dilutions were plated on 35mm x 10mm dishes in media containing 800μg/ml G-418 (Invitrogen). Cells were selected for 2 weeks until individual, separate colonies appeared. In the untransfected cells all cells had died after this time, confirming adequate selection. Using cloning rings and trypsinisation, according to standard techniques (Culture of Animal Cells, A Manual of Basic Techniques 4th Ed, R. Ian

Freshney), individual colonies were picked from plates containing cells transfected with the vector only and cells transfected with the hCCK$_2$R plasmid construct. The cells were expanded and analysed by radioligand binding analysis (see below).

Table A: Primers used in the cloning and sequence analysis of human CCK$_{2S}$R

Primer Name	Primer Orientation	Sequence (5'-3')	Gene specific or vector	Restriction Site
1	Forward	TCT**GAATTC**GCCGCC<u>ATG</u>GAGCTGCTA	GENE	*Eco* RI
2	Reverse	GTA**TCTAGAC***<u>TCA</u>*GCCAGGGCCCAGTG	GENE	*Xba* I
3 (T7)	Forward	TAATACGACTCACTATAGG	VECTOR	-
4 (T3)	Reverse	ATTAACCCTCACTAAAGGG	VECTOR	-
5	Forward	TGTCCGGACTACTCATGGTG	GENE	-

Restrictions site in bold. Start codon underlined. Stop codon italic and underlined.

Step c: Clonal Selection

Stable clones expressing hCCK$_2$R were screened for their ability to specifically bind [^{125}I]-BH-CCK-8S in tissue concentration curve studies ($0.3x10^4$ – $1x10^6$ cells per tube) using the assay conditions described below. Of those tested, clone 7 gave the highest amount of specifically bound and % specific bound label whilst also meeting the criteria that the amount of total bound label did not exceed 10% of the total added radio label (e.g. 4.2%). In addition there was a direct linear correlation between the amount of specific bound label and the cell concentration up to and including $2.5x10^5$ cells per ml. Based on the above, this clone was chosen for expansion and full binding characterisation.

Step d: Membrane Preparation

Cultured clone 7 cells were stored as frozen pellets at –70°C until required. Cell pellets were thawed in CCK$_2$ assay buffer ((mM): 10 Hepes; 130 NaCl; 5 $MgCl_2$; 4.7 KCl; 1 EGTA (pH7.2 at 21°C) with 0.125g Bacitracin added to each litre), and homogenised using a Polytron (4 x 1s). The resulting membrane preparation was centrifuged at 39,800g

for 15min at 4°C. Each cell pellet was re-suspended in fresh buffer and re-centrifuged as above. The final pellet was re-suspended by homogenisation (Teflon-in-glass), to the appropriate membrane concentration.

Step e: Incubation Conditions

For saturation and competition studies, the cell membranes prepared as in step d (3x 10^4 cells per 400µl) were incubated for 150min at 21°C in a final volume of 0.5ml with CCK_2 assay buffer containing [^{125}I]-BH-CCK-8S (50µl; 200pM). Total and non-specific binding of [^{125}I]-BH-CCK-8S were defined, respectively using 50µl of buffer and 50µl of 10µM YM022. The assays were terminated by rapid filtration through pre-soaked Whatman GF/B filters which were washed (3 x3ml) with ice-cold 50mM Tris HCl (pH7.4 @ 4°C). Filters were transferred to plastic gamma counter vials and bound radioactivity determined by counting (1 min) in a Clini-gamma counter.

Step f: Saturation analysis

The binding of [^{125}I]-BH-CCK-8S to the $hCCK_2$ receptor isoform was saturable. Scatchard plots appeared linear and the mean slope of the corresponding Hill plots was not significantly different from unity (0.97 ± 0.08; n = 4). The equilibrium dissociation constant (pK_D) and Bmax values were 10.75 ± 0.08 and 1.1 ± 0.3 fmol per 1x10^5 cells, respectively (n = 4 ± s.e. mean). Saturation data were analysed using the curve-fitting programmes, Radlig and Ligand.

Step g: Competition studies

A number of compounds of the invention as well as reference compounds were tested for their ability to displace [^{125}I]-BH-CCK-8S from the receptors prepared as above. Briefly, dilution and addition of test compounds, radioligand and cell membranes were performed using a Beckman Biomek 2000. The ability of compounds to inhibit the specific binding of to $hCCK_2$ receptors was determined in triplicate over a range of concentrations at half-log intervals. Total and non-specific binding was determined for each compound. Each compound was tested in a minimum of three experiments. Competition data were fitted to the Hill equation using Graph-pad Prism software to obtain estimates of the IC_{50} (mid-

point location parameter) and n_H (mid-point slope parameter). Dissociation constants (K_I) were determined using the Cheng & Prusoff equation (1973) to correct for the receptor occupancy by the radioligand. All compounds were dissolved in DMF to give a stock concentration of either 1 or 10mM and subsequent dilutions were made in assay buffer. The pK_I for representative examples together with a number of reference compounds are shown in the table below. All Hill slopes were not significantly different from unity.

Example no or reference	pKi±s.e.mean
Ex 22	9.45±0.04
Ex 56	9.79±0.03
Ex 58	9.48±0.08
Ex 59	9.66±0.05
Ex 121	9.96±0.01
Ex 128	9.69±0.03
Ex 160	5.49±0.05
L-365, 260	8.45±0.09
YM022	10.19±0.03

Compounds of certain examples were also tested in a CCK_1 binding assay. All the examples tested were found to have a CCK_1 pK_i not exceeding 6.5.

It is found that the compositions and products of the present invention comprising a compound of formula (I) and a proton pump inhibitor reduce hyperplasia, associated with administration of proton pump inhibitors. This was measured according to the following experimental protocol.

Animals and treatment:

40 male SPF Wistar rats (200 g) were divided into 4 treatment groups and 2 strata. The treatment of the 20 rats in the second stratum started 2 weeks after the treatment of the first stratum. The design of the study was completely randomised double blind with individual

blinding; all rats were placed in a separate cage. Animals had continuous access to water and food.

Animals were treated once daily during 14 days:

- Control group: 1 ml gastrin test drug vehicle + 1 ml p.o.(gavage) 0,25% Methocel (Dow Corning)
- PPI group: 1 ml gastrin test drug vehicle +1 ml p.o.(gavage) 25 mg/kg Rabeprazole in 0.25% Methocel.
- GRA group: 1 ml gastrin test drug + 1 ml p.o. (gavage) 0,25% Methocel
- GRA-PPI group: 1 ml gastrin test drug + 1 ml p.o.(gavage) 25 mg/kg Rabeprazole in 0.25% Methocel.

