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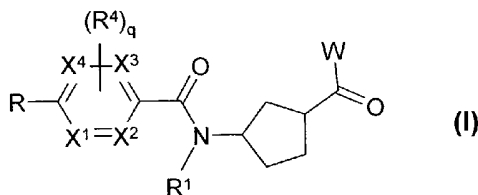
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(54) Title: 3-AMINOCYCLOPENTANE CARBOXAMIDE DERIVATIVES



(I)

(57) **Abstract:** Compounds of the formula (I) in which R¹, R⁴, R, X¹, X², X³, X⁴, q and W have the meanings indicated in Claim 1, are inhibitors of fatty acid synthase, and can be employed, inter alia, for the treatment of diseases such as cancer, cardiovascular diseases, central nervous system injury and different forms of inflammation.

3-Aminocyclopentane carboxamide derivatives

TECHNICAL FIELD OF THE INVENTION

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The present invention relates to novel hydropyrrolopyrrole derivatives which inhibit the activity of fatty acid synthase (FASN; also abbreviated as FAS), to pharmaceutical compositions comprising them, to processes for their preparation, and to their use in therapy for the treatment of cancers.

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BACKGROUND OF THE INVENTION

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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.

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FAS is also highly expressed in human sebocytes, the lipid producing cells of the sebaceous glands. Acne is the most common disorder involving the sebaceous gland. The pathogenesis of acne involves lipid (over)production by the sebaceous gland and it has been reported that inhibitors of mammalian FAS inhibit the production of sebum in sebocytes (US 2005/0053631). Acne cannot occur without sebum lipids. There is an unmet medical need in the treatment of acne for agents that reduce sebum production.

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Since fatty acid synthesis in bacteria is essential for cell survival, bacterial FAS (type II synthase) has emerged as a potential target for antibacterial therapy. Unlike in most other prokaryotes, fatty acid synthase activity in mycobacteria is carried out by a single high-molecular-weight, multifunctional peptide chain (type I synthase) related to mammalian FAS. Mycobacterial type I FAS has been described as a potential target for antimycobacterial therapy, e.g. the treatment of tuberculosis. With one-third of the world's population being infected with the tuberculosis bacillus, and multidrug-resistant strains of Mycobacterium tuberculosis developing, there is a high medical need for novel tuberculosis therapies. (Silvana C. Ngo, et al.: Inhibition of isolated Mycobacterium tuberculosis Fatty Acid Synthase I by Pyrazinamide Analogs; Antimicrobial agents and Chemotherapy 51,7 (2007) 2430-2435).

Recently, microdomains of organelle membranes rich in sphingomyelin and cholesterol (called "lipid rafts") have been considered to act as a scaffold for the hepatitis C virus (HCV) replication complex (F. Amemiya, et al.: Targeting Lipid Metabolism in the Treatment of Hepatitis C Virus Infection. The Journal of Infectious Diseases 197 (2008) 361 -70). Consequently, alterations of membrane lipid composition and/or distribution may influence viral replication. Indeed, agents related to lipid metabolism like polyunsaturated fatty acids or HMG-CoA reductase inhibitors (statins) have been shown to affect the replication of genotype 1 HCV (dto). These agents may attenuate HCV replication through the destruction of lipid rafts, according to their pharmacological actions. An alternative molecular mechanism possibly responsible for the inhibition of HCV replication is via altering localization of host proteins through alterations in lipid anchoring (S. M. Sagan, et al.: The influence of cholesterol and lipid metabolism on host cell structure and hepatitis C virus replication. Biochem. Cell Biol. 84 (2006) 67-79). Unlike polyunsaturated fatty acids, addition of saturated fatty acids or oleic acid to cultured Sfil cells promoted HCV RNA replication (S. B. Kapadia, F. V. Chisari: Hepatitis C virus RNA replication is regulated by host geranylgeranylation and fatty acids. PNAS 102 (2005) 2561 -66). In line with this, it has been reported

that expression of fatty acid synthase was increased in a human hepatoma cell line upon HCV infection (W. Yang, et al.: Fatty acid synthase is up-regulated during hepatitis C virus infection and regulates hepatitis C virus entry. *Hepatology* 48,5 (2008) 1396- 1403). Furthermore, inhibition of fatty acid biosynthesis by TOFA (an inhibitor of acetyl-CoA carboxylase) or inhibitors of fatty acid synthase (cerulenin, C75), led to decreased HCV production (dto).

The effect of fatty acid synthase (FAS) activity on viral replication or infection appears not to be restricted to HCV, but has also been reported for HIV (D. H. Nguyen, D. D. Taub: Targeting Lipids to Prevent HIV infection. *Molecular Interventions* 4,6 (2004) 318-320), Poliovirus (R. Guinea, L. Carrasco: Effects of Fatty Acids on Lipid Synthesis and Viral RNA Replication in Poliovirus-Infected Cells. *Virology* 185 (1991) 473-476), Epstein-Barr virus (Y. Li., et al.: Fatty acid synthase expression is induced by the Epstein-Barr virus immediate-early protein BRLF1 and is required for lytic viral gene expression. *Journal of Virology* 78,8 (2004) 4197-4206), human papilloma virus (L. Louw, et al.: HPV-induced recurrent laryngeal papillomatosis: fatty acid role- players. *Asia Pac J Clin Nutr* 17 (S1) (2008) 208-211), coxsackievirus B3 (A. Rassmann, et al.: The human fatty acid synthase: A new therapeutic target for coxsackievirus B3-induced diseases? *Antiviral Research* 76 (2007) 150-158), Rous sarcoma virus (H. Goldfine, et al.: Effects of inhibitors of lipid synthesis on the replication of Rous Sarcoma Virus. A specific effect of cerulenin on the processing of major non-glycosylated viral structural proteins. *Biochimica et Biophysica Acta* 512 (1978) 229-240), as well as human cytomegalovirus (HCMV), and influenza A virus (J. Munger, et al.: Systems-level metabolic flux profiling identifies fatty acid synthesis as a target for antiviral therapy. *Nature Biotechnology* 26 (2008) 1 179-1 186).

Taken together, there is growing evidence, that activity of the host's FAS plays an important role in viral infection and viral replication, suggesting FAS as a

target for antiviral therapy. The expression of FAS is strongly increased in many cancers and there is evidence that efficient fatty acid synthesis is required for tumor cell survival. Inhibition of FAS has therefore been suggested as a new direction for oncology (Expert Opin. Investig. Drugs 16,1
5 (2007)1817-1829).

Fatty acids have an essential role in a variety of cellular processes including building blocks for membranes, anchors for targeting membrane proteins, precursors in the synthesis of lipid second messengers and as a medium to
10 store energy, Menendez JS and Lupu R, Fatty acid synthase and the lipogenic phenotype in cancer pathogenesis, Nature Reviews Cancer, 7: 763-777 (2007). Fatty acids can either be obtained from the diet or can be synthesized de novo from carbohydrate precursors. The biosynthesis of the latter is
15 catalyzed by the multi-functional homodimeric FAS. FAS synthesizes long chain fatty acids by using acetyl-CoA as a primer and Malonyl Co-A as a 2 carbon donor, and NADPH as a reducing equivalents (Wakil SJ, Lipids, Structure and function of animal fatty acid synthase, 39: 1045-1053 (2004), Asturias FJ et al., Structure and molecular organization of mammalian fatty acid synthase, Nature Struct. Mol. Biol. 12:225-232 (2005), Maier T, et al.,
20 Architecture of Mammalian Fatty Acid Synthase at 4.5 Å Resolution, Science 311 : 1258-1262 (2006).

De novo fatty acid synthesis is active during embryogenesis and in fetal lungs where fatty acids are used for the production of lung surfactant. In adults, most normal human tissues preferentially acquire fatty acids from the diet. Therefore, the level of de novo lipogenesis and expression of lipogenic
25 enzymes is low, Weiss L, et al, Fatty-acid biosynthesis in man, a pathway of minor importance. Purification, optimal assay conditions, and organ distribution of fatty-acid synthase. Biological Chemistry Hoppe-Seyler 367(9):905-912 (1986). In contrast, many tumors have high rates of de novo fatty acid synthesis Medes G, et al, Metabolism of Neoplastic Tissue. IV. A
30 Study of Lipid Synthesis in Neoplastic Tissue Slices in Vitro, Can Res, 13:27-29, (1953). FAS has now been shown to be overexpressed in numerous

5 cancer types including prostate, ovary, colon, endometrium lung, bladder, stomach and kidney Kuhajda FP, Fatty-acid synthase and human cancer: new perspectives on its role in tumor biology, Nutrition; 16:202-208 (2000). This differential expression and function of FAS in tumors and normal cells provide an approach for cancer therapy with the potential of a substantial therapeutic window.

10 Pharmacological and small interference RNA mediated inhibition of FAS has demonstrated a preferential inhibition of cancer cell proliferation. Additionally these inhibitors induce apoptosis in cancers cells in vitro and retard growth in human tumors in murine xenograft models in vivo, Menendez JS and Lupu R, Nature Reviews Cancer, 7: 763-777 (2007). Based upon these findings, FAS is considered a major potential target of antineoplastic intervention.

15 The invention had the object of finding novel compounds having valuable properties, in particular those which can be used for the preparation of medicaments.

20 It has been found that the compounds according to the invention and salts thereof have very valuable pharmacological properties while being well tolerated.

25 The present invention specifically relates to compounds of the formula I which inhibit FASN, to compositions which comprise these compounds, and to processes for the use thereof for the treatment of FASN-induced diseases and complaints.

30 The compounds of the formula I can furthermore be used for the isolation and investigation of the activity or expression of FASN. In addition, they are particularly suitable for use in diagnostic methods for diseases in connection with unregulated or disturbed FASN activity.

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5 The host or patient can belong to any mammalian species, for example a primate species, particularly humans; rodents, including mice, rats and hamsters; rabbits; horses, cows, dogs, cats, etc. Animal models are of interest for experimental investigations, providing a model for treatment of human disease.

10 The susceptibility of a particular cell to treatment with the compounds according to the invention can be determined by in vitro tests. Typically, a culture of the cell is combined with a compound according to the invention at various concentrations for a period of time which is sufficient to allow active agents such as anti IgM to induce a cellular response such as expression of a surface marker, usually between about one hour and one week. In vitro testing can be carried out using cultivated cells from blood or from a biopsy sample. 15 The amount of surface marker expressed is assessed by flow cytometry using specific antibodies recognising the marker.

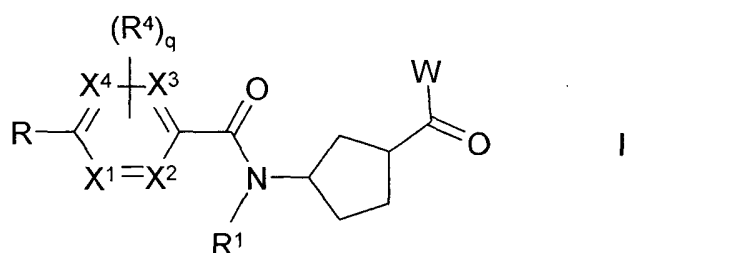
20 The dose varies depending on the specific compound used, the specific disease, the patient status, etc. A therapeutic dose is typically sufficient considerably to reduce the undesired cell population in the target tissue while the viability of the patient is maintained. The treatment is generally continued until a considerable reduction has occurred, for example an at least about 50% reduction in the cell burden, and may be continued until essentially no 25 more undesired cells are detected in the body.

PRIOR ART

30 Cyclopentanecarboxamide derivatives are described in WO 2011/048018 A1 as FAS inhibitors for the treatment of obesity and diabetes.

SUMMARY OF THE INVENTION

35 The invention relates to compounds of the formula I



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in which

- R denotes Ar, Het, $-\text{C}\equiv\text{C}-\text{Ar}$ or $-\text{C}\equiv\text{C}-\text{Het}$,
- 10 W denotes $\text{NR}^2\text{R}^{2'}$ or Het^1 ,
- R^1 denotes A, $[\text{C}(\text{R}^3)_2]_n\text{Ar}^1$ or $[\text{C}(\text{R}^3)_2]_n\text{Cyc}$,
- $\text{R}^2, \text{R}^{2'}$ each, independently of one another, denote H, A or $[\text{C}(\text{R}^3)_2]_n\text{Cyc}$,
- 15 R^4 denotes H, F, Cl, Br, OH, CN, NO_2 , A' , OA' , SA' , SO_2Me , COA' , CONH_2 , CONHA' or CONA'_2 ,
- $\text{X}^1, \text{X}^2, \text{X}^3, \text{X}^4$ each, independently of one another, denote CH or N,
- A denotes unbranched or branched alkyl with 1-10 C-atoms, wherein two adjacent carbon atoms may form a double bond and/or one or two non-adjacent CH- and/or CH_2 -groups may be replaced by N-, O- and/or S-atoms and wherein 1-7 H-atoms may be replaced by R^5 ,
- 20 Cyc denotes cycloalkyl with 3-7 C-atoms, which is unsubstituted or monosubstituted by OH, Hal or A,
- A' denotes unbranched or branched alkyl with 1-6 C-atoms, wherein 1-5 H-atoms may be replaced by F,
- 30 R^5 denotes F, Cl or OH,
- Ar denotes phenyl, which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by Hal, A, $\text{O}[\text{C}(\text{R}^3)_2]_n\text{Het}^1$, Ar^1 , $[\text{C}(\text{R}^3)_2]_p\text{OR}^3$, $[\text{C}(\text{R}^3)_2]_p\text{N}(\text{R}^3)_2$, NO_2 , CN, $[\text{C}(\text{R}^3)_2]_p\text{COOR}^3$, $\text{CON}(\text{R}^3)_2$, $[\text{C}(\text{R}^3)_2]_p\text{N}(\text{R}^3)_2$, $\text{N}(\text{R}^3)_2\text{COA}$, $\text{NR}^3\text{SO}_2\text{A}$, $[\text{C}(\text{R}^3)_2]_p\text{SO}_2\text{N}(\text{R}^3)_2$, $\text{S}(\text{O})_n\text{A}$, $\text{O}[\text{C}(\text{R}^3)_2]_m\text{N}(\text{R}^3)_2$, NHCOOA , $\text{NHCON}(\text{R}^3)_2$ and/or COA,
- 35

- Ar¹ denotes phenyl or naphthyl, which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by Hal, A, [C(R³)₂]_pOR³, [C(R³)₂]_pN(R³)₂, NO₂, CN, [C(R³)₂]_pCOOR³, [C(R³)₂]_pN(R³)₂, N(R³)₂COA, NR³SO₂A, [C(R³)₂]_pSO₂N(R³)₂, S(O)_nA, O[C(R³)₂]_mN(R³)₂, NHCOOA, NHCON(R³)₂ and/or COA,
- R³ denotes H or unbranched or branched alkyl with 1-6 C-atoms,
- Het denotes a mono- or bicyclic saturated, unsaturated or aromatic heterocycle having 1 to 4 N, O and/or S atoms, which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by Hal, A, [C(R³)₂]_nOA', [C(R³)₂]_nN(R³)₂, SR³, NO₂, CN, COOR³, CON(R³)₂, COHet¹, NR³COA, NR³SO₂A, SO₂N(R³)₂, S(O)_nA, O[C(R³)₂]_mN(R³)₂, NHCOOA, NHCON(R³)₂, CHO, COA, =S, =NH, =NA and/or =O (carbonyl oxygen),
- Het¹ denotes a mono- or bicyclic saturated, unsaturated or aromatic heterocycle having 1 to 4 N, O and/or S atoms, which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by Hal, A, [C(R³)₂]_nOR³, [C(R³)₂]_nN(R³)₂, SR³, NO₂, CN, COOR³, CON(R³)₂, NR³COA, NR³SO₂A, SO₂N(R³)₂, S(O)_nA, O[C(R³)₂]_mN(R³)₂, NHCOOA, NHCON(R³)₂, CHO, COA, =S, =NH, =NA and/or =O (carbonyl oxygen),
- Hal denotes F, Cl, Br or I,
- m denotes 1, 2 or 3,
- n denotes 0, 1 or 2,
- p denotes 0, 1, 2, 3 or 4,
- q 0, 1, 2 or 3,
- with the proviso that only one or two of X¹, X², X³, X⁴ denote N,
- and pharmaceutically acceptable salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios.

The invention also relates to the optically active forms (stereoisomers), the enantiomers, the racemates, the diastereomers and the hydrates and solvates of these compounds.

5

Moreover, the invention relates to pharmaceutically acceptable derivatives of compounds of formula I.

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The term solvates of the compounds is taken to mean adductions of inert solvent molecules onto the compounds which form owing to their mutual attractive force. Solvates are, for example, mono- or dihydrates or alkoxides. It is understood, that the invention also relates to the solvates of the salts.

15

The term pharmaceutically acceptable derivatives is taken to mean, for example, the salts of the compounds according to the invention and also so-called prodrug compounds.

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As used herein and unless otherwise indicated, the term "prodrug" means a derivative of a compound of formula I that can hydrolyze, oxidize, or otherwise react under biological conditions (in vitro or in vivo) to provide an active compound, particularly a compound of formula I. Examples of prodrugs include, but are not limited to, derivatives and metabolites of a compound of formula I that include biohydrolyzable moieties such as biohydrolyzable amides, biohydrolyzable esters, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, and biohydrolyzable phosphate analogues. In certain embodiments, prodrugs of compounds with carboxyl functional groups are the lower alkyl esters of the carboxylic acid. The carboxylate esters are conveniently formed by esterifying any of the carboxylic acid moieties present on the molecule. Prodrugs can typically be prepared using well-known methods, such as those described by Burger's Medicinal Chemistry and Drug Discovery 6th ed. (Donald J. Abraham ed., 2001, Wiley) and Design and Application of Prodrugs (H. Bundgaard ed., 1985, Harwood Academic Publishers GmbH).

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The expression "effective amount" denotes the amount of a medicament or of a pharmaceutical active ingredient which causes in a tissue, system, animal or human a biological or medical response which is sought or desired, for example, by a researcher or physician.

5 In addition, the expression "therapeutically effective amount" denotes an amount which, compared with a corresponding subject who has not received this amount, has the following consequence:

10 improved treatment, healing, prevention or elimination of a disease, syndrome, condition, complaint, disorder or side-effects or also the reduction in the advance of a disease, complaint or disorder.

The expression "therapeutically effective amount" also encompasses the amounts which are effective for increasing normal physiological function.

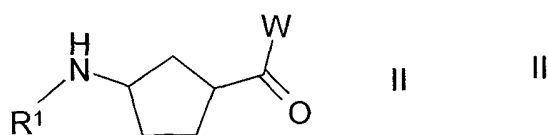
15 The invention also relates to the use of mixtures of the compounds of the formula I, for example mixtures of two diastereomers, for example in the ratio 1:1, 1:2, 1:3, 1:4, 1:5, 1:10, 1:100 or 1:1000.

20 These are particularly preferably mixtures of stereoisomeric compounds.

"Tautomers" refers to isomeric forms of a compound that are in equilibrium with each other. The concentrations of the isomeric forms will depend on the environment the compound is found in and may be different depending upon,
25 for example, whether the compound is a solid or is in an organic or aqueous solution.

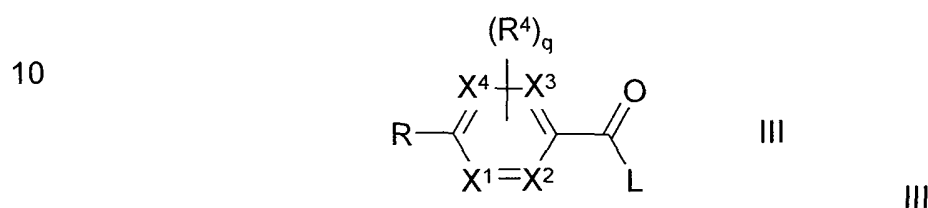
30 The invention relates to the compounds of the formula I and salts thereof and to a process for the preparation of compounds of the formula I and pharmaceutically acceptable salts, solvates, tautomers and stereoisomers thereof, characterised in that
a compound of the formula II

- 11 -



5 in which R¹ and W have the meanings indicated in Claim 1,

is reacted with a compound of the formula III



15 in which R, R⁴, X¹, X², X³, X⁴ and q have the meanings
indicated in Claim 1,
and L denotes Cl, Br, I or a free or reactively functionally
modified OH group,

20 and/or
a base or acid of the formula I is converted into one of its salts.

25 Above and below, the radicals R¹, R⁴, R, X¹, X², X³, X⁴, q and W have the
meanings indicated for the formula I, unless expressly stated otherwise.

A denotes alkyl, this is unbranched (linear) or branched, and has 1, 2, 3, 4, 5,
6, 7, 8, 9 or 10 C atoms. A preferably denotes methyl, furthermore ethyl,
30 propyl, isopropyl, butyl, isobutyl, sec-butyl or tert-butyl, furthermore also
pentyl, 1-, 2- or 3-methylbutyl, 1,1-, 1,2- or 2,2-dimethylpropyl, 1-ethylpropyl,
hexyl, 1-, 2-, 3- or 4-methylpentyl, 1,1-, 1,2-, 1,3-, 2,2-, 2,3- or 3,3-
dimethylbutyl, 1- or 2-ethylbutyl, 1-ethyl-1-methylpropyl, 1-ethyl-2-methyl-
35 propyl, 1,1,2- or 1,2,2-trimethylpropyl, furthermore preferably, for example,
trifluoromethyl.

A very particularly preferably denotes alkyl having 1, 2, 3, 4, 5 or 6 C atoms, preferably methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, trifluoromethyl, pentafluoroethyl or 1,1,1-trifluoroethyl.

Moreover, A denotes preferably CH_2OCH_3 , $\text{CH}_2\text{CH}_2\text{OH}$ or $\text{CH}_2\text{CH}_2\text{OCH}_3$.

5 Cyc denotes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl, preferably unsubstituted or monosubstituted by OH, Hal or A.

A' denotes alkyl, this is unbranched (linear) or branched, and has 1, 2, 3, 4, 5 or 6 C atoms. A preferably denotes methyl, furthermore ethyl, propyl, iso-
 10 propyl, butyl, isobutyl, sec-butyl or tert-butyl, furthermore also pentyl, 1-, 2- or 3-methylbutyl, 1,1-, 1,2- or 2,2-dimethylpropyl, 1-ethylpropyl, hexyl, 1-, 2-, 3- or 4-methylpentyl, 1,1-, 1,2-, 1,3-, 2,2-, 2,3- or 3,3-dimethylbutyl, 1- or 2-ethylbutyl, 1-ethyl-1-methylpropyl, 1-ethyl-2-methylpropyl, 1,1,2- or 1,2,2-tri-
 15 methylpropyl, furthermore preferably, for example, trifluoromethyl.

R^2 preferably denotes H.

R^{21} preferably denotes A or $[\text{C}(\text{R}^3)_2]_n\text{Cyc}$.

20 R^3 preferably denotes H, methyl, ethyl, propyl, isopropyl, butyl, pentyl or hexyl, particularly preferably H or methyl.

R^4 preferably denotes H, F, Cl, OA' or A' .

R^5 preferably denotes F or Cl.

25 Ar denotes preferably o-, m- or p-tolyl, o-, m- or p-ethylphenyl, o-, m- or p-propylphenyl, o-, m- or p-isopropylphenyl, o-, m- or p-tert-butylphenyl, o-, m- or p-hydroxyphenyl, o-, m- or p-nitrophenyl, o-, m- or p-aminophenyl, o-, m- or p-(N-methylamino)phenyl, o-, m- or p-(N-methylaminocarbonyl)phenyl, o-, m-
 30 or p-methoxyphenyl, o-, m- or p-ethoxyphenyl, o-, m- or p-ethoxycarbonylphenyl, o-, m- or p-(N,N-dimethylamino)phenyl, o-, m- or p-(N,N-dimethylaminocarbonyl)phenyl, o-, m- or p-(N-ethylamino)phenyl, o-, m- or p-(N,N-diethylamino)phenyl, o-, m- or p-fluorophenyl, o-, m- or p-bromophenyl, o-, m- or p-chlorophenyl, o-, m- or p-(methylsulfonamido)phenyl, o-, m- or p-(methylsulfonyl)phenyl, o-, m- or p-cyanophenyl, o-, m- or p-carboxyphenyl, o-, m- or
 35 p-methoxycarbonylphenyl, o-, m- or p-acetylphenyl, o-, m- or p-amino-

sulfonylphenyl, o-, m- or p-[2-(morpholin-4-yl)ethoxy]phenyl, o-, m- or p-[3-(N,N-diethylamino)propoxy]phenyl, furthermore preferably 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-difluorophenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dichlorophenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dibromophenyl, 2,4- or 2,5-dinitrophenyl, 2,5- or 3,4-dimethoxyphenyl, 3-nitro-4-chlorophenyl, 3-amino-4-chloro-, 2-amino-3-chloro-, 2-amino-4-chloro-, 2-amino-5-chloro- or 2-amino-6-chlorophenyl, 2-nitro-4-N,N-dimethylamino- or 3-nitro-4-N,N-dimethylaminophenyl, 2,3-diaminophenyl, 2,3,4-, 2,3,5-, 2,3,6-, 2,4,6- or 3,4,5-trichlorophenyl, 2,4,6-trimethoxyphenyl, 2-hydroxy-3,5-dichlorophenyl, p-iodophenyl, 3,6-dichloro-4-aminophenyl, 4-fluoro-3-chlorophenyl, 2-fluoro-4-bromophenyl, 2,5-difluoro-4-bromophenyl, 3-bromo-6-methoxyphenyl, 3-chloro-6-methoxyphenyl, 3-chloro-4-acetamidophenyl, 3-fluoro-4-methoxyphenyl, 3-amino-6-methylphenyl, 3-chloro-4-acetamidophenyl or 2,5-dimethyl-4-chlorophenyl.

Ar furthermore preferably denotes phenyl, which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by $\text{O}[\text{C}(\text{R}^3)_2]_n\text{Het}^1$, Ar^1 , A, CN and/or $[\text{C}(\text{R}^3)_2]_p\text{OR}^3$.

Ar^1 preferably denotes phenyl or naphthyl.

Irrespective of further substitutions, Het denotes, for example, 2- or 3-furyl, 2- or 3-thienyl, 1-, 2- or 3-pyrrolyl, 1-, 2, 4- or 5-imidazolyl, 1-, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 2-, 3- or 4-pyridyl, 2-, 4-, 5- or 6-pyrimidinyl, furthermore preferably 1,2,3-triazol-1-, -4- or -5-yl, 1,2,4-triazol-1-, -3- or -5-yl, 1- or 5-tetrazolyl, 1,2,3-oxadiazol-4- or -5-yl, 1,2,4-oxadiazol-3- or -5-yl, 1,3,4-thiadiazol-2- or -5-yl, 1,2,4-thiadiazol-3- or -5-yl, 1,2,3-thiadiazol-4- or -5-yl, 3- or 4-pyridazinyl, pyrazinyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 4- or 5-isoindolyl, indazolyl, 1-, 2-, 4- or 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzopyrazolyl, 2-, 4-, 5-, 6- or 7-benzoxazolyl, 3-, 4-, 5-, 6- or 7-benzisoxazolyl, 2-, 4-, 5-, 6- or 7-benzothiazolyl, 2-, 4-, 5-, 6- or 7-benzisothiazolyl, 4-, 5-, 6- or 7-benz-2,1,3-oxadiazolyl, 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolyl, 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl, 3-, 4-, 5-, 6-, 7- or 8-cinnolyl, 2-, 4-, 5-, 6-, 7- or 8-quinazolinyl, 5- or

6-quinoxaliny, 2-, 3-, 5-, 6-, 7- or 8-2H-benzo-1,4-oxaziny, further preferably 1,3-benzodioxol-5-yl, 1,4-benzodioxan-6-yl, 2,1,3-benzothiadiazol-4-, -5-yl or 2,1,3-benzoxadiazol-5-yl, azabicyclo[3.2.1]octyl or dibenzofuranyl.

