Title: PIPERIDINE DERIVATIVES FOR THE TREATMENT OF OBESITY

Abstract: A compound of formula (I) or a pharmaceutically acceptable salt thereof, processes for preparing such compounds, their use as Fatty Acid Synthase inhibitors, methods for their therapeutic use, particularly in the treatment of obesity, diabetes mellitus, cancer and infection and pharmaceutical compositions containing them.
PIPERIDINE DERIVATIVES FOR THE TREATMENT OF OBESITY

Field of invention

The present invention relates to ureas, particularly to substituted N-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]phenyl]-N'-(substitutedalkyl) ureas, to processes for preparing such compounds, to their use as Fatty Acid Synthase inhibitors, to methods for their therapeutic use, particularly in the treatment of obesity and diabetes mellitus, and to pharmaceutical compositions containing them.

Background of the invention

Obesity and diabetes are reaching epidemic proportions in the USA, EU, Japan and developing countries. Obesity is the major driver of the co-morbidities of the metabolic syndrome, particularly type 2 diabetes. Since no effective pharmacotherapies for obesity are available to date and current diabetes therapies do not stop the progression of the disease, there is a huge unmet medical need.

Fatty Acid Synthase (FAS) is a critical enzyme for endogenous lipogenesis and plays an important role in the modulation of key intermediates of lipid and carbohydrate cellular metabolism. FAS is highly expressed in the tissues with high metabolic activity (for example liver, adipose tissue and brain) and there are good reasons to believe that a FAS inhibitor would cause beneficial metabolic effects in peripheral tissues. In addition, inhibition of FAS in the hypothalamus may result in reduced food intake. The non-specific irreversible FAS inhibitors cerulenin and C-75 have been reported in the literature to decrease brain levels of orexigenic neuropeptides and to decrease food intake.

Therefore there is a need for an effective FAS inhibitor to treat obesity and diabetes.

Description of the invention

The present invention provides a compound of formula I
or a pharmaceutically acceptable salt thereof, in which

R represents 1) a C\textsubscript{1-4}alkyl group optionally substituted by one or two groups selected from A-Y below and/or by one to five groups selected from X below:

A) phenyl optionally substituted by one or more of the following: i) halo; ii) cyano; iii) a C\textsubscript{1-4}alkoxy group optionally substituted by one or more halo iv) hydroxy; v) a C\textsubscript{1-4}alkyl group optionally substituted by one or more halo; vi) a group CONR\textsubscript{e}R\textsubscript{f} in which R\textsubscript{e} and R\textsubscript{f} are as defined below; vii) C\textsubscript{1-4}alkanoyl; viii) benzoyl; ix) carboxy; x) C\textsubscript{6}alkoxycarbonyl; xi) C\textsubscript{6}alkylthio; xii) C\textsubscript{6}alkylsulfinyl; xiii) C\textsubscript{6}alkylsulfonyl; xiv) C\textsubscript{6}alkylsulfonyloxy; xv) sulfamoyl; xvi) N-C\textsubscript{6}alkylsulfamoyl; xvii) N,N-diCi.

a) H;
b) C\textsubscript{1-6}alkanoyl optionally substituted by carboxy or a C\textsubscript{1-6}alkoxycarbonyl group;
c) a carbon linked saturated or partially unsaturated 4 to 10 membered heterocyclic group containing one or more N, S or O, wherein the S may be in its oxidised form of SO or SO\textsubscript{2}, which is optionally fused to a benz ring and any ring is optionally substituted by one or more of the following: hydroxy, halo, oxo, carboxy, a C\textsubscript{1-6}alkoxycarbonyl group, a C\textsubscript{1-6}alkoxy group optionally substituted by one or more hydroxy or C\textsubscript{1-6}alkoxy, C\textsubscript{1-4}alkanoyl, benzoyl, amino, C\textsubscript{1-3}alkylamin, di(C\textsubscript{1-6}alkyl)amino or a C\textsubscript{1-6}alkyl optionally substituted by one or more hydroxy or C\textsubscript{1-4}alkoxy;
d) a C\textsubscript{1-6}alkyl group optionally substituted by one or more of the following: hydroxy; carboxy; a C\textsubscript{1-6}alkoxycarbonyl group; a C\textsubscript{1-6}alkoxy group; heteroaryl; a group of formula NR\textsubscript{e}R\textsubscript{f} in which R\textsubscript{e} and R\textsubscript{f} independently represent H; a C\textsubscript{1-4}alkanoyl group; a C\textsubscript{1-6}alkyl group.
alkylsulphonyl group; a C_{1-6}alkoxycarbonyl group; a C_{1-4}alkyl group optionally substituted by one or more hydroxy or C_{1-6}alkoxy, or R^e and R^f together with the nitrogen atom to which they are attached represent a saturated or partially unsaturated 4 to 10 membered heterocyclic ring optionally containing an additional sulphur including oxidised as SO or SO_2, oxygen or nitrogen and/or optionally fused to a benz ring and any ring is optionally substituted by one or more of the following: a C_i-oalkoxy group; carboxy; a C_i-6alkylsulfonyl group; C_{1,4}alkanoyl; benzoyl; hydroxy; oxo; carboxy; or a C_{1,4}alkyl group optionally substituted by one or more hydroxy or by one or more C_{1,4}alkoxy or by one or more carboxy;

e) R^e and R^f together with the nitrogen atom to which they are attached represent a saturated or partially unsaturated 4 to 10 membered heterocyclic ring optionally containing an additional oxygen, sulphur, SO, SO_2 or nitrogen and/or optionally fused to a benz ring and/or optionally substituted by one or more of the following: a C_i-oalkoxy group; C_i-4alkanoyl group; benzoyl; a C_i-6alkoxycarbonyl group; a C_i-6alkylsulfonyl group; carbamoyl; N-Ci.6alkylcarbamoyl; N, N-diCi.6alkylcarbamoyl; hydroxy; halo; oxo; carboxy; a C_i-oalkyl group (which is optionally substituted by one or more of the following: a C_i-oalkoxy group, hydroxy or a group of formula NR^eR^f in which R^e and R^f are as defined above) or a group of formula NR^eR^f in which R^e and R^f are as defined above;
f) a C_i-6alkylsulphonyl group;
g) phenylsulfonyl;
h) heteroarylsulfonyl;
i) benzoyl;
j) phenyl optionally substituted by one or more of the following: halo; C_{1,4}alkyl; C_i-3alkoxy; a C_{1,4}alkanoylamino group; carbamoyl; N-Ci-6alkylcarbamoyl; N, N-diCi.
k) heteroaryl optionally substituted by one or more carboxy; fluoro; hydroxy; a C_{1,4}alkyl group (which is optionally substituted by one or more of the following: a C_i-oalkoxy group, hydroxy or a group of formula NR^eR^f in which R^e and R^f are as defined above); a C_i-oalkoxy group optionally substituted on C2 or C3 by carboxy; a group NR^eR^f in which R^e and R^f are as defined above; or a group CONR^eR^f in which R^e and R^f are as defined above;
i) a C_{3,4}iocycloalkyl group which may be monocyclic, bicyclic or tricyclic and optionally may be bridged and is optionally substituted by one or more carboxy; fluoro; hydroxy; a
C^alkoxy group optionally substituted on C2 or C3 by carboxy; a group NR^eR^f in which R^e and R^f are as defined above; or a group CONR^eR^f in which R^e and R^f are as defined above;

m) a C_i-6 alkoxycarbonyl group optionally substituted by phenyl;

n) heteroarylcarbonyl;

o) sulfamoyl optionally substituted by one or two independently selected C_i-6 alkyl groups or the terminal nitrogen is included in a 5 or 6 membered saturated or partially unsaturated heterocyclic ring optionally containing an additional N, S or O, wherein the S may be in its oxidised form of SO or SO_2;

B) a heteroaryl group which is optionally substituted by groups i) to xxix) as described for phenyl above;

C) a group of formula NR^eR^d in which R^e and R^d are as defined above;

D) a C_3-γ-cycloalkyl group optionally substituted by one or more hydroxy or a group of formula NR^eR^f in which R^e and R^f are as defined above;

E) a carbon linked saturated or partially unsaturated 4 to 10 membered heterocyclic group containing one or more N, S or O, wherein the S may be in its oxidised form of SO or SO_2, which is optionally fused to a benz ring or a heteroaryl ring and is optionally substituted on any ring by one or more of the following: hydroxy; halo; oxo; a C_i-6 alkoxycarbonyl group; carboxy; hydroxy; C_1-alkanoyl; a C_i-6 alkylsulfonyl group; amino; C_1-alkylamino; di(C_i-3 alkyl)amino; a C_i-6 alkyl optionally substituted by one or more hydroxy or C_i-6 alkoxy; or a C_i-6 alkoxycarbonyl group;

F) a C_i-6 alkoxycarbonyl group;

G) a C_2-6 alkynyl group;

H) a group -CONR^eR^d in which R^e and R^d are as defined above;

I) a C_i-6 alkoxy group;

J) a C_2-6 alkenyl group;

K) a C_i-6 alkyl group;

L) a C_i-6 alkylsulphonyl group;

M) phenylsulfonyl;

N) heteroaryl sulfonyl;

O) benzoyl;

P) a CI-6 alkanoyl group
Q) C₆ alkylthio;
R) ureido optionally independently substituted by one, two or three C₆ alkyl or the terminal nitrogen is included in a 5 or 6 membered saturated or partially unsaturated heterocyclic ring optionally containing an additional N, S or O, wherein the S may be in its oxidised form of SO or SO₂;
S) phenoxy;
T) hydroxy;
U) oxo
V) carboxy;
W) cyano;
X) sulfamoyl optionally substituted by one or two independently selected C₆ alkyl groups or the nitrogen is included in a 4 or 7 membered saturated or partially unsaturated heterocyclic ring optionally containing an additional N, S or O, wherein the S may be in its oxidised form of SO or SO₂;
Y) sulfamoylamino optionally substituted by one or two independently selected C₆ alkyl groups or the terminal nitrogen is included in a 4 or 7 membered saturated or partially unsaturated heterocyclic ring optionally containing an additional N, S or O, wherein the S may be in its oxidised form of SO or SO₂;
Z) fluoro or chloro;

or R¹ represents

2) a C₃-iocycloalkyl group optionally substituted by one or two groups selected from A to Y above and/or by one to five groups selected from Z above;
3) a C₂-₆-alkynyl group optionally substituted by one or two groups selected from A to Y above and/or by one to five groups selected from Z above;
4) a carbon linked saturated or partially unsaturated 4 to 10 membered heterocyclic group containing one or more N, S or O, wherein the S may be in its oxidised form of SO or SO₂, which is optionally fused to a benz ring or a heteroaryl ring and any ring is optionally substituted by one or two groups A to Y as defined above and/or by one to five groups selected from Z above;
5) a C₂-₆-alkenyl group optionally substituted by one or two groups selected from A to Y above and/or by one to five groups selected from Z above;
wherein any alkyl chain mentioned in any of the definitions from A to Y above or in any of the definitions i to xxix above is optionally substituted by 1) one or two groups selected from: carboxy; hydroxy; a C_{1-3}alkoxy group optionally substituted on C2 or C3 by carboxy; a group NR^{e}R^{d} in which R^{e} and R^{d} are as defined above; or a group CONR^{e}R^{f} in which R^{e} and R^{f} are as defined above; a C_{1-4}alkanoyloxy group or a C_{1-alkyl} optionally substituted by one or more hydroxy, C^{alkoxy} or a group -NR^{e}R^{f} in which R^{e} and R^{f} are as defined above; and /or by 2) from one to five fluoro;

and further wherein any cycloalkyl, phenyl, heteroaryl ring or carbon linked saturated or partially saturated 4 to 10 membered heterocyclic group in the list of optional substituents from A to Y above or in any of the definitions i to xxix above, for which specific substitution has not been previously mentioned, is optionally substituted by one, two or three groups selected from: carboxy; hydroxy; a C_{1-3}alkoxy group optionally substituted on C2 or C3 by carboxy; a group NR^{e}R^{d} in which R^{e} and R^{d} are as defined above; or a group CONR^{e}R^{f} in which R^{e} and R^{f} are as defined above; and /or is optionally substituted by one to five fluoro;

R^{a} represents H; or a C_{1-4}alkyl group, a C_{3-6}cycloalkyl group or a C_{3-4}cycloalkylC_{1-alkyl} group each of which groups is optionally substituted by one or more carboxy; fluoro; hydroxy; a C_{1-3}alkoxy group optionally substituted on C2 or C3 by carboxy; a group of formula NR^{e}R^{f} in which R^{e} and R^{f} are as defined above; or a group CONR^{e}R^{f} in which R^{e} and R^{f} are as defined above;

or R^{1} and R^{4} together with the nitrogen atom to which they are attached represent a saturated or partially unsaturated 4 to 10 membered heterocyclic ring optionally containing an additional sulphur including oxidised as SO or SO_{2}, oxygen or nitrogen which is optionally fused to a benz ring and wherein any ring is optionally substituted by one or two of the groups A to Y above and/or by from 1 to 5 groups Z;

R^{b} represents H;

R^{2} represents H, halo, cyano, a Cioalkyl group which is optionally substituted by one or more of the following: halo; a C_{1-3}alkoxy group; or by a group Ci_{3-alkyl}S(O)_{u} - which is optionally substituted by one or more fluoro and u is 0, 1 or 2; or R^{2} represents a C_{3-6}alkoxy group optionally substituted by one or more halo or R^{2} represents a C_{1-alkyl}S(O)_{a}S(O)_{b} group wherein the C_{1-alkyl} is optionally substituted by one or more fluoro and a is 0, 1 or 2 and b is 0 except when a is 2 then b may also be 1;
R^3 represents H, halo, cyano, a C_{1,3}alkyl group which is optionally substituted by one or more of the following: halo; Q^alkoxy group; or by a group C_{i,3}alkylS(O)_{1,2} which is optionally substituted by one or more fluoro and t = 0, 1 or 2; or R^2 represents a C_{i,3}alkoxy group optionally substituted by one or more halo or R^2 represents a C_{6}alkylS(O)_{2}(O)d-group wherein the C_{1,6}alkyl is optionally substituted by one or more fluoro and c is 0, 1 or 2 and d is 0 except when c is 2 then d may also be 1; R^4 represents i) H

ii) a C_{i-3}alkyl group optionally substituted by cyano, hydroxy, a C_{1,3}alkoxy group or optionally substituted by one or more halo

iii) a C_{i}^alkoxy group optionally substituted by one or more halo or optionally substituted by cyano, hydroxy, a C_{i}^alkoxy group, an amino group of formula NR^aR^b in which R^a and R^b independently represent H, a C_{1,3}alkylsulphonyl group, an aminoC_{i,3}alkylsulphonyl group in which the amino is optionally substituted by one or more C_{1,3}alkyl groups, a C_{i,3}alkanoyl group, a Cioalkylcarbonyl group or a C_{1,3}alkyl group optionally substituted by hydroxy or R^a and R^b together with the nitrogen atom to which they are attached represent azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl or morpholinyl each of which is optionally substituted by one or more of the following: oxo, C_{i}^alkyl or hydroxy;

iv) halo

v) nitro

vi) cyano

vii) a C_{i,6}alkylS(O)_{y}(O)_{z} optionally substituted by one or more fluoro wherein y is 0, 1 or 2 and z is 0 except when y is 2 when z is 0 or 1

viii) a group -L-R^8 in which L represents a bond, a C_{3,6}cycloalkylene group, a C_{3,6}cycloalkylidene group, a C_{1,6}cycloalkylene group or a C_{i,6}alkoxyC_{i,6}alkylene group wherein each group is optionally substituted by one or more of the following: carboxy, hydroxy, a Cioalkyl group optionally substituted by hydroxy; and R^8 represents carboxy or a group NR^aR^b in which R^a and R^b are as defined above and additionally R^b represents cyano or R^8 represents a group CO_{2}R^w in which R^w is a C_{1,3}alkyl group; or R^8 represents a group CONR^aR^y in which R^x and R^y independently represent H, a C_{1,3}alkylsulphonyl group, a C_{i,3}alkyl group or a C_{3,6}cycloalkyl group wherein the alkyl and cycloalkyl groups are optionally substituted by one or more hydroxy, carboxy or NR^aR^b in which R^a and R^b are as previously defined, or R^x and R^y together with the nitrogen atom to which they are attached represent azetidinyl; pyrrolidinyl, piperidinyl or morpholinyl; or R^8 represents tetrazolyl, thiazolidin-2,4-dion-5-yl or R^8 represents ureido optionally independently
substituted by one, two or three C₁₋₆alkyl or the terminal nitrogen is included in a 5 or 6 membered saturated or partially unsaturated heterocyclic ring optionally containing an additional N, S or O, wherein the S may be in its oxidised form of SO or SO₂;
ix) a group -Li-N(R )SO₂-L₂-R in which Li and L₂ independently represent a bond or a C₁₋₆alkylene optionally substituted by one or more C₁₋₆alkyl groups, R is H or C₁₋₆alkyl and R represents cyano or a group NR₁R₂ in which R₁ and R₂ are as previously defined, or R represents a group CO-R* in which R* represents hydroxy, C₁₋₆alkoxy or a group NR₁R₂ in which R₁ and R₂ are as previously defined;
x) phenyl(O) -wherein f is 0 or 1 optionally substituted by one or more halo, C₁₋₆alkyl optionally substituted by one or more halo or C₁₋₆alkoxy optionally substituted by one or more halo;
xii) phenylthio optionally substituted by one or more halo, C₁₋₆alkyl optionally substituted by one or more halo or C₁₋₆alkoxy optionally substituted by one or more halo;
xiii) a nitrogen containing 5 or 6 membered heteroarylCO- wherein the heteroaryl is linked through nitrogen to the carbonyl group optionally substituted by one or more halo, C₁₋₆alkyl optionally substituted by one or more halo or C₁₋₆alkoxy optionally substituted by one or more halo;
xiv) a C₂₋₆alkynyl group optionally substituted by one or more C₁₋₆alkyl, hydroxy, Q , C₁₋₆alkoxy, C₁₋₆alkoxyC₁₋₆alkoxy, or a group - NR₁R₂ as defined above;
xv) a group - L₃-S(O)₂C₁₋₆alkyl in which L₃ is a C₁₋₆alkylene optionally substituted by one or more of the following: hydroxy or a C₁₋₆alkyl group, and e is 0, 1 or 2;
xvi) a group SO₂NR₁R₂ in which R₁ and R₂ independently represent H; a C₁₋₆alkyl group optionally substituted by one or more of the following: hydroxy, C₁₋₆alkoxy or a group - NR₁R₂ in which R₁ and R₂ are as defined above, or R₀ and R₀ together with the nitrogen atom to which they are attached represent a saturated or partially unsaturated 4 to 10 membered heterocyclic ring optionally containing an additional sulphur including oxidised as SO or SO₂, oxygen or nitrogen and/or optionally fused to a benz ring and any ring is optionally substituted by one or more of the following: a C₁₋₆alkoxy group; carboxy; a Q , C₁₋₆alkylsulfonyl group; C₁₋₆alkanoyl; benzoyl; hydroxy; oxo; carboxy; or by a C₁₋₆alkyl
group optionally substituted by one or more of the following: hydroxy, C^alkoxy or carboxy; or
xvii) -C(NH₂)=N-OH
R⁵ and R⁵' independently represent H, halo, cyano, C^aUcyl optionally substituted by one or more halo or C₁₋₃alkoxy optionally substituted by one or more halo;
R⁶ and R⁶' independently represent H, halo, cyano, Cᵢ₋₃alkyl optionally substituted by one or more halo or C₁₋₃alkoxy optionally substituted by one or more halo; and R⁷ is H or OH.

In another aspect the present invention provides a compound of formula I

![Chemical Structure](image)

or a pharmaceutically acceptable salt thereof, in which
R¹ represents 1) a Cᵢ₋₆alkyl group optionally substituted by one or two groups selected from A-W below and/or by one to five groups selected from X below:
A) phenyl optionally substituted by one or more of the following i) halo; ii) cyano; iii) a C₁₋₃alkoxy group optionally substituted by one or more halo iv) hydroxy; v) a C₁₋₃alkyl group optionally substituted by one or more halo; vi) a group CONRₑRᶠ in which Rₑ and Rᶠ are as defined below; vii) C₁₋₆alkanoyl; viii) benzoyl; ix) carboxy; x) Cᵢ₋₆alkoxycarbonyl; xi) Cᵢ₋₆alkylthio; xii) C₁₋₆alkylsulfinyl; xiii) C₁₋₆alkylsulfonyl; xiv) Cᵢ₋₆alkylsulfonyloxy; xv) sulphamoyl; xvi) N-Cᵢ₋₆alkylsulphamoyl; xvii) N,N-diC₁₋₆alkylsulphamoyl; xviii) benzyl or benzylxyloxy; xix) nitro; xx) heteroaryl; xxi) heteroaryloxy; xxii) phenyl xxiii) phenoxy xxiv) phenylsulphamoyl; xxv) heteroarylsulphamoyl; xxvi) a carbon linked saturated or partially unsaturated 4 to 8 membered heterocyclic group as defined in c) below; xxvii) phenylsulfonyl ; xxviii) heteroarylsulfonyl;
xxix) a group of formula NRₑRḏ in which Rₑ and Rḏ independently represent:
a) H;
b) C₁₋₆alkanoyl optionally substituted by carboxy or a C₁₋₆alkoxycarbonyl group;
c) a carbon linked saturated or partially unsaturated 4 to 8 membered heterocyclic group containing one or more N, S or O, wherein the S may be in its oxidised form of SO or SO₂, which is optionally fused to a benz ring and any ring is optionally substituted by one or more of the following: hydroxy, halo, oxo, carboxy, a Ci₆alkoxycarbonyl group, a Ci₆alkoxy group optionally substituted by one or more hydroxy or Ci₆alkoxy, C₁₄alkanoyl, benzoyl, amino, C₁₃alkylamino, di(Ci₃alkyl)amino or a Ci₆alkyl optionally substituted by one or more hydroxy or Ci₆alkoxy;

d) a Ci₆alkyl group optionally substituted by one or more of the following: hydroxy; carboxy; a Ci₆alkoxycarbonyl group; a Ci₆alkoxy group; heteroaryl; a group of formula NR°R⁺ in which R° and R⁺ independently represent H; a Ci₆alkanoyl group; a Ci₆alkylsulphonyl group; a Ci₆alkoxycarbonyl group; a Ci₆alkyl group optionally substituted by one or more hydroxy or Ci₆alkoxy, or R° and R⁺ together with the nitrogen atom to which they are attached represent a saturated or partially unsaturated 4 to 8 membered heterocyclic ring optionally containing an additional sulphur including oxidised as SO or SO₂, oxygen or nitrogen and/or optionally fused to a benz ring and any ring is optionally substituted by one or more of the following: a Ci₆alkoxy group; carboxy; a Ci₆alkylsulfonyl group; C₁₄alkanoyl; benzoyl; hydroxy; oxo; carboxy; or a Ci₆alkyl group optionally substituted by one or more hydroxy or by one or more Ci₆alkoxy or by one or more carboxy;

e) R° and R⁺ together with the nitrogen atom to which they are attached represent a saturated or partially unsaturated 4 to 8 membered heterocyclic ring optionally containing an additional oxygen, sulphur, SO, SO₂ or nitrogen and/or optionally fused to a benz ring and/or optionally substituted by one or more of the following: a C₁₄alkoxy group; C₄alkanoyl group; benzoyl; a Ci₆alkoxycarbonyl group; a Ci₆alkylsulfonyl group; carbamoyl; N-Ci₆alkylcarbamoyl; N,N-diC₁₄alkylcarbamoyl; hydroxy; halo; oxo; carboxy; a Ci₆alkyl group (which is optionally substituted by one or more of the following: a Ci₆alkoxy group, hydroxy or a group of formula NR°R⁺ in which R° and R⁺ are as defined above) or a group of formula NR°R⁺ in which R° and R⁺ are as defined above;

f) a Ci₆alkylsulphonyl group;

g) phenylsulfonyl;

h) heteroarylsulfonyl;

i) benzoyl;
j) phenyl optionally substituted by one or more of the following: halo; C\textsubscript{i-3}alkyl; C\textsubscript{i-3}alkoxy; a C\textsubscript{i-6}alkanoylamino group; carbamoyl; N-Q-alkylcarbamoyl; N,N-diCi. 6alkylcarbamoyl or nitro;
k) heteroaryl optionally substituted by one or more carboxy; fluoro; hydroxy; a C\textsubscript{i-6}alkyl group (which is optionally substituted by one or more of the following: a C\textsubscript{i-4}alkoxy group, hydroxy or a group of formula NR\textsubscript{e}R\textsubscript{f} in which R\textsubscript{e} and R\textsubscript{f} are as defined above); a C\textsubscript{i-3}alkoxy group optionally substituted on C2 or C3 by carboxy; a group NR\textsubscript{e}R\textsubscript{f} in which R\textsubscript{e} and R\textsubscript{f} are as defined above; or a group CONR\textsubscript{e}R\textsubscript{f} in which R\textsubscript{e} and R\textsubscript{f} are as defined above; 1) a C3.iocycloalkyl group which may be monocyclic, bicyclic or tricyclic and optionally may be bridged and is optionally substituted by one or more carboxy; fluoro; hydroxy; a C\textsubscript{1-3}alkoxy group optionally substituted on C2 or C3 by carboxy; a group NR\textsubscript{e}R\textsubscript{f} in which R\textsubscript{e} and R\textsubscript{f} are as defined above; or a group CONR\textsubscript{e}R\textsubscript{f} in which R\textsubscript{e} and R\textsubscript{f} are as defined above;
m) a Ci-alkoxycarbonyl group optionally substituted by phenyl;
n) heteroarylcarbonyl;
o) sulfamoyl optionally substituted by one or two independently selected Ci-alkyl groups or the terminal nitrogen is included in a 5 or 6 membered saturated or partially unsaturated heterocyclic ring optionally containing an additional N, S or O, wherein the S may be in its oxidised form of SO or SO\textsubscript{2};
B) a heteroaryl group which is optionally substituted by groups i) to xxix) as described for phenyl above;
C) a group of formula NR\textsubscript{e}R\textsubscript{d} in which R\textsubscript{e} and R\textsubscript{d} are as defined above;
D) a C\textsubscript{3-7}cycloalkyl group optionally substituted by one or more hydroxy or a group of formula NR\textsubscript{e}R\textsubscript{f} in which R\textsubscript{e} and R\textsubscript{f} are as defined above;
E) a carbon linked saturated or partially unsaturated 4 to 8 membered heterocyclic group containing one or more N, S or O, wherein the S may be in its oxidised form of SO or SO\textsubscript{2}, which is optionally fused to a benz ring or a heteroaryl ring and is optionally substituted on any ring by one or more of the following: hydroxy; halo; oxo; a C\textsubscript{i-4}alkoxy group; carboxy; hydroxy; C\textsubscript{i-4}alkanoyl; a C\textsubscript{i-6}alkylsulfonyl group; amino; C\textsubscript{i-3}alkylamino; di(Ci-3 alkyl)amino; a Ci-alkyl optionally substituted by one or more hydroxy or Ci-alkoxy; or a Ci-alkoxycarbonyl group;
F) a Ci-alkoxycarbonyl group;
G) a $\text{C}_2$-6alkynyl group:
H) a group -CONR$^c$R$^d$ in which R$^c$ and R$^d$ are as defined above;
  i) a Ci-alkoxy group;
J) a $\text{C}_2$-alkenyl group:
5) K) a Ci-alkyl group;
L) a Ci-alkylsulphonyl group;
M) phenylsulfonyl;
N) heteroarylsulfonyl;
O) benzoyl;
P) a Ci-alkanoyl group
Q) Ci-alkylthio;
R) ureido optionally independently substituted by one, two or three Ci^alkyl or the terminal nitrogen is included in a 5 or 6 membered saturated or partially unsaturated heterocyclic ring optionally containing an additional N, S or O, wherein the S may be in its oxidised form of SO or SO$_2$;
S) phenoxy;
T) hydroxy;
U) oxo;
V) carboxy;
W) cyano;
X) fluoro;
or R$^1$ represents
2) a C$_3$-iocycloalkyl group optionally substituted by one or two groups selected from A to X above;
3) a C$_{2-6}$alkynyl group optionally substituted by one or two groups selected from A to X above;
4) a carbon linked saturated or partially unsaturated 4 to 10 membered heterocyclic group containing one or more N, S or O, wherein the S may be in its oxidised form of SO or SO$_2$, which is optionally fused to a benz ring or a heteroaryl ring and any ring is optionally substituted by one or two groups A to X as defined above;
5) a C$_{2-6}$alkenyl group optionally substituted by one or two groups selected from A to X above;
wherein any alkyl chain mentioned in any of the definitions from A to R above or in any of the definitions i to xxix above is optionally substituted by 1) one or two groups selected from: carboxy; hydroxy; a Ci-alkoxy group optionally substituted on C2 or C3 by carboxy; a group NR<sup>e</sup>R<sup>d</sup> in which R<sup>e</sup> and R<sup>d</sup> are as defined above; or a group CONR<sup>e</sup>R<sup>f</sup> in which R<sup>e</sup> and R<sup>f</sup> are as defined above; a C<sub>1-4</sub>alkanoyloxy group or a C<sub>1-4</sub>alkyl optionally substituted by one or more hydroxy, Ci<sup>a</sup>alkoxy or a group -NR<sup>e</sup>R<sup>f</sup> in which R<sup>e</sup> and R<sup>f</sup> are as defined above; and /or by 2) from one to five fluoro;

and further wherein any cycloalkyl, phenyl, heteroaryl ring or carbon linked saturated or partially saturated 4 to 10 membered heterocyclic group in the list of optional substituents from A to P above or in any of the definitions i to xxix above, for which specific substitution has not been previously mentioned, is optionally substituted by one, two or three groups selected from: carboxy; hydroxy; a C<sub>1-4</sub>alkoxy group optionally substituted on C2 or C3 by carboxy; a group NR<sup>e</sup>R<sup>d</sup> in which R<sup>e</sup> and R<sup>d</sup> are as defined above; or a group CONR<sup>e</sup>R<sup>f</sup> in which R<sup>e</sup> and R<sup>f</sup> are as defined above; and /or is optionally substituted by one to five fluoro;

R<sup>a</sup> represents H; or a C<sub>1-4</sub>alkyl group, a C<sub>2-6</sub>Cycloalkyl group or a C<sub>3-8</sub>cycloalkylC<sub>1-4</sub>alkyl group each of which groups is optionally substituted by one or more carboxy; fluoro; hydroxy; a C<sup>a</sup>alkoxy group optionally substituted on C2 or C3 by carboxy; a group of formula NR<sup>e</sup>R<sup>f</sup> in which R<sup>e</sup> and R<sup>f</sup> are as defined above; or a group CONR<sup>e</sup>R<sup>f</sup> in which R<sup>e</sup> and R<sup>f</sup> are as defined above;

or R<sup>1</sup> and R<sup>a</sup> together with the nitrogen atom to which they are attached represent a saturated or partially unsaturated 4 to 8 membered heterocyclic ring optionally containing an additional sulphur including oxidised as SO or SO<sub>2</sub>, oxygen or nitrogen which is optionally fused to a benz ring and wherein any ring is optionally substituted by one or two of the groups A to W above and/or by from 1 to 5 groups X;

R<sup>b</sup> represents H;

R<sup>2</sup> represents H, halo, cyano, a C<sub>1-3</sub>alkyl group optionally substituted by one or more halo, or a Cioalkoxy group optionally substituted by one or more halo;

R<sup>3</sup> represents H, halo, cyano, a C<sub>1-3</sub>alkyl group optionally substituted by one or more halo, or a Cioalkoxy group optionally substituted by one or more halo;

R<sup>4</sup> represents i) H, ii) a C<sub>1-3</sub>alkyl group optionally substituted by one or more halo iii) a C<sub>1-3</sub>alkoxy group optionally substituted by one or more halo iv) halo, v) nitro, vi) cyano, vii) a
\( \text{Ci}_6\text{alkylS(O)}_y(\text{O})_z \) wherein \( y \) is 0, 1 or 2 and \( z \) is 0 except when \( y \) is 2 when \( z \) is 0 or 1.

a) a group \( \text{CH}_3\text{NR}^3\text{R}^5 \) in which \( \text{R}^3 \) and \( \text{R}^5 \) independently represent \( H \); a \( \text{C}^\text{alkylsulphonyl} \) group, a \( \text{C}_1\text{,}_{\text{alkanoyl}} \) group or a \( \text{C}_1\text{,}_{\text{3alkyl}} \) group or \( \text{R}^3 \) and \( \text{R}^5 \) together with the nitrogen atom to which they are attached represent azetidinyl, pyrrolidinyl, piperidinyl or morpholinyl; ix) a group \( \text{CO}_2\text{R}^6 \) in which \( \text{R}^6 \) is a \( \text{Ci}^\text{alkyl} \) group; or x) a group \( \text{CONR}^x\text{R}^y \) in which \( \text{R}^x \) and \( \text{R}^y \) independently represent \( H \); or a \( \text{C}_1\text{,}_{\text{alkyl}} \) group or \( \text{R}^x \) and \( \text{R}^y \) together with the nitrogen atom to which they are attached represent azetidinyl; pyrrolidinyl, piperidinyl or morpholinyl; R\(^5\) and R\(^6\) independently represent \( H \), halo, cyano, \( \text{C}_1\text{,}_{\text{3alkyl}} \) optionally substituted by one or more halo or \( \text{C}_1\text{,}_{\text{alkoxy}} \) optionally substituted by one or more halo; R\(^6\) and R\(^7\) independently represent \( H \), halo, cyano, \( \text{C}_1\text{,}_{\text{3alkyl}} \) optionally substituted by one or more halo or \( \text{C}_1\text{,}_{\text{alkoxy}} \) optionally substituted by one or more halo; and R\(^7\) is \( H \) or OH.

In a further aspect the present invention provides a compound of formula I

![Chemical Structure](image)

or a pharmaceutically acceptable salt thereof, in which

R\(^1\) represents i) a \( \text{Ci}_6\text{alkyl} \) group optionally substituted by one or two groups selected from A-S below and/or by one to five groups selected from T below:

A) phenyl optionally substituted by one or more of the following i) halo; ii) cyano; iii) a \( \text{Ci}_6\text{alkoxy} \) group optionally substituted by one or more halo iv) hydroxy; v) a \( \text{C}_1\text{,}_{\text{alkyl}} \) group optionally substituted by one or more halo; vi) carbamoyl; vii) \( N\)-\( \text{Ci}_6\text{alkylcarbamoyl} \); viii) \( N\,\text{,}\,N\text{-diCi}_6\text{alkylcarbamoyl} \); ix) carboxy; x) \( \text{Ci}_6\text{alkoxycarbonyl} \); xi) \( \text{Ci}_6\text{alkylthio} \); xii) \( \text{Ci}_6\text{alkylsulfinyl} \); xiii) \( \text{C}_1\text{,}_{\text{alkylsulfonyl}} \); xiv) \( \text{Ci}_6\text{alkylsulfonyloxy} \); xv) sulphamoyl; xvi) \( N\text{-Ci}_6\text{alkylsulphamoyl} \); xvii) \( N\,\text{,}\,N\text{-diCi}_6\text{alkylsulphamoyl} \); xviii) benzyl xix) benzyloxy; xx) heteroaryl; xxi) heteroaryloxy; xxii) phenyl xxiii) phenoxy xxiv) phenylsulphamoyl; xxv) heteroarylsulphamoyl; xxvi) a carbon linked saturated or
partially unsaturated 4 to 8 membered heterocyclic group as defined in c) below; xxvii)
phenylsulfonyl; xxviii) heteroaryl sulfonyl;
xxix) a group of formula NR\textsuperscript{e}R\textsuperscript{d} in which R\textsuperscript{e} and R\textsuperscript{d} independently represent:
\begin{itemize}
  \item a) H;
  \item b) C\textsubscript{i-6}alkanoyl;
  \item c) a carbon linked saturated or partially unsaturated 4 to 8 membered heterocyclic group containing one or more N, S or O, wherein the S may be in its oxidised form of SO or SO\textsubscript{2}, which is optionally fused to a benz ring and any ring is optionally substituted by one or more of the following: hydroxy, oxo, carboxy, a C\textsubscript{1-4}alkoxy group optionally substituted by one or more hydroxy or C\textsubscript{i-6}alkoxy, benzoyl, amino, C\textsubscript{i-3}alkylamino, di(C\textsubscript{i-3}alkyl)amino or a C\textsubscript{1-6}alkyl optionally substituted by one or more hydroxy or C\textsubscript{1-6}alkoxy;
  \item d) a C\textsubscript{i-6}alkyl group optionally substituted by one or more of the following: hydroxy, carboxy; a C\textsubscript{1-6}alkoxycarbonyl group; a C\textsubscript{1-4}alkoxy group; heteroaryl; a group of formula NR\textsuperscript{e}R\textsuperscript{f} in which R\textsuperscript{e} and R\textsuperscript{f} independently represent H; a C\textsubscript{1-4}alkanoyl group; a C\textsubscript{i-6}alkyl group optionally substituted by one or more hydroxy or C\textsubscript{i-6}alkoxy, or R\textsuperscript{e} and R\textsuperscript{f} together with the nitrogen atom to which they are attached represent a saturated or partially unsaturated 4 to 8 membered heterocyclic ring optionally containing an additional sulphur including oxidised as SO or SO\textsubscript{2}, oxygen or nitrogen and/or optionally fused to a benz ring and any ring is optionally substituted by one or more of the following: a C\textsubscript{i-6}alkoxy group; carboxy; a C\textsubscript{i-6}alkylsulphonyl group; C\textsubscript{1-4}alkanoyl; benzoyl; hydroxy; oxo; carboxy; or a C\textsubscript{1-4}alkyl group optionally substituted by one or more hydroxy or by one or more C\textsubscript{1-4}alkoxy or by one or more carboxy;
  \item e) R\textsuperscript{e} and R\textsuperscript{d} together with the nitrogen atom to which they are attached represent a saturated or partially unsaturated 4 to 8 membered heterocyclic ring optionally containing an additional oxygen, sulphur, SO or SO\textsubscript{2} or nitrogen and/or optionally fused to a benz ring and/or optionally substituted by one or more of the following: a C\textsubscript{1-6}alkoxy group; Ci\textsubscript{4}alkanoyl group; benzoyl; a C\textsubscript{1-6}alkoxycarbonyl group; a C\textsubscript{1-4}alkylsulphonyl group; carbamoyl; N-Ci\textsubscript{6}alkylcarbamoyl; N,N-diCi\textsubscript{6}alkylcarbamoyl; hydroxy; oxo; carboxy; a C\textsubscript{i-6}alkyl group (which is optionally substituted by one or more of the following: a C\textsubscript{i-6}alkoxy group, hydroxy or a group of formula NR\textsuperscript{e}R\textsuperscript{f} in which R\textsuperscript{e} and R\textsuperscript{f} are as defined above) or a group of formula NR\textsuperscript{e}R\textsuperscript{f} in which R\textsuperscript{e} and R\textsuperscript{f} are as defined above;
f) a \( \text{C}_1-\text{C}_6 \) alkylsulphonyl \( \) group;
g) phenylsulfonyl;
h) heteroarylsulfonyl;
i) benzoyl;
j) phenyl optionally substituted by one or more of the following: halo; \( \text{C}_1-\text{C}_6 \) alkyl; \( \text{C}_1-\text{C}_6 \) alkoxy; a \( \text{C}_6 \)-alkanoylamino \( \) group; carbamoyl; \( N-\text{C}_1-\text{C}_6 \) alkylcarbamoyl; \( N,N-\text{diC}_6 \) alkylcarbamoyl;
k) heteroaryl optionally substituted by one or more carboxy; fluoro; hydroxy; a \( \text{C}_1-\text{C}_6 \) alkoxy \( \) group optionally substituted on \( \text{C}_2 \) or \( \text{C}_3 \) by carboxy; a group \( \text{NR}^6 \text{R}^d \) in which \( \text{R}^e \) and \( \text{R}^d \) are as defined above; or a group \( \text{CONR}^f \text{R}^f \) in which \( \text{R}^e \) and \( \text{R}^f \) are as defined above;
l) a \( \text{C}_3-\text{C}_{10} \)-cycloalkyl \( \) group which may be monocyclic, bicyclic or tricyclic and optionally may be bridged and is optionally substituted by one or more carboxy; fluoro; hydroxy; a \( \text{C}_1-\text{C}_6 \) alkoxy \( \) group optionally substituted on \( \text{C}_2 \) or \( \text{C}_3 \) by carboxy; a group \( \text{NR}^6 \text{R}^d \) in which \( \text{R}^e \) and \( \text{R}^f \) are as defined above; or a group \( \text{CONR}^f \text{R}^f \) in which \( \text{R}^e \) and \( \text{R}^f \) are as defined above;
m) a \( \text{C}_1-\text{C}_6 \) alkoxy carbonyl \( \) group;
B) a heteroaryl \( \) group which is optionally substituted by groups i) to xxix) as described for phenyl above;
C) a group of formula \( \text{NR}^6 \text{R}^d \) in which \( \text{R}^e \) and \( \text{R}^d \) are as defined above;
D) a \( \text{C}_3-\text{C}_7 \)-cycloalkyl \( \) group optionally substituted by one or more hydroxy or a group of formula \( \text{NR}^6 \text{R}^f \) in which \( \text{R}^e \) and \( \text{R}^f \) are as defined above;
E) a carbon \( \) linked saturated or partially unsaturated \( \) 4 to 8 membered \( \) heterocyclic \( \) group containing one or more \( \) N, S or O, wherein the \( \) S may be in its oxidised \( \) form of \( \) SO or \( \) SO\(_2\), which is optionally fused to a benz \( \) ring \( \) and/or is optionally \( \) substituted by one or more of the following: hydroxy; oxo; a \( \text{C}_6 \)-alkoxy \( \) group; carboxy; hydroxy; \( \text{C}_1 \)-alkanoyl; a \( \text{C}_1-\text{C}_6 \) alkylsulfonyl \( \) group; amino; \( \text{C}_1-\text{C}_6 \) alkanoyl; di(\( \text{C}_1-\text{C}_6 \) alkyl)amino; or a \( \text{C}_1-\text{C}_6 \) alkyloxy optionally substituted by one or more hydroxy or \( \text{C}_1-\text{C}_6 \) alkoxy;
F) a \( \text{C}_1-\text{C}_6 \) alkoxy carbonyl \( \) group;
G) a \( \text{C}_2 \)-alkynyl \( \) group;
H) a group \( \) -\( \text{CONR}^c \) \( \text{R}^d \) in which \( \text{R}^c \) and \( \text{R}^d \) are as defined above;
I) a \( \text{C}_1-\text{C}_6 \) alkoxy \( \) group;
J) a \( \text{C}_2 \)-\( \text{C}_6 \) alkenyl \( \) group;
K) a C\textsubscript{1-6} alkyl group;
L) a C\textsubscript{1-6} alkylsulphonyl group;
M) phenylsulfonyl;
N) heteroarylsulfonyl;
O) ... a on C\textsubscript{2} or C\textsubscript{3} by carboxy; a group NR\textsubscript{c} R\textsubscript{d} in which R\textsubscript{c} and R\textsubscript{d} are as defined above; or a group CONR\textsubscript{e} R\textsubscript{f} in carboxy; wherein a carbon linked saturated or partially unsaturated 4 to 8 membered heterocyclic group containing one or more N, S or O, wherein the S may be in its oxidised form of SO or SO\textsubscript{2}, which is optionally fused to a benz ring and any ring is optionally substituted by a group A to T as defined above ;

5) a C\textsubscript{2-6} alkenyl group optionally substituted by one or two groups selected from A to T above;

wherein any alkyl chain mentioned in any of the definitions from A to P above or in any of the definitions i to xxix above is optionally substituted by 1) one group selected from: carboxy; hydroxy; a C\textsubscript{1-3} alkoxy group optionally substituted on C2 or C3 by carboxy; a group NR\textsubscript{e} R\textsubscript{d} in which R\textsubscript{e} and R\textsubscript{d} are as defined above; or a group CONR\textsubscript{e} R\textsubscript{f} in which R\textsubscript{e} and R\textsubscript{f} are as defined above; and /or by T) from one to five fluoro;

and further wherein any cycloalkyl, phenyl, heteroaryl ring or carbon linked saturated or partially saturated 4 to 8 membered heterocyclic group in the list of optional substituents from A to P above or in any of the definitions i to xxix above, for which specific substitution has not been previously mentioned, is optionally substituted by one group selected from: carboxy; hydroxy; a C\textsubscript{1-3} alkoxy group optionally substituted on C2 or C3 by carboxy; a group NR\textsubscript{e} R\textsubscript{d} in which R\textsubscript{e} and R\textsubscript{d} are as defined above; or a group CONR\textsubscript{e} R\textsubscript{f} in
which \( R^e \) and \( R^f \) are as defined above; and /or is optionally substituted by one to five fluoro;

\( R^a \) represents H; or a \( C_{1-4} \)alkyl group, a \( C_3^a \)cycloalkyl group or a \( C_3^b \)cycloalkyl\( C_i^c \)alkyl group each of which groups is optionally substituted by one or more carboxy; fluoro;

\( R^b \) represents \( H \) or \( \text{halo} \); or \( \text{C^alkoxy} \) optionally substituted by one or more halo; and

\( R^g \) represents \( \text{H} \) or \( \text{OH} \).

\( R^2 \) represents \( H \), halo, cyano, a \( C_{1-3} \)alkyl group optionally substituted by one or more halo, or a \( C_{1-3} \)alkoxy group optionally substituted by one or more halo;

\( R^3 \) represents \( H \), halo, cyano, a \( C_{1-3} \)alkyl group optionally substituted by one or more halo, or a \( C_{1-3} \)alkoxy group optionally substituted by one or more halo;

\( R^4 \) represents i) \( H \), ii) a \( C_{1-3} \)alkyl group optionally substituted by one or more halo iii) a \( C_{1-3} \)alkoxy group optionally substituted by one or more halo iv) halo, v) nitro, vi) cyano, vii) a \( \text{Ci}_{1-3} \text{alkylS(O)} \) \( y \) (\( O \)) \( z \) - wherein \( y \) is 0,1 or 2 and \( z \) is 0 except when \( y \) is 2 when \( z \) is 0 or 1 viii) a group \( \text{CH}_2 \text{NR}^u \text{R}^v \) in which \( R^u \) and \( R^v \) independently represent \( H \); a \( C_{1-3} \)alkylsulphonyl group, a \( C_{1-3} \)alkanoyl group or a \( \text{Cioalkyl} \) group or \( R^u \) and \( R^v \) together with the nitrogen atom to which they are attached represent azetidinyl, pyrrolidinyl, piperidinyl or morpholinyl; ix) a group \( \text{CO}_2 \text{R}^w \) in which \( R^w \) is a \( \text{Cioalkyl} \) group; or x) a group \( \text{CONR}^x \text{R}^y \) in which \( R^x \) and \( R^y \) independently represent \( H \); or a \( C_{1-3} \)alkyl group or \( R^x \) and \( R^y \) together with the nitrogen atom to which they are attached represent azetidinyl, pyrrolidinyl, piperidinyl or morpholinyl;

\( R^5 \) and \( R^6 \) independently represent \( H \), halo, cyano, \( C_{1-3} \)alkyl optionally substituted by one or more halo or \( C_{1-3} \)alkoxy optionally substituted by one or more halo;

\( R^6 \) and \( R^7 \) independently represent \( H \), halo, cyano, \( C_{1-3} \)alkyl optionally substituted by one or more halo or \( C^\text{alkoxy} \) optionally substituted by one or more halo; and

\( R^7 \) is \( H \) or \( \text{OH} \).
In a further aspect the present invention provides a compound of formula II

![Structure II]

or a pharmaceutically acceptable salt thereof, in which

R¹ represents 1) a C₁₆alkyl group optionally substituted by one or two groups selected from A-S below and/or by one to five groups selected from T below:

A) phenyl optionally substituted by one or more of the following: i) halo; ii) cyano; iii) a C₄alkoxy group optionally substituted by one or more halo iv) hydroxy; v) a C₁₆alkyl group optionally substituted by one or more halo; vi) carbamoyl; vii) N-Ci₆alkylcarbamoyl; viii) N,N-diCi₆alkylcarbamoyl; ix) carboxy; x) Ci₆alkoxycarbonyl; xi) Ci₆alkylthio; xii) Ci₆alkylsulfinyl; xiii) C₁₆alkylsulfonyl; xiv) C₁₆alkylsulfonyloxy; xv) Ci₆sulphamoyl; xvi) xvi) N-Ci₆alkylsulphamoyl; xvii) N,N-diCi₆alkylsulphamoyl; xviii) benzyl; xix) benzzyloxy; xx) heteroaryl; xx) heteroaryloxy; xxii) phenyl xxiii) phenoxy xxiv) phenylsulphamoyl; xxv) heteroarylsulphamoyl; xxvi) a carbon linked saturated or partially unsaturated 4 to 8 membered heterocyclic group as defined in c) below; xxvii) phenylsulfonyl; xxviii) heteroarylsulfonyl; xxix) a group of formula NR³R⁴ in which R³ and R⁴ independently represent:

a) H;

b) Ci₆alkanoyl;

c) a carbon linked saturated or partially unsaturated 4 to 8 membered heterocyclic group containing one or more N, S or O, wherein the S may be in its oxidised form of SO or SO₂, which is optionally fused to a benz ring and any ring is optionally substituted by one or more of the following: hydroxy, oxo, carboxy, a C₁₆alkoxy group optionally substituted by one or more hydroxy or C₁₆alkoxy, C₁₆alkanoyl, benzyol, amino, C₁₆alkylamino, di(C1₃alkyl)amino or a C₁₆alkyl optionally substituted by one or more hydroxy or C₁₆alkoxy;

d) a Ci₆alkyl group optionally substituted by one or more of the following: hydroxy; carboxy; a C₁₆alkoxycarbonyl group; a C₁₆alkoxy group; heteroaryl; a group of formula NR³R⁴ in which R³ and R⁴ independently represent H; a Ci₆alkanoyl group; a Ci₆
alkylsulphonyl group; a Ci_6alkoxycarbonyl group; a Ci_6alkyl group optionally substituted by one or more hydroxy or Q^alkoxy, or R^e and R^f together with the nitrogen atom to which they are attached represent a saturated or partially unsaturated 4 to 8 membered heterocyclic ring optionally containing an additional sulphur including oxidised as SO or SO_2, oxygen or nitrogen and/or optionally fused to a benz ring and any ring is optionally substituted by one or more of the following: a Ci_6alkoxy group; carboxy; a Ci_6alkylsulfonyl group; Ci_6alkanoyl; benzoyl; hydroxy; oxo; carboxy; or a Ci_6alkyl group optionally substituted by one or more hydroxy or by one or more Ci_6alkoxy or by one or more carboxy;

e) R^e and R^d together with the nitrogen atom to which they are attached represent a saturated or partially unsaturated 4 to 8 membered heterocyclic ring optionally containing an additional oxygen, sulphur, SO, SO_2 or nitrogen and/or optionally fused to a benz ring and/or optionally substituted by one or more of the following: a Ci_6alkoxy group; Ci_6alkanoylgroup; benzoyl; a Ci_6alkoxycarbonyl group; a Ci_6alkylsulfonyl group; carbamoyl; N-Ci_6alkylcarbamoyl; N, N-diCi_6alkylcarbamoyl; hydroxy; oxo; carboxy; a Ci_6alkyl group (which is optionally substituted by one or more of the following: a Ci_6alkoxy group, hydroxy or a group of formula NR^eR^f in which R^e and R^f are as defined above) or a group of formula NR^eR^f in which R^e and R^f are as defined above;
f) a Ci_6alkylsulphonyl group;
g) phenylsulfonyl;
h) heteroarylsulfonyl;
i) benzoyl;
j) phenyl optionally substituted by one or more of the following: halo; Ci_3alkyl; Ci_3alkoxy; a Ci_3alkanoylamino group; carbamoyl; N-Ci_3alkylcarbamoyl; N,N-diCi_4alkylcarbamoyl;
k) heteroaryl optionally substituted by one or more carboxy; fluoro; hydroxy; a Ci_3alkoxy group optionally substituted on C2 or C3 by carboxy; a group NR^eR^d in which R^e and R^d are as defined above; or a group CONR^eR^f in which R^e and R^f are as defined above; l) a Cs-iocycloalkyl group which may be monocyclic, bicyclic or tricyclic and optionally may be bridged and is optionally substituted by one or more carboxy; fluoro; hydroxy; a Ci_6alkoxy group optionally substituted on C2 or C3 by carboxy; a group NR^eR^f in which
R_e and R_f are as defined above; or a group CONR_eR_f in which R_e and R_f are as defined above;

m) a Ci_6alkoxycarbonyl group;

B) a heteroaryl group which is optionally substituted by groups i) to xxix) as described for phenyl above;

C) a group of formula NR_eR_d in which R_e and R_d are as defined above;

D) a C_3-7cycloalkyl group optionally substituted by one or more hydroxy or a group of formula NR_eR_f in which R_e and R_f are as defined above;

E) a carbon linked saturated or partially unsaturated 4 to 8 membered heterocyclic group containing one or more N, S or O, wherein the S may be in its oxidised form of SO or SO_2, which is optionally fused to a benz ring and/or is optionally substituted by one or more of the following: hydroxy; oxo; a Ci-6alkoxy group; carboxy; hydroxy; C_1,4alkanoyl; a Ci-3alkylsulfonyl group; amino; C_1,3alkylamino; di(Ci_3 alkyl)amino; or a Ci-alkyl optionally substituted by one or more hydroxy or C_1,6alkoxy;

F) a C_1-6 alkoxy carbonyl group;

G) a C_2-alkynyl group;

H) a group -CONR_cR_d in which R_c and R_d are as defined above;

i) a Ci-6alkoxy group;

J) a C_2-alkenyl group;

K) a Ci-alkyl group;

L) a Ci-6alkylsulphonyl group;

M) phenylsulfonyl;

N) heteroarylsulfonyl;

O) benzoyl;

P) a C_1,6alkanoyl group

Q) hydroxy;

R) oxo;

S) carboxy;

T) fluoro

or R^1 represents

2) a C_3-7cycloalkyl group optionally substituted by one or two groups selected from A to T above;
3) a C₇₆ alkynyl group optionally substituted by one or two groups selected from A to T above;
4) a carbon linked saturated or partially unsaturated 4 to 8 membered heterocyclic group containing one or more N, S or O, wherein the S may be in its oxidised form of SO or SO₂, which is optionally fused to a benz ring and any ring is optionally substituted by a group A to T as defined above;
5) a C₇₆ alkenyl group optionally substituted by one or two groups selected from A to T above;

wherein any alkyl chain mentioned in any of the definitions from A to P above or in any of the definitions i to xxix above is optionally substituted by 1) one group selected from: carboxy; hydroxy; a C¹alkoxy group optionally substituted on C2 or C3 by carboxy; a group NR²R³ in which R² and R³ are as defined above; or a group CONR²R³ in which R² and R³ are as defined above; and/or by 2) from one to five fluoro; and further wherein any cycloalkyl, phenyl, heteroaryl ring or carbon linked saturated or partially saturated 4 to 8 membered heterocyclic group in the list of optional substituents from A to P above or in any of the definitions i to xxix above, for which specific substitution has not been previously mentioned, is optionally substituted by one group selected from: carboxy; hydroxy; a C¹alkoxy group optionally substituted on C2 or C3 by carboxy; a group NR²R³ in which R² and R³ are as defined above; or a group CONR²R³ in which R² and R³ are as defined above; and/or is optionally substituted by one to five fluoro;

Rᵃ represents H; or a C¹alkyl group, a C₃₋₆cycloalkyl group or a C₃₋₆cycloalkylC₄₋₆alkyl group each of which groups is optionally substituted by one or more carboxy; fluoro; hydroxy; a C₃₋₆alkoxy group optionally substituted on C2 or C3 by carboxy; a group of formula NR²R³ in which R² and R³ are as defined above; or a group CONR²R³ in which R² and R³ are as defined above; or R¹ and Rᵃ together with the nitrogen atom to which they are attached represent a saturated or partially unsaturated 4 to 8 membered heterocyclic ring optionally containing an additional sulphur including oxidised as SO or SO₂, oxygen or nitrogen which is optionally fused to a benz ring and wherein any ring is optionally substituted by one or two of the groups A to S above and/or by from 1 to 5 groups T;

Rᵇ represents H,
R² represents H, halo, cyano, a C₁₋₃alkyl group optionally substituted by one or more halo, or a Cᵢ₋₃alkoxy group optionally substituted by one or more halo;

R³ represents H, halo, cyano, a C₁₋₃alkyl group optionally substituted by one or more halo, or a Cᵢ₋₃alkoxy group optionally substituted by one or more halo;

R⁴ represents cyano, halo or a C₁₋₃alkylsulphonyl group; and

R⁷ represents H or hydroxy.

In a further aspect the present invention provides a compound of formula HA

![Diagram of compound HA](image)

or a pharmaceutically acceptable salt thereof in which

R¹ represents 1) a C₁₋₃alkyl group optionally substituted by one or more of the following:

a) phenyl optionally substituted by one or more of the following: halo; a Cᵢ₋₃alkoxy group or cyano; b) pyridyl

2) a carbon linked saturated 5 or 6 membered heterocyclic group containing one N or O;

d) a Cᵢ₋₃alkoxycarbonyl group or e) a Cᵢ₋₃alkynyl group or 2) a C₃₋₇cycloalkyl group

Rᵃ represents H; or a C₁₋₃alkyl group;

or R¹ and Rᵃ together with the nitrogen atom to which they are attached represent morpholinyl, pyrrolidinyl or piperidinyl;

Rᵇ represents H,

R² represents H, halo, trifluoromethoxy, a C₁₋₃alkyl group; a Cᵢ₋₃alkoxy group; cyano; or when R¹ is other than phenyl then Rᵇ together with the nitrogen to which is attached plus the carbon on the phenyl ring to which the nitrogen is attached and R² together with the carbon to which it is attached together represent a pyrrolidine ring fused to phenyl;

R³ represents H, halo, trifluoromethoxy, a C₁₋₃alkyl group; a C₁₋₃alkoxy group; cyano;

R⁴ represents bromo, cyano or a Cᵢ₋₃alkylsulphonyl group; and

R⁷ represents H or hydroxy.

Further sub-definitions of the meaning of R¹, Rᵃ, R², Rᵇ, R³, R⁴, and R⁷, in compounds of formula I, II and HA now follow. It will be understood that any combination of these sub-
definitions may be used instead of the original definitions where appropriate in any of the
compound groups, claims or embodiments defined hereinbefore or hereinafter.
In one group of compounds of formula UA, R² represents H and R¹, R⁵, R², R⁶, R³, R⁴ are
as described above.

In a second group of compounds of formula IIA, R⁷ represents H, R¹ represents 1) a C₆₇alkyl group optionally substituted by one or more of the following: a) phenyl optionally substituted by one or more of the following: halo; a C₆alkoxy group or cyano; b) pyridyl c) oxan-4-yl d) a C₆alkoxycarbonyl group or e) a C₂alkynyl group 2) a C₅, γcycloalkyl group and R⁵ represents H or R¹ and R⁵ together with the nitrogen atom to which they are attached represent morpholino or pyrrolidino, and R², R³, R⁴ are as described above provided that one of R² and R³ is other than H.

In a third group of compounds of formula HA, R² is methyl and R³ is H.
In a fourth group of compounds of formula HA, R² and R³ are both methyl.
In a fifth group of compounds of formula IIA, R² is cyano or methylsulphonyl.
In a sixth group of compounds of formula IIA, R³ is H.
In a seventh group of compounds of formula HA, R³ is methyl and R² is H.
In an eighth group of compounds of formula IIA, R¹ represents pyrrolidinyl or piperidinyl optionally substituted on nitrogen by a C₁oalkylsulphonyl group.
In a ninth group of compounds of formula IIA, R¹ represents a C₂,₄alkylene chain terminally substituted by one of the following: a C₁₃alkylsulphonyl group or a group -NR₁₀R₁₁ in which R₁₀ represents H and R₁₁ represents H, a C₁₃alkylsulphonyl group or a sulphamoyl group which is optionally terminally substituted by one or two independently selected C₁₃alkyl groups.

In a tenth group of compounds of formula HA, R⁴ is cyano.

It will be understood that each of these ten groups also apply to formula I and to formula II.