Gastrin test drug made up to an appropriate dose in physiologically compatible solvent.

Preparation of tissue:

After removal of the fundus, the stomach were rinsed with phosphate buffered saline prior to fixation with 4% formalin in Millonig buffer. After 4 hours immersion in fixative solutions at room temperature, tissue was rinsed in phosphate buffered saline (PBS), dehydrated and embedded in paraffin using the Leitz paraffin embedding station (Leitz TP 1050; Germany) dehydration module and paraffin embedding module (Leitz EG 1160; Germany).

Cross sections (3 μm thick) of the oxyntic part of the stomach were made at 3 levels, each separated by a distance of 400 μm.

Immunostaining

The following indirect immunofluorescence labeling method was used:

- removal of paraffin and rehydratation of the sections followed by a blocking step
- primary antibodies: polyclonal guinea pig anti-histidine decarboxylase, 1/2000 (from Euro-Diagnostica) and monoclonal mouse anti PCNA 1/2500 (Clone PC10 from Sigma). All antibodies were diluted in a 0.2% BSA solution. Sections were incubated overnight at 4°C and then washed with a BSA solution.

secondary antibodies: goat anti guinea pig coupled to CY5, 1/500 (from Jackson Laboratories) and goat anti-mouse coupled to Cy3, 1/250 (from Jackson Laboratories); incubation for 4 hours at 37°C. After rinsing with BSA and PBS solutions, sections were mounted with slowfade (Molecular Probes Europe BV), and stored at 4°C.

Imaging

Fluorescence labelling was observed with an epifluorescence microscope or a Zeiss LSM510 (Carl Zeiss Jena GmbH) confocal microscope.

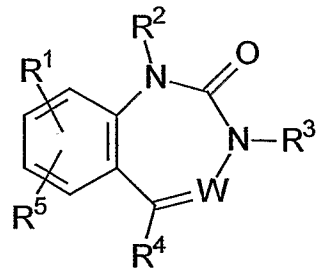
By using CY5- and CY3-coupled antibodies, the high autofluorescence properties of the oxyntic mucosa were circumvented when sections are illuminated by a 488 nm (FITC channel) light source. Negative controls, by omitting the primary antibodies, and an isotype control staining for PCNA showed complete absence of staining. The specific labelling of PCNA was checked using double staining with TOPRO-3® (Molecular Probes Europe BV), a nuclear stain. Only in the most luminal located epithelial cells, non-specific cytoplasmic labelling was present. In the glandular part of the mucosa, non-specific PCNA-staining was absent.

For determination of the labelling index of ECL cells, at least 80 confocal images per rat were taken from the 3 slides at the 3 different levels. The ratio of double labelled cells (HDC + PCNA) and all HDC labelled cells yielded the labelling index of ECL cells.

Proliferation activity of ECL cells in the PPI group is expected to be increased compared with sham, GRA and GRA-PPI groups (Eissele, R., Patberg, H., Koop, H., Krack, W., Lorenz, W., McKnight, A.T., and Arnold, R. Effect of gastrin receptor blockade on endrocine cells in rats during achlorhydria. *Gastroenterology*, 103, 1596-1601, 1992). Increased proliferation by PPI will be completely blocked by GRA.

CLAIMS

1. Use of a compound of formula (I)



(I)

wherein:

W is N or N^+-O^-;

R^1 and R^5 are independently H, C_1 to C_6 alkyl, (C_1 to C_6 alkyl)oxy, thio, (C_1 to C_6 alkyl)thio, carboxy, carboxy(C_1 to C_6 alkyl), formyl, (C_1 to C_6 alkyl)carbonyl, (C_1 to C_6 alkyl)oxycarbonyl, (C_1 to C_6 alkyl)carbonyloxy, nitro, trihalomethyl, hydroxy, hydroxy(C_1 to C_6 alkyl), amino, (C_1 to C_6 alkyl)amino, di(C_1 to C_6 alkyl)amino, aminocarbonyl, halo, halo(C_1 to C_6 alkyl), aminosulfonyl, (C_1 to C_6 alkyl)sulfonylamino, (C_1 to C_6 alkyl)aminocarbonyl, di(C_1 to C_6 alkyl)aminocarbonyl, [*N*-Z](C_1 to C_6 alkyl)carbonylamino, formyloxy, formamido, (C_1 to C_6 alkyl)aminosulfonyl, di(C_1 to C_6 alkyl)aminosulfonyl, [*N*-Z](C_1 to C_6 alkyl)sulfonylamino or cyano; or R^1 and R^5 together form a methylenedioxy group;

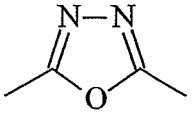
R^2 is H or an optionally substituted C_1 to C_{18} hydrocarbyl group wherein up to three C atoms may optionally be replaced by N, O and/or S atoms.

R^3 is $-(CR^{11}R^{12})_m-X-(CR^{13}R^{14})_p-R^9$;

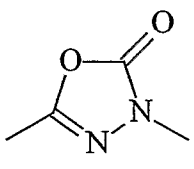
m is 0, 1, 2, 3 or 4;

p is 0, 1 or 2;

X is a bond, $-CR^{15}=CR^{16}-$, -C≡C-, C(O)NH, NHC(O), C(O)NMe, NMeC(O), C(O)O, NHC(O)NH, NHC(O)O, OC(O)NH, NH, O, CO, SO_2, SO_2NH, C(O)NHNH,



or

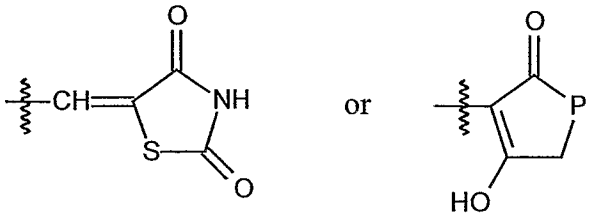


R^9 is H; C_1 to C_6 alkyl; or phenyl, naphthyl, pyridyl, benzimidazolyl, indazolyl, quinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, indolinyl, isoindolinyl, indolyl, isoindolyl or 2-pyridonyl, all optionally substituted with 1, 2 or 3 groups independently selected from -L-Q

wherein:

L is a bond, or a group of the formula $-(CR^{17}R^{18})_v-Y-(CR^{17}R^{18})_w$, wherein v and w are independently 0, 1, 2 or 3, and Y is a bond, $-CR^{15}=CR^{16}-$, phenyl, furanyl, thiophenyl, pyrrolyl, thiazolyl, imidazolyl, oxazolyl, isoxazolyl, pyrazolyl, isoxazolonyl, piperazinyl, piperidinyl, morpholinyl, pyrrolidinyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, pyridyl or pyridazyl; and

Q is H, (C_1 to C_6 alkyl)oxy, [*N*-Z](C_1 to C_6 alkyl)oxy(C_1 to C_6 alkyl)amino, thio, (C_1 to C_6 alkyl)thio, carboxy(C_1 to C_6 alkyl)thio, carboxy, carboxy(C_1 to C_6 alkyl), carboxy(C_1 to C_6 alkenyl), [*N*-Z]carboxy(C_1 to C_6 alkyl)amino, carboxy(C_1 to C_6 alkyl)oxy, formyl, (C_1 to C_6 alkyl)carbonyl, (C_1 to C_6 alkyl)oxycarbonyl, (C_1 to C_6 alkyl)carbonyloxy, nitro, trihalomethyl, hydroxy, amino, [*N*-Z](C_1 to C_6 alkyl)amino, aminocarbonyl, (C_1 to C_6 alkyl)aminocarbonyl, di(C_1 to C_6 alkyl)aminocarbonyl, [*N*-Z](C_1 to C_6 alkyl)carbonylamino, C_5 to C_8 cycloalkyl, [*N*-Z](C_1 to C_6 alkyl)carbonyl(C_1 to C_6 alkyl)amino, halo, halo(C_1 to C_6 alkyl), sulfamoyl, [*N*-Z](C_1 to C_6 alkyl)sulfonylamino, (C_1 to C_6 alkyl)sulfonylaminocarbonyl, carboxy(C_1 to C_6 alkyl)sulfonyl, carboxy(C_1 to C_6 alkyl)sulfinyl, tetrazolyl, [*N*-Z]tetrazolylamino, cyano, amidino, amidinothio, SO_3H, formyloxy, formamido, C_3 to C_8 cycloalkyl, (C_1 to C_6 alkyl)sulphamoyl, di(C_1 to C_6 alkyl)sulphamoyl, (C_1 to C_6 alkyl)carbonylaminosulfonyl, 5-oxo-2,5-dihydro[1,2,4]oxadiazolyl, carboxy(C_1 to C_6 alkyl)carbonylamino, tetrazolyl(C_1 to C_6 alkyl)thio, [*N*-Z]tetrazolyl(C_1 to C_6 alkyl)amino, 5-oxo-2,5-dihydro[1,2,4]thiadiazolyl, 5-oxo-1,2-dihydro[1,2,4]triazolyl, [*N*-Z](C_1 to C_6 alkyl)amino(C_1 to C_6 alkyl)amino, or a group of the formula



wherein P is O, S or NR^{19};

Z is H, C_1 to C_6 alkyl, t-butoxycarbonyl, acetyl, benzoyl or benzyl;

R^4 is an optionally substituted C_1 to C_{18} hydrocarbyl group wherein up to three C atoms may optionally be replaced by N, O and/or S atoms;

R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{17}, R^{18} and R^{19} are independently H or C_1 to C_3 alkyl; and

R^{16} is H, C_1 to C_3 alkyl, or acetylamino;

or a pharmaceutically acceptable salt thereof;

for the preparation of a medicament for the treatment of gastrin related disorders.

2. Use according to claim 1 wherein W is N.

3. Use according to claim 1 or claim 2 wherein R^1 and R^5 are both H.

4. Use according to any preceding claim wherein R^2 is:

$$-(CH_2)_s-C(R^6R^7)_n-(CH_2)_t-R^8$$

wherein:

R^6 and R^7 are independently selected from H, C_1 to C_6 alkyl or OH; or R^6 and R^7 together represent an =O group;

n is 0 or 1;

s is 0, 1, 2 or 3;

t is 0, 1, 2 or 3; and

R^8 is selected from H, C_1 to C_{12} alkyl, (C_1 to C_{12} alkyl)oxy, C_3 to C_{12} cycloalkyl, phenyl, naphthyl, pyridyl, pyrrolyl, imidazolyl, pyrazolyl, pyridazinyl, pyrimidinyl, triazolyl, furanyl, thienyl, furazanyl, oxazolyl, isoxazolyl, thiazolyl, thiazinyl, indolyl, indolinyl, isoindolyl, isoindolinyl, isoquinolinyl, quinolinyl, benzofuranyl, benzothienyl, piperazinyl, piperidinyl, pyrrolidinyl, pyrrolinyl, dihydropyranyl, tetrahydropyranyl, pyranyl, tetrahydrofuranyl, morpholinyl, thiazolidinyl, thiomorpholinyl or thioxanyl (all optionally substituted with 1, 2 or 3 groups independently selected from C_1 to C_6 alkyl, (C_1 to C_6 alkyl)oxy, thio, (C_1 to C_6 alkyl)thio, carboxy, carboxy(C_1 to C_6 alkyl), formyl, (C_1 to C_6 alkyl)carbonyl, (C_1 to C_6 alkyl)oxycarbonyl, (C_1 to C_6 alkyl)carbonyloxy, nitro, trihalomethyl, hydroxy, hydroxy(C_1 to C_6 alkyl), amino, (C_1 to C_6 alkyl)amino, di(C_1 to C_6 alkyl)amino, aminocarbonyl, halo, halo(C_1 to C_6 alkyl), aminosulfonyl, (C_1 to C_6 alkyl)sulfonylamino or cyano).

5. Use according to claim 4 wherein s is 1, n is 1, and R^6 and R^7 together represent an =O group.

6. Use according to claims 4 or 5 wherein t is 0 and R^8 is a C_3 to C_{12} cycloalkyl group (optionally substituted with a methyl group) or a branched C_3 to C_{12} alkyl group.

7. Use according to any one of claims 4 to 6 wherein R^8 is a t-butyl, cyclohexyl, 1-methylcyclohexyl, 1-methylcyclopentyl or cyclopentyl group.