The heterocyclic radicals may also be partially or fully hydrogenated.

5 Irrespective of further substitutions, Het can thus also denote, for example, 2,3-dihydro-2-, -3-, -4- or -5-furyl, 2,5-dihydro-2-, -3-, -4- or 5-furyl, tetrahydro-2- or -3-furyl, 1,3-dioxolan-4-yl, tetrahydro-2- or -3-thienyl, 2,3-dihydro-1-, -2-, -3-, -4- or -5-pyrrolyl, 2,5-dihydro-1-, -2-, -3-, -4- or -5-pyrrolyl, 1-, 2- or 10 3-pyrrolidinyl, tetrahydro-1-, -2- or -4-imidazolyl, 2,3-dihydro-1-, -2-, -3-, -4- or -5-pyrazolyl, tetrahydro-1-, -3- or -4-pyrazolyl, 1,4-dihydro-1-, -2-, -3- or -4-pyridyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5- or -6-pyridyl, 1-, 2-, 3- or 4-piperidinyl, 2-, 3- or 4-morpholinyl, tetrahydro-2-, -3- or -4-pyranyl, 1,4-dioxanyl, 1,3-dioxan-2-, -4- or -5-yl, hexahydro-1-, -3- or -4-pyridazinyl, 15 hexahydro-1-, -2-, -4- or -5-pyrimidinyl, 1-, 2- or 3-piperazinyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5-, -6-, -7- or -8-quinolyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5-, -6-, -7- or -8-isoquinolyl, 2-, 3-, 5-, 6-, 7- or 8- 3,4-dihydro-2H-benzo-1,4-oxaziny, furthermore preferably 2,3-methylenedioxyphenyl, 3,4-methylenedioxyphenyl, 2,3-ethylenedioxyphenyl, 3,4-ethylenedioxyphenyl, 20 3,4-(difluoromethylenedioxy)phenyl, 2,3-dihydrobenzofuran-5- or 6-yl, 2,3-(2-oxomethylenedioxy)phenyl or also 3,4-dihydro-2H-1,5-benzodioxepin-6- or -7-yl, furthermore preferably 2,3-dihydrobenzofuranyl, 2,3-dihydro-2-oxofuranyl, 25 3,4-dihydro-2-oxo-1H-quinazolinyl, 2,3-dihydrobenzoxazolyl, 2-oxo-2,3-dihydrobenzoxazolyl, 2,3-dihydrobenzimidazolyl, 1,3-dihydroindole, 2-oxo-1,3-dihydroindole or 2-oxo-2,3-dihydrobenzimidazolyl.

30 Het preferably denotes a mono- or bicyclic aromatic heterocycle having 1 to 4 N, O and/or S atoms, which is unsubstituted or mono- or disubstituted by Hal, A, $[C(R^3)_2]_nOA'$, $S(O)_nA$, CN, $SO_2N(R^3)_2$ and/or $COHet^1$.

Het furthermore preferably denotes furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, triazolyl, 35 tetrazolyl, oxadiazolyl, thiadiazolyl, pyridazinyl, pyrazinyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, benzotriazolyl, indolyl, benzo-1,3-dioxolyl,

benzodioxanyl, benzothiadiazolyl, indazolyl, benzofuranyl, quinolyl, isoquinolyl, oxazolo[5,4-b]pyridyl, imidazo[1,2-a]pyridinyl or oxazolo[5,4-c]pyridyl, each of which is unsubstituted or mono- or disubstituted by Hal, A, $[C(R^3)_2]_nOA'$, $S(O)_nA$, CN, $SO_2N(R^3)_2$ and/or COHet¹.

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Irrespective of further substitutions, Het¹ denotes, for example, 2- or 3-furyl, 2- or 3-thienyl, 1-, 2- or 3-pyrrolyl, 1-, 2, 4- or 5-imidazolyl, 1-, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 2-, 3- or 4-pyridyl, 2-, 4-, 5- or 6-pyrimidinyl, furthermore preferably 1,2,3-triazol-1-, -4- or -5-yl, 1,2,4-triazol-1-, -3- or 5-yl, 1- or 5-tetrazolyl, 1,2,3-oxadiazol-4- or -5-yl, 1,2,4-oxadiazol-3- or -5-yl, 1,3,4-thiadiazol-2- or -5-yl, 1,2,4-thiadiazol-3- or -5-yl, 1,2,3-thiadiazol-4- or -5-yl, 3- or 4-pyridazinyl, pyrazinyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 4- or 5-isoindolyl, indazolyl, 1-, 2-, 4- or 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzopyrazolyl, 2-, 4-, 5-, 6- or 7-benzoxazolyl, 3-, 4-, 5-, 6- or 7-benzisoxazolyl, 2-, 4-, 5-, 6- or 7-benzothiazolyl, 2-, 4-, 5-, 6- or 7-benzisothiazolyl, 4-, 5-, 6- or 7-benz-2,1,3-oxadiazolyl, 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolyl, 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl, 3-, 4-, 5-, 6-, 7- or 8-cinnolinyl, 2-, 4-, 5-, 6-, 7- or 8-quinazolinyl, 5- or 6-quinoxaliny, 2-, 3-, 5-, 6-, 7- or 8-2H-benzo-1,4-oxazinyl, further preferably 1,3-benzodioxol-5-yl, 1,4-benzodioxan-6-yl, 2,1,3-benzothiadiazol-4-, -5-yl or 2,1,3-benzoxadiazol-5-yl, azabicyclo[3.2.1]octyl or dibenzofuranyl.

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The heterocyclic radicals may also be partially or fully hydrogenated.

Irrespective of further substitutions, Het can thus also denote, for example, 2,3-dihydro-2-, -3-, -4- or -5-furyl, 2,5-dihydro-2-, -3-, -4- or 5-furyl, tetrahydro-2- or -3-furyl, 1,3-dioxolan-4-yl, tetrahydro-2- or -3-thienyl, 2,3-dihydro-1-, -2-, -3-, -4- or -5-pyrrolyl, 2,5-dihydro-1-, -2-, -3-, -4- or -5-pyrrolyl, 1-, 2- or 3-pyrrolidinyl, tetrahydro-1-, -2- or -4-imidazolyl, 2,3-dihydro-1-, -2-, -3-, -4- or -5-pyrazolyl, tetrahydro-1-, -3- or -4-pyrazolyl, 1,4-dihydro-1-, -2-, -3- or -4-pyridyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5- or -6-pyridyl, 1-, 2-, 3- or 4-piperidinyl, 2-, 3- or 4-morpholinyl, tetrahydro-2-, -3- or -4-pyranyl, 1,4-dioxanyl, 1,3-dioxan-2-, -4- or -5-yl, hexahydro-1-, -3- or -4-pyridazinyl, hexahydro-1-, -2-, -4- or -5-pyrimidinyl, 1-, 2- or 3-piperazinyl, 1,2,3,4-

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5 tetrahydro-1-, -2-, -3-, -4-, -5-, -6-, -7- or -8-quinolyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5-, -6-, -7- or -8-isoquinolyl, 2-, 3-, 5-, 6-, 7- or 8- 3,4-dihydro-2H-benzo-1,4-oxazinyl, furthermore preferably 2,3-methylenedioxyphenyl, 3,4-methylenedioxyphenyl, 2,3-ethylenedioxyphenyl, 3,4-ethylenedioxyphenyl,
10 3,4-(difluoromethylenedioxy)phenyl, 2,3-dihydrobenzofuran-5- or 6-yl, 2,3-(2-oxomethylenedioxy)phenyl or also 3,4-dihydro-2H-1,5-benzodioxepin-6- or -7-yl, furthermore preferably 2,3-dihydrobenzofuranyl, 2,3-dihydro-2-oxofuranyl, 3,4-dihydro-2-oxo-1*H*-quinazolinyl, 2,3-dihydrobenzoxazolyl, 2-oxo-2,3-dihydrobenzoxazolyl, 2,3-dihydrobenzimidazolyl, 1,3-dihydroindole, 2-oxo-1,3-dihydroindole or 2-oxo-2,3-dihydrobenzimidazolyl.

15 Het¹ preferably denotes a monocyclic saturated heterocycle having 1 to 4 N, O and/or S atoms, which is unsubstituted or mono- or disubstituted by A.
Het¹ furthermore preferably denotes pyrrolidinyl, azetidyl, oxetanyl, tetrahydroimidazolyl, tetrahydropyrazolyl, tetrahydrofuranyl, piperidinyl, piperazinyl, morpholinyl, hexahydropyridazinyl, hexahydropyrimidinyl, [1,3]dioxolanyl or tetrahydropyranyl, each of which is unsubstituted or mono- or disubstituted by
20 A.

Hal preferably denotes F, Cl or Br, but also I, particularly preferably F or Cl.

25 Throughout the invention, all radicals which occur more than once may be identical or different, i.e. are independent of one another.

The compounds of the formula I may have one or more chiral centres and can therefore occur in various stereoisomeric forms. The formula I encompasses
30 all these forms.

Accordingly, the invention relates, in particular, to the compounds of the formula I in which at least one of the said radicals has one of the preferred meanings indicated above. Some preferred groups of compounds may be
35 expressed by the following sub-formulae Ia to Ik, which conform to the formula

I and in which the radicals not designated in greater detail have the meaning indicated for the formula I, but in which

- 5 in Ia X^1, X^3 denote CH,
 X^2, X^4 denote N;
- in Ib X^1, X^2, X^3, X^4 denote CH,
- 10 in Ic X^1, X^3, X^4 denote CH,
 X^2 denotes N;
- in Id X^1, X^2, X^3 denote CH,
15 X^4 denotes N;
- in Ie X^1, X^2 denote CH,
 X^3, X^4 denote N;
- 20 in If X^3, X^4 denote CH,
 X^1, X^2 denote N;
- in Ig R^2 denotes H;
- 25 in Ih $R^{2'}$ denotes A or $[C(R^3)_2]_n\text{Cyc}$;
- in Ii R^4 denotes H, F, Cl, OA' or A';
- 30 in Ij R^3 denotes H or methyl;
- in Ik A denotes unbranched or branched alkyl with 1-10 C-atoms,
35 wherein one or two non-adjacent CH- and/or CH₂-groups
 may be replaced by N- and/or O-atoms and 1-7 H-atoms
 may be replaced by R⁵;

5	in II	Ar	denotes phenyl, which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by $\text{O}[\text{C}(\text{R}^3)_2]_n\text{Het}^1$, Ar^1 , A, CN and/or $[\text{C}(\text{R}^3)_2]_p\text{OR}^3$;
10	in Im	Het	denotes a mono- or bicyclic aromatic heterocycle having 1 to 4 N, O and/or S atoms, which is unsubstituted or mono- or disubstituted by Hal, A, $[\text{C}(\text{R}^3)_2]_n\text{OA}'$, $\text{S}(\text{O})_n\text{A}$, CN, $\text{SO}_2\text{N}(\text{R}^3)_2$ and/or COHet^1 ;
15	in In	Het	denotes furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, pyridazinyl, pyrazinyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, benzotriazolyl, indolyl, benzo-1,3-dioxolyl, benzodioxanyl, benzothiadiazolyl, indazolyl, benzofuranyl, quinolyl, isoquinolyl, oxazolo[5,4-b]pyridyl, imidazo[1,2-a]-pyridinyl or oxazolo[5,4-c]pyridyl, each of which is unsubstituted or mono- or disubstituted by Hal, A, $[\text{C}(\text{R}^3)_2]_n\text{OA}'$, $\text{S}(\text{O})_n\text{A}$, CN, $\text{SO}_2\text{N}(\text{R}^3)_2$ and/or COHet^1 ;
20			
25	in In	Het ¹	denotes a monocyclic saturated heterocycle having 1 to 4 N, O and/or S atoms, which is unsubstituted or mono- or disubstituted by A;
30	in Io	Het ¹	denotes pyrrolidinyl, azetidiny, oxetanyl, tetrahydroimidazolyl, tetrahydropyrazolyl, tetrahydrofuranyl, piperidinyl, piperazinyl, morpholinyl, hexahydropyridazinyl, hexahydropyrimidinyl, [1,3]dioxolanyl or tetrahydropyranyl, each of which is unsubstituted or mono- or disubstituted by A;
35			

- in Ip R denotes Ar, Het, $-C\equiv C-Ar$ or $-C\equiv C-Het$,,
W denotes $NR^2R^{2'}$ or Het^1 ,
5 R¹ denotes A, $[C(R^3)_2]_nAr^1$ or $[C(R^3)_2]_nCyc$,
R², R^{2'} each, independently of one another, denote H, A or
 $[C(R^3)_2]_nCyc$,
10 R⁴ denotes H, F, Cl, OA' or A',
X¹, X², X³, X⁴ each, independently of one another, denote CH or N,
A denotes unbranched or branched alkyl with 1-10 C-atoms,
wherein one or two non-adjacent CH- and/or CH₂-groups may
15 be replaced by N- and/or O-atoms and 1-7 H-atoms may be
replaced by R⁵,
Cyc denotes cycloalkyl with 3-7 C-atoms, which is unsubstituted or
monosubstituted by OH or A,
20 A' denotes unbranched or branched alkyl with 1-6 C-atoms,
wherein 1-5 H-atoms may be replaced by F,
R⁵ denotes F, Cl or OH,
Ar denotes phenyl, which is unsubstituted or mono-, di-, tri-, tetra- or
25 pentasubstituted by $O[C(R^3)_2]_nHet^1$, Ar^1 , A, CN and/or
 $[C(R^3)_2]_pOR^3$,
Ar¹ denotes phenyl or naphthyl,
R³ denotes H or unbranched or branched alkyl with 1-6 C-atoms,
30 Het denotes furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl,
isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, triazolyl,
tetrazolyl, oxadiazolyl, thiadiazolyl, pyridazinyl, pyrazinyl,
benzoxazolyl, benzothiazolyl, benzimidazolyl, benzotriazolyl,
35 indolyl, benzo-1,3-dioxolyl, benzodioxanyl, benzothiadiazolyl,
indazolyl, benzofuranyl, quinolyl, isoquinolyl, oxazolo[5,4-b]-

pyridyl, imidazo[1,2-a]pyridinyl or oxazolo[5,4-c]pyridyl, each of which is unsubstituted or mono- or disubstituted by Hal, A, $[C(R^3)_2]_nOA'$, $S(O)_nA$, CN, $SO_2N(R^3)_2$ and/or COHet¹,

5 Het¹ denotes pyrrolidinyl, azetidiny, oxetanyl, tetrahydroimidazolyl, tetrahydropyrazolyl, tetrahydrofuranyl, piperidinyl, piperazinyl, morpholinyl, hexahydropyridazinyl, hexahydropyrimidinyl, [1,3]dioxolanyl or tetrahydropyranyl, each of which is unsubstituted or mono- or disubstituted by A,

10 Hal denotes F, Cl, Br or I,

n denotes 0, 1 or 2,

p denotes 0, 1, 2, 3 or 4,

15 q 0, 1, 2 or 3,

with the proviso that only one or two of X¹, X², X³, X⁴ denote N, and pharmaceutically acceptable salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios.

20

The compounds of the formula I and also the starting materials for their preparation are, in addition, prepared by methods known per se, as described in the literature (for example in the standard works, such as Houben-Weyl, Methoden der organischen Chemie [Methods of Organic Chemistry], Georg-Thieme-Verlag, Stuttgart), to be precise under reaction conditions which are known and suitable for the said reactions. Use can also be made here of variants known per se which are not mentioned here in greater detail.

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The starting compounds of the formulae II and III are generally known. If they are novel, however, they can be prepared by methods known per se.

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Compounds of the formula I can preferably be obtained by reacting a compound of the formula II with a compound of the formula III.

5 In the compounds of the formula III, L preferably denotes Cl, Br, I or a free or reactively modified OH group, such as, for example, an activated ester, an imidazolidine or alkylsulfonyloxy having 1-6 C atoms (preferably methylsulfonyloxy or trifluoromethylsulfonyloxy) or arylsulfonyloxy having 6-10 C atoms (preferably phenyl- or p-tolylsulfonyloxy).

10 The reaction is generally carried out in the presence of an acid-binding agent, preferably an organic base, such as DIPEA, triethylamine, dimethylaniline, pyridine or quinoline.

The addition of an alkali or alkaline earth metal hydroxide, carbonate or bicarbonate or another salt of a weak acid of the alkali or alkaline earth metals, preferably of potassium, sodium, calcium or caesium, may also be favourable.

15 Depending on the conditions used, the reaction time is between a few minutes and 14 days, the reaction temperature is between about -30° and 140°, normally between -10° and 90°, in particular between about 0° and about 70°.

20 Examples of suitable inert solvents are hydrocarbons, such as hexane, petroleum ether, benzene, toluene or xylene; chlorinated hydrocarbons, such as trichloroethylene, 1,2-dichloroethane, carbon tetrachloride, chloroform or dichloromethane; alcohols, such as methanol, ethanol, isopropanol, n-propanol, n-butanol or tert-butanol; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran (THF) or dioxane; glycol ethers, such as ethylene glycol monomethyl or monoethyl ether, ethylene glycol dimethyl ether (diglyme); ketones, such as acetone or butanone; amides, such as acetamide, dimethylacetamide or dimethylformamide (DMF); nitriles, such as acetonitrile; sulfoxides, such as dimethyl sulfoxide (DMSO); carbon disulfide; carboxylic acids, such as formic acid or acetic acid; nitro compounds, such as nitromethane or nitrobenzene; esters, such as ethyl acetate, or mixtures of the said solvents.

35 Particular preference is given to acetonitrile, dichloromethane and/or DMF.

5

Pharmaceutical salts and other forms

10 The said compounds according to the invention can be used in their final non-salt form. On the other hand, the present invention also encompasses the use of these compounds in the form of their pharmaceutically acceptable salts, which can be derived from various organic and inorganic acids and bases by procedures known in the art. Pharmaceutically acceptable salt forms of the compounds of the formula I are for the most part prepared by conventional methods. If the compound of the formula I contains a carboxyl group, one of its suitable salts can be formed by reacting the compound with a suitable base to give the corresponding base-addition salt. Such bases are, for example, alkali metal hydroxides, including potassium hydroxide, sodium hydroxide and lithium hydroxide; alkaline earth metal hydroxides, such as barium hydroxide and calcium hydroxide; alkali metal alkoxides, for example potassium ethoxide and sodium propoxide; and various organic bases, such as piperidine, diethanolamine and N-methylglutamine. The aluminium salts of the compounds of the formula I are likewise included. In the case of certain compounds of the formula I, acid-addition salts can be formed by treating these compounds with pharmaceutically acceptable organic and inorganic acids, for example hydrogen halides, such as hydrogen chloride, hydrogen bromide or hydrogen iodide, other mineral acids and corresponding salts thereof, such as sulfate, nitrate or phosphate and the like, and alkyl- and monoarylsulfonates, such as ethanesulfonate, toluenesulfonate and benzenesulfonate, and other organic acids and corresponding salts thereof, such as acetate, trifluoroacetate, tartrate, maleate, succinate, citrate, benzoate, salicylate, ascorbate and the like. Accordingly, pharmaceutically acceptable acid-addition salts of the compounds of the formula I include the following:

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acetate, adipate, alginate, arginate, aspartate, benzoate, benzenesulfonate (besylate), bisulfate, bisulfite, bromide, butyrate, camphorate, camphor-sulfonate, caprylate, chloride, chlorobenzoate, citrate, cyclopentane-propionate, digluconate, dihydrogenphosphate, dinitrobenzoate, dodecyl-sulfate, ethanesulfonate, fumarate, formate, galacterate (from mucic acid), galacturonate, glucoheptanoate, gluconate, glutamate, glycerophosphate, hemisuccinate, hemisulfate, heptanoate, hexanoate, hippurate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, iodide, isethionate, iso-buturate, lactate, lactobionate, malate, maleate, malonate, mandelate, metaphosphate, methanesulfonate, methylbenzoate, monohydrogenphosphate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, oleate, palmoate, pectinate, persulfate, phenylacetate, 3-phenylpropionate, phosphate, phosphonate, phthalate, but this does not represent a restriction.

Furthermore, the base salts of the compounds according to the invention include aluminium, ammonium, calcium, copper, iron(III), iron(II), lithium, magnesium, manganese(III), manganese(II), potassium, sodium and zinc salts, but this is not intended to represent a restriction. Of the above-mentioned salts, preference is given to ammonium; the alkali metal salts sodium and potassium, and the alkaline earth metal salts calcium and magnesium. Salts of the compounds of the formula I which are derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary and tertiary amines, substituted amines, also including naturally occurring substituted amines, cyclic amines, and basic ion exchanger resins, for example arginine, betaine, caffeine, chloroprocaine, choline, N,N'-dibenzylethylenediamine (benzathine), dicyclohexylamine, diethanolamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lidocaine, lysine, meglumine, N-methyl-D-glucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethanolamine, triethyl-

amine, trimethylamine, tripropylamine and tris(hydroxymethyl)methylamine (tromethamine), but this is not intended to represent a restriction.

5 Compounds of the present invention which contain basic nitrogen-containing groups can be quaternised using agents such as (C₁-C₄)alkyl halides, for example methyl, ethyl, isopropyl and tert-butyl chloride, bromide and iodide; di(C₁-C₄)alkyl sulfates, for example dimethyl, diethyl and diamyl sulfate; (C₁₀-C₁₈)alkyl halides, for example decyl, dodecyl, lauryl, myristyl and stearyl
10 chloride, bromide and iodide; and aryl(C₁-C₄)alkyl halides, for example benzyl chloride and phenethyl bromide. Both water- and oil-soluble compounds according to the invention can be prepared using such salts.

15 The above-mentioned pharmaceutical salts which are preferred include acetate, trifluoroacetate, besylate, citrate, fumarate, gluconate, hemisuccinate, hippurate, hydrochloride, hydrobromide, isethionate, mandelate, meglumine, nitrate, oleate, phosphonate, pivalate, sodium phosphate, stearate, sulfate, sulfosalicylate, tartrate, thiomalate, tosylate and tromethamine, but this is not
20 intended to represent a restriction.

Particular preference is given to hydrochloride, dihydrochloride, hydrobromide, maleate, mesylate, phosphate, sulfate and succinate.

25 The acid-addition salts of basic compounds of the formula I are prepared by bringing the free base form into contact with a sufficient amount of the desired acid, causing the formation of the salt in a conventional manner. The free
30 base can be regenerated by bringing the salt form into contact with a base and isolating the free base in a conventional manner. The free base forms differ in a certain respect from the corresponding salt forms thereof with respect to certain physical properties, such as solubility in polar solvents; for the purposes of the invention, however, the salts otherwise correspond to the
35 respective free base forms thereof.

As mentioned, the pharmaceutically acceptable base-addition salts of the compounds of the formula I are formed with metals or amines, such as alkali metals and alkaline earth metals or organic amines. Preferred metals are sodium, potassium, magnesium and calcium. Preferred organic amines are
5 N,N'-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, ethylenediamine, N-methyl-D-glucamine and procaine.

The base-addition salts of acidic compounds according to the invention are
10 prepared by bringing the free acid form into contact with a sufficient amount of the desired base, causing the formation of the salt in a conventional manner. The free acid can be regenerated by bringing the salt form into contact with an acid and isolating the free acid in a conventional manner. The free acid forms
15 differ in a certain respect from the corresponding salt forms thereof with respect to certain physical properties, such as solubility in polar solvents; for the purposes of the invention, however, the salts otherwise correspond to the respective free acid forms thereof.

20 If a compound according to the invention contains more than one group which is capable of forming pharmaceutically acceptable salts of this type, the invention also encompasses multiple salts. Typical multiple salt forms include, for example, bitartrate, diacetate, difumarate, dimeglumine, diphosphate,
25 disodium and trihydrochloride, but this is not intended to represent a restriction.

With regard to that stated above, it can be seen that the expression "phar-
30 maceutically acceptable salt" in the present connection is taken to mean an active ingredient which comprises a compound of the formula I in the form of one of its salts, in particular if this salt form imparts improved pharmacokinetic properties on the active ingredient compared with the free form of the active ingredient or any other salt form of the active ingredient used earlier. The
35 pharmaceutically acceptable salt form of the active ingredient can also provide this active ingredient for the first time with a desired pharmacokinetic property

which it did not have earlier and can even have a positive influence on the pharmacodynamics of this active ingredient with respect to its therapeutic efficacy in the body.

5

Isotopes

There is furthermore intended that a compound of the formula I includes isotope-labelled forms thereof. An isotope-labelled form of a compound of the formula I is identical to this compound apart from the fact that one or more
10 atoms of the compound have been replaced by an atom or atoms having an atomic mass or mass number which differs from the atomic mass or mass number of the atom which usually occurs naturally. Exam-ples of isotopes which are readily commercially available and which can be incorporated into a
15 compound of the formula I by well-known methods include isotopes of hydrogen, carbon, nitrogen, oxygen, phos-phorus, fluo-rine and chlorine, for example ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F and ^{36}Cl , respectively. A compound of the formula I, a prodrug, thereof or a pharmaceutically acceptable salt of either which contains one or more of the
20 above-mentioned isotopes and/or other iso-topes of other atoms is intended to be part of the present invention. An isotope-labelled compound of the formula I can be used in a number of beneficial ways. For example, an isotope-labelled compound of the formula I into which, for example, a radioisotope, such as ^3H or ^{14}C , has been incorporated is suitable for medicament and/or
25 substrate tissue distribution assays. These radioisotopes, i.e. tritium (^3H) and carbon-14 (^{14}C), are particularly preferred owing to simple preparation and excellent detectability. Incor-po-ra-tion of heavier isotopes, for example deuterium (^2H), into a compound of the formula I has therapeutic advantages owing to the higher metabolic stability of this isotope-labelled compound.
30 Higher metabolic stability translates directly into an increased in vivo half-life or lower dosages, which under most circumstances would represent a preferred embodi-ment of the present invention. An isotope-labelled
35 compound of the formula I can usually be prepared by carrying out the procedures dis-closed in the synthesis schemes and the related description, in

the example part and in the preparation part in the present text, replacing a non-isotope-labelled reactant by a readily available isotope-labelled reactant.

5 Deuterium (^2H) can also be incorporated into a compound of the formula I for the purpose in order to manipulate the oxidative metabolism of the compound by way of the primary kinetic isotope effect. The primary kinetic isotope effect is a change of the rate for a chemical reaction that results from exchange of isotopic nuclei, which in turn is caused by the change in ground state energies
10 necessary for covalent bond formation after this isotopic exchange. Exchange of a heavier isotope usually results in a lowering of the ground state energy for a chemical bond and thus cause a reduction in the rate in rate-limiting bond breakage. If the bond breakage occurs in or in the vicinity of a saddle-point
15 region along the coordinate of a multi-product reaction, the product distribution ratios can be altered substantially. For explanation: if deuterium is bonded to a carbon atom at a non-exchangeable position, rate differences of $k_M/k_D = 2-7$ are typical. If this rate difference is successfully applied to a compound of the formula I that is susceptible to oxidation, the profile of this compound in vivo
20 can be drastically modified and result in improved pharmacokinetic properties.