"Pharmaceutically acceptable salt", where such salts are possible, includes both pharmaceutically acceptable acid and base addition salts. A suitable pharmaceutically acceptable salt of a compound of formula I is, for example, an acid-addition salt of a compound of formula I which is sufficiently basic, for example an acid-addition salt with an inorganic or organic acid such as hydrochloric, hydrobromic, sulphuric, trifluoroacetic, citric or maleic acid; or, for example a base-addition salt of a compound of formula I
which is sufficiently acidic, for example an alkali or alkaline earth metal salt such as a
sodium, calcium or magnesium salt, or an ammonium salt, or a salt with an organic base
such as methylamine, dimethylamine, trimethylamine, piperidine, morpholine or
tris-(2-hydroxyethyl)amine.

Throughout the specification and the appended claims, a given chemical formula or
name shall encompass all stereo and optical isomers and racemates thereof as well as
mixtures in different proportions of the separate enantiomers, where such isomers and
enantiomers exist, as well as pharmaceutically acceptable salts thereof and solvates thereof
such as for instance hydrates including solvates of the free compounds or solvates of a salt
of the compound. Isomers may be separated using conventional techniques, e.g.
chromatography or fractional crystallisation. The enantiomers may be isolated by
separation of racemate for example by fractional crystallisation, resolution or HPLC. The
diastereomers may be isolated by separation of isomer mixtures for instance by fractional
crystallisation, HPLC or flash chromatography. Alternatively the stereoisomers may be
made by chiral synthesis from chiral starting materials under conditions that will not cause
racemisation or epimerisation, or by derivatisation, with a chiral reagent. All stereoisomers
are included within the scope of the invention. AUtautomers, where possible, are included
within the scope of the invention. The present invention also encompasses compounds
containing one or more isotopes for example $^{13}$C, $^{11}$C or $^{19}$F and their use as isotopically
labelled compounds for pharmacological and metabolic studies.

The present invention also encompasses prodrugs of a compound of formula I that
is compounds which are converted into a compound of formula I in vivo.

The following definitions shall apply throughout the specification and the appended
claims.

The term "CViocycloalkyl group which may be monocyclic, bicyclic or tricyclic
and optionally may be bridged" includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,
cycloheptyl, cyclooctyl, cyclodecyl, bicyclo(2.2.1)heptyl, bicyclo(2.2.2)octyl,
perhydroindanyl and adamantyl.

The term "heteroaryl" includes an aromatic 5- or 6-membered monocyclic ring or
unless specified otherwise, an 8-, 9- or 10-membered bicyclic ring, with up to five ring
heteroatoms selected from oxygen, nitrogen and sulfur, which may, unless otherwise
specified be carbon or nitrogen linked. In one embodiment heteroaryl is an aromatic 5- or
6-membered monocyclic ring with up to five ring heteroatoms selected from oxygen, nitrogen and sulfur, which may, unless otherwise specified be carbon or nitrogen linked and includes pyrrolyl, thiienyl, furyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, triazolyl, furazanyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, 1,3,5-triazinyl and imidazothiazolyl. Other heteroaryls include quinolyl, isoquinolyl, benzthienyl, benzofuranyl, benzofurazanyl, benzoxazolyl, benzimidazolyl, indolyl, benzthiazolyl, indazolyl, cinnolinyl, quinazolinyl, quinoxaliny, phthalazinyl, 1,5-naphthyridinyl, 1,6-naphthyridinyl, 1,7-naphthyridinyl, 1,8-naphthyridinyl, pyrrolopyridinyl, pyrrolopyrazinyl, pyrazolopyridinyl or imidazopyridinyl.

The term "heteroaryl including N-oxides" includes heteroaryls as described immediately above and in addition N-oxides of such heteroaryls where such N-oxides are known to those skilled in the art to exist and are known to be stable at ambient conditions for example pyridine-N-oxides.

The term "a carbon linked saturated or partially saturated 4 to 10 (or 4 to 8) membered heterocyclic group containing containing one or more N, S or O, wherein the S may be in its oxidised form of SO or SO₂, which is optionally fused to a benz ring or a heteroaryl ring" includes oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, 2,3-dihydro-1,3-thiazolyl, 1,3-thiazolidinyl, 1,3-oxazolidinyl, oxepanyl, azetidinyl, pyrrolinyl, pyrrolidinyl, morpholinyl, thiamorpholinyl (perhydro-1,4-thiazinyl), (8-oxa-3-azabicyclo[3.2.1]octyl), (7-oxa-3-azabicyclo[3.1.1]heptyl), perhydroazepinyl, perhydrooxepinyl, tetrahydro-1,4-thiazinyl, 1-oxotetrahydrothienyl, 1,1-dioxotetrahydro-1,4-thiazinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl, dihydropyridinyl, tetrahydropyridinyl, dihydropyrimidinyl, tetrahydropyrimidinyl, or tetrahydroquinolyl each of which may be optionally substituted as previously described.

When two substituents on an amine together with the nitrogen atom to which they are attached represent a saturated or partially unsaturated 4 to 10 (or 4 to 8) membered heterocyclic ring optionally containing an additional oxygen, sulphur, SO, SO₂ or nitrogen O and/or optionally fused to a benz ring then such rings include azetidino, pyrrolidino, morpholino, piperidino, imidazolidinyl, imidazolyl, piperazino, thiamorpholino (perhydro-1,4-thiazinyl), homopiperazino, perhydroazepino, perhydrooxazepino, (2,3-dihydro-1,3-thiazolyl, 1,3-thiazolidinyl, 1,3-oxazolidinyl, oxepanyl, oxazepanyl.
dihydropyrimidinyl, tetrahydropyrimidinyl, and homopiperidinyl, each of which is optionally substituted as previously described.

Unless otherwise stated or indicated, the term "alkyl" denotes either a straight or branched alkyl group. Examples of said alkyl include methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, t-butyl, pentyl, isopentyl, neopentyl, tert-pentyl, hexyl and iso-hexyl. Preferred alkyl groups are methyl, ethyl, propyl, isopropyl, butyl and tertiary butyl.

Unless otherwise stated or indicated, the term "alkoxy" denotes a group O-alkyl, wherein alkyl is as defined above.

Unless otherwise stated or indicated, the term "halogen" shall mean fluorine, chlorine, bromine or iodine.

An example of "Ci-alkanoyloxy" is acetoxy. Examples of “Ci-alkoxycarbonyl” include C1,4alkoxycarbonyl, methoxycarbonyl, ethoxycarbonyl, n- and t-butoxycarbonyl. Examples of "Ci-alkoxycarbonamino" include methoxy-carbonamino, ethoxycarbonamino, n- and f-butoxycarbonamino. Examples of "Ci-alkoxy" include methoxy, ethoxy and propoxy. Examples of "Ci-alkanoylamino" include formamido, acetamido and propionylamino. Examples of "Ci-alkylS(O)2(O)b- group in which a is 0, 1 or 2 and b is 0 except when a is 2 then b may also be 1" include C1,alkylsulfonyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl methylsulfonyloxy and where substituted by fluoro include trifluoromethylsulfonyloxy and trifluoropropylsulfonyloxy. Examples of "Ci-alkylsulfonylamino" include methylsulfonylamino, ethylsulfonylamino and propylsulfonylamino. Examples of "Ci-alkylsulfonyl-N-(Ci-alkyl)amino" include methylsulfonyl-N-methylamino, ethylsulfonyl-N-methylamino and propylsulfonyl-N-ethylamino. Examples of "Ci-alkanoyl" include Ci-alkanoyl, propionyl and acetyl. Examples of "N-(Ci-alkyl)amino" include methylamino and ethylamino. Examples of "N,N-(Ci-alkyl)2-amino" include di-N-methylamino, di-(N-ethyl)amino and N-ethyl-N-methylamino. Examples of "C2,6alkenyl" are vinyl, allyl and 1-propenyl. Examples of "C2,6alkynyl" are ethynyl, 1-propynyl and 2-propynyl. Examples of "N-(Ci-alkyl)sulphamoyl" are N-(methyl)sulphamoyl and N-(ethyl)sulphamoyl. Examples of "N-(Ci-alkyl)2-sulphamoyl" are N,N-(dimethyl)sulphamoyl and N-(methyl)-N-(ethyl)sulphamoyl. Examples of "N-(Ci-alkyl)carbamoyl" are
$N_{-(C_{i,4} \text{alkyl})}$carbamoyl, methylaminocarbonyl and ethylaminocarbonyl. Examples of "$N_{N-(C_{i,6} \text{alkyl})}$carbamoyl" are $N_{N-(C_{i,4} \text{alkyl})}$carbamoyl, dimethylaminocarbonyl and methylethylaminocarbonyl. Examples of "(heterocyclic group)$C_{i,6}$alkyl" include pyridylmethyl, 3-morpholinopropyl and 2-pyrimid-2-ylethyl. Examples of "Cs-scycloalkylCi-ecycloalkyl" include cyclopropylmethyl and 2-cyclohexylpropyl. Examples of "$N_{-(C_{i,6} \text{alkyl})}$sulphamoylamino" are $N_{-(methyl)}$sulphamoylamino and $N_{-(ethyl)}$sulphamoylamino. Examples of "$N_{-(C_{i,6} \text{alkyl})}$sulphamoylamino" are $N_{-(methyl)}$sulphamoylamino and $N_{-(ethyl)}$sulphamoylamino. Examples of "Ci-$\text{alkyl}$sulphonylaminocarbonyl" include methylsulphonylaminocarbonyl, ethylsulphonylaminocarbonyl and propylsulphonylaminocarbonyl.

Specific compounds of the invention include one or more, for example from 1 to 418, of the following compounds below labelled as List 1:

1-butyln-3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]urea;
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-1-propan-2-yl-urea;
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-(trifluoromethoxy)phenyl]-1-propan-2-yl-urea;
3-benzyl-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-(trifluoromethoxy)phenyl]urea;
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methoxy-phenyl]-3-propan-2-yl-urea;
3-benzyl-1-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methyl-1-phenyl]urea;
3-benzyl-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-fluoro-phenyl]urea;
$N_{-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]}$m&, 4-carboxamide;
3-benzyl-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methoxy-phenyl]urea;
$N_{-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]}$pyrrolidine-1-carboxamide;
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-fluoro-phenyl]-1-propan-2-yl-urea;
3-benzyl-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2,4-dimethyl-phenyl]urea;
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2,4-dimethyl-phenyl]-1-propan-2-yl-urea;
1-benzyl-3-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]phenyl]urea;
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-cyclopentyl-urea;
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-phenethyl-urea;
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(oxan-4-ylmethyl)urea;

3-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methyl-phenyl]-1-methyl-urea;
3-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methyl-phenyl]-1-ethyl-urea;

5-1-buty1-3-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methyl-phenyl]urea;
1-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methyl-phenyl]-3-cyclopentyl-1-urea;
3-[2-cyano-5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-phenyl]-1-propan-2-yl-urea;
1-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methyl-phenyl]-3-[(2-fluorophenyl)methyl]urea;

io-1-benzyl-3-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methyl-phenyl]-1-methyl-urea;
1-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methyl-phenyl]-3-(pyridin-3-ylmethyl)urea;
1-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methyl-phenyl]-3-phenethyl-urea;
1-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methyl-phenyl]-3-(oxan-4-ylmethyl)urea;

N-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methyl-phenyl]morpholine-4-carboxamide;
N-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methyl-phenyl]pyrrolidine-1-carboxamide;

20-3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-1-ethyl-urea;
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-tert-butyl-urea;
3-benzyl-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]urea;
3-[4-cy anophenyl)methyl]-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]urea;

25-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[(2-fluorophenyl) methyl]urea;
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(pyridin-3-ylmethyl)urea;
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(pyridin-4-ylmethyl)urea;

30-3-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methyl-phenyl]-1-[(1R)-1-phenylethyl]urea;
3-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methyl-phenyl]- 1-[(1 S)-1-phenylethyl]urea;
1-[5-[4-(4-bromophenyl)-4-hydroxy-piperidine-1-carbonyl]-2-methyl-phenyl]-3-propan-2-yl-urea;
5
3-benzyl- 1-[5-[4-(4-bromophenyl)-4-hydroxy-piperidine-1-carbonyl]-2-methyl-phenyl]urea;
3-((1-benzyl-4-piperidyl)- 1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]urea;
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2-methylpropyl)urea;
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-prop-2-yny1-urea;
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[(3,4,5-trimethoxyphenyl)methyl]urea;
methyl 3-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino] propanoate;
3-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]phenyl]- 1-propan-2-yl-urea;
3-[(3-cyanophenyl)methyl]- 1-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methyl-phenyl]urea
1-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methyl-phenyl]-3-(4-hydroxycyclohexyl)urea
1-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methyl-phenyl]-3-(4-hydroxycyclohexyl)urea
1-[5-[4-(4-cyanophenyl)-4-hydroxy-piperidine-1-carbonyl]-2-methyl-phenyl]-3-propan-2-yl-urea
tert-butyl 4-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]butanoate
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(pyridin-2-ylmethyl)urea
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-1-pentan-3-yl-urea
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-1-[[3-methylphenyl]methyl]urea
N-[2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]ethyl]acetamide
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[(3,4-difluorophenyl)methyl]urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[2-(4-sulfamoylphenyl)ethyl]urea
2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]acetamide
3-(1-anilino-2-methyl-propan-2-yl)-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2-pyridin-2-ylethyl)urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2-thiophen-2-ylethyl)urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2-thiophen-2-ylethyl)urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2-thiophen-2-ylethyl)urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2-thiophen-2-ylethyl)urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2-thiophen-2-ylethyl)urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2-thiophen-2-ylethyl)urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2-thiophen-2-ylethyl)urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2-thiophen-2-ylethyl)urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2-thiophen-2-ylethyl)urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2-thiophen-2-ylethyl)urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2-thiophen-2-ylethyl)urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2-thiophen-2-ylethyl)urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2-thiophen-2-ylethyl)urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2-thiophen-2-ylethyl)urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2-thiophen-2-ylethyl)urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[2-(3,5-dimethyl-1,2-oxazol-4-yl)ethyl]urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[2-(3,5-dimethyl-1,2-oxazol-4-yl)ethyl]urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[2-(3,5-dimethyl-1,2-oxazol-4-yl)ethyl]urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[2-(3,5-dimethyl-1,2-oxazol-4-yl)ethyl]urea
tert-butyl N-[4-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]butyl]carbamate
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[1-(1H-indol-3-yl)propan-2-yl]urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[2,2-dimethylpropyl]urea
Methyl 2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]acetate

(2S)-2-[[5- [4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]-4-methyl-pentanamide

1-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(3-pyrrolidinylpropyl)urea

1-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[4-(thiadiazol-4-yl)phenyl]methyl]urea

1-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[2-(3,5-dimethylpyrazol-1-yl)ethyl]urea

1-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2,2-dimethyloxan-4-yl)urea

(2S)-2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]-3-[[2-methylpropan-2-yl]oxy]propanamide

3-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-1-(1-propyl-4-piperidyl)urea

1-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[(1,1-dioxothiolan-3-yl)methyl]urea

Benzyl N-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]ethyl carbamate

1-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[[1H-tetrazol-5-yl]methyl]urea

1-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[2-(2-methoxyphenoxy)ethyl]urea

2-[(4-nitrophenyl)amino]ethyl]-1-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]urea

3-[[2-(benzenesulfonamido)ethyl]-1-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]urea

1-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[[4-nitrophenyl]amino]ethyl]urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]-3-[1-(4-
fluorophenyl)ethyl]urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]-3-(3-flu-
ylmethyl)urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]-3-(2-hydroxyethyl)urea
5 N-[2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]carba-
moxyamino]ethyl]pyridine-2-carboxamide
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]-3-[2-
(dimethylsulfamoylamino)ethyl]urea
N-[2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]carba-
moxyamino]-2-methyl-propyl]pyridine-3-carboxamide
3-[2-[(2-amino-5,6-dimethyl-pyrimidin-4-yl)amino]ethyl]-1-[5-[4-(4-
cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]-3-[2-(9H-purin-6-
ylamino)ethyl]urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]-3-[(3-
-methylbut-2-enyl)urea
tert-butyl 3-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-
phenyl]carbamoylamino]azetidine-1-carboxylate
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]-3-[1-(4-
methylsulfonylphenyl)ethyl]urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]-3-(2-oxo-3,4-dihydro-
1,7-naphthyridin-3-yl)urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]-3-[3-(3-methyl-l-
piperidyl)propyl]urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]-3-[2-[(4-
methoxyphenyl)amino]ethyl]urea
tert-butyl N-[2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methy-
phenyl]carbamoylamino]ethyl]carbamate
3-(2-aminoethyl)-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-
phenyl]carbamoylformic acid
2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]carba-
moxyamino]ethyl]carbamoylformic acid
2-[2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]ethylcarbamoyl]acetic acid
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[(1S)-1-phenylethyl]urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[(4-hydroxycyclohexyl)urea
3-[(3-cyanophenyl)methyl]-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2-methanesulfonamidoethyl)urea
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-1-[2-(ethylsulfonylamino)ethyl]urea
N-[2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]ethyl]propanamide
N-[2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]ethyl]-2-methyl-propanamide
2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]ethylcarbamoylmethyl acetate
N-[2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]ethyl]-2-hydroxy-acetamide
tert-butyl N-[2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]ethyl]-N-methyl-carbamate
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2-methylaminoethyl)urea
N-[2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]ethyl]thiophene-2-carboxamide
N-[2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]ethyl]-1-methyl-pyrrole-2-carboxamide
N-[2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]ethyl]-5-methyl-1,2-oxazole-4-carboxamide
N-[2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]carbamoylamino]ethyl]-N-methylacetamide
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[2-(methylsulfonyl-amino)ethyl]urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[2-(propan-2-ylsulfonylamino)ethyl]urea
4-[l-[3-(benzylcarbamoylamino)-4-methyl-benzoyl]-4-piperidyl]-N,N-dimethylbenzamide
N,N-dimethyl-4-[l-[4-methyl-3-(propan-2-ylcarbamoylamino)benzoyl]-4-piperidyl]benzamide
3-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]propanoic acid
3-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]propanamide
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(3-morpholin-4-yl-3-oxo-propyl)urea
3-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]-N-(2-methoxyethyl)propanamide
3-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]-N,N-dimethyl-propanamide
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[3-(2-oxopyrrolidin-1-yl)propyl]urea
ethyl 4-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]piperidine-1-carboxylate
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2-oxazepan-3-yl)urea
(IS)-2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino)cyclohexane-1-carboxamide
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[2-(2-oximidazolidin-1-yl)ethyl]urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[3-oxo-1,2-oxazol-5-yl]methyl]urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2-pyrrolidin-1-ylethyl)urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[3-(3-dimethylaminopropyl)urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[2-(1H-imidazol-4-yl)ethyl]urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[3-(4-methylpiperazin-1-yl)propyl]urea
3-[3-(bis(2-hydroxyethyl)amino)propyl]-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(4-dimethylaminobutyl)urea
3-(1-azabicyclo[2.2.2]oct-8-yl)-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[2-(1-methylpyrrolidin-2-yl)ethyl]urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2-dimethylaminoethyl)urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[3-(3-morpholin-4-ylpropyl)urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[1-(2-methoxyethyl)-4-piperidyl]urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(1-methyl-4-piperidyl)urea
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-1-[(2S)-1-ethylpyrrolidin-2-yl]methyl]urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[(3-methylimidazol-4-yl)methyl]urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(oxolan-2-ylmethyl)urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2-methoxyethyl)urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(3-propan-2-yl oxypropyl)urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(3-methoxypropyl)urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2-methoxy-2-methyl propyl)urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(oxan-4-yl)urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[(1,4-dioxan-2-yl)methyl]urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[(2-methoxyethoxy) propyl]urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(oxan-4-yl)urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[3-(2,6-dioxabicyclo[5.4.0]undeca-8,10,12-trien-4-yl)methyl]urea
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-l-(3-ethoxypropyl)urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2-methoxy-2-methyl propyl)urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(oxan-2-ylmethyl)urea
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-l-(2-propoxyethyl)urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(7,10-dioxabicyclo[4.4.0]deca-2,4,11-trien-8-ylmethyl)urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(oxan-2-ylmethyl)urea
3-(cyanomethyl)-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2,2,2-trifluoroethyl)urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(1,1-dioxothiolan-3 yl)urea
3-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-1-phenyl]carbamoylamino]-N- pyridin-2-yl-propanamide
2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]-N-propan-2-yl-acetamide

1-butyl-3-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]ethyl]urea

N-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]pentyl)morpholine-4-carboxamide

3-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]ethyl)cyclohexanecarboxamide

1-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]-2-(2-methylpropan-2-yl)oxycarbonylamino]propanoate

1-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]-3-[3-(2-oxoazepan-1-yl)propyl]urea

3-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]-N-niethyl-propanamide

tert-butyl (2S)-2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]-4-methylsulfonyl-butanoate

Methyl 4-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino][cyclohexane-1-carboxylate

1-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]-3-(1-hydroxypropan-2-yl)urea

1-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]-3-(2-hydroxypropyl)urea

1-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]-3-(2,3-dihydroxypropyl)urea

1-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]-3-(4-hydroxybutyl)urea

1-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]-3-(1,3-dihydroxypropan-2-yl)urea

1-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]-3-(2-hydroxycyclohexyl)urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(3-hydroxy-2,2-dimethyl-propyl)urea

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[2-(2-hydroxyethoxy)ethyl]urea

5 1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(1-hydroxy-2-methyl-propan-2-yl)urea

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(3-hydroxypropyl)urea

5 1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(3-hydroxy-2,2-dimethyl-propyl)urea

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[2-(2-hydroxyethoxy)ethyl]urea

(2S)-2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]-3-hydroxy-propanamide

10 1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(4-hydroxy-cyclohexyl)urea

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[1-(hydroxymethyl)cyclopentyl]urea

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(3,3,3-trifluoro-2-hydroxy-propyl)urea

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(3,3,3-trifluoro-2-hydroxy-propyl)urea

3-[3-(2-chlorophenoxy)-2-hydroxy-propyl]-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]urea

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(3-hydroxyadamantyl)urea

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2-methanesulfonamido-2-methyl-propyl)urea

3-(2-amino-2-methyl-propyl)-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]urea

3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-1-[2-(ethylsulfonylamino)-2-methyl-propyl]urea
N-[1-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]-2-methyl-propan-2-yl]-2,2-dimethyl-propanamide
tert-butyl N-[3-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]propyl]carbamate

5 3-(3-aminopropyl)-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]urea
tert-butyl 4-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino)piperidine-1-carboxylate
tert-butyl (3R)-3-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]pyrrolidine-1-carboxylate
tert-butyl (3S)-3-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]pyrrolidine-1-carboxylate

10 tert-butyl (3S)-3-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]pyrrolidine-1-carboxylate
l-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(3R)-pyrrolidin-3-yl]urea
l-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(3S)-pyrrolidin-3-yl]urea
l-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[2-(methyl-propan-2-ylsulfonyl-amino)ethyl]urea
l-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(3-methanesulfonamidopropyl)]urea

20 3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-1-[3-(ethylsulfonylamino)propyl]urea
l-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[3-(propan-2-ylsulfonylamino)propyl]urea
l-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[(3R)-1-methylsulfonylpyrrolidin-3-yl]urea
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-1-[(3R)-1-ethylsulfonylpyrrolidin-3-yl]urea
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-1-[[(3S)-1-propanoylpyrrolidin-3-yl]urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[[(3S)-1-methylsulfonylpyrrolidin-3-yl]urea
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-1-[(3S)-I-ethylsulfonylpyrrolidin-3-yl]urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(3-methylsulfonylpropyl)urea
1-benzyl-3-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-fluoro-phenyl]urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-cyclopropyl-urea
1-butyl-2-yl-3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]urea
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-1-propyl-urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-cyclohexyl-urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(3-methylbutan-2-yl)urea
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]-N-(2-hydroxyethyl)propanamide
N-[2-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino][ethyl]-N',N'-dimethyl-propanediamide
N-[2-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino][propyl]acetamide
N-[3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino][propyl]morpholine-4-carboxamide
3-(2-(carbamoylamino)ethyl]-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]urea
4-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]-N-propyl-butanamide
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2-oxo-3-piperidyl)urea
Methyl 2-[2-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino][acetyl]amino]acetate
2-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]-N,N-dimethyl-acetamide
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2-oxo-3,4-dihydro-IH-1,8-naphthyridin-3-yl)urea
(2S)-2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]-4-methylsulfonyl-butanoic acid
3-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]-N-(5-methyl-1,2-oxazol-4-yl)propanamide
3-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]-N,N-bis(2-hydroxyethyl)propanamide
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[(4-methylsulfonylphenyl)methyl]urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(3-pyrazol-1-yl)propyl]urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[(3-methyl-1,2-oxazol-5-yl)methyl]urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[(6-methylpyridin-2-yl)methyl]urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[(3-methyl-1,2-thiazol-2-yl)methyl]urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[(3-methylpyridin-2-yl)methyl]urea
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-1-[(3-methylpyridin-2-yl)methyl]urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[[3-(2-methoxypyridin-3-yl)-1,2-oxazol-5-yl]methyl]urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[(4-methoxybutyl)urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[(1-phenoxypropan-2-yl)urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[[2-(3,3-difluoropyrrolidin-1-yl)ethyl]urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(1-methyl-3-piperidyl)urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(4-dimethylaminocyclohexyl)urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[(1,5-dimethylpyrazol-3-yl)methyl]urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[(1,3-dimethylpyrazol-4-yl)methyl]urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[(1,3-dimethylpyrazol-4-yl)methyl]urea
3-[(1-amino-2-methyl-propan-2-yl)-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]urea
N-[1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]-2-methyl-propan-2-ylacetamide
N-[1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]-2-methyl-propan-2-ylpropamamide
3-[(3R)-6-oxo-3-piperidyl]urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[(1,3-oxazol-2-yl)methyl]urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[(3R)-6-oxo-3-piperidyl]urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[(4-methyl-1,3-thiazol-2-yl)methyl]urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[(3R)-6-oxo-3-piperidyl]urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[(1,3-oxazol-2-yl)methyl]urea
3-[(8S)-1-azabicyclo[2.2.2]oct-8-yl]-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]urea
N-[2-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]ethyl]-N,2-dimethyl-propanamide
3-[(3R)-1-acetylpyrrolidin-3-yl]-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]urea
3-[(3S)-1-acetylpyrrolidin-3-yl]-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]urea
l-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methyl-phenyl]-3-(3-methylsulfonylpropyl)urea and
tert-butyl 3-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino)piperidine-1-carboxylate
1-benzyl-3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-(trifluoromethyl)phenyl]urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(1-methylsulfonyl-4-piperidyl)urea
3-(1-acetyl-4-piperidyl)-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[1-(2-methylpropanoyl)-4-piperidyl]urea
4-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]N,N-dimethyl-piperidine-1-carboxamide
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[1-(dimethylsulfamoyl)-4-piperidyl]urea
l-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(3-piperidyl)urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-cyclobutyl-urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(cyclopropylmethyl)urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(1H-pyrazol-3-ylmethyl)urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[[1-methylpyrazol-3-yl)methyl]urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(pyrimidin-2-ylmethyl)urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[[5-methyl-2H-pyrazol-3-yl]methyl]urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(pyrazin-2-ylmethyl)urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(3-(3-methylsulfonylpropyl)urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(1-propanoyl-3-piperidyl)urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-ethyl-phenyl]-3-(1-methylsulfanyl-3-piperidyl)urea
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-1-(1-propanoyl-3-piperidyl)urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(oxetan-3-yl)urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(dimethylsulfamoyl)azetidin-3-yl)urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(1-methylsulfanylazetidin-3-yl)urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[[1-(dimethylsulfamoyl)azetidin-3-yl]urea
3-[(cw)-2-aminocyclohexyl]-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]urea
3-[(rr)<5>-2-aminocyclohexyl]-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]urea
3-amino-N-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]azetidine-1-carboxamide
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[(trans)-2-methanesulfonamidocyclohexyl]urea
N-[(lS,3S)-3-[(5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]cyclohexyl]acetamide
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-1-[(trans)-2-(ethylsulfonylamino)cyclohexyl]urea
3-[(1-acetylamidin-3-yl)-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]urea
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-methanesulfonamidoazetidine-1-carboxamide
N-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-methanesulfonamidocyclohexyl]urea
5-
N-[(lS,3S)-3-[(5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]cyclopentyl]carbamate
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[(c/s)-2-(dimethylsulfamoylamino)cyclohexyl]urea
3-[(lS,3S)-3-aminocyclopentyl]-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[(1R,2R)-2-(dimethylsulfamoylamino)cyclohexyl]urea
N-[(lS,3S)-3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]cyclopentyl]acetamide
N-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-4-methylsulfonyl-piperazine-1-carboxamide

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-1-phenyl]-3-[(1S,3S)-3-(dimethylsulfamoylamino)cyclopentyl]urea

3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-1-phenyl]-1-[(1S,3S)-3-(ethylsulfonylamino)cyclopentyl]urea

1-[5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-propan-2-yl-urea


Ethyl 4-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylpiperazine-1-carboxylate

N-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-4-(2-methylpropanoyl)piperazine-1-carboxamide

N-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-N',N'-dimethylpiperazine-1,4-dicarboxamide

3-(2-dimethylaminoethyl)-1-[2-methyl-5-[4-(trifluoromethyl)phenyl]piperidine-1-carbonyl]phenyl]urea

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(3-methyl-1,1-dioxothiolan-3-yl)urea

1-[2-methyl-5-[4-(trifluoromethyl)phenyl]piperidine-1-carbonyl]phenyl]-3-(3-piperidyl)urea

N-[2-[5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]ethyl]acetamide
tert-butyl 3-[[5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]azetidine-1-carboxylate
3-[2-(dimethylsulfamoylamino)ethyl]-l-[2-methyl-5-[4-[4-(trifluoromethyl)phenyl]piperidine-1-carbonyl]phenyl]urea
3-(2-methanesulfonamidoethyl)-l-[2-methyl-5-[4-[4-(trifluoromethyl)phenyl]piperidine-1-carbonyl]phenyl]urea
3-(2-aminoethyl)-l-[2-methyl-5-[4-[4-(trifluoromethyl)phenyl]piperidine-1-carbonyl]phenyl]urea
tert-butyl 3-[[5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]pyrrolidine-1-carboxylate
N-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-methylsulfonyl-pyrrolidine-1-carboxamide
N-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-hydroxy-azetidine-1-carboxamide
N-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]azetidine-1-carboxamide
tert-butyl N-[2-[[5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]ethyl]-N-methyl-carbamate
3-((1-acetylpyrrolidin-3-yl)-l-[5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]urea
1-[5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-pyrrolidin-3-yl-urea
1-[5-[4-(4-chlorophenyl)-4-hydroxy-piperidine-1-carbonyl]-2-methyl-phenyl]-3-propan-2-yl-urea
1-[5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[2-(methylmethylsulfonyl-amino)ethyl]urea
N-[2-[[5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]ethyl]-N-methyl-acetamide
N-[2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoyl-methyl-amino]ethyl]propanamide
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(1-pyridin-3-yl)ethyl]urea
1-[5-[4-(4-chlorophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(pyridin-2-ylmethyl)urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-1-phenyl]-3-[(1-methylpyrazol-4-yl)methyl]urea
l-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(1-pyridin-4-yethyl)urea
l-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[(6-mo φ holin-4-ylpyridin-2-yl)methyl]urea
l-[5-[4-(4-chlorophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-propan-2-yl-urea
l-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylsulfanylphenyl]-1-propan-2-ylurea
3-benzyl-l-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylsulfanylphenyl]urea
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methoxymethyl]phenyl]-1-propan-2-ylurea
[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]urea
l-[5-[4-(4-sulfamoylphenyl)piperidine-1-carbonyl]-2-methylphenyl]-3-[(3,5-difluoropyridin-2-yl)methyl]urea
l-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylsulfonylphenyl]-1-propan-2-ylurea
2-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]carbamoylamino]-3-(4-fluorophenyl)propanoic acid
(2R)-3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]carbamoylamino]-2-[2-methylpropan-2-yl]oxycarbonylamino]propanoic acid
2-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]carbamoylamino]-3-methylbutanoic acid
4-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]carbamoylamino]butanoic acid
2-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]carbamoylamino]acetic acid
l-[2-methyl-5-[4-(4-methylsulfonylphenyl)piperidine-1-carbonyl]-phenyl]-3-propan-2-ylurea
l-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methylphenyl]-3-propan-2-ylurea
3-tert-butyl-l-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methylphenyl]urea
3-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-fluorophenyl]-l-propan-2-ylurea
3-[4-(cyanophenyl)methyl]-1-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-A-methylphenyl]urea

1-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methylphenyl]-3-(pyridin-4-ylmethy)lurea
3-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methylphenyl]-1,1-dimethylurea
1-benzyl-3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]-1-methylurea
1-[5-[4-(4-bromophenyl)-4-hydroxypiperidine-1-carbonyl]-2-methylphenyl]-3-propan-2-ylurea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]-3-(3-oxo-1,2-oxazolidin-4-yl)urea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]-3-(2-methylbut-3-yn-2-yl)urea

Ethyl 2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]carbamoylamino]propanoate
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylsulfinylphenyl]-1-propan-2-ylurea
3-benzyl-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylsulfinylphenyl]urea
2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]carbamoylamino]cyclopentane-1-carboxylic acid
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]-3-(1-methylcyclopropyl)urea
3-[(1-acetil)piperidin-3-yl]-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]urea

1-[2-methyl-5-(4-phenylpiperidine-1-carbonyl)phenyl]-3-propan-2-ylurea
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]-1-(2-hydroxyethyl)-1-methylurea
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]-1-methyl-1-(1-methylpiperidin-4-yl)urea

3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]-1-(2-dimethylaminoethyl)-1-methylurea
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]-1-(2-hydroxyethyl)-1-propan-2-ylurea
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]-1-methyl-1-(oxan-4-yl)urea
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]-1-(1,1-dioxothiolan-3-yl)-1-propylurea
2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]carbamoyl-methylamino]-N-propan-2-ylacetamide
N-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]-2-(ethoxymethyl)pyrrolidine-1-carboxamide
1-[5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-2-methylphenyl]-3-(2-methylaminoethyl)urea
N-[2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]carbamoyl-methylamino]ethyl]acetamide
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]-1-[2-(ethylsulfonylamino)ethyl]-1-methylurea
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-(methylsulfonylmethyl)phenyl]-1-propan-2-ylurea
1-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methylphenyl]-3-propan-2-ylurea
3-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methylsulfanylphenyl]-1-propan-2-ylurea
4-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]carbamoylamino]cyclohexane-1-carboxylic acid
4-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]carbamoylamino]butanoic acid
2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]carbamoylamino]acetic acid
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2,4-dimethylphenyl]-3-(pyridin-2-ylmethyl)urea
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2,4-dimethylphenyl]-1-ethylurea
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2,4-dimethylphenyl]-3-cyclopropylurea
In another embodiment there is provided a compound or compounds selected from one or more of the following compounds labelled as List 2:

3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-1-propan-2-yl-urea;
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-1-ethyl-urea;
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(pyridin-2-ylmethyl)urea;
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2-methoxyethyl)urea;
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-ethyl-phenyl]-3-propan-2-yl-urea;
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(3-methanesulfonamidopropyl) urea;
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[(3S)-1-methylsulfonylpyrrolidin-3-yl]urea;
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-1-[(3S)-1-ethylsulfonylpyrrolidin-3-yl]urea;
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(4-dimethylaminocyclohexyl)urea;
3-(azetidin-3-yl)-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]urea; or
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]-3-[(3,5-difluoropyridin-2-yl)methyl]urea

or a pharmaceutically-acceptable salt thereof.

A compound of the Formula I, or a pharmaceutically-acceptable salt thereof, may be prepared by any process known to be applicable to the preparation of chemically-related
compounds. Such processes, when used to prepare a compound of the formula I are provided as a further feature of the invention and are illustrated by the following representative process variants. Necessary starting materials may be obtained by standard procedures of organic chemistry. The preparation of such starting materials is described in conjunction with the following representative process variants and within the accompanying Examples. Alternatively necessary starting materials are obtainable by analogous procedures to those illustrated that are within the ordinary skill of an organic chemist. Unless otherwise stated R¹, R², R³, R⁴, R⁵, R⁶, R⁶' and R⁷ are as described above.

According to a further aspect, the present invention provides a process for preparing a compound of formula I

![Chemical Structure I](image)

or a pharmaceutically acceptable salt thereof wherein R¹, R², R³, R⁴, R⁵, R⁶', R⁶ and R⁷ are, unless otherwise specified which comprises:

(a) reacting a compound of formula VI

![Chemical Structure VI](image)

with an isocyanate of formula VII

\[ R^1 \cdot N=C=O \]

VII

to give compounds of formula I in which R⁸ is H or

b) reacting a compound of formula VI
with phosgene or an equivalent thereof, for example triphosgene, and then further reacting the intermediate obtained with an amine of formula VIII

VIII

Compounds of formula I may also be prepared by reacting a compound of formula IX

IX

in which X represents a leaving group for example halo, e.g. chloro with a compound of formula X

X

in the presence of a diluent for example a solvent e.g. dichloromethane and optionally in the presence of a base, for example an organic amine e.g. DIPEA, at a temperature in the range of 0-150 °C.

Compounds of formula I may also be prepared by reacting a compound of formula XI
with a compound of formula X optionally in the presence of a coupling agent and optionally in the presence of a diluent for example a solvent at a temperature in the range of 0-150°C.

Compounds of formula I may also be prepared by reacting a compound of formula XII

in which X represents a replaceable group, eg. Cl, Br, I, OMesyl, or OTriflyl with a compound of formula X in the presence of carbon monoxide and in the presence of a metal catalyst, eg. Pd or derivatives thereof, and in a solvent such as an alcohol, THF, toluene, or DMF, and in the temperature range 0 - 150°C. The carbon monoxide may be gaseous or in the form of a metal carbonyl, eg. Molybdenum hexacarbonyl.

Compounds of formula I in which R^b is H may also be prepared by reacting a compound of formula XIII

with a compound of formula XIV
in which X represents a replaceable group, eg. F, Cl, Br, I, O Mesyl, or O Triflyl, in the presence of a metal catalyst, for example Pd (0), Pd (II) or Cu (I), in an organic diluent for example, dioxan, DMF, NMP or DMA at a temperature in the range 0 - 150\(^{0}\)C.

Examples of coupling agents are Dichlorotriphenyl phosphorane (DCTPP), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDAC), O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate (HTBU), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) and 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM).

Examples of optional additives are: 1-hydroxy benzotriazole (HOBt), 4-dimethylamino pyridine (DMAP), di-iso-propylethylamine (DIPEA), and triethylamine (TEA).

Examples of suitable solvents are: dimethyl formamide (DMF), chloroform, dichloromethane (DCM), and tetrahydrofuran (THF).

Certain compounds of formula I may be converted into other compounds of formula I by methods known to those skilled in the art. For example, compounds of formula I

Compounds of formula I in which \(R^1\) represents an optionally substituted pyridyl-\(N\)-oxide may be prepared by reacting a compound of formula I in which \(R^1\) represents an optionally substituted pyridyl with an oxidising agent for example urea hydrogen peroxide or 3-chloroperbenzoic acid, in the presence of a diluent for example dichloromethane or acetonitrile at a temperature in the range of 0-150\(^{0}\)C.

In other processes compounds of formula I containing a sulphide group may be oxidised to \(\text{SO}\) or \(\text{SO}_2\) for example by use of potassium peroxymonosulfate, nitriles may be reduce to aminomethyl compounds, amines may be acylated or sulphonated to give amides or
sulphonamides, respectively, activated heteroaryl halides may be hydrolysed to hydroxy
groups, esters may be hydrolysed to acids, and carboxylic acids may be esterified.
It will be appreciated by those skilled in the art that certain functional groups may require
protection before certain transformations are attempted followed by deprotection after the
particular transformation. Such methods are well known to those skilled in the art and are

Certain intermediates of formula VI are believed to be novel and are herein claimed
as another aspect of the present invention.

**Pharmaceutical preparations**

The compounds of the invention will normally be administered via the oral,
parenteral, intravenous, intramuscular, subcutaneous or in other injectable ways, buccal,
rectal, vaginal, transdermal and/or nasal route and/or via inhalation, in the form of
pharmaceutical preparations comprising the active ingredient or a pharmaceutically
acceptable addition salt, in a pharmaceutically acceptable dosage form. Depending upon
the disorder and patient to be treated and the route of administration, the compositions may
be administered at varying doses.

Suitable daily doses of the compounds of the invention in the therapeutic treatment
of humans are about 0.001-10 mg/kg body weight, preferably 0.01-1 mg/kg body weight.
Oral formulations are preferred particularly tablets or capsules which may be formulated
by methods known to those skilled in the art to provide doses of the active compound in
the range of 0.5mg to 500mg for example 1 mg, 3 mg, 5 mg, 10 mg, 25mg, 50mg, 100mg
and 250mg.

According to a further aspect of the invention there is also provided a
pharmaceutical formulation comprising a compound of formula I, or pharmaceutically
acceptable salt thereof, in admixture with pharmaceutically acceptable adjuvants, diluents
and/or carriers.

**Pharmacological properties**

The compounds of formula (I) are useful for the treatment of obesity or being
overweight, (e.g., promotion of weight loss and maintenance of weight loss), prevention of
weight gain (e.g., medication-induced or subsequent to cessation of smoking), for
modulation of appetite and/or satiety, eating disorders (e.g. binge eating, bulimia and compulsive eating), dyslipidaemia and the treatment of type 2 diabetes mellitus.

The present compounds of formula (I) are useful for the prophylaxis and/or treatment of clinical conditions associated with inherent or induced reduced sensitivity to insulin (insulin resistance) and associated metabolic disorders (also known as the metabolic syndrome). These clinical conditions will include, but will not be limited to, general obesity, abdominal obesity, arterial hypertension, hyperinsulinaemia, hyperglycaemia, type 2 diabetes and the dyslipidaemia characteristically appearing with insulin resistance. This dyslipidaemia, also known as the atherogenic lipoprotein profile, is characterised by moderately elevated non-esterified fatty acids, elevated very low density lipoprotein (VLDL) triglyceride rich particles, high Apo B levels, low high density lipoprotein (HDL) levels associated with low apoAI particle levels and high Apo B levels in the presence of small, dense, low density lipoproteins (LDL) particles, phenotype B.

The compounds of the present invention are expected to be useful in treating patients with combined or mixed hyperlipidemias or various degrees of hypertriglyceridemias and postprandial dyslipidemia with or without other manifestations of the metabolic syndrome.

Treatment with the present compounds is expected to lower the cardiovascular morbidity and mortality associated with atherosclerosis due to their antidyslipidaemic as well as antiinflammatory properties. The cardiovascular disease conditions include macroangiopathies of various internal organs causing myocardial infarction, congestive heart failure, cerebrovascular disease and peripheral arterial insufficiency of the lower extremities. Because of their insulin sensitizing effect the compounds of formula I are also expected to prevent or delay the development of type 2 diabetes from the metabolic syndrome and diabetes of pregnancy. Therefore the development of long-term complications associated with chronic hyperglycaemia in diabetes mellitus, such as the micro-angiopathies causing renal disease, retinal damage and peripheral vascular disease of the lower limbs, is expected to be delayed. Furthermore the compounds may be useful in treatment of various conditions outside the cardiovascular system whether or not associated with insulin resistance, like polycystic ovarian syndrome, obesity, cancer and states of inflammatory disease including neurodegenerative disorders such as mild cognitive impairment, Alzheimer's disease, Parkinson's disease and multiple sclerosis.
The compounds of formula I may also be useful in the treatment of metabolic syndrome and Prader-Willi syndrome.

In another aspect the present invention provides a compound of formula I as previously defined for use as a medicament.

In a further aspect the present invention provides the use of a compound of formula I in the preparation of a medicament for the treatment or prophylaxis of obesity or being overweight, (e.g., promotion of weight loss and maintenance of weight loss), prevention of weight gain (e.g., medication-induced or subsequent to cessation of smoking), for modulation of appetite and/or satiety, eating disorders (e.g. binge eating, bulimia and compulsive eating) and for the treatment or prophylaxis of dyslipidaemia and for the treatment of obesity or being overweight, (e.g., promotion of weight loss and maintenance of weight loss), prevention of weight gain (e.g., medication-induced or subsequent to cessation of smoking), for modulation of appetite and/or satiety, eating disorders (e.g. binge eating, bulimia and compulsive eating) dyslipidaemia and type 2 diabetes mellitus.

In a still further aspect the present invention provides a method of treating obesity or being overweight, (e.g., promotion of weight loss and maintenance of weight loss), prevention of weight gain (e.g., medication-induced or subsequent to cessation of smoking), for modulation of appetite and/or satiety, eating disorders (e.g. binge eating, bulimia and compulsive eating) dyslipidaemia and type 2 diabetes mellitus comprising administering a pharmacologically effective amount of a compound of formula I, to a patient in need thereof.

Combination Therapy

The compounds of the invention may be combined with another therapeutic agent that is useful in the treatment of obesity such as other anti-obesity drugs, that affect energy expenditure, glycolysis, gluconeogenesis, glucogenolysis, lipolysis, lipogenesis, fat absorption, fat storage, fat excretion, hunger and/or satiety and/or craving mechanisms, appetite/motivation, food intake, or G-I motility.

The compounds of the invention may further be combined with another therapeutic agent that is useful in the treatment of disorders associated with obesity such as hypertension, hyperlipidaemias, dyslipidaemias, diabetes, sleep apnea, asthma, heart disorders, atherosclerosis, macro and micro vascular diseases, liver steatosis, cancer, joint disorders, and gallbladder disorders. For example, a compound of the present invention may be used in combination with a another therapeutic agent that lowers blood pressure or that decreases the ratio of LDL:HDL or an agent that causes a decrease in circulating levels of LDL-cholesterol. In patients with diabetes mellitus the compounds of the invention may
also be combined with therapeutic agents used to treat complications related to micro-
angiopathies.

The compounds of the invention may be used alongside other therapies for the
treatment of obesity and its associated complications the metabolic syndrome and type 2
diabetes, these include biguanide drugs, insulin (synthetic insulin analogues) and oral
antihyperglycemics (these are divided into prandial glucose regulators and alpha-
glucosidase inhibitors).

In another aspect of the invention, the compound of formula I, or a
pharmaceutically acceptable salt thereof may be administered in association with a PPAR
modulating agent. PPAR modulating agents include but are not limited to a PPAR alpha
and/or gamma agonist, or pharmaceutically acceptable salts, solvates, solvates of such salts
or prodrugs thereof. Suitable PPAR alpha and/or gamma agonists, pharmaceutically
acceptable salts, solvates, solvates of such salts or prodrugs thereof are well known in the
art.

In addition the combination of the invention may be used in conjunction with a
sulfonylurea. The present invention also includes a compound of the present invention in
combination with a cholesterol-lowering agent. The cholesterol-lowering agents referred to
in this application include but are not limited to inhibitors of HMG-CoA reductase (3-
hydroxy-3-methylglutaryl coenzyme A reductase). Suitably the HMG-CoA reductase
inhibitor is a statin.

In the present application, the term "cholesterol-lowering agent" also includes
chemical modifications of the HMG-CoA reductase inhibitors, such as esters, prodrugs and
metabolites, whether active or inactive.

The present invention also includes a compound of the present invention in
combination with an inhibitor of the ileal bile acid transport system (IBAT inhibitor). The
present invention also includes a compound of the present invention in combination with a
bile acid binding resin.

The present invention also includes a compound of the present invention in
combination with a bile acid sequestering agent, for example colestipol or cholestyramine
or cholestagel.

According to an additional further aspect of the present invention there is provided a
combination treatment comprising the administration of an effective amount of a
compound of the formula I, or a pharmaceutically acceptable salt thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration one or more of the following agents selected from:

- a CETP (cholesteryl ester transfer protein) inhibitor;
- a cholesterol absorption antagonist;
- a MTP (microsomal transfer protein) inhibitor;
- a nicotinic acid derivative, including slow release and combination products;
- a phytosterol compound;
- probucol;
- an anti-coagulant;
- an omega-3 fatty acid;
- another anti-obesity compound for example sibutramine, phentermine, orlistat, bupropion, ephedrine, thyroxine;
- an aldose reductase inhibitor;
- a glycogen phosphorylase inhibitor;
- a glycogen synthase kinase inhibitors;
- a glucokinase activator;
- a haemostasis modulator;
- an antithrombotic;
- an activator of fibrinolysis;
- an antiplatelet agent;
- a thrombin antagonist;
- a factor Xa inhibitor;
- a factor Vila inhibitor;
- an antiplatelet agents;
- a 5 HT transporter inhibitor;
- an antihypertensive compound for example an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor antagonist, an adrenergic blocker, an alpha adrenergic blocker, a beta adrenergic blocker, a mixed alpha/beta adrenergic blocker, an adrenergic stimulant, calcium channel blocker, an AT-I blocker, a saluretic, a diuretic or a vasodilator;
- a melanin concentrating hormone (MCH) modulator;
an NPY receptor modulator; for example an NPY agonist or an NPY2 agonist or an NPY5 antagonist;
an Mc4r modulator for example an Mc4r agonist;
an Mc3r modulator for example an Mc3r agonist;
an orexin receptor modulator for example an antagonist;
a phosphoinositide-dependent protein kinase (PDK) modulator; or
modulators of nuclear receptors for example LXR, FXR, RXR, GR, ERRα, β, PPARα, β, γ, δ and RORalpha;
a monoamine transmission-modulating agent, for example a selective serotonin reuptake inhibitor (SSRI), a noradrenaline reuptake inhibitor (NARI), a noradrenaline-serotonin reuptake inhibitor (SNRI), a monoamine oxidase inhibitor (MAOI), a tricyclic antidepressive agent (TCA), a noradrenergic and specific serotonergic antidepressant (NaSSA);
an antipsychotic agent for example olanzapine and clozapine;
a serotonin receptor modulator;
a leptin/leptin receptor modulator;
a CBl receptor modulator for example an inverse agonist or an antagonist;
a GLK receptor modulator;
a DPP-IV inhibitor;
a cholesterol absorption inhibitor;
a GLP-I agonist;
an SGLT-2 inhibitor;
a DGAT1 inhibitor;
a DGAT2 inhibitor;
a DGAT2 anti-sense oligonucleotide;
a ghrelin antibody;
a ghrelin antagonist;
an 11β HSD-I inhibitor;
an UCP-1,2 or 3 activator;
or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.
According to an additional further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of very low calorie diets (VLCD) or low-calorie diets (LCD).

Therefore in an additional feature of the invention, there is provided a method for the treatment of obesity and its associated complications in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof in simultaneous, sequential or separate administration with an effective amount of a compound from one of the other classes of compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Therefore in an additional feature of the invention, there is provided a method of treating hyperlipidemic conditions in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof in simultaneous, sequential or separate administration with an effective amount of a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula I, or a pharmaceutically acceptable salt thereof, and a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the present invention there is provided a kit comprising a compound of formula I, or a pharmaceutically acceptable salt thereof, and a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.
According to a further aspect of the present invention there is provided a kit comprising:

a) a compound of formula I, or a pharmaceutically acceptable salt thereof, in a first unit dosage form;

b) a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof; in a second unit dosage form; and

c) container means for containing said first and second dosage forms.

According to a further aspect of the present invention there is provided a kit comprising:

a) a compound of formula I, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier, in a first unit dosage form;

b) a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof; in a second unit dosage form; and

c) container means for containing said first and second dosage forms.

According to another feature of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt thereof, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment of obesity and its associated complications in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt thereof, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

According to a further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous,
sequential or separate administration of an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

Furthermore, a compound of the invention may also be combined with therapeutic agents that are useful in the treatment of disorders or conditions associated with obesity (such as type II diabetes, metabolic syndrome, dyslipidemia, impaired glucose tolerance, hypertension, coronary heart disease, non-alcoholic steatohepatitis, osteoarthritis and some cancers) and psychiatric and neurological conditions.

It will be understood that there are medically accepted definitions of obesity and being overweight. A patient may be identified by, for example, measuring body mass index (BMI), which is calculated by dividing weight in kilograms by height in metres squared, and comparing the result with the definitions.

The compounds of the invention may also be useful as anti-cell-proliferation (such as anti-cancer) agents and are therefore useful in methods of treatment of the human or animal body.

Such properties are expected to be of value in the treatment of disease states associated with cell cycle and cell proliferation such as cancers (solid tumors and leukemias), fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi’s sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation.

The anti-cancer treatment defined herein may be applied as a sole therapy or may involve, in addition to the compound of the invention, conventional surgery or radiotherapy or chemotherapy. Such chemotherapy may include one or more of the following categories of anti-tumour agents:

(i) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan and nitrosoureas); antimetabolites (for example antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside and
hydroxyurea); antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin);

(ii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene and idoxofylene), oestrogen receptor down regulators (for example fulvestrant), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprolelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5α-reductase such as finasteride;

(iii) agents which inhibit cancer cell invasion (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function);

(iv) inhibitors of growth factor function, for example such inhibitors include growth factor antibodies, growth factor receptor antibodies (for example the anti-erbb2 antibody trastuzumab [Herceptin™] and the anti-erbbl antibody cetuximab [C225]), farnesyl transferase inhibitors, tyrosine kinase inhibitors and serine/threonine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine, N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033), for example inhibitors of the platelet-derived growth factor family and for example inhibitors of the hepatocyte growth factor family;

(v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, (for example the anti-vascular endothelial cell growth factor antibody bevacizumab [Avastin™], compounds such as those disclosed in International Patent Applications WO 97/22596, WO 97/30035, WO 97/32856 and WO 98/13354) and compounds that work by other mechanisms (for example linomide, inhibitors of integrin αvβ3 function and angiostatin);
vascular damaging agents such as Combretastatin A4 and compounds disclosed in International Patent Applications WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 and WO 02/08213;

(vii) antisense therapies, for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense;

(viii) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; and

(ix) immunotherapy approaches, including for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment. Such combination products employ the compounds of this invention within the dosage range described hereinbefore and the other pharmaceutically-active agent within its approved dosage range.

The compounds of the present invention may also be useful as anti-infective agents or as anti-bacterial agents.

The compounds of the present invention may also be useful as in decreasing sebum production following topical application.

Pharmacological Activity

The compounds of the present invention are Fatty Acid Synthase inhibitors. The activity of the compounds of the invention was demonstrated using the following assay. Human and Rat FAS Enzyme Assay.

Fatty acid synthase is an enzyme complex that harbours seven enzymatic activities catalysing the reductive synthesis of long chain fatty acids from acetyl CoA and malonyl CoA to palmitate. When acetyl CoA and malonyl CoA are forming palmitate NADPH is
consumed forming NADP. Since NADPH is fluorescent but not NADP the reaction can be measured by analysing the decrease in fluorescence.

Compounds were added to a black 384 well plate (Matrix) in a volume of 5µl consisting of 20% DMSO and 80% Tris buffer pH 7.5, at a top concentration of 1mM. NADPH, 30µl of 166.6µM, formulated in assay buffer (0.1M Tris ph7.5, 0.1mM EDTA, 1mM glutathione, 0.05%BSA), was then added to all of the wells of the plate. Fatty acid synthase Human or rat enzyme (0.4µg, produced in house), dissolved in 20mM Tris/HCl pH 7.5, 5mM BOG, 10% TCEP, 10% glycerol, 1mM EDTA, 150mM NaCl, was then added to the plate in a volume of 10µl. Enzyme was added to all but the last two columns of the plate, to which, 10µl of assay buffer was added (0.1M Tris ph7.5, 0.1mM EDTA, 1mM glutathione, 0.05%BSA) to provide a no enzyme assay control. Following a 15-minute incubation period, at room temperature, the plates were read on an Envision plate reader using 340nm excitation and 460nm emission filters. This served as a time zero background read. Substrates (an equal mix of both malonyl and acetyl CoA) were then added to the plates in a total volume of 5µl. The concentrations of malonyl and acetyl CoA in the mixture were 500µM and 150µM respectively. Both were prepared as 10mM stock solutions in distilled water and were subsequently diluted to working concentrations in assay buffer. Plates were then incubated for a further 60 minutes, at room temperature, before being read again on the Envision reader using the same parameters as previously used. The data was analysed by subtracting the background time zero data from that generated following the final 60 minute incubate and the percent inhibition compared to the maximum and minimum assay controls was determined. Sigmoid curves were fitted using Origin 7.5 Client software and IC50 values were determined.

The compounds of the present invention were found to inhibit the activation of human Fatty Acid Synthase with IC50s in a range of about 0.0001 µM to about 0.1µM. The examples of the present invention inhibited the activation of human Fatty Acid Synthase with IC50s in a range of about 0.0001 µM to about 0.1µM. In another embodiment, the compounds inhibit the activation of Fatty Acid Synthase with IC50s in a range of about 0.0001 µM to about 0.1µM.
The results obtained are given in Table 1 in which Ex No stands for Example Number and Inhib (%) stands for the % inhibition at a concentration of 100µmolar.

**Table 1**

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The following compounds do not have IC₅₀ S in the range of about 0.001 µM to about 30 µM in the above assay:

3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]-1,1-dimethylurea
3-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methoxyphenyl]-1-propan-2-ylurea
3-benzyl-1-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methoxyphenyl]urea
Methyl (2S)-2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl] carbamoylamino]-3-methylbutanoate
Methyl (2S)-2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]carbamoylamino]-2-phenylacetate
Methyl 2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]carbamoylamino]-3-(4-fluorophenyl)propanoate
Methyl 2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]carbamoylamino]-4-(tetrazol-1-yl)butanoate
Methyl (2S)-2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]carbamoylamino]-3-(l-methylimidazol-4-yl)propanoate
Ethyl (2S)-2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]carbamoylamino]-3-hydroxypropanoate
3-benzyl-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylsulfonylphenyl]urea
N-[[3α(5)-2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]carbamoylamino]cyclohexyl]acetamide
1-[5-(4-hydroxy-4-phenylpiperidine-1-carbonyl)-2-methylphenyl]-3-propan-2-ylurea
1-[5-[4-(2-methoxyphenyl)piperidine-1-carbonyl]-2-methylphenyl]-3-propan-2-ylurea
1-[5-[4-hydroxy-4-[3-(trifluoromethyl)phenyl]piperidine-1-carbonyl]-2-methylphenyl]-3-propan-2-ylurea
1-[5-[4-(2-fluorophenyl)-4-hydroxypiperidine-1-carbonyl]-2-methylphenyl]-3-propan-2-ylurea
3-[5-[4-(cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]-1-methyl-1-(oxolan-2-ylmethyl)urea
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]-1-(2-methoxyethyl)-1-methylurea
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]-1-(2-cyanopropan-2-yl)-1-methylurea
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]-1-cyclopropyl-1-(1,1-dioxothiolan-3-yl)urea
N-[2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]carbamoyl-
methylamino]ethyl]-2-methylpropanamide
N-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]-1,1-dioxo-1,4-thiazinane-
4-carboxamide

1-[5-[4-(3-fluorophenyl)piperidine-1-carbonyl]-2-methylphenyl]-3-propan-2-ylurea
1-[5-[4-(3-chlorophenyl)piperidine-1-carbonyl]-2-methylphenyl]-3-propan-2-ylurea
1-[5-[4-(3-methoxyphenyl)piperidine-1-carbonyl]-2-methylphenyl]-3-propan-2-ylurea
1-[5-[4-(2-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]-3-propan-2-ylurea
3-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methylsulfonylphenyl]-1-propan-2-ylurea
and
3-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methylsulfonylphenyl]-1-propan-2-
ylurea.

In an alternative embodiment these compounds are excluded from the claims of the present application.