8. Use according to any one of the preceding claims wherein m is 1, R^{11} is H and R^{12} is H

9. Use according to any one of the preceding claims wherein p is 0.

10. Use according to any one of the preceding claims wherein X is C(O)NH

11. Use according to any one of the preceding claims wherein R^9 is phenyl substituted with a carboxy, carboxy(C_1 to C_6 alkyl), tetrazolyl, tetrazolyl-*N*-(C_1 to C_6 alkyl)amino, carboxy(C_1 to C_6 alkyl)thio, carboxy(C_1 to C_6 alkyl)sulfonyl, (C_1 to C_6 alkyl)amino, or 5-oxo-2,5-dihydro[1,2,4]oxadiazolyl group; or R^9 is a *N*-[carboxy(C_1 to C_6 alkyl)]indolinyl or *N*-[carboxy(C_1 to C_6 alkyl)]indolyl group.

12. Use according to claim 11 wherein the phenyl group is substituted at its 3-position.

13. Use according to any one of the preceding claims wherein R^4 is

$$-(CH_2)_q\text{-}T\text{-}R^{10}$$

wherein:

q is 0, 1, 2 or 3;

T is a bond, O, S, NH or N(C_1 to C_6 alkyl); and

R^{10} is C_1 to C_{12} alkyl, C_3 to C_{12} cycloalkyl, phenyl, naphthyl, pyridyl, pyrrolyl, imidazolyl, pyrazolyl, pyridazinyl, pyrimidinyl, triazolyl, furanyl, thienyl, furazanyl, oxazolyl, isoxazolyl, thiazolyl, thiazinyl, indolyl, indolinyl, isoindolyl, isoindolinyl, isoquinolinyl, quinolinyl, benzofuranyl, benzothienyl, piperazinyl, piperidinyl, pyrrolidinyl, pyrrolinyl, dihydropyranyl, tetrahydropyranyl, pyranyl, tetrahydrofuranyl, morpholinyl, thiazolidinyl, thiomorpholinyl or thioxanyl (all optionally substituted with 1, 2 or 3 groups independently selected from C_1 to C_6 alkyl, (C_1 to C_6 alkyl)oxy, C_3 to C_8 cycloalkyl, (C_3 to C_8 cycloalkyl)oxy, thio, (C_1 to C_6 alkyl)thio, carboxy, carboxy(C_1 to C_6 alkyl), formyl, (C_1 to C_6 alkyl)carbonyl, (C_1 to C_6 alkyl)oxycarbonyl, (C_1 to C_6 alkyl)carbonyloxy, nitro, trihalomethyl, hydroxy, hydroxy(C_1 to C_6 alkyl), amino, (C_1 to C_6 alkyl)amino, di(C_1 to C_6 alkyl)amino, aminocarbonyl, halo, halo(C_1 to C_6 alkyl), aminosulfonyl, (C_1 to C_6 alkyl)sulfonylamino or cyano).

14. Use according to claim 13 wherein q is 0, T is a bond and R^{10} is C_1 to C_{12} alkyl, C_3 to C_{12} cycloalkyl, pyridyl or phenyl (all optionally substituted with OMe, NMe_2, CF_3, Me, F, Cl, Br or I).

15. Use according to any one of the preceding claims wherein R^4 is cyclohexyl.

16. A method of treating a gastrin related disorder comprising administering a therapeutically effective amount of a compound of formula (I), as defined in any one of the preceding claims, to a patient in need thereof.

17. A method according to claim 16 wherein the gastrin related disorder is a gastrointestinal disorder.

18. A pharmaceutical composition comprising a proton pump inhibitor and a compound of formula (I), as defined in any one of claims 1 to 15, together with a pharmaceutically acceptable diluent or carrier.

19. A composition according to claim 16 wherein the proton pump inhibitor is selected from (RS)-rabeprazole, (RS)-omeprazole, lansoprazole, pantoprazole, (R)-omeprazole, (S)-omeprazole, perprazole, (R)-rabeprazole, (S)-rabeprazole, or the alkaline salts thereof.

20. A composition according to claim 18 or 19 wherein the proton pump inhibitor and the compound of formula (I) are each in an amount producing a therapeutically beneficial effect in patients suffering from gastrointestinal disorders.

21. A composition according to claim 20 wherein said therapeutically beneficial effect is a synergistic effect on the reduction of acid secretion in patients suffering from gastrointestinal disorders, or the prevention of gastrointestinal disorders in said patients, or the reduction of adverse effects associated with the one of the active ingredients by the other active ingredients.

22. A composition according to any one of claims 18 to 21 wherein the amount of each of the active ingredients is equal to or less than that which is approved or indicated in monotherapy with said active ingredient.

23. A kit containing as a first active ingredient a compound of formula (I), as defined in any one of claims 1 to 15, and as a second active ingredient a proton pump inhibitor, as a combined preparation for simultaneous, separate or sequential use in the treatment of patients suffering from gastrointestinal disorders.

24. Use of a composition according to any one of claims 18 to 22 or a kit according to claim 23 for the preparation of a medicament for the treatment of gastrointestinal disorders.

25. Use of a proton pump inhibitor for the preparation of a medicament for the treatment of gastrointestinal disorders, said treatment comprising the simultaneous or sequential administration of said proton pump inhibitor and a compound of formula (I), as defined in any one of claims 1 to 15, wherein said proton pump inhibitor enhances the effect of the compound of formula (I) on gastrin-related disorders in patients suffering from gastrointestinal disorders.

26. Use of a compound of formula (I), as defined in any one of claims 1 to 15, for the preparation of a medicament for the treatment of gastrointestinal disorders, said treatment comprising the simultaneous or sequential administration of said proton pump inhibitor

and a compound of formula (I), wherein said compound of formula (I) enhances the effect of the proton pump inhibitor on the reduction of acid secretion in patients suffering from gastrointestinal disorders.

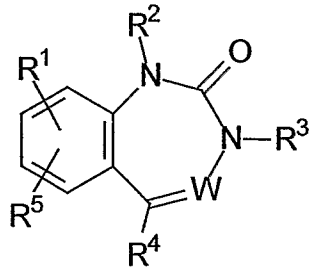
27. Use of a compound of formula (I), as defined in any one of claims 1 to 15, for the preparation of a medicament for reducing adverse effects associated with administration of proton pump inhibitors in patients suffering from gastrointestinal disorders.