When discovering and developing therapeutic agents, the person skilled in the art attempts to optimise pharmacokinetic parameters while retaining desirable
25 in vitro properties. It is reasonable to assume that many compounds with poor pharmacokinetic profiles are susceptible to oxidative metabolism. In vitro liver microsomal assays currently available provide valuable information on the course of oxidative metabolism of this type, which in turn permits the
30 rational design of deuterated compounds of the formula I with improved stability through resistance to such oxidative metabolism. Significant improvements in the pharmacokinetic profiles of compounds of the formula I are thereby obtained, and can be expressed quantitatively in terms of
35 increases in the in vivo half-life ($t/2$), concentration at maximum therapeutic effect ($C_{\max}$), area under the dose response curve (AUC), and F; and in terms of reduced clearance, dose and materials costs.

The following is intended to illustrate the above: a compound of the formula I which has multiple potential sites of attack for oxidative metabolism, for example benzylic hydrogen atoms and hydrogen atoms bonded to a nitrogen atom, is prepared as a series of analogues in which various combinations of hydrogen atoms are replaced by deuterium atoms, so that some, most or all of these hydrogen atoms have been replaced by deuterium atoms. Half-life determinations enable favourable and accurate determination of the extent of the extent to which the improvement in resistance to oxidative metabolism has improved. In this way, it is determined that the half-life of the parent compound can be extended by up to 100% as the result of deuterium-hydrogen exchange of this type.

Deuterium-hydrogen exchange in a compound of the formula I can also be used to achieve a favourable modification of the metabolite spectrum of the starting compound in order to diminish or eliminate undesired toxic metabolites. For example, if a toxic metabolite arises through oxidative carbon-hydrogen (C-H) bond cleavage, it can reasonably be assumed that the deuterated analogue will greatly diminish or eliminate production of the unwanted metabolite, even if the particular oxidation is not a rate-determining step. Further information on the state of the art with respect to deuterium-hydrogen exchange may be found, for example in Hanzlik et al., J. Org. Chem. **55**, 3992-3997, 1990, Reider et al., J. Org. Chem. **52**, 3326-3334, 1987, Foster, Adv. Drug Res. **14**, 1-40, 1985, Gillette et al, Biochemistry **33**(10) 2927-2937, 1994, and Jarman et al. Carcinogenesis **16**(4), 683-688, 1993.

The invention furthermore relates to medicaments comprising at least one compound of the formula I and/or pharmaceutically acceptable salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios, and optionally excipients and/or adjuvants.

Pharmaceutical formulations can be administered in the form of dosage units which comprise a predetermined amount of active ingredient per dosage unit. Such a unit can comprise, for example, 0.5 mg to 1 g, preferably 1 mg to 700 mg, particularly preferably 5 mg to 100 mg, of a compound according to the invention, depending on the condition treated, the method of administration and the age, weight and condition of the patient, or pharmaceutical formulations can be administered in the form of dosage units which comprise a predetermined amount of active ingredient per dosage unit. Preferred dosage unit formulations are those which comprise a daily dose or part-dose, as indicated above, or a corresponding fraction thereof of an active ingredient. Furthermore, pharmaceutical formulations of this type can be prepared using a process which is generally known in the pharmaceutical art.

Pharmaceutical formulations can be adapted for administration via any desired suitable method, for example by oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual or transdermal), vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) methods. Such formulations can be prepared using all processes known in the pharmaceutical art by, for example, combining the active ingredient with the excipient(s) or adjuvant(s).

Pharmaceutical formulations adapted for oral administration can be administered as separate units, such as, for example, capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or foam foods; or oil-in-water liquid emulsions or water-in-oil liquid emulsions.

Thus, for example, in the case of oral administration in the form of a tablet or capsule, the active-ingredient component can be combined with an oral, non-toxic and pharmaceutically acceptable inert excipient, such as, for example, ethanol, glycerol, water and the like. Powders are prepared by comminuting

the compound to a suitable fine size and mixing it with a pharmaceutical excipient comminuted in a similar manner, such as, for example, an edible carbohydrate, such as, for example, starch or mannitol. A flavour, preservative, dispersant and dye may likewise be present.

5

Capsules are produced by preparing a powder mixture as described above and filling shaped gelatine shells therewith. Glidants and lubricants, such as, for example, highly disperse silicic acid, talc, magnesium stearate, calcium stearate or polyethylene glycol in solid form, can be added to the powder mixture before the filling operation. A disintegrant or solubiliser, such as, for example, agar-agar, calcium carbonate or sodium carbonate, may likewise be added in order to improve the availability of the medicament after the capsule has been taken.

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In addition, if desired or necessary, suitable binders, lubricants and disintegrants as well as dyes can likewise be incorporated into the mixture.

Suitable binders include starch, gelatine, natural sugars, such as, for example, glucose or beta-lactose, sweeteners made from maize, natural and synthetic rubber, such as, for example, acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. The lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. The disintegrants include, without being restricted thereto, starch, methylcellulose, agar, bentonite, xanthan gum and the like.

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The tablets are formulated by, for example, preparing a powder mixture, granulating or dry-pressing the mixture, adding a lubricant and a disintegrant and pressing the entire mixture to give tablets. A powder mixture is prepared by mixing the compound comminuted in a suitable manner with a diluent or a base, as described above, and optionally with a binder, such as, for example, carboxymethylcellulose, an alginate, gelatine or polyvinylpyrrolidone, a dissolution retardant, such as, for example, paraffin, an absorption accelerator, such as, for example, a quaternary salt, and/or an absorbant,

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such as, for example, bentonite, kaolin or dicalcium phosphate. The powder mixture can be granulated by wetting it with a binder, such as, for example, syrup, starch paste, acacia mucilage or solutions of cellulose or polymer materials and pressing it through a sieve. As an alternative to granulation, the powder mixture can be run through a tabletting machine, giving lumps of non-uniform shape, which are broken up to form granules. The granules can be lubricated by addition of stearic acid, a stearate salt, talc or mineral oil in order to prevent sticking to the tablet casting moulds. The lubricated mixture is then pressed to give tablets. The compounds according to the invention can also be combined with a free-flowing inert excipient and then pressed directly to give tablets without carrying out the granulation or dry-pressing steps. A transparent or opaque protective layer consisting of a shellac sealing layer, a layer of sugar or polymer material and a gloss layer of wax may be present. Dyes can be added to these coatings in order to be able to differentiate between different dosage units.

Oral liquids, such as, for example, solution, syrups and elixirs, can be prepared in the form of dosage units so that a given quantity comprises a pre-specified amount of the compound. Syrups can be prepared by dissolving the compound in an aqueous solution with a suitable flavour, while elixirs are prepared using a non-toxic alcoholic vehicle. Suspensions can be formulated by dispersion of the compound in a non-toxic vehicle. Solubilisers and emulsifiers, such as, for example, ethoxylated isostearyl alcohols and polyoxyethylene sorbitol ethers, preservatives, flavour additives, such as, for example, peppermint oil or natural sweeteners or saccharin, or other artificial sweeteners and the like, can likewise be added.

The dosage unit formulations for oral administration can, if desired, be encapsulated in microcapsules. The formulation can also be prepared in such a way that the release is extended or retarded, such as, for example, by coating or embedding of particulate material in polymers, wax and the like.

5 The compounds of the formula I and pharmaceutically acceptable salts, tautomers and stereoisomers thereof can also be administered in the form of liposome delivery systems, such as, for example, small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from various phospholipids, such as, for example, cholesterol, stearylamine or phosphatidylcholines.

10 The compounds of the formula I and the pharmaceutically acceptable salts, tautomers and physiologically functional derivatives thereof can also be delivered using monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds can also be coupled to soluble polymers as targeted medicament carriers. Such polymers may encompass polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmeth-
15 acrylamidophenol, polyhydroxyethylaspartamidophenol or polyethylene oxide polylysine, substituted by palmitoyl radicals. The compounds may furthermore be coupled to a class of biodegradable polymers which are suitable for achieving controlled release of a medicament, for example polylactic acid,
20 poly-epsilon-caprolactone, polyhydroxybutyric acid, polyorthoesters, polyacetals, polydihydroxypyranes, polycyanoacrylates and crosslinked or amphipathic block copolymers of hydrogels.

25 Pharmaceutical formulations adapted for transdermal administration can be administered as independent plasters for extended, close contact with the epidermis of the recipient. Thus, for example, the active ingredient can be delivered from the plaster by iontophoresis, as described in general terms in
30 Pharmaceutical Research, 3(6), 318 (1986).

Pharmaceutical compounds adapted for topical administration can be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols or oils.

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For the treatment of the eye or other external tissue, for example mouth and skin, the formulations are preferably applied as topical ointment or cream. In the case of formulation to give an ointment, the active ingredient can be

5 employed either with a paraffinic or a water-miscible cream base.
Alternatively, the active ingredient can be formulated to give a cream with an oil-in-water cream base or a water-in-oil base.

10 Pharmaceutical formulations adapted for topical application to the eye include eye drops, in which the active ingredient is dissolved or suspended in a suitable carrier, in particular an aqueous solvent.

15 Pharmaceutical formulations adapted for topical application in the mouth encompass lozenges, pastilles and mouthwashes.

Pharmaceutical formulations adapted for rectal administration can be administered in the form of suppositories or enemas.

20 Pharmaceutical formulations adapted for nasal administration in which the carrier substance is a solid comprise a coarse powder having a particle size, for example, in the range 20-500 microns, which is administered in the manner in which snuff is taken, i.e. by rapid inhalation via the nasal passages
25 from a container containing the powder held close to the nose. Suitable formulations for administration as nasal spray or nose drops with a liquid as carrier substance encompass active-ingredient solutions in water or oil.

30 Pharmaceutical formulations adapted for administration by inhalation encompass finely particulate dusts or mists, which can be generated by various types of pressurised dispensers with aerosols, nebulisers or insufflators.

35 Pharmaceutical formulations adapted for vaginal administration can be administered as pessaries, tampons, creams, gels, pastes, foams or spray formulations.

Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions comprising antioxidants, buffers, bacteriostatics and solutes, by means of which the formulation is rendered isotonic with the blood of the recipient to be treated; and aqueous and non-aqueous sterile suspensions, which may comprise suspension media and thickeners. The formulations can be administered in single-dose or multidose containers, for example sealed ampoules and vials, and stored in freeze-dried (lyophilised) state, so that only the addition of the sterile carrier liquid, for example water for injection purposes, immediately before use is necessary. Injection solutions and suspensions prepared in accordance with the recipe can be prepared from sterile powders, granules and tablets.

It goes without saying that, in addition to the above particularly mentioned constituents, the formulations may also comprise other agents usual in the art with respect to the particular type of formulation; thus, for example, formulations which are suitable for oral administration may comprise flavours.

A therapeutically effective amount of a compound of the formula I depends on a number of factors, including, for example, the age and weight of the animal, the precise condition that requires treatment, and its severity, the nature of the formulation and the method of administration, and is ultimately determined by the treating doctor or vet. However, an effective amount of a compound according to the invention is generally in the range from 0.1 to 100 mg/kg of body weight of the recipient (mammal) per day and particularly typically in the range from 1 to 10 mg/kg of body weight per day. Thus, the actual amount per day for an adult mammal weighing 70 kg is usually between 70 and 700 mg, where this amount can be administered as a single dose per day or usually in a series of part-doses (such as, for example, two, three, four, five or six) per day, so that the total daily dose is the same. An effective amount of a salt or solvate or of a physiologically functional derivative thereof can be determined as the fraction of the effective amount of the compound according to the

invention *per se*. It can be assumed that similar doses are suitable for the treatment of other conditions mentioned above.

5 A combined treatment of this type can be achieved with the aid of simultaneous, consecutive or separate dispensing of the individual components of the treatment. Combination products of this type employ the compounds according to the invention.

10 The invention furthermore relates to medicaments comprising at least one compound of the formula I and/or pharmaceutically acceptable salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios, and at least one further medicament active ingredient.

15 The invention also relates to a set (kit) consisting of separate packs of
(a) an effective amount of a compound of the formula I and/or pharmaceutically acceptable salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios,
20 and
(b) an effective amount of a further medicament active ingredient.

The set comprises suitable containers, such as boxes, individual bottles, bags
25 or ampoules. The set may, for example, comprise separate ampoules, each containing an effective amount of a compound of the formula I and/or pharmaceutically acceptable salts, solvates and stereoisomers thereof, including mixtures thereof in all ratios,
30 and an effective amount of a further medicament active ingredient in dissolved or lyophilised form.

"Treating" as used herein, means an alleviation, in whole or in part, of
35 symptoms associated with a disorder or disease, or slowing, or halting of further progression or worsening of those symptoms, or prevention or

prophylaxis of the disease or disorder in a subject at risk for developing the disease or disorder.

5 The term "effective amount" in connection with a compound of formula (I) can mean an amount capable of alleviating, in whole or in part, symptoms associated with a disorder or disease, or slowing or halting further progression or worsening of those symptoms, or preventing or providing prophylaxis for the disease or disorder in a subject having or at risk for developing a disease
10 disclosed herein, such as inflammatory conditions, immunological conditions, cancer or metabolic conditions.

In one embodiment an effective amount of a compound of formula (I) is an amount that inhibits a tankyrase in a cell, such as, for example, in vitro or in
15 vivo. In some embodiments, the effective amount of the compound of formula (I) inhibits tankyrase in a cell by 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or 99%, compared to the activity of tankyrase in an untreated cell. The effective amount of the compound of formula (I), for example in a
20 pharmaceutical composition, may be at a level that will exercise the desired effect; for example, about 0.005 mg/kg of a subject's body weight to about 10 mg/kg of a subject's body weight in unit dosage for both oral and parenteral administration.

25 **USE**

The present compounds of formula I are useful for treating or preventing cardiovascular disorders and/or conditions. Treatment with the present
30 compounds is expected to lower the cardiovascular morbidity and mortality associated with atherosclerosis due to their antidyslipidaemic as well as anti-inflammatory properties. The cardiovascular disease conditions include macro-angiopathies of various internal organs causing myocardial infarction, congestive heart failure, cerebrovascular disease and peripheral arterial
35 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-
5 angiopathies causing renal disease, retinal damage and peripheral vascular disease of the lower limbs, is expected to be delayed.

In addition the present compounds of formula I are useful for treating or preventing inflammatory and/ or neurodegenerative disorders and/or
10 conditions. Examples of such disorders or conditions are polycystic ovarian syndrome and states of inflammatory disease including neurodegenerative disorders such as mild cognitive impairment, Alzheimer's disease, Parkinson's disease and multiple sclerosis.

15 The compounds of the present invention may also be useful for decreasing sebum production in sebaceous glands of the skin following systemic or topical application. Diseases of the sebaceous gland are acne, seborrhea, sebaceoma and sebaceous carcinoma. The pathogenesis of acne involves
20 lipid (over)production by the sebaceous gland and therefore compound of the present invention may be particularly useful in the treatment of acne. Moreover, compounds of formula I may be useful as antimycobacterial agents in the treatment of mycobacterial infections, such as e.g. tuberculosis.

25 Compounds of the invention may be useful to treat conditions associated with viral infection like e.g. Hepatitis C, AIDS, Polio, Influenza, warts.

Examples of inflammatory diseases include rheumatoid arthritis, psoriasis, contact dermatitis, delayed hypersensitivity reaction and the like.

30 Also encompassed is the use of the compounds of the formula I and/or pharmaceutically acceptable salts, tautomers and stereoisomers thereof for the preparation of a medicament for the treatment or prevention of a FASN-induced disease or a FASN-induced condition in a mammal, in which to this
35 method a therapeutically effective amount of a compound according to the

invention is administered to a sick mammal in need of such treatment. The therapeutic amount varies according to the specific disease and can be determined by the person skilled in the art without undue effort.

5 The expression "FASN-induced diseases or conditions" refers to pathological conditions that depend on the activity of FASN. Diseases associated with FASN activity include cancer, multiple sclerosis, cardiovascular diseases, central nervous system injury and different forms of inflammation.

10 The present invention specifically relates to compounds of the formula I and pharmaceutically acceptable salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios,
15 for the use for the treatment of diseases in which the inhibition, regulation and/or modulation inhibition of FASN plays a role.

The present invention specifically relates to compounds of the formula I and pharmaceutically acceptable salts, tautomers and stereoisomers
20 thereof, including mixtures thereof in all ratios, for the use for the inhibition of FASN.

The present invention specifically relates to compounds of the formula I and pharmaceutically acceptable salts, tautomers and stereoisomers
25 thereof, including mixtures thereof in all ratios, for the use for the treatment of cancer, multiple sclerosis, cardiovascular diseases, central nervous system injury and different forms of inflammation.

30 The present invention specifically relates to methods for treating or preventing cancer, multiple sclerosis, cardiovascular diseases, central nervous system injury and different forms of inflammation, comprising administering to a
35 subject in need thereof an effective amount of a compound of formula I or a pharmaceutically acceptable salt, tautomer, stereoisomer or solvate thereof.

Representative cancers that compounds of formula I are useful for treating or preventing include, but are not limited to, cancer of the head, neck, eye, mouth, throat, esophagus, bronchus, larynx, pharynx, chest, bone, lung, colon, rectum, stomach, prostate, urinary bladder, uterine, cervix, breast, ovaries, testicles or other reproductive organs, skin, thyroid, blood, lymph nodes, kidney, liver, pancreas, brain, central nervous system, solid tumors and blood-borne tumors.

Moreover, representative cancers that compounds of formula I are useful for treating or preventing include cancer of brain (gliomas), glioblastomas, leukemias, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, breast, inflammatory breast cancer, Wilm's tumor, Ewing's sarcoma, Rhabdomyosarcoma, ependymoma, medulloblastoma, colon, head and neck, kidney, lung, liver, melanoma, ovarian, pancreatic, prostate, sarcoma, osteosarcoma, giant cell tumor of bone and thyroid.

Representative cardiovascular diseases that compounds of formula I are useful for treating or preventing include, but are not limited to, restenosis, atherosclerosis and its consequences such as stroke, myocardial infarction, ischemic damage to the heart, lung, gut, kidney, liver, pancreas, spleen or brain.

The present invention relates to a method of treating a proliferative, autoimmune, anti inflammatory or infectious disease disorder that comprises administering to a subject in need thereof a therapeutically effective amount of a compound of formula I.

Preferably, the present invention relates to a method wherein the disease is a cancer.

Particularly preferable, the present invention relates to a method wherein the disease is a cancer, wherein administration is simultaneous, sequential or in alternation with administration of at least one other active drug agent.

The disclosed compounds of the formula I can be administered in combination with other known therapeutic agents, including anticancer agents.

As used here, the term "anticancer agent" relates to any agent which is administered to a patient with cancer for the purposes of treating the cancer.

5 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:

10 (i) antiproliferative/antineoplastic/DNA-damaging agents and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chloroambucil, busulphan and nitrosoureas); anti-
15 metabolites (for example antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside, hydroxyurea and gemcitabine); antitumour antibiotics (for example anthra-cyclines, like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin) ; antimitotic
20 agents (for example vinca alkaloids, like vincristine, vinblastine, vindesine and vinorelbine, and taxoids, like taxol and taxotere) ; topoisomerase inhibitors (for example epipodophyllotoxins, like etoposide and teniposide, amsacrine, topotecan, irinotecan and camptothecin) and cell-differentiating
25 agents (for example all-trans-retinoic acid, 13-cis-retinoic acid and fenretinide);

(ii) cytostatic agents, such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene and iodoxifene), oestrogen receptor
30 downregulators (for example fulvestrant), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progesterones (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibi-
35 tors of 5 α -reductase, such as finasteride;

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

5 (iv) inhibitors of growth factor function, for example such inhibitors include growth factor antibodies, growth factor receptor antibodies (for example the anti-erb2 antibody trastuzumab [HerceptinTM] and the anti-erbB1 antibody cetuximab [C225]), farnesyl transferase inhibitors, tyrosine kinase inhibitors and serine/threonine kinase inhibitors, for example inhibitors of
10 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 (gefitinib, AZD1839), 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)-
15 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;

20 (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 [AvastinTM], compounds such as those disclosed in published international patent applications WO 97/22596, WO 97/30035, WO 97/32856 and WO 98/13354) and
25 compounds that work by other mechanisms (for example linomide, inhibitors of integrin $\alpha v \beta 3$ function and angiostatin);

(vi) vessel-damaging agents, such as combretastatin A4 and compounds disclosed in international patent applications WO 99/02166,
30 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;

35 (viii) gene therapy approaches, including, for example, approaches for replacement of 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 for increasing 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 for increasing the immunogenicity of patient tumour cells, such as transfection with cytokines, such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches for decreasing 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.

The medicaments from Table 1 below are preferably, but not exclusively, combined with the compounds of the formula I.

Table 1.		
Alkylating agents	Cyclophosphamide Busulfan Ifosfamide Melphalan Hexamethylmelamine Thiotepa chloroambucil Dacarbazine Carmustine	Lomustine Procarbazine Altretamine Estramustine phosphate Mechloroethamine Streptozocin Temozolomide Semustine
Platinum agents	Cisplatin Oxaliplatin Spiroplatin Carboxyphthalatoplatinum Tetraplatin Ormiplatin Iproplatin	Carboplatin ZD-0473 (AnorMED) Lobaplatin (Aetema) Satraplatin (Johnson Matthey) BBR-3464 (Hoffmann-La Roche) SM-11355 (Sumitomo) AP-5280 (Access)

5	Antimetabolites	Azacytidine Gemcitabine Capecitabine 5-fluorouracil Floxuridine 2-chlorodesoxyadenosine 6-Mercaptopurine 6-Thioguanine Cytarabine 2-fluorodesoxycytidine Methotrexate Idatrexate	Tomudex Trimetrexate Deoxycoformycin Fludarabine Pentostatin Raltitrexed Hydroxyurea Decitabine (SuperGen) Clofarabine (Bioenvision) Irofulven (MGI Pharrna) DMDC (Hoffmann-La Roche) Ethynylcytidine (Taiho)
10			
15	Topoisomerase inhibitors	Amsacrine Epirubicin Etoposide Teniposide or mitoxantrone Irinotecan (CPT-11) 7-ethyl-10-hydroxycamptothecin Topotecan Dexrazoxanet (TopoTarget) Pixantrone (Novuspharna) Rebeccamycin analogue (Exelixis) BBR-3576 (Novuspharna)	Rubitecan (SuperGen) Exatecan mesylate (Daiichi) Quinamed (ChemGenex) Gimatecan (Sigma- Tau) Diflomotecan (Beaufour-Ipsen) TAS-103 (Taiho) Elsamitrucin (Spectrum) J-107088 (Merck & Co) BNP-1350 (BioNumerik) CKD-602 (Chong Kun Dang) KW-2170 (Kyowa Hakko)
20			
25	Antitumour antibiotics	Dactinomycin (Actinomycin D) Doxorubicin (Adriamycin) Deoxyrubicin Valrubicin Daunorubicin (Daunomycin) Epirubicin Therarubicin Idarubicin Rubidazon Plicamycinp Porfiromycin Cyanomorpholinodoxo-rubicin Mitoxantron (Novantron)	Amonafide Azonafide Anthrapyrazole Oxantrazole Losoxantrone Bleomycin sulfate (Blenoxan) Bleomycinic acid Bleomycin A Bleomycin B Mitomycin C MEN-10755 (Menarini) GPX-100 (Gem Pharmaceuticals)
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Antimitotic agents	Paclitaxel Docetaxel Colchicine Vinblastine Vincristine Vinorelbine Vindesine Dolastatin 10 (NCI) Rhizoxin (Fujisawa) Mivobulin (Warner-Lambert) Cemadotin (BASF) RPR 109881A (Aventis) TXD 258 (Aventis) Epothilone B (Novartis) T 900607 (Tularik) T 138067 (Tularik) Cryptophycin 52 (Eli Lilly) Vinflunine (Fabre) Auristatin PE (Teikoku Hormone) BMS 247550 (BMS) BMS 184476 (BMS) BMS 188797 (BMS) Taxoprexin (Protarga)	SB 408075 (GlaxoSmithKline) E7010 (Abbott) PG-TXL (Cell Therapeutics) IDN 5109 (Bayer) A 105972 (Abbott) A 204197 (Abbott) LU 223651 (BASF) D 24851 (ASTA Medica) ER-86526 (Eisai) Combretastatin A4 (BMS) Isohomohalichondrin-B (PharmaMar) ZD 6126 (AstraZeneca) PEG-Paclitaxel (Enzon) AZ10992 (Asahi) IDN-5109 (Indena) AVLB (Prescient NeuroPharma) Azaepothilon B (BMS) BNP- 7787 (BioNumerik) CA-4-prodrug (OXiGENE) Dolastatin-10 (NrH) CA-4 (OXiGENE)
Aromatase inhibitors	Aminoglutethimide Letrozole Anastrozole Formestan	Exemestan Atamestan (BioMedicines) YM-511 (Yamanouchi)
Thymidylate synthase inhibitors	Pemetrexed (Eli Lilly) ZD-9331 (BTG)	Nolatrexed (Eximias) CoFactor™ (BioKeys)
DNA antagonists	Trabectedin (PharmaMar) Glufosfamide (Baxter International) Albumin + 32P (Isotope Solutions) Thymectacin (NewBiotics) Edotreotid (Novartis)	Mafosfamide (Baxter International) Apaziquone (Spectrum Pharmaceuticals) O6-benzylguanine (Paligent)

5	Farnesyl transferase inhibitors	Arglabin (NuOncology Labs) lonafarnib (Schering-Plough) BAY-43-9006 (Bayer)	Tipifarnib (Johnson & Johnson) Perillyl alcohol (DOR BioPharma)
	Pump inhibitors	CBT-1 (CBA Pharma) Tariquidar (Xenova) MS-209 (Schering AG)	Zosuquidar trihydrochloride (Eli Lilly) Biricodar dicitrate (Vertex)
10	Histone acetyl transferase inhibitors	Tacedinaline (Pfizer) SAHA (Aton Pharma) MS-275 (Schering AG)	Pivaloyloxymethyl butyrate (Titan) Depsipeptide (Fujisawa)
	Metalloproteinase inhibitors Ribonucleoside reductase inhibitors	Neovastat (Aeterna Laboratories) Marimastat (British Biotech) Gallium maltolate (Titan) Triapin (Vion)	CMT -3 (CollaGenex) BMS-275291 (Celltech) Tezacitabine (Aventis) Didox (Molecules for Health)
20	TNF-alpha agonists/antagonists	Virulizin (Lorus Therapeutics) CDC-394 (Celgene)	Revimid (Celgene)
	Endothelin-A receptor antagonists	Atrasentan (Abbot) ZD-4054 (AstraZeneca)	YM-598 (Yamanouchi)
25	Retinoic acid receptor agonists	Fenretinide (Johnson & Johnson) LGD-1550 (Ligand)	Alitretinoin (Ligand)
	Immunomodulators	Interferon Oncophage (Antigenics) GMK (Progenics) Adenocarcinoma vaccine (Biomira) CTP-37 (AVI BioPharma) JRX-2 (Immuno-Rx) PEP-005 (Peplin Biotech) Synchrovax vaccines (CTL Immuno) Melanoma vaccine (CTL Immuno) p21-RAS vaccine (Gem-Vax)	Dexosome therapy (Anosys) Pentrix (Australian Cancer Technology) JSF-154 (Tragen) Cancer vaccine (Intercell) Norelin (Biostar) BLP-25 (Biomira) MGV (Progenics) !3-Alethin (Dovetail) CLL-Thera (Vasogen)
30			
35			