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:
(i) temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25 °C, unless otherwise stated;
(ii) organic solutions were dried over anhydrous magnesium sulfate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals; 4.5-30 mmHg) with a bath temperature of up to 60 °C;
(iii) chromatography means flash chromatography on silica gel; thin layer chromatography (TLC) was carried out on silica gel plates;
(iv) in general, the course of reactions was followed by TLC and / or analytical LC-MS, and reaction times are given for illustration only;
The following methods were used for liquid chromatography (LC) / mass spectral (MS) analysis :
HPLC: Agilent 1100 or Waters Alliance HT (2790 & 2795)
Mass Spectrometer: Waters ZQ ESCi
(v) final products had satisfactory proton nuclear magnetic resonance (NMR) spectra and/or mass spectral data;
(vi) yields are given for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;
(vii) when given, NMR data is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard when the solvent is CDCl₃ (when the solvent is d₆-DMSO, it locks on to the 2.49 DMSO peak), determined at 300 MHz unless otherwise indicated; the following abbreviations have been used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad;
(viii) chemical symbols have their usual meanings; SI units and symbols are used;
(ix) solvent ratios are given in volume:volume (v/v) terms; and
(x) mass spectra (MS) were run with an electron energy of 70 electron volts in the chemical ionization (CI) mode using a direct exposure probe; where indicated ionization was effected by electron impact (EI), fast atom bombardment (FAB) or electrospray (ESP); values for m/z are given; generally, only ions which indicate the parent mass are reported; and unless otherwise stated, the mass ion quoted is MH⁺;
[A] When Cl is present in the molecule, the m/z value for the (M+H)⁺ molecular ion is based on the ³⁵Cl isotope. When there are multiple chlorine atoms in the molecule, the m/z is based on the first peak of the isotope pattern.
[B] When Br is present in the molecule, the m/z value for the (M+H)⁺ and / or (M-H)⁻ molecular ions may be based either on the ⁷⁹Br isotope or the ⁸¹Br isotope. As the isotopes are of approximately equal abundance, in many cases both isotopes are seen in the spectrum, but only one is reported.
(xi) unless stated otherwise compounds containing an asymmetrically substituted carbon and/or sulphur atom have not been resolved;
(xii) where a synthesis is described as being analogous to that described in a previous example the amounts used are the millimolar ratio equivalents to those used in the previous example;
(xvi) the following abbreviations have been used:

<table>
<thead>
<tr>
<th>Abbreviations</th>
<th>Description</th>
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<tr>
<td>ACN</td>
<td>Acetonitrile</td>
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<tr>
<td>DIPEA</td>
<td>Di-wo-propylethylamine</td>
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<td>DMA</td>
<td>Dimethyl acetamide</td>
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</table>
DMAP 4-dimethylamino pyridine
DMTMM 4-(4,6-Dimethoxy-1,3,5-Triazin-2-yl)-4-Methylmorpholinium Chloride
DMSO (dms)dimethyl sulfoxide (in NMR data the solvent is $d_6$-deuterioDMSO)
EDAC N-ethyl-N’-(3-dimethylaminopropyl)-carbodiimide hydrochloride
EtOAc Ethyl acetate
EtOH Ethanol
HATU O-(7-Azabenzotriazol-1-Yl)-N,N,N',N'-Tetramethyluronium Hexafluorophosphate
HOBT 1-Hydroxybenzotriazole
hrs hours
HTBU O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate
MeOH Methanol
mins minutes
TEA Triethylamine
TFAA Trifluoroacetic Anhydride
THF Tetrahydrofuran

Method 1
Example 1
1-butyl-3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]urea

A suspension of 4-[1-(3-amino-4-methyl-benzoyl)-4-piperidyl]benzonitrile (Intermediate A, 200 mg, 0.63mmol) in DCM (5 mL) was treated with n-butyl isocyanate (0.28 mL, 2.5mmol), and the reaction stirred at ambient temperature for 24 hrs. Analysis of the reaction mixture indicated only partial reaction so extra isocyanate was added and stirring was continued; triethylamine (0.1 mL) was also added and stirring for a further 24 hrs. A parallel experiment was carried out on the same scale as the above, using acetonitrile (5 mL) as solvent, and using Microwave heating (10 mins at 100°C, 30 mins at 120°C and 60 mins at 130°C.)
The reaction mixtures from the two experiments were combined and reduced *in vacuo.* EtOAc (30ml) was added and the solution was washed sequentially with water (30ml) and brine (30ml), dried (MgSO$_4$), filtered and reduced *in vacuo* to give a brown oil which was chromatographed (Optix, 12 g silica column, eluting with a gradient consisting of 40-100% EtOAc in isohexane) to give the title compound as a colourless solid (201mg), $^1$H NMR (300.072 MHz, CDCl$_3$) δ 0.93 (3H, t), 1.30 - 1.42 (2H, m), 1.44 - 1.54 (2H, m), 1.57 - 1.99 (4H, m), 2.04 (3H, s), 2.79 - 2.92 (2H, m), 2.99 - 3.13 (IH, m), 3.20 (2H, t), 3.90 - 4.04 (IH, m), 4.74 - 4.95 (IH, m), 5.55 (IH, s), 6.69 (IH, s), 7.07 (2H, m), 7.32 (2H, d), 7.51 (IH, s), 7.60 (2H, d), m/z 419 (M+H)$^+$.

**Method 2**

**Example 2**

N-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]morpholine-4-carboxamide

A suspension of 4-[1-(3-amino-4-methyl-benzoyl)-4-piperidyl]benzonitrile (Intermediate A, 200 mg, 0.63mmol) in THF (15 mL) was blanketed with nitrogen and treated with triphosgene (63 mg, 0.31 mmol, 0.5 eq) and DIPEA (218 µL, 1.25 mmol, 2 eq), and the reaction stirred at ambient temperature for 0.5 hr. Morpholine (274 µL, 3.13 mmol, 5 eq) was added and the reaction mixture stirred for a further four hours. The reaction mixture was then concentrated and the solid residue dissolved in DCM; the suspension was filtered and the filtrate purified by column chromatography (4 g silica column, eluting with a gradient consisting of 0-10% methanol in DCM) to give the title compound as a colourless solid (91 mg), $^1$H NMR (300.073 MHz, d$_6$-DMSO) δ 1.50 - 1.91 (m, 4H), 2.19 (s, 3H), 2.85 - 3.02 (m, 3H), 3.38 - 3.65 (m, 8H), 3.72 - 3.86 (m, IH), 4.42 - 4.78 (m, IH), 7.10 (d, J = 7.7 Hz, IH), 7.23 (d, J = 7.8 Hz, IH), 7.29 (s, IH), 7.50 (d, J = 8.3 Hz, 2H), 7.76 (d, J = 8.3 Hz, 2H), 8.10 (s, IH), m/z 433 (M+H)$^+$.

It will be appreciated that alternative solvents, reagents, additives and conditions may be used in the above reactions. Examples of solvents are THF, DCM, other; examples of
additives are TEA, DIPEA and pyridine, and the reactions may be performed at temperatures between 0°C and the boiling point of the solvent.

The following examples were prepared using the method indicated, and starting from the appropriate intermediate and reagents:

Example 3 3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-1-propan-2-yl-urea

\[
\begin{align*}
\text{Method 1 from Intermediate A} \\
^{1}\text{H NMR (300.072 MHz, CDCl}_3\right) \delta & 1.16 (6H, d), 1.60 - 1.98 (4H, m), 2.01 (3H, s), 2.75 - 2.89 (2H, m), 2.97 - 3.22 (IH, m), 3.85 - 4.07 (2H, m), 4.77 - 4.94 (IH, m), 5.49 (IH, s), 6.71 (IH, s), 6.90 - 7.08 (2H, m), 7.31 (2H, d), 7.53 (IH, s), 7.61 (2H, d), m/z 405 (M+H)^+. 
\end{align*}
\]

Example 4 3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-(trifluoromethoxy)phenyl]-1-propan-2-yl-urea

\[
\begin{align*}
\text{Method 1 from Intermediate B} \\
^{1}\text{H NMR (300.072 MHz, CDCl}_3\right) \delta & 1.21 (6H, d), 1.60 - 1.95 (4H, m), 2.77 - 2.91 (2H, m), 3.10 - 3.26 (IH, m), 3.86 - 4.02 (2H, m), 4.79 - 4.98 (IH, m), 5.05 (IH, d), 6.81 (IH, s), 7.07 - 7.13 (IH, m), 7.22 - 7.25 (IH, m), 7.33 (2H, d), 7.61 (2H, d), 8.29 (IH, s), m/z 475 (M+H)^+. 
\end{align*}
\]

Example 5 3-benzyl-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-(trifluoromethoxy)phenyl]urea

\[
\begin{align*}
\text{Method 1 from Intermediate B} \\
^{1}\text{H NMR (300.072 MHz, CDCl}_3\right) \delta & 1.73 - 2.02 (4H, m), 2.73 - 2.90 (2H, m), 3.02 - 3.26 (IH, m), 3.84 - 3.99 (IH, m), 4.39 (2H, d), 4.70 - 4.88 (IH, m), 5.91 (IH, t), 6.94 - 7.00 (IH, m), 7.11 - 7.17 (IH, m), 7.19 - 7.22 (IH, m), 7.26 - 7.34 (7H, m), 7.60 (2H, d), 8.25 (IH, d), m/z 523 (M+H)^+. 
\end{align*}
\]
Example 6
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methoxy-phenyl]-3-propan-2-yl-urea

Method 1 from Intermediate C

\(^1\)H NMR (300.072 MHz, CDCl\(_3\), 30°C) \(\delta\) 1.21 (6H, \(d, J = 7.9\) Hz), 1.50 - 1.99 (4H, m), range 2.75 - 3.21 (3H, m, br s, br s), 3.87 (3H, s), 3.90 - 4.03 (IH, m), 4.06 - 4.40 (IH, m), 4.50 - 4.98 (IH, m), 6.80 - 6.93 (2H, m), 7.07 - 7.15 (IH, m), 7.33 (2H, \(d, J = 7.9\) Hz), 7.61 (2H, \(d = 8.6\) Hz), 8.20 (IH, \(d = 3.0\) Hz) (NB. Integration is imprecise as spectrum contains signals due to presence of water and also displays extensive peak broadening due to rotational isomerism), m/z 421 (M+H)\(^+\).

Example 7
3-benzyl- 1-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methyl-phenyl]urea

Method 1 from Intermediate D

\(^1\)H NMR (400.132 MHz, CDC\(\text{13}\)) \(\delta\) 1.37 - 1.74 (3H, m), 1.89 - 1.97 (IH, m), 2.14 (3H, d), 2.68 - 2.85 (2H, m), 2.95 - 3.08 (IH, m), 3.54 - 3.63 (IH, m), 4.33 (2H, d), 4.72 - 4.79 (IH, m), 6.02 (IH, t), 6.92 - 7.12 (3H, m), 7.17 - 7.32 (7H, m), 7.58 - 7.70 (3H, m), m/z 453 (M+H)\(^+\).

Example 8
3-benzyl- 1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-fluoro-phenyl]urea

Method 1 from Intermediate E

\(^1\)H NMR (400.132 MHz, d\(_6\)-DMSO) \(\delta\) 1.47 - 1.94 (m, 4H), 2.76 - 3.26 (m, 3H), 3.62 - 3.85 (m, IH), 4.32 (d, 2H), 4.48 - 4.74 (m, IH), 6.98 - 7.06 (m, IH), 7.13 (t, IH), 7.21 - 7.39 (m, 6H), 7.51 (d, 2H), 7.78 (d, 2H), 8.21 - 8.29 (m, IH), 8.56 (d, IH), m/z 457 (M+H)\(^+\).
Example 9
3-benzyl-L-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methoxy-phenyl]urea

\[
\text{Method 1 from Intermediate C}
\]

\[^1\text{H NMR (300.073 MHz, d\textsubscript{6}-DMSO, 30° C) } \delta 1.49 - 1.70 (2H, m), 1.71 - 1.88 (2H, m), 2.79 - 3.19 (3H, m), 3.87 (3H, s), 3.93 - 4.21 (IH, m), 4.29 (2H, d, J = 5.6 Hz), 4.35 - 4.98 (IH, m), 6.94 - 7.04 (2H, m), 7.18 - 7.38 (6H, m), 7.49 (2H, d, J = 7.1 Hz), 7.75 (2H, d, J = 7.9 Hz), 8.11 (IH, s), 8.22 (IH, s) (NB. Integration is imprecise as spectrum displays extensive peak broadening due to rotational isomerism), m/z 469 (M+H)^{+}.\]

Example 10
N-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]pyrroldine-1-carboxamide

\[
\text{Method 2 from Intermediate A}
\]

\[^1\text{H NMR (300.073 MHz, d\textsubscript{6}-DMSO) } \delta 1.54 - 1.71 (m, 2H), 1.79 - 1.95 (m, 6H), 2.25 (s, 3H), 2.88 - 3.10 (m, 3H), 3.36 - 3.46 (m, 4H), 4.15 - 4.31 (m, 2H), 7.04 (d, J = 7.6 Hz, IH), 7.16 - 7.28 (m, 2H), 7.44 - 7.58 (m, 3H), 7.71 (d, J = 8.3 Hz, 2H), m/z 417 (M+H)^{+}.\]

Example 11
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-fluoro-phenyl]-1-propan-2-yl-urea

\[
\text{Method 1 from Intermediate E}
\]

\[^1\text{H NMR (300.073 MHz, d\textsubscript{6}-DMSO) } \delta 1.09 (d, 6H), 1.44 - 1.94 (m, 4H), 2.77 - 3.30 (m, 3H), 3.67 - 3.90 (m, 2H), 4.34 - 4.82 (m, IH), 6.51 - 6.64 (m, IH), 6.93 - 7.05 (m, IH), 7.22 (t, IH), 7.50 (d, 2H), 7.76 (d, 2H), 8.18 - 8.38 (m, 2H), m/z 409 (M+H)^{+}.\]
Example 1
3-benzyl-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2,4-dimethyl-phenyl]urea

Method 1 from Intermediate F

$^1$H NMR (300.072 MHz, CDCl$_3$) $\delta$ 1.65 (2H, m), 1.93 (IH, m), 2.06 (3H, s), 2.19 - 2.26 (3H, m), 2.77 (2H, m), 3.06 (IH, m), 3.67 (IH, m), 4.42 (2H, m), 4.84 (IH, m), 5.40 (IH, m), 6.35 (IH, m), 6.94 (IH, s), 7.31 (7H, s), 7.59 - 7.62 (2H, d), m/z 467 (M+H)$^+$. 

Example 1
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2,4-dimethyl-phenyl]-1-propan-2-yl-urea

Method 1 from Intermediate F

$^1$H NMR (300.072 MHz, CDCl$_3$) $\delta$ 1.13 - 1.16 (6H, m), 1.73 (2H, m), 1.98 - 2.05 (IH, m), 2.08 (3H, s), 2.25 (3H, d), 2.84 (2H, m), 3.13 (IH, m), 3.71 (IH, d), 3.92 - 3.99 (IH, m), 4.94 (2H, m), 6.11 - 6.22 (IH, m), 6.95 (IH, s), 7.31 (2H, d), 7.61 (2H, d), m/z 419 (M+H)$^+$. 

Example 1
5-1-benzyl-3-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]phenyl]urea

Method 1 from Intermediate I

$^1$H NMR (300.073 MHz, dmso, 30°C) $\delta$ 1.48 - 1.97 (4H, m), 2.69 - 3.25 (3H, m), 3.60 - 3.90 (IH, m), 4.29 (2H, dJ = 5.3 Hz), 4.48 - 4.76 (IH, m), 6.60 - 6.70 (IH, m), 6.94 (IH, dJ = 6.7 Hz), 7.18 - 7.42 (7H, m), 7.45 - 7.56 (3H, m), 7.76 (2H, dJ = 8.0 Hz), 8.67 (IH, s), m/z 439 (M+H)$^+$. 

Example 1
5-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-1-phenyl]-3-cyclopentyl-1-urea
Example 16

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-phenethyl-urea

Method 2 from Intermediate A

$^1$H NMR (300.072 MHz, CDCl$_3$) $\delta$ 1.35 - 1.45 (2H, m), 1.53 - 2.01 (13H, m), 2.79 - 3.20 (3H, m), 3.90 - 4.12 (2H, m), 4.85 (IH, m), 5.64 (IH, d), 6.71 (IH, s), 6.90 - 6.94 (IH, m), 7.03 (IH, d), 7.32 (2H, d), 7.54 (IH, s), 7.60 (2H, d), m/z 431 (M+H)$^+$. 

Example 17

3-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methyl-phenyl]-1-methyl-urea

Method 2 from Intermediate A

$^1$H NMR (300.072 MHz, CDCl$_3$) $\delta$ 1.49 - 1.82 (IH, m), 1.33 - 1.38 (IH, m), 1.55 - 2.00 (7H, m), 2.00 (3H, s), 2.80 - 2.88 (2H, m), 3.10 (3H, t), 3.34 (IH, d), 3.38 (IH, d), 3.94 - 3.98 (3H, m), 4.84 (IH, m), 5.86 (IH, t), 6.79 (IH, s), 6.90 - 6.93 (IH, m), 7.02 (IH, d), 7.31 (2H, d), 7.50 (IH, d), 7.61 (2H, d), m/z 461 (M+H)$^+$. 

Example 18

3-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methyl-phenyl]-1-methyl-urea

Method 1 from Intermediate D

$^1$H NMR (400.132 MHz, CDCl$_3$) $\delta$ 1.49 - 1.82 (m, 3H), 1.97 - 2.03 (m, IH), 2.24 (d, 3H), 2.75 (d, 3H), 2.79 - 2.93 (m, 2H), 3.04 - 3.14 (m, IH), 3.62 - 3.69 (m, IH), 4.88 - 4.99 (m,
Example 1
93-[3-[(4-cyanophenyl)piperidine-1-carbonyl]-4-methyl-phenyl]-1-ethyl-urea

\[
\begin{align*}
\text{Method 1 from Intermediate D} \\
{^1}\text{H NMR (400.132 MHz, CDCl}_3 \delta 1.1 (t, 3H), 1.48 - 1.81 (m, 3H), 1.97 - 2.03 (m, IH), 2.24 (d, 3H), 2.79 - 2.92 (m, 2H), 3.04 - 3.15 (m, IH), 3.19 - 3.25 (m, 2H), 3.62 - 3.68 (m, IH), 4.92 - 4.99 (m, IH), 5.39 (s, IH), 6.96 (d, IH), 7.06 (d, IH), 7.15 (d, IH), 7.21 (t, IH), 7.31 (d, 2H), 7.62 (d, 2H), m/z 377 (M+H)^{+}.}
\end{align*}
\]

Example 2
21-butyl-3-[(4-cyanophenyl)piperidine-1-carbonyl]-4-methyl-phenyl]urea

\[
\begin{align*}
\text{Method 1 from Intermediate D} \\
{^1}\text{H NMR (400.132 MHz, CDCl}_3 \delta 0.90 (t, 3H), 1.32 (sextet, 2H), 1.43 (quintet, 2H), 1.53 - 1.80 (m, 3H), 1.95 - 2.01 (m, IH), 2.22 (d, 3H), 2.78 - 2.92 (m, 2H), 3.04 - 3.18 (m, 3H), 3.60 - 3.66 (m, IH), 4.91 - 4.97 (m, IH), 5.64 (t, IH), 6.98 - 7.18 (m, 3H), 7.31 (d, 2H), 7.52 - 7.63 (m, 3H), m/z 419 (M+H)^{+}.}
\end{align*}
\]

Example 21
1-[3-[(4-cyanophenyl)piperidine-1-carbonyl]-methyl-phenyl]-S-cyclopentyl-urea

\[
\begin{align*}
\text{Method 1 from Intermediate D} \\
{^1}\text{H NMR (400.132 MHz, CDCl}_3 \delta 1.30 - 1.39 (m, 2H), 1.49 - 1.81 (m, 7H), 1.87 - 1.96 (m, 2H), 1.99 - 2.03 (m, IH), 2.23 (d, 3H), 2.78 - 2.92 (m, 2H), 3.02 - 3.13 (m, IH), 3.61 - 3.68 (m, IH), 4.00 - 4.08 (m, IH), 4.89 - 4.94 (m, IH), 5.65 (s, IH), 6.91 - 7.04 (m, 2H), 7.08 - 7.21 (m, IH), 7.31 (d, 2H), 7.42 (d, IH), 7.61 (d, 2H), m/z 431 (M+H)^{+}.}
\end{align*}
\]

Example 22
3-[2-cyano-5-[(4-cyanophenyl)piperidine-1-carbonyl]-phenyl]-1-propan-2-yl-urea
Method 2 from Intermediate G

$^1$H NMR (400.132 MHz, CDCl$_3$) $\delta$ 1.22 (d, 6H), 1.69 - 1.84 (m, 3H), 1.95 - 2.03 (m, IH), 2.80 - 2.93 (m, 2H), 3.15 - 3.25 (m, IH), 3.81 - 3.89 (m, IH), 3.97 (octet, IH), 4.84 - 4.93 (m, IH), 5.32 (d, IH), 7.07 - 7.10 (m, IH), 7.24 (s, IH), 7.33 (d, 2H), 7.51 (d, IH), 7.62 (d, 2H), 8.30 (d, IH), m/z 416 (M+H)$^+$. 

Example 23
1-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methyl-phenyl]-3-[2-fluorophenyl)methyl]urea

Method 2 from Intermediate D

$^1$H NMR (300.072 MHz, cdcl3) $\delta$ 1.45 - 1.80 (m, 3H), 1.91 - 1.99 (m, IH), 2.16 (d, 3H), 2.72 - 2.87 (m, 2H), 3.00 - 3.12 (m, IH), 3.57 - 3.66 (m, IH), 4.41 (d, 2H), 4.82 - 4.89 (m, IH), 5.91 - 5.97 (m, IH), 6.87 - 7.08 (m, 4H), 7.11 - 7.23 (m, 2H), 7.27 - 7.36 (m, 3H), 7.49 - 7.63 (m, 3H), m/z 471 (M+H)$^+$. 

Example 24
1-benzy 1-3-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methyl-phenyl]-1-methyl-urea

Method 2 from Intermediate D

$^1$H NMR (300.072 MHz, CDCl$_3$) $\delta$ 1.62 - 1.82 (m, 3H), 1.93 - 2.02 (m, IH), 2.27 (d, 3H), 2.75 - 2.91 (m, 2H), 3.02 (s, 3H), 3.06 - 3.12 (m, IH), 3.66 - 3.72 (m, IH), 4.53 - 4.60 (m, 2H), 4.90 - 4.99 (m, IH), 6.41 (s, IH), 7.09 - 7.14 (m, 2H), 7.27 - 7.39 (m, 8H), 7.60 (d, 2H), m/z 467 (M+H)$^+$. 

Example 25
1-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methyl-phenyl]-3-(pyridin-3-ylmethyl)urea
Method 2 from Intermediate D

$^1$H NMR (300.072 MHz, CDCl$_3$) $\delta$ 1.48 - 1.82 (m, 3H), 1.91 - 2.00 (m, IH), 2.17 (d, 3H), 2.73 - 2.87 (m, 2H), 3.00 - 3.13 (m, IH), 3.57 - 3.66 (m, IH), 4.38 (d, 2H), 4.79 - 4.86 (m, IH), 5.99 - 6.09 (m, IH), 6.90 - 7.06 (m, 2H), 7.15 - 7.34 (m, 4H), 7.51 (d, IH), 7.60 - 7.67 (m, 3H), 8.45 - 8.55 (m, 2H), m/z 454 (M+H)$^+$.  

Example 26
1-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methyl-phenyl]-3-phenethyl-urea

$^1$H NMR (300.072 MHz, CDCl$_3$) $\delta$ 1.42 - 1.69 (m, 3H), 1.91 - 2.00 (m, IH), 2.19 (d, 3H), 2.74 - 2.85 (m, 4H), 2.97 - 3.12 (m, IH), 3.37 - 3.46 (m, 2H), 3.57 - 3.65 (m, IH), 4.77 - 4.87 (m, IH), 5.44 (s, IH), 6.91 - 7.07 (m, 3H), 7.16 - 7.31 (m, 8H), 7.60 (d, 2H), m/z 467 (M+H)$^+$.  

Example 27
1-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methyl-phenyl]-3-(oxan-4-ylmethyl)urea

$^1$H NMR (300.072 MHz, CDCl$_3$) $\delta$ 1.21-1.37 (m, 3H), 1.42 - 1.85 (m, 3H), 1.91 - 2.01 (m, IH), 2.23 (d, 3H), 2.77 - 2.90 (m, 2H), 3.03 - 3.18 (m, 3H), 3.30-3.40 (m, 2H), 3.63 - 3.67 (m, IH), 3.91-3.98 (dd, 2H), 4.90 - 4.99 (m, IH), 5.62 (s, IH), 6.96 (d, IH), 7.03 (d, IH), 7.10 - 7.27 (m, 2H), 7.30 (d, 2H), 7.61 (d, 2H), m/z 461 (M+H)$^+$.  

Example 28
N-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methyl-phenyl]morpholine-4-carboxamide
Method 2 from Intermediate D

\[ ^1 \text{H NMR (300.072 MHz, CDCl}_3) \delta 1.63 - 1.82 (m, 3H), 1.91 - 2.01 (m, IH), 2.26 (d, 3H), 2.77 - 2.90 (m, 2H), 3.03 - 3.15 (m, IH), 3.47 (t, 4H), 3.63 - 3.67 (m, IH), 3.71 (t, 4H), 4.90 - 4.99 (m, IH), 6.82 (s, IH), 7.11 (d, IH), 7.17 - 7.22 (m, IH), 7.27 - 7.34 (m, 3H), 7.61 (d, 2H), m/z 432 (M+H)^+ . \]

Example 29

N-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methyl-phenyl]pyrrolidine-1-carboxamide

Method 2 from Intermediate D

\[ ^1 \text{H NMR (300.072 MHz, CDCl}_3) \delta 1.45 - 1.81 (m, 3H), 1.92 - 2.00 (m, 5H), 2.27 (d, 3H), 2.77 - 2.88 (m, 2H), 3.03 - 3.15 (m, IH), 3.39 - 3.49 (m, 4H), 3.65 - 3.75 (m, IH), 4.91 - 5.00 (m, IH), 6.23 (s, IH), 7.11 (d, IH), 7.23 - 7.37 (m, 4H), 7.60 (d, 2H), m/z 417 (M+H)^+ . \]

Example 30

3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-tert-butyl-urea

Method 2 from Intermediate A

\[ ^1 \text{H NMR (300.072 MHz, CDCl}_3) \delta 1.05 - 1.11 (3H, m), 1.14 - 1.67 (3H, m), 2.03 (4H, d), 2.79 - 2.88 (2H, m), 3.11 - 3.18 (IH, m), 3.20 - 3.22 (2H, m), 3.95 (IH, m), 4.85 (IH, m), 5.77 (IH, s), 6.91 - 6.94 (2H, m), 7.03 (IH, d), 7.31 (2H, d), 7.58 (2H, q), 7.61 (IH, s), m/z 391 (M+H)^+ . \]

Example 31

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-tert-butyl-urea
Method 2 from Intermediate A

\(^1\)H NMR (300.072 MHz, CDCl\(_3\)) \(\delta\) 1.35 (9H, s), 1.66 - 1.90 (4H, m), 1.96 (3H, s), 2.79 - 2.88 (2H, m), 3.10 (IH, m), 3.95 (IH, m), 4.85 (IH, m), 5.74 (IH, s), 6.81 - 6.85 (IH, m), 6.86 (IH, s), 6.96 (IH, d), 7.31 - 7.34 (2H, m), 7.57 - 7.59 (2H, m), 7.61 (IH, s), m/z 419 (M+H)\(^+\).

Example 32

3-benzyl- 1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]urea

Method 2 from Intermediate A

\(^1\)H NMR (300.072 MHz, CDCl\(_3\)) \(\delta\) 1.50 - 1.90 (4H, m), 1.97 (3H, s), 2.68 - 2.81 (2H, m), 3.05 (IH, s), 3.90 (IH, s), 4.34 (2H, d), 4.69 (IH, s), 6.21 (IH, t), 6.85 - 6.89 (IH, m), 6.98 (IH, d), 7.07 - 7.11 (IH, m), 7.16 - 7.28 (7H, m), 7.56 (IH, s), 7.58 (2H, t), m/z 453 (M+H)\(^+\).

Example 33

3-[(4-cyanophenyl)methyl]- 1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]urea

Method 2 from Intermediate A

\(^1\)H NMR (300.072 MHz, CDCl\(_3\)) \(\delta\) 1.76 - 1.97 (4H, m), 1.98 (3H, s), 2.78 - 2.82 (2H, m), 3.11 (IH, s), 3.92 (IH, m), 4.42 (2H, d), 4.74 (IH, m), 6.51 (IH, t), 6.86 - 6.89 (IH, m), 7.00 (IH, d), 7.12 (IH, d), 7.26 - 7.30 (2H, m), 7.37 (2H, d), 7.55 - 7.61 (5H, m), m/z 478 (M+H)\(^+\).

Example 34

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[(2-fluorophenyl)methyl]urea
Method 2 from Intermediate A

1H NMR (300.072 MHz, CDCl₃) δ 1.74 - 1.90 (4H, m), 1.96 (3H, s), 2.70 - 2.86 (2H, m), 3.02 - 3.08 (IH, m), 3.91 (IH, s), 4.39 (2H, d), 4.75 (IH, s), 6.29 (IH, t), 6.85 - 7.10 (4H, m), 7.12 - 7.21 (2H, m), 7.29 - 7.35 (3H, m), 7.50 - 7.60 (IH, m), 7.55 - 7.58 (2H, m), m/z 471 (M+H)+.

Example 3

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(pyridin-3-ylmethyl)urea

Method 2 from Intermediate A

1H NMR (300.072 MHz, CDCl₃) δ 1.50 - 1.99 (4H, m), 1.99 (3H, s), 2.77 - 2.81 (2H, m), 2.84 (IH, t), 3.11 (IH, s), 3.92 (IH, s), 4.38 (2H, d), 4.74 (IH, s), 6.45 (IH, t), 6.87 - 6.90 (IH, m), 7.02 (IH, t), 7.12 (IH, d), 7.21 - 7.25 (IH, m), 7.30 (3H, d), 7.51 - 7.67 (4H, m), 8.45 - 8.47 (IH, m), 8.51 - 8.52 (IH, m), m/z 454 (M+H)+.

Example 36

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(pyridin-4-ylmethyl)urea

Method 2 from Intermediate A

1H NMR (300.072 MHz, CDCl₃) δ 1.61 (2H, s), 1.75 - 1.91 (4H, m), 2.02 (4H, m), 2.77 - 2.85 (2H, m), 2.99 (IH, d), 3.11 (IH, s), 3.92 (IH, s), 4.36 (2H, d), 4.76 (IH, s), 6.66 (IH, t), 6.88 - 6.91 (IH, m), 7.01 (IH, d), 7.18 (2H, q), 7.29 (IH, d), 7.33 (IH, s), 7.57 - 7.60 (2H, m), 7.70 (IH, d), 8.47 - 8.49 (2H, m), m/z 454 (M+H)+.

Example 37

3-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methyl-phenyl]-1-[(1R)-1-phenylethyl]urea
Method 2 from Intermediate D

$^1$H NMR (300.072 MHz, CDCl$_3$) δ 1.44 (3H, d), 1.48 - 1.78 (3H, m), 1.87 - 2.00 (IH, m), 2.09 - 2.27 (3H, m), 2.73 - 2.84 (2H, m), 2.96 - 3.09 (IH, m), 3.58 - 3.62 (IH, m), 4.77 - 4.95 (2H, m), 5.69 - 5.84 (IH, m), 6.82 - 7.05 (2H, m), 7.15 - 7.35 (9H, m), 7.61 (2H, d), m/z 467 M+H$^+$.

Example 38

3-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methy-1-phenyl]-1-[(1S)-1-phenylethyl]urea

Method 2 from Intermediate D

$^1$H NMR (300.072 MHz, CDCl$_3$) δ 1.15 (d, 6H), 1.47 - 1.83 (m, 3H), 1.83 - 2.00 (m, IH), 2.08 - 2.26 (m, 3H), 2.64 - 2.87 (m, 2H), 2.93 - 3.11 (m, IH), 3.53 - 3.65 (m, IH), 4.75 - 4.99 (m, 2H), 5.86 - 5.94 (m, IH), 6.84 - 7.05 (m, 2H), 7.17 - 7.42 (m, 9H), 7.61 (d, 2H), m/z 474 M+H$^+$ and 476 M+H$^+$.

Example 39

1-[5-[4-(4-bromophenyl)-4-hydroxy-piperidine-1-carbonyl]-2-methyl-phenyl]-3-propan-2-yl-urea

Method 2 from Intermediate H

$^1$H NMR (300.072 MHz, CDCl$_3$) δ 1.15 (d, 6H), 1.45 - 1.56 (m, IH), 1.76 - 1.90 (m, 3H), 1.96 (s, 3H), 3.04 (s, IH), 3.17 - 3.31 (m, 2H), 3.40 - 3.51 (m, IH), 3.89 (octet, IH), 4.47 - 4.60 (m, IH), 5.73 (d, IH), 6.85 (d, IH), 6.95 - 7.00 (m, 2H), 7.35 (d, 2H), 7.46 (d, 3H), m/z 474 and 476 M+H$^+$ [B].
Example 40
3-benzyl-l-[5-[4-(4-bromophenyl)-4-hydroxy-piperidine-1-carbonyl]-2-methyl-phenyl]urea

Method 2 from Intermediate H

1H NMR (300.072 MHz, CDCl$_3$) δ 1.41 - 1.51 (m, 1H), 1.67 - 1.83 (m, 3H), 1.88 (s, 3H), 2.97 (s, IH), 3.06 - 3.24 (m, 2H), 3.32 - 3.45 (m, 1H), 4.25 (d, 2H), 4.35 - 4.44 (m, 1H), 6.26 (t, IH), 6.79 - 6.82 (m, IH), 6.94 (d, IH), 7.18 - 7.33 (m, 8H), 7.44 (d, 3H), m/z 522 and 524 (M+H)$^+$ [B].

Example 41
3-(1-benzyl-4-piperidyl)-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]urea

Method 2 from Intermediate A

1H NMR (300.072 MHz, CDCl$_3$) δ 0.86 - 0.93 (6H, m), 1.62 - 1.79 (4H, m), 1.87 (IH, s), 2.02 (3H, d), 2.79 - 2.87 (2H, m), 2.92 - 2.96 (IH, m), 3.02 (2H, t), 3.95 (IH, m), 4.60 - 4.84 (IH, m), 5.83 (IH, t), 6.90 - 6.93 (IH, m), 6.93 (IH, d), 7.02 (IH, d), 7.31 (2H, d), 7.54 - 7.62 (3H, m), m/z 419 (M+H)$^+$.

Example 42
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2-methylpropyl)urea

Method 2 from Intermediate A

1H NMR (300.072 MHz, CDCl$_3$) δ 0.86 - 0.93 (6H, m), 1.62 - 1.79 (4H, m), 1.87 (IH, s), 2.02 (3H, d), 2.79 - 2.87 (2H, m), 2.92 - 2.96 (IH, m), 3.02 (2H, t), 3.95 (IH, m), 4.60 - 4.84 (IH, m), 5.83 (IH, t), 6.90 - 6.93 (IH, m), 6.93 (IH, d), 7.02 (IH, d), 7.31 (2H, d), 7.54 - 7.62 (3H, m), m/z 419 (M+H)$^+$.
Example 43
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-prop-2-ynyl-urea

Method 2 from Intermediate A

\(^1\)H NMR (300.072 MHz, CDCl\(_3\)) \(\delta 1.50 - 2.00\) (4H, m), 2.00 (3H, s), 2.20 (IH, m), 2.84 - 3.20 (3H, m), 3.96 - 3.99 (3H, m), 4.86 (IH, s), 6.12 (IH, t), 6.93 - 6.96 (IH, m), 7.03 (IH, d), 7.17 (IH, s), 7.32 (2H, d), 7.54 - 7.59 (2H, m), 7.61 (IH, s), m/z 401 (M+H)\(^+\).

Example 44
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[(3,4,5-trimethoxyphenyl)methyl]urea

Method 2 from Intermediate A

\(^1\)H NMR (300.072 MHz, CDCl\(_3\)) \(\delta 1.50 - 2.04\) (4H, m), 2.04 (3H, s), 2.77 - 3.10 (3H, m), 3.80 - 3.83 (9H, m), 3.95 (IH, m), 4.26 - 4.33 (2H, m), 4.70 (IH, m), 6.07 (IH, t), 6.53 - 6.54 (2H, m), 6.90 - 6.93 (IH, m), 6.97 (IH, s), 7.02 - 7.10 (IH, m), 7.30 (2H, d), 7.59 (2H, d), 7.60 (IH, s), m/z 543 (M+H)\(^+\).

Example 45
methyl 3-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]propanoate

Method 2 from Intermediate A

\(^1\)H NMR (300.072 MHz, CDCl\(_3\)) \(\delta 1.50 - 2.04\) (4H, m), 2.04 (3H, d), 2.48 - 2.58 (2H, m), 2.80 - 3.20 (3H, m), 3.41 - 3.48 (2H, m), 3.68 (3H, s), 3.95 (IH, m), 4.88 (IH, s), 5.99 (IH, t), 6.92 - 6.95 (IH, m), 7.04 (2H, d), 7.32 (2H, d), 7.46 - 7.52 (IH, m), 7.58 - 7.61 (2H, m), m/z 449 (M+H)\(^+\).

Example 46
3-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]phenyl]l-propan-2-yl-urea
Method 2 from Intermediate I

$^1$H NMR (300.073 MHz, de-DMSO, 300°C) δ 1.09 (6H, d J = 6.1 Hz), 1.48 - 1.95 (4H, m), 2.69 - 3.22 (3H, m), 3.63 - 3.84 (2H, m), 4.43 - 4.75 (IH, m), 6.03 (IH, d J = 6.8 Hz), 6.92 (IH, d J = 7.5 Hz), 7.21 - 7.38 (2H, m), 7.45 - 7.54 (3H, m), 7.76 (2H, d J = 9.6 Hz), 8.41 (IH, s), m/z 391 (M+H)$^+$. 

Example 47

3-[(3-cyanophenyl)methyl]-1-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methyl-phenyl]urea

Method 2 from Intermediate D

$^1$H NMR (300.072 MHz, CDCl$_3$) δ 1.46 - 1.83 (m, 3H), 1.94 - 2.00 (m, IH), 2.19 (d, 3H), 2.76 - 2.93 (m, 2H), 3.03 - 3.19 (m, IH), 3.60 - 3.66 (m, IH), 4.38 (d, 2H), 4.82 - 4.90 (m, IH), 6.15 - 6.25 (m, IH), 6.90 - 7.07 (m, 2H), 7.13 - 7.24 (m, IH), 7.30 (d, 2H), 7.41 (d, IH), 7.50 - 7.62 (m, 6H), m/z 478 (M+H)$^+$. 

Example 48

1-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methyl-phenyl]-3-c/s-(4-hydroxycyclohexyl)urea

Method 2 from Intermediate D

$^1$H NMR (300.072 MHz, CDCl$_3$) δ 1.55 - 1.83 (m, HH), 1.96 - 2.01 (m, IH), 2.11 (s, IH), 2.25 (d, 3H), 2.79 - 2.91 (m, 2H), 3.03 - 3.20 (m, IH), 3.62 - 3.77 (m, 2H), 3.83 - 3.88 (m, IH), 4.91 - 4.99 (m, IH), 5.44 - 5.51 (m, IH), 7.04 - 7.20 (m, 3H), 7.31 (d, 2H), 7.41 (s, IH), 7.61 (d, 2H)(probably cis), m/z 461 (M+H)$^+$. 
Example 49
1-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methyl-phenyl]-3-5-(4-hydroxycyclohexyl)urea

Method 2 from Intermediate D

$^1$H NMR (300.072 MHz, CDCl$_3$) δ 1.04 - 2.02 (m, 13H), 2.24 (d, 3H), 2.76 - 2.93 (m, 2H), 3.05 - 3.15 (m, IH), 3.61 - 3.67 (m, IH), 4.88 - 4.97 (m, IH), 5.33 - 5.40 (m, IH), 7.02 - 7.18 (m, 3H), 7.29 - 7.34 (m, 2H), 7.39 (s, IH), 7.61 (d, 2H) (probably trans), m/z 461 (M+H)$^+$. 

Example 50
1-[5-[4-(4-cyanophenyl)-4-hydroxy-piperidine-1-carbonyl]-2-methyl-phenyl]-3-propan-2-yl-urea

Method 2 from Intermediate J

$^1$H NMR (300.072 MHz, CDCl$_3$) δ 1.14 (d, 6H), 1.42 - 1.54 (m, IH), 1.75 - 1.85 (m, 3H), 1.94 (s, 3H), 3.10 - 3.24 (m, 2H), 3.34 - 3.43 (m, IH), 3.80 (s, IH), 3.85 - 3.89 (m, IH), 4.47 - 4.61 (m, IH), 5.88 (d, IH), 6.82 (d, IH), 6.98 (d, IH), 7.12 (s, IH), 7.51 (s, IH), 7.57 - 7.64 (m, 4H), m/z 421 (M+H)$^+$. 

Example 51
tert-butyl 4-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoyl amino] butanoate

Method 2 from Intermediate A

$^1$H NMR (300.072 MHz, CDCl$_3$) δ 1.72 - 2.04 (9H, m), 2.29 (2H, t), 2.83 (IH, m), 3.20 (4H, m), 3.95 (IH, m), 4.85 (IH, m), 5.78 (IH, s), 6.88 (IH, s), 6.92 - 6.96 (IH, m), 7.05 (IH, d), 7.30 - 7.33 (2H, m), 7.52 (IH, d), 7.58 - 7.61 (2H, m), m/z 505 (M+H)$^+$. 
Example 5

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(pyridin-2-
ylmethyl)urea

Method 2 from Intermediate A

$^1$H NMR (300.072 MHz, CDCl$_3$) $\delta$ 1.55 - 2.00 (4H, m), 2.04 - 2.09 (3H, m), 2.77 - 3.20
(3H, m), 4.00 (IH, m), 4.51 (2H, d), 4.85 (IH, m), 6.58 (IH, t), 6.95 - 6.98 (IH, m), 7.04 (IH, d), 7.12 - 7.16 (IH, m), 7.30 (3H, d), 7.48 (IH, s), 7.57 - 7.60 (2H, m), 7.62 - 7.65 (IH, m), 7.69 (IH, d), 8.46 - 8.48 (IH, m), m/z 454 (M+H)$^+$. 

Example 5

3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-1-pentan-3-yl-urea

Method 2 from Intermediate A

$^1$H NMR (300.072 MHz, CDCl$_3$) $\delta$ 0.90 (6H, t), 1.44 - 2.00 (HH, m), 2.82 (2H, t), 3.10 (IH, m), 3.60 (IH, m), 3.94 (IH, m), 4.83 (IH, m), 5.55 - 5.58 (IH, d), 6.90 (2H, d), 7.00 (IH, d), 7.31 (2H, d), 7.51 (IH, d), 7.59 (2H, d), m/z 433 (M+H)$^+$. 

Example 5

3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-1-[3-(3-
methylphenyl)methyl]urea

Method 2 from Intermediate A

$^1$H NMR (300.072 MHz, CDCl$_3$) $\delta$ 0.90 (6H, t), 1.44 - 2.00 (IH, m), 2.82 (2H, t), 3.10 (IH, m), 3.60 (IH, m), 3.94 (IH, m), 4.83 (IH, m), 5.55 - 5.58 (IH, d), 6.90 (2H, d), 7.00 (IH, d), 7.31 (2H, d), 7.51 (IH, d), 7.59 (2H, d), m/z 467 (M+H)$^+$. 

Example 5

N-[2-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-
phenyl]carbamoylamino]ethyl]acetamide
Method 2 from Intermediate A

1H NMR (300.072 MHz, CDCl₃) δ 0.50 - 2.00 (7H, m), 2.02 (3H, s), 2.70 - 3.22 (3H, m), 3.20 (4H, m), 3.94 (IH, m), 4.75 (IH, m), 6.38 (IH, m), 6.84 - 6.87 (IH, m), 7.01 (IH, t), 7.11 (IH, s), 7.27 (3H, m), 7.53 (2H, d), 7.73 - 7.78 (IH, m), m/z 448 (M+H)⁺.

Example 56
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[(3,4-difluorophenyl)methyl]urea

Method 2 from Intermediate A

1H NMR (300.072 MHz, CDCl₃) δ 1.50 - 2.00 (7H, m), 2.02 (3H, s), 2.70 - 3.22 (3H, m), 3.20 (4H, m), 3.94 (IH, m), 4.75 (IH, m), 6.38 (IH, m), 6.84 - 6.87 (IH, m), 7.01 (IH, t), 7.11 (IH, s), 7.27 (3H, m), 7.53 (2H, d), 7.73 - 7.78 (IH, m), m/z 489 (M+H)⁺.

Example 57
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[(2-(4-sulfamoylphenyl)ethyl]urea

Method 2 from Intermediate A

1H NMR (400.132 MHz, d₆-DMSO) δ 1.47 - 1.96 (m, 4H), 2.18 (s, 3H), 2.84 (t, 2H), 2.88 - 3.24 (m, 3H), 3.35 - 3.44 (m, 2H), 3.67 - 3.88 (m, 1H), 4.50 - 4.73 (m, 1H), 6.67 (t, 1H), 6.89 - 6.97 (m, 1H), 7.18 (d, 1H), 7.32 (s, 2H), 7.44 (d, 2H), 7.51 (d, 2H), 7.73 - 7.81 (m, 5H), 7.96 (s, 1H), m/z 546 (M+H)⁺.

Example 58
2-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]acetamide
Example 59
3-(1-anilino-2-methyl-propan-2-yl)-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]urea

\[
\text{Method 2 from Intermediate A}
\]

\(^1\text{H NMR (300.072 MHz, CDCl}_3) \delta \ 0.50 - 2.20 (7H, m), 2.73 (2H, m), 3.02 (IH, m), 3.53 - 3.62 (2H, m), 3.72 (2H, s), 3.80 - 6.67 (IH, m), 6.85 (IH, d), 7.00 (2H, t), 7.22 (3H, d), 7.48 (2H, d), 7.82 (IH, s), 8.08 - 10.77 (2H, m), m/z 420 (M+H)^+.

Example 60
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2-pyridin-2-yethyl)urea

\[
\text{Method 2 from Intermediate A}
\]

\(^1\text{H NMR (400.132 MHz, de-DMSO) \delta 1.54 - 2.02 (m, 4H), 2.23 (s, 3H), 2.82 - 3.28 (m, 5H), 3.55 (q, 2H), 3.75 - 3.96 (m, IH), 4.58 - 4.78 (m, IH), 6.74 (t, IH), 6.95 - 7.01 (m, IH), 7.23 (d, IH), 7.26 - 7.33 (m, IH), 7.35 (d, IH), 7.57 (d, 2H), 7.75 - 7.81 (m, IH), 7.84 (d, 3H), 8.01 (s, IH), 8.56 - 8.61 (m, IH), m/z 468 (M+H)^+.

Example 61
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[2-(2-methoxyphenyl)ethyl]urea

\[
\text{Method 2 from Intermediate A}
\]
Method 2 from Intermediate A

$^1$H NMR (400.132 MHz, DMSO) $\delta$ 1.49 - 1.95 (m, 4H), 2.19 (s, 3H), 2.73 (t, 2H), 2.78 - 3.21 (m, 3H), 3.25 - 3.33 (m, 2H), 3.65 - 3.88 (m, 4H), 4.51 - 4.73 (m, 1H), 6.63 (t, 1H), 6.85 - 7.00 (m, 3H), 7.12 - 7.26 (m, 3H), 7.51 (d, 2H), 7.71 (s, 1H), 7.78 (d, 2H), 7.97 (s, 1H), m/z 497 (M+H)$^+$. 

Example 62
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2-pyridin-4-ylethyl)urea

Method 2 from Intermediate A

$^1$H NMR (400.132 MHz, de-DMSO) $\delta$ 1.46 - 1.96 (m, 4H), 2.18 (s, 3H), 2.78 (t, 2H), 2.82 - 3.25 (m, 3H), 3.40 (q, 2H), 3.67 - 3.89 (m, 1H), 4.49 - 4.74 (m, 1H), 6.66 (t, 1H), 6.90 - 6.97 (m, 1H), 7.18 (d, 1H), 7.28 (d, 2H), 7.51 (d, 2H), 7.77 (t, 3H), 7.94 (s, 1H), 8.49 (d, 2H), m/z 468 (M+H)$^+$. 

Example 63
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2-thiophen-2-ylethyl)urea

Method 2 from Intermediate A

$^1$H NMR (400.132 MHz, de-DMSO) $\delta$ 1.48 - 1.95 (m, 4H), 2.20 (s, 3H), 2.71 - 3.25 (m, 5H), 3.29 - 3.42 (m, 2H), 3.67 - 3.90 (m, 1H), 4.49 - 4.74 (m, 1H), 6.75 (t, 1H), 6.89 - 7.00 (m, 3H), 7.18 (d, 1H), 7.33 - 7.39 (m, 1H), 7.51 (d, 2H), 7.77 (d, 2H), 7.82 (s, 1H), 7.96 (s, 1H), m/z 473 (M+H)$^+$. 
Example 64

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[2-(4-methoxyphenyl)ethyl]urea

Method 2 from Intermediate A

$^1$H NMR (400.132 MHz, d$_6$-DMSO) $\delta$ 1.47 - 1.95 (m, 4H), 2.19 (s, 3H), 2.62 - 2.72 (m, 2H), 2.73 - 3.20 (m, 3H), 3.22 - 3.33 (m, 2H), 3.65 - 3.92 (m, 4H), 4.51 - 4.76 (m, 1H), 6.62 (t, 1H), 6.81 - 6.96 (m, 4H), 7.09 - 7.21 (m, 4H), 7.51 (d, 2H), 7.71 - 7.84 (m, 2H), 7.93 - 8.00 (m, 1H) Some base line imps.; m/z 497 (M+H)$^+$. 

Example 65

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[2-(3-methoxyphenyl)ethyl]urea

Method 2 from Intermediate A

$^1$H NMR (400.132 MHz, de-DMSO) $\delta$ 1.49 - 1.95 (m, 4H), 2.18 (s, 3H), 2.73 (t, 2H), 2.78 - 3.24 (m, 3H), 3.27 - 3.33 (m, 2H), 3.67 - 3.87 (m, 4H), 4.52 - 4.74 (m, 1H), 6.64 (t, 1H), 6.73 - 6.85 (m, 3H), 6.93 (d, 1H), 7.14 - 7.26 (m, 2H), 7.51 (d, 2H), 7.78 (d, 3H), 7.93 - 8.02 (m, 1H), m/z 497 (M+H)$^+$. 

Example 66

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2-pyridin-3-ylethyl)urea

Method 2 from Intermediate A
**Example 67**

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[2-(3,5-dimethyl-1,2-oxazol-4-yl)ethyl]urea

Method 2 from Intermediate A

1H NMR (400.132 MHz, d<sub>6</sub>-DMSO) δ 1.46 - 1.94 (m, 4H), 2.18 (s, 3H), 2.64 - 3.27 (m, 5H), 3.35 - 3.43 (m, 2H), 3.66 - 3.93 (m, IH), 4.48 - 4.75 (m, IH), 6.66 (t, IH), 6.93 (d, IH), 7.18 (d, IH), 7.31 - 7.38 (m, IH), 7.51 (d, 2H), 7.68 (d, IH), 7.72 - 7.82 (m, 3H), 7.93 (s, IH), 8.39 - 8.50 (m, 2H), m/z 468 (M+H)+.

**Example 68**

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[2-(3,5-dimethyl-1,2-oxazol-4-yl)ethyl]urea

Method 2 from Intermediate A

1H NMR (400.132 MHz, d<sub>6</sub>-DMSO) δ 2.16 (s, 3H), 2.19 (s, 3H), 2.29 (s, 3H), 2.46 (t, 2H), 2.71 - 3.27 (m, 5H), 3.69 - 3.88 (m, IH), 4.53 - 4.72 (m, IH), 6.62 (t, IH), 6.90 - 6.97 (m, IH), 7.18 (d, IH), 7.51 (d, 2H), 7.73 - 7.81 (m, 3H), 7.89 - 7.95 (m, IH), m/z 486 (M+H)+.

**Example 69**

tert-buty 1N-[4-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]butyl]carbamate

1H NMR (400.132 MHz, d<sub>6</sub>-DMSO) δ 1.49 - 1.94 (m, 4H), 2.18 (s, 3H), 2.78 (t, 2H), 2.82 - 3.25 (m, 3H), 3.30 - 3.42 (m, 2H), 3.68 - 3.91 (m, IH), 4.52 - 4.73 (m, IH), 6.65 (t, IH), 6.89 - 6.96 (m, IH), 7.00 - 7.13 (m, 3H), 7.18 (d, IH), 7.31 - 7.40 (m, IH), 7.51 (d, 2H), 7.72 - 7.81 (m, 3H), 7.92 - 7.98 (m, IH), m/z 485 (M+H)+.
Method 2 from Intermediate A

$^1$H NMR (300.072 MHz, CDCl$_3$) $\delta$ 1.37 (4H, s), 1.44 (9H, s), 1.65 - 1.68 (2H, m), 1.97 (2H, s), 2.14 (3H, s), 2.84 (2H, t), 3.01 - 3.03 (4H, m), 4.00 (IH, m), 4.85 (IH, m), 5.02 (IH, s), 5.29 (3H, s), 6.05 (IH, s), 6.94 - 6.97 (IH, m), 7.10 (IH, d), 7.32 (3H, m), 7.59 (2H, d), 7.83 (IH, s), m/z 534 (M+H)$^+$.  

**Example 70**

(RS)-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[1-(IH-indol-3-yl)propan-2-yl]urea

Method 2 from Intermediate A

$^1$H NMR (300.072 MHz, CDCl$_3$) $\delta$ 1.25 - 1.95 (1OH, m), 2.85 - 3.20 (3H, m), 3.40 (IH, m), 3.75 (IH, m), 4.38 (2H, m), 4.70 (IH, m), 5.71 (IH, d), 6.62 - 7.60 (13H, m), 9.88 (IH, s), m/z 520 (M+H)$^+$.  

**Example 71**

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2,2-dimethylpropyl)urea

Method 2 from Intermediate A

$^1$H NMR (300.072 MHz, CDCl$_3$) $\delta$ 0.92 (9H, s), 1.50 - 1.98 (7H, m), 2.79 - 2.87 (2H, m), 3.01 (2H, d), 3.00 - 3.20 (IH, m), 3.95 (IH, m), 4.85 (IH, m), 5.88 (IH, t), 6.87 - 6.90 (IH, m), 7.00 (2H, d), 7.31 (2H, d), 7.50 (IH, d), 7.60 (2H, d), m/z 433 (M+H)$^+$.  

**Example 72**

Methyl 2-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]acetate

Method 2 from Intermediate A

$^1$H NMR (300.072 MHz, CDCl$_3$) $\delta$ 0.92 (9H, s), 1.50 - 1.98 (7H, m), 2.79 - 2.87 (2H, m), 3.01 (2H, d), 3.00 - 3.20 (IH, m), 3.95 (IH, m), 4.85 (IH, m), 5.88 (IH, t), 6.87 - 6.90 (IH, m), 7.00 (2H, d), 7.31 (2H, d), 7.50 (IH, d), 7.60 (2H, d), m/z 433 (M+H)$^+$.  

**Example 72**

Methyl 2-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]acetate
Method 2 from Intermediate A

\[ ^1H \text{NMR } (300.072 \text{ MHz, CDCl}_3) \delta 1.50 - 2.00 \ (4H, \text{ m}), 2.04 \ (3H, \text{ s}), 2.74 - 2.83 \ (1H, \text{ m}), 2.83 - 2.87 \ (1H, \text{ m}), 3.11 \ (3H, \text{ s}), 3.72 \ (3H, \text{ s}), 3.92 - 3.99 \ (3H, \text{ m}), 4.90 \ (1H, \text{ m}), 6.17 \ (1H, \text{ t}), 6.96 - 6.99 \ (1H, \text{ m}), 7.04 \ (1H, \text{ d}), 7.32 \ (3H, \text{ m}), 7.54 - 7.61 \ (3H, \text{ m}), \text{ m/z 435 (M+H)}^+. \]

Example 73

(2S)-2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-1-phenylcarbamoylamino]-4-methyl-pentanamide

Method 2 from Intermediate A

\[ ^1H \text{NMR } (300.072 \text{ MHz, CDCl}_3) \delta 0.91 - 0.94 \ (6H, \text{ m}), 1.48 - 1.58 \ (1H, \text{ m}), 1.62 - 1.68 \ (2H, \text{ m}), 1.72 - 1.83 \ (3H, \text{ m}), 2.05 \ (3H, \text{ s}), 2.81 - 2.85 \ (2H, \text{ m}), 3.09 \ (1H, \text{ s}), 3.90 \ (1H, \text{ m}), 4.40 - 4.48 \ (1H, \text{ m}), 4.84 \ (1H, \text{ s}), 6.77 \ (1H, \text{ d}), 6.85 \ (2H, \text{ d}), 6.98 \ (1H, \text{ d}), 7.31 \ (3H, \text{ d}), 7.58 \ (3H, \text{ d}), 7.76 \ (1H, \text{ s}), \text{ m/z 476 (M+H)}^+. \]

Example 74

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(3-pyrrolidin-1-ylpropyl)urea

Method 2 from Intermediate A

\[ ^1H \text{NMR } (300.072 \text{ MHz, CDCl}_3) \delta 1.60 - 2.10 \ (10H, \text{ m}), 2.14 \ (3H, \text{ s}), 2.47 - 2.60 \ (6H, \text{ m}), 2.84 - 3.20 \ (3H, \text{ m}), 3.29 \ (2H, \text{ t}), 4.00 \ (1H, \text{ m}), 4.85 \ (1H, \text{ m}), 6.00 \ (1H, \text{ m}), 6.99 - 7.11 \ (3H, \text{ m}), 7.31 - 7.33 \ (2H, \text{ m}), 7.59 - 7.62 \ (3H, \text{ m}), \text{ m/z 474 (M+H)}^+. \]

Example 75

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[[4-(thiadiazol-4-yl)phenyl]methyl]urea
Method 2 from Intermediate A

$^1$H NMR (300.072 MHz, CDCl$_3$) δ 1.50 - 2.00 (4H, m), 2.00 (3H, s), 2.75 (2H, m), 3.07 (IH, m), 3.92 (IH, s), 4.40 (2H, d), 4.74 (IH, m), 6.43 (IH, t), 6.89 - 6.92 (IH, m), 7.01 (IH, d), 7.23 - 7.27 (3H, m), 7.35 (2H, d), 7.54 (2H, d), 7.68 (IH, d), 7.91 (2H, d), 8.63 (IH, s), m/z 537 (M+H)$^+$. 

Example 76
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[2-(3,5-dimethylpyrazol-1-yl)ethyl]urea

Method 2 from Intermediate A

$^1$H NMR (300.072 MHz, CDCl$_3$) δ 1.28 - 1.32 (1OH, m), 1.50 - 2.00 (4H, m), 2.05 - 2.22 (9H, m), 2.80 - 3.20 (3H, m), 3.53 (IH, q), 4.07 (3H, m), 4.85 (IH, m), 5.77 (IH, s), 6.05 (IH, t), 6.98 - 7.01 (IH, m), 7.11 (IH, d), 7.33 (3H, d), 7.61 (3H, d), m/z 485 (M+H)$^+$. 

Example 77
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2,2-dimethyloxan-4-yl)urea

Method 2 from Intermediate A

$^1$H NMR (300.072 MHz, CDCl$_3$) δ 1.18 - 1.32 (1OH, m), 1.50 - 2.00 (4H, m), 2.01 (3H, s), 2.81 - 3.20 (3H, m), 3.66 - 3.79 (2H, m), 3.95 - 4.02 (IH, m), 5.69 (IH, d), 6.86 (IH, s), 6.90 - 6.93 (IH, m), 7.03 (IH, d), 7.31 - 7.34 (2H, m), 7.54 (IH, d), 7.59 - 7.62 (2H, m), m/z 475 (M+H)$^+$. 

Example 78
(2S)-2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]-3-[(2-methylpropan-2-yl)oxy]propanamide
Method 2 from Intermediate A

1H NMR (300.072 MHz, CDCl₃) δ 1.20 (9H, s), 1.50 - 2.00 (4H, m), 2.11 (3H, s), 2.83 - 3.20 (3H, m), 3.45 (IH, m), 3.79 - 3.83 (IH, m), 3.95 (IH, m), 4.43 - 4.46 (IH, m), 4.85 (IH, m), 6.43 (IH, s), 6.60 (IH, d), 6.93 - 6.97 (2H, m), 7.04 (IH, d), 7.32 (2H, d), 7.60 (2H, d), 7.69 (IH, s), 7.75 (IH, s), m/z 506 (M+H)⁺.