28. Use according to claim 27 wherein the adverse effect is hyperplasia.

29. Use of a proton pump inhibitor for the preparation of a medicament for reducing adverse effects associated with administration of a compound of formula (I), as defined in any one of claims 1 to 15, in patients suffering from gastrointestinal disorders.

30. A method of making a pharmaceutical composition according to any one of claims 18 to 22, comprising mixing a compound of formula (I), as defined in any one of claims 1 to 15, and a proton pump inhibitor with a pharmaceutically acceptable diluent or carrier.

31. A compound of formula (IIa)



(IIa)

wherein:

W is N or N^+-O^-;

R^1 and R^5 are independently H, C_1 to C_6 alkyl, (C_1 to C_6 alkyl)oxy, thio, (C_1 to C_6 alkyl)thio, carboxy, carboxy(C_1 to C_6 alkyl), formyl, (C_1 to C_6 alkyl)carbonyl, (C_1 to C_6 alkyl)oxycarbonyl, (C_1 to C_6 alkyl)carbonyloxy, nitro, trihalomethyl, hydroxy, hydroxy(C_1 to C_6 alkyl), amino, (C_1 to C_6 alkyl)amino, di(C_1 to C_6 alkyl)amino, aminocarbonyl, halo, halo(C_1 to C_6 alkyl), aminosulfonyl, (C_1 to C_6 alkyl)sulfonylamino, (C_1 to C_6 alkyl)aminocarbonyl, di(C_1 to C_6 alkyl)aminocarbonyl, [*N*-Z](C_1 to C_6

alkyl)carbonylamino, formyloxy, formamido, (C_1 to C_6 alkyl)aminosulfonyl, di(C_1 to C_6 alkyl)aminosulfonyl, [*N*-Z](C_1 to C_6 alkyl)sulfonylamino or cyano; or R^1 and R^5 together form a methylenedioxy group;

R^2 is $-(CH_2)_s-C(O)-(CH_2)_t-R^8$

s is 0, 1, 2 or 3;

t is 0, 1, 2 or 3;

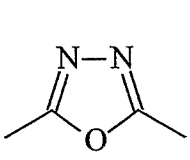
R^8 is selected from H, OH, C_1 to C_{12} alkyl, (C_1 to C_{12} alkyl)oxy, C_3 to C_{12} cycloalkyl, phenyl, naphthyl, pyridyl, pyrrolyl, imidazolyl, pyrazolyl, pyridazinyl, pyrimidinyl, triazolyl, furanyl, thienyl, furazanyl, oxazolyl, isoxazolyl, thiazolyl, thiazinyl, indolyl, indolinyl, isoindolyl, isoindolinyl, isoquinolinyl, quinolinyl, benzofuranyl, benzothienyl, piperazinyl, piperidinyl, pyrrolidinyl, pyrrolinyl, dihydropyranyl, tetrahydropyranyl, pyranyl, tetrahydrofuranyl, morpholinyl, thiazolidinyl, thiomorpholinyl or thioxanyl (all optionally substituted with 1, 2 or 3 groups independently selected from C_1 to C_6 alkyl, (C_1 to C_6 alkyl)oxy, thio, (C_1 to C_6 alkyl)thio, carboxy, carboxy(C_1 to C_6 alkyl), formyl, (C_1 to C_6 alkyl)carbonyl, (C_1 to C_6 alkyl)oxycarbonyl, (C_1 to C_6 alkyl)carbonyloxy, nitro, trihalomethyl, hydroxy, hydroxy(C_1 to C_6 alkyl), amino, (C_1 to C_6 alkyl)amino, di(C_1 to C_6 alkyl)amino, aminocarbonyl, halo, halo(C_1 to C_6 alkyl), aminosulfonyl, (C_1 to C_6 alkyl)sulfonylamino or cyano);

R^3 is $-(CR^{11}R^{12})_m-X-(CR^{13}R^{14})_p-R^9$;

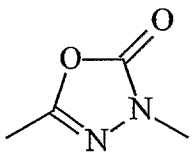
m is 0, 1, 2, 3 or 4;

p is 0, 1 or 2;

X is a bond, $-CR^{15}=CR^{16}-$, $-C\equiv C-$, C(O)NH, NHC(O), C(O)NMe, NMeC(O), C(O)O, NHC(O)NH, NHC(O)O, OC(O)NH, NH, O, CO, SO_2, SO_2NH, C(O)NHNH,



or



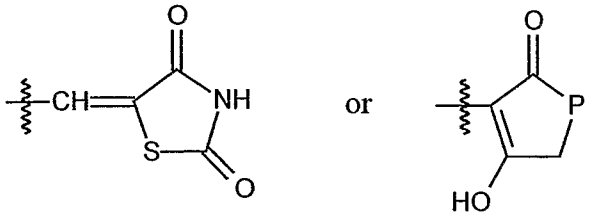
R^9 is H; C_1 to C_6 alkyl; or phenyl, naphthyl, pyridyl, benzimidazolyl, indazolyl, quinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, indolinyl, isoindolinyl, indolyl, isoindolyl or 2-pyridonyl, all optionally substituted with 1, 2 or 3 groups independently selected from

-L-Q

wherein:

L is a bond, or a group of the formula -($CR^{17}R^{18}$)$_v$-Y-($CR^{17}R^{18}$)$_w$, wherein v and w are independently 0, 1, 2 or 3, and Y is a bond, -CR^{15}=CR^{16}-, phenyl, furanyl, thiophenyl, pyrrolyl, thiazolyl, imidazolyl, oxazolyl, isoxazolyl, pyrazolyl, isoxazolonyl, piperazinyl, piperidinyl, morpholinyl, pyrrolidinyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, pyridyl or pyridazyl; and