5	Hormonal and antihormonal agents	Oestrogens Conjugated oestrogens Ethinylloestradiol chlorotrianisene Idenestrol Hydroxyprogesterone caproate Medroxyprogesterone Testosterone Testosterone propionate Fluoxymesterone Methyltestosterone Diethylstilbestrol Megestrol Tamoxifen Toremofin Dexamethasone	Prednisone Methylprednisolone Prednisolone Aminoglutethimide Leuprolide Goserelin Leuporelin Bicalutamide Flutamide Octreotide Nilutamide Mitotan P-04 (Novogen) 2-Methoxyoestradiol (EntreMed) Arzoxifen (Eli Lilly)
15	Photodynamic agents	Talaporfin (Light Sciences) Theralux (Theratechnologies) Motexafin-Gadolinium (Pharmacyclics)	Pd-Bacteriopheophorbid (Yeda) Lutetium-Texaphyrin (Pharmacyclics) Hypericin
20	Tyrosine kinase inhibitors	Imatinib (Novartis) Leflunomide (Sugen/Pharmacia) ZD1839 (AstraZeneca) Erlotinib (Oncogene Science) Canertinib (Pfizer) Squalamine (Genaera) SU5416 (Pharmacia) SU6668 (Pharmacia) ZD4190 (AstraZeneca) ZD6474 (AstraZeneca) Vatalanib (Novartis) PKI166 (Novartis) GW2016 (GlaxoSmith-Kline) EKB-509 (Wyeth) EKB-569 (Wyeth)	Kahalide F (PharmaMar) CEP-701 (Cephalon) CEP-751 (Cephalon) MLN518 (Millenium) PKC412 (Novartis) Phenoxodiol O Trastuzumab (Genentech) C225 (ImClone) rhu-Mab (Genentech) MDX-H210 (Medarex) 2C4 (Genentech) MDX-447 (Medarex) ABX-EGF (Abgenix) IMC-1C11 (ImClone)
35	Various agents	SR-27897 (CCK-A inhibitor, Sanofi-Synthelabo) Tocladesine (cyclic AMP agonist, Ribapharm) Alvocidib (CDK inhibitor,	BCX-1777 (PNP inhibitor, BioCryst) Ranpirnase (ribonuclease stimulant, Alfacell) Galarubicin (RNA synthe-

5	Aventis) CV-247 (COX-2 inhibitor, Ivy Medical) P54 (COX-2 inhibitor, Phytopharm) CapCell™ (CYP450 stimulant, Bavarian Nordic) GCS-IOO (gal3 antagonist, GlycoGenesys) G17DT immunogen (gas-trin inhibitor, Aphton) Efaproxiral (oxygenator, Allos Therapeutics)	sis inhibitor, Dong-A) Tirapazamine (reducing agent, SRI International) N-Acetylcysteine (reducing agent, Zambon) R-Flurbiprofen (NF-kappaB inhibitor, Encore) 3CPA (NF-kappaB inhibitor, Active Biotech) Seocalcitol (vitamin D receptor agonist, Leo) 131-I-TM-601 (DNA antagonist, TransMolecular)
10	PI-88 (heparanase inhibitor, Progen) Tesmilifen (histamine antagonist, YM BioSciences) Histamine (histamine H2 receptor agonist, Maxim) Tiazofurin (IMPDH inhibitor, Ribapharm)	Eflornithin (ODC inhibitor, ILEX Oncology) Minodronic acid (osteoclast inhibitor, Yamanouchi) Indisulam (p53 stimulant, Eisai)
15	Cilengitide (integrin antagonist, Merck KGaA) SR-31747 (IL-1 antagonist, Sanofi-Synthelabo) CCI-779 (mTOR kinase inhibitor, Wyeth) Exisulind (PDE-V inhibitor, Cell Pathways)	Aplidin (PPT inhibitor, PharmaMar) Rituximab (CD20 antibody, Genentech) Gemtuzumab (CD33 antibody, Wyeth Ayerst) PG2 (haematopoiesis promoter, Pharmagenesis)
20	CP-461 (PDE-V inhibitor, Cell Pathways) AG-2037 (GART inhibitor, Pfizer) WX-UK1 (plasminogen activator inhibitor, Willex) PBI-1402 (PMN stimulant, ProMetic LifeSciences)	Immunol™ (triclosan mouthwash, Endo) Triacetyluridine (uridine prodrug, Wellstat) SN-4071 (sarcoma agent, Signature BioScience) TransMID-107™ (immunotoxin, KS Biomedix)
25	Bortezomib (proteasome inhibitor, Millennium) SRL-172 (T-cell stimulant, SR Pharma) TLK-286 (glutathione-S transferase inhibitor, Telik) PT-100 (growth factor agonist, Point Therapeutics)	PCK-3145 (apoptosis promoter, Procyon) Doranidazole (apoptosis promoter, Pola) CHS-828 (cytotoxic agent, Leo) Trans-retinic acid (differentiator, NIH)
30	Midostaurin (PKC inhibitor,	MX6 (apoptosis promoter,
35		

5

	Novartis) Bryostatin-1 (PKC stimu- lant, GPC Biotech) CDA-II (apoptosis pro- moter, Everlife) SDX-101 (apoptosis pro- moter, Salmedix) Ceflatonin (apoptosis pro- moter, ChemGenex)	MAXIA) Apomine (apoptosis promoter, ILEX Oncology) Urocidin (apoptosis promoter, Bioniche) Ro-31-7453 (apoptosis promoter, La Roche) Brostallicin (apoptosis promoter, Pharmacia)
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The following abbreviations refer respectively to the definitions below:

15

aq (aqueous), h (hour), g (gram), L (liter), mg (milligram), MHz (Megahertz),
min. (minute), mm (millimeter), mmol (millimole), mM (millimolar), m.p.
(melting point), eq (equivalent), mL (milliliter), μ L (microliter), ACN (acetonitrile),
AcOH (acetic acid), CDCl_3 (deuterated chloroform), CD_3OD (deuterated
methanol), CH_3CN (acetonitrile), c-hex (cyclohexane), DCC (dicyclohexyl
carbodiimide), DCM (dichloromethane), DIC (diisopropyl carbodiimide), DIEA
(diisopropylethyl-amine), DMF (dimethylformamide), DMSO

20

(dimethylsulfoxide), DMSO-d_6 (deuterated dimethylsulfoxide), EDC (1-(3-
dimethyl-amino-propyl)-3-ethylcarbodiimide), ESI (Electro-spray ionization),
EtOAc (ethyl acetate), Et_2O (diethyl ether), EtOH (ethanol), HATU
(dimethylamino-([1,2,3]triazolo[4,5-b]pyridin-3-yloxy)-methylene]-dimethyl-
ammonium hexafluorophosphate), HPLC (High Performance Liquid

25

Chromatography), i-PrOH (2-propanol), K_2CO_3 (potassium carbonate), LC
(Liquid Chromatography), MeOH (methanol), MgSO_4 (magnesium sulfate), MS
(mass spectrometry), MTBE (Methyl tert-butyl ether), NaHCO_3 (sodium
bicarbonate), NaBH_4 (sodium borohydride), NMM (N-methyl morpholine),

30

NMR (Nuclear Magnetic Resonance), PyBOP (benzotriazole-1-yl-oxy-tris-
pyrrolidino-phosphonium hexafluorophosphate), RT (room temperature), Rt
(retention time), SPE (solid phase extraction), TBTU (2-(1-H-benzotriazole-1-
yl)-1,1,3,3-tetramethyluromium tetrafluoro borate), TEA (triethylamine), TFA
(trifluoroacetic acid), THF (tetrahydrofuran), TLC (Thin Layer

35

Chromatography), UV (Ultraviolet).

Description of the in vitro assays

Abbreviations:

GST = Glutathione-S-transferase

5 FRET= Fluorescence resonance energy transfer

HTRF® = (homogenous time resolved fluorescence)

HEPES = 4-(2-hydroxyethyl)-1-piperazine ethanesulfonic acid buffer

10 DTT = Dithiothreitol

BSA = bovine serum albumin

CHAPS = detergent;

15 CHAPS = 3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonate

Biochemical activity testing of human fatty acid synthase FASN

20 Fatty acid synthase FASN is a multifunctional enzyme with seven catalytic activities thereby synthesising long chain fatty acids especially palmitoyl-CoA in the presence of co-factor NADPH starting from the substrates acetyl-CoA and malonyl-CoA. The reductive synthesis is realized by the oxidation of NADPH to NADP. Since NADPH has a high fluorescence intensity quantum yield compared to NADP with excitation at 340 nm and emission at 460 nm,
25 the reaction can be monitored via the decrease in fluorescence intensity. The biochemical FASN activity testing was performed as 384 well two-time-point kinetic fluorescence intensity assay format in Greiner low volume medium binding 384-well black microtiter plates in a total assay volume of 8 µl
30 and was used for high throughput screen. In each well 3 µl 40 nM human recombinant full-length fatty acid synthase (produced in-house in SF9 cells) were dispensed in the following assay buffer: 50 mM potassium phosphate buffer pH 7.0, 0.005 % (w/v) BSA, 2 mM Glutathione, 0.02 % Tween-20. Then
35 2 µl of 200 µM NADPH in assay buffer were added, followed by the addition of the test compounds in 10 dilution concentrations starting with 30 µM (final

concentration) to get a final DMSO content of 1 % (v/v). The mixture was incubated for at least 15 min at room temperature. After the pre-incubation the enzymatic reaction was started by the addition of 2 µl substrate solution (80 µM acetyl-CoA, 240 µM malonyl-CoA). A first fluorescence intensity measurement (time point one) was performed with an Envision multimode reader (Perkin Elmer LAS Germany GmbH) at excitation wavelength 340 nm (lamp mode) and emission wavelength 460 nm. The reaction was incubated for 30 minutes at room temperature. After this the fluorescence intensity was measured again in the Envision using the same parameters as described above (second time point measurement). The data were analysed by subtracting the first time point measurement value from the second time point measurement value (after the enzymatic reaction). The differences of the emission signals were determined. These reflect directly the conversion rate of NADPH. The full value used was the inhibitor-free reaction. A pharmacological zero value was used like GSK837149A (Sigma-Aldrich) in a final concentration of 5-10 µM. The inhibitory values (IC₅₀) were determined using either the program Symyx Assay Explorer® or Condosseo® from GeneData.

Above and below, all temperatures are indicated in°C. In the following examples, "conventional work-up" means: water is added if necessary, the pH is adjusted, if necessary, to values between 2 and 10, depending on the constitution of the end product, the mixture is extracted with ethyl acetate or dichloromethane, the phases are separated, the organic phase is dried over sodium sulfate and evaporated, and the residue is purified by chromatography on silica gel and/or by crystallisation. R_f values on silica gel; eluent: ethyl acetate/methanol 9:1.

LCMS:

Method A

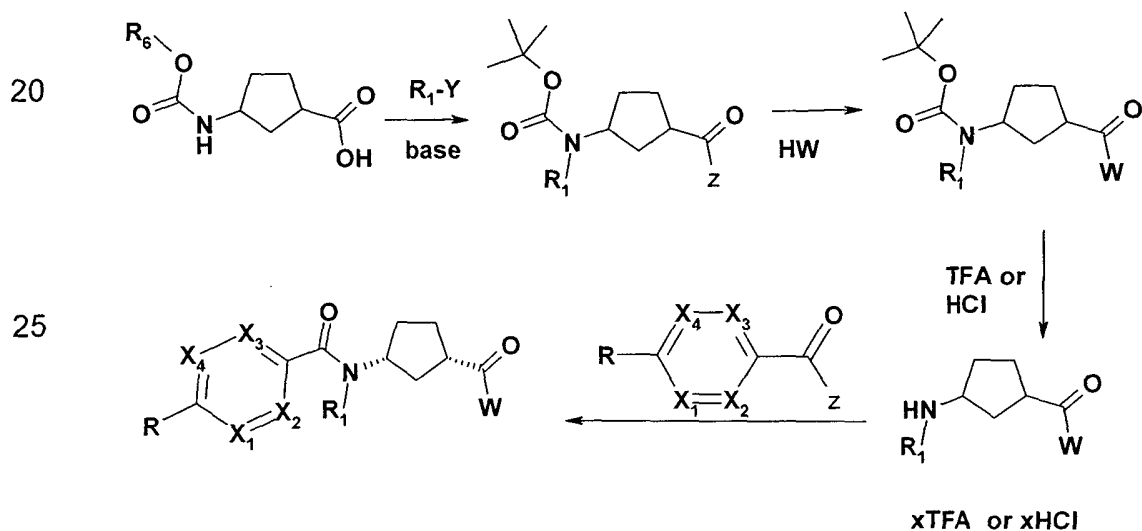
Method: A-0.1 % HCOOH in H₂O, B-0.1 % HCOOH in ACN: Flow- 2.4 mL/min. Column: Chromolith SpeedRod RP-18e (50x4.6mm)

Method B

Method: A-0.1 % TFA in H₂O, B-0.1 % TFA in ACN: Flow- 2.4 mL/min.

Column: Chromolith SpeedRod RP-18e (50x4.6mm) (50 x 4.6mm)

¹H NMR was recorded on Bruker DPX-300, DRX-400 or AVII-400 spectrometer, using residual signal of deuterated solvent as internal reference. Chemical shifts (δ) are reported in ppm relative to the residual solvent signal (δ = 2.49 ppm for ¹H NMR in DMSO-d₆). ¹H NMR data are reported as follows: chemical shift (multiplicity, coupling constants, and number of hydrogens). Multiplicity is abbreviated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad).

General Synthesis

R₆ : Methyl, tert-Butyl, Benzyl, Allyl

Y : Cl, Br, I or -OSO₂-R₇

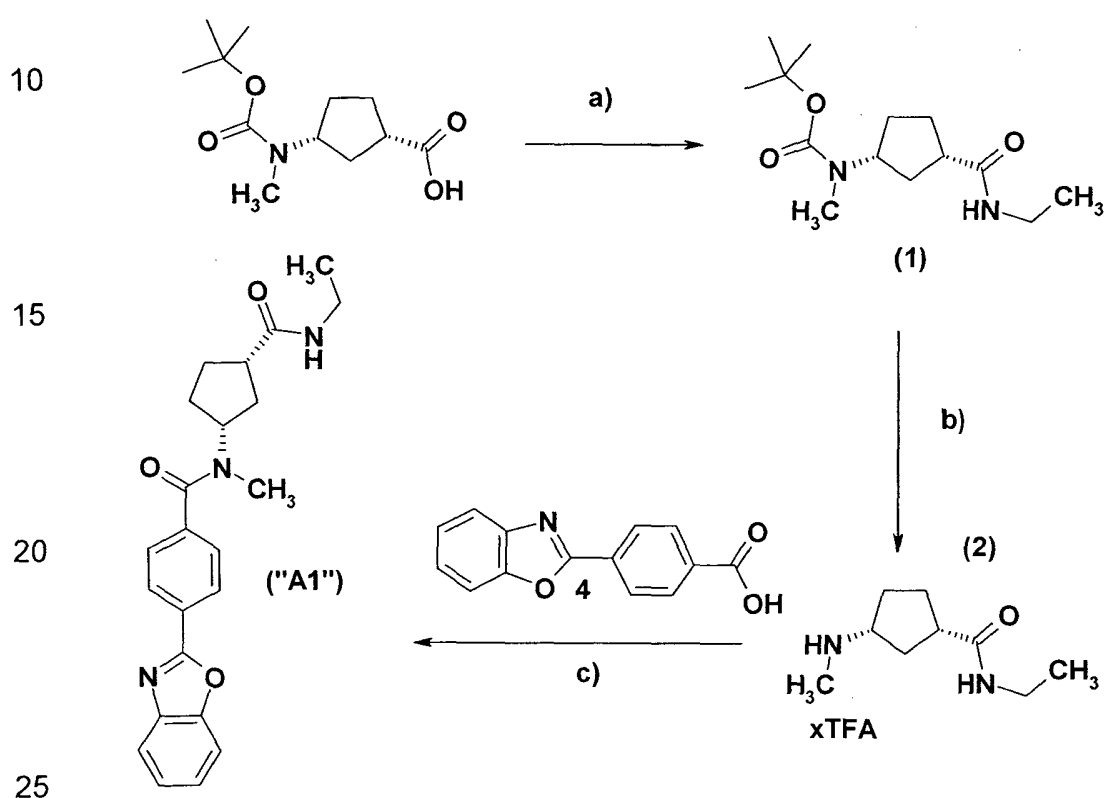
R₇ : Methyl, Trifluoromethyl, Phenyl, Toluolyl

Base : NaH, KH, LiN(i-Propyl)₂, LiN((CH₃)₃Si)₂, Na₂CO₃, K₂CO₃, Cs₂CO₃, NaOH, KOH

Z = -Cl, Br, OH or activated carboxylic acid ester -O-CO-CH₃ or -OCO-C₂H₅.

Example 1

4-(1,3-benzoxazol-2-yl)-N-[(1R,3S)-3-(ethylcarbamoyl)cyclopentyl]-N-methylbenzamide ("A1")



1.1 (1S,3R)-3-(tert-Butoxycarbonyl-methyl-amino)-cyclopentanecarboxylic acid (Roberto J. Brea Angew. Chem. Int. Ed. 2005, 44, 5710 –5713) (90 mg; 0,37 mmol), ethylamine (2.0 M solution in tetrahydrofurane) (555 µl; 1,11 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimidhydrochlorid (142 mg; 0,74 mmol) and 1-hydroxybenzotriazol hydrat (56,65 mg; 0,37 mmol) are dissolved in 5 ml N,N-dimethylformamide. 4-Methylmorpholine (0,122 ml; 1,11 mmol) is added and the mixture is stirred at r. t. for 14 h. The reaction solution is diluted with water (10 ml) and extracted 2 x with 10 ml of ethylacetate. The combined organic layer is washed 3 x with 10 ml of water

and 1 x with 10 ml of brine, dried over Na₂SO₄, filtered and evaporated to dryness to yield 100 mg (100%) tert-butyl N-[(1R,3S)-3-(ethylcarbamoyl)cyclopentyl]-N-methyl-carbamate (**1**); LC/MS : 271 (M+H).

5

1.2 To tert-butyl N-[(1R,3S)-3-(ethylcarbamoyl)cyclopentyl]-N-methyl-carbamate (**1**) (100 mg; 0,37 mmol) in 15 ml of dichloromethane is added trifluoroacetic acid (1 ml; 13 mmol). The solution is stirred for 14 h at room temperature and then reduced to dryness under vacuo to afford 105 mg (100%) (1S,3R)-N-ethyl-3-(methylamino)cyclopentanecarboxamide (**2**) as the TFA salt; LC/MS : 171 (M+H).

10

1.3 4-Benzoxazol-2-yl-benzoic acid (**4**) (Dinesh Kumar Aust. J. Chem. 2008 (61) 881 - 887) (50 mg; 0,21 mmol), (1S,3R)-N-ethyl-3-(methylamino)-cyclopentanecarboxamide trifluoroacetate (**2**) (59,42 mg; 0,21 mmol.), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride for synthesis (60,1 mg; 0,314 mmol), and 1-hydroxybenzotriazole (32 mg; 0,21 mmol) are dissolved in 3 ml of N,N-dimethylformamide and then was added 4-methylmorpholine for synthesis (91,9 µl; 0,84 mmol). The reaction mixture is stirred at r.t. for 14 h. The reaction solution is diluted with 10 ml of water and extracted 3 x with 10 ml of ethylacetate. The combined organic layers are washed 3 x with water and 1 x with brine, dried over Na₂SO₄, filtered, evaporated to dryness and the residue is purified by flash chromatography (dichloromethane:methanol 95:5) to yield 65 mg (78.1%) 4-(1,3-benzoxazol-2-yl)-N-[(1R,3S)-3-(ethylcarbamoyl)cyclopentyl]-N-methyl-benzamide ("A1") as a white solid; LC/MS : 392 (M+H); ¹H NMR (500 MHz, DMSO-d₆) δ [ppm] 8.26 (d, J = 8.3 Hz, 2H), 7.86-7.80 (m, 2H), 7.72 (br. s, 1H; NH), 7.65-7.55 (m, 2H), 7.45 (pd, J = 7.4, 1.3 Hz, 2H), 4.89, 4.00 (2x br. s, 1H, ratio=1:1.8 mixture of rotamers), 3.06 (q, J = 6.6 Hz, 2H, NCH₂), 2.91 (br. s, 3H, CH₃), 2.67, 2.49 (2x br.s, 1H, , ratio=1:1.8 mixture of rotamers), 2.20 – 1.52 (m, 6H), 1.00 (t, J = 7.1 Hz, 3H, CH₃).

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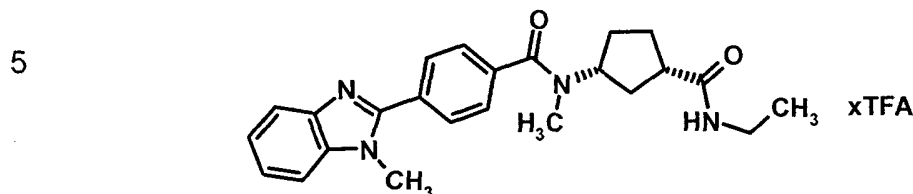
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Example 2

N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-N-methyl-4-(1-methyl-1H-benzimidazol-2-yl)-benzamide ("A2")



The compound is synthesized analogously to the method described above (example 1.3) with the amine (2) (example 1.2) and 4-(1-methyl-1H-benzimidazol-2-yl)-benzoic acid as educts; LC/MS: M+H = 405; ¹H NMR (500 MHz, DMSO-d₆) δ [ppm] 7.97 (d, J = 8.3 Hz, 2H), 7.88 (d, J = 7.6 Hz, 1H), 7.80 (d, J = 7.8 Hz, 1H), 7.73 (s, 1H; NH), 7.70 – 7.60 (m, 2H), 7.51 (dq, J = 15.0, 7.0 Hz, 2H), 4.90, 4.00 (2x br. s, 1H, ratio=1.6:1, mixture of rotamers), 4.00 (s, 3H), 3.06 (q, J = 7.0 Hz, 2H), 2.92 (s, 3H), 2.64, 2.44 (2x br. s, 1H, ratio=1.6:1 mixture of rotamers), 2.08 – 1.51 (m, 6H), 1.00 (t, J = 7.1 Hz, 3H).

Synthesis of 4-(1-methyl-1H-benzimidazol-2-yl)-benzoic acid:

0,50 g (4,1 mmol) N-methyl-1,2-phenylenediamine and (0,67 g; 4,1 mmol) methyl 4-formylbenzoate for synthesis are dissolved in 20 ml methanol dried (max. 0,005% H₂O). After addition of 1.17 ml acetic acid (glacial 100%) the mixture is stirred at r.t. for 14 h. The reaction solution is evaporated to dryness and the residue is dissolved in 10 ml of 5% NaHCO₃-solution and extracted 2x with 10 ml ethyl acetate. The combined organic layer are washed with brine, dried over Na₂SO₄, filtered and evaporated to dryness. The residue, 1,15 g, is purified by silica gel column chromatography with CombiFlash. Eluent: 100% dichlormethane to 65:35 dichlormethane:ethyl acetate to yield 367 mg (33.7%) 4-(1-methyl-1H-benzimidazol-2-yl)-benzoic acid methyl ester as a beige solid; LC/MS: M+H 267. This solid is dissolved in 15 ml tetrahydrofuran and 5 ml water. After addition of 99.02 mg lithiumhydroxid the reaction mixture is stirred 2 h at room temperature and concentrated under reduced pressure. The residue is diluted with 5 ml water, acidified (pH~3) using 1 N HCl and the

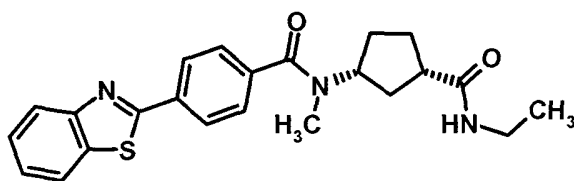
resulting precipitate is filtered with suction, washed with water and dried at 50°C in a vacuum cabinet dryer to yield 280 mg (80.5%) 4-(1-methyl-1H-benzothiazol-2-yl)-benzoic acid as a beige solid; LC/MS: M+H 253.

5

Example 3

4-benzothiazol-2-yl-N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-N-methylbenzamide ("A3")

10



15

The compound is synthesized analogously to the method described above (example 1.3) with the amine (2) (example 1.2) and 4-benzothiazol-2-ylbenzoic (Lloyd J. Nadeau, Chem. Commun., 2006, 564–565) as educts. LC/MS: M+H = 408; ¹H NMR (500 MHz, DMSO-d₆) δ [ppm] 8.17 (dd, J = 12.1, 7.9 Hz, 3H), 8.09 (d, J = 8.0 Hz, 1H), 7.73 (s, 1H; NH), 7.63 – 7.52 (m, 3H), 7.49 (t, J = 7.6 Hz, 1H), 4.88, 4.02 (2x br. s, 1H, ratio=1:2 mixture of rotamers) 3.06 (q, J = 7.0 Hz, 2H), 2.90 (s, 3H), 2.90, 2.44 (2x br.s, 1H, ratio=1:2 mixture of rotamers), 2.20 – 1.63 (m, 6H), 1.00 (t, J = 7.2 Hz, 3H).

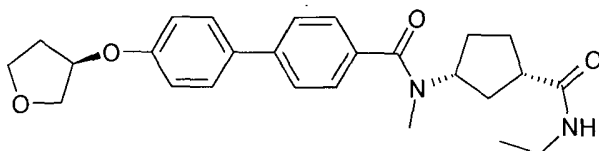
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Example 4

4'-[(R)-(tetrahydro-furan-3-yl)oxy]-biphenyl-4-carboxylic acid ((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-methyl-amide

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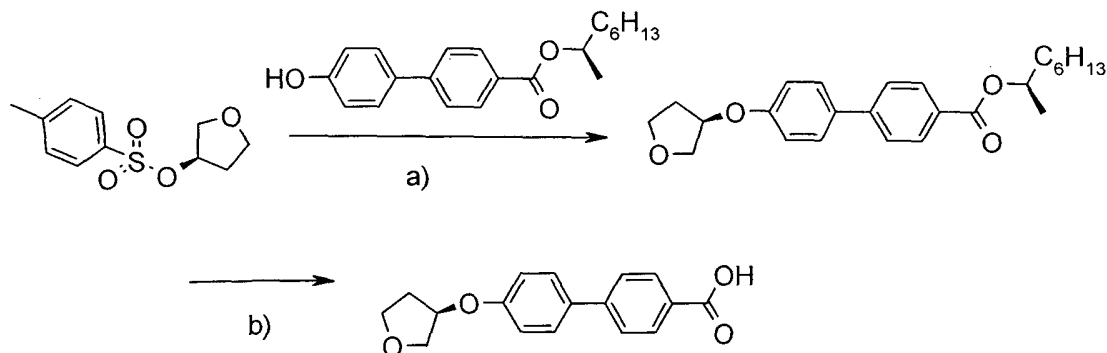


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The compound is synthesized analogously to the method described above (example 1.3) with the amine (2) (example 1.2) and 4'-[(R)-(tetrahydro-furan-3-yl)oxy]-biphenyl-4-carboxylic acid as educts.