Example 79

3-[[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-1-(1-propyl-4-piperidyl)urea

Method 2 from Intermediate A

1H NMR (300.072 MHz, CDCl₃) δ 0.83 - 0.94 (4H, m), 1.04 (3H, t), 1.40 - 2.10 (1OH, m), 2.23 - 2.35 (2H, m), 2.42 (IH, s), 2.81 (4H, m), 3.06 (IH, m), 3.65 (IH, m), 3.95 (IH, m), 4.85 (IH, m), 5.74 (IH, d), 6.89 - 6.92 (IH, m), 6.94 (IH, s), 7.02 (IH, d), 7.32 (2H, d), 7.52 (IH, d), 7.60 (2H, d), m/z 488 (M+H)⁺.

Example 80

1-[[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[(1,1-dioxothiolan-3-yl)methyl]urea

Method 2 from Intermediate A

1H NMR (300.072 MHz, CDCl₃) δ 1.55 - 2.10 (8H, m), 2.30 (IH, m), 2.60 - 3.40 (1OH, m), 3.98 (IH, m), 4.85 (IH, m), 6.39 (IH, t), 6.93 (2H, d), 7.08 (IH, d), 7.33 (2H, d), 7.61 (2H, d), 7.67 (IH, d), m/z 495 (M+H)⁺.

Example 81

Benzyl N-[[5-[[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-1-phenyl]carbamoylamino] ethyl]carbamate
Example 82
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(1 H-tetrazol-5-ylmethyl)urea

\[ \text{Method 2 from Intermediate A} \]
\[ \text{H NMR (300.072 MHz, CDCl}_3) \delta 1.50 - 2.00 (7H, m), 2.74 \text{ - 3.20 (3H, m), 3.29 (4H, s),} \]
\[ 3.95 (IH, m), 4.80 (IH, m), 5.07 (2H, s), 5.75 (IH, s), 6.15 (IH, s), 6.85 (IH, d), 6.92 (IH, d), 7.02 (IH, d), 7.26 - 7.30 (7H, m), 7.58 (2H, d), 7.62 (IH, s), m/z 540 (M+H)^+. \]

Example 83
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[2-((2-methoxyphenoxy)ethyl)urea

\[ \text{Method 2 from Intermediate A} \]
\[ \text{H NMR (300.072 MHz, CDCl}_3) \delta 1.42 (3H, d), 1.50 - 2.00 (7H, m), 2.75 \text{ - 3.20 (3H, m),} \]
\[ 3.74 (3H, s), 3.92 (IH, s), 4.75 \text{ - 4.81 (IH, m), 4.85 (IH, t), 6.04 (IH, d), 6.80 \text{ - 6.88 (4H, m),} \]
\[ 6.97 \text{ - 6.99 (IH, m), 7.23 (IH, d), 7.26 \text{ - 7.30 (3H, m), 7.57 \text{ - 7.60 (3H, m), m/z 497 (M+H)^+}.} \]

Example 84
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-1-phenyl]-3-[(1R)-1-(4-methoxyphenyl)ethyl]urea

\[ \text{Method 2 from Intermediate A} \]
\[ \text{H NMR (300.072 MHz, CDCl}_3) \delta 1.42 (3H, d), 1.50 \text{ - 2.00 (7H, m), 2.75 \text{ - 3.20 (3H, m),} \]
\[ 3.74 (3H, s), 3.92 (IH, s), 4.75 \text{ - 4.81 (IH, m), 4.85 (IH, t), 6.04 (IH, d), 6.80 \text{ - 6.88 (4H, m),} \]
\[ 6.97 \text{ - 6.99 (IH, m), 7.23 (IH, d), 7.26 \text{ - 7.30 (3H, m), 7.57 \text{ - 7.60 (3H, m), m/z 497 (M+H)^+.} \]
Example 85
3-[(3-aminophenyl)methyl]-L-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]urea

\[
\begin{align*}
&\text{Method 2 from Intermediate A} \\
&^1H \text{ NMR (300.072 MHz, CDCl}_3\text{) } \delta 1.40 - 1.90 (4H, m), 1.97 (3H, d), 2.67 - 2.75 (2H, m), \\
&3.05 (IH, s), 3.89 (IH, m), 4.30 (2H, d), 4.68 (IH, m), 6.18 - 7.75 (13H, m), m/z 468 (M+H)^+. \\
\end{align*}
\]

Example 86
3-[2-(benzenesulfonamido)ethyl]-L-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]urea

\[
\begin{align*}
&\text{Method 2 from Intermediate A} \\
&^1H \text{ NMR (300.072 MHz, CDCl}_3\text{) } \delta 1.73 (2H, s), 1.86 (2H, d), 1.94 (3H, s), 2.79 - 2.91 (2H, m), \\
&2.96 - 3.01 (3H, m), 3.25 (2H, m), 3.94 - 4.00 (IH, m), 4.87 (IH, d), 6.46 (IH, t), 6.55 (IH, t), 6.84 - 6.87 (IH, m), 6.97 (IH, d), 7.16 (IH, s), 7.33 (2H, d), 7.45 - 7.48 (2H, m), \\
&7.52 (2H, d), 7.53 (IH, d), 7.83 - 7.87 (3H, m), m/z 546 (M+H)^+. \\
\end{align*}
\]

Example 87
L-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[2-[(4-nitrophenyl)amino]ethyl]urea

\[
\begin{align*}
&\text{Method 2 from Intermediate A} \\
&^1H \text{ NMR (300.072 MHz, CDCl}_3\text{) } \delta 1.50 - 2.00 (7H, m), 2.63 (IH, m), 2.77 (IH, m), 3.00 (IH, m), 3.37 (2H, d), 3.51 - 3.55 (2H, m), 3.93 (IH, d), 4.70 (IH, d), 6.33 (IH, t), 6.52 \\
\end{align*}
\]
(IH, t), 6.56 - 6.61 (2H, m), 6.80 - 6.83 (IH, m), 6.94 - 6.96 (2H, m), 7.30 (2H, d), 7.59 (2H, d), 7.86 (IH, d), 7.98 - 8.02 (2H, m), m/z 527 (M+H)^+.

Example 88
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[1-(4-fluorophenyl)ethyl]urea

\[
\text{Method 2 from Intermediate A}
\]

\(^1\)H NMR (300.072 MHz, CDCl\(_3\)) \(\delta 1.41 - 1.49 (3H, d), 1.50 - 2.00 (7H, m), 2.77 - 2.81 (2H, m), 3.09 (IH, m), 3.88 (IH, m), 4.73 - 4.80 (IH, m), 4.86 - 4.95 (IH, m), 5.99 (IH, d), 6.73 (IH, s), 6.86 - 6.89 (IH, m), 6.93 - 7.00 (3H, m), 7.28 (IH, s), 7.30 - 7.32 (3H, m), 7.52 (IH, d), 7.59 - 7.61 (2H, m), m/z 485 (M+H)^+.

Example 89
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(3-furylmethyl)urea

\[
\text{Method 2 from Intermediate A}
\]

\(^1\)H NMR (300.072 MHz, CDCl\(_3\)) \(\delta 1.50 - 2.02 (7H, m), 2.78 - 3.20 (3H, m), 3.95 (IH, m), 4.24 (2H, d), 4.80 (IH, m), 5.82 (IH, t), 6.39 - 6.40 (IH, m), 6.82 (IH, s), 6.90 - 6.93 (IH, m), 7.02 (IH, d), 7.29 (IH, s), 7.32 - 7.38 (3H, m), 7.51 (IH, d), 7.59 - 7.62 (2H, m), m/z 443 (M+H)^+.

Example 90
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2-hydroxyethyl)urea

\[
\text{Method 2 from Intermediate A}
\]

\(^1\)H NMR (300.072 MHz, CDCl\(_3\)) \(\delta 1.60 - 2.02 (7H, m), 2.80 - 2.88 (2H, m), 3.13 (IH, m), 3.35 (2H, q), 3.70 (2H, t), 3.96 (IH, m), 4.82 - 4.88 (IH, m), 6.20 (IH, t), 6.89 - 6.92 (IH, m), 7.02 (IH, d), 7.11 (IH, s), 7.33 (2H, d), 7.60 (2H, d), 7.74 (IH, d), m/z 407 (M+H)^+.

Example 91
N-[2-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]ethyl]pyridine-2-carboxamide
**Example 92**

1-[[5-[[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]-2-methyl-propyl]pyridine-3-carboxamide

**Method 2 from Intermediate A**

$^1$H NMR (300.072 MHz, CDCl$_3$) δ 1.36 (6H, s), 1.40 - 2.00 (7H, m), 2.81 (2H, m), 2.98 (IH, m), 3.73 (2H, d), 3.90 - 3.96 (IH, m), 4.83 (IH, d), 6.14 (IH, s), 6.79 - 6.82 (IH, m), 6.91 - 6.95 (2H, m), 7.21 (2H, d), 7.25 - 7.30 (IH, m), 7.57 (2H, d), 7.78 (IH, d), 8.31 - 8.35 (IH, m), 8.57 - 8.59 (IH, m), 8.95 (IH, t), 9.21 (IH, d), m/z 539 (M+H)$^+$. 

**Example 93**

N-[2-[[5-[[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]-2-methyl-propyl]pyridine-3-carboxamide

**Method 2 from Intermediate A**

$^1$H NMR (300.072 MHz, CDCl$_3$) δ 1.50 - 2.00 (4H, m), 2.10 (3H, s), 2.78 - 3.20 (3H, m), 3.47 (2H, q), 3.54 - 3.66 (2H, m), 4.00 (IH, m), 5.95 (IH, t), 6.84 (IH, s), 6.99 - 7.03 (IH, m), 7.10 (IH, d), 7.31 (2H, d), 7.37 - 7.42 (IH, m), 7.60 (3H, d), 7.78 - 7.84 (IH, m), 8.11 - 8.15 (IH, m), 8.41 (IH, t), 8.52 - 8.57 (IH, m), m/z 511 (M+H)$^+$. 

**Example 94**

3-[2-amino-5,6-dimethyl-pyrimidin-4-yl]amino|ethyl|l-[5-[[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]urea

**Method 2 from Intermediate A**

$^1$H NMR (300.072 MHz, CDCl$_3$) δ 1.60 - 2.04 (7H, m), 2.80 (8H, m), 3.20 - 3.26 (3H, m), 3.38 (2H, q), 3.98 (IH, m), 4.90 (IH, m), 5.93 (IH, t), 6.33 (IH, t), 6.87 (IH, d), 6.96 - 7.00 (2H, m), 7.35 (2H, d), 7.60 (2H, d), 7.78 (IH, s), m/z 513 (M+H)$^+$. 

Example 95

Example 96
Method 2 from Intermediate A

$^1$H NMR (300.072 MHz, CDCl$_3$) $^\delta$ 1.43 - 2.05 (7H, m), 2.61 - 3.20 (5H, m), 3.43 - 3.55 (2H, m), 6.87 - 7.00 (4H, m), 6.97 - 7.31 (3H, m), 7.51 - 7.60 (3H, d), 7.60 - 8.00 (2H, m), 8.22 (IH, s), m/z 524 (M+H)$^+$.

Example 95

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(3-methylbut-2-enyl)urea

Method 2 from Intermediate A

$^1$H NMR (300.072 MHz, CDCl$_3$) $^\delta$ 1.50 - 2.05 (7H, m), 2.06 (3H, s), 2.18 (3H, s), 2.79 - 3.20 (3H, m), 3.43 - 3.55 (4H, m), 3.95 (IH, m), 4.63 (2H, s), 4.85 (IH, m), 5.47 (IH, t), 6.14 (IH, t), 6.81 (IH, s), 6.95 - 6.98 (IH, m), 7.05 (IH, d), 7.31 (2H, d), 7.61 (3H, d), m/z 527 (M+H)$^+$.

Example 96

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(3-methylbut-2-enyl)urea

Method 2 from Intermediate A

$^1$H NMR (300.072 MHz, CDCl$_3$) $^\delta$ 1.50 - 2.04 (13H, m), 2.79 - 2.87 (2H, m), 3.09 - 3.14 (IH, m), 3.80 - 4.82 (2H, m), 3.95 (IH, m), 4.85 (IH, m), 5.17 - 5.22 (IH, m), 5.57 (IH, t), 6.86 (IH, s), 6.93 - 6.96 (IH, m), 7.04 (IH, d), 7.32 (2H, d), 7.57 (IH, d), 7.60 (2H, d), m/z 431 (M+H)$^+$.

Example 97

tert-butyl 3-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]carbamoylamino] azetidine-1-carboxylate
Method 2 from Intermediate A

$^1$H NMR (300.072 MHz, CDCl$_3$) $\delta$ 1.44 (9H, d), 1.50 - 2.00 (7H, s), 2.85 - 3.25 (3H, m), 3.70 - 3.75 (2H, m), 3.95 (IH, m), 4.22 (2H, m), 4.49 (IH, m), 4.85 (IH, m), 6.51 (IH, d), 6.95 (2H, d), 7.05 - 7.07 (IH, m), 7.33 (2H, d), 7.52 - 7.52 (IH, m), 7.61 (2H, d), m/z 516 (M-H)$^+$. 

Example 98

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[1-(4-methylsulfonylphenyl)ethyl]urea

Method 2 from Intermediate A

$^1$H NMR (300.073 MHz, DMSO-d$_6$) $\delta$ 1.50 - 1.90 (4H, m), 2.23 (3H, s), 2.70 - 3.40 (5H, m), 3.60 - 4.00 (IH, m), 4.35 - 4.80 (2H, m), 6.91 - 6.94 (IH, m), 7.15 - 7.20 (3H, m), 7.46 (2H, d), 7.71 (2H, d), 7.97 (IH, d), 8.14 (2H, m), 10.55 (IH, s), m/z 509 (M+H)$^+$. 

Example 99

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2-oxo-3,4-dihydro-1H-1,7-naphthyridin-3-yl)urea
Example 100
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[3-(3-methyl-1-piperidyl)propyl]urea

Method 2 from Intermediate A

$^1$H NMR (300.072 MHz, CDCl$_3$) $\delta$ 0.84 (4H, m), 1.41 - 2.00 (9H, m), 2.12 (3H, s), 2.39 (3H, m), 2.79 (3H, d), 2.85 (2H, t), 3.23 - 3.29 (2H, m), 4.00 (IH, m), 4.85 (IH, s), 6.16 (IH, m), 6.89 (IH, s), 6.98 - 7.01 (IH, m), 7.09 (IH, d), 7.32 (2H, d), 7.59 - 7.63 (3H, m), m/z 502 (M+H)$^+$. 

Example 101
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[2-[(4-methoxyphenyl)amino]ethyl]urea

Method 2 from Intermediate A

$^1$H NMR (300.072 MHz, CDCl$_3$) $\delta$ 1.50 - 2.00 (7H, m), 2.77 - 3.30 (5H, m), 3.41 - 3.48 (2H, m), 3.70 (3H, s), 3.95 (IH, m), 4.76 (IH, d), 6.13 (IH, t), 6.51 - 6.65 (3H, m), 6.72 - 6.75 (3H, m), 6.87 - 7.00 (3H, m), 7.29 (IH, d), 7.58 (2H, d), 7.65 (IH, d), m/z 512 (M+H)$^+$. 

Example 102
tert-butyl N-[2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]ethyl]carbamate

Method 2 from Intermediate A

$^1$H NMR (300.072 MHz, CDCl$_3$) $\delta$ 1.42 (s, 9H), 1.62 - 2.01 (m, 4H), 2.05 (s, 3H), 2.78 - 2.93 (m, 2H), 3.06 - 3.15 (m, IH), 3.24 (t, 2H), 3.29 (t, 2H), 3.89 - 4.06 (m, IH), 4.78 -
4.97 (m, IH), 5.21 (s, IH), 5.92 (s, IH), 6.81 (s, IH), 6.94 - 7.11 (m, 2H), 7.33 (d, 2H), 7.56 - 7.63 (m, 3H), m/z 506 (M+H)^+.

**Example 103**

3-(2-aminoethyl)-L-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]urea

![Chemical Structure](image)

**Method 3**

A solution of tert-butyl N-[2-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino] ethylcarbamate (Example 102) (3.5 g, 6.92 mmol) in DCM (35 mL) was treated with hydrogen chloride (35 mL of a saturated solution in EtOAc), and the reaction stirred at ambient temperature for 2 hrs. The reaction mixture was reduced in vacuo and the residue triturated with ether. The residue was dried in vacuo to give the title compound as a white solid (3.05 g). \(^1\)H NMR (300.073 MHz, d\(_6\)-DMSO) \(\delta\) 1.47 - 1.83 (m, 4H), 2.24 (s, 3H), 2.82 - 2.98 (m, 4H), 3.03 - 3.12 (m, IH), 3.32 - 3.42 (m, 2H), 3.68 - 3.89 (m, IH), 4.21 - 4.65 (m, 3H), 6.93 (d, IH), 7.17 (d, IH), 7.37 (s, IH), 7.48 (d, 2H), 7.75 (d, 2H), 7.92 (s, IH), 8.24 (s, IH), m/z 406 (M+H)^+.

**Example 104**

2-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino ethylcarbamoylformic acid

![Chemical Structure](image)

**Method 4**

Pyridine (0.15 mL, 1.81 mmol) was added to a solution of 3-(2-aminoethyl)-L-[5-[4-(4-cyanophenyl) piperidine-1-carbonyl]-2-methyl-phenyl]urea (Example 103) (0.2 g, 0.45 mmol) and methyl oxalyl chloride (42 \(\mu\)L, 0.45 mmol) in DCM (3 mL), and the reaction mixture stirred at ambient temperature for 24 hrs. It was then diluted with DCM (10 mL) and the resulting solution washed sequentially with dilute hydrochloric acid (10 mL of IM), saturated sodium bicarbonate solution (10 mL), brine (10 mL), dried (MgSO\(_4\)) and evaporated in vacuo to give a brown oil. This was dissolved in MeOH (4 mL) and a
solution of potassium carbonate (240 mg, 5 eq) in water (4 mL) added. The reaction mixture was heated to reflux for 5 mins, and the MeOH then removed in vacuo. The resulting aqueous portion was acidified and extracted with ethyl acetate (30 mL) and the organic extracts washed with brine (30 mL), dried (MgSO₄), and evaporated in vacuo to give a beige solid which was purified by chromatography on silica, eluting with 0-40% MeOH in DCM, to give the title compound as a colourless solid, ¹H NMR (300.073 MHz,) δ 1.48 - 1.86 (m, 4H), 2.19 (s, 3H), 2.84 - 2.96 (m, 2H), 3.01 - 3.09 (m, 1H), 3.20 - 3.24 (m, 4H), 3.62 - 3.89 (m, 1H), 4.49 - 4.75 (m, 1H), 6.86 (s, 2H), 6.91 - 6.94 (m, 1H), 7.15 (d, 1H), 7.49 (d, 2H), 7.75 (d, 2H), 7.91 (s, 1H), 7.95 (s, 1H), m/z 478 (M+H)⁺.

Example 104A

2-[2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]ethylcarbamoyl] acetic acid

Method 4 from Example 103

¹H NMR (300.073 MHz, de-DMSO) δ 1.48 - 1.86 (m, 4H), 2.20 (s, 3H), 2.79 - 2.94 (m, 2H), 3.00 (s, 2H), 3.06 - 3.12 (m, 1H), 3.17 - 3.23 (m, 4H), 3.71 - 3.92 (m, 1H), 4.40 - 4.72 (m, 1H), 6.88 - 6.93 (m, 1H), 7.14 (d, 2H), 7.49 (d, 2H), 7.75 (d, 2H), 7.91 (s, 1H), 8.10 (s, 1H), 8.62 (s, 1H), m/z 492 (M+H)⁺.

Example 105

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-1-pheny]-3-[((IS)-1-phenylethyl]urea

Method 2 from Intermediate A

¹H NMR (300.072 MHz, CDCl₃) δ 1.44 (3H, d), 1.67 -2.00 (7H, m), 2.74 - 3.20 (3H, m), 3.90 (IH, m), 4.76 (IH, m), 4.86 - 4.95 (IH, m), 6.07 (IH, d), 6.87 (2H, d), 6.98 (IH, d), 7.17 - 7.23 (IH, m), 7.28 (3H, d), 7.30 - 7.34 (3H, m), 7.57 (IH, d), 7.59 (2H, d), m/z 467 (M+H)⁺.
Example 106
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[(IR)-I-phenylethyljurea

Method 2 from Intermediate A

\(^1\)H NMR (300.072 MHz, CDCl\(_3\)) \(\delta\) 1.41 - 1.49 (3H, d), 1.67 - 2.00 (7H, m), 2.74 - 3.07 (3H, m), 3.87 - 3.91 (IH, m), 4.73 (IH, m), 4.85 - 4.94 (IH, m), 6.19 (IH, d), 6.85 - 6.96 (3H, m), 7.11 - 7.31 (7H, m), 7.56 - 7.59 (3H, m), m/z 467 (M+H)^+.

Example 107
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(4-hydroxycyclohexyl)urea

Method 2 from Intermediate A

\(^1\)H NMR (300.072 MHz, CDCl\(_3\)) \(\delta\) 1.09 - 2.10 (15H, m), 2.83 - 3.20 (3H, t), 3.51 - 3.56 (IH, m), 3.73 - 4.10 (2H, s), 4.83 (IH, s), 5.68 - 5.91 (IH, m), 6.85 - 7.10 (3H, m), 7.32 (2H, d), 7.58 - 7.71 (3H, m), m/z 461 (M+H)^+.

Example 108
3-[(3-cyanophenyl)methyl]-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]urea

Method 2 from Intermediate A

\(^1\)H NMR (300.072 MHz, CDCl\(_3\)) \(\delta\) 6.63 - 2.02 (7H, m), 2.80 - 3.20 (3H, m), 3.91 (IH, m), 4.38 (2H, d), 4.77 (IH, m), 6.51 (IH, t), 6.89 - 6.92 (IH, m), 7.02 - 7.08 (2H, m), 7.29 - 7.32 (2H, m), 7.41 (IH, q), 7.49 - 7.52 (2H, m), 7.58 (4H, t), m/z 478 (M+H)^+. 
Example 109
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2-methanesulfonamidoethyl)urea

Method 5
Pyridine (0.15 mL, 1.81 mmol) was added to a solution of 3-(2-aminoethyl)-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]urea (Example 103) (0.2g, 0.45mmol) and methane sulfonyl chloride (43 µL, 0.54mmol) in DCM (3 mL), and the reaction mixture stirred at ambient temperature for 48 hrs. It was then diluted with DCM (10 mL) and the resulting solution washed sequentially with dilute hydrochloric acid (10 mL of 1M), saturated sodium bicarbonate solution (10 mL), brine (10 mL), dried (MgSO4) and evaporated in vacuo to give a brown oil. This was purified by chromatography on silica, eluting with 0-10% MeOH in EtOAc, to give the title compound as a colourless solid, \(^1\)H NMR (300.072 MHz, CDCl₃) \(\delta\) 1.63 - 1.83 (m, 4H), 1.95 (s, 3H), 2.80 - 2.90 (m, 2H), 2.97 (s, 3H), 3.11 - 3.20 (m, IH), 3.25 - 3.32 (m, 2H), 3.37 - 3.44 (m, 2H), 3.90 - 4.05 (m, IH), 4.81 - 4.92 (m, IH), 6.02 (t, IH), 6.38 (t, IH), 6.85 (d, IH), 6.96 (s, IH), 6.97 (d, IH), 7.35 (d, 2H), 7.61 (d, 2H), 7.82 (s, IH), m/z 484 (M+H)⁺.

Example 110
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-1-[2-(ethylsulfonylamino)ethyl]urea

Method 5 from Example 103
\(^1\)H NMR (300.072 MHz, CDCl₃) \(\delta\) 1.36 (t, 3H), 1.66 - 1.91 (m, 4H), 2.00 (s, 3H), 2.81 - 2.92 (m, 2H), 3.05 (q, 2H), 3.14 - 3.20 (m, IH), 3.23 - 3.29 (m, 2H), 3.33 - 3.39 (m, 2H), 3.93 - 4.03 (m, IH), 4.75 - 4.96 (m, IH), 5.96 - 6.04 (m, IH), 6.42 - 6.50 (m, IH), 6.87 (d, IH), 7.00 (d, IH), 7.09 (s, IH), 7.35 (d, 2H), 7.60 (d, 2H), 7.80 (s, IH), m/z 498 (M+H)⁺.\(^1\)H NMR (300.072 MHz, CDCl₃) \(\delta\) 1.52 - 1.87 (m, 4H), 2.09 (s, 3H), 2.19 (q, 2H), 2.79 - 2.90 (m, 2H), 3.02 - 3.23 (m, IH), 3.28 - 3.37 (m, 4H), 3.90 - 4.06 (m,
Example 111
N-[2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]carbamoylamino] ethyl] propanamide

Method 5 from Example 103

$^1$H NMR (300.072 MHz, CDCl$_3$) δ 1.10 (t, 3H), 1.52 - 1.87 (m, 4H), 2.09 (s, 3H), 2.19 (q, 2H), 2.79 - 2.90 (m, 2H), 3.02 - 3.23 (m, 1H), 3.28 - 3.37 (m, 4H), 3.90 - 4.06 (m, 1H), 4.73 - 4.92 (m, 1H), 6.34 - 6.38 (m, 1H), 6.92 - 6.98 (m, 2H), 7.07 (d, 1H), 7.26 (s, 1H), 7.33 (d, 2H), 7.61 (d, 2H), 7.78 - 7.80 (m, 1H), m/z 462 (M+H)$^+$. 

Example 112
N-[2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]carbamoylamino] ethyl]-2-methyl-1-propanamide

Method 5 from Example 103

$^1$H NMR (300.072 MHz, CDCl$_3$) δ 1.11 (d, 6H), 1.61 - 1.97 (m, 4H), 2.10 (s, 3H), 2.38 (septet, 1H), 2.81 - 2.89 (m, 2H), 2.99 - 3.23 (m, 1H), 3.30 - 3.37 (m, 4H), 3.90 - 4.02 (m, 1H), 4.72 - 4.91 (m, 1H), 6.29 (s, 1H), 6.84 (s, 1H), 6.96 (d, 1H), 7.08 (d, 1H), 7.21 (s, 1H), 7.33 (d, 2H), 7.61 (d, 2H), 7.76 (s, 1H), m/z 476 (M+H)$^+$. 

Example 113
2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyln[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl phenyl]carbamoylamino] ethylcarbamoylmethyl acetate

Method 5 from Example 103

$^1$H NMR (300.072 MHz, CDCl$_3$) δ 1.59 - 1.88 (m, 4H), 2.05 (s, 3H), 2.08 (s, 3H), 2.78 - 2.89 (m, 2H), 3.00 - 3.18 (m, 1H), 3.34 - 3.43 (m, 4H), 3.89 - 4.06 (m, 1H), 4.53 (s, 2H),
4.74 - 4.93 (m, IH), 6.10 - 6.16 (m, IH), 6.93 - 6.97 (m, IH), 7.04 - 7.10 (m, 2H), 7.33 (d, 2H), 7.47 - 7.52 (m, IH), 7.60 (d, 2H), 7.68 - 7.72 (m, IH), m/z 506 (M+H)+.

Example 114
N-[2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]ethyl]-2-hydroxy-acetamide

Method 6
DIPEA (0.31 mL, 1.81 mmol) was added to a mixture of 3-(2-aminoethyl)-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]urea (Example 103) (0.2 g, 0.45 mmol), glycolic acid (104 mg, 1.36 mmol) and HATU (0.36 g 0.95 mmol) in DMF (3 mL) and stirred at ambient temperature for 24 hrs. It was then diluted with EtOAc (30 mL) and the resulting solution washed sequentially with water and brine (30 mL of each), dried (MgSO₄) and evaporated in vacuo to give a brown oil. This was purified by chromatography on silica, eluting with 0-20% MeOH in EtOAc, to give the title compound as a colourless solid, ¹H NMR (300.072 MHz, CDCl₃) δ 1.71 - 1.86 (m, 4H), 1.98 (s, 3H), 2.80 - 2.99 (m, 2H), 3.09 - 3.25 (m, IH), 3.36 - 3.48 (m, 4H), 3.91 - 3.97 (m, IH), 4.00 - 4.05 (m, 2H), 4.78 - 4.90 (m, IH), 4.97 - 5.04 (m, IH), 6.12 - 6.17 (m, IH), 6.83 - 6.87 (m, IH), 6.99 (d, IH), 7.14 (s, IH), 7.30 - 7.37 (m, 3H), 7.61 (d, 2H), 7.69 (d, IH), m/z 462 (M-H)-.

Example 115
tert-butyl N-[2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]ethyl]-N-methyl-carbamate

Method 2 from Intermediate A

¹H NMR (300.072 MHz, CDCl₃) δ 1.42 (s, 9H), 1.64 - 1.97 (m, 4H), 2.19 (s, 3H), 2.78 - 2.86 (m, 2H), 2.89 (s, 3H), 3.02 - 3.22 (m, IH), 3.34 - 3.41 (m, 4H), 3.91 - 4.07 (m, IH),
Example 116

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2-methylaminoethyl) urea

Method 3 from Example 115

$^1$H NMR (300.073 MHz, $d_6$-DMSO) $\delta$ 1.51 - 1.86 (m, 4H), 2.24 (s, 3H), 2.53 - 2.57 (m, 3H), 2.88 - 3.03 (m, 4H), 3.09 - 3.16 (m, 1H), 3.36 - 3.41 (m, 2H), 3.76 - 3.85 (m, 1H), 4.44 - 4.71 (m, 1H), 6.92 - 6.96 (m, 1H), 7.18 (d, 2H), 7.49 (d, 2H), 7.76 (d, 2H), 7.89 - 7.92 (m, 1H), 8.15 (s, 1H), 8.96 (s, 1H), m/z 420 (M+H)$^+$. 

Example 117 N-[2-[5-[4-(cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]ethyl thiophene-2-carboxamide

Method 5 from Example 103

$^1$H NMR (300.072 MHz, CDCl$_3$) $\delta$ 1.45 - 1.81 (m, 4H), 1.97 (s, 3H), 2.70 - 2.98 (m, 3H), 3.41 - 3.49 (m, 2H), 3.52 - 3.59 (m, 2H), 3.81 - 3.95 (m, 1H), 4.70 - 4.91 (m, 1H), 6.52 (s, IH), 6.82 - 6.87 (m, IH), 6.91 - 6.94 (m, IH), 6.98 (d, IH), 7.14 (s, IH), 7.29 (d, 2H), 7.36 (d, IH), 7.59 (d, 2H), 7.66 (d, IH), 7.85 (s, IH), 7.91 (t, IH), m/z 516 (M+H)$^+$. 

Example 118

N-[2-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]ethyl]-1-methyl-pyrrole-2-carboxamide

Method 5 from Example 103

$^1$H NMR (300.072 MHz, CDCl$_3$) $\delta$ 1.58 - 1.93 (m, 4H), 1.98 (s, 3H), 2.75 - 2.85 (m, 2H), 2.98 - 3.18 (m, IH), 3.35 - 3.54 (m, 4H), 3.91 (s, 3H), 3.98 - 4.08 (m, IH), 4.68 - 4.83 (m,
IH), 5.94 - 5.97 (m, IH), 6.25 (t, IH), 6.63 - 6.68 (m, 2H), 6.89 - 6.93 (m, IH), 6.98 - 7.03 (m, 2H), 7.20 (t, IH), 7.30 (d, 2H), 7.59 (d, 2H), 7.69 (s, IH), \textbf{m/z} 513 (M+H)^+.

**Example 119**

N-[2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]ethyl]-5-methyl-1,2-oxazole-4-carboxamide

\[
\text{Method 5 from Example 103}
\]

\(^1\)H NMR (300.072 MHz, CDCl\(_3\) \(\delta\) 1.47 - 1.81 (m, 4H), 1.90 (s, 3H), 2.69 (s, 3H), 2.75 - 2.86 (m, 2H), 2.93 - 3.07 (m, IH), 3.40 - 3.56 (m, 4H), 3.82 - 3.98 (m, IH), 4.75 - 4.88 (m, IH), 6.46 - 6.51 (m, IH), 6.84 (d, IH), 6.94 (d, IH), 7.05 (s, IH), 7.32 (d, 2H), 7.62 (d, 2H), 7.70 (s, IH), 7.98 (t, IH), 8.67 (s, IH), \textbf{m/z} 515 (M+H)^+.

**Example 120**

N-[2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]ethyl]-N-methyl-acetamide

\[
\text{Method 5 from Example 116}
\]

\(^1\)H NMR (300.072 MHz, CDCl\(_3\) \(\delta\) 1.63 - 1.95 (m, 4H), 2.10 & 2.12 (2xs, 3H), 2.13 & 2.20 (2xs, 3H), 2.78 - 2.90 (m, 2H), 2.93 & 3.07 (2xs, 3H), 3.11 - 3.19 (m, 1H), 3.36 - 3.54 (m, 4H), 3.87 - 4.14 (m, 1H), 4.79 - 4.93 (m, 1H), 5.85 & 6.26 (2xt, 1H), 6.88 (s, 1H), 7.01 - 7.17 (m, 2H), 7.32 (d, 2H), 7.60 (d, 2H), 7.66 - 7.72 (m, IH) (NB: spectrum is complicated due to rotamers), \textbf{m/z} 462 (M+H)^+.

**Example 121**

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[2-(methylmethylsulfonyl-amino)ethyl]urea

\[
\text{Method 5 from Example 116}
\]
1H NMR (300.072 MHz, CDCl$_3$) $\delta$ 1.62 - 1.98 (m, 4H), 2.13 (s, 3H), 2.81 (s, 3H), 2.82 - 2.87 (m, 2H), 2.90 (s, 3H), 3.05 - 3.19 (m, IH), 3.23 - 3.28 (m, 2H), 3.38 - 3.46 (m, 2H), 3.88 - 4.05 (m, IH), 4.75 - 4.97 (m, IH), 5.72 (s, IH), 6.81 (s, IH), 7.01 - 7.13 (m, 2H), 7.34 (d, 2H), 7.53 (s, IH), 7.62 (d, 2H), m/z 498 (M+H)$^+$.  

Example 122

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[2-(propan-2-ylsulfbnylamino)ethyl]urea

Method 5 from Example 103

1H NMR (300.072 MHz, CDCl$_3$) $\delta$ 1.37 (d, 6H), 1.54 - 1.82 (m, 4H), 1.98 (s, 3H), 2.79 - 2.88 (m, 2H), 2.97 - 3.09 (m, IH), 3.19 (septet, IH), 3.27 - 3.32 (m, 2H), 3.36 - 3.43 (m, 2H), 3.92 - 4.04 (m, IH), 4.81 - 4.95 (m, IH), 5.72 (t, IH), 6.24 (s, IH), 6.84 (s, IH), 6.87 - 6.91 (m, IH), 6.97 - 7.02 (m, IH), 7.36 (d, 2H), 7.60 (d, 2H), 7.76 - 7.80 (m, IH), m/z 512 (M+H)$^+$.  

Example 123

4-[1-[3-(benzylcarbamoylamino)-4-methyl-1-benzoyl-4-piperidyl]-N,N-dimethyl-benzamide

Method 1 from Intermediate K

1H NMR (300.073 MHz, de-DMSO) $\delta$ 1.47 - 1.88 (m, 4H), 2.21 (s, 3H), 2.74 - 3.02 (m, 9H), 3.67 - 3.90 (m, IH), 4.30 (d, $J = 5.7$ Hz, 2H), 4.47 - 4.70 (m, IH), 6.93 (d, $J = 7.5$ Hz, IH), 7.02 - 7.09 (m, IH), 7.18 (d, $J = 7.7$ Hz, IH), 7.22 - 7.27 (m, IH), 7.32 (s, 8H), 7.81 (s, IH), 7.98 (s, IH), m/z 499 (M+H)$^+$.  

Example 124

N,N-dimethyl-4-[1-[4-methyl-3-(propan-2-ylcarbamoylamino)benzoyl]-4-piperidyl] benzamide
Example 125

3-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]propanoic acid

Method 7

A solution of methyl 3-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]propanoate (Example 45) (1.6g, 3.56mmol) in THF (10 mL) was treated with a solution of lithium hydroxide (299 mg, 7.12 mmol) in water (5 mL), and the reaction mixture was stirred for 16 hours at ambient temperature. It was then evaporated in vacuo to remove the THF and the aqueous phase was diluted with water (10 mL) and washed with EtOAc (10mL). Citric acid solution (10% aqueous) was added to the aqueous phase until the pH was 4-5. The precipitate thus formed was extracted into EtOAc (3 x 15 mL), the combined organic phases dried (MgSO₄) and concentrated in vacuo to yield a colourless foam, ¹H NMR (300.073 MHz, d₆-DMSO) δ 1.5-1.9 (4H, m), 2.1 (3H, s), 2.4 (2H, t), 2.8-3.2 (2H, m), 3.3 (2H, m), 3.6-3.9 (IH, m), 4.4-4.7 (IH, m), 6.7 (IH, t), 6.9 (IH, dd), 7.1 (IH, d), 7.5 (2H, d), 7.7 (2H, d), 7.9 (IH, s), 8.0 (IH, s), m/z 435 (M+H)⁺.

Example 126

3-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]propanamide
Method 6 from Example 125

\[ 1^1H \text{NMR} \ (300.073 \text{ MHz}, \text{d}_2\text{-DMSO}) \delta \ 1.4-2.0 \ (4H, m), 2.2 \ (3H, s), 2.3 \ (2H, t), 2.8-3.2 \ (2H, m), 3.3 \ (2H, m), 3.6-4.0 \ (IH, m), 4.4-4.6 \ (IH, m), 6.7 \ (IH, t), 6.8 \ (IH, bs), 6.9 \ (IH, dd), 7.1 \ (IH, d), 7.3 \ (IH, bs), 7.5 \ (2H, d), 7.8 \ (2H, d), 7.8 \ (IH, s), 8.0 \ (IH, s), \text{ m/z } 434 \ (\text{M+H})^+ .

Example 127

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(3-morpholin-4-y1)-3-oxo-propyl)urea

\[ 1^1H \text{NMR} \ (300.073 \text{ MHz}, \text{d}_2\text{-DMSO}) \delta \ 1.50-1.80 \ (4H, m), 2.26 \ (3H, s), 2.27-2.87 \ (2H, t), 2.67-3.02 \ (3H, m), 3.21-3.36 \ (6H, m), 3.23 \ (3H, s), 3.73-3.83 \ (8H, m), 3.65-3.98 \ (IH, m), 4.58-4.62 \ (IH, m), 6.74 \ (IH, dt), 6.90 \ (IH, d, J 7.7), 7.15 \ (IH, d, J 7.9), 7.49 \ (2H, d, J 8.3), 7.75 \ (IH, d, J 8.3), 7.87 \ (IH, s), 7.95 \ (IH, s), \text{ m/z } 504 \ (\text{M+H})^+ .

Example 128

3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]-N-(2-methoxyethyl)propanamide

\[ 1^1H \text{NMR} \ (300.073 \text{ MHz}, \text{d}_2\text{-DMSO}) \delta \ 1.57-1.78 \ (4H, m), 2.18 \ (3H, s), 2.28 \ (2H, t, J 6.4), 2.68-3.02 \ (3H, m), 3.21-3.36 \ (6H, m), 3.23 \ (3H, s), 3.73-3.83 \ (IH, m), 4.50-4.61 \ (IH, m), 6.68 \ (IH, t, J 5.7), 6.90 \ (IH, dd, J 8.0, 1.7), 7.15 \ (IH, d, J 8.0), 7.49 \ (2H, d, J 8.3), 7.76 \ (2H, d, J 8.3), 7.81 \ (IH, s), 7.96 \ (2H, bs), \text{ m/z } 492 \ (\text{M+H})^+ .

Example 129
3-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]-N,N-propan-2-yl-propanamide

Method 6 from Example 125

\[^1\text{H} \text{NMR} \ (300.073 \text{ MHz, } d_6\text{-DMSO}) \ \delta \ 1.04 \ (3\text{H}, \text{s}), \ 1.06 \ (3\text{H}, \text{s}), \ 1.36-1.89 \ (4\text{H}, \text{m}), \ 2.19 \ (3\text{H}, \text{s}), \ 2.24 \ (2\text{H}, \text{t}, J6.3), \ 2.74-3.24 \ (3\text{H}, \text{m}), \ 3.24-3.29 \ (2\text{H}, \text{m}), \ 3.69-3.80 \ (1\text{H}, \text{m}), \ 3.87 \ (1\text{H}, \text{p}, J6.6), \ 4.64-4.78 \ (1\text{H}, \text{m}), \ 6.72 \ (1\text{H}, \text{t}, J6.0), \ 6.92 \ (1\text{H}, \text{dd}, Jl. \beta, 1.5), \ 7.17 \ (1\text{H}, \text{d}, J7.8), \ 7.51 \ (2\text{H}, \text{d}, J8.3), \ 7.78 \ (3\text{H}, \text{d}, J8.3), \ 7.85 \ (1\text{H}, \text{s}), \ 7.97 \ (1\text{H}, \text{d}, J1.5), \ m/z \ 476 (M+H)^+.

Example 130
3-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]-N,N-dimethyl-propanamide

Method 6 from Example 125

\[^1\text{H} \text{NMR} \ (300.073 \text{ MHz, } d_6\text{-DMSO}) \ \delta \ 1.58-1.99 \ (4\text{H}, \text{m}), \ 2.19 \ (3\text{H}, \text{s}), \ 2.45-2.50 \ (2\text{H}, \text{m}), \ 2.85 \ (3\text{H}, \text{s}), \ 2.94 \ (3\text{H}, \text{s}), \ 2.70-2.99 \ (3\text{H}, \text{m}), \ 3.30 \ (2\text{H}, \text{m}), \ 3.75-3.93 \ (1\text{H}, \text{m}), \ 4.5-4.7 \ (1\text{H}, \text{m}), \ 6.78 \ (1\text{H}, \text{t}, J6.3), \ 6.91 \ (1\text{H}, \text{dd}, J7.6, 1.5), \ 7.17 \ (1\text{H}, \text{d}, J8.3), \ 7.51 \ (2\text{H}, \text{d}, J8.3), \ 7.78 \ (2\text{H}, \text{d}, J8.3), \ 7.91 \ (1\text{H}, \text{s}), \ 7.98 \ (1\text{H}, \text{d}, J1.5), \ m/z \ 462 (M+H)^+.

Example 131
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[3-(2-oxopyrrolidin-1-yl)propyl]urea

Method 2 from Intermediate A

\[^1\text{H} \text{NMR} \ (300.073 \text{ MHz, } d_6\text{-DMSO}) \ \delta \ 1.49 - 2.01 \ (m, 8\text{H}), \ 2.14 - 2.29 \ (m, 5\text{H}), \ 2.76 - 3.12 \ (m, 5\text{H}), \ 3.21 \ (t, 2\text{H}), \ 3.25 - 3.38 \ (m, 2\text{H}), \ 3.57 - 4.00 \ (m, \text{IH}), \ 4.38 - 4.80 \ (m, \text{IH}), \ 4.88 - 5.00 \ (m, \text{IH}), \ 5.97 - 6.12 \ (s, 1\text{H}), \ 7.00 - 7.39 \ (m, 20\text{H}), \ 7.70 - 7.80 \ (m, 1\text{H}), \ 8.00 - 8.12 \ (m, 1\text{H}), \ 8.30 - 8.40 \ (m, 1\text{H}).
6.62 (t, IH), 6.91 (d, IH), 7.17 (d, IH), 7.49 (d, 2H), 7.71 - 7.83 (m, 3H), 7.93 (s, IH), m/z 488 (M+H)⁺.

**Example 132**

ethyl 4-[[5-[(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]piperidine-1-carboxylate

\[
\text{Method 2 from Intermediate A}
\]

\[
^1\text{H NMR (300.073 MHz, } d_6\text{-DMSO) } \delta 1.06 - 1.36 \text{ (m, 5H), 1.48 - 1.93 \text{ (m, 6H), 2.19 \text{ (s, 3H), 2.73 - 3.21 \text{ (m, 5H), 3.52 - 3.92 \text{ (m, 4H), 4.03 \text{ (q, 2H), 4.34 - 4.83 \text{ (m, IH), 6.67 \text{ (d, IH), 6.91 \text{ (d, IH), 7.17 \text{ (d, IH), 7.49 \text{ (d, 2H), 7.65 \text{ (s, IH), 7.76 \text{ (d, 2H), 7.97 \text{ (s, IH), m/z 518 (M+H)⁺).}}}}}}}}}
\]

**Example 133**

1-[5-(4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2-oxazepan-3-yl)urea

\[
\text{Method 2 from Intermediate A}
\]

\[
^1\text{H NMR (300.073 MHz, } d_6\text{-DMSO) } \delta 1.09 - 1.45 \text{ (m, 2H), 1.48 - 1.99 \text{ (m, 8H), 2.21 \text{ (s, 3H), 2.75 - 3.24 \text{ (m, 5H), 3.55 - 4.05 \text{ (m, 1H), 4.25 - 4.39 \text{ (m, 1H), 4.44 - 4.79 \text{ (m, 1H), 6.91 \text{ (d, IH), 7.16 \text{ (d, 2H), 7.49 \text{ (d, 2H), 7.75 \text{ (d, 2H), 7.83 \text{ (t, 2H), 7.94 \text{ (s, IH), 8.22 \text{ (s, IH), m/z 474 (M+H)⁺).}}}}}}}}}
\]

**Example 134**

(1S)-2-[[5-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]cyclohexane-1-carboxamide

\[
\text{Method 2 from Intermediate A}
\]
\[ \text{Example 135} \]

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[2-(2-oximidazolidin-1-yl)ethyl]urea

\[ \text{Method 2 from Intermediate A} \]

\[ \text{Example 136} \]

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(3-oxo-1,2-oxazol-5-yl)methyl]urea

\[ \text{Method 2 from Intermediate A} \]

\[ \text{Example 137} \]

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2-pyrrolidin-1-ylethyl)urea
Method 2 from Intermediate A

$^1$H NMR (300.072 MHz, CDCl$_3$) $\delta$ 1.50 - 2.05 (6H, m), 2.15 (3H, s), 2.53 - 2.59 (2H, m), 2.55 - 2.61 (4H, m), 2.64 (2H, d), 2.79 - 3.25 (3H, m), 3.35 (2H, q), 4.00 (IH, m), 4.85 (IH, m), 5.95 (IH, t), 6.98 - 7.02 (IH, m), 7.11 (IH, d), 7.31 (3H, t), 7.59 - 7.61 (2H, m), 7.68 (IH, d), m/z 460 (M+H)$^+$.

**Example 138**

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(3-dimethylaminopropyl) urea

Method 2 from Intermediate A

$^1$H NMR (300.072 MHz, CDCl$_3$) $\delta$ 1.55 - 2.10 (4H, m), 2.05 (3H, s), 2.70 (2H, t), 2.48 (2H, s), 2.80 - 2.88 (IH, m), 3.00 - 3.28 (3H, m), 4.00 (IH, m), 4.85 (IH, m), 6.15 (IH, m), 6.64 (IH, s), 6.89 - 6.92 (IH, m), 7.05 (IH, d), 7.32 (2H, d), 7.59 - 7.64 (3H, m), m/z 448 (M+H)$^+$.

**Example 139**

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[2-([H-imidazol-4-yl)ethyl]urea

Method 2 from Intermediate A

$^1$H NMR (300.072 MHz, CDCl$_3$) $\delta$ 1.50 - 2.05 (4H, m), 2.05 (3H, s), 2.70 (2H, t), 2.83 - 3.20 (3H, m), 3.41 - 3.44 (2H, m), 3.95 (IH, m), 4.80 (IH, m), 5.20 (IH, s), 6.56 (IH, t), 6.64 (IH, s), 6.89 - 6.92 (IH, m), 7.05 (IH, d), 7.31 (3H, d), 7.58 (2H, d), 7.85 (IH, s), 7.89 (IH, d), m/z 457 (M+H)$^+$.
Example 140

1-[[5-[[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[3-(4-methylpiperazin-1-yl)propyl]urea

Method 2 from Intermediate A

$^1$H NMR (300.072 MHz, CDCl$_3$) δ 1.50 - 2.10 (6H, m), 2.16 (3H, s), 2.25 (3H, s), 2.30 - 2.55 (1OH, m), 2.80 - 3.20 (3H, m), 3.29 (2H, q), 4.00 (IH, m), 4.85 (IH, m), 5.98 (IH, s), 6.61 (IH, s), 7.01 - 7.04 (IH, m), 7.13 (IH, d), 7.32 (2H, d), 7.59 - 7.62 (3H, m), m/z 503 (M+H)$^+$.

Example 141

3-[[3-((bis(2-hydroxyethyl)amino)propyl] - 1-[5-[[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]urea

Method 2 from Intermediate A

$^1$H NMR (300.072 MHz, CDCl$_3$) δ 1.47 - 2.10 (6H, m), 2.06 (3H, s), 2.58 (4H, d), 2.60 (2H, s), 2.83 - 3.25 (3H, m), 3.30 - 3.32 (2H, m), 3.64 (4H, t), 4.00 (IH, m), 4.85 (IH, m), 6.81 (IH, s), 6.91 - 6.94 (IH, m), 7.06 (IH, d), 7.12 (IH, s), 7.33 (2H, d), 7.58 - 7.61 (2H, m), 7.84 (IH, d), m/z 508 (M+H)$^+$.

Example 142

1-[5-[[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-([4-dimethylaminobutyl] urea

Method 2 from Intermediate A

$^1$H NMR (300.072 MHz, CDCl$_3$) δ 1.47 - 2.10 (6H, m), 2.11 (3H, s), 2.21 (6H, s), 2.26 - 2.29 (2H, m), 2.45 (2H, s), 2.79 - 3.23 (5H, m), 4.00 (IH, m), 4.85 (IH, m), 6.05 (IH, s),...
6.96 (IH, d), 6.96 (IH, d), 7.08 (IH, d), 7.32 (2H, d), 7.59 - 7.61 (2H, m), 7.67 (IH, d), m/z 462 (M+H)+.

**Example 143**

3-(1-azabicyclo[2.2.2]oct-8-yl)-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]urea

Method 2 from Intermediate A

^1H NMR (300.072 MHz, CDCl$_3$) δ: 1.69 - 2.05 (6H, m), 2.13 (7H, d), 2.55 (IH, m), 2.75 - 3.25 (7H, m), 3.26 - 3.34 (IH, m), 4.85 (IH, m), 6.45 (IH, d), 6.92 - 6.95 (IH, m), 7.10 (2H, t), 7.27 - 7.33 (2H, m), 7.60 - 7.62 (2H, m), 7.68 (IH, d), m/z 472 (M+H)+.

**Example 144**

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-1-phenyl]-3-[2-(1-methylpyrrolidin-2-yl)ethyl]urea

Method 2 from Intermediate A

^1H NMR (300.072 MHz, CDCl$_3$) δ: 1.46 - 2.05 (6H, m), 2.15 (5H, m), 2.27 (4H, m), 2.50 (3H, s), 2.80 - 3.30 (6H, m), 4.00 (IH, m), 4.85 (IH, m), 6.17 (IH, s), 6.98 (2H, d), 7.10 (IH, d), 7.33 (2H, d), 7.60 (3H, d), m/z 474 (M+H)+.

**Example 145**

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2-dimethylaminoethyl)urea

Method 2 from Intermediate A
H NMR (300.072 MHz, CDCl₃) δ 1.55 - 2.05 (4H, m), 2.15 (3H, s), 2.25 (6H, s), 2.45 (2H, t), 2.79 - 3.25 (3H, m), 3.31 (2H, q), 4.00 (IH, m), 4.85 (IH, m), 5.97 (IH, t), 6.99 - 7.02 (IH, m), 7.11 (IH, d), 7.31 - 7.45 (3H, m), 7.59 - 7.61 (2H, m), 7.70 (IH, d), m/z 434 (M+H)⁺.

Example 146
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(3-morpholin-4-ylpropyl)urea

1H NMR (300.072 MHz, CDCl₃) δ 1.50 - 2.05 (6H, m), 2.09 (3H, s), 2.42 (2H, d), 2.42 (4H, d), 2.80 - 3.20 (3H, m), 3.24 - 3.30 (2H, m), 3.66 (4H, t), 4.00 (IH, m), 4.85 (IH, m), 5.97 (IH, s), 6.82 (IH, s), 6.95 - 6.98 (IH, m), 7.08 (IH, d), 7.32 (2H, d), 7.57 (IH, d), 7.61 (2H, d), m/z 490 (M+H)⁺.

Example 147
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[1-(2-methoxyethyl)-4-piperidyl]urea

1H NMR (300.072 MHz, CDCl₃) δ 1.20 - 2.15 (1OH, m), 2.15 (3H, s), 2.55 (2H, t), 2.79 - 3.25 (5H, m), 3.39 (3H, s), 3.52 (2H, t), 3.58 - 3.63 (IH, m), 4.00 (IH, m), 4.85 (IH, m), 5.74 (IH, d), 6.93 - 6.96 (IH, m), 7.10 (IH, d), 7.31 (2H, d), 7.60 (2H, d), 7.75 (IH, d), m/z 504 (M+H)⁺.

Example 148
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[1-methyl-1-4-piperidyl]urea
Method 2 from Intermediate A

$^1$H NMR (300.072 MHz, CDCl$_3$) δ1.40 - 2.20 (1H, m), 2.28 (3H, s), 2.64 - 3.25 (7H, m), 3.59 - 3.67 (1H, m), 3.95 (IH, m), 4.85 (IH, d), 5.85 - 6.93 (IH, m), 7.02 (2H, d), 7.32 (2H, d), 7.57 - 7.62 (3H, m), m/z 460 (M+H)$^+$.  

**Example 149**

3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-1-[[2S]-1-ethylpyrrolidin-2-yl]methyl]urea

Method 2 from Intermediate A

$^1$H NMR (300.072 MHz, CDCl$_3$) δ1.50 - 2.05 (3H, t), 1.55 - 2.10 (6H, m), 2.15 - 2.34 (5H, m), 2.51 - 2.59 (IH, m), 2.56 - 2.62 (IH, m), 2.80 - 3.20 (6H, m), 3.37 - 3.45 (IH, m), 4.00 (IH, m), 4.85 (IH, m), 5.87 (IH, s), 6.99 - 7.02 (IH, m), 7.11 (IH, d), 7.32 (2H, d), 7.60 (2H, d), 7.66 (IH, d), m/z 474 (M+H)$^+$.  

**Example 150**

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[(3-methylimidazol-4-yl)methyl]urea

Method 2 from Intermediate A

$^1$H NMR (300.072 MHz, CDCl$_3$) δ1.50 - 2.05 (4H, m), 2.07 (3H, s), 2.80 - 2.88 (2H, m), 3.14 (IH, s), 3.61 (3H, s), 4.00 (IH, m), 4.37 (2H, d), 4.77 (IH, s), 6.38 (IH, t), 6.81 (IH, s), 6.91 - 6.94 (IH, m), 7.06 (IH, d), 7.32 (2H, d), 7.37 (IH, s), 7.46 (IH, s), 7.59 - 7.62 (2H, m), 7.72 (IH, d), m/z 457 (M+H)$^+$.  

**Example 151**

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(oxolan-2-ylmethyl]urea
Example 152
1-[(5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2-methoxyethyl)urea

\[ \text{Method } 2 \text{ from Intermediate A} \]

$^1$H NMR (300.072 MHz, CDCl$_3$) $\delta$ 1.58 - 2.03 (m, 8H), 2.19 (s, 3H), 2.78 - 2.87 (m, 2H), 2.96 - 3.10 (m, IH), 3.10 - 3.20 (m, IH), 3.47 - 3.58 (m, IH), 3.71 - 3.78 (m, IH), 3.82 - 3.89 (m, IH), 3.96 - 4.03 (m, IH), 4.04 - 4.11 (m, IH), 4.76 - 5.00 (m, IH), 5.32 - 5.38 (m, IH), 6.94 (s, IH), 7.04 - 7.16 (m, 2H), 7.32 (d, 2H), 7.57 (d, 2H), 7.61 (d, 2H), 7.65 (s, IH), m/z 447 (M+H)$^+$.  

Example 153
1-[(5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(3-propan-2-yloxypropyl)urea

\[ \text{Method } 2 \text{ from Intermediate A} \]

$^1$H NMR (300.072 MHz, CDCl$_3$) $\delta$ 1.09 (d, 6H), 1.61 - 1.96 (m, 4H), 1.77 (quintet, 2H), 2.18 (s, 3H), 2.79 - 2.90 (m, 2H), 2.95 - 3.20 (m, IH), 3.34 (q, 2H), 3.49 (t, 2H), 3.53 (septet, IH), 3.89 - 4.15 (m, IH), 4.72 - 4.98 (m, IH), 5.43 (t, IH), 6.33 (s, IH), 7.04 - 7.17 (m, 2H), 7.32 (d, 2H), 7.54 - 7.56 (m, IH), 7.61 (d, 2H), m/z 463 (M+H)$^+$.  

Example 154
1-[(5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(3-methoxypropyl)urea
1H NMR (300.072 MHz, CDCl\textsubscript{3}) $\delta$ 1.64 - 1.97 (m, 4H), 1.78 (quintet, 2H), 2.19 (s, 3H), 2.79 - 2.90 (m, 2H), 3.05 - 3.16 (m, 1H), 3.28 (s, 3H), 3.34 (q, 2H), 3.46 (t, 2H), 3.89 - 4.09 (m, 1H), 4.76 - 4.94 (m, 1H), 5.33 - 5.41 (m, 1H), 6.33 (s, 1H), 7.05 - 7.19 (m, 2H), 7.33 (d, 2H), 7.53 - 7.56 (m, 1H), 7.61 (d, 2H), m/z 435 (M+H)$^+$. 

Example 155
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(1-methoxypropan-2-yl)urea

1H NMR (300.072 MHz, CDCl\textsubscript{3}) $\delta$ 1.19 (d, 3H), 1.53 - 1.96 (m, 4H), 2.12 (s, 3H), 2.78 - 2.88 (m, 2H), 3.08 - 3.23 (m, 1H), 3.33 - 3.43 (m, 2H), 3.37 (s, 3H), 3.91 - 4.10 (m, 2H), 4.75 - 4.94 (m, 1H), 5.37 (d, 1H), 6.93 (s, 1H), 6.98 - 7.10 (m, 2H), 7.32 (d, 2H), 7.57 - 7.63 (m, 3H), m/z 435 (M+H)$^+$. 

Example 156
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2-methylsulfanylethyl)urea

1H NMR (300.072 MHz, CDCl\textsubscript{3}) $\delta$ 1.64 - 1.80 (m, 4H), 2.09 (s, 3H), 2.12 (s, 3H), 2.66 (t, 2H), 2.79 - 2.90 (m, 2H), 3.10 - 3.19 (m, 1H), 3.44 (q, 2H), 3.86 - 4.07 (m, 1H), 4.81 - 4.99 (m, 1H), 5.68 (t, 1H), 6.68 (s, 1H), 6.98 - 7.11 (m, 2H), 7.32 (d, 2H), 7.49 - 7.52 (m, 1H), 7.61 (d, 2H), m/z 437 (M+H)$^+$. 

Example 157
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-1-phenyl]-3-(3-methylsulfanylpropyl)urea
**Example 158**

3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-1-(3-ethoxypropyl)urea

**Example 159**

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2-methoxy-2-methylpropyl)urea

**Example 160**

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(1,4-dioxan-2-ylmethyl)urea
Example 161

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[3-(2-methoxyethoxy)propyl]urea

Method 2 from Intermediate A

\[ \text{Method 2 from Intermediate A} \]

\[ ^1\text{H NMR (300.072 MHz, CDCl}_3 \] $\delta$ 1.65 - 1.94 (m, 4H), 2.15 (s, 3H), 2.78 - 2.91 (m, 2H), 3.06 - 3.21 (m, 2H), 3.32 - 3.83 (m, 8H), 3.91 - 4.10 (m, IH), 4.76 - 4.96 (m, IH), 5.39 (t, IH), 6.70 (s, IH), 7.02 - 7.15 (m, 2H), 7.32 (d, 2H), 7.53 - 7.55 (m, IH), 7.61 (d, 2H), m/z 463 (M+H)$^+$.  