Q is H, (C_1 to C_6 alkyl)oxy, [*N*-Z](C_1 to C_6 alkyl)oxy(C_1 to C_6 alkyl)amino, thio, (C_1 to C_6 alkyl)thio, carboxy(C_1 to C_6 alkyl)thio, carboxy, carboxy(C_1 to C_6 alkyl), carboxy(C_1 to C_6 alkenyl), [*N*-Z]carboxy(C_1 to C_6 alkyl)amino, carboxy(C_1 to C_6 alkyl)oxy, formyl, (C_1 to C_6 alkyl)carbonyl, (C_1 to C_6 alkyl)oxycarbonyl, (C_1 to C_6 alkyl)carbonyloxy, nitro, trihalomethyl, hydroxy, amino, [*N*-Z](C_1 to C_6 alkyl)amino, aminocarbonyl, (C_1 to C_6 alkyl)aminocarbonyl, di(C_1 to C_6 alkyl)aminocarbonyl, [*N*-Z](C_1 to C_6 alkyl)carbonylamino, C_5 to C_8 cycloalkyl, [*N*-Z](C_1 to C_6 alkyl)carbonyl(C_1 to C_6 alkyl)amino, halo, halo(C_1 to C_6 alkyl), sulfamoyl, [*N*-Z](C_1 to C_6 alkyl)sulfonylamino, (C_1 to C_6 alkyl)sulfonylaminocarbonyl, carboxy(C_1 to C_6 alkyl)sulfonyl, carboxy(C_1 to C_6 alkyl)sulfinyl, tetrazolyl, [*N*-Z]tetrazolylamino, cyano, amidino, amidinothio, SO_3H, formyloxy, formamido, C_3 to C_8 cycloalkyl, (C_1 to C_6 alkyl)sulphamoyl, di(C_1 to C_6 alkyl)sulphamoyl, (C_1 to C_6 alkyl)carbonylaminosulfonyl, 5-oxo-2,5-dihydro[1,2,4]oxadiazolyl, carboxy(C_1 to C_6 alkyl)carbonylamino, tetrazolyl(C_1 to C_6 alkyl)thio, [*N*-Z]tetrazolyl(C_1 to C_6 alkyl)amino, 5-oxo-2,5-dihydro[1,2,4]thiadiazolyl, 5-oxo-1,2-dihydro[1,2,4]triazolyl, [*N*-Z](C_1 to C_6 alkyl)amino(C_1 to C_6 alkyl)amino, or a group of the formula



wherein P is O, S or NR^{19};

Z is H, C_1 to C_6 alkyl, t-butoxycarbonyl, acetyl, benzoyl or benzyl;

R^4 is an optionally substituted C_1 to C_{18} hydrocarbyl group wherein up to three C atoms may optionally be replaced by N, O and/or S atoms;

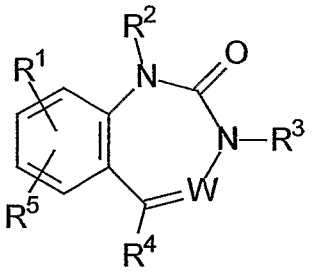
R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{17}, R^{18} and R^{19} are independently H or C_1 to C_3 alkyl; and

R^{16} is H or C_1 to C_3 alkyl, or acetylamino;

or a pharmaceutically acceptable salt thereof;

with the proviso that R^2 is not CH_2CO_2H or $C(O)CH_3$ when R^4 is phenyl.

32. A compound of formula (IIb)



(IIb)

wherein:

W is N or N^+-O^-;

R^1 and R^5 are independently H, C_1 to C_6 alkyl, (C_1 to C_6 alkyl)oxy, thio, (C_1 to C_6 alkyl)thio, carboxy, carboxy(C_1 to C_6 alkyl), formyl, (C_1 to C_6 alkyl)carbonyl, (C_1 to C_6 alkyl)oxycarbonyl, (C_1 to C_6 alkyl)carbonyloxy, nitro, trihalomethyl, hydroxy, hydroxy(C_1 to C_6 alkyl), amino, (C_1 to C_6 alkyl)amino, di(C_1 to C_6 alkyl)amino, aminocarbonyl, halo, halo(C_1 to C_6 alkyl), aminosulfonyl, (C_1 to C_6 alkyl)sulfonylamino, (C_1 to C_6 alkyl)aminocarbonyl, di(C_1 to C_6 alkyl)aminocarbonyl, [*N*-Z](C_1 to C_6 alkyl)carbonylamino, formyloxy, formamido, (C_1 to C_6 alkyl)aminosulfonyl, di(C_1 to C_6 alkyl)aminosulfonyl, [*N*-Z](C_1 to C_6 alkyl)sulfonylamino or cyano; or R^1 and R^5 together form a methylenedioxy group;

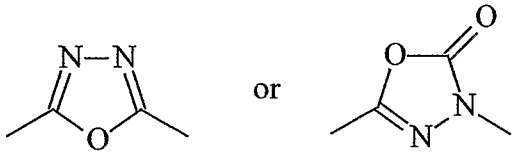
R^2 is H or an optionally substituted C_1 to C_{18} hydrocarbyl group wherein up to three C atoms may optionally be replaced by N, O and/or S atoms;

R^3 is $-(CR^{11}R^{12})_m-X-(CR^{13}R^{14})_p-R^9$;

m is 0, 1, 2, 3 or 4;

p is 0, 1 or 2;

X is a bond, $-CR^{15}=CR^{16}-$, -C≡C-, C(O)NH, NHC(O), C(O)NMe, NMeC(O), C(O)O, NHC(O)NH, NHC(O)O, OC(O)NH, NH, O, CO, SO_2, SO_2NH, C(O)NHNH,



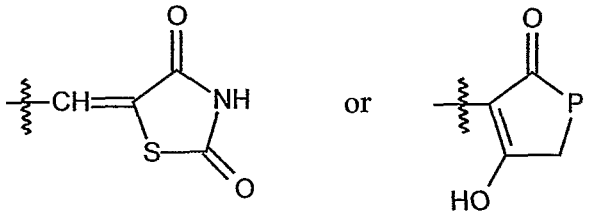
R^9 is H; C_1 to C_6 alkyl; or phenyl, naphthyl, pyridyl, benzimidazolyl, indazolyl, quinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, indolinyl, isoindolinyl, indolyl, isoindolyl or 2-pyridonyl, all optionally substituted with 1, 2 or 3 groups independently selected from

-L-Q

wherein:

L is a bond, or a group of the formula -($CR^{17}R^{18}$)$_v$-Y-($CR^{17}R^{18}$)$_w$, wherein v and w are independently 0, 1, 2 or 3, and Y is a bond, -CR^{15}=CR^{16}-, phenyl, furanyl, thiophenyl, pyrrolyl, thiazolyl, imidazolyl, oxazolyl, isoxazolyl, pyrazolyl, isoxazolonyl, piperazinyl, piperidinyl, morpholinyl, pyrrolidinyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, pyridyl or pyridazyl; and