LC/MS: $M+H = 437$; ^1H NMR (500 MHz, DMSO- d_6) δ [ppm] 7.73 (s, 1H; NH), 7.70 – 7.61 (m, 4H), 7.41 (d, $J = 7.9$ Hz, 2H), 7.02 (d, $J = 8.8$ Hz, 2H), 5.11 – 5.05 (m, 1H), 4.83, 4.12 (2x br. s, 1H, ratio=1:1.6 mixture of rotamers) 3.92 (dd, $J = 10.1, 4.6$ Hz, 1H), 3.86 (q, $J = 8.1$ Hz, 1H), 3.81 (d, $J = 10.1$ Hz, 1H), 3.77 (td, $J = 8.3, 4.6$ Hz, 1H), 3.05 (q, $J = 7.2$ Hz, 2H), 2.88 (s, 3H), 2.31 – 2.18 (m, 1H), 1.99 (dt, $J = 12.6, 5.8$ Hz, 1H), 1.95 – 1.58 (m, 6H), 1.00 (t, $J = 7.2$ Hz, 3H).

Synthesis of 4'-[(R)-(tetrahydro-furan-3-yl)oxy]-biphenyl-4-carboxylic acid



a) A mixture of 4'-hydroxy-biphenyl-4-carboxylic acid (R)-1-methyl-heptyl ester (269.5 mg; 0.825 mmol), toluene-4-sulfonic acid (R)-(tetrahydro-furan-3-yl) ester (200 mg; 0.825 mmol) and cesium carbonate (350 mg; 1.07 mmol) in of N,N-dimethylformamide (5 mL) is heated to 60 °C for 4 hours. The reaction mixture is diluted with 10 ml water and extracted 3x with 10 ml ethyl acetate. The organic layer is dried over Na_2SO_4 , filtered and the solvent removed in vacuo. The residue is crystallized with methanol, filtered with suction, washed with cold methanol and dried at 40°C under vacuo to give 300 mg (91,7%) 4'-[(R)-(tetrahydro-furan-3-yl)oxy]-biphenyl-4-carboxylic acid (R)-1-methyl-heptyl ester as white powder; LC/MS: $M+Na = 419$.

b) 4'-[(R)-(tetrahydro-furan-3-yl)oxy]-biphenyl-4-carboxylic acid (R)-1-methyl-heptyl ester (300 mg) is dissolved in 15 ml tetrahydrofuran and 3 ml water. After addition of 54.36 mg lithiumhydroxid the reaction mixture is stirred for 14 h at 70 °C and concentrated under reduced pressure. The residue is

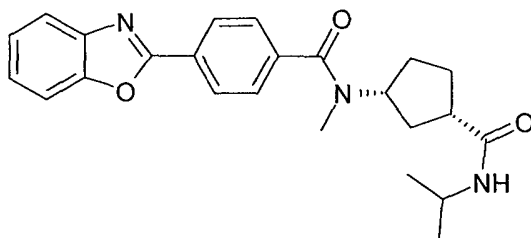
diluted with 5 ml water, acidified (pH~3) using 1 N HCl and the resulting precipitate is filtered with suction, washed with water and dried at 50°C in a vacuum cabinet dryer to yield 210 mg (97.6%) 4'-[(R)-(tetrahydro-furan-3-yl)oxy]-biphenyl-4-carboxylic acid as beige solid; LC/MS: M+H 285.

5

The following compounds are synthesized analogously to methods 1.1 to 1.3 (example 1):

10 4-benzoxazol-2-yl-N-((1R,3S)-3-isopropylcarbamoyl-cyclopentyl)-N-methylbenzamide ("A5")

15



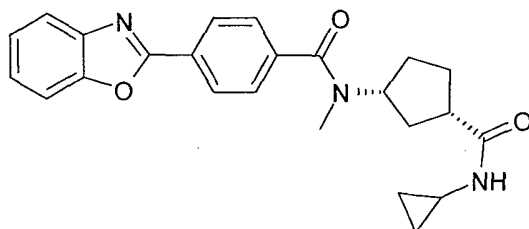
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LC/MS: M+H 406; ¹H NMR (500 MHz, DMSO-d₆) δ [ppm] 8.26 (d, J = 8.3 Hz, 2H), 7.83 (dd, J = 14.3, 7.3 Hz, 2H), 7.60 (m, 3H; 2xCH+NH), 7.53 – 7.37 (m, 2H), 4.89, 3.98 (2x br. s, 1H, ratio=1:1.6 mixture of rotamers), 3.82 (dq, J = 13.2, 6.6 Hz, 1H), 2.91 (br. s, 3H, CH₃), 2.63, 2.41 (2x br.s, 1H, ratio=1:1.6 mixture of rotamers) 2.00 – 1.61 (m, 6H), 1.03 (d, J = 6.3 Hz, 6H);

25

4-benzoxazol-2-yl-N-((1R,3S)-3-cyclopropylcarbamoyl-cyclopentyl)-N-methylbenzamide ("A6")

30

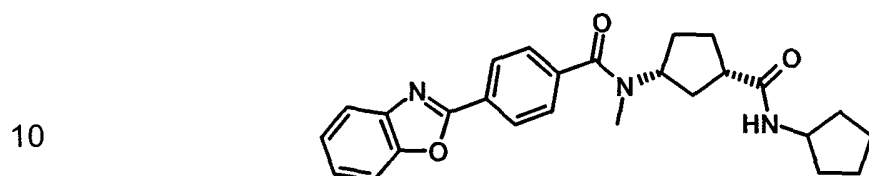


35

LC/MS: M+H 404; ¹H NMR (500 MHz, DMSO-d₆) δ [ppm] 8.25 (d, J = 8.4 Hz, 2H), 7.92 – 7.70 (m, 3H; 2xCH+NH), 7.59 (br. d, J = 5.6 Hz, 2H), 7.52 – 7.35 (m, 2H), 4.88, 3.98 (2x br. s, 1H, ratio=1:1.7 mixture of rotamers), 2.91 (br. s,

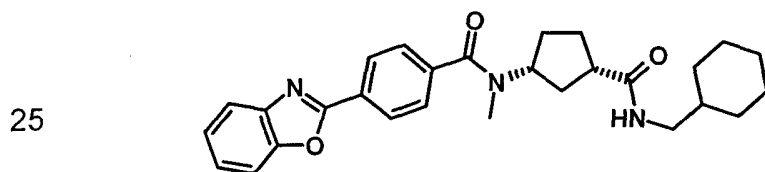
3H), 2.67, 2.38 (2x br. s, 1H, ratio=1:1.7 mixture of rotamers), 2.64 – 2.55 (m, 1H), 2.03 – 1.52 (m, 6H), 0.58 (d, $J = 5.2$ Hz, 2H), 0.36 (br. s, 2H);

5 4-benzoxazol-2-yl-N-((1R,3S)-3-cyclopentylcarbamoyl-cyclopentyl)-N-methyl-benzamide ("A7")



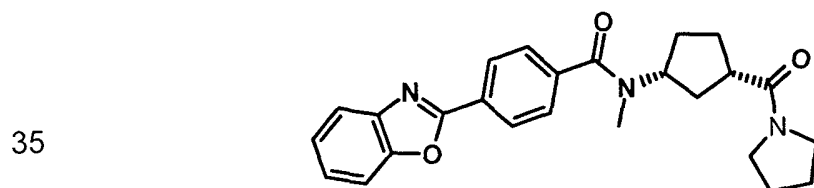
LC/MS: M+H 432; ^1H NMR (500 MHz, DMSO- d_6) δ [ppm] 8.26 (d, $J = 8.4$ Hz, 2H), 7.83 (dd, $J = 14.3, 7.3$ Hz, 2H), 7.68 (s, 1H; NH), 7.60 (d, $J = 7.0$ Hz, 2H), 7.45 (pd, $J = 7.4, 1.4$ Hz, 2H), 4.89, 3.98 (2x br. s, 1H, ratio=1:2 mixture of rotamers), 3.97 (q, $J = 6.8$ Hz, 2H), 2.91 (br. s, 3H), 2.73, 2.43 (2x br. s, 1H, ratio=1:2 mixture of rotamers), 2.10 – 1.54 (m, 10H), 1.53 – 1.41 (m, 2H), 1.40 – 1.24 (m, 2H);

20 4-benzoxazol-2-yl-N-[(1R,3S)-3-(cyclohexylmethyl-carbamoyl)-cyclopentyl]-N-methyl-benzamide ("A8")



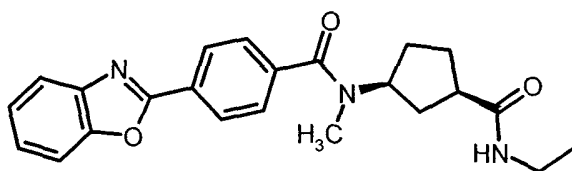
LC/MS: M+H 460;

30 4-benzoxazol-2-yl-N-methyl-N-[(1R,3S)-3-(pyrrolidine-1-carbonyl)-cyclopentyl]-benzamide ("A9")



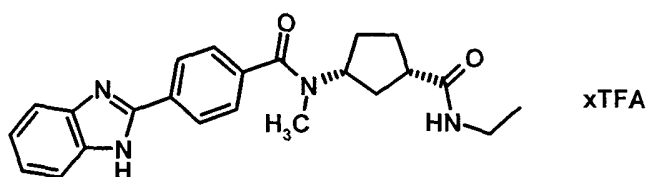
LC/MS: M+H 418; ¹H NMR (500 MHz, DMSO-d₆) δ [ppm] 8.26 (d, *J* = 8.3 Hz, 2H), 7.83 (dd, *J* = 14.2, 7.3 Hz, 2H), 7.60 (d, *J* = 7.3 Hz, 2H), 7.45 (pd, *J* = 7.4, 1.4 Hz, 2H), 4.90, 4.00 (2x br. s, 1H, ratio=1:1.8, mixture of rotamers), 3.51 – 3.24 (m, 4H), 2.91 (s, 3H), 303, 2.78 (2x br. s, 1H, ratio=1:1.8 mixture of rotamers), 2.09 – 1.56 (m, 10H);

4-(1,3-benzoxazol-2-yl)-N-[(1S,3R)-3-(ethylcarbamoyl)cyclopentyl]-N-methylbenzamide ("A10")



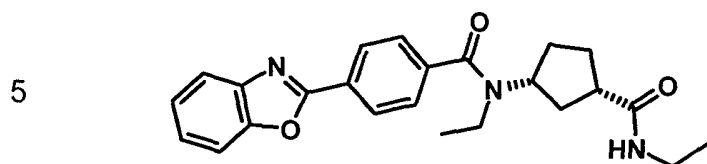
LC/MS: 392 (M+H); ¹H NMR (500 MHz, DMSO-d₆) δ [ppm] 8.26 (d, *J* = 8.3 Hz, 2H), 7.86-7.80 (m, 2H), 7.72 (br. s, 1H; NH), 7.65-7.55 (m, 2H), 7.45 (pd, *J* = 7.4, 1.3 Hz, 2H), 4.89, 4.00 (2x br. s, 1H, ratio=1:1.8 mixture of rotamers), 3.06 (q, *J* = 6.6 Hz, 2H, NCH₂), 2.91 (br. s, 3H, CH₃), 2.67, 2.49 (2x br.s, 1H, , ratio=1:1.8 mixture of rotamers) 2.20 – 1.52 (m, 6H), 1.00 (t, *J* = 7.1 Hz, 3H, CH₃);

4-(1H-benzimidazol-2-yl)-N-[(1R,3S)-3-(ethylcarbamoyl)cyclopentyl]-N-methylbenzamide ("A11")



LC/MS: M+H 391; ¹H NMR (500 MHz, DMSO-d₆) δ [ppm] 8.23 (d, *J* = 8.4 Hz, 2H), 7.75 (s, 1H, NH), 7.71 (dd, *J* = 6.0, 3.2 Hz, 2H), 7.69 – 7.55 (m, 2H), 7.36 (dd, *J* = 5.9, 3.0 Hz, 2H), 4.90, 4.00 (2x br. s, 1H, ratio=1:1.4, mixture of rotamers), 3.06 (q, *J* = 7.2 Hz, 2H), 2.90 (s, 3H), 2.71, 2.46 (2x br. s, 1H, ratio=1:1.4 mixture of rotamers) 2.05 – 1.53 (m, 6H), 1.00 (t, *J* = 7.2 Hz, 3H);

4-benzoxazol-2-yl-N-ethyl-N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-benzamide ("A12")



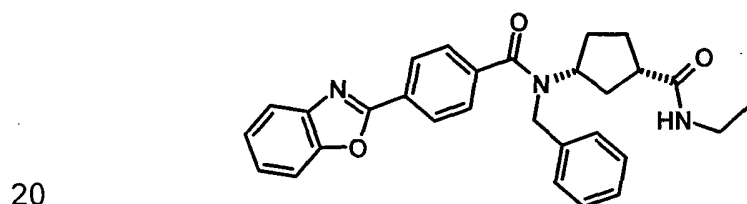
LC/MS: M+H 406;

¹H NMR (500 MHz, DMSO-d₆), mixture of rotamers, δ [ppm] 8.26 (d, *J* = 8.3 Hz, 2H), 7.83 (ddd, *J* = 12.2, 7.3, 1.9 Hz, 2H), 7.72 (s, 1H; NH), 7.57 (d, *J* = 8.3 Hz, 2H), 7.51 – 7.39 (m, 2H), 3.38 (br. s, 2H), 3.16 – 2.98 (m, 2H), 2.16 – 1.52 (m, 6H), 1.38 – 1.06 (m, 3H), 1.07 – 0.91 (m, 3H);

10

4-benzoxazol-2-yl-N-benzyl-N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-benzamide ("A13")

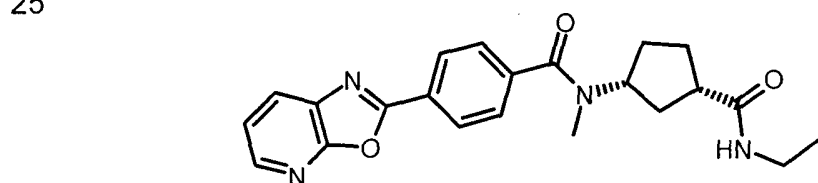
15



LC/MS: M+H 468;

N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-N-methyl-4-oxazolo[5,4-b]pyridin-2-yl-benzamide ("A14")

25



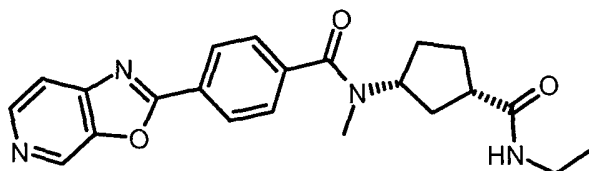
LC/MS: M+H 393;

¹H NMR (500 MHz, DMSO-d₆) δ [ppm] 8.42 (dd, *J* = 4.9, 1.5 Hz, 1H), 8.31 (dd, *J* = 7.9, 1.5 Hz, 1H), 8.29 (d, *J* = 8.3 Hz, 2H), 7.72 (s, 1H; NH), 7.62 (d, *J* = 6.6 Hz, 2H), 7.53 (dd, *J* = 7.8, 4.9 Hz, 1H), 4.89, 3.97 (2x br.s, 1H, ratio=1:1,9, mixture of rotamers), 3.05 (q, *J* = 6.0, 1.0 Hz, 2H), 2.92 (s, 3H), 2.41 (br. s, 1H), 2.13 – 1.49 (m, 6H), 1.00 (t, *J* = 7.0 Hz, 3H);

35

N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-N-methyl-4-oxazolo[5,4-c]pyridin-2-yl-benzamide ("A15")

5

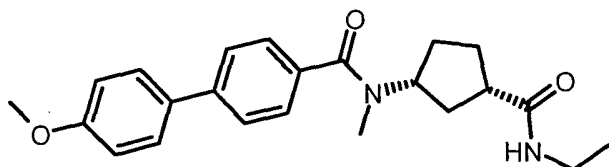


LC/MS: M+H 393;

10

4'-methoxy-biphenyl-4-carboxylic acid ((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-methyl-amide ("A16")

15

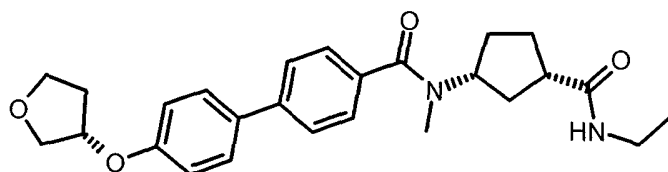


20

LC/MS: M+H 381; ^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 7.74 (s, 1H; NH), 7.66 (t, J = 8.6 Hz, 4H), 7.41 (d, J = 8.1 Hz, 2H), 7.04 (d, J = 8.8 Hz, 2H), 4.41 (br. s, 1H), 3.81 (s, 3H; CH₃O), 3.05 (dd, J = 7.2, 5.6 Hz, 2H), 2.88 (s, 3H; CH₃N), 1.94 – 1.58 (m, 6H), 1.00 (t, J = 7.2 Hz, 3H);

25

4'-[(S)-(tetrahydro-furan-3-yl)oxy]-biphenyl-4-carboxylic acid ((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-methyl-amide ("A17")



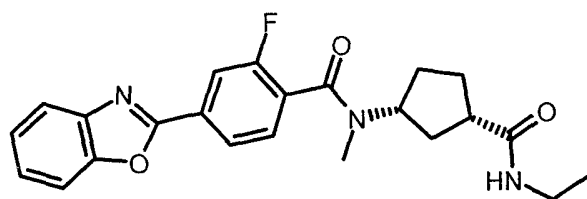
LC/MS: M+H 437;

30

4-benzoxazol-2-yl-N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-2-fluoro-N-methyl-benzamide ("A18")

35

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LC/MS: M+H 410;

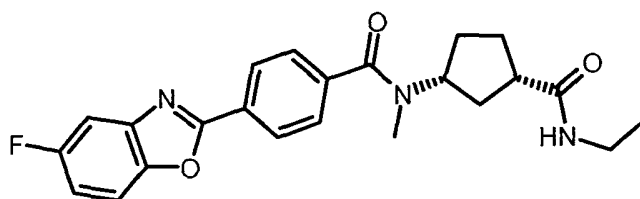
5

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.10 (d, J = 7.9 Hz, 1H), 8.04 (d, J = 9.8 Hz, 1H), 7.85 (dd, J = 14.2, 7.8 Hz, 2H), 7.72 (t, J = 5.4 Hz, 1H; NH), 7.62 (q, J = 8.0 Hz, 1H), 7.47 (pd, J = 7.4, 1.4 Hz, 2H), 4.92, 3.91 (2x br.s, 1H, , ratio=1:7, mixture of rotamers), 3.06 (dp, J = 14.3, 7.2 Hz, 2H), 2.96, 2.79 (2x s, ratio=1:1,6, mixture of rotamers, 3H), 2.65, 2.43 (2x br. s, ratio=1:1,6, mixture of rotamers, 1H), 2.06 – 1.52 (m, 6H), 1.00 (dt, J = 14.3, 7.2 Hz, 3H);

10

N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-4-(5-fluoro-benzoxazol-2-yl)-N-methyl-benzamide ("A19")

15



20

LC/MS: M+H 410;

^1H NMR (500 MHz, DMSO- d_6) δ [ppm] 8.25 (d, J = 8.3 Hz, 2H), 7.85 (dd, J = 8.9, 4.4 Hz, 1H), 7.72 (dd, J = 8.7, 2.6 Hz, 1H+1H, NH), 7.60 (d, J = 6.8 Hz, 2H), 7.32 (td, J = 9.4, 2.6 Hz, 1H), .4.89, 3.97 (2x br.s, 1H, ratio=1:1,6, mixture of rotamers) 3.05 (q, J = 6.7 Hz, 2H), 2.91 (br. s, 3H), 2.63, 2.42 (2x br.s, 1H, ratio=1:1,6, mixture of rotamers) 2.05 – 1.52 (m, 6H), 1.00 (t, J = 7.1 Hz, 3H);

25

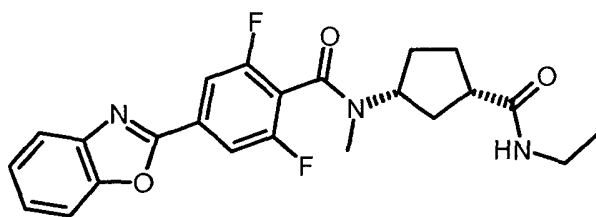
4-benzoxazol-2-yl-N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-2,6-difluoro-N-methyl-benzamide ("A20")

30

35

- 63 -

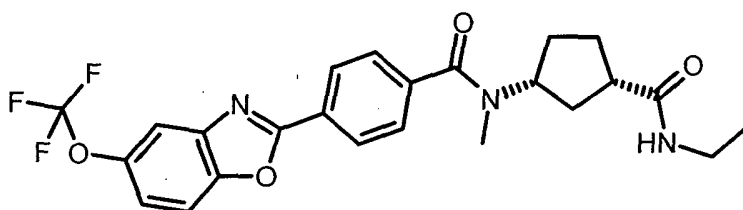
5



LC/MS: M+H 428;

N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-N-methyl-4-(5-trifluoromethoxy-benzoxazol-2-yl)-benzamide ("A21")

10

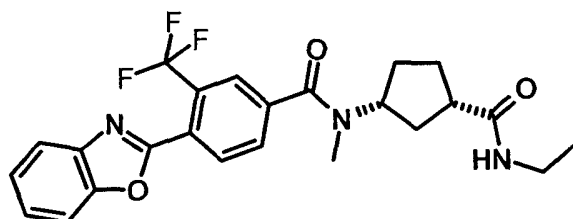


LC/MS: M+H 476;

15

4-benzoxazol-2-yl-N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-N-methyl-3-trifluoromethyl-benzamide ("A22")

20

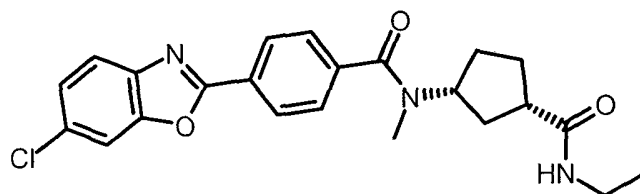


LC/MS: M+H 460;

25

4-(6-chloro-benzoxazol-2-yl)-N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-N-methyl-benzamide ("A23")

30



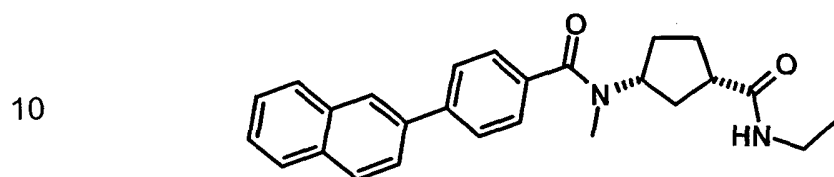
LC/MS: M+H 426;

35

^1H NMR (500 MHz, DMSO- d_6) δ [ppm] 8.24 (d, J = 8.3 Hz, 2H), 8.03 (d, J = 1.9 Hz, 1H), 7.86 (d, J = 8.5 Hz, 1H), 7.72 (s, 1H; NH), 7.60 (d, J = 6.8 Hz, 2H), 7.49 (dd, J = 8.5, 2.0 Hz, 1H), , 4.87, 3.96 (2x br.s, 1H, ratio=1:1,46,

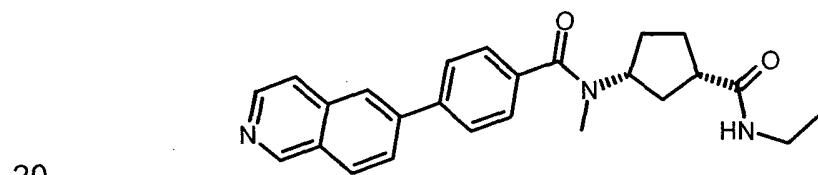
mixture of rotamers), 3.05 (q, $J = 6.6$ Hz, 2H), 2.91 (br. s, 3H), 2.61, 2.43 (2x br.s, 1H, , ratio=1:1,46, mixture of rotamers), 2.06 – 1.49 (m, 6H), 1.00 (t, $J = 7.1$ Hz, 3H);

5 N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-N-methyl-4-naphthalen-2-yl-benzamide ("A24")



LC/MS: M+H 401;

15 N-((1R,3S)-3-Ethylcarbamoyl-cyclopentyl)-4-isoquinolin-6-yl-N-methyl-benzamide ("A25")

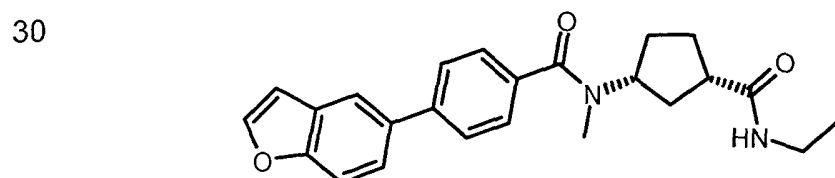


LC/MS: M+H 402;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 9.66 (s, 1H), 8.64 (d, $J = 6.2$ Hz, 1H), 8.54 (s, 1H), 8.46 (d, $J = 8.7$ Hz, 1H), 8.33 – 8.16 (m, 2H), 7.99 (d, $J = 8.3$ Hz, 2H), 7.75 (s, 1H; NH), 7.57 (d, $J = 7.6$ Hz, 2H), 3.06 (p, $J = 7.1$ Hz, 2H), 2.91 (br. s, 3H), 2.09 – 1.54 (m, 6H), 1.00 (t, $J = 7.2$ Hz, 3H);

25

4-benzofuran-5-yl-N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-N-methyl-benzamide ("A26")

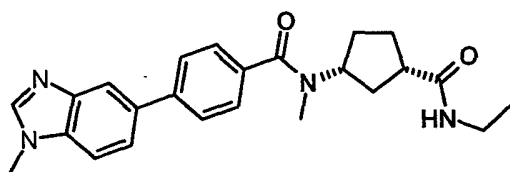


LC/MS: M+H 391;

35

N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-N-methyl-4-(1-methyl-1H-benzimidazol-5-yl)-benzamide ("A27")

5

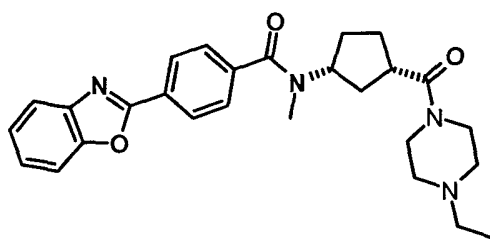


LC/MS: M+H 391;

10

4-benzoxazol-2-yl-N-[(1R,3S)-3-(4-ethyl-piperazine-1-carbonyl)-cyclopentyl]-N-methyl-benzamide ("A28")

15

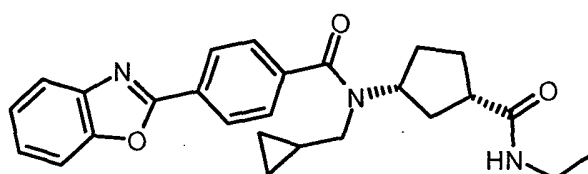


LC/MS: M+H 461;

20

4-benzoxazol-2-yl-N-cyclopropylmethyl-N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-benzamide ("A29")

25

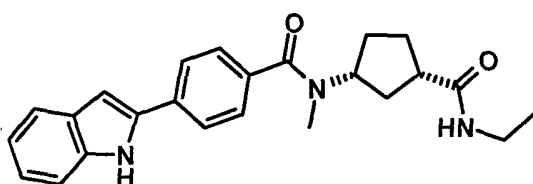


LC/MS: M+H 432;