Example 162

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(oxan-4-yl)urea

Method 2 from Intermediate A

\[ \text{Method 2 from Intermediate A} \]

\[ ^1\text{H NMR (400.132 MHz, CDCl}_3 \] $\delta$ 1.44 - 1.55 (m, 2H), 1.58 - 1.80 (m, 4H), 1.89 - 1.96 (m, 2H), 1.99 (s, 3H), 2.80 - 2.93 (m, 2H), 3.10 - 3.21 (m, IH), 3.49 (t, 2H), 3.81 - 3.87 (m, IH), 3.94 - 3.99 (m, 3H), 4.83 - 4.95 (m, IH), 5.67 (d, IH), 6.64 (s, IH), 6.92 - 7.06 (m, 2H), 7.33 (d, 2H), 7.45 - 7.50 (m, IH), 7.62 (d, 2H), m/z 479 (M+H)$^+$.  

Example 163

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2,6-dioxabicyclo[5.4.0]undeca-8,10,12-trien-4-yl)urea
Method 2 from Intermediate A

1H NMR (400.132 MHz, CDCl$_3$) δ 1.48 - 1.83 (m, 4H), 2.05 (s, 3H), 2.59 - 2.81 (m, 2H), 2.99 - 3.17 (m, IH), 3.89 - 3.96 (m, IH), 4.08 - 4.12 (m, 2H), 4.25 - 4.30 (m, 2H), 4.34 - 4.43 (m, IH), 4.72 - 4.82 (m, IH), 6.48 (d, IH), 6.91 - 7.05 (m, 6H), 7.20 (s, IH), 7.27 (d, 2H), 7.47 - 7.50 (m, IH), 7.60 (d, 2H), m/z 511 (M+H)$^+$.  

Example 164

3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-1-(2-propoxyethyl)urea

Method 2 from Intermediate A

1H NMR (400.132 MHz, CDCl$_3$) δ 0.89 (t, 3H), 1.52 - 1.58 (m, 2H), 1.71 - 2.03 (m, 4H), 2.23 (s, 3H), 2.80 - 2.88 (m, 2H), 3.08 - 3.22 (m, IH), 3.39 - 3.45 (m, 4H), 3.53 (t, 2H), 3.95 - 4.09 (m, IH), 4.79 - 4.94 (m, IH), 5.15 (t, IH), 6.52 (s, IH), 7.09 - 7.20 (m, 2H), 7.33 (d, 2H), 7.59 - 7.63 (m, 3H), m/z 449 (M+H)$^+$.  

Example 165

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(7,10-dioxabicyclo[4.4.0]deca-2,4,10-trien-8-ylmethyl)urea

Method 2 from Intermediate A

1H NMR (400.132 MHz, CDCl$_3$) δ 1.70 - 1.98 (m, 4H), 2.09 (s, 3H), 2.76 - 2.88 (m, 2H), 3.08 - 3.24 (m, IH), 3.46 - 3.64 (m, 2H), 3.92 - 4.01 (m, 2H), 4.26 - 4.34 (m, 2H), 4.80 - 4.91 (m, IH), 5.77 (t, IH), 6.77 (s, IH), 6.82 - 6.90 (m, 4H), 6.97 - 7.08 (m, 2H), 7.31 (d, 2H), 7.41 (s, IH), 7.62 (d, 2H), m/z 511 (M+H)$^+$.  

Example 166

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(oxan-2-ylmethyl)urea
Method 2 from Intermediate A

**Example 167**

3-(cyanomethyl)-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]urea

**Example 168**

l-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2,2,2-trifluoroethyl)urea

**Example 169**

l-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(1,1-dioxothiolan-3-yl)urea
Method 2 from Intermediate A

1H NMR (400.132 MHz, CDCl3) δ 1.70 - 1.85 (m, 3H), 1.94 (s, 3H), 1.98 - 2.04 (m, IH), 2.26 - 2.35 (m, IH), 2.48 - 2.57 (m, IH), 2.81 - 2.95 (m, 2H), 3.05 - 3.21 (m, 3H), 3.27 - 3.35 (m, IH), 3.39 - 3.44 (m, IH), 3.95 - 4.00 (m, IH), 4.64 (sextet, IH), 4.83 - 4.94 (m, IH), 6.62 (d, IH), 6.77 (s, IH), 6.92 - 7.06 (m, 2H), 7.34 (d, 2H), 7.52 (s, IH), 7.63 (d, 2H), m/z 481 (M+H)+.

Example 170

3-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-1-phenyl]carbamoylamino]-N-pyridin-2-yl-propanamide

Method 6 from Example 125

1H NMR (300.073 MHz, de-DMSO) δ 1.54-1.96 (4H, m), 2.17 (3H, s), 2.61 (2H, t, J5.9), 2.84-3.10 (3H, m), 3.38-3.40 (2H, m), 3.62-3.80 (IH, m), 4.49-4.75 (IH, m), 6.76 (IH, t, J5.5), 6.90 (IH, d, J7.1), 7.07 (IH, t, J5.3), 7.15 (IH, d, J7.7), 7.49 (2H, d, J7.9), 7.76 (2H, d, J7.9), 7.70-7.80 (IH, m), 7.80 (IH, s), 7.97 (IH, s), 8.10 (IH, d, J5.2), 8.29 (IH, d, J3.7), 10.49 (IH, bs), m/z 511 (M+H)+.

Example 171

2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]-N-propan-2-yl-acetamide

Method 2 from Intermediate A

1H NMR (300.073 MHz, t6-DMSO, 30° C) δ 1.05 (6H, d, J = 7.3 Hz), 1.46 - 1.93 (4H, m), 2.20 (3H, s), 2.60 - 3.19 (3H, m), 3.51 - 3.95 (4H, m), 4.40 - 4.70 (IH, m), 6.82 - 6.96 (2H, m), 7.17 (IH, d J = 6.8 Hz), 7.49 (2H, d J = 7.3 Hz), 7.70 - 7.85 (3H, m), 7.94 (IH, s), 8.03 (IH, s), m/z 462 (M+H)+.
Example 172
1-butyl-3-[2-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino] ethylurea

Method 2 from Intermediate A

$^1$H NMR (300.073 MHz, d$_6$-DMSO, 30°C) δ 0.85 (3H, t J = 8.4 Hz), 1.16 - 1.40 (4H, m),
1.47 - 1.95 (4H, m), 2.20 (3H, s), 2.68 - 3.23 (9H, m), 3.60 - 4.01 (IH, m appears as a
broad flat singlet), 4.37 - 4.71 (IH, m appears as a broad flat singlet), 5.73 - 5.91 (2H, m),
6.59 - 6.70 (IH, m), 6.92 (IH, d J = 8.6 Hz), 7.17 (IH, d J = 8.1 Hz), 7.49 (2H, d J = 8.1
Hz), 7.72 - 7.82 (3H, m), 7.93 (IH, s), m/z 505 (M+H)+.

Example 173
N-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-1-phenyl]carbamoylamino]
pentyl)morpholine-4-carboxamide

Method 2 from Intermediate A

$^1$H NMR (300.073 MHz, d$_6$-DMSO, 30°C) δ 1.21 - 1.35 (2H, m), 1.36 - 1.50 (4H, m),
1.50 - 1.69 (2H, m), 1.69 - 1.91 (2H, m), 2.20 (3H, s), 2.69 - 3.15 (7H, m), 3.16 - 3.25 (4H,
m), 3.45 - 3.56 (4H, m), 3.64 - 3.96 (IH, m appears as a broad flat singlet), 4.40 - 4.80
(IH, m appears as a broad flat singlet), 6.45 (IH, t J = 5.1 Hz), 6.59 (IH, t J = 5.1 Hz),
6.91 (IH, d J = 6.8 Hz), 7.16 (IH, d J = 7.7 Hz), 7.49 (2H, d J = 8.6 Hz), 7.66 (IH, s),
7.76 (2H, d J = 8.5 Hz), 7.95 (IH, s), m/z 561 (M+H)+.

Example 174
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-l-[2-(propylsulfonlamino)ethyl] urea

Method 2 from Intermediate A
1H NMR (300.073 MHz, d$_6$-DMSO, 30° C) δ 0.95 (3H, t, J = 7.6 Hz), 1.49 - 1.93 (6H, m), 2.20 (3H, s), 2.75 - 3.08 (7H, m), 3.14 - 3.23 (2H, m), 3.58 - 3.95 (IH, m appears as a broad flat singlet), 4.34 - 4.78 (IH, m appears as a broad flat singlet), 6.73 (IH, t, J = 5.7 Hz), 6.93 (IH, d, J = 6.7 Hz), 7.08 (IH, t, J = 5.8 Hz), 7.17 (IH, d, J = 9.1 Hz), 7.49 (2H, d, J = 8.5 Hz), 7.76 (2H, d, J = 8.5 Hz), 7.84 (IH, s), 7.91 (IH, s), m/z 512 (M+H)+.

Example 175

N-[2-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]ethyl)cyclohexanecarboxamide

Method 2 from Intermediate A

1H NMR (300.073 MHz, d$_6$-DMSO, 30° C) δ 1.02 - 1.40 (6H, m), 1.45 - 1.92 (10H, m), 1.96 - 2.12 (IH, m), 2.19 (3H, s), 2.68 - 3.20 (7H, m), 3.59 - 3.96 (IH, m), 4.40 - 4.80 (IH, m), 6.54 - 6.65 (IH, m), 6.92 (IH, d, J = 8.2 Hz), 7.17 (IH, d, J = 8.9 Hz), 7.49 (2H, d, J = 8.2 Hz), 7.59 - 7.73 (IH, m), 7.73 - 7.83 (3H, m), 7.91 (IH, s), m/z 516 (M+H)+.

Example 176

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[2-(2-oxopyrrolidin-1-yl)ethyl]urea

Method 2 from Intermediate A

1H NMR (300.073 MHz, d$_6$-DMSO, 30° C) δ 1.46 - 1.69 (2H, m), 1.70 - 1.98 (4H, m), 2.08 - 2.29 (5H, m), 2.67 - 3.18 (3H, m), 3.18 - 3.27 (4H, m), 3.32 - 3.42 (2H, m), 3.60 - 3.94 (IH, m), 4.41 - 4.81 (IH, m), 6.53 - 6.62 (IH, m), 6.93 (IH, d, J = 7.5 Hz), 7.17 (IH, d, J = 8.1 Hz), 7.50 (2H, d, J = 8.1 Hz), 7.72 - 7.79 (3H, m), 7.88 (IH, s), m/z (M+H)+.

Example 177

Methyl (2S)-3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]-2-[(2-methylpropan-2-yl)oxycarbonylamino]propanoate
Method 2 from Intermediate A

$^1$H NMR (300.073 MHz, d$_6$-DMSO, 30°C) δ 1.37 (9H, s), 1.49 - 1.94 (4H, m), 2.20 (3H, s), 2.67 - 3.23 (5H, m), 3.47 - 3.94 (5H, m), 3.96 - 4.18 (2H, m), 4.32 - 4.76 (IH, m), 6.67 - 6.83 (IH, m), 6.93 - 6.96 (IH, m), 7.13 - 7.28 (2H, m), 7.50 (2H, d J = 7.2 Hz), 7.74 - 7.77 (2H, m), 7.88 - 7.93 (2H, m), m/z 564 (M+H)$^+$.  

Example 178  
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[3-(2-oxazepanyl)propyl]urea

Method 2 from Intermediate A

$^1$H NMR (300.073 MHz, d$_6$-DMSO, 30°C) δ 1.42 - 1.95 (12H, m), 2.20 (3H, s), 2.33 - 2.45 (2H, m), 2.69 - 3.22 (6H, m), 3.24 - 3.40 (3H, m), 3.61 - 3.95 (IH, m), 4.39 - 4.79 (IH, m), 6.61 (IH, t J = 5.3 Hz), 6.92 (IH, d J = 9.7 Hz), 7.17 (IH, d J = 8.1 Hz), 7.50 (2H, d J = 8.8 Hz), 7.71 - 7.85 (3H, m), 7.92 (IH, s), m/z 516 (M+H)$^+$.  

Example 179  
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]-N-methyl-propanamide

Method 6 from Example 125

$^1$H NMR (400 MHz, d$_6$-DMSO, 30°C) 1.50-1.80 (4H, m), 2.19 (3H, s), 2.27 (2H, t, J6.0), 2.83-3.17 (3H, m), 3.30 (2H, bs), 3.54 (3H, s), 3.78-3.86 (IH, m), 4.55-4.70 (IH, m), 6.73
(IH, bs), 6.92 (IH, d, J 6), 7.17 (IH, d, J 7.6), 7.51 (2H, d, J 7.8), 7.78 (2H, d, J 7.8), 7.84 (IH, s), 7.77-7.84 (IH, m), 7.98 (IH, s), m/z 448 (M+H)+.

**Example 180**
tert-butyl (2S)-2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl] carbamoylamino]-4-methylsulfonyl-butanoate

![Chemical Structure](image)

Method 2 from Intermediate A

^1H NMR (300.073 MHz, d6-DMSO) δ 1.42 (s, 9H), 1.51 - 1.87 (m, 4H), 1.89 - 2.08 (m, IH), 2.10 - 2.28 (m, 4H), 2.76 - 3.26 (m, 8H), 3.63 - 3.95 (m, 1H), 4.17 - 4.31 (m, 4H), 4.40 - 4.75 (m, 1H), 6.91 - 6.98 (m, 1H), 7.08 (d, 1H), 7.19 (d, 1H), 7.49 (d, 2H), 7.76 (d, 2H), 7.89 - 7.98 (m, 2H), m/z 583 (M+H)+.

**Example 181**
Methyl 4-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino] cyclohexane-1-carboxylate

![Chemical Structure](image)

Method 2 from Intermediate A

^1H NMR (300.073 MHz, d6-DMSO) δ 1.08 - 1.27 (m, 2H), 1.32 - 1.49 (m, 2H), 1.51 - 1.84 (m, 4H), 1.86 - 2.01 (m, 4H), 2.18 (s, 3H), 2.24 - 2.38 (m, 1H), 2.75 - 3.24 (m, 3H), 3.31 - 3.47 (m, 1H), 3.59 (s, 3H), 3.67 - 3.96 (m, 1H), 4.36 - 4.81 (m, 1H), 6.57 (d, 1H), 6.90 (d, 1H), 7.16 (d, 1H), 7.49 (d, 2H), 7.60 (s, 1H), 7.76 (d, 2H), 7.98 (s, 1H), m/z 583 (M+H)+.

**Example 182**
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(1-hydroxypropan-2-yl)urea
Method 2 from Intermediate A

{\textsuperscript{1}H NMR (400.132 MHz, CDCl\textsubscript{3}) \delta 1.19 (d, 3H), 1.59 - 1.86 (m, 4H), 1.96 (s, 3H), 2.82 - 2.92 (m, 2H), 3.09 - 3.22 (m, IH), 3.47 - 3.55 (m, IH), 3.75 (s, IH), 3.89 - 4.02 (m, 3H), 4.81 - 4.92 (m, IH), 5.86 (s, IH), 6.87 - 6.93 (m, 2H), 7.00 (d, IH), 7.34 (d, 2H), 7.62 (d, 2H), 7.68 - 7.72 (m, IH), m/z 421 (M+H){+}.}

Example 183

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2-hydroxypropyl)urea

Method 2 from Intermediate A

{\textsuperscript{1}H NMR (400.132 MHz, CDCl\textsubscript{3}) \delta 1.66 - 2.00 (m, 4H), 2.07 (s, 3H), 2.82 - 2.93 (m, 2H), 3.12 - 3.20 (m, IH), 3.29 - 3.44 (m, 2H), 3.57 - 3.63 (m, 3H), 3.70 (s, IH), 3.78 - 3.83 (m, IH), 3.94 - 4.01 (m, IH), 4.84 - 4.91 (m, IH), 5.96 (s, IH), 6.86 (s, IH), 6.97 (d, IH), 7.08 (d, IH), 7.34 (d, 2H), 7.60 - 7.64 (m, 3H), m/z 437 (M+H){+}.}

Example 184

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2,3-dihydroxypropyl)urea

Method 2 from Intermediate A

{\textsuperscript{1}H NMR (400.132 MHz, CDCl\textsubscript{3}) \delta 1.19 (d, 3H), 1.59 - 1.86 (m, 4H), 1.96 (s, 3H), 2.82 - 2.92 (m, 2H), 3.09 - 3.22 (m, IH), 3.47 - 3.55 (m, IH), 3.75 (s, IH), 3.89 - 4.02 (m, 3H), 4.81 - 4.92 (m, IH), 5.86 (s, IH), 6.87 - 6.93 (m, 2H), 7.00 (d, IH), 7.34 (d, 2H), 7.62 (d, 2H), 7.68 - 7.72 (m, IH), m/z 421 (M+H){+}.}

Example 185

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(4-hydroxybutyl)urea

Method 2 from Intermediate A
$^1$H NMR (400.132 MHz, CDCl$_3$) $\delta$ 1.60 - 1.66 (m, 4H), 1.71 - 2.01 (m, 4H), 2.05 (s, 3H), 2.80 - 2.92 (m, 2H), 3.10 - 3.20 (m, IH), 3.25 - 3.31 (m, 2H), 3.55 (s, IH), 3.64 - 3.70 (m, 2H), 3.94 - 4.04 (m, IH), 4.86 - 4.91 (m, IH), 6.06 (t, IH), 6.66 (s, IH), 6.91 (d, IH), 7.05 (d, IH), 7.34 (d, 2H), 7.60 - 7.64 (m, 3H), m/z 435 (M+H)$^+$.  

Example 186

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(1,3-dihydroxypropan-2-yl)urea

Method 2 from Intermediate A

$^1$H NMR (400.132 MHz, CDCl$_3$) $\delta$ 1.63 - 1.96 (m, 4H), 2.04 (s, 3H), 2.80 - 2.91 (m, 2H), 3.12 - 3.22 (m, IH), 3.58 (s, 2H), 3.78 - 3.91 (m, 5H), 3.95 - 4.02 (m, IH), 4.79 - 4.89 (m, IH), 6.25 (s, IH), 6.89 (s, IH), 6.94 (d, IH), 7.06 (d, IH), 7.33 (d, 2H), 7.62 (d, 2H), 7.81 - 7.83 (m, IH), m/z 437 (M+H)$^+$.  

Example 187

(RS) 1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2-hydroxycyclohexyl) urea

Method 2 from Intermediate A

$^1$H NMR (400.132 MHz, CDCl$_3$) $\delta$ 1.16 - 1.37 (m, 4H), 1.60 - 1.82 (m, 6H), 1.98 (s, 3H), 1.98 - 2.05 (m, 2H), 2.78 - 2.90 (m, 2H), 3.08 - 3.16 (m, IH), 3.28 - 3.36 (m, IH), 3.41 - 3.45 (m, IH), 3.93 - 4.01 (m, IH), 4.53 (s, IH), 4.81 - 4.90 (m, IH), 5.74 (s, IH), 6.92 (d, IH), 7.02 (d, IH), 7.18 (s, IH), 7.34 (d, 2H), 7.61 (d, 2H), 7.63 - 7.64 (m, IH), m/z 461 (M+H)$^+$.  

Example 188

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(3-hydroxy-2,2-dimethyl-propyl)urea
**Example 189**

1-[5-[4-(4-cyanophenyl)piperidin-1-carbonyl]-2-methyl-phenyl]-3-[2-(2-hydroxyethoxy)ethyl]urea

**Example 190**

1-[5-[4-(4-cyanophenyl)piperidin-1-carbonyl]-2-methyl-phenyl]-3-(1-hydroxy-2-methylpropan-2-yl)urea

**Example 191**

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(3-hydroxypropyl)]urea
Method 2 from Intermediate A

$^1$H NMR (400.132 MHz, CDCl$_3$) $\delta$ 1.69 - 1.72 (m, 2H), 1.77 - 2.02 (m, 4H), 2.07 (s, 3H), 2.81 - 2.94 (m, 2H), 3.08 - 3.21 (m, IH), 3.41 (q, 2H), 3.71 (q, 2H), 3.94 - 4.03 (m, IH), 4.09 (t, IH), 4.82 - 4.93 (m, IH), 6.00 (t, IH), 6.67 (s, IH), 6.96 (d, IH), 7.08 (d, IH), 7.34 (d, 2H), 7.48 (s, IH), 7.62 (d, 2H), m/z 421 (M+H$^+$.)

Example 192
(2S)-2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]-3-hydroxy-propanamide

Method 2 from Intermediate A

$^1$H NMR (400.132 MHz, CDCl$_3$) $\delta$ 1.55 - 2.02 (m, 4H), 2.08 (s, 3H), 2.70 - 2.86 (m, 2H), 3.01 - 3.15 (m, IH), 3.62 - 3.73 (m, IH), 3.85 - 4.00 (m, 2H), 4.37 (s, IH), 4.66 - 4.91 (m, 2H), 6.82 - 7.10 (m, 4H), 7.29 - 7.36 (m, 3H), 7.56 (d, 2H), 7.80 (s, IH), 7.92 (s, IH), m/z 450 (M+H$^+$.)

Example 193
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(4-hydroxycyclohexyl) urea

Method 2 from Intermediate A

$^1$H NMR (400.132 MHz, CDCl$_3$) $\delta$ 1.15 - 1.26 (m, 2H), 1.35 - 1.45 (m, 2H), 1.53 (d, IH), 1.66 - 1.86 (m, 4H), 1.93 - 2.04 (m, 4H), 2.08 (s, 3H), 2.80 - 2.93 (m, 2H), 3.10 - 3.22 (m, IH), 3.58 - 3.66 (m, 2H), 3.91 - 4.01 (m, IH), 4.82 - 4.90 (m, IH), 5.18 (d, IH), 6.42 (s, IH), 6.99 (d, IH), 7.09 (d, IH), 7.32 (d, 2H), 7.49 - 7.51 (m, IH), 7.62 (d, 2H), m/z 461 (M+H$^+$.).
Example 194
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[1-(hydroxymethyl)cyclopentyl] urea

Method 2 from Intermediate A

$^1$H NMR (400.132 MHz, CDCl$_3$) $\delta$ 1.64 - 1.86 (m, 1H), 1.92 (s, 3H), 1.97 - 2.02 (m, 1H), 2.81 - 2.93 (m, 2H), 3.10 - 3.19 (m, 1H), 3.72 - 3.80 (m, 2H), 3.93 - 3.98 (m, 1H), 4.85 - 4.91 (m, 1H), 5.09 (t, 1H), 6.10 (s, 1H), 6.82 (d, 1H), 6.93 (d, 1H), 7.04 (s, 1H), 7.35 (d, 2H), 7.60 - 7.67 (m, 3H), m/z 461 (M+H)$^+$.  

Example 195

(RS)-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(3,3,3-trifluoro-2-hydroxy-propyl)urea

Method 2 from Intermediate A

$^1$H NMR (400.132 MHz, CDCl$_3$) $\delta$ 1.61 - 1.87 (m, 4H), 2.04 (s, 3H), 2.79 - 2.95 (m, 2H), 3.14 - 3.19 (m, 1H), 3.66 - 3.74 (m, 1H), 3.87 (t, 2H), 3.95 - 4.15 (m, 1H), 4.86 - 4.95 (m, 2H), 6.22 - 6.25 (m, 1H), 6.36 - 6.39 (m, 1H), 6.91 - 7.08 (m, 2H), 7.35 (d, 2H), 7.61 - 7.63 (m, 3H), m/z 475 (M+H)$^+$.  

Example 196

3-[3-(2-chlorophenoxy)-2-hydroxy-propyl]-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]urea

Method 2 from Intermediate A

$^1$H NMR (400.132 MHz, CDCl$_3$) $\delta$ 1.70 - 2.00 (m, 4H), 2.05 (s, 3H), 2.72 - 2.86 (m, 2H), 3.08 - 3.17 (m, 1H), 3.40 - 3.50 (m, 1H), 3.64 - 3.71 (m, 1H), 3.93 - 4.09 (m, 3H), 4.16 -
4.23 (m, IH), 4.39 (s, IH), 4.79 - 4.88 (m, IH), 6.02 (s, IH), 6.89 - 7.06 (m, 5H), 7.19 - 7.24 (m, IH), 7.30 - 7.36 (m, 3H), 7.58 - 7.61 (m, 3H), m/z 548 (M+H)^+.

**Example 197**
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-1-phenyl]-3-(3-hydroxy-1-adamantyl)urea

![Chemical Structure](image)

**Method 2 from Intermediate A**

$^1$H NMR (400.132 MHz, CDCl$_3$) δ 1.50 - 1.75 (m, HH), 1.83 - 1.88 (m, 2H), 1.97 (s, 3H), 1.98 - 2.03 (m, 2H), 2.10 - 2.15 (m, 2H), 2.25 - 2.29 (m, 2H), 2.79 - 2.91 (m, 2H), 3.07 - 3.21 (m, IH), 3.91 - 4.02 (m, IH), 4.82 - 4.92 (m, IH), 5.58 (s, IH), 6.71 (s, IH), 6.82 (d, IH), 6.95 (d, IH), 7.34 (d, 2H), 7.60 - 7.67 (m, 3H), m/z 513 (M+H)^+.

**Example 198**
1-[5-[4-(cyanophenyl)piperidine-1-carbonyl]-2-methyl-1-phenyl]-3-[(2R)-1-hydroxy-3-methoxy-propan-2-yl]urea

![Chemical Structure](image)

**Method 2 from Intermediate A**

$^1$H NMR (400.132 MHz, CDCl$_3$) δ 1.69 - 2.03 (m, 4H), 2.11 (s, 3H), 2.80 - 2.87 (m, 2H), 3.07 - 3.20 (m, IH), 3.34 - 3.38 (m, IH), 3.38 (s, 3H), 3.59 (d, 2H), 3.75 - 3.85 (m, 2H), 3.96 - 4.03 (m, 2H), 4.82 - 4.93 (m, IH), 5.83 (d, IH), 6.78 (s, IH), 6.99 (d, IH), 7.09 (d, IH), 7.33 (d, 2H), 7.62 (d, 2H), 7.70 (s, IH), m/z 451 (M+H)^+.

**Example 199**
1-[5-[4-(cyanophenyl)piperidine-1-carbonyl]-2-methyl-1-phenyl]-3-[(3R)-oxolan-3-yl]urea

![Chemical Structure](image)

**Method 2 from Intermediate A**

$^1$H NMR (400.132 MHz, CDCl$_3$) δ 1.73 - 1.89 (m, 4H), 1.95 - 1.99 (m, IH), 2.02 (s, 3H), 2.21 - 2.30 (m, IH), 2.81 - 2.88 (m, 2H), 3.10 - 3.16 (m, IH), 3.66 - 3.70 (m, IH), 3.80 -
4.03 (m, 4H), 4.38 - 4.45 (m, IH), 4.81 - 4.92 (m, IH), 5.83 (d, IH), 6.63 (s, IH), 6.95 (d, IH), 7.06 (d, IH), 7.33 (d, 2H), 7.48 (s, IH), 7.62 (d, 2H), m/z 433 (M+H)+.

**Example 200**

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[3-(3-methyl-1H-pyrazol-4-yl)propyl]urea

Method 2 from Intermediate A

$^1$H NMR (300.072 MHz, CDCl$_3$) $\delta$ 1.60 - 1.93 (m, 6H), 2.04 (s, 3H), 2.15 (s, 3H), 2.38 (t, 2H), 2.75 - 2.89 (m, 2H), 3.08 - 3.24 (m, 3H), 3.86 - 4.06 (m, IH), 4.76 - 4.91 (m, IH), 5.82 - 5.93 (m, IH), 6.93 - 7.08 (m, 3H), 7.21 (s, IH), 7.29 (d, 2H), 7.58 (d, 2H), 7.67 (s, IH) [NB the signal due to the imidazole was not apparent], m/z 485 (M+H)+.

**Example 201**

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-ethyl-phenyl]-3-propan-2-yl-urea

Method 2 from Intermediate L

$^1$H NMR (300.073 MHz, de-DMSO, 30° C) $\delta$ 1.03 - 1.21 (9H, m), 1.46 - 1.93 (4H, m), 2.42 - 2.62 (2H, m, partially obscured by DMSO signal), 2.66 - 3.20 (3H, m), 3.55 - 3.98 (2H, m, appears as a broad flat singlet containing a multiplet), 4.39 - 4.76 (IH, m), 6.52 (IH, dJ = 7.2Hz), 6.95 (IH, dJ = 7.2Hz), 7.16 (IH, dJ = 8.4Hz), 7.49 (2H, dJ = 8.3Hz), 7.57 (IH, s), 7.75 (2H, dJ = 7.7Hz), 7.95 (IH, s), m/z 419 (M+H)+.

**Example 202**

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2-methanesulfonamido-2-methyl-propyl)urea

Method 5 from Example 203

$^1$H NMR (300.072 MHz, CDCl$_3$) $\delta$ 1.38 (s, 6H), 1.69 - 1.84 (m, 4H), 2.00 (s, 3H), 2.77 - 2.93 (m, 2H), 3.01 (s, 3H), 3.08 - 3.19 (m, IH), 3.31 (d, 2H), 3.89 - 4.00 (m, IH), 4.76 -
4.98 (m, IH), 5.64 (s, IH), 6.24 - 6.32 (m, IH), 6.92 (d, IH), 6.99 - 7.05 (m, 2H), 7.34 (d, 2H), 7.58 - 7.64 (m, 3H), m/z 512 (M+H)^+.

Example 203
3-(2-amino-2-methyl-propyl)-l-[5-[4-(4-cyanophenyl)piperidine-I-carbonyl]-2-methyl-phenyl]urea

\[ \text{Method 2 from Intermediate A} \]

\[ ^1\text{H NMR (300.072 MHz, CDCl}_3\text{)} \delta 1.12 (s, 6H), 1.56 - 2.03 (m, 4H), 2.20 (s, 3H), 2.77 - 2.96 (m, 4H), 3.03 - 3.09 (m, IH), 3.15 (d, 2H), 3.93 - 4.09 (m, IH), 4.70 - 5.03 (m, IH), 6.45 - 6.53 (m, IH), 6.97 (d, IH), 7.11 (d, IH), 7.31 (d, 2H), 7.60 (d, 2H), 7.71 (m, 2H), m/z 434 (M+H)^+ \].

Example 204
3-[5-[4-(4-cyanophenyl)piperidine-I-carbonyl]-2-methyl-phenyl]-1-[2-(ethylsulfbylamino)-2-methyl-propyl]urea

\[ \text{Method 5 from Example 203} \]

\[ ^1\text{H NMR (300.072 MHz, CDCl}_3\text{)} \delta 1.32 - 1.38 (m, 9H), 1.63 - 1.83 (m, 4H), 2.03 (s, 3H), 2.80 - 2.88 (m, 2H), 3.05 (q, 2H), 3.12 - 3.22 (m, IH), 3.32 (d, 2H), 3.89 - 4.09 (m, IH), 4.77 - 5.01 (m, IH), 5.40 (s, IH), 6.23 (t, IH), 6.88 (s, IH), 6.92 - 7.08 (m, 2H), 7.34 (d, 2H), 7.57 - 7.63 (m, 3H), m/z 526 (M+H)^+ \].

Example 205
N-[1-[5-[4-(4-cyanophenyl)piperidine-I-carbonyl]-2-methyl-phenyl]carbamoylamino]-2-methyl-propan-2-yl]-2,2-dimethyl-propanamide

\[ \text{Method 5 from Example 203} \]

\[ ^1\text{H NMR (300.072 MHz, CDCl}_3\text{)} \delta 1.13 (s, 9H), 1.33 (s, 6H), 1.57 - 1.78 (m, 4H), 2.15 (s, 3H), 2.79 - 2.91 (m, 2H), 3.00 - 3.18 (m, IH), 3.28 (d, 2H), 3.89 - 4.08 (m, IH), 4.71 - 4.96 \]
(m, IH), 6.16 (t, IH), 6.63 (s, IH), 6.79 (s, IH), 7.03 - 7.16 (m, 2H), 7.31 (d, 2H), 7.53 - 7.55 (m, IH), 7.61 (d, 2H), m/z 518 (M+H)+.

**Example 206**

tert-buty 1N-[3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]propyl]carbamate

Method 2 from Intermediate A

IH NMR (300.072 MHz, CDCl$_3$) δ  1.42 (s, 9H), 1.59 - 1.70 (m, 2H), 1.76 - 2.00 (m, 4H), 2.12 (s, 3H), 2.78 - 2.91 (m, 2H), 2.97 - 3.07 (m, 1H), 3.17 (q, 2H), 3.26 (q, 2H), 3.92 - 4.05 (m, IH), 4.77 - 4.94 (m, IH), 5.06 (s, IH), 5.73 (s, IH), 6.57 (s, IH), 6.97 - 7.14 (m, 2H), 7.32 (d, 2H), 7.58 - 7.64 (m, 3H), m/z (ESI+) (M+H)+ = 520; HPLC tR = 2.32 min

**Example 207**

3-(3-aminopropyl)- 1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]urea

Method 3 from Example 206

IH NMR (300.073 MHz, de-DMSO) δ 1.56 - 1.85 (m, 6H), 2.23 (s, 3H), 2.76 - 3.00 (m, 4H), 3.07 - 3.22 (m, 3H), 3.63 - 3.93 (m, 1H), 4.57 (s, 3H), 6.92 (d, IH), 7.16 (d, IH), 7.22 (s, IH), 7.49 (d, 2H), 7.76 (d, 2H), 7.93 (s, IH), 8.12 (s, IH), m/z (ESI+) (M+H)+ = 420; HPLC tR = 1.24 min.

**Example 208**

tert-butyl 4-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]piperidine-1-carboxylate

Method 2 from Intermediate A
1H NMR (300.073 MHz, d₆-DMSO) δ 1.20 - 1.33 (m, 2H), 1.39 (s, 9H), 1.48 - 1.94 (m, 6H), 2.19 (s, 3H), 2.65 - 3.22 (m, 5H), 3.50 - 3.95 (m, 4H), 4.37 - 4.83 (m, 1H), 6.66 (d, IH), 6.91 (d, IH), 7.16 (d, IH), 7.49 (d, 2H), 7.64 (s, IH), 7.75 (d, 2H), 7.97 (s, IH), [also contains signals due to EtOAc], m/z 546 (M+H)+.

Example 209
tert-butyl (3R)-3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl] carbamoylamino]pyrrolidine-1-carboxylate

Example 210
tert-butyl (3S)-3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl] carbamoylamino]pyrrolidine-1-carboxylate

Example 211
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(4-piperidyl)urea

1H NMR (300.073 MHz, d₆-DMSO) δ 1.24 - 1.94 (m, 8H), 2.21 (s, 3H), 2.58 - 3.25 (m, 6H), 3.38 - 3.96 (m, 2H), 4.11 - 4.85 (m, 2H), 6.90 (d, IH), 6.96 (d, IH), 7.15 (d, IH), 7.48 (d, 2H), 7.75 (d, 2H), 7.81 (s, IH), 7.99 (s, IH), m/z 446 (M+H)+.

Example 212
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[(3R)-pyrrolidin-3-yl]urea
Example 213

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[3S]-pyrrolidin-3-yl]urea

Example 214

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[2-(methyl-propan-2-ylsulfonyl-amino)ethyl]urea

Example 215

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(3-methanesulfonamidopropyl) urea

Example 216

3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-1-[3-(ethylsulfonylamino)propyl]urea
Example 217
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[3-(propan-2-ylsulfonylamino)propyl]urea

m/z (ESI+) (M+H)+ = 512; HPLC tR = 2.00 min.

Example 218
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[(3R)-1-methylsulfonylpyrrolidin-3-yl]urea

m/z (ESI+) (M+H)+ = 526; HPLC tR = 2.08 min.

Example 219
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-1-[(3S)-1-ethylsulfonylpyrrolidin-3-yl]urea

Example 220
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-1-[(3S)-1-propanoylpyrrolidin-3-yl]urea
Example 221

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[(3S)-1-methylsulfonylpyrrolidin-3-yl]urea

Example 222

3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-1-[(3S)-1-ethylsulfonylpyrrolidin-3-yl]urea

Example 223

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(3-methylsulfonylpropyl)urea

Method 2 from Intermediate A

$^1$H NMR (300.073 MHz, de-DMSO, 30° C) δ 1.44 - 2.03 (6H, m), 2.21 (3H, s), 2.70 - 3.25 (1OH, m), 3.57 - 4.01 (IH, m appears as a broad flat singlet), 4.32 - 4.78 (IH, m appears as a broad flat singlet), 6.72 (IH, tJ = 5.4Hz), 6.93 (IH, dJ = 6.7Hz), 7.17 (IH, dJ = 7.5Hz), 7.49 (2H, dJ = 8.3Hz), 7.70 - 7.80 (3H, m), 7.93 (IH, s), m/z 483 (M+H)$^+$. 

Example 224

1-benzyl-3-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-fluoro-phenyl]urea
Method 2 from Intermediate M

$^1$H NMR (300.073 MHz, d$_6$-DMSO, 30° C) $\delta$ 1.38 - 1.95 (4H, m), 2.77 - 3.25 (3H, m), 3.46 - 3.60 (IH, m), 4.28 (2H, dJ = 6.6 Hz), 4.59 - 4.72 (IH, m), 5.34 (2H, dJ = 6.6 Hz), 4.59 - 4.72 (IH, m), 6.66 (IH, tJ = 5.9 Hz), 7.09 - 7.42 (7H, m), 7.43 - 7.56 (3H, m), 7.75 (2H, dJ = 9.6 Hz), 8.67 (IH, s), m/z 457 (M+H)$^+$.  

**Example 225**

1-[5-(4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-cyclopropyl-urea

Method 2 from Intermediate A

$^1$H NMR (300.073 MHz, de-DMSO) $\delta$ -0.01 - 0.39 (m, 4H), 1.21 - 1.61 (m, 4H), 1.90 (s, 3H), 2.32 - 2.96 (m, 4H), 3.39 - 3.68 (m, IH), 4.18 - 4.49 (m, IH), 6.49 - 6.54 (m, IH), 6.65 (d, J = 7.6 Hz, IH), 6.89 (d, J = 7.8 Hz, IH), 7.21 (d, J = 8.3 Hz, 2H), 7.30 (s, IH), 7.48 (d, J = 8.2 Hz, 2H), 7.65 (s, IH), m/z 403 (M+H)$^+$.  

**Example 226**

1-butan-2-yl-3-[5-(4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]urea

$^1$H NMR (300.073 MHz, d$_6$-DMSO) $\delta$ 0.75 - 1.49 (m, 8H), 1.52 - 1.68 (m, 2H), 1.70 - 1.90 (m, 2H), 2.19 (s, 3H), 2.60 - 3.18 (m, 3H), 3.52 - 3.65 (m, IH), 3.68 - 3.93 (m, IH), 4.43 - 4.72 (m, IH), 6.48 (d, J = 7.9 Hz, IH), 6.89 (d, J = 6.1 Hz, IH), 7.16 (d, J = 7.7 Hz, IH), 7.49 (d, J = 8.3 Hz, 2H), 7.60 (s, IH), 7.76 (d, J = 8.2 Hz, 2H), 8.00 (s, IH), m/z 419 (M+H)$^+$.  

**Example 227**

3-[5-(4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-1-phenyl]-1-propyl-urea
Method 2 from Intermediate A

$^1$H NMR (300.073 MHz, d$_6$-DMSO) $\delta$ 0.77 - 1.49 (m, 5H), 1.51 - 1.66 (m, 2H), 1.69 - 1.91 (m, 2H), 2.20 (s, 3H), 2.78 - 3.14 (m, 5H), 3.66 - 3.97 (m, 1H), 4.42 - 4.79 (m, 1H), 6.56 - 6.64 (m, 1H), 6.90 (d, $J$ = 7.7 Hz, 1H), 7.16 (d, $J$ = 7.7 Hz, 1H), 7.49 (d, $J$ = 8.2 Hz, 2H), 7.66 (s, 1H), 7.76 (d, $J$ = 8.1 Hz, 2H), 7.96 (s, 1H), m/z 405 (M+H)$^+$.  

**Example 228**

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-cyclohexyl-urea

$^1$H NMR (300.073 MHz, de-DMSO) $\delta$ 0.92 - 1.88 (m, 14H), 2.19 (s, 3H), 2.77 - 3.09 (m, 3H), 3.38 - 3.53 (m, 1H), 3.65 - 3.98 (m, 1H), 4.42 - 4.75 (m, 1H), 6.58 (d, $J$ = 7.7 Hz, 1H), 6.89 (d, $J$ = 9.2 Hz, 1H), 7.16 (d, $J$ = 7.8 Hz, 1H), 7.49 (d, $J$ = 8.3 Hz, 2H), 7.61 (s, 1H), 7.76 (d, $J$ = 8.2 Hz, 2H), 7.99 (s, 1H), m/z 445 (M+H)$^+$.  

**Example 229**

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(3-methylbutan-2-yl)urea

$^1$H NMR (300.073 MHz, de-DMSO) $\delta$ 0.75 - 1.92 (m, 14H), 2.20 (s, 3H), 2.71 - 3.17 (m, 3H), 3.49 - 3.65 (m, 1H), 3.67 - 3.95 (m, 1H), 4.46 - 4.75 (m, 1H), 6.50 (d, $J$ = 8.4 Hz, 1H), 6.89 (d, $J$ = 8.9 Hz, 1H), 7.16 (d, $J$ = 7.7 Hz, 1H), 7.49 (d, $J$ = 8.2 Hz, 2H), 7.63 (s, 1H), 7.76 (d, $J$ = 8.1 Hz, 2H), 8.01 (s, 1H), m/z 433 (M+H)$^+$.  

**Example 230**

3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]-N-(2-hydroxyethyl)propanamide
The title compound was prepared by the procedure described in Method 6, starting from 3-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]propanoic acid (Example 125).

$$^1$$H NMR (300.073 MHz, d$_6$-DMSO) δ 1.45-1.92 (4H, m), 2.18 (3H, s), 2.29 (2H, t, J6.4), 2.72-3.08 (4H, m), 3.67-3.42 (2H, m), 3.79 (IH, bs), 4.05 (2H, q, J5.3), 4.62 (2H, t, J5.4), 6.68 (IH, t, J5.7), 6.90 (IH, dd, J7.5, 1.4), 7.15 (IH, d, J7.7), 7.49 (2H, d, J8.3), 7.76 (2H, d, J8.3), 7.81 (IH, s), 7.86 (IH, t, J5.5), 7.96 (1H, s), m/z 477 (M+H)$^+$.  

**Example 231**

N-[2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]ethyl]-N',N'-dimethyl-propanediamide

$$^1$$H NMR (300.073 MHz, de-DMSO) δ 1.54 - 1.86 (m, 4H), 2.19 (s, 3H), 2.68 (s, 3H), 2.80 (s, 3H), 2.90 - 2.93 (m, 2H), 2.95 (s, 2H), 2.99 - 3.04 (m, IH), 3.12 - 3.18 (m, 4H), 3.67 - 3.94 (m, IH), 4.44 - 4.71 (m, IH), 6.65 (s, IH), 6.91 - 6.94 (m, IH), 7.17 (d, IH), 7.49 (d, 2H), 7.72 - 7.79 (m, 3H), 7.91 (s, IH), 8.03 - 8.09 (m, IH), m/z 519 (M+H)$^+$.  

**Example 232**

N-[2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]propyl]acetamide

$$^1$$H NMR (300.073 MHz, d$_6$-DMSO) δ 1.45-1.92 (4H, m), 2.18 (3H, s), 2.29 (2H, t, J6.4), 2.72-3.08 (4H, m), 3.67-3.42 (2H, m), 3.79 (IH, bs), 4.05 (2H, q, J5.3), 4.62 (2H, t, J5.4), 6.68 (IH, t, J5.7), 6.90 (IH, dd, J7.5, 1.4), 7.15 (IH, d, J7.7), 7.49 (2H, d, J8.3), 7.76 (2H, d, J8.3), 7.81 (IH, s), 7.86 (IH, t, J5.5), 7.96 (1H, s), m/z 477 (M+H)$^+$.  

Method 6 from Example 103
1H NMR (300.073 MHz, d$_6$-DMSO, 30°C) δ 1.04 (3H, d J = 6.5 Hz), 1.21 - 1.30 (2H, m possible impurity), 1.48 - 1.69 (2H, m 1.69 - 1.90), 3.51 - 4.00 (2H, m), 4.40 - 4.80 (IH, m appears as a broad flat singlet), 6.53 (IH, d J = 7.4 Hz), 6.91 (IH, d J = 8.1 Hz), 7.17 (IH, d J = 8.1 Hz), 7.49 (2H, d J = 8.8 Hz), 7.66 - 7.80 (3H, m), 7.81 - 7.89 (IH, m), 7.95 (IH, s), m/z 462 (M+H)$^+$.  

**Example 233**

N-[3-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]propyl]morpholine-4-carboxamide

![Chemical structure](image)

**Method 2 from Intermediate A**

1H NMR (300.073 MHz, d$_6$-DMSO, 30°C) δ 1.20 - 1.30 (2H, m, possible impurity), 1.47 - 1.68 (4H, m), 1.70 - 1.90 (2H, m), 2.20 (3H, s), 2.70 - 3.00 (2H, m), 3.01 - 3.16 (5H, m), 3.19 - 3.26 (4H, m), 3.47 - 3.55 (4H, m), 3.67 - 3.91 (IH, m), 4.40 - 4.74 (IH, m), 6.50 (IH, t J = 5.3 Hz), 6.64 (IH, t J = 5.6 Hz), 6.92 (IH, d J = 7.6 Hz), 7.17 (IH, d J = 7.6 Hz), 7.49 (2H, d J = 7.1 Hz), 7.72 - 7.80 (3H, m), 7.92 (IH, s), m/z 533 (M+H)$^+$.  

**Example 234**

3-[2-(carbamoylamino)ethyl]-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]urea

![Chemical structure](image)

**Method 2 from Intermediate A**

1H NMR (300.073 MHz, d$_6$-DMSO, 30°C) δ 1.44 - 1.95 (4H, m), 2.20 (3H, s), 2.66 - 3.21 (7H, m), 3.58 - 4.00 (IH, m appears as a broad flat singlet), 4.40 - 4.78 (IH, m appears as a broad flat singlet), 5.46 (2H, s), 5.93 - 6.03 (IH, m), 6.60 - 6.71 (IH, m),
6.92 (IH, d J = 7.4 Hz), 7.17 (IH, d J = 8.8 Hz), 7.50 (2H, d J = 8.8 Hz), 7.71 - 7.82 (3H, m), 7.94 (IH, s), m/z 449 (M+H)+.

Example 235

4-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-1-phenyl]carbamoylamino]-N-propyl-butanamide

\[
\begin{align*}
\text{Method 2 from Intermediate A}
\end{align*}
\]

\[^{1}H\text{ NMR (300.073 MHz, d}_{6}\text{-DMSO, } 30^\circ\text{ C) } \delta 0.82 (3H, t, J = 7.5 Hz), 1.30 - 1.46 (2H, m), 1.49 - 1.93 (6H, m), 2.10 (2H, t, J = 7.5 Hz), 2.19 (3H, s), 2.69 - 3.15 (7H, m), 3.63 - 3.93 (IH, m appears as a broad flat singlet), 4.39 - 4.78 (IH, m appears as a broad flat singlet), 6.62 (IH, t, J = 5.2 Hz), 6.91 (IH, d, J = 8.4 Hz), 7.16 (IH, d, J = 8.5 Hz), 7.49 (2H, d, J = 8.4 Hz), 7.69 (IH, s), 7.71 - 7.82 (3H, m), 7.95 (IH, s), m/z 490 (M+H)+.\]

Example 236

(RS)-1-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2-oxo-3-piperidyl)urea

\[
\begin{align*}
\text{Method 2 from Intermediate A}
\end{align*}
\]

\[^{1}H\text{ NMR (300.073 MHz, d}_{6}\text{-DMSO, } 30^\circ\text{ C) } \delta 1.43 - 1.94 (7H, m), 2.13 - 2.30 (4H, m), 2.76 - 3.22 (5H, m), 3.61 - 3.93 (IH, m), 3.95 - 4.09 (IH, m), 4.40 - 4.80 (IH, m), 6.87 - 7.02 (2H, m), 7.17 (IH, d, J = 8.5 Hz), 7.49 (2H, d, J = 7.7 Hz), 7.63 (IH, s), 7.75 (2H, d, J = 6.2 Hz), 7.97 (IH, s), 8.02 (IH, s), m/z 460 (M+H)+.\]

Example 237

Methyl 2-[[2-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino] acetyl] amino] acetate

\[
\begin{align*}
\text{Method 2 from Intermediate A}
\end{align*}
\]
Example 238

2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]-N,N-dimethyl-acetamide

\[
\text{Method 2 from Intermediate A}
\]

\[\text{H NMR (300.073 MHz, d}_6\text{-DMSO, 30° C) } \delta 1.46 - 1.93 (4H, m), 2.21 (3H, s), 2.67 - 3.20 (9H, m), 3.63 - 3.92 (IH, m), 3.96 (2H, d J = 6.7 Hz), 4.40 - 4.74 (IH, m), 6.83 - 6.97 (2H, m), 7.18 (IH, d J = 7.7 Hz), 7.49 (2H, d J = 9.3 Hz), 7.76 (2H, d J = 7.0 Hz), 7.93 (IH, s), 8.16 (IH, s), m/z 448 (M+H)^+.
\]

Example 239

(RS)-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2-oxo-3,4-dihydro-1H-1,8-naphthyridin-3-yl)urea

\[
\text{Method 2 from Intermediate A}
\]

\[\text{H NMR (300.073 MHz, d}_6\text{-DMSO, 30° C) } \delta 1.43 - 1.95 (4H, m), 2.24 (3H, s), 2.64 - 3.20 (4H, m), 3.29 (IH, s, obscured by HOD signal), 3.59 - 3.98 (IH, m), 4.32 - 4.48 (IH, m), 4.49 - 4.74 (IH, m), 6.89 - 7.06 (2H, m), 7.19 (2H, d J = 6.8 Hz), 7.50 (2H, d J = 7.7 Hz), 7.64 (IH, d J = 6.0 Hz), 7.75 (2H, d J = 6.0 Hz), 7.97 (IH, s), 8.09 - 8.24 (2H, m), 10.76 (IH, s), m/z 507 (M-H)- 509 (M+H)^+.
\]
Example 240

(2S)-2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]-4-methylsulfonyl-butanoic acid

The title compound was prepared by hydrolysis as described in Method 7 (Example 180), starting from tert-butyl (2S)-2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]-4-methylsulfonyl-butanoate (Example 180), but using NaOH instead of LiOH. 

1H NMR (300.073 MHz, d6-DMSO) δ 1.47 - 1.89 (m, 4H), 1.92 - 2.11 (m, IH), 2.13 - 2.34 (m, 4H), 2.76 - 3.28 (m, 8H), 3.62 - 3.95 (m, IH), 4.26 - 4.38 (m, IH), 4.45 - 4.79 (m, IH), 6.94 (d, IH), 7.11 (d, IH), 7.19 (d, IH), 7.49 (d, 2H), 7.76 (d, 2H), 7.96 (d, 2H), 12.69 - 13.23 (m, IH), m/z 527 (M+H)+.

Example 241

3-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]-N-(5-methyl-1,2-oxazol-4-yl)propanamide

The title compound was prepared by the process described in Method 6 (Example 125), starting from 3-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]propanoic acid (Example 125), (d6-DMSO) 1.57-1.90 (4H, m), 2.18 (3H, s), 2.36 (3H, s), 2.52-2.54 (2H, m), 2.71-2.96 (3H, m), 3.38 (2H, q, J6.1), 3.70-4.04 (IH, m), 4.57-4.72 (IH, m), 6.77 (IH, t, J5.9), 6.91 (IH, dd, 77.7, 1.6), 7.16 (IH, d, 77.7), 7.49 (2H, d, J8.2), 7.76 (2H, d, J8.2), 7.82 (IH, s), 7.96 (IH, d, J1.6), 8.70 (IH, s), 9.70 (IH, s), m/z 513 (M-H)- 515 (M+H)+.

Example 242

3-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]-N,N-bis(2-hydroxyethyl)propanamide
The title compound was prepared by the process described in Method 6, starting from 3-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-1-phenyl]carbamoyl amino]-propanoic acid (Example 125), (d<sub>6</sub>-DMSO) 1.57-1.97 (4H, m), 2.18 (3H, s), 2.50-2.57 (2H, m), 2.69-3.12 (3H, m), 3.30-3.40 (4H, m), 3.46-3.51 (4H, m), 3.73-3.95 (IH, m), 4.39-4.65 (IH, m), 4.63 (IH, t, J=5.3), 4.78 (IH, t, J=5.3), 6.71 (IH, t, J=5.9), 6.90 (IH, dd, J=7.5, 1.4), 7.15 (IH, d, J=7.9), 7.49 (2H, d, J=8.1), 7.76 (2H, d, J=8.1), 7.87 (IH, s), 7.95 (IH, s), m/z 522 (M+H)+.

**Example 243**

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[(3-pyrazol-1-ylpropyl)urea

\[\begin{align*}
\text{Method 2 from Intermediate A} \\
\text{1H NMR (300.072 MHz, CDCl}_3\text{) } &\delta 1.66 - 1.93 (m, 4H), 2.05 (s, 3H), 2.79 - 2.86 (m, 2H), 3.03 (s, 3H), 3.10 - 3.16 (m, IH), 3.88 - 3.98 (m, IH), 4.48 (d, 2H), 4.69 - 4.83 (m, IH), 6.34 (t, IH), 6.89 - 6.98 (m, 2H), 7.05 (d, IH), 7.29 - 7.32 (m, 2H), 7.47 (d, 2H), 7.54 - 7.64 (m, 3H), 7.85 (d, 2H), m/z 531 (M+H)+. 
\end{align*}\]

**Example 244**

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(3-pyrazol-1-ylpropyl)urea

\[\begin{align*}
\text{Method 2 from Intermediate A} \\
\text{1H NMR (300.072 MHz, CDCl}_3\text{) } &\delta 1.64 - 1.90 (m, 4H), 2.06 (quintet, 2H), 2.16 (s, 3H), 2.76 - 2.90 (m, 2H), 3.05 - 3.18 (m, IH), 3.20 - 3.27 (m, 2H), 3.89 - 4.03 (m, IH), 4.22 (t, 2H), 4.69 - 4.99 (m, IH), 5.48 (t, IH), 6.23 (s, IH), 6.44 (s, IH), 7.05 (d, IH), 7.15 (d, IH), 7.31 (d, 2H), 7.42 - 7.46 (m, 2H), 7.58 - 7.64 (m, 3H), m/z 471 (M+H)+. 
\end{align*}\]
Example 245
1-[5-[(4-(4-cyanophenyl)piperidin-1-carbonyl)]-2-methyl-phenyl]-3-[(3-methyl-1,2-oxazol-5-yl)methyl]urea

\[
\text{Method 2 from Intermediate A}
\]

\[^{1}\text{H NMR (300.072 MHz, CDCl}_3\text{) } \delta 1.70 - 1.85 (m, 4H), 2.01 (s, 3H), 2.26 (s, 3H), 2.76 - 2.88 (m, 2H), 3.07 - 3.20 (m, IH), 3.85 - 4.04 (m, IH), 4.46 (d, 2H), 4.79 - 4.90 (m, IH), 6.04 (s, IH), 6.20 (t, IH), 6.90 - 7.04 (m, 3H), 7.33 (d, 2H), 7.46 (s, IH), 7.61 (d, 2H), m/z 458 (M+H)^{+}.
\]

Example 246
1-[5-[(4-(4-cyanophenyl)piperidin-1-carbonyl)]-2-methyl-phenyl]-3-[(5-methylsulfonylphenyl)methyl]urea

\[
\text{Method 2 from Intermediate A}
\]

\[^{1}\text{H NMR (300.072 MHz, CDCl}_3\text{) } \delta 1.56 - 2.00 (m, 4H), 2.09 (s, 3H), 2.38 (s, 3H), 2.77 - 2.89 (m, 2H), 3.08 - 3.19 (m, IH), 3.86 - 4.10 (m, IH), 4.44 (d, 2H), 4.73 - 4.94 (m, IH), 5.92 (t, IH), 6.02 (s, IH), 6.88 (s, IH), 6.96 - 7.10 (m, 2H), 7.33 (d, 2H), 7.52 - 7.55 (m, IH), 7.61 (d, 2H), m/z 531 (M+H)^{+}.
\]

Example 247
1-[5-[(4-(4-cyanophenyl)piperidin-1-carbonyl)]-2-methyl-phenyl]-3-[(3-methylsulfonylphenyl)methyl]urea

\[
\text{Method 2 from Intermediate A}
\]

\[^{1}\text{H NMR (300.072 MHz, CDCl}_3\text{) } \delta 1.56 - 1.97 (m, 4H), 2.04 (s, 3H), 2.75 - 2.89 (m, 2H), 3.04 (s, 3H), 3.11 - 3.25 (m, IH), 3.87 - 4.07 (m, IH), 4.45 (d, 2H), 4.66 - 4.86 (m, IH), 6.31 (t, IH), 6.92 - 6.97 (m, 2H), 7.05 (d, IH), 7.31 (d, 2H), 7.50 (t, IH), 7.57 - 7.62 (m, 4H), 7.79 (d, IH), 7.85 (s, IH), m/z 531 (M+H)^{+}.
\]
Example 248
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(1,3-thiazol-2-ylmethyl)urea

\[
\begin{array}{c}
\text{Method 2 from Intermediate A}
\end{array}
\]

\[\text{H NMR (400.132 MHz, CDCl}_3\text{) } \delta 1.65 - 1.98 (m, 4H), 2.10 (s, 3H), 2.79 - 2.88 (m, 2H), 2.99 - 3.19 (m, IH), 3.83 - 4.08 (m, IH), 4.73 (d, 2H), 4.77 - 4.90 (m, IH), 6.20 (t, IH), 6.96 - 7.01 (m, 2H), 7.07 (d, IH), 7.25 (s, IH), 7.31 (d, 2H), 7.54 - 7.56 (m, IH), 7.60 (d, 2H), 7.69 (d, IH), m/z 460 (M+H)^+.
\]

Example 249
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[(6-methylpyridin-2-yl)methyl]urea

\[
\begin{array}{c}
\text{Method 2 from Intermediate A}
\end{array}
\]

\[\text{H NMR (400.132 MHz, CDCl}_3\text{) } \delta 1.56 - 1.93 (m, 4H), 2.22 (s, 3H), 2.50 (s, 3H), 2.77 - 2.87 (m, 2H), 2.94 - 3.14 (m, IH), 3.87 - 4.13 (m, IH), 4.50 (d, 2H), 4.51 - 4.88 (m, IH), 6.01 - 6.05 (m, IH), 6.82 - 6.86 (m, IH), 7.03 (d, IH), 7.09 (t, 2H), 7.16 (d, IH), 7.30 (d, 2H), 7.54 (t, IH), 7.60 (d, 2H), 7.67 - 7.68 (m, IH), m/z 468 (M+H)^+.
\]

Example 250
3-[5-[4-(4-cyanopheny l)piperidine-1-carbony l]-2-methyl-1-phenyl]-1-[(3-methyl pyridin-2-yl)methyl]urea

\[
\begin{array}{c}
\text{Method 2 from Intermediate A}
\end{array}
\]

\[\text{H NMR (400.132 MHz, CDCl}_3\text{) } \delta 1.66 - 1.96 (m, 4H), 2.26 (s, 3H), 2.31 (s, 3H), 2.78 - 2.86 (m, 2H), 2.95 - 3.19 (m, IH), 3.95 - 4.15 (m, IH), 4.53 (d, 2H), 4.73 - 4.93 (m, IH), 6.64 (s, IH), 6.87 (s, IH), 7.09 - 7.12 (m, 2H), 7.19 (d, IH), 7.30 (d, 2H), 7.46 (d, IH), 7.59 (d, 2H), 7.72 - 7.76 (m, IH), 8.29 (d, IH), m/z 468 (M+H)^+.
\]
Example 251
l-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[[3-(2-methoxypyridin-3-yl)-1,2-oxazol-5-yl]methyl]urea

Method 2 from Intermediate A

\[ \text{Method 2 from Intermediate A} \]

\[ \text{Method 2 from Intermediate A} \]

Example 252
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(4-methoxybutyl)urea

\[ \text{Method 2 from Intermediate A} \]

\[ \text{Method 2 from Intermediate A} \]

Example 253
(RS)-l-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[(l-phenoxypyropan-2-yl)urea

\[ \text{Method 2 from Intermediate A} \]

\[ \text{Method 2 from Intermediate A} \]
Example 254

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[2-(3,3-difluoropyrrolidin-1-yl)ethyl]urea

Method 2 from Intermediate A

$^1$H NMR (300.072 MHz, CDCl$_3$) $\delta$ 1.55 - 2.05 (4H, m), 2.05 (3H, s), 2.18 - 2.33 (2H, m), 2.57 - 2.60 (IH, m), 2.62 - 2.68 (IH, m), 2.77 - 3.20 (7H, t), 3.30 - 3.39 (2H, m), 3.86 - 3.99 (IH, m), 4.85 (IH, s), 5.91 (IH, t), 6.93 - 6.96 (IH, m), 7.02 (IH, s), 7.06 (IH, t), 7.32 (2H, d), 7.54 (IH, d), 7.59 - 7.62 (2H, m), m/z 496 (M+H)$^+$. 