Q is H, (C_1 to C_6 alkyl)oxy, [*N*-Z](C_1 to C_6 alkyl)oxy(C_1 to C_6 alkyl)amino, thio, (C_1 to C_6 alkyl)thio, carboxy(C_1 to C_6 alkyl)thio, carboxy, carboxy(C_1 to C_6 alkyl), carboxy(C_1 to C_6 alkenyl), [*N*-Z]carboxy(C_1 to C_6 alkyl)amino, carboxy(C_1 to C_6 alkyl)oxy, formyl, (C_1 to C_6 alkyl)carbonyl, (C_1 to C_6 alkyl)oxycarbonyl, (C_1 to C_6 alkyl)carbonyloxy, nitro, trihalomethyl, hydroxy, amino, [*N*-Z](C_1 to C_6 alkyl)amino, aminocarbonyl, (C_1 to C_6 alkyl)aminocarbonyl, di(C_1 to C_6 alkyl)aminocarbonyl, [*N*-Z](C_1 to C_6 alkyl)carbonylamino, C_5 to C_8 cycloalkyl, [*N*-Z](C_1 to C_6 alkyl)carbonyl(C_1 to C_6 alkyl)amino, halo, halo(C_1 to C_6 alkyl), sulfamoyl, [*N*-Z](C_1 to C_6 alkyl)sulfonylamino, (C_1 to C_6 alkyl)sulfonylaminocarbonyl, carboxy(C_1 to C_6 alkyl)sulfonyl, carboxy(C_1 to C_6 alkyl)sulfinyl, tetrazolyl, [*N*-Z]tetrazolylamino, cyano, amidino, amidinothio, SO_3H, formyloxy, formamido, C_3 to C_8 cycloalkyl, (C_1 to C_6 alkyl)sulphamoyl, di(C_1 to C_6 alkyl)sulphamoyl, (C_1 to C_6 alkyl)carbonylaminosulfonyl, 5-oxo-2,5-dihydro[1,2,4]oxadiazolyl, carboxy(C_1 to C_6 alkyl)carbonylamino, tetrazolyl(C_1 to C_6 alkyl)thio, [*N*-Z]tetrazolyl(C_1 to C_6 alkyl)amino, 5-oxo-2,5-dihydro[1,2,4]thiadiazolyl, 5-oxo-1,2-dihydro[1,2,4]triazolyl, [*N*-Z](C_1 to C_6 alkyl)amino(C_1 to C_6 alkyl)amino, or a group of the formula



wherein P is O, S or NR^{19};

Z is H, C_1 to C_6 alkyl, t-butoxycarbonyl, acetyl, benzoyl or benzyl;

R^4 is of formula

$$-(CH_2)_q\text{-}T\text{-}R^{10}$$

wherein:

q is 0, 1, 2 or 3;

T is a bond, O, S, NH or N(C_1 to C_6 alkyl); and

R^{10} is C_1 to C_{12} alkyl, C_3 to C_{12} cycloalkyl, phenyl, naphthyl, pyridyl, pyrrolyl, imidazolyl, pyrazolyl, pyridazinyl, pyrimidinyl, triazolyl, furanyl, thienyl, furazanyl, oxazolyl, isoxazolyl, thiazolyl, thiazinyl, indolyl, indolinyl, isoindolyl, isoindolinyl, isoquinolinyl, quinolinyl, benzofuranyl, benzothienyl, piperazinyl, piperidinyl, pyrrolidinyl, pyrrolinyl, dihydropyranyl, tetrahydropyranyl, pyranyl, tetrahydrofuranyl, morpholinyl, thiazolidinyl, thiomorpholinyl or thioxanyl (all optionally substituted with 1, 2 or 3 groups independently selected from C_1 to C_6 alkyl, (C_1 to C_6 alkyl)oxy, C_3 to C_8 cycloalkyl, (C_3 to C_8 cycloalkyl)oxy, thio, (C_1 to C_6 alkyl)thio, carboxy, carboxy(C_1 to C_6 alkyl), formyl, (C_1 to C_6 alkyl)carbonyl, (C_1 to C_6 alkyl)oxycarbonyl, (C_1 to C_6 alkyl)carbonyloxy, nitro, trihalomethyl, hydroxy, hydroxy(C_1 to C_6 alkyl), amino, (C_1 to C_6 alkyl)amino, di(C_1 to C_6 alkyl)amino, aminocarbonyl, halo, halo(C_1 to C_6 alkyl), aminosulfonyl, (C_1 to C_6 alkyl)sulfonylamino or cyano);

R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{17}, R^{18} and R^{19} are independently H or C_1 to C_3 alkyl; and

R^{16} is H, C_1 to C_3 alkyl, or acetylamino;

or a pharmaceutically acceptable salt thereof;

with the proviso that R^{10} is not phenyl or substituted phenyl when q is 0 and T is a bond.

33. A compound of formula (IIa) or (IIb) according to claim 31 or 32 wherein W is N.

34. A compound of formula (IIa) or (IIb) according to any one of claims 31 to 33 wherein R^1 and R^5 are both H.

35. A compound of formula (IIb) according to any of claims 32 to 34 wherein R^2 is:

$$-(CH_2)_s-C(R^6R^7)_n-(CH_2)_t-R^8$$

wherein:

R^6 and R^7 are independently selected from H, C_1 to C_6 alkyl or OH; or R^6 and R^7 together represent an =O group;

n is 0 or 1;

s is 0, 1, 2 or 3;

t is 0, 1, 2 or 3; and

R^8 is selected from H, C_1 to C_{12} alkyl, (C_1 to C_{12} alkyl)oxy, C_3 to C_{12} cycloalkyl, phenyl, naphthyl, pyridyl, pyrrolyl, imidazolyl, pyrazolyl, pyridazinyl, pyrimidinyl, triazolyl, furanyl, thienyl, furazanyl, oxazolyl, isoxazolyl, thiazolyl, thiazinyl, indolyl, indolinyl, isoindolyl, isoindolinyl, isoquinolinyl, quinolinyl, benzofuranyl, benzothienyl, piperazinyl, piperidinyl, pyrrolidinyl, pyrrolinyl, dihydropyranyl, tetrahydropyranyl, pyranyl, tetrahydrofuranyl, morpholinyl, thiazolidinyl, thiomorpholinyl or thioxanyl (all optionally substituted with 1, 2 or 3 groups independently selected from C_1 to C_6 alkyl, (C_1 to C_6 alkyl)oxy, thio, (C_1 to C_6 alkyl)thio, carboxy, carboxy(C_1 to C_6 alkyl), formyl, (C_1 to C_6 alkyl)carbonyl, (C_1 to C_6 alkyl)oxycarbonyl, (C_1 to C_6 alkyl)carbonyloxy, nitro, trihalomethyl, hydroxy, hydroxy(C_1 to C_6 alkyl), amino, (C_1 to C_6 alkyl)amino, di(C_1 to C_6 alkyl)amino, aminocarbonyl, halo, halo(C_1 to C_6 alkyl), aminosulfonyl, (C_1 to C_6 alkyl)sulfonylamino or cyano).