30

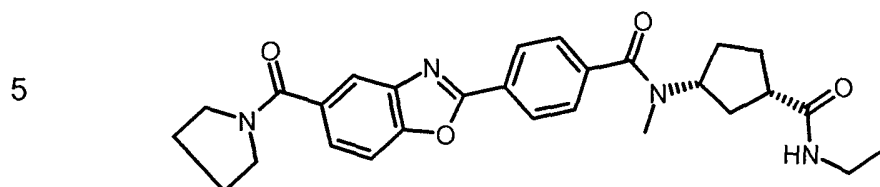
N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-4-(1H-indol-2-yl)-N-methyl-benzamide ("A30")

35



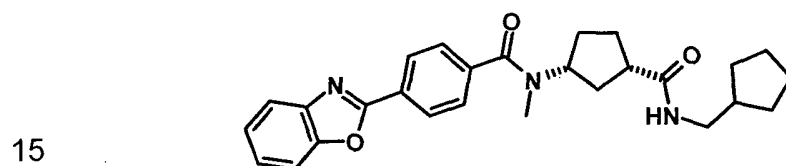
LC/MS: M+H 390;

N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-N-methyl-4-[5-(pyrrolidine-1-carbonyl)-benzoxazol-2-yl]-benzamide ("A31")



LC/MS: M+H 489;

10 4-benzoxazol-2-yl-N-[(1R,3S)-3-(cyclopentylmethyl-carbamoyl)-cyclopentyl]-N-methyl-benzamide ("A32")

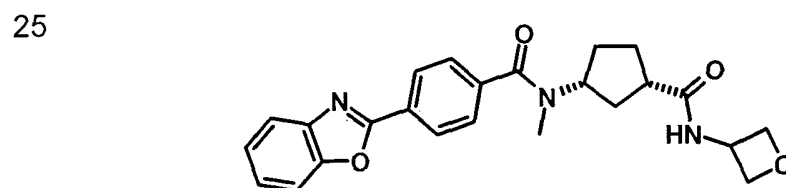


LC/MS: M+H 446;

¹H NMR (500 MHz, DMSO-d₆) δ [ppm] 8.26 (d, *J* = 8.4 Hz, 2H), 7.83 (dd, *J* = 13.4, 8.0 Hz, 2H), 7.73 (s, 1H; NH), 7.60 (d, *J* = 7.1 Hz, 2H), 7.49 – 7.37 (m, 2H), 4.89, 3.99 (2x br.s, 1H, ratio=1:1.7, mixture of rotamers) 3.11 – 2.72 (m, 5H), 2.10 – 1.34 (m, 13H), 1.23 – 0.97 (m, 2H);

20

4-benzoxazol-2-yl-N-methyl-N-[(1R,3S)-3-(oxetan-3-ylcarbamoyl)-cyclopentyl]-benzamide ("A33")



LC/MS: M+H 420;

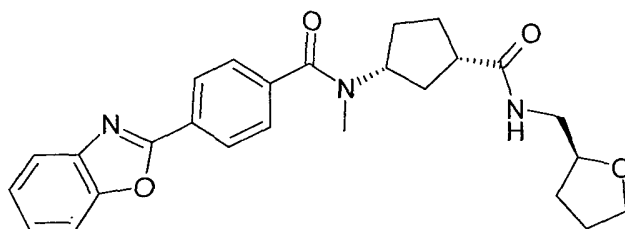
30

4-benzoxazol-2-yl-N-methyl-N-((1R,3S)-3-[(S)-1-(tetrahydro-furan-2-yl)methyl]-carbamoyl)-cyclopentyl)-benzamide ("A34")

35

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5



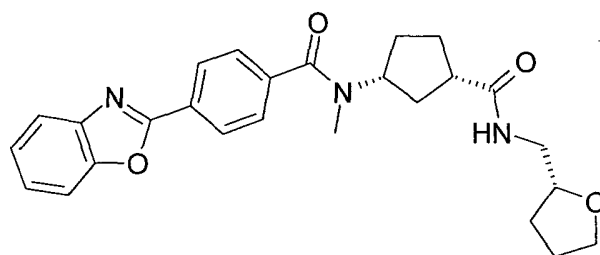
10

LC/MS: M+H 448; ^1H NMR (500 MHz, DMSO- d_6) δ [ppm] 8.27 (d, J = 8.3 Hz, 2H), 7.98 – 7.72 (m, 3H), 7.61 (d, J = 6.9 Hz, 2H), 7.46 (pd, J = 7.4, 1.4 Hz, 2H), 4.91, 4.00 (2x br. s, 1H, ratio=1:1.8 mixture of rotamers) 3.89 – 3.78 (m, 1H), 3.75 (q, J = 6.9 Hz, 1H), 3.61 (q, J = 7.2 Hz, 1H), 3.16 - 3.06 (m, 2H), 2.92 (s, 3H), 2.90 (s, 3H), 2.72, 2.55 (2x br.s, 1H, , ratio=1:1.8 mixture of rotamers), 2.03 - 1.58 m, 9H), 1.49 (dq, J = 14.4, 7.2 Hz, 1H).

15

4-benzoxazol-2-yl-N-methyl-N-((1R,3S)-3-(((R)-1-(tetrahydro-furan-2-yl)methyl)-carbamoyl)-cyclopentyl)-benzamide ("A35")

20



25

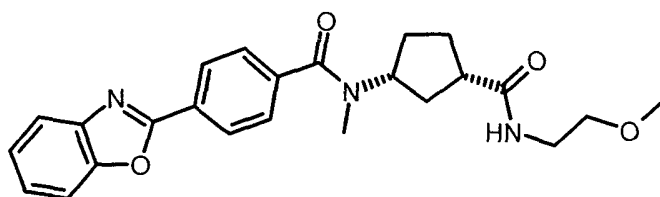
LC/MS: M+H 448; ^1H NMR (500 MHz, DMSO- d_6) δ [ppm] 8.27 (d, J = 8.3 Hz, 2H), 7.98 – 7.72 (m, 3H), 7.61 (d, J = 6.9 Hz, 2H), 7.46 (pd, J = 7.4, 1.4 Hz, 2H), 4.91, 4.00 (2x br. s, 1H, ratio=1:1.8 mixture of rotamers) 3.89 – 3.78 (m, 1H), 3.75 (q, J = 6.9 Hz, 1H), 3.61 (q, J = 7.2 Hz, 1H), 3.16 - 3.06 (m, 2H), 2.92 (s, 3H), 2.90 (s, 3H), 2.72, 2.55 (2x br.s, 1H, , ratio=1:1.8 mixture of rotamers), 2.03 - 1.58 m, 9H), 1.49 (dq, J = 14.4, 7.2 Hz, 1H);

30

4-benzoxazol-2-yl-N-[(1R,3S)-3-(2-methoxy-ethylcarbamoyl)-cyclopentyl]-N-methyl-benzamide ("A36")

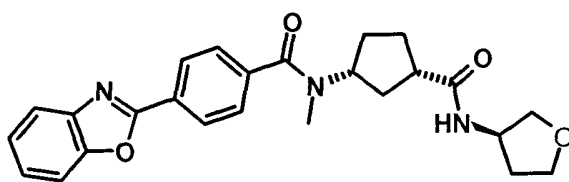
35

- 68 -



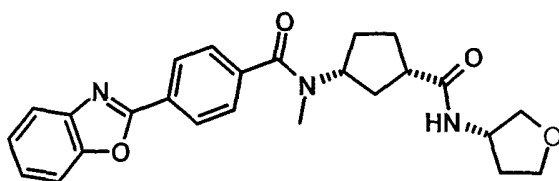
5 LC/MS: M+H 422; ^1H NMR (500 MHz, DMSO- d_6) δ [ppm] 8.27 (d, J = 8.3 Hz, 2H), 7.89 – 7.79 (m, 3H), 7.61 (d, J = 6.7 Hz, 2H), 7.46 (pd, J = 7.4, 1.4 Hz, 2H), 4.90, 4.00 (2x br. s, 1H, ratio=1:2 mixture of rotamers) 3.34 (t, J = 5.6 Hz, 2H), 3.31 (s, 3H; OCH₃), 3.24 – 3.18 (m, 2H), 2.92 (s, 3H), 2.08 – 1.52 (m, 6H);

4-benzoxazol-2-yl-N-methyl-N-((1R,3S)-3-[(R)-(tetrahydro-furan-3-yl)carbamoyl]-cyclopentyl)-benzamide ("A37")



15 LC/MS: M+H 434;
 20 ^1H NMR (500 MHz, DMSO- d_6) δ [ppm] 8.26 (d, J = 8.3 Hz, 2H), 7.98 (s, 1H; NH), 7.83 (ddd, J = 12.7, 7.3, 1.8 Hz, 2H), 7.60 (d, J = 6.9 Hz, 2H), 7.50 – 7.40 (m, 2H), 4.90, 3.99 (2x br.s, 1H, ratio=1:1.5, mixture of rotamers) 4.25 – 4.17 (m, 1H), 3.83 – 3.70 (m, 2H), 3.65 (q, J = 8.1 Hz, 1H), 3.41 (dd, J = 8.6, 3.3 Hz, 1H), 2.91 (br. s, 3H), 2.12 – 1.99 (m, 1H), 2.00 – 1.54 (m, 7H);

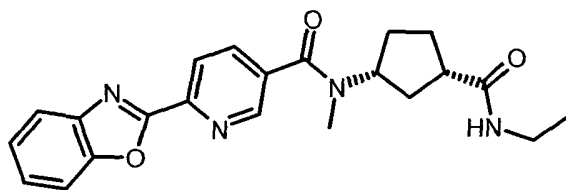
4-benzoxazol-2-yl-N-methyl-N-((1R,3S)-3-[(S)-(tetrahydro-furan-3-yl)carbamoyl]-cyclopentyl)-benzamide ("A38")



30 LC/MS: M+H 434;
 35 ^1H NMR (500 MHz, DMSO- d_6) δ [ppm] 8.26 (d, J = 8.3 Hz, 2H), 7.98 (s, 1H; NH), 7.83 (ddd, J = 12.7, 7.3, 1.8 Hz, 2H), 7.60 (d, J = 6.9 Hz, 2H), 7.50 – 7.40 (m, 2H), 4.90, 3.99 (2x br.s, 1H, ratio=1:1.5, mixture of rotamers) 4.25 –

4.17 (m, 1H), 3.83 – 3.70 (m, 2H), 3.65 (q, $J = 8.1$ Hz, 1H), 3.41 (dd, $J = 8.6$, 3.3 Hz, 1H), 2.91 (br. s, 3H), 2.12 – 1.99 (m, 1H), 2.00 – 1.54 (m, 7H);

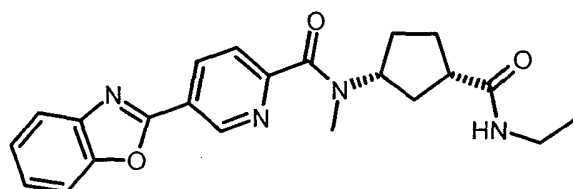
5 6-benzoxazol-2-yl-N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-N-methyl-nicotinamide ("A39")



LC/MS: M+H 393;

^1H NMR (500 MHz, DMSO- d_6) δ [ppm] 8.79 (s, 1H), 8.39 (d, $J = 8.1$ Hz, 1H), 8.07 (s, 1H), 7.90 (d, $J = 7.6$ Hz, 1H), 7.86 (d, $J = 7.7$ Hz, 1H), 7.73 (s, 1H; NH), 7.52 (td, $J = 7.8$, 1.4 Hz, 1H), 7.47 (td, $J = 7.7$, 1.2 Hz, 1H), 4.91, 3.99 (2x br.s, 1H, ratio=1:1.5, mixture of rotamers), 3.14 – 3.00 (m, 2H), 2.95 (s, 3H), 2.44 (br. s, 1H), 2.11 – 1.52 (m, 6H), 1.13 – 0.89 (m, 3H);

20 5-benzoxazol-2-yl-pyridine-2-carboxylic acid ((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-methyl-amide ("A40")

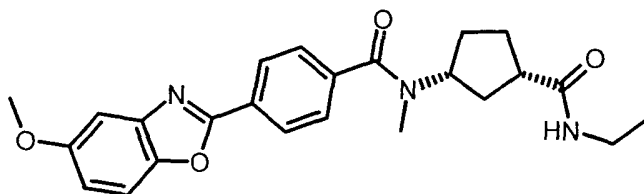


LC/MS: M+H 393;

^1H NMR (500 MHz, DMSO- d_6) mixture of rotamers: δ [ppm] 9.35 (s, 1H), 8.63 (d, $J = 8.1$ Hz, 1H), 7.87 (dd, $J = 16.0$, 7.1 Hz, 2H), 7.83 – 7.62 (m, 2H), 7.60 – 7.32 (m, 2H), 4.93, 4.00 (m, 1H), 3.11- 3.01 (m, 2H), 2.96, 2.85 (s, 3H), 2.65, 2.44 (m, 1H), 2.08 – 1.53 (m, 6H), 1.10 – 0.93 (m, 3H);

N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-4-(5-methoxy-benzoxazol-2-yl)-N-methyl-benzamide ("A41")

- 70 -



LC/MS: M+H 422;

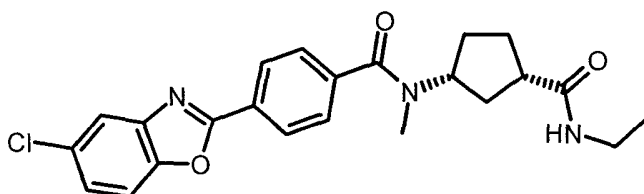
5

^1H NMR (500 MHz, DMSO- d_6) δ [ppm] 8.22 (d, J = 8.1 Hz, 2H), 7.73 (br. s, 1H; NH), 7.70 (d, J = 8.9 Hz, 1H), 7.58 (d, J = 6.5 Hz, 2H), 7.38 (d, J = 2.4 Hz, 1H), 7.03 (dd, J = 8.9, 2.5 Hz, 1H), 4.89, 3.97 (2x br.s, 1H, ratio=1:2, mixture of rotamers), 3.84 (s, 3H), 3.14 – 2.99 (m, 2H), 2.90 (br. s, 3H), 2.33 (br. s, 1H), 2.07 – 1.49 (m, 6H), 1.00 (t, J = 7.0 Hz, 3H);

10

4-(5-chloro-benzoxazol-2-yl)-N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-N-methyl-benzamide ("A42")

15



LC/MS: M+H 426

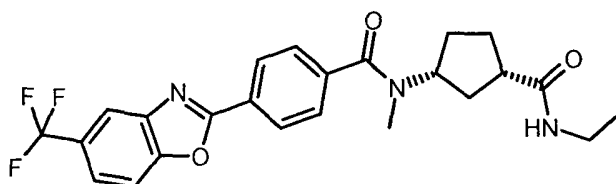
20

^1H NMR (500 MHz, DMSO- d_6) δ [ppm] 8.25 (d, J = 8.3 Hz, 2H), 7.95 (d, J = 2.1 Hz, 1H), 7.86 (d, J = 8.7 Hz, 1H), 7.72 (s, 1H; NH), 7.60 (d, J = 6.4 Hz, 2H), 7.50 (dd, J = 8.7, 2.1 Hz, 1H), 4.89, 3.97 (2x br.s, 1H, ratio=1:1.9, mixture of rotamers) 3.05 (q, J = 6.7 Hz, 2H), 2.91 (br. s, 3H), 2.42 (br. s, 1H), 2.10 – 1.50 (m, 6H), 1.00 (t, J = 7.1 Hz, 3H);

25

N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-N-methyl-4-(5-trifluoromethyl-benzoxazol-2-yl)-benzamide ("A43")

30



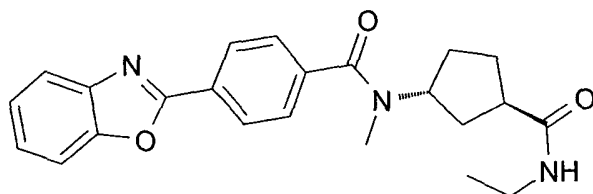
LC/MS: M+H 460;

35

^1H NMR (500 MHz, DMSO- d_6) δ [ppm] 8.34 – 8.24 (m, 3H), 8.06 (d, J = 8.5 Hz, 1H), 7.87 – 7.80 (m, 1H), 7.74 (s, 1H; NH), 7.63 (s, 2H), 4.90, 3.96 (2x

br.s, 1H, ratio=1:1.7, mixture of rotamers) 3.05 (q, $J = 6.7, 5.8$ Hz, 2H), 2.93 (br. s, 3H), 2.15 – 1.50 (m, 6H), 0.99 (t, $J = 6.4$ Hz, 3H);

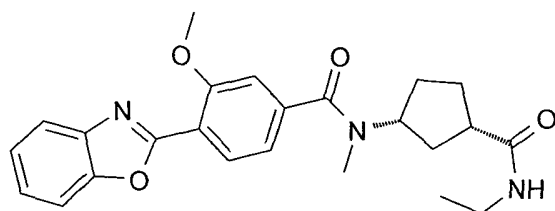
4-(1,3-benzoxazol-2-yl)-N-[(1R,3R)-3-(ethylcarbamoyl)cyclopentyl]-N-methyl-benzamide ("A44")



LC/MS: M+H 392;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.26 (d, $J = 8.3$ Hz, 2H), 7.88 – 7.78 (m, 2H), 7.74 (s, 1H; NH), 7.58 (d, $J = 7.3$ Hz, 2H), 7.51 – 7.39 (m, 2H), 4.94, 4.17 (2x br.s, 1H, ratio=1:2.2, mixture of rotamers), 3.01 (br. s, 2H), 2.86 (br. s, 3H), 2.80 – 2.64 (m, 1H), 2.15 – 1.53 (m, 6H), 0.96 (br. s, 3H);

4-benzoxazol-2-yl-N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-3-methoxy-N-methyl-benzamide ("A45")

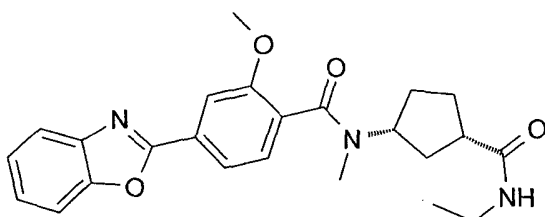


LC/MS: M+H 422;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.09 (d, $J = 7.9$ Hz, 1H), 7.85 (d, $J = 8.8$ Hz, 1H), 7.80 (d, $J = 6.9$ Hz, 1H), 7.75 (s, 1H; NH), 7.49 – 7.39 (m, 2H), 7.24 (s, 1H), 7.12 (d, $J = 7.3$ Hz, 1H), 4.93, 4.07 (2x br.s, 1H, ratio=1:1.5, mixture of rotamers), 3.98 (s, 3H), 3.15 – 3.00 (m, 2H), 2.93 (br. s, 3H), 2.09 – 1.58 (m, 6H), 1.02 (t, $J = 7.0$ Hz, 3H);

4-benzoxazol-2-yl-N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-2-methoxy-N-methyl-benzamide ("A46")

- 72 -

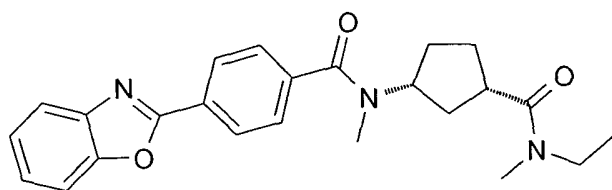


LC/MS: M+H 422;

¹H NMR (400 MHz, DMSO-d₆) δ [ppm] mixture of rotamers

7.90 – 7.78 (m, 4H), 7.69 (s, 1H, NH), 7.46 (td, *J* = 7.2, 1.4 Hz, 2H), 7.39 (d, *J* = 7.7 Hz, 1H), 4.95, 3.83 (2x m, 1H, ratio=1:1.8, mixture of rotamers), 3.95 (s, 3H), 3.15 – 2.98 (m, 2H), 2.92, 2.70 (2xs, 3H), 2.04 – 1.44 (m, 6H), 1.08 – 0.92 (m, 3H);

4-benzoxazol-2-yl-N-[(1R,3S)-3-(ethyl-methyl-carbamoyl)-cyclopentyl]-N-methyl-benzamide ("A47")

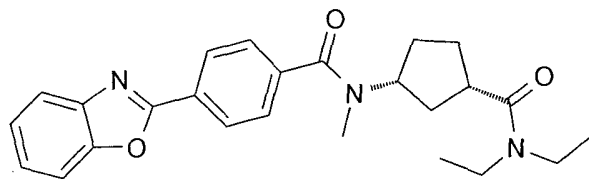


LC/MS: M+H 406;

¹H NMR (400 MHz, DMSO-d₆) δ [ppm] mixture of rotamers

8.26 (d, *J* = 8.3 Hz, 2H), 7.83 (dd, *J* = 13.7, 6.9 Hz, 2H), 7.60 (d, *J* = 7.2 Hz, 2H), 7.45 (pd, *J* = 7.4, 1.4 Hz, 2H), 4.93, 4.04 (2x s, 1H, ratio=1:1.7, mixture of rotamers), 3.29 – 3.16 (m, 2H), 3.10 – 2.70 (m, 6H), 2.13 – 1.57 (m, 6H), 1.19 – 0.84 (m, 3H);

4-benzoxazol-2-yl-N-[(1R,3S)-3-diethylcarbamoyl-cyclopentyl]-N-methyl-benzamide ("A48")



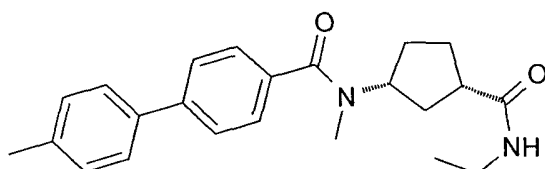
LC/MS: M+H 420;

¹H NMR (400 MHz, DMSO-d₆) δ [ppm] 8.26 (d, *J* = 8.4 Hz, 2H), 7.87 – 7.78 (m, 2H), 7.60 (d, *J* = 7.1 Hz, 2H), 7.45 (td, *J* = 7.5, 1.5 Hz, 2H), 4.95, 4.04 (2x

s, 1H, ratio=1:1.7, mixture of rotamers), 3.30 – 3.11 (m, 2H), 2.91 (br. s, 3H), 2.09 – 1.53 (m, 6H), 1.21 – 0.84 (m, 6H);

5

4'-methyl-biphenyl-4-carboxylic acid ((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-methyl-amide ("A49")



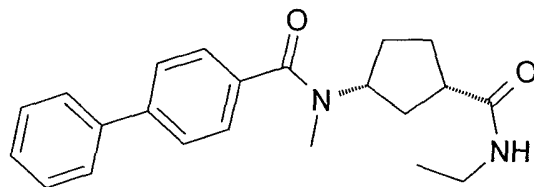
10

LC/MS: M+H 365;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 7.73 (s, 1H; NH), 7.70 (d, J = 8.3 Hz, 2H), 7.60 (d, J = 8.1 Hz, 2H), 7.43 (d, J = 7.9 Hz, 2H), 7.29 (d, J = 7.9 Hz, 2H), 4.83, 4.09 (2x s, 1H, ratio=1:1.8, mixture of rotamers), 3.05 (p, J = 7.2 Hz, 2H), 2.88 (s, 3H), 2.35 (s, 3H), 2.05 – 1.54 (m, 6H), 1.00 (t, J = 7.2 Hz, 3H);

15

biphenyl-4-carboxylic acid ((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-methyl-amide ("A50")



20

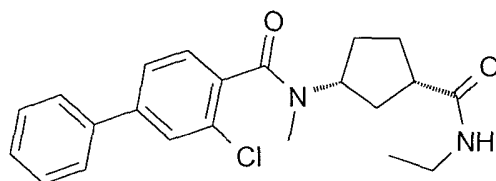
LC/MS: M+H 351;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 7.81 – 7.63 (m, 5H), 7.49 (t, J = 7.7 Hz, 2H), 7.45 (d, J = 7.9 Hz, 2H), 7.40 (t, J = 7.4 Hz, 1H), 4.84, 4.08 (2x s, 1H, ratio=1:1.8, mixture of rotamers), 3.06 (p, J = 7.2 Hz, 2H), 2.88 (br. s, 3H), 2.05 – 1.54 (m, 6H), 1.00 (t, J = 7.2 Hz, 3H);

25

30

3-chloro-biphenyl-4-carboxylic acid ((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-methyl-amide ("A51")



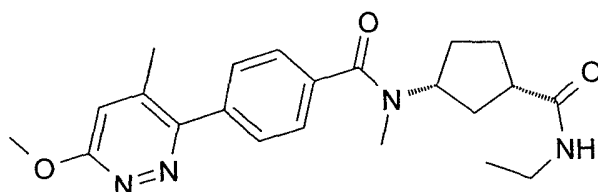
35

LC/MS: M+H 385;

- 74 -

¹H NMR (400 MHz, DMSO-d₆) δ [ppm] 7.81 (d, *J* = 6.9 Hz, 1H), 7.77 – 7.65 (m, 4H), 7.50 (t, *J* = 7.6 Hz, 2H), 7.41 (q, *J* = 7.4, 6.8 Hz, 2H), 7.40 (t, *J* = 7.4 Hz, 1H), 4.95, 3.82 (2x m, 1H, ratio=1:1.6, mixture of rotamers), 3.15 – 2.98 (m, 2H), 2.94, 2.72 (2x s, 3H, ratio=1:1.6, mixture of rotamers), 2.65, 2.41 (2x m, 1H ratio=1:1.6, mixture of rotamers), 2.02 – 1.50 (m, 6H), 1.07 – 0.91 (m, 3H);

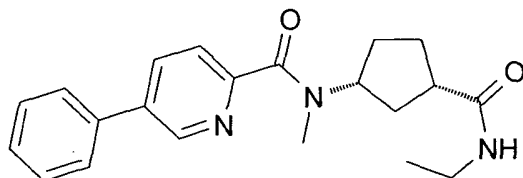
N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-4-(6-methoxy-4-methyl-pyridazin-3-yl)-N-methyl-benzamide ("A52")



LC/MS: M+H 397;

¹H NMR (400 MHz, DMSO-d₆) δ [ppm] 7.74 (s, 1H; NH), 7.62 (d, *J* = 8.2 Hz, 2H), 7.48 (d, *J* = 7.7 Hz, 2H), 7.20 (s, 1H), 4.87, 4.04 (2x s, 1H, ratio=1:1.2, mixture of rotamers), 4.06 (s, 3H), 3.06 (p, *J* = 7.1 Hz, 2H), 2.90 (br. s, 3H), 2.29 (s, 3H), 2.04 – 1.55 (m, 6H), 1.00 (t, *J* = 7.2 Hz, 3H);

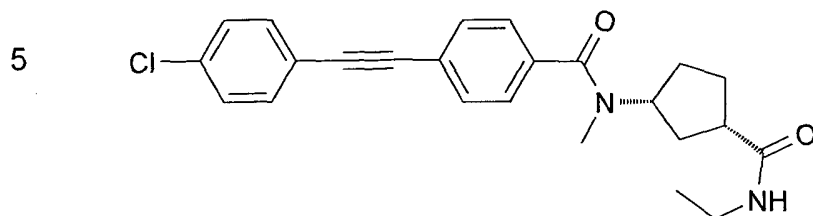
5-phenyl-pyridine-2-carboxylic acid ((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-methyl-amide ("A53")



LC/MS: M+H 352;