Example 255

(RS)- 1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(1-methyl-3-piperidyl)urea

Method 2 from Intermediate A

$^1$H NMR (300.072 MHz, CDCl$_3$) $\delta$ 1.12 (2H, d), 1.41 (IH, d), 1.50 - 2.40 (13H, m), 2.54 - 3.25 (5H, m), 3.92 (2H, m), 4.86 (IH, s), 5.98 (IH, d), 6.96 - 6.99 (IH, m), 7.07 - 7.10 (2H, m), 7.31 (2H, t), 7.60 (2H, d), 7.67 (IH, d), m/z 460 (M+H)$^+$. 

Example 256

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(4-dimethylaminocyclohexyl)urea

Method 2 from Intermediate A

$^1$H NMR (300.072 MHz, CDCl$_3$) $\delta$ 0.98 - 1.20 (4H, m), 1.23 - 2.25 (1OH, m), 2.30 (6H, s), 2.79 - 3.25 (4H, m), 3.46 - 3.53 (IH, m), 4.01 (IH, m), 4.85 (IH, m), 5.80 (0.5H, d), 6.06 (0.5H, d), 6.93 - 7.19 (3H, m), 7.32 (2H, d), 7.60 (2H, d), 7.67 - 7.69 (IH, m), m/z 488 (M+H)$^+$. 

Example 257

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[(1,5-dimethylpyrazol-3-yl)methyl]urea

Method 2 from Intermediate A

1H NMR (300.072 MHz, CDCl₃) δ 1.56 - 1.94 (m, 4H), 2.11 (s, 3H), 2.20 (s, 3H), 2.76 - 2.86 (m, 2H), 3.01 - 3.18 (m, IH), 3.68 (s, 3H), 3.89 - 4.02 (m, IH), 4.33 (d, 2H), 4.72 - 5.01 (m, IH), 5.84 - 5.90 (m, IH), 5.97 (s, IH), 6.97 - 7.11 (m, 3H), 7.31 (d, 2H), 7.60 (d, 2H), 7.69 (d, IH), m/z 471 (M+H)⁺.

Example 258

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[(1,3-dimethylpyrazol-4-yl)methyl]urea

Method 2 from Intermediate A

1H NMR (300.072 MHz, CDCl₃) δ 1.55 - 1.85 (m, 4H), 2.02 (s, 3H), 2.23 (s, 3H), 2.79 - 2.87 (m, 2H), 3.01 - 3.13 (m, IH), 3.77 (s, 3H), 3.88 - 4.04 (m, IH), 4.21 (d, 2H), 4.74 - 4.81 (m, IH), 5.61 (t, IH), 6.67 (s, IH), 6.91 - 7.07 (m, 2H), 7.26 - 7.35 (m, 3H), 7.53 (s, IH), 7.63 (d, 2H), m/z 471 (M+H)⁺.

Example 259

(RS)-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-ethyl-1-phenyl]-3-(1,4-dioxan-2-ylmethyl)urea

Method 2 from Intermediate L

1H NMR (300.073 MHz, (d₆-DMSO, 30 °C) δ 1.15 (3H, U = 7.7Hz), 1.48 - 1.92 (4H, m), 2.45 - 2.64 (2H, m ~ assumed to be 2H under the DMSO), 2.70 - 3.29 (6H, m), 3.37 - 3.98 (7H, m), 4.41 - 4.79 (IH, m), 6.76 (IH, U = 6.0Hz), 6.97 (IH, dJ = 7.6Hz), 7.18 (IH, dJ = 10.1Hz), 7.49 (2H, dJ = 7.6Hz), 7.76 (2H, dJ = 9.3Hz), 7.81 (IH, s), 7.92 (IH, s), m/z 477 (M+H)⁺.
Example 260

3-(1-amino-2-methyl-propan-2-yl)-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]urea

Method 2 from Intermediate A

\[^{1}\text{H NMR (300.072 MHz, CDCl}_3 \text{)}\delta 1.21 (s, 6H), 1.56 - 1.98 (m, 4H), 2.31 (s, 3H), 2.80 - 2.93 (m, 2H), 3.11 - 3.23 (m, IH), 3.30 - 3.38 (m, 2H), 3.95 - 4.09 (m, IH), 4.57 - 5.03 (m, 3H), 6.93 (d, IH), 7.11 (d, IH), 7.32 (d, 2H), 7.54 (s, IH), 7.59 (d, 2H), 7.84 (s, IH), 8.26 (s, IH), m/z 434 (M+H)^+.\]

Example 261

N-[1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]-2-methyl-propan-2-yl]acetamide

Method 5 from Example 203

\[^{1}\text{H NMR (300.072 MHz, CDCl}_3 \text{)}\delta 1.33 (s, 6H), 1.50 - 1.89 (m, 4H), 1.86 (s, 3H), 2.1 (s, 3H), 2.78 - 2.92 (m, 2H), 3.03 - 3.16 (m, IH), 3.31 (d, 2H), 3.93 - 4.03 (m, IH), 4.77 - 4.94 (m, IH), 6.28 (t, IH), 6.63 (s, IH), 6.89 (s, IH), 6.97 - 7.13 (m, 2H), 7.32 (d, 2H), 7.58 - 7.65 (m, 3H), m/z 476 (M+H)^+.\]

Example 262

N-[1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]-2-methyl-propan-2-yl]propanamide

Method 5 from Example 203

\[^{1}\text{H NMR (300.072 MHz, CDCl}_3 \text{)}\delta 1.07 (t, 3H), 1.34 (s, 6H), 1.60 - 2.01 (m, 4H), 2.1 (q, 2H), 2.14 (s, 3H), 2.80 - 2.89 (m, 2H), 3.02 - 3.19 (m, IH), 3.32 (d, 2H), 3.92 - 4.04 (m,
Example 263

N-[1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-1-phenyl]carbamoylamino]-2-methyl-propan-2-yl]-2-methyl-propanamide

Method 5 from Example 203

\[\text{\textsuperscript{1}H NMR (300.072 MHz, CDCl\textsubscript{3})} \ \delta 1.06 (d, 6H), 1.33 (s, 6H), 1.55 - 1.79 (m, 4H), 2.14 (s, 3H), 2.25 (sept, IH), 2.79 - 2.91 (m, 2H), 3.03 - 3.20 (m, IH), 3.30 (d, 2H), 3.91 - 4.05 (m, 1H), 4.74 - 4.97 (m, IH), 6.21 (t, IH), 6.49 (s, IH), 6.77 (s, IH), 7.01 - 7.15 (m, 2H), 7.31 (d, 2H), 7.54 - 7.64 (m, 3H), m/z 504 (M+H)^{+}.\]

Example 264

1-[5-[4-(4-cyanophenyl)piperidin-1-carbonyl]-2-methyl-phenyl]-3-[4-methyl-1,3-thiazol-2-yl)methyl]urea

Method 2 from Intermediate A

\[\text{\textsuperscript{1}H NMR (300.072 MHz, CDCl\textsubscript{3})} \ \delta 1.50 - 2.04 (4H, m), 2.03 - 2.04 (3H, m), 2.40 (3H, d), 2.78 - 2.86 (2H, m), 3.11 (IH, m), 3.94 (IH, m), 4.65 (2H, d), 4.82 (IH, m), 6.45 (IH, t), 6.77 (IH, d), 6.91 - 6.95 (IH, m), 7.00 - 7.03 (IH, m), 7.32 (3H, m), 7.55 - 7.60 (3H, m), m/z 474 (M+H)^{+}.\]

Example 265

1-[5-[4-(4-cyanophenyl)piperidin-1-carbonyl]-2-methyl-1-phenyl]-3-[(3R)-6-oxo-3-piperidinyl]urea

Method 2 from Intermediate A

\[\text{\textsuperscript{1}H NMR (300.072 MHz, CDCl\textsubscript{3})} \ \delta 1.50 - 2.05 (4H, m), 2.14 (3H, m), 2.40 - 2.60 (2H, m), 2.75 - 3.30 (6H, m), 3.62 (IH, m), 4.00 (IH, m), 4.20 (IH, m), 4.85 (IH, m), 6.45 (IH, s),\]
Example 266
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(pyrimidin-4-ylmethyl)urea

![Chemical Structure](image)

Method 2 from Intermediate A

\[ ^1H\text{ NMR} (300.072\text{ MHz, CDCl}_3) \delta 1.50 - 2.05 (4H, m), 2.09 (3H, s), 2.79 - 2.87 (2H, m), 3.22 - 3.25 (IH, m), 3.99 (IH, m), 4.49 (2H, d), 4.85 (IH, m), 6.79 (IH, t), 6.92 - 6.96 (IH, m), 7.03 - 7.06 (IH, m), 7.28 - 7.35 (3H, m), 7.44 (IH, s), 7.58 - 7.61 (2H, m), 7.71 (IH, d), 8.62 - 8.64 (IH, m), 9.09 (IH, d), m/z 455 (M+H)^+.

Example 267
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[(1-methylimidazol-4-yl)methyl]urea

![Chemical Structure](image)

Method 2 from Intermediate A

\[ ^1H\text{ NMR} (300.072\text{ MHz, CDCl}_3) \delta 1.45 - 2.05 (6H, m), 2.10 (3H, s), 2.78 - 3.25 (3H, m), 3.61 (3H, s), 4.05 (IH, m), 4.29 (2H, d), 4.85 (IH, m), 6.66 (IH, t), 6.84 (IH, d), 6.97 - 7.00 (IH, m), 7.07 - 7.10 (IH, m), 7.32 (2H, t), 7.34 (IH, s), 7.59 - 7.61 (2H, m), 7.67 (IH, s), 7.84 (IH, d), m/z 457 (M+H)^+.

Example 268
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[(1-methylpyrrolidin-3-yl)methyl]urea

![Chemical Structure](image)

Method 2 from Intermediate A

\[ ^1H\text{ NMR} (300.072\text{ MHz, CDCl}_3) \delta 1.45 - 2.05 (6H, m), 2.17 (3H, s), 2.32 - 2.34 (3H, m), 2.40 (IH, d), 2.46 - 2.67 (3H, m), 2.80 - 3.20 (3H, m), 3.20 (2H, t), 4.00 (IH, m), 4.85
Example 269
1-{[5-{4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(1,3-oxazol-2-
5 ylmethyl)urea

\[
\text{Method 2 from Intermediate A}
\]
\[\delta \text{ ppm} \]
\[
1.50 - 2.05 (4H, m), 2.05 (3H, s), 2.78 - 3.20 (3H, m),
3.95 (IH, m), 4.52 (2H, d), 4.85 (IH, m), 6.53 (IH, t), 6.92 - 6.96 (IH, m), 7.03 (2H, d),
7.33 (3H, t), 7.59 - 7.61 (3H, m), 7.62 (IH, d), m/z 460 (M+H)^+.
\]

Example 270
3-{[8S]-l-azabicyclo[2.2.2]oct-8-yl]-l-{[5-{4-(4-cyanophenyl)piperidine-1-carbonyl]-2-
10 methyl-phenyl]urea

\[
\text{Method 2 from Intermediate A}
\]
\[\delta \text{ ppm} \]
\[
1.50 - 2.05 (4H, m), 2.05 (3H, s), 2.18 (2H, s), 2.38 (2H, s), 2.60
\]
\[(IH, m), 2.75 - 3.25 (5H, m), 3.25 - 3.62 (3H, m), 4.00 (2H, m), 4.85 (IH, m), 5.10 (IH, m),
6.45 (IH, s), 6.95 (IH, m), 7.10 - 7.25 (2H, m), 7.33 (2H, m), 7.59 - 7.62 (2H, d), 7.98
\[(IH, m), m/z 472 (M+H)^+.
\]

Example 271
N-[2-{[5-{4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-
15 phenyl|carbamoylamino]ethyl]-N,2-dimethyl-propanamide

\[
\text{Method 5 from Example 116}
\]
\[\delta \text{ ppm} \]
\[
1.08 (d, 6H), 1.56 - 1.98 (m, 4H), 2.18 (s, 3H), 2.74 - 2.96 (m, 3H), 3.12 (s, 3H), 3.04 - 3.15 (m, IH),
3.35 - 3.42 (m, 2H), 3.45 - 3.53 (m, 2H), 3.92 - 4.19 (m, IH), 4.72 - 4.93 (m, IH), 5.98 (t, IH),
6.98 - 7.16 (m, 3H), 7.32 (d, 2H),
\]
7.58 - 7.66 (m, 2H), 7.74 (s, IH) Complicated due to rotamers, m/z 490 (M+H)^+; HPLC tR = 2.02 min.

**Example 272**

3-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-l-2-(ethylsulfonyl-methyl-amino)ethyl]urea

\[
\text{Method 5 from Example 116}
\]

\(^1\)H NMR (300.072 MHz, CDCl\(_3\)) d 1.33 (t, 3H), 1.52 - 2.04 (m, 4H), 2.10 (s, 3H), 2.79 - 2.88 (m, 2H), 2.92 (s, 3H), 2.98 (q, 2H), 3.06 - 3.19 (m, IH), 3.26 - 3.32 (m, 2H), 3.36 - 3.41 (m, 2H), 3.88 - 4.09 (m, IH), 4.74 - 5.02 (m, IH), 5.80 - 5.86 (m, IH), 6.95 (s, IH), 6.98 - 7.10 (m, 2H), 7.34 (d, 2H), 7.55 (d, IH), 7.60 (d, 2H), m/z 512 (M+H)^+; HPLC tR = 2.07 min.

**Example 273**

N-[3-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-carbamoylamino]propyl]-acetamide

\[
\text{Method 5 from Example 207}
\]

\(^1\)H NMR (300.072 MHz, CDCl\(_3\)) d 1.59 - 1.65 (m, 2H), 1.74 - 1.90 (m, 4H), 1.95 (s, 3H), 2.13 (s, 3H), 2.80 - 2.94 (m, 2H), 3.01 - 3.15 (m, IH), 3.19 - 3.29 (m, 4H), 3.93 - 4.07 (m, IH), 4.75 - 4.96 (m, IH), 5.95 (t, IH), 6.63 (t, IH), 6.89 (s, IH), 6.97 - 7.13 (m, 2H), 7.32 (d, 2H), 7.61 (d, 2H), 7.69 (s, IH), m/z 462 (M+H)^+; HPLC tR = 1.79 min.

**Example 274**

N-[3-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-carbamoylamino]propyl]-2-methyl-propanamide

\[
\text{Method 5 from Example 207}
\]
\(^1\)H NMR (300.072 MHz, CDCl\(_3\)) d 1.12 (d, 6H), 1.60 (quintet, 2H), 1.68 - 2.01 (m, 4H), 2.14 (s, 3H), 2.36 (septet, IH), 2.78 - 2.91 (m, 2H), 3.08 - 3.30 (m, 5H), 3.91 - 4.16 (m, IH), 4.75 - 4.96 (m, IH), 5.99 (t, IH), 6.54 (t, IH), 6.91 (s, IH), 6.96 - 7.01 (m, IH), 7.12 (d, IH), 7.32 (d, 2H), 7.61 (d, 2H), 7.68 - 7.71 (m, IH), m/z 490 (M+H)\(^+\); HPLC tR = 1.99 min.

Example 275

3-[(3R)-l-acetylpyrrolidin-3-yl]-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]urea

\[\text{Method 5 from Example 212}\]

\(^1\)H NMR (300.072 MHz, CDCl\(_3\)) d 1.61 - 1.96 (m, 4H), 2.04 (s, 3H), 2.08 (s, 3H), 2.10 - 2.30 (m, 2H), 2.77 - 2.93 (m, 2H), 3.07 - 3.26 (m, IH), 3.31 - 3.44 (m, IH), 3.48 - 3.73 (m, 3H), 3.90 - 4.09 (m, IH), 4.33 - 4.48 (m, IH), 4.75 - 4.94 (m, IH), 6.29 - 6.49 (m, IH), 6.92 - 6.97 (m, IH), 7.03 - 7.12 (m, 2H), 7.33 (d, 2H), 7.61 (d, 2H), 7.75 (d, IH), m/z 474 (M+H)\(^+\); HPLC tR = 1.82 min.

Example 276

3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]-1-[(3R)-l-propanoy lpyrrolidin-3-yl]urea

\[\text{Method 5 from Example 212}\]

\(^1\)H NMR (300.072 MHz, CDCl\(_3\)) d 1.09 - 1.18 (m, 3H), 1.56 - 1.98 (m, 4H), 2.04 - 2.37 (m, 7H), 2.77 - 2.91 (m, 2H), 3.02 - 3.23 (m, IH), 3.32 - 3.43 (m, IH), 3.48 - 3.69 (m, 3H), 3.91 - 4.14 (m, IH), 4.30 - 4.49 (m, IH), 4.72 - 4.94 (m, IH), 6.36 - 6.53 (m, IH), 6.93 - 6.99 (m, IH), 7.06 - 7.11 (m, IH), 7.20 (d, IH), 7.33 (d, 2H), 7.61 (d, 2H), 7.79 (d, IH), m/z 488 (M+H)\(^+\); HPLC tR= 1.92 min.

Example 277

3-[(3S)-l-acetylpyrrolidin-3-yl]-l-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]urea
Method 5 from Example 2

\( ^1 \)H NMR (300.072 MHz, CDCl\(_3\)) δ 1.62 - 1.97 (m, 5H), 2.05 (s, 3H), 2.09 (d, 3H), 2.14 - 2.30 (m, 3H), 2.78 - 2.90 (m, 2H), 3.06 - 3.30 (m, 1H), 3.32 - 3.43 (m, 1H), 3.50 - 3.71 (m, 3H), 3.95 - 4.10 (m, 1H), 4.31 - 4.47 (m, 1H), 4.75 - 4.97 (m, 1H), 6.27 - 6.50 (m, 1H), 6.92 - 6.99 (m, 1H), 7.03 - 7.11 (m, 2H), 7.34 (d, 2H), 7.61 (d, 2H), 7.72 - 7.77 (m, 1H), m/z 474 (M+H)

Example 278

tert-butyl 3-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]piperidine-1-carboxylate

Method 2 from Intermediate A

\( ^1 \)H NMR (300.072 MHz, CDCl\(_3\)) δ 1.44 (9H, s), 1.48 - 1.58 (2H, m), 1.65 - 1.75 (4H, m), 1.85 - 2.01 (2H, m), 2.11 (3H, s), 2.75 - 2.94 (2H, m), 3.04 - 3.27 (3H, m), 3.45 - 3.58 (IH, m), 3.68 - 3.86 (2H, m), 3.90 - 4.06 (IH, m), 4.73 - 4.95 (IH, m), 5.37 - 5.48 (IH, m), 6.54 (IH, s), 6.99 - 7.14 (2H, m), 7.32 (2H, d), 7.52 (IH, s), 7.61 (2H, d), m/z 546 (M+H)

HPLC tR = 2.52 min.
Example 280

1-benzyl-3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-(trifluoromethyl)phenyl]urea

Method 2 from Intermediate N

$^1$H NMR (300.072 MHz, CDCl$_3$, 30° C) $\delta$ 1.48 - 2.00 (5H, m), 2.66 - 2.93 (2H, m), 3.03 - 3.24 (IH, m), 3.74 - 3.94 (IH, m), 4.67 - 4.90 (IH, m), 6.25 (IH, s), 7.01 (IH, dJ = 8.8 Hz), 7.15 - 7.39 (8H, m), 7.46 (IH, dJ = 8.1 Hz), 7.59 (2H, dJ = 8.8 Hz), 7.87 (IH, s), m/z 507 (M+H)$^+$.  

Example 281

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(1-methylsulfonyl-4-piperidyl)urea

Method 5 from Example 211

$^1$H NMR (300.073 MHz, d$_6$-DMSO) $\delta$ 1.31 - 1.97 (8H, m), 2.20 (3H, s), 2.75 - 3.21 (8H, m), 3.41 - 3.95 (4H, m), 4.34 - 4.88 (IH, m), 6.71 (IH, d), 6.92 (IH, d), 7.17 (IH, d), 7.49 (2H, d), 7.67 (IH, s), 7.76 (2H, d), 7.97 (IH, s), m/z 524 (M+H)$^+$.  

Example 282

3-(1-acetyl-4-piperidyl)-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]urea

Method 5 from Example 211

$^1$H NMR (300.073 MHz, d$_6$-DMSO) $\delta$ 1.23 - 1.93 (8H, m), 2.00 (3H, s), 2.19 (3H, s), 2.75 - 3.22 (5H, m), 3.55 - 3.96 (3H, m), 4.07 - 4.21 (IH, m), 4.38 - 4.79 (IH, m), 6.68 (IH, d), 6.91 (IH, d), 7.17 (IH, d), 7.49 (2H, d), 7.66 (IH, s), 7.76 (2H, d), 7.97 (IH, s), m/z 488 (M+H)$^+$.  

Example 283
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[1-(2-methylpropanoyl)-4-piperidyl]urea

Method 5 from Example 211

$^1$H NMR (300.073 MHz, d$_6$-DMSO) δ 0.99 (6H, d), 1.11 - 1.37 (2H, m), 1.45 - 1.95 (6H, m), 2.19 (3H, s), 2.32 - 2.45 (IH, m), 2.76 - 3.23 (5H, m), 3.59 - 3.94 (3H, m), 4.09 - 4.24 (IH, m), 4.35 - 4.80 (IH, m), 6.68 (IH, d), 6.87 - 6.96 (IH, m), 7.17 (IH, d), 7.49 (2H, d), 7.64 (IH, s), 7.76 (2H, d), 7.97 (IH, d), m/z 516 (M+H)$^+$. 

Example 284

4-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]-N,N-dimethyl-piperidine-1-carboxamide

Method 5 from Example 211

$^1$H NMR (300.073 MHz, d$_6$-DMSO) δ 1.25 - 1.93 (8H, m), 2.19 (3H, s), 2.72 (6H, s), 2.76 - 3.24 (5H, m), 3.36 - 3.51 (2H, m), 3.52 - 3.96 (2H, m), 4.37 - 4.82 (IH, m), 6.68 (IH, d), 6.91 (IH, d), 7.17 (IH, d), 7.49 (2H, d), 7.63 (IH, s), 7.76 (2H, d), 7.97 (IH, s), m/z 517 (M+H)$^+$. 

Example 285

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[1-(dimethylsulfamoyl)-4-piperidyl]urea

Method 5 from Example 211

The reaction mixture was heated at 60° C overnight. $^1$H NMR (300.073 MHz, d$_6$-DMSO) δ 1.29 - 1.95 (8H, m), 2.20 (3H, s), 2.75 (6H, s), 2.83 - 3.23 (5H, m), 3.38 - 3.95 (4H, m),
4.37 - 4.84 (IH, m), 6.71 (IH, d), 6.91 (IH, d), 7.17 (IH, d), 7.49 (2H, d), 7.65 (IH, s),
7.76 (2H, d), 7.97 (IH, s), m/z 517 (M+H)+.

**Example 286**

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(3-piperidyl)urea

![Chemical structure](image)

Method 3 from Example 279

1H NMR (300.072 MHz, CDCl₃) δ 1.46 - 1.98 (9H, m), 2.14 (3H, s), 2.53 - 2.72 (2H, m),
2.76 - 2.93 (3H, m), 2.99 - 3.22 (2H, m), 3.74 - 3.83 (IH, m), 3.91 - 4.16 (IH, m), 4.75 -
5.00 (IH, m), 5.71 - 5.85 (IH, m), 6.70 (IH, s), 6.96 - 7.14 (2H, m), 7.32 (2H, d), 7.56 -
7.66 (3H, m), m/z (EI+) (M+H)+ = 446; HPLC tR = 1.27 min.

**Example 287**

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-cyclobutyl-urea

![Chemical structure](image)

Method 2 from Intermediate A

1H NMR (300.072 MHz, CDCl₃) δ 1.50 - 2.10 (1H, m), 2.30 (IH, m), 2.85 (2H, m), 3.10
(IH, m), 3.95 (IH, m), 4.90 (IH, m), 6.02 (IH, d), 6.87 (IH, s), 6.95 (IH, m), 7.03 (IH,
m), 7.35 (2H, d), 7.60 (3H, m), m/z 417 (M+H)+.

**Example 288**

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(cyclopropylmethyl)urea

![Chemical structure](image)

Method 2 from Intermediate A

1H NMR (300.072 MHz, CDCl₃) δ 0.19 (2H, m), 0.45 - 0.51 (2H, m), 1.50 - 2.10 (7H, m),
2.79 - 2.91 (2H, m), 3.00 - 3.15 (4H, m), 3.95 (IH, m), 4.90 (IH, m), 5.83 (IH, t), 6.90 -
6.95 (2H, m), 7.02 - 7.04 (IH, m), 7.32 (2H, d), 7.56 - 7.59 (2H, m), 7.62 (IH, s), m/z 417
(M+H)+.
Example 289
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(1H-pyrazol-3-ylmethyl)urea

Method 2 from Intermediate A

^1^H NMR (300.072 MHz, CDCl₃) δ 1.40 - 2.05 (7H, m), 2.80 - 2.84 (IH, m), 2.76 - 2.88 (IH, m), 3.01 - 3.16 (IH, m), 3.85 - 3.95 (IH, m), 4.33 (2H, d), 4.79 - 4.84 (IH, m), 6.06 (IH, d), 6.67 (IH, t), 6.87 - 6.90 (IH, m), 7.00 (IH, d), 7.27 - 7.30 (2H, m), 7.34 (IH, s), 7.38 (IH, d), 7.57 - 7.59 (2H, m), 7.82 (IH, s), m/z 443 (M+H)^+.  

Example 290
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(pyrimidin-2-ylmethyl)urea

Method 2 from Intermediate A

^1^H NMR (300.072 MHz, CDCl₃) δ 1.50 - 2.00 (7H, m), 2.70 - 2.86 (2H, m), 3.10 (IH, d), 3.81 (3H, s), 3.85 - 4.04 (IH, m), 4.39 (2H, d), 4.90 (IH, m), 5.95 (IH, t), 6.18 (IH, d), 6.95 - 6.99 (IH, m), 7.05 - 7.09 (2H, m), 7.25 (IH, d), 7.31 (2H, d), 7.58 - 7.61 (2H, m), 7.64 (IH, d), m/z 457 (M+H)^+.  

Example 291
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(pyrimidin-2-ylmethyl)urea

Method 2 from Intermediate A

^1^H NMR (300.072 MHz, CDCl₃) δ 1.50 - 2.00 (4H, m), 2.12 (3H, s), 2.76 - 2.85 (2H, m), 3.01 - 3.11 (IH, m), 3.95 (IH, m), 4.68 (2H, d), 4.85 (IH, m), 6.55 (IH, t), 6.96 - 7.00 (IH, m), 7.05 (IH, d), 7.14 (IH, t), 7.29 (2H, m), 7.43 (IH, s), 7.57 - 7.60 (2H, m), 7.69 - 7.72 (IH, m), 8.66 - 8.71 (2H, d), m/z 455 (M+H)^+.  

Example 290
Example 292
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[(5-methyl-2H-pyrazol-3-yl)methyl]urea

\[
\text{Method 2 from Intermediate A}
\]

\[\text{H NMR (300.072 MHz, CDCl}_3\text{) } \delta 1.50 - 2.05 (7H, m), 2.16 (3H, s), 2.76 - 2.84 (2H, m), 3.01 - 3.10 (IH, m), 3.95 (IH, m), 4.32 (2H, d), 4.80 (IH, m), 5.86 (IH, s), 6.59 (IH, t), 6.89 - 6.92 (IH, m), 7.00 (IH, d), 7.28 (2H, d), 7.39 (IH, s), 7.48 (3H, d), 7.79 (IH, d), m/z 457 (M+H)\].

Example 293
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(pyrazin-2-ylmethyl)urea

\[
\text{Method 2 from Intermediate A}
\]

\[\text{H NMR (300.072 MHz, CDCl}_3\text{) } \delta 1.38 - 1.88 (3H, m), 1.88 - 2.11 (6H, m), 2.12 - 2.35 (3H, m), 2.74 - 2.99 (5H, m), 3.01 - 3.22 (3H, m), 3.26 - 3.41 (2H, m), 3.70 (IH, dJ = 13.6Hz), 4.93 (IH, dJ = 12.5Hz), 5.90 (IH, s), 6.61 - 6.83 (IH, m), 6.87 (IH, s), 7.16 - 7.40 (3H, m), 7.60 (2H, dJ = 8.3Hz), m/z 497 (M+H)\].

Example 294
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2,4-dimethyl-phenyl]-3-(3-methylsulfonylpropyl)urea

\[
\text{Method 2 from Intermediate F}
\]

\[\text{H NMR (300.072 MHz, CDCl}_3, 30^\circ C ) \delta 1.38 - 1.88 (3H, m), 1.88 - 2.11 (6H, m), 2.12 - 2.35 (3H, m), 2.74 - 2.99 (5H, m), 3.01 - 3.22 (3H, m), 3.26 - 3.41 (2H, m), 3.70 (IH, dJ = 13.6Hz), 4.93 (IH, dJ = 12.5Hz), 5.90 (IH, s), 6.61 - 6.83 (IH, m), 6.87 (IH, s), 7.16 - 7.40 (3H, m), 7.60 (2H, dJ = 8.3Hz), m/z 497 (M+H)\].
Example 295

3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-1-(1-propanoyl-3-piperidyl)urea

Method 5 from Example 286

$^1$H NMR (400.132 MHz, CDCl$_3$) $\delta$ 1.15 (3H, t), 1.48 - 1.97 (8H, m), 2.16 (3H, d), 2.37 (2H, q), 2.79 - 2.89 (2H, m), 3.05 - 3.25 (IH, m), 3.30 - 3.41 (IH, m), 3.48 - 3.59 (2H, m), 3.63 - 3.71 (IH, m), 3.78 - 3.96 (IH, m), 4.00 - 4.07 (IH, m), 4.75 - 4.96 (IH, m), 5.66 (IH, d), 6.55 - 6.81 (IH, m), 7.01 - 7.17 (2H, m), 7.33 (2H, d), 7.57 - 7.64 (3H, m), m/z (ESI+) (M+H)$^+$ = 502; HPLC tR = 2.04 min.

Example 296

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(1-methylsulfonyl-3-piperidyl)urea

Method 5a from Example 286

The title compound was prepared by a procedure essentially analogous to that described in Method 5 using sodium carbonate as the base in place of pyridine, and performing the reaction in a 2-phase solvent system consisting of DCM - Water. $^1$H NMR (400.132 MHz, CDCl$_3$) $\delta$ 1.63 - 1.86 (8H, m), 2.11 (3H, s), 2.78 (3H, s), 2.82 - 2.89 (2H, m), 2.97 - 3.08 (IH, m), 3.12 - 3.19 (IH, m), 3.24 - 3.28 (2H, m), 3.34 - 3.40 (IH, m), 3.92 - 4.07 (2H, m), 4.80 - 5.04 (IH, m), 5.67 - 5.76 (IH, m), 6.69 (IH, s), 6.98 - 7.12 (2H, m), 7.33 (2H, d), 7.52 - 7.56 (IH, m), 7.60 (2H, d), m/z (ESI+) (M+H)$^+$ = 524; HPLC tR = 2.12 min.

Example 297

3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-1-(1-ethylsulfonyl-3-piperidyl)urea
Method 5a from Example 286

\(^1\)H NMR (400.132 MHz, CDCl\(_3\)) \(\delta\) 1.34 (3H, t), 1.60 - 1.98 (8H, m), 2.18 (3H, s), 2.77 - 2.87 (2H, m), 2.95 (2H, q), 3.08 - 3.17 (2H, m), 3.25 - 3.47 (3H, m), 3.94 - 4.03 (2H, m), 4.77 - 4.97 (IH, m), 5.49 (IH, d), 6.46 (IH, s), 7.05 - 7.16 (2H, m), 7.33 (2H, d), 7.56 - 7.63 (3H, m), m/z (ESI+) (M+H\(^+\)) = 538; HPLC t\(R\) = 2.19 min.

Example 298
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-ethyl-phenyl]-3-(oxetan-3-yl)urea

Method 2 from Intermediate L

\(^1\)H NMR (300.073 MHz, de-DMSO) \(\delta\) 1.16 (3H, t), 1.48 - 1.92 (4H, m), 2.58 (2H, q), 2.67 - 3.24 (3H, m), 3.60 - 3.91 (IH, m), 4.34 - 4.48 (2H, m), 4.49 - 4.68 (IH, m), 4.68 - 4.82 (3H, m), 7.00 ( IH, d), 7.19 (IH, d), 7.34 (IH, d), 7.49 (2H, d), 7.71 - 7.81 (3H, m), 7.85 (IH, s), m/z (ESI+) (M+H\(^+\)) = 433.44; HPLC t\(R\) = 1.95 min.

Example 299
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(oxetan-3-yl)urea

Method 2 from Intermediate A

\(^1\)H NMR (300.073 MHz, de-DMSO) \(\delta\) 1.49 - 1.91 (4H, m), 2.21 (3H, s), 2.67 - 3.22 (3H, m), 3.58 - 3.94 (IH, m), 4.35 - 4.44 (2H, m), 4.48 - 4.67 (IH, m), 4.69 - 4.81 (3H, m), 6.94 (IH, d), 7.19 (IH, d), 7.33 (IH, d), 7.49 (2H, d), 7.72 - 7.81 (3H, m), 7.88 (IH, s), m/z (ESI+) (M+H\(^+\)) = 419.42; HPLC t\(R\) = 1.85 min.

Example 300
3-(azetidin-3-yl)-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-1-phenyl]urea
Method 3 from Example 97

$^1$H NMR (300.072 MHz, CDCl$_3$) $\delta$ 1.58 - 2.05 (4H, m), 2.11 (3H, s), 2.78 - 2.93 (2H, m), 2.99 - 3.34 (IH, m), 3.44 - 3.59 (2H, m), 3.81 - 4.08 (3H, m), 4.23 - 4.44 (IH, m), 4.55 - 4.67 (IH, m), 4.79 - 4.91 (IH, m), 6.35 (IH, d), 6.97 - 7.13 (3H, m), 7.32 (2H, d), 7.57 - 7.64 (3H, m), m/z (ESI+) (M+H)+ = 418; HPLC $t_R$ = 1.22 min.

Example 301

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[1-(2-methylpropanoyl)azetidin-3-y]urea

Method 5 from Example 300

$^1$H NMR (300.072 MHz, CDCl$_3$) $\delta$ 1.10 (6H, d), 1.58 - 1.94 (4H, m), 2.04 (3H, s), 2.45 (IH, septet), 2.78 - 2.93 (2H, m), 3.05 - 3.26 (IH, m), 3.71 - 3.81 (IH, m), 3.92 - 4.06 (2H, m), 4.29 (IH, t), 4.45 (IH, t), 4.52 - 4.60 (IH, m), 4.75 - 4.94 (IH, m), 6.61 (IH, d), 6.91 - 7.00 (2H, m), 7.08 (IH, d), 7.32 (2H, d), 7.57 - 7.65 (3H, m), m/z (ESI+) (M+H)+ = 488; HPLC $t_R$ = 1.96 min.

Example 302

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(1-methylsulfonylazetidin-3-y)urea

Method 5a from Example 300

$^1$H NMR (300.072 MHz, CDCl$_3$) $\delta$ 1.52 - 1.90 (4H, m), 1.97 (3H, s), 2.80 - 2.89 (2H, m), 2.92 (3H, s), 3.06 - 3.24 (IH, m), 3.88 - 4.00 (3H, m), 4.06 - 4.14 (2H, m), 4.57 (IH, sextet), 4.82 - 4.99 (IH, m), 6.58 (IH, d), 6.73 (IH, s), 6.94 - 7.08 (2H, m), 7.34 (2H, d), 7.49 - 7.51 (IH, m), 7.62 (2H, d), m/z (ESI+) (M+H)+ = 496; HPLC $t_R$ = 1.97 min.
Example 303
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[1-(dimethylsulfamoyl)azetidin-3-y1]urea

Method 5a from Example 300

$^1$H NMR (300.072 MHz, CDCl$_3$) $\delta$ 1.70 - 1.92 (4H, m), 2.00 (3H, s), 2.81 (6H, s), 2.87 - 2.94 (2H, m), 3.09 - 3.28 (IH, m), 3.83 (2H, t), 3.91 - 3.99 (IH, m), 4.04 (2H, t), 4.62 (IH, sextet), 4.87 - 5.00 (IH, m), 6.43 (IH, d), 6.75 (IH, s), 6.95 - 7.09 (2H, m), 7.34 (2H, d), 7.44 - 7.47 (IH, m), 7.61 (2H, d), m/z (ESI+) (M+H)$^+$ = 525; HPLC tR = 2.16 min.

Example 304
3-[(c/5)-2-aminocyclohexyl]-1-[5-[4-(cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]urea

Method 2 from Intermediate A

$^1$H NMR (300.072 MHz, CDCl$_3$) $\delta$ 2.02 - 0.90 (16H, m), 2.49 (3H, s), 3.07 - 2.87 (3H, m), 3.60 - 3.48 (2H, m), 4.04 (IH, d), 4.79 (IH, t), 6.89 (IH, s), 7.37 - 7.24 (4H, m), 7.71 - 7.54 (4H, m), 8.62 (IH, s), m/z (EI+) (M+H)$^+$ = 460.37; HPLC tR = 1.43 min; m/z (EI-) (M-H)$^-$ = 458.13; HPLC tR = 1.43 min.

Example 305
3-[(fr-<ms)-2-aminocyclohexyl]-1-[5-[4-(cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]urea

Method 8
Hydrazine monohydrate (0.049 mL, 1.02 mmol) was added to a suspension of 1-(5-(4-(4-cyanophenyl)piperidine-1-carbonyl)-2-methylphenyl)-3-((IR,2R)-2-(1,3-dioxoisindolin-2-yl)cyclohexyl)urea (Intermediate O) (601 mg, 1.02 mmol) in ethanol (3 mL) at ambient
temperature, and the resulting solution was heated to reflux for 30 minutes. The mixture was then cooled to room temperature and the solid collected by filtration. The filtrate was concentrated under reduced pressure to give crude product as a yellow foam (428 mg). This was purified by flash silica chromatography, elution gradient 0 to 20% MeOH in DCM to give the desired product (35 mg, 7.5%) as a colourless dry film.

Example 306
3-amino-N-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]azetidine-1-carboxamide

Method 3 from Intermediate P

\[ \text{H NMR (300.072 MHz, CDCl}_3 \delta 1.56 - 1.93 (4H, m), 2.13 (2H, s), 2.24 (3H, s), 2.78 - 2.89 (2H, m), 3.00 - 3.23 (IH, m), 3.72 - 3.77 (2H, m), 3.90 (IH, quintet), 3.98 - 4.09 (IH, m), 4.26 (2H, t), 4.69 - 4.92 (IH, m), 6.06 (IH, s), 7.06 - 7.20 (2H, m), 7.32 (2H, d), 7.60 (2H, d), 7.80 (IH, s), m/z (ESI+) (M+H)+ = 418; HPLC tR = 1.16 min.} \]

Example 307
l-[5-[4-(4-cyanophenyl)piperidine-l-carbonyl]-2-methyl-phenyl]-3-[(cw)-2-methanesulfonamidocyclohexyl]urea

Method 5a from Example 304

\[ \text{H NMR (300.072 MHz, CDCl}_3 \delta 1.86 - 1.39 (1H, m), 2.00 (3H, s), 2.89 - 2.74 (2H, m), 2.97 (3H, s), 3.20 - 2.97 (3H, m), 3.61 - 3.51 (IH, m), 4.16 - 3.91 (2H, m), 5.00 - 4.71 (IH, m), 5.69 (IH, d), 6.18 (IH, d), 6.91 (IH, d), 7.01 (IH, s), 7.05 (IH, d), 7.33 (2H, d), 7.61 (2H, d), 7.71 (IH, s), m/z (EI+) (M+H)+ = 538.41; HPLC tR = 2.17 min; m/z (EI-) (M-H)- = 536.42; HPLC tR = 2.17 min.} \]
Example 308
N-[((cw)-2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]cyclohexyl]acetamide

\[
\text{Method 5 from Example 304}
\]

\[
\begin{align*}
{^1}H \text{ NMR (300.072 MHz, CDCl}_3) \delta 1.90 - 1.37 (13H, m), 1.95 (3H, s), 2.01 (3H, s), 2.90 - 2.82 (2H, m), 3.27 - 3.06 (IH, m), 4.08 - 3.86 (2H, m), 5.00 - 4.61 (IH, m), 6.27 (IH, d), 6.92 - 6.87 (2H, m), 7.02 (IH, d), 7.22 (IH, s), 7.31 (2H, d), 7.61 (2H, d), 7.73 (IH, s), m/z (EI+) (M+H)+ = 502.48; HPLC tR = 2.01 min; m/z (EI-) (M-H)- = 500.45; HPLC tR = 2.01 min.
\end{align*}
\]

Example 309
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-1-[(cis)-2-(ethylsulfonylamino)cyclohexyl]urea

\[
\text{Method 5a from Example 304}
\]

\[
\begin{align*}
{^1}H \text{ NMR (300.072 MHz, CDCl}_3) \delta 1.33 (3H, t), 1.91 - 1.38 (12H, m), 2.03 (3H, s), 3.15 - 2.81 (5H, m), 3.57 - 3.52 (IH, m), 4.08 - 3.86 (2H, m), 5.00 - 4.69 (IH, m), 5.62 (IH, d), 6.14 (IH, d), 6.94 (IH, d), 7.05 (2H, d), 7.33 (2H, d), 7.61 (2H, d), 7.66 (IH, s), m/z (EI+) (M+H)+ = 552.45; HPLC tR = 2.23 min; m/z (EI-) (M-H)- = 550.43; HPLC tR = 2.23 min; m/z (EI+) (M+H)+ = 552.45; HPLC tR = 2.23 min; m/z (EI-) (M-H)- = 550.43; HPLC tR = 2.23 min.
\end{align*}
\]

Example 310
3-(1-acetylazetidin-3-yl)-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]urea

\[
\text{Method 5 from Example 300}
\]
Example 311
3-[5-[(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-1-(1-ethylsulfonyl)azetidin-3-yl)urea

Method 5a from Example 300

Example 312
3-acetamido-N-[5-[(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]azetidine-1-carboxamide

Method 5 from Example 306

Example 313
N-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-methanesulfonamido-azetidine-1-carboxamide
Method 5a from Example 306

$^1$H NMR (300.072 MHz, CDCl$_3$) δ 1.47 - 2.01 (4H, m), 2.19 (3H, s), 2.75 - 2.84 (2H, m), 2.88 (3H, s), 3.01 - 3.21 (IH, m), 3.83 - 3.98 (3H, m), 4.18 - 4.28 (3H, m), 4.70 - 4.96 (IH, m), 6.52 (IH, s), 6.79 (IH, d), 7.05 - 7.20 (2H, m), 7.31 (2H, d), 7.58 (2H, d), 7.62 - 7.65 (IH, m), m/z (ESI+) (M+H)$^+$ = 496; HPLC t$_R$ = 1.89 min.

Example 314

N-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(dimethylsulfamoylamino)azetidine-1-carboxamide

Method 5a from Example 306

$^1$H NMR (300.072 MHz, CDCl$_3$) δ 1.53 - 1.93 (4H, m), 2.18 (3H, s), 2.75 (6H, s), 2.80 - 2.87 (2H, m), 2.97 - 3.19 (IH, m), 3.85 - 3.99 (3H, m), 4.10 - 4.25 (3H, m), 4.73 - 4.89 (IH, m), 6.41 (IH, d), 6.51 (IH, s), 7.03 - 7.19 (2H, m), 7.30 (2H, d), 7.57 (2H, d), 7.62 - 7.64 (IH, m), m/z (ESI+) (M+H)$^+$ = 525; HPLC t$_R$ = 2.04 min.

Example 315

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[(trans)-2-methanesulfonamidocyclohexyl]urea

Method 5a from Example 305

$^1$H NMR (300.072 MHz, CDCl$_3$) δ 2.04 - 1.25 (13H, m), 2.17 (3H, s), 2.92 (3H, s), 3.31 - 3.02 (3H, m), 3.54 - 3.48 (2H, m), 4.16 - 3.92 (IH, m), 4.95 - 4.67 (IH, m), 6.92 (IH, d), 7.10 (IH, d), 7.35 (3H, d), 7.41 (2H, s), 7.61 (3H, d), m/z (EI+) (M+H)$^+$ = 538.42; HPLC t$_R$ = 2.20 min; m/z (EI-) (M-H)$^-$ = 536.40; HPLC t$_R$ = 2.20 min.
Example 316
tert-butyl N-[(lS,3S)-3-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]carbamoylamino]cyclopentyl]carbamate

The title compound was prepared according to Method 2, starting from Intermediate A and tert-butyl (lS,3S)-3-aminocyclopentylcarbamate (preparation described in WO 2004 / 004726). $^1$H NMR (300.073 MHz, d$_6$-DMSO) $\delta$ 1.38 (9H, s), 1.46 - 1.90 (8H, m), 2.19 (3H, s), 2.55 - 3.17 (5H, m), 3.54 - 4.11 (3H, m), 4.46 - 4.75 (IH, m), 6.70 (IH, d), 6.90 (2H, d), 7.16 (IH, d), 7.49 (2H, d), 7.56 (IH, s), 7.76 (2H, d), 7.98 (IH, s), m/z (ESI+) (M+H)$^+$ = 546.48; HPLC tR = 2.44 min.

Example 317
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[(c/s)-2-(dimethylsulfamoylamino)cyclohexyl]urea

$^1$H NMR (300.072 MHz, CDCl$_3$) $\delta$ 1.94 - 1.36 (13H, m), 2.05 (3H, s), 2.78 (6H, s), 3.26 - 2.80 (2H, m), 3.50 - 3.45 (IH, m), 4.13 - 3.89 (2H, m), 5.00 - 4.67 (IH, m), 5.46 (IH, d), 5.94 (IH, d), 6.78 (IH, s), 6.98 (IH, dd), 7.07 (IH, d), 7.33 (2H, d), 7.62 - 7.58 (3H, m), m/z (EI+) (M+H)$^+$ = 567.42; HPLC tR = 2.32 min; m/z (EI-) (M-H)$^-$ = 565.42; HPLC tR = 2.32 min.

Example 318
3-[(lS,3S)-3-aminocyclopentyl]-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]urea
Method 3 from Example 316

\[ \text{H NMR (300.073 MHz, } d_6\text{-DMSO)} \delta 1.36 - 2.15 (1OH, m), 2.20 (3H, s), 2.56 - 3.40 (3H, m), 3.58 - 3.70 (IH, m), 3.72 - 3.88 (IH, m), 4.06 - 4.20 (IH, m), 4.27 - 4.90 (IH, m), 6.91 (IH, d), 7.16 (IH, d), 7.49 (2H, d), 7.76 (2H, d), 7.96 (IH, s), m/z (ESI+) (M+H)+ = 446.46; \]

\[ \text{HPLC tR } = 1.32 \text{ min.} \]

Example 319

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[(trans)-2-(dimethylsulfamoylamino)cyclohexyl]urea

Method 5a from Example 305

\[ \text{H NMR (300.072 MHz, } CDCl_3)} \delta 1.38 - 1.13 (4H, m), 1.92 - 1.58 (6H, m), 2.10 (4H, s), 2.73 (6H, s), 3.11 - 2.79 (3H, m), 3.57 - 3.46 (IH, m), 4.17 - 3.88 (IH, m), 4.99 - 4.62 (IH, m), 5.79 - 5.71 (IH, m), 5.84 (IH, d), 7.00 (IH, d), 7.03 (IH, s), 7.09 (IH, d), 7.17 (IH, d), 7.24 (IH, d), 7.35 (2H, d), 7.60 (3H, d), m/z (EI+) (M+H)+ = 567.49; \text{HPLC tR } = 2.36 \text{ min; m/z (EI-) (M-H)- } = 565.47; \text{HPLC tR } = 2.36 \text{ min.} \]

Example 320

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[[(S,3S)-3-methanesulfonamidocyclopentyl]urea

Method 5a from Example 318

\[ \text{H NMR (300.073 MHz, } d_6\text{-DMSO)} \delta 1.20 - 2.12 (1OH, m), 2.19 (3H, s), 2.69 - 2.99 (6H, m), 3.69 - 4.11 (3H, m), 4.45 - 4.74 (IH, m), 6.71 (IH, d), 6.90 (IH, d), 7.07 - 7.19 (2H, m), 7.49 (2H, d), 7.57 (IH, s), 7.76 (2H, d), 7.98 (IH, s), m/z (ESI+) (M+H)+ = 524.41; \text{HPLC tR } = 2.03 \text{ min.} \]
Example 321
N-[(lS,3S)-3-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoyl]amino)cyclopentyl]acetamide

Method 5 from Example 318

\(^1\)H NMR (300.073 MHz, \(d_6\)-DMSO) \(\delta\) 1.10 - 2.14 (13H, m), 2.19 (3H, s), 2.61 - 3.20 (3H, m), 3.64 - 3.93 (IH, m), 3.98 - 4.23 (2H, m), 4.47 - 4.76 (IH, m), 6.40 (IH, d), 6.90 (IH, d), 7.16 (IH, d), 7.49 (2H, d), 7.57 (IH, s), 7.75 (2H, d), 7.87 (IH, d), 7.99 (IH, s), m/z (ESI+) (M+H)+ = 488.49; HPLC tR = 1.89 min.

Example 322
N-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-4-methylsulfonyl-piperazine-1-carboxamide

Method 2 from Intermediate A

\(^1\)H NMR (300.073 MHz, \(d_6\)-DMSO) \(\delta\) 1.49 - 1.90 (4H, m), 2.19 (3H, s), 2.83 - 2.97 (5H, m), 3.09 - 3.17 (5H, m), 3.50 - 3.59 (4H, m), 3.69 - 3.87 (IH, m), 4.34 - 4.87 (IH, m), 7.11 (IH, d), 7.20 - 7.29 (2H, m), 7.50 (2H, d), 7.76 (2H, d), 8.24 (IH, s), m/z (ESI+) (M+H)+ = 510.39; HPLC tR = 2.02 min.

Example 323
l-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[(lS,3S)-3-(dimethylsulfamoyl)amino)cyclopentyl]urea

Method 5a from Example 318

\(^1\)H NMR (300.073 MHz, \(d_6\)-DMSO) \(\delta\) 1.21 - 2.08 (1OH, m), 2.19 (3H, s), 2.64 (6H, s), 2.77 - 3.19 (3H, m), 3.60 - 3.85 (2H, m), 3.97 - 4.10 (IH, m), 4.46 - 4.71 (IH, m), 6.71
(IH, d), 6.90 (IH, d), 7.16 (IH, d), 7.23 (IH, d), 7.50 (2H, d), 7.56 (IH, s), 7.76 (2H, d),
7.98 (IH, s), m/z (ESI+) (M+H)+ = 553.44; HPLC tR = 2.16 min.

Example 324

3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-1-{[1S,3S]-3-
(ethylsulfonylamino)cyclopentyl]urea

Method 5a from Example 318

1H NMR (300.073 MHz, d6-DMSO) δ 1.19 (3H, t), 1.27 - 2.12 (10H, m), 2.18 (3H, s), 2.77
- 3.16 (5H, m), 3.60 - 3.90 (2H, m), 3.96 - 4.12 (IH, m), 4.40 - 4.75 (IH, m), 6.70 (IH, d),
6.90 (IH, d), 7.10 - 7.19 (2H, m), 7.49 (2H, d), 7.56 (IH, s), 7.76 (2H, d), 7.97 (IH, s), m/z
(ESI+) (M+H)+ = 538.45; HPLC tR = 2.10 min.

Example 325

1-[5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-propan-2-yl-urea

Method 6b

The title compound was prepared by means of a standard amide coupling as described in
Method 6 (EDAC, DMAP in DMF as solvent), starting from 4-methyl-3-(propan-2-
ylcarbamoylamino) benzoic acid (Intermediate Q) and 4-(4-fluorophenyl)piperidine
hydrochloride, 1H NMR (300.073 MHz, d6-DMSO) δ 1.10 (6H, d), 1.40 - 1.90 (4H, m),
2.19 (3H, s), 2.70 - 3.24 (3H, m), 3.60 - 3.87 (2H, m), 4.40 - 4.70 (IH, m), 6.52 (IH, d),
6.89 (IH, d), 7.04 - 7.19 (3H, m), 7.25 - 7.35 (2H, m), 7.57 (IH, s), 7.99 (IH, s), m/z 398
(M+H)+.

Example 326

N-[2-[2-methyl-5-[4-[4-(trifluoromethyl)phenyl]piperidine-1-carbonyl]
phenyl]carbamoylamino]ethyl]acetamide
Method 2 from Intermediate R

$^1$H NMR (300.073 MHz, $d_6$-DMSO) $\delta$ 1.51 - 1.90 (7H, m), 2.20 (3H, s), 2.77 - 3.07 (3H, m), 3.09 - 3.17 (4H, m), 3.62 - 3.96 (IH, m), 4.42 - 4.72 (IH, m), 6.58 - 6.69 (IH, m), 6.93 (IH, d), 7.17 (IH, d), 7.51 (2H, d), 7.65 (2H, d), 7.76 (IH, s), 7.84 - 7.94 (2H, m), m/z (ESI$^+$) (M+H)$^+$ = 491.43; HPLC tR = 2.17 min.

Example 327

1-[5-[4-(3-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-propan-2-yl-urea

Method 6b from Intermediate Q

$^1$H NMR (300.073 MHz, d$_6$-DMSO) $\delta$ 1.10 (6H, d), 1.50 - 1.94 (4H, m), 2.19 (3H, s), 2.62 - 3.20 (3H, m), 3.60 - 3.89 (2H, m), 4.41 - 4.76 (IH, m), 6.52 (IH, d), 6.91 (IH, d), 7.16 (IH, d), 7.45 - 7.70 (4H, m), 7.77 (IH, s), 7.99 (IH, s), m/z 405 (M+H)$^+$. 

Example 328

1-[5-[4-(4-methoxyphenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-propan-2-yl-urea

Method 6b from Intermediate Q

$^1$H NMR (300.073 MHz, de-DMSO) $\delta$ 1.10 (6H, d), 1.39 - 1.90 (4H, m), 2.19 (3H, s), 2.64 - 3.23 (3H, m), 3.60 - 3.90 (5H, m), 4.40 - 4.70 (IH, m), 6.52 (IH, d), 6.80 - 6.92 (3H, m), 7.11 - 7.21 (3H, m), 7.57 (IH, s), 7.99 (IH, s), m/z 410 (M+H)$^+$. 

Example 329

N-methyl-4-[1-[4-methyl-3-(propan-2-ylcarbamoylamino)benzoyl]-4-piperidyl]benzamide
Method 6b from Intermediate Q

\(^1\)H NMR (300.073 MHz, \(\text{d}_6\)-DMSO) \(\delta\) 1.10 (6H, d), 1.43 - 1.93 (4H, m), 2.19 (3H, s), 2.68 - 3.19 (6H, m), 3.60 - 3.90 (2H, m), 4.40 - 4.72 (IH, m), 6.52 (IH, d), 6.90 (IH, d), 7.16 (IH, d), 7.34 (2H, d), 7.58 (IH, s), 7.75 (2H, d), 8.00 (IH, s), 8.27 - 8.36 (IH, m), m/z 437 (M+H)^+.

Example 330

Ethyl 4-[[5-[[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoyl]piperazine-1-carboxylate

Method 2 from Intermediate A

\(^1\)H NMR (400.132 MHz, \(\text{d}_6\)-DMSO) \(\delta\) 1.03 (6H, d), 1.51 - 1.91 (4H, m), 2.21 (3H, s), 2.77 - 3.21 (4H, m), 3.40 - 3.60 (8H, m), 3.71 - 3.97 (IH, m), 4.43 - 4.77 (IH, m), 7.12 (IH, d), 7.25 (IH, d), 7.31 (IH, s), 7.51 (2H, d), 7.77 (2H, d), 8.17 (IH, s), m/z (ESI+) (M+H)+ = 504.46; HPLC tR = 2.15 min.

Example 331

N-[[5-[[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-4-(2-methylpropanoyl)piperazine-1-carboxamide

Method 2 from Intermediate A

\(^1\)H NMR (400.132 MHz, \(\text{d}_6\)-DMSO) \(\delta\) 1.03 (6H, d), 1.51 - 1.91 (4H, m), 2.21 (3H, s), 2.77 - 3.21 (4H, m), 3.40 - 3.60 (8H, m), 3.71 - 3.97 (IH, m), 4.43 - 4.77 (IH, m), 7.12 (IH, d), 7.25 (IH, d), 7.31 (IH, s), 7.51 (2H, d), 7.77 (2H, d), 8.17 (IH, s), m/z (ESI+) (M+H)+ = 502.36; HPLC tR = 2.08 min.
Example 332
N-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-N',N'-dimethyl-
piperazine- 1,4-dicarboxamide

\[
\text{Method 2 from Intermediate } A
\]

\[\begin{align*}
^{1}H \text{ NMR } (300.072 \text{ MHz, CDCl}_3) & \delta 1.61 - 2.00 (4H, m), 2.26 (3H, s), 2.61 - 3.09 (9H, m), \\
& 3.28 - 3.35 (4H, m), 3.50 - 3.57 (4H, m), 3.92 - 4.19 (IH, m), 4.71 - 5.00 (IH, m), 6.44 \\
& (IH, s), 7.08 (IH, d), 7.19 (IH, d), 7.32 (2H, d), 7.60 (2H, d), 7.67 (IH, s), m/z (ESI+) \\
& (M+H)^+ = 503.47; \text{HPLC } t_R = 1.90 \text{ min.}
\end{align*}\]

Example 333

\[
\text{Method 2 from Intermediate } R
\]

\[\begin{align*}
^{1}H \text{ NMR } (400.132 \text{ MHz, de-DMSO}) & \delta 1.32 - 1.42 (m, 9H), 1.42 - 1.55 (m, 3H), 1.57 - 1.75 \\
& (m, 3H), 1.76 - 1.93 (m, 3H), 2.22 (s, 3H), 2.62 - 3.25 (m, 5H), 3.39 - 3.99 (m, 3H), 4.47 - \\
& 4.82 (m, 1H), 6.74 (d, 1H), 6.93 - 7.00 (m, 1H), 7.23 (d, 1H), 7.56 (d, 2H), 7.70 (d, 2H), 7.74 \\
& (s, 1H), 8.04 (s, IH), m/z (ESI+) (M+H)^+ = 589.51; \text{HPLC } t_R = 2.93 \text{ min.}
\end{align*}\]

Example 334
3-(2-dimethylaminoethyl)-l-[2-methyl-5-[4-[4-(trifluoromethyl)phenyl]piperidine-1-
carbonyl]phenyl]urea

\[
\text{Method 2 from Intermediate } R
\]

\[\begin{align*}
^{1}H \text{ NMR } (300.073 \text{ MHz, d}_6-\text{DMSO}) & \delta 1.48 - 1.91 (4H, m), 2.17 - 2.25 (9H, m), 2.38 (2H, \\
& t), 2.77 - 3.11 (3H, m), 3.15 - 3.24 (2H, m), 3.66 - 3.92 (IH, m), 4.44 - 4.74 (IH, m), 6.66
\end{align*}\]
Example 335
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(3-methyl-1,1-dioxo-thiolan-3-yl)urea

Method 2 from Intermediate A

\(^1\)H NMR (300.072 MHz, CDCl\(_3\)) \(\delta\) 1.65 (3H, s), 1.89 - 1.70 (3H, m), 1.89 (3H, s), 2.22 - 1.95 (2H, m), 2.97 - 2.79 (3H, m), 3.04 (IH, d), 3.23 - 3.15 (2H, m), 3.56 - 3.45 (IH, m), 3.74 (IH, d), 4.05 - 3.89 (IH, m), 4.92 - 4.79 (IH, m), 6.45 (IH, s), 6.66 (IH, s), 6.90 (IH, d), 7.00 (IH, d), 7.34 (2H, d), 7.53 (IH, s), 7.62 (2H, d), m/z (EI+) (M+H)+ = 495.43;

HPLC tR = 2.09 min.