36. A compound of formula (IIb) according to claim 35 wherein s is 1, n is 1, and R^6 and R^7 together represent an =O group.

37 A compound of formula (IIb) according to claims 35 or 36 wherein t is 0 and R^8 is a C_3 to C_{12} cycloalkyl group or a branched C_3 to C_{12} alkyl or group.

38. A compound of formula (IIa) according to claims 31, 33 or 34 wherein s is 1, t is 0 and R^8 is a C_3 to C_{12} cycloalkyl group or a branched C_3 to C_{12} alkyl or group.

39. A compound of formula (IIa) or (IIb) according to claim 37 or 38 wherein R^8 is a t-butyl or cyclopentyl group.

40. A compound of formula (IIa) or (IIb) according to any one of claims 31 to 39 wherein m is 1, R^{11} is H and R^{12} is H.

41. A compound of formula (IIa) or (IIb) according to any one of the claims 31 to 40 wherein p is 0.

42. A compound of formula (IIa) or (IIb) according to any one of claims 31 to 41 wherein X is C(O)NH.

43. A compound of formula (IIa) or (IIb) according to any one of claims 31 to 42 wherein R^9 is phenyl substituted with a carboxy, carboxy(C_1 to C_6 alkyl), tetrazolyl, tetrazolyl-*N*-(C_1 to C_6 alkyl)amino, carboxy(C_1 to C_6 alkyl)thio, carboxy(C_1 to C_6 alkyl)sulfonyl, (C_1 to C_6 alkyl)amino, or 5-oxo-2,5-dihydro[1,2,4]oxadiazolyl group; or R^9 is a *N*-[carboxy(C_1 to C_6 alkyl)]indolinyl or *N*-[carboxy(C_1 to C_6 alkyl)]indolyl group.

44. A compound of formula (IIa) or (IIb) according to claim 43 wherein the phenyl group is substituted at its 3-position.

45. A compound of formula (IIa) according to any one of claims 31, 33, 34 or 38-44 wherein R^4 is

$$-(CH_2)_q\text{-}T\text{-}R^{10}$$

wherein:

q is 0, 1, 2 or 3;

T is a bond, O, S, NH or N(C_1 to C_6 alkyl); and

R^{10} is C_1 to C_{12} alkyl, C_3 to C_{12} cycloalkyl, phenyl, naphthyl, pyridyl, pyrrolyl, imidazolyl, pyrazolyl, pyridazinyl, pyrimidinyl, triazolyl, furanyl, thienyl, furazanyl, oxazolyl, isoxazolyl, thiazolyl, thiazinyl, indolyl, indolinyl, isoindolyl, isoindolinyl, isoquinolinyl, quinolinyl, benzofuranyl, benzothienyl, piperazinyl, piperidinyl, pyrrolidinyl, pyrrolinyl, dihydropyranyl, tetrahydropyranyl, pyranyl, tetrahydrofuranyl, morpholinyl, thiazolidinyl, thiomorpholinyl or thioxanyl (all optionally substituted with 1, 2 or 3 groups independently selected from C_1 to C_6 alkyl, (C_1 to C_6 alkyl)oxy, C_3 to C_8 cycloalkyl, (C_3 to C_8 cycloalkyl)oxy, thio, (C_1 to C_6 alkyl)thio, carboxy, carboxy(C_1 to C_6 alkyl), formyl, (C_1 to C_6 alkyl)carbonyl, (C_1 to C_6 alkyl)oxycarbonyl, (C_1 to C_6 alkyl)carbonyloxy, nitro, trihalomethyl, hydroxy, hydroxy(C_1 to C_6 alkyl), amino, (C_1 to C_6 alkyl)amino, di(C_1 to C_6 alkyl)amino, aminocarbonyl, halo, halo(C_1 to C_6 alkyl), aminosulfonyl, (C_1 to C_6 alkyl)sulfonylamino or cyano).

46. A compound of formula (IIa) according to claim 45 wherein q is 0, T is a bond and R^{10} is C_1 to C_{12} alkyl, C_3 to C_{12} cycloalkyl, pyridyl or phenyl (all optionally substituted with OMe, NMe_2, CF_3, Me, F, Cl, Br or I).

47. A compound of formula (IIb) according to claims 32-37 or 39-44 wherein q is 0, T is a bond and R^{10} is C_1 to C_{12} alkyl, C_3 to C_{12} cycloalkyl or pyridyl (all optionally substituted with OMe, NMe_2, CF_3, Me, F, Cl, Br or I).

48. A compound of formula (IIa) or (IIb) according to claim 46 or 47 wherein R^4 is C_{3-12} cycloalkyl.

49. A compound of formula (IIa) or (IIb) according to any one of claims 46 to 48 wherein R^4 is cyclohexyl.

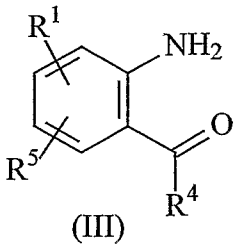
50. A compound of formula (IIa) or (IIb) which is degraded *in vivo* to yield a compound according to any one of claims 31 to 49.

51. A pharmaceutical composition comprising a compound of formula (IIa) or (IIb) according to any of claims 31 to 50 together with a pharmaceutically acceptable diluent or carrier.

52. A compound of formula (IIa) or (IIb) according to any one of claims 31 to 50 or a composition according to claim 51 for use in medicine.

53. A method of making a pharmaceutical composition according to claim 51 comprising mixing a compound of formula (IIa) or (IIb) with a pharmaceutically acceptable diluent or carrier.

54. A method of making a compound according to formula (I), (IIa) or (IIb) comprising the steps of reacting a compound of formula (III) with $NH_2NHR^{3'}$ and cyclising the resulting hydrazone compound with a bifunctional carbonyl reagent;



(III)

wherein $R^{3'}$ is R^3 or a suitable precursor thereof and R^1, R^4 and R^5 are as defined in claim 1.