¹H NMR (400 MHz, DMSO-d₆) δ [ppm] 8.89 (s, 1H), 8.19 (dd, *J* = 8.1, 2.3 Hz, 1H), 7.78 (d, *J* = 7.5 Hz, 2H), 7.69 (t, *J* = 4.2 Hz, 1H; NH), 7.66 – 7.57 (m, 1H), 7.53 (t, *J* = 7.5 Hz, 2H), 7.45 (t, *J* = 7.4 Hz, 1H), 4.93, 4.132 (2x m, 1H, ratio=1:1.5, mixture of rotamers), 3.17 – 2.97 (m, 2H), 2.94, 2.86 (2x s, 3H, ratio=1:1.5, mixture of rotamers; N-CH₃), 2.64, 2.41 (2x m, 1H ratio=1:1.5, mixture of rotamers), 2.10 – 1.49 (m, 6H), 1.08 – 0.90 (m, 3H);

4-(4-chloro-phenylethynyl)-N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-N-methyl-benzamide ("A54")

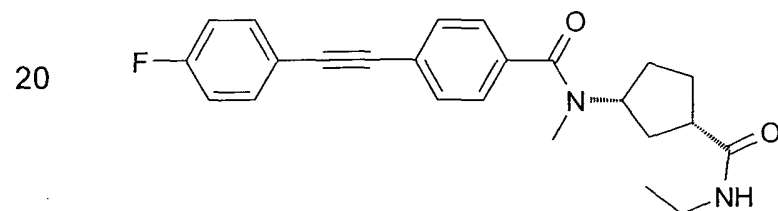


LC/MS: M+H 409;

10 ^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 7.73 (br. s, 1H; NH), 7.61 (t, J = 8.2 Hz, 4H), 7.51 (d, J = 8.6 Hz, 2H), 7.41 (d, J = 7.4 Hz, 2H), 4.86, 3.95 (2x br. s, 1H, ratio=1:1.8, mixture of rotamers), 3.05 (p, J = 7.1 Hz, 2H), 2.86 (br. s, 3H), 2.56, 2.43 (2x br. s, 1H, ratio=1:1.8, mixture of rotamers), 2.08 – 1.46 (m, 6H), 1.00 (t, J = 7.2 Hz, 3H);

15

N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-4-(4-fluoro-phenylethynyl)-N-methyl-benzamide ("A55")



LC/MS: M+H 393;

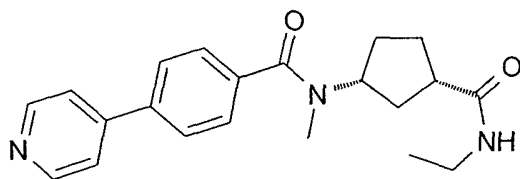
25 ^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 7.73 (br. s, 1H; NH), 7.64 (dd, J = 8.9, 5.5 Hz, 2H), 7.60 (d, J = 8.3 Hz, 2H), 7.41 (d, J = 8.3 Hz, 2H), 7.29 (t, J = 8.9 Hz, 2H), 4.87, 3.94 (2x br. s, 1H, ratio=1:1.8, mixture of rotamers), 3.05 (p, J = 7.1 Hz, 2H), 2.86 (br. s, 3H), 2.56, 2.43 (2x br. s, 1H, ratio=1:1.8, mixture of rotamers), 2.11 – 1.50 (m, 6H), 1.00 (t, J = 7.2 Hz, 3H);

30

N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-N-methyl-4-pyridin-4-yl-benzamide ("A56")

35

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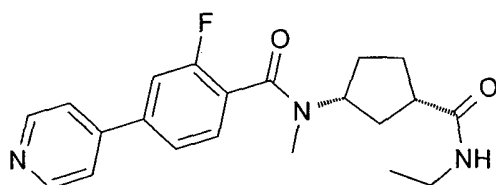


LC/MS: M+H 352;

5 ^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.66 (d, J = 6.1 Hz, 2H), 7.87 (d, J = 8.3 Hz, 2H), 7.82 – 7.61 (m, 3H), 7.50 (d, J = 7.6 Hz, 2H), 4.87, 4.04 (2x s, 1H, ratio=1:1.9, mixture of rotamers), 3.05 (p, J = 7.1 Hz, 2H), 2.89 (br. s, 3H), 2.13 – 1.52 (m, 6H), 1.00 (t, J = 7.2 Hz, 3H);

10

N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-2-fluoro-N-methyl-4-pyridin-4-yl-benzamide ("A57")



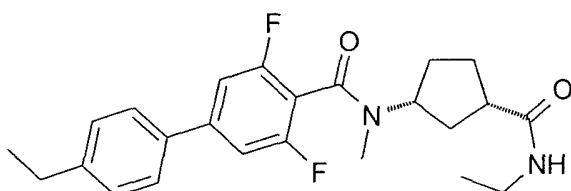
15

LC/MS: M+H 370;

20 ^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.67 (d, J = 4.6 Hz, 2H), 7.84 – 7.76 (m, 3H), 7.74 (dd, J = 7.9, 1.6 Hz, 1H), 7.70 (t, J = 5.2 Hz, 1H; NH), 7.50 (q, J = 7.6 Hz, 1H), 4.93, 3.92 (2x p, J = 8.2 Hz, 1H, ratio=1:1.8, mixture of rotamers), 3.17 – 2.97 (m, 2H), 2.94, 2.78 (2x s, 3H), 2.65, 2.40 (2x m, 1H, ratio=1:1.8, mixture of rotamers), 2.09 – 1.51 (m, 6H), 1.07 – 0.91 (m, 3H);

25

4'-ethyl-3,5-difluoro-biphenyl-4-carboxylic acid ((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-methyl-amide ("A58")



30

LC/MS: M+H 415;

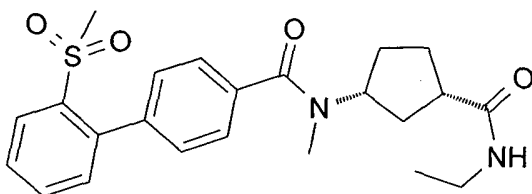
35 ^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 7.84 – 7.66 (m, 3H), 7.54 (dd, J = 9.3, 2.9 Hz, 2H), 7.34 (d, J = 8.3 Hz, 2H), 4.93, 3.99 (2x m, 1H, ratio=1:1.7, mixture of rotamers), 3.14 – 2.99 (m, 2H), 2.96, 2.81 (2x s, 3H, ratio=1:1.7, mixture of

rotamers), 2.66 (q, $J = 7.6$ Hz, 2H), 2.04 – 1.54 (m, 6H), 1.28 – 1.17 (m, 3H), 1.07 – 0.91 (m, 3H);

5

2'-methanesulfonyl-biphenyl-4-carboxylic acid ((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-methyl-amide ("A59")

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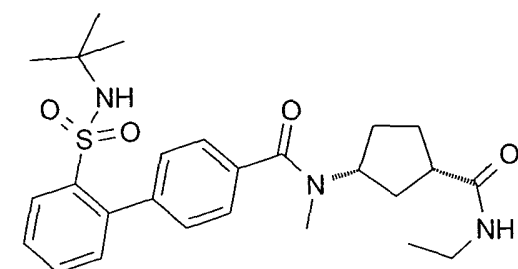


LC/MS: M+H 429;

15

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.11 (dd, $J = 8.0, 1.3$ Hz, 1H), 7.82 – 7.72 (m, 2H), 7.70 (td, $J = 7.7, 1.4$ Hz, 1H), 7.54 – 7.31 (m, 5H), 3.06 (p, $J = 7.1$ Hz, 2H), 4.87, 4.02 (2x br. s, 1H, ratio=1:1.4, mixture of rotamers), 2.94 – 2.78 (m, 6H), 2.09 – 1.54 (m, 6H), 1.00 (t, $J = 7.2$ Hz, 3H);

20



25

LC/MS: M+H 486;

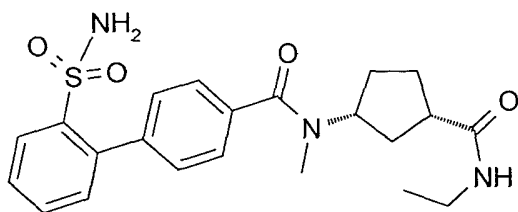
30

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.11 – 7.98 (m, 1H), 7.75 (s, 1H; NH), 7.65 (td, $J = 7.5, 1.3$ Hz, 1H), 7.58 (td, $J = 7.7, 1.4$ Hz, 1H), 7.46 (d, $J = 8.1$ Hz, 2H), 7.38 (d, $J = 7.5$ Hz, 2H), 7.34 (dd, $J = 7.5, 1.1$ Hz, 1H), 6.67 (s, 1H; NH), 4.82, 4.13 (2x br. s, 1H, ratio=1:1.7, mixture of rotamers), 3.06 (p, $J = 7.2$ Hz, 2H), 2.90 (s, 3H), 2.04 – 1.48 (m, 6H), 1.05 – 0.92 (m, 12H);

35

2'-sulfamoyl-biphenyl-4-carboxylic acid ((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-methyl-amide ("A61")

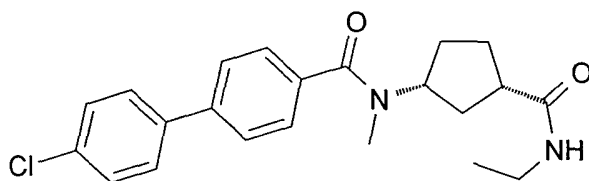
- 78 -



LC/MS: M+H 430;

¹H NMR (400 MHz, DMSO-d₆) δ [ppm] 8.05 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.76 (s, 1H; NH), 7.67 – 7.55 (m, 2H), 7.44 (d, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 7.8 Hz, 2H), 7.34 (dd, *J* = 7.4, 1.3 Hz, 1H), 7.27 (s, 2H), 4.87, 4.13 (2x br. s, 1H, ratio=1:1.8, mixture of rotamers), 3.06 (p, *J* = 7.1 Hz, 2H), 2.89 (s, 3H), 2.02 – 1.55 (m, 6H), 1.00 (t, *J* = 7.2 Hz, 3H);

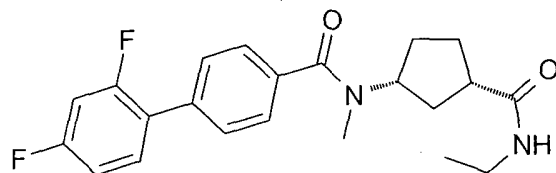
4'-chloro-biphenyl-4-carboxylic acid ((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-methyl-amide ("A62")



LC/MS: M+H 385;

¹H NMR (400 MHz, DMSO-d₆) δ [ppm] 7.80 – 7.69 (m, 5H), 7.55 (d, *J* = 8.6 Hz, 2H), 7.47 (d, *J* = 7.8 Hz, 2H), 4.84, 4.08 (2x br. s, 1H, ratio=1:2.1, mixture of rotamers), 3.07 (p, *J* = 7.1 Hz, 2H), 2.89 (s, 3H), 2.09 – 1.50 (m, 6H), 1.01 (t, *J* = 7.2 Hz, 3H);

2',4'-difluoro-biphenyl-4-carboxylic acid ((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-methyl-amide ("A63")

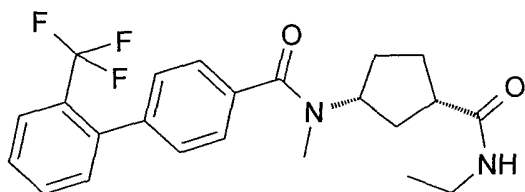


LC/MS: M+H 387;

¹H NMR (400 MHz, DMSO-d₆) δ [ppm] 7.75 (s, 1H; NH), 7.65 (td, *J* = 8.9, 6.6 Hz, 1H), 7.60 (d, *J* = 6.8 Hz, 2H), 7.48 (d, *J* = 7.8 Hz, 2H), 7.40 (ddd, *J* = 11.6, 9.3, 2.6 Hz, 1H), 7.23 (td, *J* = 8.8, 2.3 Hz, 1H), 4.84, 4.08 (2x br. s, 1H,

ratio=1:1.7, mixture of rotamers), 3.07 (p, $J = 7.1$ Hz, 2H), 2.89 (s, 3H), 2.04 – 1.57 (m, 6H), 1.01 (t, $J = 7.2$ Hz, 3H);

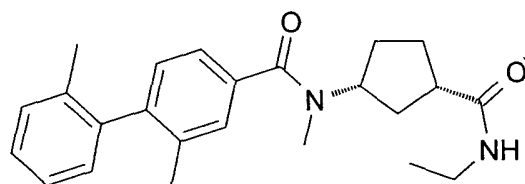
2'-trifluoromethyl-biphenyl-4-carboxylic acid ((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-methyl-amide ("A64")



LC/MS: M+H 419;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 7.86 (d, $J = 7.7$ Hz, 1H), 7.82 – 7.69 (m, 2H), 7.65 (t, $J = 7.7$ Hz, 1H), 7.49 – 7.42 (m, 3H), 7.38 (d, $J = 8.0$ Hz, 2H), 4.88, 4.05 (2x br. s, 1H, ratio=1:1.5, mixture of rotamers), 3.07 (p, $J = 7.1$ Hz, 2H), 2.90 (s, 3H), 2.02 – 1.56 (m, 6H), 1.01 (t, $J = 7.2$ Hz, 3H);

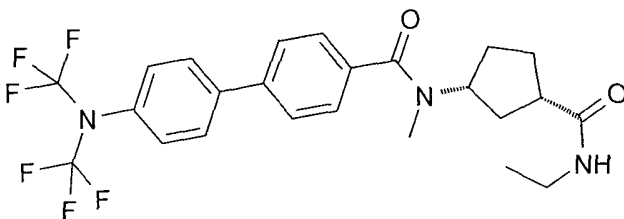
2,2'-dimethyl-biphenyl-4-carboxylic acid ((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-methyl-amide ("A65")



LC/MS: M+H 379;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 7.77 (s, 1H; NH), 7.39 – 7.16 (m, 5H), 7.16 – 7.03 (m, 2H), 4.87, 4.14 (2x br. s, 1H, ratio=1:1.5, mixture of rotamers), 3.07 (p, $J = 7.2$ Hz, 2H), 2.89 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H), 2.00 – 1.58 (m, 6H), 1.01 (t, $J = 7.2$ Hz, 3H);

4'-(bis-trifluoromethyl-amino)-biphenyl-4-carboxylic acid ((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-methyl-amide ("A66")



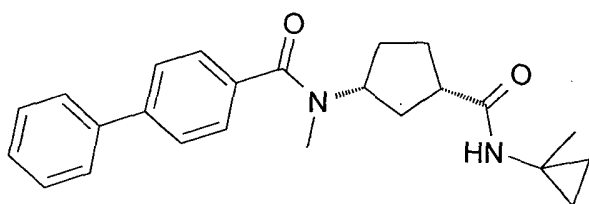
LC/MS: M+H 502;

¹H NMR (400 MHz, DMSO-d₆) δ [ppm] 7.90 (d, *J* = 8.6 Hz, 2H), 7.79 (d, *J* = 8.3 Hz, 2H), 7.73 (s, 1H; NH), 7.63 (d, *J* = 8.4 Hz, 2H), 7.49 (d, *J* = 7.8 Hz, 2H), 4.82, 4.04 (2x br. s, 1H, ratio=1:1.8, mixture of rotamers), 3.06 (p, *J* = 7.1 Hz, 2H), 2.89 (s, 3H), 2.07 – 1.54 (m, 6H), 1.00 (t, *J* = 7.2 Hz, 3H);

5

biphenyl-4-carboxylic acid methyl-[(1R,3S)-3-(1-methyl-cyclopropylcarbamoyl)-cyclopentyl]-amide ("A67")

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LC/MS: M+H 377;

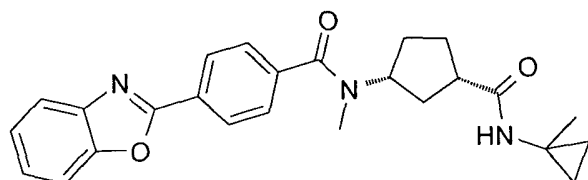
¹H NMR (400 MHz, DMSO-d₆) δ [ppm] 7.95 (s, 1H; NH), 7.75 – 7.67 (m, 4H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.45 (d, *J* = 7.8 Hz, 2H), 7.40 (t, *J* = 7.4 Hz, 1H), 4.83, 4.05 (2x br. s, 1H, ratio=1:1.8, mixture of rotamers), 2.88 (s, 3H), 2.47 – 2.23 (m, 1H), 2.11 – 1.45 (m, 6H), 1.25 (s, 3H), 0.64 – 0.41 (m, 4H);

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4-benzoxazol-2-yl-N-methyl-N-[(1R,3S)-3-(1-methyl-cyclopropylcarbamoyl)-cyclopentyl]-benzamide ("A68")

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LC/MS: M+H 418;

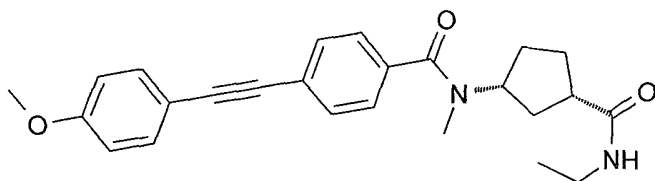
¹H NMR (400 MHz, DMSO-d₆) δ [ppm] 8.25 (d, *J* = 8.4 Hz, 2H), 7.94 (s, 1H; NH), 7.88 – 7.75 (m, 2H), 7.59 (d, *J* = 5.8 Hz, 2H), 7.51 – 7.35 (m, 2H), 4.86, 3.96 (2x br. s, 1H, ratio=1:1.7, mixture of rotamers), 2.90 (s, 3H), 2.45 – 2.23 (m, 1H), 2.09 – 1.42 (m, 6H), 1.25 (s, 3H), 0.66 – 0.36 (m, 4H);

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N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-4-(4-methoxy-phenylethynyl)-N-methyl-benzamide ("A69")

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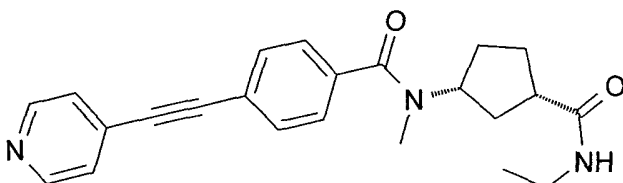
- 81 -



LC/MS: M+H 405;

5 ^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 7.73 (s, 1H; NH), 7.56 (d, J = 8.3 Hz, 2H), 7.51 (d, J = 8.9 Hz, 2H), 7.39 (d, J = 7.5 Hz, 2H), 7.00 (d, J = 8.9 Hz, 2H), 4.84, 3.97 (2x br. s, 1H, ratio=1:1.9, mixture of rotamers), 3.80 (s, 3H; CH₃O), 3.05 (p, J = 7.1 Hz, 2H), 2.86 (s, 3H), 2.01 – 1.49 (m, 6H), 1.00 (t, J = 7.2 Hz, 3H);

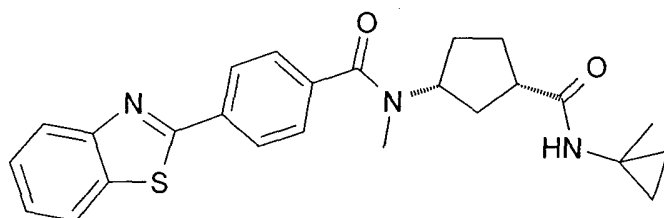
N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-N-methyl-4-pyridin-4-ylethynylbenzamide ("A70")



LC/MS: M+H 376;

15 ^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.65 (d, J = 6.0 Hz, 2H), 7.73 (s, 1H; NH), 7.67 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 6.1 Hz, 2H), 7.44 (d, J = 7.7 Hz, 2H), 4.83, 3.94 (2x br. s, 1H, ratio=1:1.9, mixture of rotamers), 3.11 – 3.00 (m, 2H), 2.86 (br. s, 3H), 2.10 – 1.49 (m, 6H), 1.00 (t, J = 7.2 Hz, 3H);

25 4-benzothiazol-2-yl-N-methyl-N-[(1R,3S)-3-(1-methyl-cyclopropylcarbamoyl)-cyclopentyl]-benzamide ("A71")



LC/MS: M+H 434;

30 ^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.18 (d, J = 8.0 Hz, 1H), 8.15 (d, J = 8.4 Hz, 2H), 8.09 (d, J = 7.8 Hz, 1H), 7.94 (s, 1H; NH), 7.61 – 7.52 (m, 3H), 7.49 (t, J = 7.6 Hz, 1H), 4.84, 3.97 (2x br. s, 1H, ratio=1:1.6, mixture of

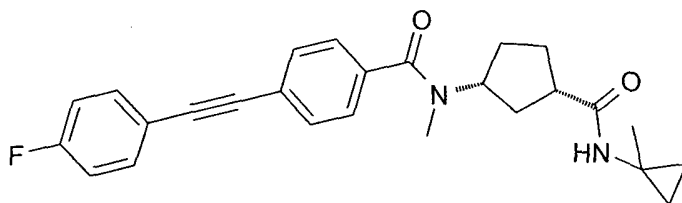
35

rotamers), 2.90 (br. s, 3H), 2.00 – 1.58 (m, 6H), 1.25 (s, 3H), 0.66 – 0.40 (m, 4H);

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4-(4-fluorophenylethynyl)-N-methyl-N-[(1R,3S)-3-(1-methylcyclopropylcarbamoyl)-cyclopentyl]-benzamide ("A72")

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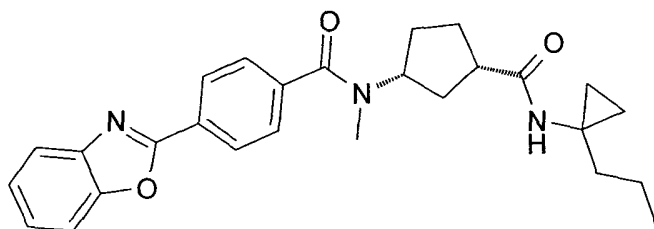
LC/MS: M+H 419;

15

¹H NMR (400 MHz, DMSO-d₆) δ [ppm] 7.94 (s, 1H; NH), 7.68 – 7.56 (m, 4H), 7.40 (d, *J* = 7.8 Hz, 2H), 7.28 (t, *J* = 8.9 Hz, 2H), 4.83, 3.92 (2x br. s, 1H, ratio=1:1.3, mixture of rotamers), 2.86 (s, 3H), 1.99 – 1.48 (m, 6H), 1.25 (s, 3H), 0.64 – 0.39 (m, 4H);

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4-benzoxazol-2-yl-N-methyl-N-[(1R,3S)-3-(1-propylcyclopropylcarbamoyl)-cyclopentyl]-benzamide ("A73")



LC/MS: M+H 446;

25

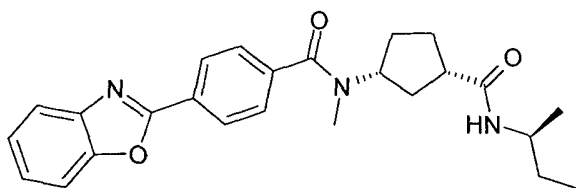
¹H NMR (400 MHz, DMSO-d₆) δ [ppm] 8.25 (d, *J* = 8.4 Hz, 2H), 7.89 (br. s, 1H; NH), 7.86 – 7.79 (m, 2H), 7.59 (d, *J* = 6.1 Hz, 2H), 7.45 (pd, *J* = 7.4, 1.4 Hz, 2H), 2.90 (s, 3H), 4.86, 3.95 (2x m, 1H, ratio=1:1.9, mixture of rotamers), 2.39 (br. s, 1H), 2.02 – 1.53 (m, 6H), 1.51 – 1.38 (m, 2H), 1.39 – 1.25 (m, 2H), 0.86 (t, *J* = 7.3 Hz, 3H), 0.60 – 0.39 (m, 4H);

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4-(1,3-benzoxazol-2-yl)-N-methyl-N-[(1R,3S)-3-[(1S)-1-methylpropyl]carbamoyl]cyclopentyl]benzamide ("A74")

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LC/MS: M+H 420;

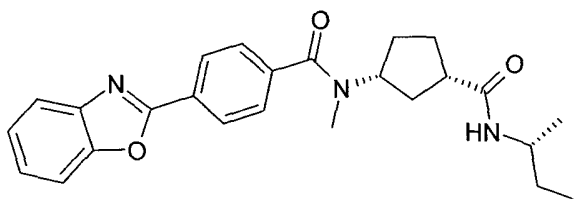
5

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.26 (d, J = 8.4 Hz, 2H), 7.83 (dd, J = 14.4, 7.3 Hz, 2H), 7.60 (d, J = 7.0 Hz, 2H), 7.50 (s, 1H; NH), 7.45 (pd, J = 7.4, 1.4 Hz, 2H), 4.85, 3.97 (2x br. s, 1H, ratio=1:1.7, mixture of rotamers), 3.65 (dt, J = 13.6, 6.7 Hz, 1H), 2.91 (br. s, 3H), 2.11 – 1.50 (m, 6H), 1.36 (p, J = 6.5 Hz, 2H), 1.00 (d, J = 6.2 Hz, 3H), 0.81 (t, J = 7.4 Hz, 3H);

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4-(1,3-benzoxazol-2-yl)-N-methyl-N-[(1R,3S)-3-[(1R)-1-methylpropyl]carbamoyl]cyclopentyl]benzamide ("A75")

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LC/MS: M+H 420;

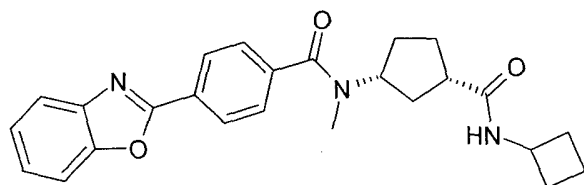
20

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.26 (d, J = 8.4 Hz, 2H), 7.83 (dd, J = 14.4, 7.3 Hz, 2H), 7.60 (d, J = 7.0 Hz, 2H), 7.50 (s, 1H; NH), 7.45 (pd, J = 7.4, 1.4 Hz, 2H), 4.85, 3.97 (2x br. s, 1H, ratio=1:1.7, mixture of rotamers), 3.65 (dt, J = 13.6, 6.7 Hz, 1H), 2.91 (br. s, 3H), 2.11 – 1.50 (m, 6H), 1.36 (p, J = 6.5 Hz, 2H), 1.00 (d, J = 6.2 Hz, 3H), 0.81 (t, J = 7.4 Hz, 3H);

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4-(1,3-benzoxazol-2-yl)-N-[(1R,3S)-3-(cyclobutylcarbamoyl)cyclopentyl]-N-methylbenzamide ("A76")

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LC/MS: M+H 418;

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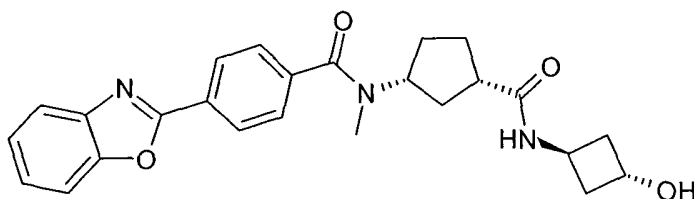
^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.26 (d, J = 8.4 Hz, 2H), 7.99 (s, 1H; NH), 7.89 – 7.76 (m, 2H), 7.60 (d, J = 7.2 Hz, 2H), 7.45 (pd, J = 7.4, 1.4 Hz,

2H), 4.86, 3.98 (2x br. s, 1H, ratio=1:1.9, mixture of rotamers), 4.17 (h, $J = 8.2$ Hz, 1H), 2.90 (br. s, 3H), 2.22 – 2.04 (m, 2H), 2.02 – 1.48 (m, 10H);