Example 336

Method 2 from Intermediate R

\(^1\)H NMR (300.073 MHz, d6-DMSO) \(\delta\) 1.30 (s, 9H), 1.51 - 1.70 (3H, m), 2H),2.15 (s, 3H),2.82 - 2.96 (m, 1H),2.96 - 3.06 (m, 3H),3.06 - 3.18 (m, 3H),3.58 - 3.98 (m, 1H),4.28 - 4.80 (m, 1H),6.59 - 6.70 (m, 1H),6.75 - 6.86 (m, 1H),6.92 (d, 1H),7.17 (d, 1H),7.51 (d, 2H),7.65 (d, 2H),7.73 (s, 1H),7.89 (s, IH), m/z (EI+) (M+H)+ = 549.51;

HPLC tR = 2.69 min.

Example 337
1-[2-methyl-5-[4-(trifluoromethyl)phenyl]piperidine-1-carbonyl]phenyl]-3-(3- piperidyl)urea
Method 3 from Example 333

\[ \text{H NMR (300.073 MHz, } d_6\text{-DMSO)} \delta 0.39 - 1.50 (m, 1H), 1.54 - 1.73 (m, 3H), 1.74 - 1.94 (m, 4H), 2.20 (s, 3H), 2.62 - 2.77 (m, 1H), 2.82 - 3.00 (m, 2H), 3.03 - 3.20 (m, 2H), 3.23 - 3.34 (m, 1H), 3.74 - 3.98 (m, 2H), 4.40 - 4.81 (m, 1H), 6.90 - 6.98 (m, 1H), 7.12 - 7.25 (m, 2H), 7.50 (d, 2H), 7.66 (d, 2H), 7.92 (s, 1H)], m/z (EI+) = 489.50 (M+H)+; HPLC tR = 1.54 min.

Example 338

N-[[2-[[5-[[4-(4-fluorophenyl)piperidine-1-carbonyl]-2-methyl-phenyl] carbamoylamino]ethyl]acetamide

\[ \text{H NMR (500.133 MHz, } d_6\text{-DMSO)} \delta 1.53 - 1.64 (2H, m), 1.79 - 1.86 (5H, m), 2.23 (3H, s), 2.79 - 2.87 (IH, m), 2.96 - 3.04 (2H, m), 3.19 (4H, t), 4.12 - 4.28 (2H, m), 6.94 (IH, d), 7.04 - 7.09 (2H, m), 7.17 (IH, d), 7.26 - 7.33 (2H, m), 7.39 - 7.50 (IH, m), 7.40 - 7.50 (IH, m), 7.56 (IH, s), 7.82 (IH, s), m/z (ESI+) (M+H)+ = 441.46; HPLC tR = 1.93 min.

Example 339

tert-butyl 3-[[5-[[4-(4-fluorophenyl)piperidine-1-carbonyl]-2-methyl-phenyl] carbamoylamino]azetidine-1-carboxylate

\[ \text{H NMR (300.073 MHz, } d_6\text{-DMSO)} \delta 0.98 - 1.08 (IH, m), 1.38 (9H, s), 1.49 - 1.88 (4H, m), 2.20 (3H, s), 2.69 - 3.00 (3H, m), 3.62 - 3.72 (2H, m), 4.03 - 4.12 (2H, m), 4.29 - 4.43 (IH, m), 4.47 - 4.74 (IH, m), 6.94 (IH, d), 7.06 - 7.15 (2H, m), 7.16 - 7.23 (2H, m), 7.26 - 7.34 (2H, m), 7.76 (IH, s), 8.72 - 9.07 (s, 2H), m/z (ESI-) (M-H)- = 509.57; HPLC tR = 2.09 min.
Example 340

3-[2-(dimethylsulfamoylamino)ethyl]-l-[2-methyl-5-[4-(trifluoromethyl)phenyl]piperidine-1-carbonyl]phenyl]urea

Method 5a from Example 342

\[ \text{H NMR (300.073 MHz, de-DMSO)} \delta 1.48 - 1.91 (4H, m), 2.20 (3H, s), 2.65 (6H, s), 2.82 - 3.23 (7H, m), 3.66 - 3.92 (IH, m), 4.49 - 4.73 (IH, m), 6.71 (IH, t), 6.93 (IH, d), 7.15 - 7.25 (2H, m), 7.51 (2H, d), 7.65 (2H, d), 7.83 (IH, s), 7.91 (IH, s), m/z (ESI+) (M+H)+ = 556.51; HPLC tR = 2.45 min. \]

Example 341

3-(2-methanesulfonamidoethyl)-l-[2-methyl-5-[4-(trifluoromethyl)phenyl]piperidine-1-carbonyl]phenyl]urea

Method 5a from Example 342

\[ \text{H NMR (300.073 MHz, de-DMSO)} \delta 1.47 - 1.92 (4H, m), 2.20 (3H, s), 2.83 - 3.24 (1OH, m), 3.62 - 4.02 (IH, m), 4.48 - 4.71 (IH, m), 6.74 (IH, t), 6.93 (IH, d), 7.06 (IH, t), 7.18 (IH, d), 7.51 (2H, d), 7.65 (2H, d), 7.84 (IH, s), 7.92 (IH, s), m/z (ESI+) (M+H)+ = 527.47; HPLC tR = 2.32 min. \]

Example 342

3-(2-aminoethyl)-l-[2-methyl-5-[4-(trifluoromethyl)phenyl]piperidine-1-carbonyl]phenyl]urea

Method 3 from Example 336

\[ \text{H NMR (300.072 MHz, CDCl}_3) \delta 1.58 - 2.00 (4H, m), 2.30 (3H, s), 2.75 - 3.21 (5H, m), 3.28 - 3.41 (2H, m), 3.85 - 4.02 (IH, m), 4.68 - 4.85 (IH, m), 6.92 (IH, d), 7.12 (IH, d), \]
7.30 (2H, d), 7.54 (2H, d), 7.85 (IH, s), 8.08 - 8.30 (4H, m), m/z (ESI+) (M+H)+ = 449.49;
HPLC tR = 1.42 min.

Example 343
tert-butyl 3-[[5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]pyrrolidine-1-carboxylate

Method 2 from Intermediate S

\[
\delta \begin{align*}
&1.41 (9H, s), 1.51 - 1.64 (2H, m), 1.71 - 1.85 (3H, m), 2.02 - 2.11 (IH, m), 2.21 (3H, s), 2.78 - 2.88 (2H, m), 3.06 - 3.14 (2H, m), 3.33 (2H, t), \\
&3.42 - 3.55 (IH, m), 3.68 - 3.92 (IH, m), 4.11 - 4.20 (IH, m), 4.51 - 4.69 (IH, m), 6.90 - 6.95 (2H, m), 7.09 - 7.15 (2H, m), 7.19 (IH, d), 7.29 - 7.35 (2H, m), 7.66 (IH, s), 7.99
\end{align*}
\]

Example 344
N-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-methylsulfonyl-pyrrolidine-1-carboxamide

Method 2 from Intermediate A

\[
\delta \begin{align*}
&1.50 - 1.90 (4H, m), 2.22 (3H, s), 2.25 - 2.37 (2H, m), 2.70 - 3.23 (3H, m), 3.04 (3H, s), 3.40 - 4.07 (6H, m), 4.40 - 4.80 (IH, m), 7.10 (IH, d), 7.24 (IH, d), 7.38 (IH, s), 7.50 (2H, d), 7.76 (2H, d), 7.81 (IH, s), m/z 495 (M+H)+.
\end{align*}
\]

Example 345
N-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-hydroxy-azetidine-1-carboxamide

Method 2 from Intermediate A
1H NMR (300.073 MHz, d6-DMSO) δ 1.50 - 1.91 (4H, m), 2.21 (3H, s), 2.66 - 3.22 (3H, m), 3.65 - 3.73 (2H, m), 3.74 - 4.00 (IH, m), 4.04 - 4.15 (2H, m), 4.37 - 4.49 (IH, m), 4.48 - 4.75 (IH, m), 5.60 (IH, d), 7.07 (IH, d), 7.22 (IH, d), 7.40 (IH, s), 7.50 (2H, d), 7.73 - 7.80 (3H, m), m/z 419 (M+H)+.

Example 346
N-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]azetidine-1-carboxamide

Method 2 from Intermediate A

1H NMR (300.073 MHz, d6-DMSO) δ 1.50 - 1.95 (4H, m), 2.10 - 2.29 (5H, m), 2.70 - 3.22 (3H, m), 3.61 - 4.01 (5H, m), 4.39 - 4.70 (IH, m), 7.07 (IH, d), 7.22 (IH, d), 7.41 (IH, s), 7.50 (2H, d), 7.70 - 7.80 (3H, m), m/z 403 (M+H)+.

Example 347
tert-butyl N-[2-[5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino] ethyl]-N-methyl 1-carbamate

Method 2 from Intermediate S

1H NMR (300.072 MHz, CDCl3) δ 1.43 (9H, s), 1.69 - 1.99 (4H, m), 2.10 - 2.22 (3H, m), 2.68 - 3.22 (6H, m), 3.36 (4H, s), 3.88 - 4.04 (IH, m), 4.74 - 4.95 (IH, m), 5.45 - 5.59 (IH, m), 6.53 (IH, s), 6.94 - 7.08 (3H, m), 7.10 - 7.21 (3H, m), 7.60 (IH, s), m/z (ESI+) (M+H)+ = 513.54; HPLC tR = 2.55 min.

Example 348
3-(1-acetylpyrrolidin-3-yl)-1-[5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]urea

Method 5 from Example 349

1H NMR (300.073 MHz, t6-DMSO) δ 1.49 - 1.66 (2H, m), 1.76 - 1.87 (2H, m), 1.94 (3H, s), 2.03 - 2.16 (IH, m), 2.22 (3H, s), 2.76 - 3.08 (5H, m), 3.18 - 3.31 (IH, m), 3.39 - 3.58
Example 349

1-[5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-pyrrolidin-3-yl-urea

\[
\text{Method 3 from Example 343}
\]

\[^1\text{H NMR (400.132 MHz, d}_6\text{-DMSO) } \delta 0.84 - 0.92 (2H, m), 1.23 - 1.41 (4H, m), 1.46 - 1.86 (4H, m), 2.22 (3H, s), 2.73 - 3.07 (3H, m), 3.67 - 3.87 (IH, m), 4.12 - 4.18 (IH, m), 4.51 - 4.71 (IH, m), 6.90 (IH, d), 7.06 - 7.19 (4H, m), 7.28 - 7.35 (2H, m), 7.65 - 7.75 (IH, m), 7.83 (IH, s), 7.99 (IH, s), m/z (ESI+) (M+H)+ = 425.45; HPLC tR = 1.43 min.\]

Example 350

1-[5-[4-(4-chlorophenyl)-4-hydroxy-piperidine-1-carbonyl]-2-methyl-phenyl]-3-propan-2-yl-urea

\[
\text{Method 6b from Intermediate Q}
\]

m/z (ESI+) (M+H)+ = 431; HPLC tR = 2.10 min.

Example 351

1-[5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[2-(methylmethylsulfonyl-amino)ethyl]urea

\[
\text{Method 5a from Intermediate T}
\]

\[^1\text{H NMR (300.073 MHz, d}_6\text{-DMSO) } \delta 1.46 - 1.86 (4H, m), 2.20 (3H, s), 2.70 - 2.92 (9H, m), 3.13 (4H, t), 3.69 - 3.85 (IH, m), 4.51 - 4.67 (IH, m), 6.69 (IH, t), 6.92 (IH, d), 7.06 - 7.20 (3H, m), 7.26 - 7.34 (2H, m), 7.88 (2H, d), m/z (ESI+) (M+H)+ = 491.43; HPLC tR = 2.17 min.\]
Example 352
N-[2-[5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]ethyl]-N-methyl-acetamide

\[
\text{Method 5 from Intermediate T}
\]

\[
\begin{align*}
^1\text{H NMR} (300.073 \text{ MHz, } d_6\text{-DMSO}) & \delta 1.43 - 1.87 \text{ (4H, m), } 1.97 \text{ (3H, d), } 2.19 \text{ (3H, s), } 2.68 - 3.10 \text{ (8H, m), } 3.32 - 3.40 \text{ (2H, m), } 3.60 - 3.91 \text{ (IH, m), } 4.40 - 4.71 \text{ (IH, m), } 6.53 - 6.75 \text{ (IH, m), } 6.89 - 6.97 \text{ (IH, m), } 7.05 - 7.21 \text{ (3H, m), } 7.26 - 7.35 \text{ (2H, m), } 7.71 - 7.91 \text{ (2H, m), } \\
\text{m/z (ESI+) (M+H)+} & = 455.46; \text{ HPLC } t_R = 1.99 \text{ min.}
\end{align*}
\]

Example 353
N-[2-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoyl-1-methyl- amino]ethyl]propanamide

\[
\text{Method 5 from Intermediate U}
\]

\[
\begin{align*}
^1\text{H NMR} (300.073 \text{ MHz, } d_6\text{-DMSO}) & \delta 0.96 \text{ (3H, t), } 1.50 - 1.89 \text{ (4H, m), } 2.05 \text{ (2H, q), } 2.21 \text{ (3H, s), } 2.74 - 3.04 \text{ (6H, m), } 3.23 \text{ (2H, t), } 3.34 \text{ (2H, t), } 3.69 - 3.93 \text{ (IH, m), } 4.45 - 4.72 \text{ (IH, m), } \\
7.08 \text{ (IH, d), } 7.22 \text{ (IH, d), } 7.34 \text{ (IH, s), } 7.50 \text{ (2H, d), } 7.72 - 7.88 \text{ (4H, m), } \text{m/z (ESI+)} (M+H)+ & = 476.43; \text{ HPLC } t_R = 1.83 \text{ min.}
\end{align*}
\]

Example 354
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(1-pyridin-3-yl)ethyl]urea

\[
\text{Method 2 from Intermediate A}
\]

\[
\begin{align*}
^1\text{H NMR} (400.132 \text{ MHz, } d_6\text{-DMSO}) & \delta 1.43 \text{ (3H, d), } 1.48 - 1.92 \text{ (4H, m), } 2.21 \text{ (3H, s), } 2.72 - 2.96 \text{ (2H, m), } 2.98 - 3.21 \text{ (IH, m), } 3.67 - 3.84 \text{ (IH, m), } 4.80 - 4.90 \text{ (IH, m), } 6.93 \text{ (IH, d), } \\
7.18 \text{ (2H, d), } 7.24 \text{ (IH, d), } 7.35 - 7.40 \text{ (IH, m), } 7.49 \text{ (2H, d), } 7.72 - 7.80 \text{ (4H, m), } 7.96 \text{ (IH, d), } 8.46 \text{ (IH, d), } 8.59 \text{ (IH, d), } \text{m/z (ESI+)} (M+H)+ & = 468.49; \text{ HPLC } t_R = 1.53 \text{ min.}
\end{align*}
\]
Example 355

1-[5-[4-(4-chlorophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(pyridin-2-ylmethyl)urea

Method 2 from Intermediate V

$^1$H NMR (400.132 MHz, d$_6$-DMSO) $\delta$ 1.41 - 1.95 (4H, m), 2.23 (3H, s), 2.71 - 2.92 (2H, m), 3.00 - 3.21 (IH, m), 3.68 - 3.87 (IH, m), 4.42 (2H, d), 4.50 - 4.69 (IH, m), 6.94 (IH, d), 7.20 (IH, d), 7.25 - 7.40 (7H, m), 7.75 - 7.82 (IH, m), 7.97 (IH, s), 8.05 (IH, s), 8.54 (IH, d), m/z (ESI+) (M+H)$^+$ = 463.45; HPLC $t_R$ = 1.79 min.

Example 356

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[1-methylpyrazol-4-yl)methyl]urea

Method 2 from Intermediate A

$^1$H NMR (400.132 MHz, d$_6$-DMSO) $\delta$ 1.50 - 1.94 (4H, m), 2.19 (3H, s), 2.74 - 2.99 (2H, m), 3.00 - 3.22 (IH, m), 3.68 - 3.87 (4H, m), 4.11 (2H, d), 4.53 - 4.70 (IH, m), 6.85 (IH, t), 6.93 (IH, d), 7.18 (IH, d), 7.37 (IH, s), 7.51 (2H, d), 7.62 (IH, s), 7.73 (IH, s), 7.76 - 7.81 (2H, m), 8.01 (IH, d), m/z (ESI+) (M+H)$^+$ = 457.49; HPLC $t_R$ = 1.94 min.

Example 357

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[1-pyridin-4-ylyethyl]urea

Method 2 from Intermediate A

$^1$H NMR (400.132 MHz, d$_6$-DMSO) $\delta$ 1.39 (3H, d), 1.47 - 1.90 (4H, m), 2.23 (3H, s), 2.71 - 2.97 (2H, m), 3.00 - 3.21 (IH, m), 3.67 - 3.84 (IH, m), 4.52 - 4.68 (IH, m), 4.75 - 4.85 (IH, m), 6.91 - 6.95 (IH, m), 7.19 (IH, d), 7.26 (IH, d), 7.35 (2H, d), 7.49 (2H, d), 7.77
Example 358

1-[[5-[[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-[[6-morpholin-4-ylpyridin-2-yl)methyl]urea

\[
\text{Method 2 from Intermediate A}
\]

\[\text{H NMR (400.132 MHz, d}_6\text{-DMSO) } \delta 1.46 \text{ - 1.95 (4H, m), 2.23 (3H, s), 2.70 - 3.00 (2H, m), 3.01 - 3.21 (IH, m), 3.40 - 3.49 (4H, m), 3.65 - 3.87 (5H, m), 4.25 (2H, d), 4.52 - 4.69 (IH, m), 6.65 (IH, d), 6.70 (IH, d), 6.95 (IH, d), 7.03 - 7.09 (IH, m), 7.20 (IH, d), 7.47 - 7.58 (3H, m), 7.77 (2H, d), 7.94 (IH, s), 7.99 (IH, s), m/z (ESI+) (M+H)+ = 539.56;}
\]

HPLC t\text{R} = 1.84 min.

Example 359

1-[[5-[[4-(4-chlorophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-propan-2-yl-urea

\[
\text{Method 6b from Intermediate Q}
\]

\[\text{H NMR (400.132 MHz, d}_6\text{-DMSO) } \delta 1.04 (6H, d), 1.36 - 1.86 (4H, m), 2.13 (3H, s), 2.70 - 2.81 (2H, m), 2.95 - 3.14 (IH, m), 3.61 - 3.77 (2H, m), 4.45 - 4.63 (IH, m), 6.50 (IH, d), 6.83 (IH, d), 7.10 (IH, d), 7.24 (2H, d), 7.29 (2H, d), 7.54 (IH, s), 7.94 (IH, s), m/z (ESI+) (M+H)+ = 414.37; HPLC t\text{R} = 2.53.
\]

Example 360

1-[[2-methyl-5-[[4-(4-sulfamoylphenyl)piperidine-1-carbonyl]-phenyl]-3-propan-2-yl-urea

\[
\text{Method 6b from Intermediate Q}
\]

\[\text{H NMR (400.132 MHz, de-DMSO) } \delta 1.11 (6H, d), 1.50 - 1.93 (4H, m), 2.20 (3H, s), 2.70 - 3.23 (3H, m), 3.65 - 3.88 (2H, m), 4.52 - 4.73 (IH, m), 6.57 (IH, d), 6.91 (IH, d), 7.18
\]
(IH, d), 7.29 (2H, s), 7.48 (2H, d), 7.62 (IH, s), 7.76 (2H, d), 8.02 (IH, s), m/z (ESI+) (M+H)+ = 459.3 1; HPLC tR = 1.77.

Example 361

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-methyl-urea

\[
\text{Method 2 from Intermediate A}
\]

\[\text{H NMR (400.132 MHz, d}_6\text{-DMSO) } \delta \text{ 1.51 - 1.95 (4H, m), 2.20 (3H, s), 2.66 (3H, d), 2.76 - 3.23 (3H, m), 3.64 - 3.94 (IH, m), 4.45 - 4.73 (IH, m), 6.43 - 6.50 (IH, m), 6.93 (IH, d), 7.18 (IH, d), 7.51 (2H, d), 7.72 (IH, s), 7.77 (2H, d), 7.93 (IH, s), m/z (ESI+) (M+H)+ = 377.43 ; HPLC tR = 2.03 min.}\]

Example 362

3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylsulfanylphenyl]-1-propan-2-ylurea

\[
\text{Method 2 from Intermediate W}
\]

\[\text{H NMR (300.072 MHz, CDCl}_3\text{) } \delta \text{ 1.21 (d, 6H), 1.67 - 1.95 (m, 4H), 2.36 (s, 3H), 2.78 - 2.89 (m, 2H), 3.06 - 3.32 (m, IH), 3.96 (septet, IH), 4.04 - 4.09 (m, IH), 4.78 - 4.96 (m, 2H), 7.05 - 7.08 (m, IH), 7.22 (s, IH), 7.32 (d, 2H), 7.40 (d, IH), 7.60 (d, 2H), 8.08 (s, IH), m/z (ESI+) (M+H)+ = 437; HPLC tR = 2.32 min.}\]

Example 363

3-benzyl-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylsulfanylphenyl]urea

\[
\text{Method 2 from Intermediate W}
\]

\[\text{H NMR (300.072 MHz, CDCl}_3\text{) } \delta \text{ 1.63 - 1.97 (m, 4H), 2.32 (s, 3H), 2.75 - 2.88 (m, 2H), 3.05 - 3.23 (m, IH), 3.82 - 4.13 (m, IH), 4.46 (d, 2H), 4.74 - 4.96 (m, IH), 5.37 (t, IH),}\]
7.03 - 7.08 (m, 1H), 7.27 - 7.40 (m, 9H), 7.60 (d, 2H), 8.07 - 8.10 (m, 1H), m/z (ESI+) (M+H)+ = 485; HPLC tR = 2.52 min.

**Example 364**
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylsulfonylphenyl]-1-propan-2-ylurea

[Chemical structure image]

Method 2 from Intermediate X

H NMR (300.072 MHz, CDCl3) δ 1.22 (d, 6H), 1.64 - 1.99 (m, 4H), 2.80 - 2.94 (m, 2H), 3.08 (s, 3H), 3.16 - 3.27 (m, 1H), 3.79 - 4.01 (m, 2H), 4.81 - 4.94 (m, 1H), 5.14 (d, 1H), 7.16 - 7.21 (m, 1H), 7.34 (d, 2H), 7.61 (d, 2H), 7.90 (d, 2H), 8.32 - 8.35 (m, 1H), 8.51 (s, 1H), m/z (ESI+) (M-H)- = 467; HPLC tR = 2.19 min.

**Example 365**
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-(methoxymethyl)phenyl]-1-propan-2-ylurea

[Chemical structure image]

Method 2 from Intermediate Y

1H NMR (300.073 MHz, d6-DMSO) δ 1.10 (6H, d), 1.45 - 2.00 (4H, m), 2.68 - 3.23 (3H, m), 3.30 (3H, s), 3.64 - 3.83 (2H, m), 4.40 (2H, s), 4.49 - 4.75 (IH, m), 6.80 (IH, d), 6.97 (IH, d), 7.29 (IH, d), 7.50 (2H, d), 7.64 (IH, s), 7.76 (2H, d), 8.01 (IH, s), m/z (ESI+) (M+H)+ = 435.35; HPLC tR = 2.21 min.

**Example 366**
[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]urea

[Chemical structure image]

Method 2 from Intermediate A
IH NMR (400.132 MHz, d<sub>6</sub>-DMSO) δ 1.54 - 1.69 (2H, m), 1.71 - 1.92 (2H, m), 2.22 (3H, s), 2.63 - 3.22 (3H, m), 3.66 - 3.97 (IH, m), 4.44 - 4.78 (IH, m), 6.09 (2H, s), 6.94 (IH, d), 7.18 (IH, d), 7.50 (2H, d), 7.74 - 7.81 (3H, m), 7.97 (IH, s),
m/z (ESI+) (M+H)+ = 363.33; HPLC tR = 1.85 min.

Example 367

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]-3-[(3,5-difluoropyridin-2-yl)methyl]urea

Method 2 from Intermediate A

IH NMR (400.132 MHz, d<sub>6</sub>-DMSO) δ 1.47 - 1.94 (4H, m), 2.21 (3H, d), 2.71 - 3.23 (3H, m), 3.65 - 3.88 (IH, m), 4.49 (2H, d), 4.53 - 4.72 (IH, m), 6.94 (IH, dd), 7.19 (IH, d), 7.28 (IH, t), 7.50 (2H, d), 7.77 (2H, dd), 7.91 - 8.00 (2H, m), 8.07 (IH, s), 8.51 (IH, d), m/z (ESI+) (M+H)+ = 490.48; HPLC tR = 2.33 min.

Example 368

1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]-3-[(1-pyridin-2-ylethyl)urea

Method 2 from Intermediate A

IH NMR (400.132 MHz, d<sub>6</sub>-DMSO) δ 1.39 (3H, d), 1.47 - 1.92 (4H, m), 2.22 (3H, s), 2.64 - 3.23 (3H, m), 3.63 - 3.87 (IH, m), 4.49 - 4.70 (IH, m), 4.91 (IH, quintet), 6.92 (IH, dd), 7.18 (IH, d), 7.24 - 7.36 (2H, m), 7.39 (IH, d), 7.49 (2H, d), 7.73 - 7.81 (3H, m), 7.96 - 8.01 (2H, m), 8.56 (IH, ddd), m/z (ESI+) (M+H)+ = 468.54; HPLC tR = 1.76 min.

Example 369

2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]carbamoylamino]-3-(4-fluorophenyl)propanoic acid

Example 370

(2R)-3-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]carbamoylamino]-2-[[2-methylpropan-2-yl]oxycarbonylamino]propanoic acid
Example 371
2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]carbamoylamino]-3-methylbutanoic acid
Example 372
4-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]carbamoylamino]butanoic acid
Example 373
2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]carbamoylamino]acetic acid
Example 374
1-[2-methyl-5-[4-(4-methylsulfonylphenyl)piperidine-1-carbonyl]phenyl]-3-propan-2-ylurea
Example 375
1-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methylphenyl]-3-propan-2-ylurea
Example 376
3-tert-butyl-1-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methylphenyl]urea
Example 377
3-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-fluorophenyl]-1-propan-2-ylurea
Example 378
3-[4-(cyanophenyl)methyl]-1-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methylphenyl]urea
Example 379
1-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methylphenyl]-3-(pyridin-4-ylmethyl)urea
Example 380
3-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methylphenyl]-1,1-dimethylurea
Example 381
1-benzyl-3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]-1-methylurea
Example 383
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]-3-(3-oxo-1,2-oxazolidin-4-yl)urea
Example 384
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]-3-(2-methylbut-3-yn-2-yl)urea

Example 385
Ethyl 2-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]carbamoylamino]-propanoate

Example 386
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylsulfinylphenyl]-1-propan-2-ylurea

Example 387
3-benzyl-l-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylsulfinylphenyl]urea

Example 388
2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]carbamoylamino]-cyclopentane-1-carboxylic acid

Example 389
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]-3-(1-methylcyclopropyl)-urea

Example 390
3-(1-acetylpiperidin-3-yl)-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]urea

Example 391
1-[2-methyl-5-(4-phenylpiperidine-1-carbonyl)phenyl]-3-propan-2-ylurea

Example 392
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]-1-(2-hydroxyethyl)-1-methylurea

Example 393
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]-1-methyl-1-(1-methylpiperidin-4-yl)urea

Example 394
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]-1-(2-dimethylaminoethyl)-1-methylurea
Example 395
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]-1-(2-hydroxyethyl)-1-propan-2-ylurea
Example 396
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]-1-methyl-1-(oxan-4-yl)urea
Example 397
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]-1-(1,1-dioxothiolan-3-yl)-1-propylurea
Example 398
2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]carbamoyl-methylamino]-N-propan-2-ylacetamide
Example 399
N-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]-2-(ethoxymethyl)pyrrolidine-1-carboxamide
Example 400
1-[5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-2-methylphenyl]-3-(2-methylaminoethyl)urea
Example 401
N-[2-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]carbamoyl-methylamino[ethyl]acetamide
Example 402
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]-1-[2-(ethylsulfonylamino)ethyl]-1-methylurea
Example 403
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-(methylsulfonylmethyl)phenyl]-1-propan-2-ylurea
Example 404
1-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methylphenyl]-3-propan-2-ylurea
Example 405
3-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methylsulfanylphenyl]-1-propan-2-ylurea
Example 406
4-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]carbamoylamino]cyclohexane-1-carboxylic acid

Example 407
4-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]carbamoylamino]butanoic acid

Example 408
2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]carbamoylamino]acetic acid

Example 409
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2,4-dimethylphenyl]-3-(pyridin-2-ylmethyl)urea

Example 410
3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2,4-dimethylphenyl]-1-ethylurea

Example 411
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2,4-dimethylphenyl]-3-cyclopropylurea

Example 412
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2,4-dimethylphenyl]-3-(2-methoxyethyl)urea

Example 413
1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2,4-dimethylphenyl]-3-prop-2-ynylurea

Example 414
1-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methylphenyl]-3-(pyridin-2-ylmethyl)urea

Example 415
1-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methylphenyl]-3-cyclopropylurea

Example 416
3-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methylphenyl]-1-(3-ethoxypropyl)urea

Example 417
1-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methylphenyl]-3-(2-methoxyethyl)urea

Example 418
1-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methylphenyl]-3-prop-2-ynylurea
Preparation of Intermediates

Intermediate A

4-[1-(3-amino-4-methyl-benzoyl)-4-piperidyl]benzonitrile

A solution of 3-amino-4-methyl benzoic acid (4.05 g, 26.792 mmol), 4-(4'-cyanophenyl) piperidine (5 g, 26.79 mmol), N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride [EDAC] (5.64 g, 29.47 mmol, 1.1 eq) and DMAP (328 mg, 2.68 mmol, 0.1 eq) in DMF (60 mL) was stirred at ambient temperature for 2 hrs. Ethyl acetate (200 mL) was added and the resulting solution was washed sequentially with KHSO₄ solution (100 mL of 2M), and brine (100ml); a precipitate formed and was filtered off to give the title compound as a colourless solid (5.25 g). ¹H NMR (300.073 MHz, d₆-DMSO, 30 °C) δ 1.47 - 1.67 (2H, m), 1.68 - 1.89 (2H, m), 2.05 (3H, s), 2.68 - 3.15 (3H, m), 3.59 - 4.13 (IH, m), 4.22 - 4.76 (IH, m), 4.97 (2H, s), 6.45 - 6.53 (IH, m), 6.63 (IH, s), 6.90 - 6.99 (IH, m), 7.44 - 7.54 (2H, m), 7.71 - 7.81 (2H, m), m/z 320 (M+H)+.

Intermediate B

4-[1-[3-amino-4-(trifluoromethoxy)benzoyl]-4-piperidyl]benzonitrile

Step 1: 3-nitro-4-(trifluoromethoxy)benzoic acid

4-(trifluoromethoxy) benzoic acid (4 g, 26.3 mmol) was added slowly to a stirred mixture of concentrated sulfuric acid ((6.6 mL, 65.7 mmol) and concentrated nitric acid (4 mL, 44.7 mmol) at 40°C. When the addition was complete, the reaction mixture was heated to 50°C and became a pale yellow slurry. After 1h the reaction appeared to have gone to completion and so was poured onto ice and water. A white precipitate formed which was
isolated by filtration and washed with water to give the title compound as a colourless crystalline solid (4.2 g). $^1$H NMR (300.073 MHz, DMSO-de) $\delta$ 7.83 - 7.87 (IH, m), 8.32 - 8.36 (IH, m), 8.56 (IH, d), m/z 198 (M+H)$^+$.  

**Step 2:** 3-amino-4-(trifluoromethoxy)benzoic acid

![Chemical structure](image)

A solution of 3-nitro-4-(trifluoromethoxy)benzoic acid (Step 1) (3.51 g, 14 mmol) in MeOH (150 mL) was hydrogenated at ambient temperature and pressure in the presence of 10% palladium on charcoal catalyst (500 mg). The catalyst was removed by filtration and washed through with more MeOH; the filtrate and washings were combined and evaporated to give the title compound as a pale cream solid (2.9 g), $^1$H NMR (300.073 MHz, $d_6$-DMSO) $\delta$ 5.60 (br s, 2H), 7.07 - 7.23 (m, 2H), 7.39 - 7.46 (m, 1H), 12.02 - 13.40 (br s, IH), m/z 220 (M-H)$^-$.  

**Step 3:** 4-[(1-3-amino-4-(trifluoromethoxy)benzoyl)-4-piperidyl]benzonitrile

![Chemical structure](image)

A mixture of 3-amino-4-trifluoromethoxy benzoic acid (Step 2) (2.8 g, 12.66 mmol), 4-(4'-cyanophenyl)piperidine (2.36 g, 12.66 mmol, 1 eq), N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (EDAC) (2.67 g, 13.93 mmol, 1.1 eq) and DMAP (155 mg, 1.27 mmol, 0.1 eq) in DMF (30 mL) was stirred at room temperature for 2 hrs. EtOAc (200 mL) was added and the resulting mixture washed sequentially with aqueous potassium bisulfate solution (100 mL of 2M KHSO$_4$), brine (100 mL), dried (MgSO$_4$), filtered and reduced in vacuo to give a brown oil. Ethyl acetate was added and the resulting colourless solid isolated by filtration. A precipitate also appeared during the extraction process; this was isolated and the solids combined to give the title compound (3.16 g), $^1$H NMR (300.072 MHz, CDCl$_3$) $\delta$ 1.43 - 2.02 (4H, m), 2.77 - 3.22 (3H, m), 3.80 - 4.21 (3H, m), 4.63 - 5.03 (IH, m), 6.72 - 6.77 (IH, m), 6.87 (IH, d), 7.13 - 7.18 (IH, m), 7.32 (2H, d), 7.61 (2H, d), m/z 390 (M+H)$^+$. 
Intermediate C

4-[l-(3-amino-4-methoxy-benzoyl)-4-piperidyl]benzonitrile

A stirred mixture of 4-(4'-cyanophenyl)piperidine (3 g, 16 mmol); 3-amino-4-

methoxybenzoic acid (2.675 g, 16 mmol, 1 eq) and DIPEA (4.2 ml, 24 mmol, 1.5 eq) in

DCM (100 mL) was blanketed with nitrogen and treated with N-(3-Dimethylaminopropyl) -

N'-ethylcarbodiimide hydrochloride (EDAC) (3.4 g, 17.6 mmol, 1.1 eq). The reaction

mixture was stirred for three days. Addition of water to the reaction mixture resulted in an

emulsion and a colourless precipitate. The solid was isolated by filtration and washed with

EtOAc (2 x 75 mL portions) to give a colourless solid (2.5 g). The ethyl acetate washings

were combined, washed with water, dried (MgSO₄) and evaporated to give a further 2 g;

the solids thus prepared were identical and combined to give the title compound as (4.5 g,

83%). ¹H NMR (300.073 MHz, d₆-DMSO, 300°C) δ 1.48 - 1.67 (2H, m), 1.71 - 1.87 (2H,
m), 2.80 - 3.08 (3H, m), 3.78 (3H, s), 3.88 - 4.63 (2H, m), 4.84 (2H, s), 6.56 - 6.64 (IH,
m), 6.67 - 6.73 (IH, m), 6.80 (IH, d J = 8.1 Hz), 7.49 (2H, d J = 8.1 Hz), 7.76 (2H, d J = 9.4

Hz), m/z 336 (M+H)+.

Intermediate D

4-[1-(5-amino-2-methyl-benzoyl)-4-piperidyl]benzonitrile

Step 1:

4-[1-(2-methyl-5-nitro-benzoyl)-4-piperidyl]benzonitrile

The title compound was prepared in a manner similar to that described for Intermediate A,

starting from 2-methyl-5-nitrobenzoic acid and 4-(4'-cyanophenyl)piperidine. ³H NMR

(300.072 MHz, CDCl₃) δ 1.64 - 2.11 (4H, m), 2.42 - 2.53 (3H, m), 2.79 - 3.00 (2H, m), 3.09

- 3.23 (IH, m), 3.55 (IH, d), 4.98 (IH, d J = 29 - 7.36 (2H, m), 7.42 (IH, d), 7.63 (2H, d), 8.04

- 8.18 (2H, m), m/z 348 (M-H)
Step 2:
4-[1-(5-amino-2-methyl-benzoyl)-4-piperidyl]benzonitrile

10% Palladium on carbon (0.6g, 15% by weight) was added to a solution of 4-[1-(2-methyl-5-nitro-benzoyl)-4-piperidyl]benzonitrile (Step 1) (4g, 11.45mmol) in ethanol (100 mL) and THF (100 mL). After purging the reaction flask with nitrogen, hydrogen was introduced and the resulting reaction mixture was stirred for 4hrs. The catalyst was removed by filtration through celite and the filtrate was evaporated in vacuo to give a yellow foam. This still contained unreacted starting material so the hydrogenation procedure was repeated for a further 1 hr. The catalyst was removed by filtration through celite and the solvent removed in vacuo to give a yellow foam. This was dissolved in EtOAc and the solution was then washed sequentially with water and brine, dried (MgSO₄) and the solvent removed in vacuo to give the title compound as a yellow solid (3.3 g). ¹H NMR (400.132 MHz, d₆-DMSO) δ 1.39 - 1.62 (2H, m), 1.69 - 1.78 (IH, m), 1.88 (IH, d), 1.99 - 2.12 (3H, m), 2.80 (IH, t), 2.90 - 2.99 (IH, m), 3.08 (IH, t), 3.45 - 3.51 (IH, m), 4.63 - 4.72 (IH, m), 5.01 (2H, s), 6.37 (IH, d), 6.48 - 6.52 (IH, m), 6.89 (IH, d), 7.46 - 7.52 (2H, m), 7.78 (2H, d), m/z 320 (M+H)⁺.

Intermediate E
4-[1-(3-amino-4-fluoro-benzoyl)-4-piperidyl]benzonitrile

The title compound was prepared in a manner similar to that described for Intermediate A, starting from 3-amino-4-fluoro-benzoic acid and 4-(4'-cyanophenyl)piperidine. After work-up of the reaction, the crude product was purified by trituration with ethanol to give a colourless solid. ¹H NMR (300.073 MHz, d₆-DMSO) δ 1.43 - 2.00 (m, 4H), 2.68 - 3.23 (m, 3H), 3.59 - 4.05 (m, IH), 4.21 - 4.88 (m, IH), 5.29 (s, 2H), 6.49 - 6.61 (m, IH), 6.80 (d, IH), 6.95 - 7.08 (m, IH), 7.49 (d, 2H), 7.76 (d, 2H), m/z 324 (M+H)⁺.
Intermediate F

4-[(5-amino-2,4-dimethyl-benzoyl)-4-piperidyl]benzonitrile

\[
\begin{align*}
\text{HN} & \quad \text{O} \\
\text{N} & \quad \text{N}
\end{align*}
\]

Step 1: 4-[(2,4-dimethyl-5-nitro-benzoyl)-4-piperidyl]benzonitrile

The title compound was prepared in a manner similar to that described for Intermediate A, starting from 2,4-dimethyl-5-nitro-benzoic acid and 4-(4'-cyanophenyl)piperidine; \(^1\)H NMR (300.072 MHz, CDCl\(_3\)) \(\delta\) 1.44 - 1.64 (m, IH), 1.66 - 1.91 (m, 2H), 1.95 - 2.09 (m, IH), 2.30 - 2.49 (br s, 3H), 2.61 (s, 3H), 2.79 - 2.95 (m, 2H), 3.05 - 3.26 (m, IH), 3.59 (d, IH), 4.95 (d, IH), 7.22 (s, IH), 7.32 (d, 2H), 7.61 (d, 2H), 7.81 (br s, IH), m/z 405 (M+MeCN+H)\(^+\).

Step 2: 4-[(5-amino-2,4-dimethyl-benzoyl)-4-piperidyl]benzonitrile

The title compound was prepared in a manner similar to that described for Intermediate D, Step 2, starting from 4-[(2,4-dimethyl-5-nitro-benzoyl)-4-piperidyl]benzonitrile (Step 1), and using a methanol / THF mixture (1:1) as solvent; \(^1\)H NMR (300.073 MHz, \(\alpha\)/DMSO) \(\delta\) 1.36 - 1.63 (m, 2H), 1.64 - 1.79 (m, IH), 1.80 - 1.95 (m, IH), 1.96 - 2.08 (br s, 3H), 2.02 (s, 3H), 2.69 - 2.85 (m, IH), 2.85 - 2.97 (m, IH), 2.98 - 3.12 (m, IH), 3.40 - 3.56 (m, IH), 4.59 - 4.70 (m, IH), 4.73 (br s, 2H), 6.30 - 6.55 (br m, IH), 6.78 (s, IH), 7.47 (d, 2H), 7.77 (d, 2H); peak broadening is observed due to conformations of amide group, m/z 334 (M+H)\(^+\).
Intermediate G

2-amino-4-[4-(4-cyanophenyl)piperidine-1-carbonyl]benzonitrile

\[
\text{H}_2\text{N} \begin{array}{c}
\text{N} \\
\text{=}
\end{array}
\text{C} \begin{array}{c}
\text{O} \\
\text{O} \\
\text{O} \\
\text{O}
\end{array} 
\text{N}
\begin{array}{c}
\text{N} \\
\text{=}
\end{array}
\text{N} \begin{array}{c}
\text{C} \\
\text{N}
\end{array}
\text{N}
\]

**Step 1:** Ethyl 4-cyano-3-nitro-benzoate

Water (0.01 mL) was added to a solution of 4-iodo-3-nitro benzoic acid ethyl ester (0.4 g, 1.25 mmol) and zinc cyanide (79 mg, 0.67 mmol) in NMP (5 mL) and nitrogen was bubbled through the mixture for 5 mins. Bis(dibenzylideneacetone)palladium(0) (29 mg, 0.05 mmol) and 1,1'-Bis(diphenylphosphino)ferrocene (83 mg, 0.15 mmol) were added and the vessel sealed and filled with nitrogen. The reaction was heated in the microwave oven at 150°C for 5 mins. EtOAc (50 mL) was added and the resulting mixture was filtered through celite and then washed sequentially with dilute aqueous hydrochloric acid (50 mL of IM), saturated aqueous sodium bicarbonate solution (50 mL), water (50 mL) and brine (50 mL), dried (MgSO\textsubscript{4}), filtered and reduced in vacuo to give a brown oil which was chromatographed (40 g silica column, Companion, eluting with a gradient consisting of isohexane containing 0-20% EtOAc to give the title compound as a yellow solid (200 mg).

\(^1\)H NMR (300.072 MHz, CDCl\textsubscript{3}) \(\delta\) 1.45 (t, 3H), 4.49 (q, 2H), 8.01 (d, 1H), 8.42 - 8.47 (m, 1H), 8.92 (d, 1H), m/z 220 (M\(^+\)).

**Step 2** Ethyl 3-amino-4-cyano-benzoate

This was prepared by hydrogenation of ethyl 4-cyano-3-nitro-benzoate (Step 1) using a procedure similar to that described in Intermediate B, Step 2, to give the title compound as a yellow solid, \(^1\)H NMR (300.072 MHz, CDCl\textsubscript{3}) \(\delta\) 1.39 (3H, t), 4.38 (2H, q), 4.57 (2H, s), 7.34 - 7.47 (3H, m), m/z 190 (M\(^+\)).
A solution of ethyl 3-amino-4-cyano-benzoate (Step 2) (140 mg, 0.74 mmol) in THF (6 mL) was treated with a solution of lithium hydroxide monohydrate (47 mg, 1.10 mmol) in water (3 ml), and the mixture stirred at ambient temperature for 2 hrs. The THF was removed in vacuo and the aqueous residue washed with EtOAc (30 mL) to remove any unreacted starting material. The aqueous was then adjusted to pH 3 with citric acid solution (IM), and extracted with EtOAc (20 mL). The organic extracts were washed with brine (20 mL), dried (MgSO₄), filtered and reduced in vacuo to give the title compound as a yellow solid (60 mg). ¹H NMR (300.073 MHz, d₆-DMSO) δ 6.27 (s, 2H), 7.04 - 7.08 (m, 1H), 7.38 - 7.40 (m, 1H), 7.47 (d, 1H), 13.03 (s, 1H), m/z 161 (M-H)⁺.

**Step 3:** 3-amino-4-cyano-benzoic acid

![结构式](image)

The title compound was prepared in a manner similar to that described for Intermediate A, starting from 3-amino-4-cyano-benzoic acid (Step 3) and 4-(4'-cyanophenyl) piperidine, ¹H NMR (300.072 MHz, CDCl₃) δ 1.53 - 2.06 (m, 4H), 2.78 - 2.92 (m, 2H), 3.05 - 3.22 (m, 1H), 3.71 - 3.96 (m, 1H), 4.61 (s, 2H), 4.79 - 4.97 (m, 1H), 6.71 - 6.75 (m, 1H), 6.78 - 6.81 (m, 1H), 7.32 (d, 2H), 7.42 (d, 1H), 7.62 (d, 2H), m/z 331 (M+H)⁺.

**Intermediate H**

(3-amino-4-methyl-phenyl)-[4-(4-bromophenyl)-4-hydroxy- 1-piperidyl]methanone

![结构式](image)

**Step 1:** [4-(4-bromophenyl)-4-hydroxy- 1-piperidyl]- (4-methyl-3-nitrophenyl)methanone
DIPEA (2.04 mL, 14.05 mmol) was added to a stirred solution of 4-(4-bromophenyl) piperidin-4-ol (2.5g, 9.76 mmol) and 4-methyl-3-nitrobenzoyl chloride (1.42 mL, 9.76 mmol) in DCM (30 mL), and the reaction mixture stirred at room temperature for 20 hrs. It was then washed sequentially with 1M citric acid (40 mL), saturated sodium bicarbonate solution (40 mL), brine (40 mL), dried (MgSO₄), filtered and reduced in vacuo to give a yellow oil. DCM was added and the resulting colourless solid isolated by filtration (2.1 g). The filtrate was chromatographed (120 g silica column, eluting with a gradient consisting of 20-70% EtOAc in isohexane) to give a colourless solid (0.97 g). This was combined with the product isolated previously to give the title compound as a colourless solid (3.07 g, 75%).

**Step 2:** (3-amino-4-methy1-phenyl)-[4-(4-bromophenyl)-4-hydroxy-1-piperidyl]methanone

A mixture of [4-(4-bromophenyl)-4-hydroxy-1-piperidyl]-[4-methyl-3-nitrophenyl]methanone (Step 1, 0.5 g, 1.19 mmol), iron (III) chloride hexahydrate (968 mg, 3.58 mmol) and zinc dust (778 mg, 11.9 mmol) in DMF (10 mL) and water (5 mL) was heated at 100°C for 4 hrs. The reaction mixture was filtered through celite and reduced in vacuo. EtOAc (30 mL) was added and the solution washed sequentially with water (2x30 mL) and brine (30 mL), dried (MgSO₄), filtered and reduced in vacuo to give the title compound as a colourless solid (0.43 g, 93%), which was used without further purification.

**1H NMR (300.072 MHz, CDCl₃)** δ 1.61 - 2.06 (m, 5H), 2.16 (s, 3H), 3.19 - 3.55 (m, 3H), 3.65 - 3.81 (m, 2H), 4.52 - 4.78 (m, 1H), 6.68 - 6.74 (m, 2H), 7.05 (d, 1H), 7.34 (d, 2H), 7.48 (d, 2H), m/z 389, 391 (M+H)+ [B].
Intermediate I

4-[(3-aminobenzoyl)-4-piperidyl]benzonitrile

The title compound was prepared in a manner similar to that described for Intermediate A, starting from 3-amino benzoic acid and 4-(4'-cyanophenyl)piperidine. After work-up of the reaction, the crude product was triturated with ether and recrystallised from EtOAc to give a pink solid. $^1$H NMR (300.072 MHz, CDCl$_3$) δ 1.50 - 2.04 (4H, m), 2.79 - 2.89 - 3.20 (3H, m), 3.76 - 3.97 (2H, s), 4.00 (1H, s), 4.90 (1H, s), 6.70 - 6.78 (3H, m), 7.15 - 7.20 (IH, m), 7.32 (2H, d), 7.60 - 7.63 (2H, m), m/z 306 (M+H)$^+$.  

Intermediate J

4-[(3-amino-4-methyl-benzoyl)-4-hydroxy-4-piperidyl]benzonitrile

**Step 1: [4-(4-bromophenyl)-4-hydroxy-1-piperidyl]-(4-methyl-3-nitro-phenyl)methanone**

A solution of 4-(4-bromophenyl)-4-piperidinol (2.5 g, 9.76 mmol) and 4-methyl-3-nitrobenzoyl chloride (1.42 mL, 9.76 mmol) in DCM (30 mL) was treated with DIPEA (2.04 mL, 14.05 mmol) and the reaction mixture stirred at ambient temperature for 20 hrs. It was then washed sequentially with aqueous citric acid (40 mL of IM), saturated sodium bicarbonate solution (40 mL) and brine (40 mL), dried (MgSO$_4$), and evaporated *in vacuo* to give a yellow oil. DCM was added and a colourless solid filtered off (2.1 g). The filtrate was purified by chromatography (120 g silica column, gradient eluting with 20-70% EtOAc in isohexane) to give a colourless solid (0.97 g). This was combined with the product isolated previously to give the title compound (3.07 g), $^1$H NMR (300.072 MHz, CDCl$_3$) δ 1.67 (s, IH), 1.73 - 2.20 (m, 4H), 2.65 (s, 3H), 3.25 - 3.74 (m, 3H), 4.51 - 4.81
Step 2: 4-[4-hydroxy-1-(4-methyl-3-nitro-benzoyl)-4-piperidyl]benzonitrile

A mixture of [4-(4-bromophenyl)-4-hydroxy-1-piperidyl]-(4-methyl-3-nitrophenyl)methanone (1.57 g, 3.74 mmol) and copper (I) cyanide (504 mg, 5.62 mmol) in NMP (20 mL) was stirred in the microwave at 190°C for 12 hrs. EtOAc (30 mL) was added and the resulting mixture was washed sequentially with water (30 mL) and brine (30 mL), dried (MgSO₄) and evaporated in vacuo to give a brown oil which was purified by chromatograph (12 g silica column, eluting with 20-70% EtOAc in isohexane to give the title compound as a colourless solid (0.2 g). 1H NMR (300.072 MHz, CDCl₃) δ 1.49 - 2.30 (m, 5H), 2.66 (s, 3H), 3.22 - 3.85 (m, 3H), 4.53 - 4.89 (m, 1H), 7.43 (d, 1H), 7.58 - 7.64 (m, 3H), 7.67 - 7.71 (m, 2H), 8.07 (d, 1H), m/z 366 (M+H)⁺.

Step 3: 4-[1-(3-amino-4-methyl-benzoyl)-4-hydroxy-4-piperidyl]benzonitrile

A mixture of 4-[4-hydroxy-1-(4-methyl-3-nitro-benzoyl)-4-piperidyl]benzonitrile (Step 2) (0.2 g, 0.55 mmol), iron (III) chloride hexahydrate (444 mg, 1.64 mmol) and zinc dust (360 mg, 5.5 mmol) in DMF (6 mL) and water (3 mL) was heated at 100°C for 4 hrs. The reaction mixture was filtered through celite and the filtrate evaporated in vacuo. EtOAc (30 ml) was added to the residue and the resulting solution was washed sequentialall with water (2x30 mL) and brine (30 mL), dried (MgSO₄) and evaporated in vacuo to give the title compound as a colourless solid (0.17 g). 1H NMR (300.072 MHz, CDCl₃) δ 1.59 - 2.10 (m, 5H), 2.18 (s, 3H), 3.10 - 3.48 (m, 3H), 3.60 - 4.02 (m, 2H), 4.47 - 4.73 (m, 1H), 6.69 - 6.75 (m, 2H), 7.06 (d, 1H), 7.57 - 7.68 (m, 4H), m/z 336 (M+H)⁺.

Intermediate K
4-[1-(3-amino-4-methyl-benzoyl)-4-piperidyl]-N,N-dimethyl-benzamide
Methyl 4-[1-(4-methyl-3-nitro-benzoyl)-4-piperidyl]benzoate

A solution of 4-methyl-3-nitrobenzoyl chloride (3.9 g, 19.55 mmol) in DCM (50 mL) was added dropwise to a solution of methyl 4-(4-piperidyl)benzoate (5 g, 19.55 mmol) and DIPEA in DCM (100 mL). The reaction mixture was stirred at ambient temperature for 72 hrs. The reaction mixture was then washed sequentially with saturated aqueous sodium hydrogen carbonate solution, 1M aqueous citric acid and water. The solvent was dried (phase separating cartridge) and evaporated to give the title compound as a brown waxy solid (6.85 g, 92%). 1H NMR (300.073 MHz, DMSO-de) δ 1.56-1.95 (4H, m), 2.56 (3H, s), 2.94 (2H, t), 3.60 - 3.67 (IH, m), 3.86 (3H, s), 4.64 (IH, s), 7.46 (2H, d), 7.60 (IH, d), 7.71 - 7.74 (IH, m), 7.92 (2H, d), 8.05 (IH, d), m/z 383 (M+H)+.

Step 2: 4-[1-(4-methyl-3-nitro-benzoyl)-4-piperidyl]benzoic acid

A suspension of methyl 4-[1-(4-methyl-3-nitro-benzoyl)-4-piperidyl]benzoate (Step 1) (5.68 g, 14.9 mmol) in MeOH (57 mL) was treated with aqueous sodium hydroxide solution (19 mL of 2M, 37.1 mmol, 2 eq.) and the reaction mixture stirred at 50°C for two hrs. More MeOH (25 mL) was added and stirring for continued for one hr. The reaction mixture was cooled and treated with 2M aqueous hydrochloric acid to <pH5, diluted with EtOAc, and the organic layer separated. The aqueous portion was shaken with more EtOAc and the organic layer again separated. The organic extracts were combined, washed with brine, dried over MgSO4, filtered and evaporated to give the title compound as a
yellow solid (4.92 g). $^1$H NMR (300.073 MHz, $d_6$-DMSO) $\delta$ 1.56 - 1.77 (m, 4H), 2.54 (s, 3H), 2.68 - 3.00 (m, 3H), 3.51 - 3.73 (m, 1H), 4.52 - 4.71 (m, 1H), 7.41 (d, $J = 8.3$ Hz, 2H), 7.58 (d, $J = 7.9$ Hz, 1H), 7.70 (d, $J = 9.4$ Hz, 1H), 7.87 (d, $J = 8.2$ Hz, 2H), 8.02 (s, 1H), 12.69 - 12.99 (m, 1H), m/z 367 (M-H)$^\text{+}$.

**Step 3**: N,N-dimethyl-4-[l-(4-methyl-3-nitro-benzoyl)-4-piperidyl]benzamide

A solution of 4-[l-(4-methyl-3-nitro-benzoyl)-4-piperidyl]benzoic acid (Step 2) (2.89 g, 7.84 mmol), dimethylamine (5.89 mL of a 2M solution in THF, 11.8 mmol, 1.5 eq.), DIPEA (2.7 mL, 15.7 mmol, 2 eq.), and DMAP (2.1 g, 17.3 mmol, 2.2 eq.) in DCM (58 mL) was treated with EDAC (1.8 g, 9.4 mmol, 1.2 eq.), and the reaction mixture stirred for 16 hrs at ambient temperature. Further reagents were added and the reaction mixture stirred for a further 16 hrs, by which time reaction was essentially complete. The reaction mixture was dwashed with water and the phases separated; the organic portion was concentrated to a brown solid. The crude product was re-dissolved in DCM and the solution washed sequentially with water, citric acid solution (IM in water) and saturated sodium bicarbonate solution. The organic phase was dried (MgSO$_4$), filtered and concentrated to a brown solid, which was purified by chromatography (120g silica column, gradient eluting with 10 - 50% EtOAc in iso-hexane) to give the title compound as a yellow gum, (1.74 g). $^1$H NMR (300.073 MHz, $d_6$-DMSO) $\delta$ 1.57 - 1.92 (m, 4H), 2.54 (s, 3H), 2.76 - 3.03 (m, 9H), 3.57 - 3.71 (m, 1H), 4.51 - 4.70 (m, 1H), 7.34 (s, 4H), 7.58 (d, $J = 7.9$ Hz, 1H), 7.70 (d, $J = 6.2$ Hz, 1H), 8.02 (s, 1H), m/z 396 (M+H)$^\text{+}$.

**Step 4**: 4-[l-(3-amino-4-methy 1-benzoyl)-4-piperidyl] -N,N-dimethy 1-benzamide

A solution of N,N-dimethyl-4-[l-(4-methyl-3-nitro-benzoyl)-4-piperidyl] benzamide (Step 3) (1.74 g) in MeOH (35 mL) was treated with palladium-on-charcoal catalyst (122 mg of
10% Pd/C). The reaction mixture was stirred in an atmosphere of hydrogen at ambient temperature and pressure for 2 hours. The catalyst was removed by filtration and the filtrate concentrated to give the title compound as a colourless solid (1.5 g). \(^1\)H NMR (300.073 MHz, \(d_6\)-DMSO) \(\delta\) 1.46 - 1.68 (m, 2H), 1.69 - 1.88 (m, 2H), 2.06 (s, 3H), 2.74 - 3.07 (m, 9H), 3.64 - 3.97 (m, 1H), 4.43 - 4.70 (m, 1H), 4.97 (s, 2H), 6.49 (d, \(J = 7.4\) Hz, 1H), 6.64 (s, 1H), 6.95 (d, \(J = 7.5\) Hz, 1H), 7.32 (s, 4H), m/z 366 (M+H).

**Intermediate L**

4-[(3-amino-4-ethyl-benzoyl)-4-piperidyl]benzonitrile

**Step 1**: 4-ethyl-3-nitro-benzoic acid

Concentrated nitric acid (80 mL) was cooled to approximately 0 - 5°C in an ice bath and 4-ethyl benzoic acid (10 g, 66.59 mmol) was added portionwise. The resultant mixture was allowed to warm up to ambient temperature and the reaction mixture was stirred for approx. 72 hrs. It was then warmed to 60°C at which it was maintained overnight at this temperature. The reaction mixture was quenched into ice / water (200 mL) and the resulting precipitate isolated by filtration and washed with water to give the title compounds as a colourless solid (9.52 g, 73%). \(^1\)H NMR (300.073 MHz, \(t_6\)-DMSO, 30°C) \(\delta\) 1.22 (3H, t \(J = 8.3\) Hz), 2.87 (2H, q \(J = 7.8\) Hz), 7.65 (IH, d \(J = 8.3\) Hz), 8.13 (IH, d \(J = 9.0\) Hz), 8.34 (IH, s ), 13.00 - 13.80 (IH, m), m/z 194 (M-Hy).

**Step 2**: 4-[(4-ethyl-3-nitro-benzoyl)-4-piperidyl]benzonitrile

The title compound was prepared by an amide coupling reaction starting from 4-ethyl-3-nitro-benzoic acid (Step 1) and 4-(4-piperidyl)benzonitrile as described for Intermediate A.
1H NMR (300.073 MHz, (\textsuperscript{1}H-DMSO, 30° C) δ 1.22 (3H, U = 7.4Hz), 1.56 - 1.96 (4H, m), 2.77 - 3.01 (4H, m - contains q from ethyl), 3.04 - 3.25 (IH, m), 3.63 (IH, br s), 4.61 (IH, br s), 7.50 (2H, dJ = 9.1Hz), 7.59 (2H, dJ = 7.4Hz), 7.67 - 7.81 (3H, m), 7.94 - 7.98 (IH, m).

Step 3: 4-[l-(3-amino-4-ethyl-benzoyl)-4-piperidyl]benzonitrile

The title compound was prepared by hydrogenation of 4-[l-(4-ethyl-3-nitro-benzoyl)-4-piperidyl]benzonitrile (Step 2) as described for Intermediate I, Step 3, 1H NMR (300.073 MHz, de-DMSO, 30° C) δ 1.13 (2H, d), 1.46 - 1.67 (2H, m), 1.67 - 1.91 (2H, m), 2.38 - 2.48 (2H, m), 2.64 - 3.21 (3H, m), 3.59 - 4.05 (IH, m), 4.33 - 4.72 (IH, m), 4.98 (2H, s), 6.53 (IH, dJ = 7.3Hz), 6.64 (IH, s), 6.95 (IH, dJ = 6.1Hz), 7.49 (2H, dJ = 7.2Hz), 7.76 (2H, dJ = 9.5Hz), m/z 334 (M+H) +.

Intermediate M

4-[l-(5-amino-2-fluoro-benzoyl)-4-piperidyl]benzonitrile

The title compound was prepared by the method described for Intermediate A, starting from 5-amino-2-fluoro-benzoic acid and 4-(4'-cyanophenyl) piperidine, 1H NMR (300.073 MHz, DMSO-d\textsubscript{6}) δ1.55 (2H, d), 1.74 - 1.79 (IH, m), 1.88 (IH, d), 2.88 (2H, d), 3.13 (IH, d), 3.57 (IH, d), 4.64 (IH, d), 5.10 (2H, s), 6.50 (IH, s), 6.56 - 6.60 (IH, m), 6.89 (IH, d), 7.46 (2H, d), 7.76 (2H, d), m/z 324 (M+H) +.
Step 1:
3-amino-4-(trifluoromethyl)benzoic acid

A mixture of 3-nitro-4-(trifluoromethyl)benzoic acid (4.56 g, 19.39 mmol) and palladium-on-charcoal catalyst (500 mg, 10% Pd) in methanol (100 ml) was stirred under an atmosphere of hydrogen until uptake of hydrogen was complete. The solvent was removed under reduced pressure to give the title compound as a cream solid (3.7 g), \( ^1\)H NMR (300.073 MHz, DMSO-d6) 55.81 (2H, s), 7.12 (IH, d), 7.40 - 7.45 (2H, m).

Step 2:
4-[1-[3-amino-4-(trifluoromethyl)benzoyl]-4-piperidyl]benzonitrile

A stirred solution of 17029/82/1 (3.7 g, 18 mmol), 4-(4'-cyanophenyl)piperidine (3.36 g, 18 mmol) and DIPEA (9.4 ml, 54.1 mmol) in DCM (100 ml) was treated with N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (EDAC) (3.8 g, 19.8 mmol), and the reaction mixture stirred for 24 hrs and then allowed to stand for a further 24 hrs at ambient temperature. The bulk of the DCM was removed in vacuo and the residue partitioned between water and EtOAc was attempted. The organic phase was separated and dried (MgSO₄); evaporation of the solvent gave a gum (~ 5.8 g) which was recrystallised from EtOH (100 mL) to give a solid (2.2 g) which was purified by column chromatography (120 g silica cartridge, eluting with a gradient of 0 - 50 % MeOH in DCM) to give the title compound as a pale yellow solid (1.6 g 24 %), \( ^1\)H NMR (300.073 MHz, d6-DMSO, 30° C) \( \delta \) 1.49 - 1.95 (4H, m), 2.70 - 3.01 (2H, m), 3.02 - 3.23 (IH, m), 3.54 - 3.78 (IH, m), 4.49 - 4.71 (IH, m), 5.75 (2H, s), 6.63 (IH, \( dJ = 7.3 \) Hz), 6.83 (IH, s), 7.37 (IH, \( dJ = 8.5 \) Hz), 7.49 (2H, \( dJ = 7.3 \) Hz), 7.77 (2H, \( dJ = 7.9 \) Hz).
**Intermediate O**

\[ \text{1-}(5-(4-(4-cyanophenyl)piperidine-1-carbonyl)-2-methylphenyl)-3-((trans)-2-(1,3-dioxoisooindolin-2-yl)cyclohexyl)urea} \]

\[
\begin{array}{c}
\text{N} \\
\text{O} \\
\text{O} \\
\text{NH} \\
\text{O} \\
\text{O} \\
\text{N} \\
\text{O} \\
\text{N} \\
\end{array}
\]

**Step 1:**

2-[(trans)-2-aminocyclohexyl] isoindole-1,3-dione

\[
\begin{array}{c}
\text{N} \\
\text{O} \\
\text{N} \\
\text{N} \\
\end{array}
\]

The title compound was prepared as described in Tetrahedron Asymmetry 14, 1559-1563 (2003).

**Step B:**

\[ \text{1-}(5-(4-(4-cyanophenyl)piperidine-1-carbonyl)-2-methylphenyl)-3-((trans)-2-(1,3-dioxoisooindolin-2-yl)cyclohexyl)urea} \]

\[
\begin{array}{c}
\text{N} \\
\text{O} \\
\text{O} \\
\text{O} \\
\text{N} \\
\text{N} \\
\end{array}
\]

The title compound was prepared by the procedure described in Method 2, starting from 4-\[1-(3-amino-4-methyl-benzoyl)-4-piperidyl]benzonitrile (Intermediate A) and 2-[(trans)-2-aminocyclohexyl]isoindole-1,3-dione (Step 1), 1H NMR (300.072 MHz, CDCl\textsubscript{3}) \( \delta \) 1.85 - 1.21 (1H, m), 1.89 (3H, s), 2.58 - 2.47 (IH, m), 3.11 - 2.80 (2H, m), 3.70 - 3.63 (IH, m), 3.94 - 3.86 (IH, m), 4.44 - 4.33 (IH, m), 5.03 - 4.75 (2H, m), 6.16 (IH, s), 7.00 (IH, s),
7.19 - 7.02 (2H, m), 7.37 - 7.31 (3H, m), 7.66 - 7.60 (2H, m), 7.75 (2H, s), m/z (EI+) (M+H)+ = 590.52; HPLC tR = 2.57 min. m/z (EI-) (M-H)- = 588.45; HPLC tR = 2.57 min.

**Intermediate P**

tert-butyl N-[1-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]carbamoyl]azetidin-3-yl]carbamate

The title compound was prepared by the procedure described in Method 2, starting from 4-[[1-(3-amino-4-methyl-benzoyl)-4-piperidyl]benzonitrile (Intermediate A) and 3-N-Boc-amino-azetidine, 1H NMR (300.072 MHz, CDCl3) δ 1.45 (9H, s), 1.66 - 1.95 (4H, m), 2.20 (3H, s), 2.76 - 2.89 (2H, m), 2.97 - 3.05 (IH, m), 3.84 - 3.90 (2H, m), 3.97 - 4.03 (IH, m), 4.30 (2H, t), 4.42 - 4.54 (IH, m), 4.77 - 4.93 (IH, m), 5.11 - 5.24 (IH, m), 6.12 (IH, s), 7.05 - 7.19 (2H, m), 7.32 (2H, d), 7.60 (2H, d), 7.76 (IH, s), m/z (ESI+) (M+H)+ = 518; HPLC tR = 2.27 min.

**Intermediate Q**

4-methyl 1-(propan-2-yl)carbamoylamino)benzoic acid

**Step 1:**

Methyl 4-methyl-3-(propan-2-yl)carbamoylamino)benzoate

Isopropyl isocyanate (5.07 mL, 51.76 mmol) was added to methyl 3-amino-4-methyl benzoate (5.7 g, 34.51 mmol) and DMAP (4.22 g, 34.51 mmol) in MeCN (125mL) and the reaction mixture warmed to 55°C over a period of 5 minutes under nitrogen. The resulting solution was stirred at 55 °C for 6 hours. The precipitate which formed was collected by filtration, washed with MeCN (100 mL) and dried under vacuum to afford methyl 3-(3-25
isopropylureido)-4-methylbenzoate (3.38 g, 39.1 %) as a colourless solid, which was used without further purification, \( \text{IH NMR (300.073 MHz, d}_6\text{-DMSO)} \delta 1.11 (6H, d), 2.22 (3H, s), 3.68 - 3.86 (4H, m), 6.50 - 6.59 (IH, m), 7.23 (IH, d), 7.44 (IH, d), 7.62 (IH, s), 8.58 (IH, s), m/z (ESI+) (M+H)+ = 251.33; HPLC tR = 1.80 min.

**Step 2:**

4-methyl-3-(propan-2-ylcarbamoylamino)benzoic acid

The material from Step 1 was hydrolysed using aqueous sodium hydroxide in a similar procedure to that described in Method 7 to give the title compound as a colourless solid, \( \text{IH NMR (300.073 MHz, d}_6\text{-DMSO)} \delta 1.11 (6H, d), 2.21 (3H, s), 3.66 - 3.84 (IH, m), 6.50 (IH, d), 7.20 (IH, d), 7.42 (IH, d), 7.59 (IH, s), 8.52 (IH, s), 12.56 (IH, s), m/z (ESI+) (M+H)+ = 237.26; HPLC tR = 1.45 min.

**Intermediate R**

(3-amino-4-methyl-phenyl)-[4-[4-(trifluoromethyl)phenyl]-1-piperidyl]methanone

The title compound was prepared by the method described for Intermediate A, starting from 3-amino-4-methyl-benzoic acid and 4-[4-(trifluoromethyl)phenyl]piperidine hydrochloride,

\( \text{IH NMR (300.073 MHz, d}_6\text{-DMSO)} \) dl.48 - 1.68 (m, 2H), 1.69 - 1.94 (m, 2H),2.06 (s, 3H),2.84 - 3.02 (m, 3H),3.49 - 4.20 (m, 1H),4.23 - 4.82 (m, 1H),4.91 - 5.03 (m, 2H),6.49 (d, 1H),6.62 (s, 1H),6.95 (d, 1H),7.51 (d, 2H),7.65 (d, 2H), m/z (ESI+) (M+H)+ = 363.37; HPLC tR = 2.53 min.

**Intermediate S**

(3-amino-4-methyl-phenyl)-[4-(4-fluorophenyl)-1-piperidyl]methanone
The title compound was prepared by the method described for Intermediate A, starting from 3-amino-4-methyl-benzoic acid and 4-(4-fluorophenyl)piperidine hydrochloride. \(^1\)H NMR (300.073 MHz, d\(_6\)-DMSO) δ 1.43 - 1.62 (m, 2H), 1.65 - 1.87 (m, 2H), 2.01 (s, 3H), 2.73 - 2.87 (m, 2H), 2.89 - 3.13 (m, 1H), 3.54 - 4.14 (m, 1H), 4.20 - 4.76 (m, 1H), 4.88 (s, 2H), 6.45 - 6.51 (m, 1H), 6.61 - 6.66 (m, 1H), 6.94 (d, 1H), 7.05 - 7.15 (m, 2H), 7.24 - 7.35 (m, 2H), m/z (ESI+) (M+H)+ = 313.33; HPLC tR = 2.22 min.

**Intermediate T**

1-[5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-3-(2-methylaminoethyl)urea

The title compound was prepared by the method described in Method 3, starting from tert-butyl N-[2-[[5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]carbamoylamino]ethyl]-N-methyl-carbamate (Example 347). \(^1\)H NMR (300.073 MHz, d\(_6\)-DMSO) δ 1.44 - 1.86 (4H, m), 1.90 (3H, s), 2.24 (3H, s), 2.55 (2H, t), 2.71 - 3.06 (3H, m), 3.30 - 3.43 (2H, m), 3.70 - 3.87 (IH, m), 4.51 - 4.67 (IH, m), 6.94 (IH, d), 7.04 - 7.35 (6H, m), 7.92 (IH, s), 8.16 (IH, s), 8.63 - 8.76 (2H, m), m/z (ESI+) (M+H)+ = 413.54; HPLC tR = 1.33 min.

**Intermediate U**

1-(2-aminoethyl)-3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-1-methyl-urea

**Step 1:**

tert-butyl N-[2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]carbamoyl-methylamino]ethyl]carbamate
The title compound was prepared by the procedure described in Method 2, starting from 4-
[1-(3-amino-4-methyl-benzoyl)-4-piperidyl]benzonitrile (Intermediate A) and tert-butyl N-
(2-methylaminoethyl)carbamate, $^1$H NMR (300.073 MHz, $d_6$-DMSO) $\delta$ 1.35 (9H, s), 1.49 -
1.91 (4H, m), 2.21 (3H, s), 2.75 - 3.16 (8H, m), 3.30 - 3.56 (2H, m), 3.57 - 4.05 (IH, m),
4.30 - 4.80 (IH, m), 6.75 - 6.85 (IH, m), 7.08 (IH, d), 7.22 (IH, d), 7.35 (IH, s), 7.49 (2H, d),
7.68 - 7.81 (3H, m), m/z (ESI+) (M+H)+ = 420.39; HPLC tR = 2.32 min.

Step 2:
1-(2-aminoethyl)-3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methyl-phenyl]-1-
methyl-urea

The title compound was prepared by the process described in Method 3, starting from tert-
butyl N-[2-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]carbamoyl-
methylamino]ethyl]carbamate (Step 1) to give the title compound as the hydrochloride salt,
$^1$H NMR (300.073 MHz, $d_6$-DMSO) $\delta$ 1.51 - 1.87 (4H, m), 2.23 (3H, s), 2.80 - 3.22 (8H, m),
3.49 - 3.59 (2H, m), 3.64 - 3.97 (IH, m), 4.09 - 4.77 (IH, m), 7.10 (IH, d), 7.23 (IH, d), 7.37 (IH, s), 7.50 (2H, d), 7.77 (2H, d), 7.93 - 8.18 (4H, m), m/z (ESI+) (M+H)+ = 420.47; HPLC tR = 1.19 min.

Intermediate V
(3-amino-4-methylphenyl)-[4-(4-chlorophenyl)piperidin-1-yl]methanone

The title compound was prepared by the process described for Intermediate A, staring from
3-amino-4-methylbenzoic acid and 4-(4-chlorophenyl)piperidine hydrochloride, $^1$H NMR
(300.073 MHz, $d_6$-DMSO) $\delta$ 1.40 - 1.63 (2H, m), 1.63 - 1.89 (2H, m), 2.06 (3H, s), 2.65 -
3.17 (3H, m), 3.61 - 4.05 (IH, m), 4.32 - 4.73 (IH, m), 4.97 (2H, s), 6.48 (IH, d), 6.63
(IH, s), 6.95 (IH, d), 7.29 (2H, d), 7.35 (2H, d), m/z (ESI+) (M+H)+ = 329.36 ; HPLC tR
= 2.44 min.
Intermediate W

4-[(3-amino-4-methylsulfanylbenzoyl)piperidin-4-yl]benzonitrile

Step 1:

4-[1-(4-methylsulfanyl-3-nitrobenzoyl)piperidin-4-yl]benzonitrile

Oxalyl chloride (2.5 mL, 28 mmol) was added to a stirred suspension of 4-methylsulfanyl-3-nitro-benzoic acid (5 g, 23.45 mmol) in dichloromethane (50 mL), followed by the addition of DMF (2 drops), and the reaction mixture was stirred at ambient temperature for 2 hrs. The volatiles were removed in vacuo and the residue redissolved in dichloromethane (25 mL). This solution was added to a stirred solution of 4-(4'-cyanophenyOpiperidine (4.36 g, 23.45 mmol) and DIPEA (8.99 mL, 51.59 mmol) in DCM (25 mL) and the reaction mixture stirred for 20hrs. It was then diluted with DCM and the resulting solution was washed sequentially with 0.5M HCl solution, saturated NaHCO₃ solution, and brine. The organic phase was dried and concentrated in vacuo to give a yellow solid which was purified by chromatography on silica (120 g column, eluting with 10-100% EtOAc in isohexane) to give the title compound as a yellow solid (2.6 g). ¹H NMR (300.072 MHz, CDCl₃) δ 1.59 - 2.04 (m, 4H), 2.54 (s, 3H), 2.80 - 2.93 (m, 2H), 3.01 - 3.18 (m, IH), 3.77 - 4.20 (m, IH), 4.44 - 5.03 (m, IH), 7.33 (d, 2H), 7.44 (d, IH), 7.63 (d, 2H), 7.68 - 7.72 (m, IH), 8.34 (d, IH), m/z (ESI+) (M+H)+ = 382; HPLC tR = 2.54 min.

Step 2:

4-[1-(3-amino-4-methylsulfanylbenzoyl)piperidin-4-yl]benzonitrile

A mixture of 4-[1-(4-methylsulfanyl-3-nitrobenzoyl)piperidin-4-yl]benzonitrile
(Step 1) (2.6g, 6.82mmol), iron (III) chloride hexahydrate (5.53g, 20.45mmol) and zinc dust (4.46g, 68.2mmol) in DMF (70ml) and water (35ml) was heated at 100°C for 4 hrs. The reaction mixture was filtered through celite and evaporated in vacuo. Ethyl acetate (30ml) was added to the filtrate and the resulting mixture was washed sequentially with water (2x30 mL) and saturated brine (30 mL). A beige solid impurity was removed by filtration and the organic filtrate was dried (MgSO₄) and evaporated in vacuo to give a yellow foam which was purified by chromatography on silica (40 g column, eluting with 20-80% EtOAc in isohexane) to give the title compound as a colourless solid (0.83 g).

**Intermediate X**

4-[1-(3-amino-4-methylsulfonylbenzoyl)piperidin-4-yl]benzonitrile

The title compound was prepared by the method described for Intermediate W, Step 1, starting from 4-methylsulfonyl-3-nitrobenzoic acid and 4-(4'-cyanophenyl)piperidine, ¹H NMR (300.072 MHz, CDCl₃) δ 1.62 - 2.12 (m, 4H), 2.84 - 2.97 (m, 2H), 3.11 - 3.34 (m, IH), 3.45 (s, 3H), 3.61 - 3.82 (m, IH), 4.72 - 5.08 (m, IH), 7.33 (d, 2H), 7.63 (d, 2H), 7.79 - 7.82 (m, IH), 7.89 (d, IH), 8.27 (d, IH), m/z (ESI+) (M+H+) = 455; HPLC tR = 2.28 min.

**Step 2:**

4-[1-(3-amino-4-methylsulfonylbenzoyl)piperidin-4-yl]benzonitrile
The title compound was prepared by the method described for Intermediate W, Step 2, starting from 4-[1-(4-methylsulfonyl-3-nitrobenzoyl)piperidin-4-yl]benzonitrile (Step 1).

\[ \text{H}N\text{M}R \ (300.072 \text{ MHz, CDCl}_3) \delta 1.51 - 2.08 (m, 4H), 2.79 - 2.93 (m, 2H), 3.06 (s, 3H), 3.11 - 3.24 (m, 1H), 3.74 - 3.91 (m, 1H), 4.74 - 4.92 (m, 1H), 5.16 (s, 2H), 6.79 - 6.83 (m, 2H), 7.32 (d, 2H), 7.62 (d, 2H), 7.78 (d, 1H), m/z (ESI-) (M-H)$^-$ = 382; HPLC $t_R = 2.03$ min.

**Intermediate Y**

4-[1-[3-amino-4-(methoxymethyl)benzoyl]piperidin-4-yl]benzonitrile

\[ \text{H}N\text{M}R \ (300.073 \text{ MHz, de-DMSO}) \delta 3.39 (3H, s), 4.82 (2H, s), 7.86 (IH, d), 8.22 - 8.28 (IH, m), 8.47 (IH, d), 13.58 (IH, s), m/z (ESI-) (M-H)$^-$ = 210.25; HPLC $t_R = 1.69$ min.

**Step 1:**  
4-(methoxymethyl)-3-nitrobenzoic acid

A solution of sodium methoxide in methanol (0.5 M,15 mL, 57.68 mmol) was added dropwise to a stirred mixture of 4-(bromomethyl)-3-nitrobenzoic acid (5g, 19.23 mmol) in methanol (100 mL) over a period of 5 minutes. The resulting mixture was stirred at 62 °C for 1 hour and was then quenched with water (100 mL) and the bulk of the methanol removed under reduced pressure. The reaction mixture was acidified with 2M HCl. The resulting precipitate was collected by filtration, washed with water (150 mL) and dried in the vacuum oven to give the title compound as a pale orange solid (2.96 g, 72.9 %), which was used without further purification, \[ \text{H}N\text{M}R \ (300.073 \text{ MHz, de-DMSO}) \delta 3.39 (3H, s), 4.82 (2H, s), 7.86 (IH, d), 8.22 - 8.28 (IH, m), 8.47 (IH, d), 13.58 (IH, s), m/z (ESI-) (M-H)$^-$ = 210.25; HPLC $t_R = 1.69$ min.

**Step 2:**

4-[1-[4-(methoxymethyl)-3-nitrobenzoyl]piperidin-4-yl]benzonitrile
The title compound was prepared by the method described for Intermediate W, Step 1, starting from 4-(methoxymethyl)-3-nitrobenzoic acid and 4-(4'-cyanophenyl)piperidine (Step 1). $^1$H NMR (300.073 MHz, $d_6$-DMSO) $\delta$ 1.59 - 1.97 (4H, m), 2.74 - 3.02 (2H, m), 3.06 - 3.24 (IH, m), 3.37 (3H, s), 3.50 - 3.80 (IH, m), 4.50 - 4.72 (IH, m), 4.77 (2H, s), 7.51 (2H, d), 7.73 - 7.85 (4H, m), 8.09 (IH, s), m/z - no mass ion observed; HPLC tR = 2.45 min.

**Step 3:**
4-[l-[3-amino-4-(methoxymethyl)benzoyl]piperidin-4-yl]benzonitrile

The title compound was prepared by the method described for Intermediate D, Step 2, starting from 4-[l-[4-(methoxymethyl)-3-nitrobenzoyl]piperidin-4-yl]benzonitrile (Step 2), and using a MeOH and THF mixture (1:1.5 by volume) as solvent. $^1$H NMR (300.073 MHz, $\alpha_6$-DMSO) $\delta$ 1.48 - 1.67 (2H, m), 1.68 - 1.92 (2H, m), 2.65 - 3.22 (3H, m), 3.27 (3H, s), 3.58 - 3.96 (IH, m), 4.32 (2H, s), 4.40 - 4.75 (IH, m), 5.09 (2H, s), 6.55 (IH, d), 6.67 (IH, s), 7.07 (IH, d), 7.49 (2H, d), 7.76 (2H, d), m/z (ESI+) (M+H)$^+$ = 350.28; HPLC tR = 2.01 min.
Claims

1) A compound of formula I

![Chemical structure image]

or a pharmaceutically acceptable salt thereof, in which

R₁ represents 1) a C₁₋₆alkyl group optionally substituted by one or two groups selected from A-Y below and/or by one to five groups selected from X below:

A) phenyl optionally substituted by one or more of the following i) halo; ii) cyano; iii) a C₁₋₄alkoxy group optionally substituted by one or more halo iv) hydroxy; v) a C₁₋₄alkyl group optionally substituted by one or more halo; vi) a group CONRₑRᵢ in which Rₑ and Rᵢ are as defined below; vii) C₁₋₆alkanoyl; viii) benzoyl; ix) carboxy; x) C₁₋₆alkoxycarbonyl; xi) C₁₋₆alkylothio; xii) C₁₋₆alkylsulfinyl; xiii) C₁₋₆alkylsulfonyl; xiv) C₁₋₆alkylsulfonyloxy; xv) sulfamoyl; xvi) N-C₁₋₆alkylsulfamoyl; xvii) N,N-diC₁₋₆alkylsulfamoyl; xviii) benzyl or benzyloxy; xix) nitro; xx) heteroaryl; xxi) heteroaryloxy; xxii) phenyl xxiii) phenoxy xxiv) phenylsulfamoyl; xxv) heteroarylsulfamoyl; xxvi) a carbon linked saturated or partially unsaturated 4 to 10 membered heterocyclic group as defined in c) below; xxvii) phenylsulfonoyl; xxviii) heteroarylsulfonoyl; xxix) a group of formula NRₑRᵣ in which Rₑ and Rᵣ independently represent:

a) H;
b) C₁₋₆alkanoyl optionally substituted by carboxy or a C₁₋₆alkoxycarbonyl group;
c) a carbon linked saturated or partially unsaturated 4 to 10 membered heterocyclic group containing one or more N, S or O, wherein the S may be in its oxidised form of SO or SO₂ , which is optionally fused to a benz ring and any ring is optionally substituted by one or more of the following: hydroxy, halo, oxo, carboxy, a C₁₋₆alkoxycarbonyl group, a C₁₋₆alkoxy group optionally substituted by one or more hydroxy or C₁₋₆alkoxy, C₁₋₆alkanoyl, benzoyl, amino, C₁₋₆alkylamino, di(C₁₋₆alkyl)amino or a C₁₋₆alkyl optionally substituted by one or more hydroxy or C₁₋₆alkoxy;
d) a C_i-alkyl group optionally substituted by one or more of the following: hydroxy; carboxy; a C_i-alkoxycarbonyl group; a C_{1-6}alkoxy group; heteroaryl; a group of formula NR^eR^f in which R^e and R^f independently represent H; a C_{1-6}alkanoyl group; a C_i-
6-alkylsulphonyl group; a C_{1-6}alkoxycarbonyl group; a C_{1-6}alkyl group optionally
substituted by one or more hydroxy or C_i-alkoxy, or R^e and R^f together with the nitrogen
atom to which they are attached represent a saturated or partially unsaturated 4 to 10
membered heterocyclic ring optionally containing an additional sulphur including oxidised
as SO or SO_2, oxygen or nitrogen and/or optionally fused to a benz ring and any ring is
optionally substituted by one or more of the following: a C_i-alkoxy group; carboxy; a C_i-
6-alkylsulphonyl group; C_{1-6}alkanoyl; benzoyl; hydroxy; oxo; carboxy; or a C_{1-6}alkyl group
optionally substituted by one or more hydroxy or by one or more C_{1-6}alkoxy or by one or
more carboxy;

e) R^e and R^f together with the nitrogen atom to which they are attached represent a
saturated or partially unsaturated 4 to 10 membered heterocyclic ring optionally containing
an additional oxygen, sulphur, SO, SO_2 or nitrogen and/or optionally fused to a benz ring
and/or optionally substituted by one or more of the following: a C_{1-6}alkoxy group; C_i-
4-alkanoyl group; benzoyl; a C_{1-6}alkoxycarbonyl group; a C_i-alkylsulphonyl group;
carbamoyl; N-C_i-alkylcarbamoyl; N, N-diC_{1-6}alkylcarbamoyl; hydroxy; halo; oxo;
carboxy; a C_i-alkyl group (which is optionally substituted by one or more of the
following: a C_{1-6}alkoxy group, hydroxy or a group of formula NR^eR^f in which R^e and R^f
are as defined above) or a group of formula NR^eR^f in which R^e and R^f are as defined above;
f) a C_i-alkylsulphonyl group;
g) phenylsulfonyl;
h) heteroarylsulphonyl;
i) benzoyl;
j) phenyl optionally substituted by one or more of the following: halo; C_i-3alkyl; C_i-
3-alkoxy; a C_i-alkanoylamino group; carbamoyl; N-C_i-alkylcarbamoyl; N,N-diC_i-
6-alkylcarbamoyl or nitro;
k) heteroaryl optionally substituted by one or more carboxy; fluoro; hydroxy; a C_i-alkyl
group (which is optionally substituted by one or more of the following: a C_{1-6}alkoxy group,
hydroxy or a group of formula NR^eR^f in which R^e and R^f are as defined above); a C_i-
alkoxy group optionally substituted on C2 or C3 by carboxy; a group NR\textsuperscript{e}R\textsuperscript{f} in which R\textsuperscript{e} and R\textsuperscript{f} are as defined above; or a group CONR\textsuperscript{e}R\textsuperscript{f} in which R\textsuperscript{e} and R\textsuperscript{f} are as defined above; 
1) a C\textsubscript{3}ioiocycloalkyl group which may be monocyclic, bicyclic or tricyclic and optionally may be bridged and is optionally substituted by one or more carboxy; fluoro; hydroxy; a 
Ci\textsubscript{3}alkoxy group optionally substituted on C2 or C3 by carboxy; a group NR\textsuperscript{e}R\textsuperscript{f} in which R\textsuperscript{e} and R\textsuperscript{f} are as defined above; or a group CONR\textsuperscript{e}R\textsuperscript{f} in which R\textsuperscript{e} and R\textsuperscript{f} are as defined above; 
m) a Ci\textsubscript{6}alkoxycarbonyl group optionally substituted by phenyl; 
n) heteroarylcarbonyl; 
o) sulfamoyl optionally substituted by one or two independently selected C\textsubscript{1-6}alkyl groups or the terminal nitrogen is included in a 5 or 6 membered saturated or partially unsaturated heterocyclic ring optionally containing an additional N, S or O, wherein the S may be in its oxidised form of SO or SO\textsubscript{2}; 
B) a heteroaryl group which is optionally substituted by groups i) to xxix) as described for phenyl above; 
C) a group of formula NR\textsuperscript{e}R\textsuperscript{d} in which R\textsuperscript{e} and R\textsuperscript{d} are as defined above; 
D) a C\textsubscript{3}-cycloalkyl group optionally substituted by one or more hydroxy or a group of formula NR\textsuperscript{e}R\textsuperscript{f} in which R\textsuperscript{e} and R\textsuperscript{f} are as defined above; 
E) a carbon linked saturated or partially unsaturated 4 to 10 membered heterocyclic group containing one or more N, S or O, wherein the S may be in its oxidised form of SO or SO\textsubscript{2}, which is optionally fused to a benz ring or a heteroaryl ring and is optionally substituted on any ring by one or more of the following: hydroxy; halo; o xo; a C\textsubscript{1-6}alkoxy group; carboxy; hydroxy; C\textsubscript{1-6}alkanoyl; a Ci\textsubscript{2}alkylsulfonyl group; amino; C\textsubscript{1-6}alkylamino; di(Ci\textsubscript{3} alkyl)amino; a C\textsubscript{1-6}alkyl optionally substituted by one or more hydroxy or Ci\textsubscript{6}alkoxy; or a C\textsubscript{1-6}alkoxycarbonyl group;
M) phenylsulfonyl;
N) heteroarylsulfonyl;
O) benzoyl;
P) a C₃₋₆ alkanoyl group
Q) C₁₋₆ alkylthio;
R) ureido optionally independently substituted by one, two or three C₁₋₆ alkyl or the terminal nitrogen is included in a 5 or 6 membered saturated or partially unsaturated heterocyclic ring optionally containing an additional N, S or O, wherein the S may be in its oxidised form of SO or SO₂;
S) phenoxy;
T) hydroxy;
U) oxo
V) carboxy;
W) cyano;
X) sulfamoyl optionally substituted by one or two independently selected C₁₋₆ alkyl groups or the nitrogen is included in a 4 or 7 membered saturated or partially unsaturated heterocyclic ring optionally containing an additional N, S or O, wherein the S may be in its oxidised form of SO or SO₂;
Y) sulfamoylamino optionally substituted by one or two independently selected C₁₋₆ alkyl groups or the terminal nitrogen is included in a 4 or 7 membered saturated or partially unsaturated heterocyclic ring optionally containing an additional N, S or O, wherein the S may be in its oxidised form of SO or SO₂;
Z) fluoro or chloro;
or R¹ represents
2) a C₂₋₃ cycloalkyl group optionally substituted by one or two groups selected from A to Y above and/or by one to five groups selected from Z above;
3) a C₂₋₆ alkynyl group optionally substituted by one or two groups selected from A to Y above and/or by one to five groups selected from Z above;
4) a carbon linked saturated or partially unsaturated 4 to 10 membered heterocyclic group containing one or more N, S or O, wherein the S may be in its oxidised form of SO or SO₂, which is optionally fused to a benz ring or a heteroaryl ring and any ring is optionally
substituted by one or two groups A to Y as defined above and/or by one to five groups selected from Z above;

5) a C_{2-5}alkenyl group optionally substituted by one or two groups selected from A to Y above and/or by one to five groups selected from Z above;

wherein any alkyl chain mentioned in any of the definitions from A to Y above or in any of the definitions i to xxix above is optionally substituted by 1) one or two groups selected from: carboxy; hydroxy; a C_{1-3}alkoxy group optionally substituted on C2 or C3 by carboxy; a group NR^eR^d in which R^e and R^d are as defined above; or a group CONR^eR^f in which R^e and R^f are as defined above; a C_{1-4}alkanoyloxy group or a C^aalkyl optionally substituted by one or more hydroxy, C_{1-3}alkoxy or a group -NR^eR^f in which R^e and R^f are as defined above; and/or by 2) from one to five fluoro;

and further wherein any cycloalkyl, phenyl, heteroaryl ring or carbon linked saturated or partially saturated 4 to 10 membered heterocyclic group in the list of optional substituents from A to Y above or in any of the definitions i to xxix above, for which specific substitution has not been previously mentioned, is optionally substituted by one, two or three groups selected from: carboxy; hydroxy; a C^aalkoxy group optionally substituted on C2 or C3 by carboxy; a group NR^eR^d in which R^e and R^d are as defined above; or a group CONR^eR^f in which R^e and R^f are as defined above; and/or is optionally substituted by one to five fluoro;

R^a represents H; or a C_{1-4}alkyl group, a C_{3-6}cycloalkyl group or a C_{3-6}cycloalkylC_{1-4}alkyl group each of which groups is optionally substituted by one or more carboxy; fluoro; hydroxy; a C_{1-3}alkoxy group optionally substituted on C2 or C3 by carboxy; a group of formula NR^eR^f in which R^e and R^f are as defined above; or a group CONR^eR^f in which R^e and R^f are as defined above;

or R^1 and R^4 together with the nitrogen atom to which they are attached represent a saturated or partially unsaturated 4 to 10 membered heterocyclic ring optionally containing an additional sulphur including oxidised as SO or SO_2, oxygen or nitrogen which is optionally fused to a benz ring and wherein any ring is optionally substituted by one or two of the groups A to Y above and/or by from 1 to 5 groups Z;

R^b represents H;

R^2 represents H, halo, cyano, a C_{1-3}alkyl group which is optionally substituted by one or more of the following: halo; a C_{1-3}alkoxy group; or by a group Ci_3alkylS(O)_n^t, which is
optionally substituted by one or more fluoro and u is 0, 1 or 2; or R² represents a C_i₃alkoxy group optionally substituted by one or more halo or R² represents a C_i₃alkylS(O)₃(O)₅ group wherein the C_i₃alkyl is optionally substituted by one or more fluoro and a is 0, 1 or 2 and b is 0 except when a is 2 then b may also be 1;

R³ represents H, halo, cyano, a C₁₃alkyl group which is optionally substituted by one or more of the following: halo; C_i₃alkoxy group; or by a group C_i₃alkylS(O)₅ which is optionally substituted by one or more fluoro and t is 0, 1 or 2; or R² represents a C_i₃alkoxy group optionally substituted by one or more halo or R² represents a C_i₃alkylS(O)₅ group wherein the C_i₃alkyl is optionally substituted by one or more fluoro and c is 0, 1 or 2 and d is 0 except when c is 2 then d may also be 1;

R⁴ represents i) H

ii) a C₃oalkyl group optionally substituted by cyano, hydroxy, a C₁₃alkoxy group or optionally substituted by one or more halo

iii) a C₁₃alkoxy group optionally substituted by one or more halo or optionally substituted by cyano, hydroxy, a C₁₃alkoxy group, an amino group of formula NR¹R⁵ in which R⁴ and R⁵ independently represent H, a C_i₃alkylsulphonyl group, an aminoC_i₃alkylsulphonyl group in which the amino is optionally substituted by one or more C₁₃alkyl groups, a C_i₃alkanoyl group, a C₁₃alkoxycarbonyl group or a C₁₃alkyl group optionally substituted by hydroxy or R⁴ and R⁵ together with the nitrogen atom to which they are attached represent azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl or morpholinyl each of which is optionally substituted by one or more of the following: o xo, C₁₃alkyl or hydroxy;

iv) halo

v) nitro

vi) cyano

vii) a C_i₃alkylS(O)y(O)z optionally substituted by one or more fluoro wherein y is 0, 1 or 2 and z is 0 except when y is 2 when z is 0 or 1

viii) a group -L-R⁸ in which L represents a bond, a C₃cycloalkylene group, a C₃cycloalkylidene group, a C_i₃alkylene group or a C_i₃alkoxyCi₃alkylene group wherein each group is optionally substituted by one or more of the following: carboxy, hydroxy, a Cioalkyl group optionally substituted by hydroxy; and R⁸ represents carboxy or a group NR¹R⁵ in which R⁴ and R⁵ are as defined above and additionally R⁵ represents cyano or R⁸ represents a group CO₂R⁹ in which R¹⁰ is a C₁₃alkyl group; or R⁸ represents a group CONR¹R⁵ in which R⁴ and R⁵ independently represent H, a C₁₃alkylsulphonyl group, a C₁₃alkyl group or a C₃cycloalkyl group wherein the alkyl and cycloalkyl groups are
optionally substituted by one or more hydroxy, carboxy or NR₃R⁴ in which R⁵ and R⁶ are as previously defined, or R⁷ and R⁸ together with the nitrogen atom to which they are attached represent azetidinyl; pyrrolidinyl, piperidinyl or morpholinyl; or R⁷ represents tetrazolyl, thiazolidin-2,4-dion-5-yl or R⁷ represents ureido optionally independently substituted by one, two or three C₆alkyl or the terminal nitrogen is included in a 5 or 6 membered saturated or partially unsaturated heterocyclic ring optionally containing an additional N, S or O, wherein the S may be in its oxidised form of SO or SO₂; ix) a group -Li-N(R₄)SO₂-L₂-R¹ in which Li and L₂ independently represent a bond or a C₆alkylene optionally substituted by one or more C₁,₃alkyl groups, R⁵ is H or C₁,₃alkyl and R¹ represents cyano or a group NR₃R⁴ in which R⁵ and R⁶ are as previously defined, or R¹ represents a group CO-R¹ in which R¹ represents hydroxy, C₁,₃alkoxy or a group NR₃R⁴ in which R⁵ and R⁶ are as previously defined; x) phenyl(O)₁₋ wherein f is 0 or 1 optionally substituted by one or more halo, C₁,₃alkyl optionally substituted by one or more halo or C₁,₃alkoxy optionally substituted by one or more halo; xi) phenylthio optionally substituted by one or more halo, C₁,₃alkyl optionally substituted by one or more halo or C₁,₃alkoxy optionally substituted by one or more halo; xii) monocyclic heteroaryl(O)₁₋ wherein g is 0 or 1 optionally substituted by one or more halo, C₁,₃alkyl optionally substituted by one or more halo or C₁,₃alkoxy optionally substituted by one or more halo; xiii) a nitrogen containing 5 or 6 membered heteroarylCO- wherein the heteroaryl is linked through nitrogen to the carbonyl group optionally substituted by one or more halo, C₆alkyl optionally substituted by one or more halo or C₁,₃alkoxy optionally substituted by one or more halo; xiv) a C₂,₆alkynyl group optionally substituted by one or more C₁,₃alkyl, hydroxy, C₁,₃alkoxy, C₁,₃alkoxyC₁,₃alkoxy, or a group - NR₃R⁴ as defined above; xv) a group - L₃-S(0)ₑC₆alkyl in which L₃ is a C₁,₃alkylene optionally substituted by one or more of the following: hydroxy or a C₁,₃alkyl group, and e is 0, 1 or 2; xvi) a group SO₂NR₃R⁴ in which R⁵ and R⁶ independently represent H; a C₆alkyl group optionally substituted by one or more of the following: hydroxy, C₁,₃alkoxy or a group - NR₃R⁴ in which R⁵ and R⁶ are as defined above, or R⁵ and R⁶ together with the nitrogen atom to which they are attached represent a saturated or partially unsaturated 4 to 10
membered heterocyclic ring optionally containing an additional sulphur including oxidised as SO or SO₂, oxygen or nitrogen and/or optionally fused to a benz ring and any ring is optionally substituted by one or more of the following: a C₁₃alkoxy group; carboxy; a C₃alkylsulfonyl group; C₁₃alkanoyl; benzoyl; hydroxy; oxo; carboxy; or by a Cioalkyl group optionally substituted by one or more of the following: hydroxy, C₁₃alkoxy or carboxy; or

R⁵ and R⁷ independently represent H, halo, cyano, C₃alkyl optionally substituted by one or more halo or C₁₃alkoxy optionally substituted by one or more halo;

R⁶ and R⁸ independently represent H, halo, cyano, C₁₃alkyl optionally substituted by one or more halo or C₁₃alkoxy optionally substituted by one or more halo; and

R⁷ is H or OH; with the proviso that the compound is not one of the following:

3-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]-1,1-dimethylurea
3-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methoxyphenyl]-1-propan-2-ylurea
3-benzyl-1-[3-[4-(4-cyanophenyl)piperidine-1-carbonyl]-4-methoxyphenyl]urea
Methyl (2S)-2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]carbamoylamino]-3-methylbutanoate
Methyl (2S)-2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]carbamoylamino]-2-phenylacetate
Methyl 2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]carbamoylamino]-3-(4-fluorophenyl)propanoate
Methyl 2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]carbamoylamino]-4-(tetrazol-1-yl)butanoate
Methyl (2S)-2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]carbamoylamino]-4-(1H-tetrazol-5-yl)butanoate
Methyl (2S)-2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]carbamoylamino]-3-1-methylimidazol-4-yl)propanoate
Methyl 2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]carbamoylamino]-2-methylpropanoate
Ethyl (2S)-2-[[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylphenyl]carbamoylamino]-3-hydroxypropanoate
3-benzyl-1-[5-[4-(4-cyanophenyl)piperidine-1-carbonyl]-2-methylsulfonylphenyl]urea
N-[(4-methylphenyl)carbamoylamino]cyclohexylacetamide

1-[5-(4-hydroxy-4-phenylpiperidine-1-carbonyl)-2-methylphenyl]-3-propan-2-ylurea

1-[5-(4-(2-methoxyphenyl)piperidine-1-carbonyl)-2-methylphenyl]-3-propan-2-ylurea

1-[5-(4-hydroxy-4-[3-(trifluoromethyl)phenyl]piperidine-1-carbonyl)-2-methylphenyl]-3-propan-2-ylurea

1-[5-(4-(2-fluorophenyl)-4-hydroxypiperidine-1-carbonyl)-2-methylphenyl]-3-propan-2-ylurea

3-[5-(4-(4-cyanophenyl)piperidine-1-carbonyl)-2-methylphenyl]-1-methyl-1-(oxolan-2-yl)urea

3-[5-(4-(4-cyanophenyl)piperidine-1-carbonyl)-2-methylphenyl]-1-(2-methoxyethyl)-1-methylurea

3-[5-(4-(4-cyanophenyl)piperidine-1-carbonyl)-2-methylphenyl]-1-(2-cyanopropan-2-yl)-1-methylurea

3-[5-(4-(4-cyanophenyl)piperidine-1-carbonyl)-2-methylphenyl]-1-cyclopropyl-1-(1,1-dioxothiolan-3-yl)urea

N-[2-[[5-(4-(4-cyanophenyl)piperidine-1-carbonyl)-2-methylphenyl]carbamoyl-methylamino]ethyl]-2-methylpropanamide

N-[5-(4-(4-cyanophenyl)piperidine-1-carbonyl)-2-methylphenyl]-1,1-dioxo-1,4-thiazinane-4-carboxamide

1-[5-(4-(3-fluorophenyl)piperidine-1-carbonyl)-2-methylphenyl]-3-propan-2-ylurea

1-[5-(4-(3-chlorophenyl)piperidine-1-carbonyl)-2-methylphenyl]-3-propan-2-ylurea

1-[5-(4-(3-methoxyphenyl)piperidine-1-carbonyl)-2-methylphenyl]-3-propan-2-ylurea

1-[5-(4-(2-cyanophenyl)piperidine-1-carbonyl)-2-methylphenyl]-3-propan-2-ylurea

3-[3-(4-(4-cyanophenyl)piperidine-1-carbonyl)-4-methylsulfinylphenyl]-1-propan-2-ylurea

or

3-[3-(4-(4-cyanophenyl)piperidine-1-carbonyl)-4-methylsulfonylphenyl]-1-propan-2-ylurea.

2) A compound according to claim 1 as represented by formula II
or a pharmaceutically acceptable salt thereof, in which

R^1 represents 1) a C_{1-6}alkyl group optionally substituted by one or two groups selected from A-S below and/or by one to five groups selected from T below:

A) phenyl optionally substituted by one or more of the following i) halo; ii) cyano; iii) a C_{1-6}alkoxy group optionally substituted by one or more halo iv) hydroxy; v) a C_{1-6}alkyl group optionally substituted by one or more halo; vi) carbamoyl; vii) N-C_{1-6}alkylcarbamoyl; viii) N,N-diC_{1-6}alkylcarbamoyl; ix) carboxy; x) C_{1-6}alkoxycarbonyl; xi) C_{1-6}alkylthio; xii) C_{1-6}alkylsulfanyl; xiii) C_{1-6}alkylsulfonyl; xiv) C_{1-6}alkylsulfonyloxy; xv) sulphasoyl; xvi) N-C_{1-6}alkylsulphamoyl; xvii) N,N-diC_{1-6}alkylsulphamoyl; xviii) benzyl xix) benzyloxy; xx) heteroaryl; xxi) heteroaryloxy; xii) phenyl xiii) phenoxy xiv) phenylsulphonyl; xv) heteroaryl sulphonyl; xxv) a carbon linked saturated or partially unsaturated 4 to 8 membered heterocyclic group as defined in c) below; xxvi) phenylsulphonyl; xxvii) heteroaryl sulphonyl;

xxviii) a group of formula NR^cR^d in which R^c and R^d independently represent:

a) H;
b) C_{1-6}alkanoyl;
c) a carbon linked saturated or partially unsaturated 4 to 8 membered heterocyclic group containing one or more N, S or O, wherein the S may be in its oxidised form of SO or SO_2, which is optionally fused to a benz ring and any ring is optionally substituted by one or more of the following: hydroxy, oxo, carboxy, a C_{1-6}alkoxy group optionally substituted by one or more hydroxy or C_{1-6}alkoxy, C_{1-6}alkanoyl, benzoyl, amino, C_{1-3}alkylamino, di(C_{1-3}alkyl)amino or a C_{1-6}alkyl group optionally substituted by one or more hydroxy or C_{1-6}alkoxy; d) a C_{1-6}alkyl group optionally substituted by one or more of the following: hydroxy; carboxy; a C_{1-6}alkoxycarbonyl group; a C^alkoxy group; heteroaryl; a group of formula NR^eR^f in which R^e and R^f independently represent H; a C_{1-6}alkanoyl group; a C_{1-6}alkylsulphonyl group; a C_{1-6}alkoxycarbonyl group; a C_{1-6}alkyl group optionally
substituted by one or more hydroxy or C₅₋₆alkoxy, or Rₑ and Rᶠ together with the nitrogen atom to which they are attached represent a saturated or partially unsaturated 4 to 8 membered heterocyclic ring optionally containing an additional sulphur including oxidised as SO or SO₂, oxygen or nitrogen and/or optionally fused to a benz ring and any ring is optionally substituted by one or more of the following: a C₁₋₆alkoxy group; carboxy; a C₁₋₆alkylsulfonyl group; C₁₋₆alkanoyl; benzoyl; hydroxy; oxo; carboxy; or a C₁₋₆alkyl group optionally substituted by one or more hydroxy or by one or more C₁₋₆alkoxy or by one or more carboxy;
e) Rₑ and Rᶠ together with the nitrogen atom to which they are attached represent a saturated or partially unsaturated 4 to 8 membered heterocyclic ring optionally containing an additional oxygen, sulphur, SO, SO₂ or nitrogen and/or optionally fused to a benz ring and/or optionally substituted by one or more of the following: a C₁₋₆alkoxy group; C₁₋₆alkanoyl group; benzoyl; a C₁₋₆alkoxycarbonyl group; a C₁₋₆alkylsulfonyl group; carboxamoyl; N-C₁₋₆alkylcarbamoyl; N, N-diC₁₋₆alkylcarbamoyl; hydroxy; oxo; carboxy; a C₁₋₆alkyl group (which is optionally substituted by one or more of the following: a C₁₋₆alkoxy group, hydroxy or a group of formula NRₑRᶠ in which Rₑ and Rᶠ are as defined above) or a group of formula NRₑRᶠ in which Rₑ and Rᶠ are as defined above;
f) a C₁₋₆alkylsulphonyl group;
g) phenylsulfonyl;
h) heteroarylsulfonyl;
i) benzoyl;
j) phenyl optionally substituted by one or more of the following: halo; C₁₋₃alkyl; C₁₋₃alkoxy; a C₁₋₆alkanoylamino group; carboxamoyl; N-C₁₋₆alkylcarbamoyl; N, N-diC₁₋₆alkylcarbamoyl;
k) heteroaryl optionally substituted by one or more carboxy; fluoro; hydroxy; a C₁₋₃alkoxy group optionally substituted on C₂ or C₃ by carboxy; a group NRₑRᶠ in which Rₑ and Rᶠ are as defined above; or a group CONRₑRᶠ in which Rₑ and Rᶠ are as defined above;
i) a Cs-iocycloalkyl group which may be monocyclic, bicyclic or tricyclic and optionally may be bridged and is optionally substituted by one or more carboxy; fluoro; hydroxy; a C₅₋₁₀alkoxy group optionally substituted on C₂ or C₃ by carboxy; a group NRₑRᶠ in which Rₑ and Rᶠ are as defined above; or a group CONRₑRᶠ in which Rₑ and Rᶠ are as defined above;
m) a $\text{Ci}_6\text{alkoxycarbonyl}$ group;
B) a heteroaryl group which is optionally substituted by groups i) to xxix) as described for phenyl above;
C) a group of formula NR$c$R$d$ in which R$c$ and R$d$ are as defined above;
D) a C$3$-$7$cycloalkyl group optionally substituted by one or more hydroxy or a group of formula NR$e$R$f$ in which R$e$ and R$f$ are as defined above;
E) a carbon linked saturated or partially unsaturated 4 to 8 membered heterocyclic group containing one or more N, S or O, wherein the S may be in its oxidised form of SO or SO$_2$, which is optionally fused to a benz ring and/or is optionally substituted by one or more of the following: hydroxy; oxo; a $\text{C}_1\text{,}_6\text{alkoxy}$ group; carboxy; hydroxy; C$1$-$4$alkanoyl; a $\text{C}_1$-$6$alkylsulfonyl group; amino; C$1$-$3$alkylamino; di(C$1$-$3$ alkyl)amino; or a C$1$-$6$alkyl optionally substituted by one or more hydroxy or C$1$-$6$alkoxy;
F) a $\text{C}_1$-$6$ alkoxy carbonyl group;
G) a C$2$-$6$alkynyl group;
H) a group -CONR$c$R$d$ in which R$c$ and R$d$ are as defined above;
i) a Ci$6$alkoxy group;
J) a C$2$-$6$alkenyl group;
K) a Ci$6$alkyl group;
L) a Ci$6$alkylsulphonyl group;
M) phenylsulfonyl;
N) heteroarylsulfonyl;
O) benzoyl;
P) a Ci$6$alkanoyl group
Q) hydroxy;
R) oxo;
S) carboxy;
T) fluoro
or R$^1$ represents
2) a C$3$-$7$cycloalkyl group optionally substituted by one or two groups selected from A to T above;
3) a C$2$-$6$alkynyl group optionally substituted by one or two groups selected from A to T above;
4) a carbon linked saturated or partially unsaturated 4 to 8 membered heterocyclic group containing one or more N, S or O, wherein the S may be in its oxidised form of SO or SO$_2$, which is optionally fused to a benz ring and any ring is optionally substituted by a group A to T as defined above;

5) a C$_{2-6}$ alkenyl group optionally substituted by one or two groups selected from A to T above;

wherein any alkyl chain mentioned in any of the definitions from A to P above or in any of the definitions i to xxix above is optionally substituted by 1) one group selected from: carboxy; hydroxy; a C$_{1-3}$ alkoxy group optionally substituted on C2 or C3 by carboxy; a group NR$_e$R$_d$ in which R$_e$ and R$_d$ are as defined above; or a group CONR$_e$R$_f$ in which R$_e$ and R$_f$ are as defined above; and/or by 2) from one to five fluoro;

and further wherein any cycloalkyl, phenyl, heteroaryl ring or carbon linked saturated or partially saturated 4 to 8 membered heterocyclic group in the list of optional substituents from A to P above or in any of the definitions i to xxix above, for which specific substitution has not been previously mentioned, is optionally substituted by one group selected from: carboxy; hydroxy; a C$_{1-3}$ alkoxy group optionally substituted on C2 or C3 by carboxy; a group NR$_e$R$_d$ in which R$_e$ and R$_d$ are as defined above; or a group CONR$_e$R$_f$ in which R$_e$ and R$_f$ are as defined above; and/or is optionally substituted by one to five fluoro;

R$_e$ represents H; or a d$_a$alkyl group, a C$_{3-6}$cloalkyl group or a C$_{3-6}$cycloalkylC$_{1-4}$alkyl group each of which groups is optionally substituted by one or more carboxy; fluoro; hydroxy; a C$_{1-3}$ alkoxy group optionally substituted on C2 or C3 by carboxy; a group of formula NR$_e$R$_f$ in which R$_e$ and R$_f$ are as defined above; or a group CONR$_e$R$_f$ in which R$_e$ and R$_f$ are as defined above; or R$_f$ and R$_d$ together with the nitrogen atom to which they are attached represent a saturated or partially unsaturated 4 to 8 membered heterocyclic ring optionally containing an additional sulphur including oxidised as SO or SO$_2$, oxygen or nitrogen which is optionally fused to a benz ring and wherein any ring is optionally substituted by one or two of the groups A to S above and/or by from 1 to 5 groups T;

R$_b$ represents H.

R$_2$ represents H, halo, cyano, a C$_{1-3}$ alkyl group optionally substituted by one or more halo, or a C$_{1-3}$ alkoxy group optionally substituted by one or more halo;
R³ represents H, halo, cyano, a C₁₋₃alkyl group optionally substituted by one or more halo, or a C₁₋₃alkoxy group optionally substituted by one or more halo; R⁴ represents cyano, halo or a C₁₋₃alkylsulphonyl group; and R⁷ represents H or hydroxy.

3) A compound according to claim 1 as represented by formula HA

![Diagram of a molecular structure]

or a pharmaceutically acceptable salt thereof, in which
R¹ represents 1) a C₁₋₃alkyl group optionally substituted by one or more of the following:
a) phenyl optionally substituted by one or more of the following: halo; a C₁₋₃alkoxy group or cyano; b) pyridyl c) a carbon linked saturated 5 or 6 membered heterocyclic group containing one N or O; d) a C₁₋₄alkoxycarbonyl group or e) a C₂₋₄alkynyl group or 2) a C₃₋₇cycloalkyl group
R³ represents H; or a C₈alkyl group;
or R¹ and R³ together with the nitrogen atom to which they are attached represent morpholinyl, pyrrolidinyl or piperidinyl;
R² represents H, halo, trifluoromethoxy, a C₁₋₃alkyl group; a C₁₋₃alkoxy group; cyano; or when R¹ is other than phenyl then R² together with the nitrogen to which it is attached plus the carbon on the phenyl ring to which the nitrogen is attached and R² together with the carbon to which it is attached together represent a pyrrolidine ring fused to phenyl;
R³ represents H, halo, trifluoromethoxy, a C₁₋₃alkyl group; a C₁₋₃alkoxy group; cyano; R⁴ represents bromo, cyano or a C₁₋₂alkylsulphonyl group; and R⁷ represents H or hydroxy.

4) A compound according to any previous claim in which R⁷ represents H.
A compound according to any previous claim in which R⁷ represents H, R¹ represents 1) a Ci₆-alkyl group optionally substituted by one or more of the following: a) phenyl optionally substituted by one or more of the following: halo; a Ci₅-alkoxy group or cyano; b) pyridyl c) oxan-4-yl d) a C₁₄alkoxycarbonyl group or e) a C₂₄-alkynyl group 2) a C₃-₇-cycloalkyl group and R⁸ represents H or R¹ and R⁸ together with the nitrogen atom to which they are attached represent morpholino or pyrrolidino, and R², R⁵, R³, R⁴ are as described above provided that one of R² and R³ is other than H.

A compound according to any previous claim in which R² is methyl and R³ is H.

A compound according to any one of claims 1 to 5 in which R² and R³ are both methyl.

A compound according to any previous claim in which R⁴ is cyano or methylsulphonyl.

A compound according to any previous claim in which R⁸ is H.

A compound according to any one of claims 1 to 5 or claim 8 or claim 9 in which R³ is methyl and R² is H.

A compound selected from one or more of the compounds described in List 1 in the specification or a pharmaceutically acceptable salt thereof.

A compound selected from one or more of the compounds described in List 2 in the specification or a pharmaceutically acceptable salt thereof.

A method of treating obesity or being overweight, eating disorders, dyslipidaemia and type 2 diabetes mellitus comprising administering a pharmacologically effective amount of a compound of formula I as defined in any one of claims 1 to 12 to a patient in need thereof.
14) A method of treating cancer comprising administering a pharmacologically effective amount of a compound of formula I as defined in any one of claims 1 to 12 to a patient in need thereof.

15) A method of treating infection comprising administering a pharmacologically effective amount of a compound of formula I as defined in any one of claims 1 to 12 to a patient in need thereof.

16) A pharmaceutical formulation comprising a compound of formula I as defined in any one of claims 1 to 12, or pharmaceutically acceptable salt thereof, in admixture with pharmaceutically acceptable adjuvants, diluents and/or carriers.

17) A process for preparing a compound of formula I as claimed in claim 1 wherein R^1, R^a, R^2, R^b, R^3, R^4, R^5, R^6, R^6' and R^7 are as claimed in claim 1 unless otherwise specified which comprises:

(a) reacting a compound of formula VI

\[
\begin{align*}
\text{VI} & \quad R^1, R^a, R^2, R^b, R^3, R^4, \ldots \end{align*}
\]

with an isocyanate of formula VII

\[
\begin{align*}
\text{VII} & \quad R^1 \text{N=C=O} \\
\end{align*}
\]

(b) reacting a compound of formula VI with an isocyanate of formula VII
with phosgene or an equivalent thereof and then further reacting the intermediate obtained with an amine of formula VIII

or c) reacting a compound of formula IX

in which X represents a leaving group with a compound of formula X

in the presence of a diluent and optionally in the presence of a base at a temperature in the range of 0-150°C

or d) reacting a compound of formula XI
with a compound of formula X optionally in the presence of a coupling agent and optionally in the presence of a diluent at a temperature in the range of 0-150°C.

e) reacting a compound of formula XII

in which X represents a replaceable group, with a compound of formula X in the presence of carbon monoxide and in the presence of a metal catalyst in a solvent in the temperature range 0 - 150°C or

f) reacting a compound of formula XIII

with a compound of formula XIV
in which X represents a replaceable group in the presence of a metal catalyst in an organic diluent at a temperature in the range 0 - 150°C.

18) A compound of formula VI as described in the previous claim.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

| INV. | C07D211/34 | C07D401/12 | C07D211/16 | C07D211/18 | C07D211/22 | C07D211/24 | C07D211/52 | C07D405/12 | C07D211/24 | C07D417/12 | C07D471/04 | C07D471/18 | C07D473/34 | A61K31/451 |
|------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|

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

B. REELS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

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

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

EPO-Internal, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<th>Relevant to claim No.</th>
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<tr>
<td>A</td>
<td>US 5 981 575 A (KUHAJDA ET. AL.) 9 November 1999 (1999-11-09) column 4, line 55 - column 6, line 34; claims; examples</td>
<td>1-18</td>
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</table>

Further documents are listed in the continuation of Box C.

See patent family annex.

Date of the actual completion of the international search

6 March 2008

Date of mailing of the international search report

26/03/2008

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk

Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016

Authorized officer

Helsp. Ian
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<tr>
<td>A</td>
<td>WO 02/055661 A (SMITHKLINE BEECHAM CORPORATION) 18 July 2002 (2002-07-18) claims; examples</td>
<td>1-18</td>
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<td>A</td>
<td>WO 01/90101 A (AVENTIS) 29 November 2001 (2001-11-29) claims; tables 5-7</td>
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</table>
INTERNATIONAL SEARCH REPORT

Box No. II  Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [ ] claims Nos.: 13-15(part)
   because they relate to subject matter not required to be searched by this Authority, namely:
   Although claims 13-15 are drawn to a therapeutic method of treatment, the search has been carried out based of the alleged effects of the compounds.

2. [ ] Claims Nos.:
   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III  Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant’s protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant’s protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.
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<td>US 5981575</td>
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