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4-(1,3-benzoxazol-2-yl)-N-[(1R,3S)-3-[(trans-3-hydroxycyclobutyl)-carbamoyl]cyclopentyl]-N-methyl-benzamide ("A77")

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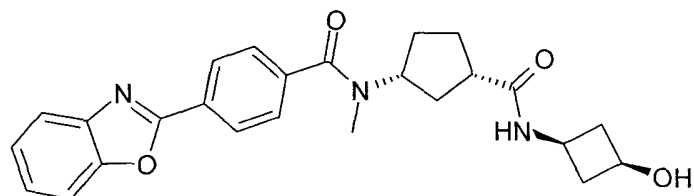
LC/MS: M+H 434;

15

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.26 (d, $J = 8.4$ Hz, 2H), 7.98 (s, 1H; NH), 7.88 – 7.77 (m, 2H), 7.60 (d, $J = 7.2$ Hz, 2H), 7.45 (pd, $J = 7.4, 1.4$ Hz, 2H), 4.95 (d, $J = 5.4$ Hz, 1H), 4.89, 3.98 (2x br. s, 1H, ratio=1:1.7, mixture of rotamers), 4.22 (dt, $J = 13.0, 3.8$ Hz, 1H), 4.16 (q, $J = 6.5$ Hz, 1H), 2.90 (br. s, 3H), 2.19 – 1.95 (m, 4H), 1.99 – 1.53 (m, 6H);

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4-(1,3-benzoxazol-2-yl)-N-[(1R,3S)-3-[(cis-3-hydroxycyclobutyl)-carbamoyl]cyclopentyl]-N-methyl-benzamide ("A78")



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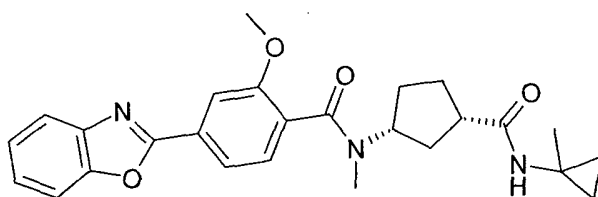
LC/MS: M+H 434;

30

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.26 (d, $J = 8.4$ Hz, 2H), 7.90 (s, 1H; NH), 7.83 (dd, $J = 13.8, 8.0$ Hz, 2H), 7.59 (d, $J = 7.0$ Hz, 2H), 7.45 (pd, $J = 7.4, 1.4$ Hz, 2H), 5.00 (d, $J = 5.7$ Hz, 1H; OH), 4.88, 3.98 (2x br. s, 1H, ratio=1:1.5, mixture of rotamers), 3.77 (h, $J = 7.0$ Hz, 1H), 3.65 (h, $J = 8.5$ Hz, 1H), 2.90 (br. s, 3H), 2.46 (d, $J = 7.0$ Hz, 2H), 2.03 – 1.49 (m, 8H);

35

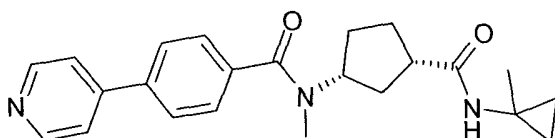
4-(1,3-benzoxazol-2-yl)-2-methoxy-N-methyl-N-[(1R,3S)-3-[(1-methylcyclopropyl)carbamoyl]cyclopentyl]benzamide ("A79")



LC/MS: M+H 448;

¹H NMR (400 MHz, DMSO-d₆) δ [ppm] 7.92, 7.89 (2x s, 1H, NH; ratio=1:1.9, mixture of rotamers), 7.87 – 7.75 (m, 4H), 7.45 (pd, J = 7.4, 1.4 Hz, 2H), 7.41 – 7.33 (m, 1H), 4.91, 3.80 (2x m, 1H, ratio=1:1.9, mixture of rotamers) 3.97 – 3.90 (m, 3H), 2.90, 2.69 (2x s, 3H, ratio=1:1.9, mixture of rotamers), 1.96 – 1.46 (m, 6H), 1.29 – 1.19 (m, 3H), 0.65 – 0.39 (m, 4H);

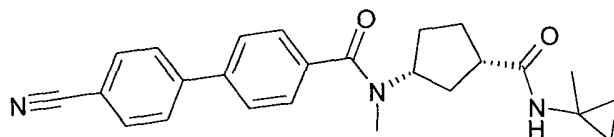
N-methyl-N-[(1R,3S)-3-[(1-methylcyclopropyl)carbamoyl]cyclopentyl]-4-(4-pyridyl)benzamide ("A80")



LC/MS: M+H 378;

¹H NMR (400 MHz, DMSO-d₆) δ [ppm] 8.66 (d, J = 6.1 Hz, 2H), 7.94 (s, 1H; NH), 7.86 (d, J = 8.4 Hz, 2H), 7.75 (d, J = 6.2 Hz, 2H), 7.50 (d, J = 7.4 Hz, 2H), 4.85, 3.97 (2x br. s, 1H, ratio=1:1.7, mixture of rotamers), 2.88 (br. s, 3H), 2.08 – 1.45 (m, 6H), 1.25 (s, 3H), 0.64 – 0.41 (m, 4H);

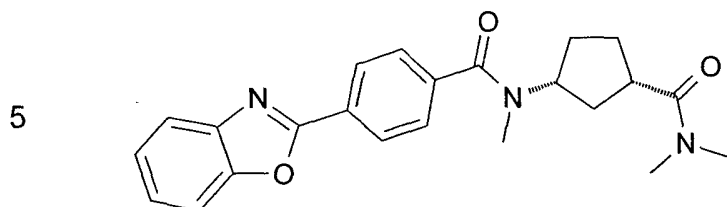
4-(4-cyanophenyl)-N-methyl-N-[(1R,3S)-3-[(1-methylcyclopropyl)-carbamoyl]cyclopentyl]benzamide ("A81")



LC/MS: M+H 402;

¹H NMR (400 MHz, DMSO-d₆) δ [ppm] 7.97 – 7.90 (m, 5H), 7.81 (d, J = 8.4 Hz, 2H), 7.49 (d, J = 7.5 Hz, 2H), 2.88 (br. s, 3H), 4.82, 4.02 (2x br. s, 1H, ratio=1:1.8, mixture of rotamers), 2.08 – 1.45 (m, 6H), 1.25 (s, 3H), 0.63 – 0.40 (m, 4H);

4-benzoxazol-2-yl-N-((1R,3S)-3-dimethylcarbamoyl-cyclopentyl)-N-methyl-benzamide ("A82")



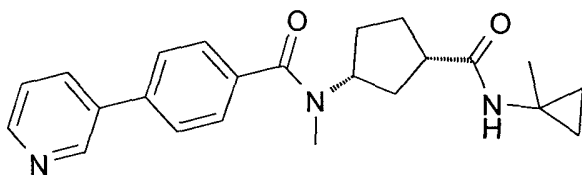
LC/MS: M+H 392;

¹H NMR (400 MHz, DMSO-d₆) δ [ppm] 8.26 (d, *J* = 8.3 Hz, 2H), 7.83 (ddd, *J* = 12.4, 7.0, 1.6 Hz, 2H), 7.60 (d, *J* = 7.3 Hz, 2H), 7.45 (pd, *J* = 7.4, 1.4 Hz, 2H), 4.92, 4.00 (2x br. s, 1H, ratio=1:2.5, mixture of rotamers), 3.16 – 2.83 (m, 6H), 2.82 (s, 3H), 2.10 – 1.57 (m, 6H);

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N-methyl-N-[(1R,3S)-3-(1-methyl-cyclopropylcarbamoyl)-cyclopentyl]-4-pyridin-3-yl-benzamide ("A83")

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LC/MS: M+H 378;

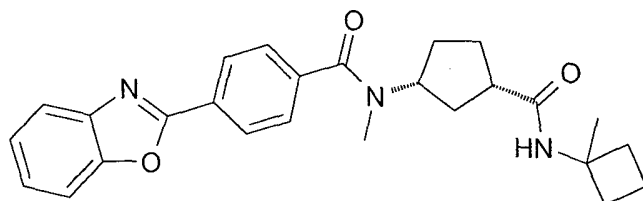
¹H NMR (400 MHz, DMSO-d₆) δ [ppm] 8.93 (dd, *J* = 2.4, 0.7 Hz, 1H), 8.60 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.12 (ddd, *J* = 8.0, 2.4, 1.7 Hz, 1H), 7.95 (s, 1H; NH), 7.79 (d, *J* = 8.4 Hz, 2H), 7.59 – 7.33 (m, 3H), 4.83, 4.04 (2x br. s, 1H, ratio=1:1.8, mixture of rotamers), 2.88 (s, 3H), 1.98 – 1.53 (m, 6H), 1.25 (s, 3H), 0.64 – 0.41 (m, 4H);

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4-benzoxazol-2-yl-N-methyl-N-[(1R,3S)-3-(1-methyl-cyclobutylcarbamoyl)-cyclopentyl]-benzamide ("A84")

30



LC/MS: M+H 432;

¹H NMR (400 MHz, DMSO-d₆) δ [ppm] 8.26 (d, *J* = 8.4 Hz, 2H), 7.87 – 7.78 (m, 2H), 7.74 (s, 1H; NH), 7.60 (d, *J* = 7.8 Hz, 2H), 7.51 – 7.37 (m, 2H), 2.90

35

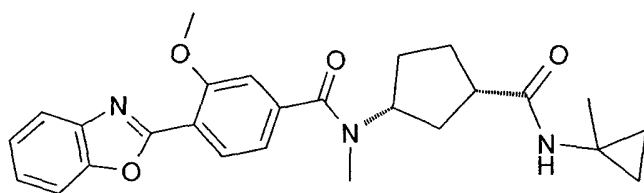
- 87 -

(br. s, 3H), 4.84, 3.95 (2x br. s, 1H, ratio=1:1.5, mixture of rotamers), 2.26 – 2.12 (m, 2H), 2.01 – 1.60 (m, 10H), 1.34 (s, 3H);

5

4-benzoxazol-2-yl-3-methoxy-N-methyl-N-[(1R,3S)-3-(1-methyl-cyclopropyl-carbamoyl)-cyclopentyl]-benzamide ("A85")

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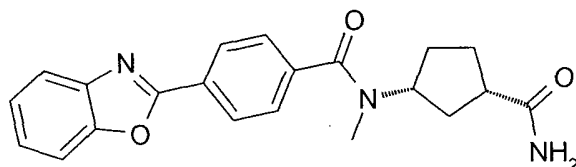
LC/MS: M+H 448;

15

¹H NMR (400 MHz, DMSO-d₆) δ [ppm] 8.09 (d, *J* = 7.9 Hz, 1H), 7.96 (s, 1H; NH), 7.88 – 7.73 (m, 2H), 7.50 – 7.39 (m, 2H), 7.23 (s, 1H), 7.11 (d, *J* = 7.9 Hz, 1H), 3.98 (s, 3H), , 4.89, 4.02 (2x br. s, 1H, ratio=1:1.4, mixture of rotamers), 2.92 (br. s, 3H), 2.11 – 1.55 (m, 6H), 1.26 (s, 3H), 0.66 – 0.37 (m, 4H);

20

4-benzoxazol-2-yl-N-((1R,3S)-3-carbamoyl-cyclopentyl)-N-methyl-benzamide ("A86")



LC/MS: M+H 364;

25

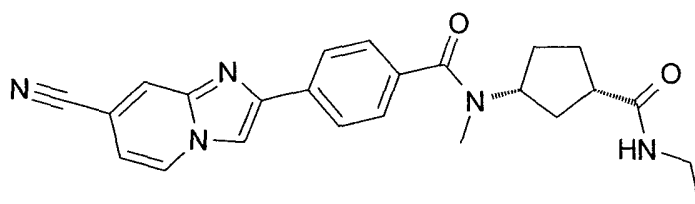
¹H NMR (400 MHz, DMSO-d₆) δ [ppm] 8.26 (d, *J* = 8.3 Hz, 2H), 7.83 (ddd, *J* = 13.1, 7.3, 1.7 Hz, 2H), 7.60 (d, *J* = 6.7 Hz, 2H), 7.45 (pd, *J* = 7.4, 1.3 Hz, 2H), 7.23 (s, 1H; NH), 6.74 (s, 1H; NH), , 4.89, 3.99 (2x br. s, 1H, ratio=1:2.0, mixture of rotamers), 2.91 (br. s, 3H), 2.45 (br. s, 1H), 2.15 – 1.51 (m, 6H);

30

4-(7-cyano-imidazo[1,2-a]pyridin-2-yl)-N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-N-methyl-benzamide ("A87")

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- 88 -



LC/MS: M+H 416;

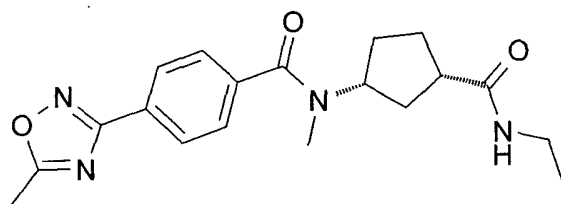
5

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.72 (d, J = 7.0 Hz, 1H), 8.69 (s, 1H), 8.36 (s, 1H), 8.06 (d, J = 8.3 Hz, 2H), 7.73 (s, 1H; NH), 7.47 (d, J = 7.8 Hz, 2H), 7.22 (dd, J = 7.0, 1.6 Hz, 1H), 4.85, 4.07 (2x br. s, 1H, ratio=1:2.0, mixture of rotamers), 3.05 (p, J = 7.1 Hz, 2H), 2.88 (br. s, 3H), 2.01 – 1.51 (m, 6H), 1.00 (t, J = 7.2 Hz, 3H);

10

N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-N-methyl-4-(5-methyl-1,2,4-oxadiazol-3-yl)-benzamide ("A88")

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LC/MS: M+H 357;

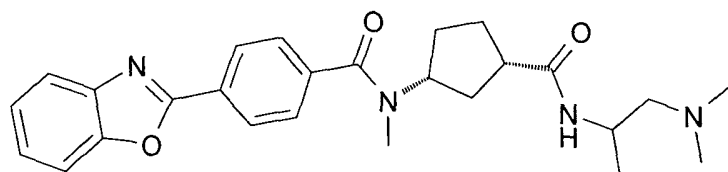
20

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.04 (d, J = 8.3 Hz, 2H), 7.72 (s, 1H; NH), 7.54 (d, J = 7.2 Hz, 2H), 4.88, 3.96 (2x br. s, 1H, ratio=1:1.7, mixture of rotamers), 3.05 (p, J = 7.1 Hz, 2H), 2.89 (br. s, 3H), 2.68 (s, 3H), 2.42 (br. s, 1H), 2.06 – 1.49 (m, 6H), 0.99 (t, J = 7.1 Hz, 3H);

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4-benzoxazol-2-yl-N-[(1R,3S)-3-(2-dimethylamino-1-methyl-ethylcarbamoyl)-cyclopentyl]-N-methyl-benzamide ("A89")

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LC/MS: M+H 449;

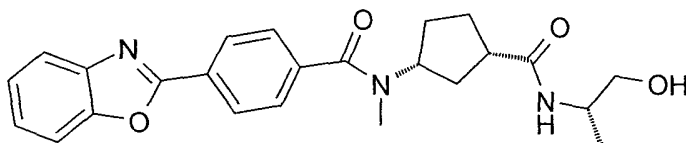
35

^1H NMR (400 MHz, DMSO- d_6 + CF_3COOD) δ [ppm] 8.31 (d, J = 8.1 Hz, 2H), 7.84 (d, J = 7.2 Hz, 1H), 7.78 (d, J = 8.1 Hz, 1H), 7.61 (d, J = 7.4 Hz, 2H), 7.45 (p, J = 7.3 Hz, 2H), 4.95, 4.09 (2x br. s, 1H, ratio=1:1.8, mixture of rotamers), 4.35 – 4.17 (m, 1H), 3.13 (d, J = 4.8 Hz, 2H), 2.95

(s, 3H), 2.85 (s, 3H), 2.83 (s, 3H), 2.18 – 1.60 (m, 6H), 1.19 – 1.03 (m, 3H);

5

4-benzoxazol-2-yl-N-[(1R,3S)-3-((S)-2-hydroxy-1-methyl-ethylcarbamoyl)-cyclopentyl]-N-methyl-benzamide ("A90")



LC/MS: M+H 422;

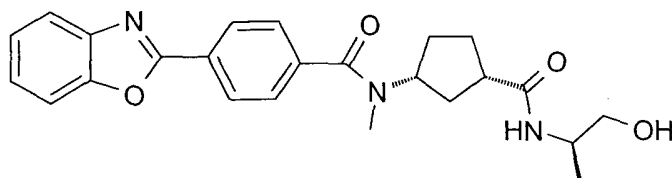
10

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.26 (d, J = 8.2 Hz, 2H), 7.83 (dd, J = 14.3, 7.3 Hz, 2H), 7.60 (d, J = 6.4 Hz, 2H), 7.54 – 7.39 (m, 3H), 4.88, 3.99 (2x br. s, 1H, ratio=1:1.7, mixture of rotamers), 4.61 (t, J = 5.4 Hz, 1H; OH), 3.85 – 3.64 (m, 1H), 3.40 – 3.29 (m, 1H), 3.26 – 3.12 (m, 1H), 2.91 (br. s, 3H), 2.15 – 1.45 (m, 6H), 1.00 (d, J = 6.0 Hz, 3H);

15

4-benzoxazol-2-yl-N-[(1R,3S)-3-((R)-2-hydroxy-1-methyl-ethylcarbamoyl)-cyclopentyl]-N-methyl-benzamide ("A91")

20



LC/MS: M+H 422;

25

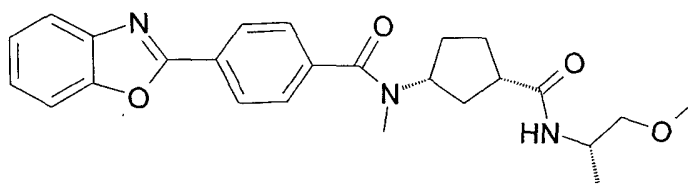
^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.26 (d, J = 8.2 Hz, 2H), 7.83 (dd, J = 14.3, 7.3 Hz, 2H), 7.60 (d, J = 6.4 Hz, 2H), 7.54 – 7.39 (m, 3H), 4.88, 3.99 (2x br. s, 1H, ratio=1:1.7, mixture of rotamers), 4.61 (t, J = 5.4 Hz, 1H; OH), 3.85 – 3.64 (m, 1H), 3.40 – 3.29 (m, 1H), 3.26 – 3.12 (m, 1H), 2.91 (br. s, 3H), 2.15 – 1.45 (m, 6H), 1.00 (d, J = 6.0 Hz, 3H);

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4-benzoxazol-2-yl-N-[(1R,3S)-3-((S)-2-methoxy-1-methyl-ethylcarbamoyl)-cyclopentyl]-N-methyl-benzamide ("A92")

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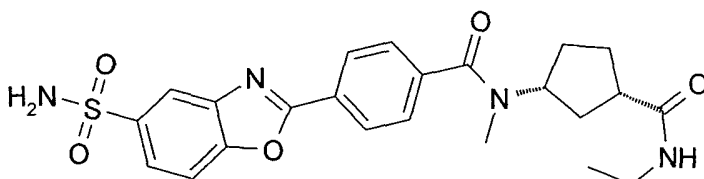
- 90 -



LC/MS: M+H 436;

5 ^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.26 (d, J = 8.3 Hz, 2H), 7.87 – 7.78 (m, 2H), 7.71 – 7.53 (m, 3H), 7.45 (pd, J = 7.4, 1.4 Hz, 2H), 4.87, 3.98 (2x br. s, 1H, ratio=1:1.9, mixture of rotamers), 3.91 (p, J = 6.7 Hz, 1H), 3.27 – 3.24 (m, 1H), 3.24 (s, 3H; CH_3O), 3.15 (dd, J = 9.4, 6.1 Hz, 1H), 2.89 (br. s, 3H),
10 2.08 – 1.53 (m, 6H), 1.01 (d, J = 6.4 Hz, 3H);

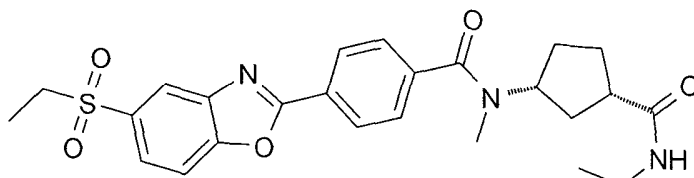
N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-N-methyl-4-(5-sulfamoyl-benzooxazol-2-yl)-benzamide ("A93")



LC/MS: M+H 471;

15 ^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.29 (d, J = 8.3 Hz, 2H), 8.23 (d, J = 1.6 Hz, 1H), 8.01 (d, J = 8.6 Hz, 1H), 7.93 (dd, J = 8.6, 1.8 Hz, 1H), 7.72 (s, 1H; NH), 7.62 (d, J = 6.5 Hz, 2H), 7.47 (s, 2H; NH_2), , 1H; NH), 7.63 (d, J = 6.6 Hz, 2H), 4.90, 3.97 (2x m, 1H, ratio=1:1.8, mixture of rotamers), 3.05 (p, J = 6.9 Hz, 2H), 2.92 (bt. s, 3H), 2.42 (br. s, 1H), 2.12 – 1.46 (m, 6H), 1.00 (t, J =
20 7.1 Hz, 3H);
25

4-(5-ethanesulfonyl-benzooxazol-2-yl)-N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-N-methyl-benzamide ("A94")



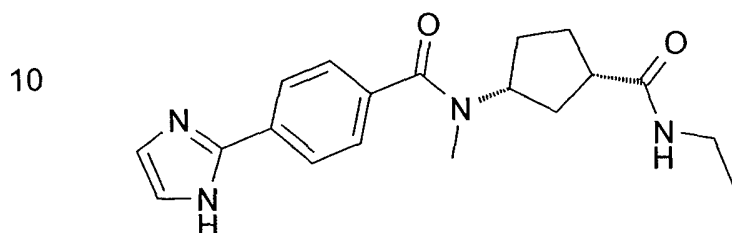
LC/MS: M+H 484;

30 ^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.34 (d, J = 1.7 Hz, 1H), 8.30 (d, J = 8.3 Hz, 1H), 8.10 (d, J = 8.6 Hz, 1H), 7.98 (dd, J = 8.6, 1.8 Hz, 1H), 7.72 (br. s,
35

1H; NH), 7.63 (d, $J = 6.6$ Hz, 2H), 4.90, 3.97 (2x m, 1H, ratio=1:1.6, mixture of rotamers), 3.39 (q, $J = 7.3$ Hz, 2H), 3.06 (p, $J = 6.9, 6.5$ Hz, 2H), 2.92 (br. s, 3H), 2.41 (br. s, 1H), 2.07 – 1.50 (m, 6H), 1.14 (t, $J = 7.3$ Hz, 3H), 1.00 (t, $J = 7.1$ Hz, 3H);

5

N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-4-(1H-imidazol-2-yl)-N-methyl-benzamide ("A95")

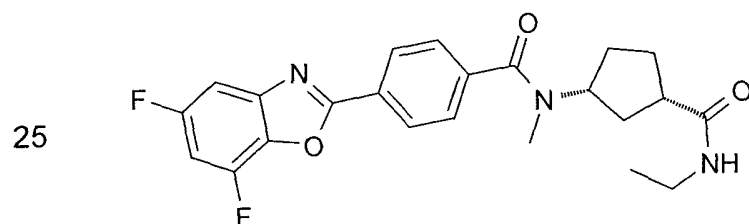


LC/MS: M+H 341;

15 ^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 12.59 (s, 1H; NH), 7.99 (d, $J = 8.3$ Hz, 2H), 7.75 (s, 1H; NH), 7.44 (d, $J = 7.7$ Hz, 2H), 7.29 (s, 1H), 7.07 (s, 1H), 4.85, 4.05 (2x br. s, 1H, ratio=1:2.0, mixture of rotamers), 3.07 (p, $J = 7.1$ Hz, 2H), 2.88 (br. s, 3H), 2.46 (br. s, 1H), 2.00 – 1.55 (m, 6H), 1.01 (t, $J = 7.2$ Hz, 3H);

20

4-(5,7-difluoro-benzoxazol-2-yl)-N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-N-methyl-benzamide ("A96")



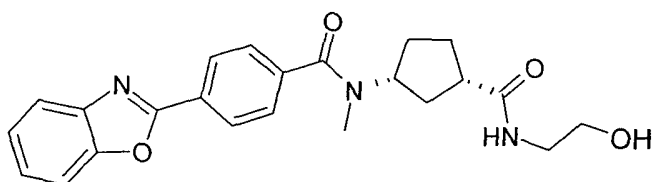
LC/MS: M+H 428;

30 ^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.27 (d, $J = 8.4$ Hz, 2H), 7.74 (s, 1H; NH), 7.66 (dd, $J = 8.4, 2.0$ Hz, 1H), 7.61 (d, $J = 3.2$ Hz, 2H), 7.51 (td, $J = 10.3, 2.3$ Hz, 1H), 4.89, 3.96 (2x m, 1H, ratio=1:1.5, mixture of rotamers), 3.05 (q, $J = 7.0, 5.9$ Hz, 2H), 2.91 (br. s, 3H), 2.43 (br. s, 1H), 2.09 – 1.48 (m, 6H), 0.99 (t, $J = 7.1$ Hz, 3H);

35

4-benzoxazol-2-yl-N-[(1R,3S)-3-(2-hydroxy-ethylcarbamoyl)-cyclopentyl]-N-methyl-benzamide ("A97")

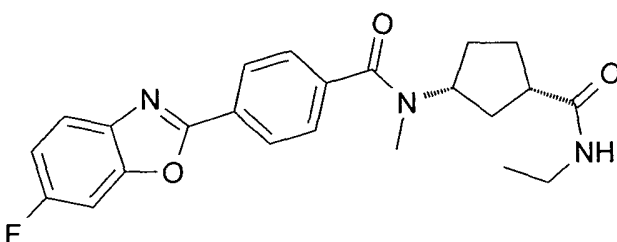
- 92 -



LC/MS: M+H 407;

5 ^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.27 (d, J = 8.4 Hz, 2H), 7.89 – 7.81 (m, 2H), 7.77 (s, 1H; NH), 7.61 (d, J = 7.4 Hz, 2H), 7.53 – 7.39 (m, 2H), 4.63 (t, J = 5.4 Hz, 1H; OH), 4.91, 4.00 (2x m, 1H, ratio=1:1.7, mixture of rotamers), 3.39 (q, J = 5.7 Hz, 2H), 3.12 (q, J = 5.8 Hz, 2H), 2.92 (br. s, 3H),
10 2.19 – 1.47 (m, 6H);

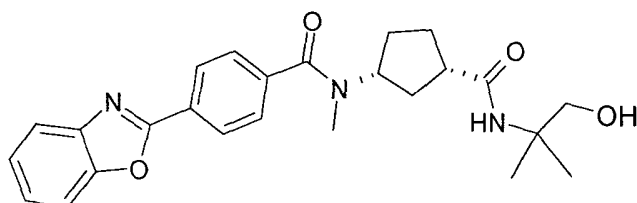
N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-4-(6-fluoro-benzoxazol-2-yl)-N-methyl-benzamide ("A98")



LC/MS: M+H 410;

15 ^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.22 (d, J = 8.3 Hz, 2H), 7.86 (dd, J = 8.8, 5.0 Hz, 1H), 7.82 (dd, J = 8.4, 2.4 Hz, 1H), 7.72 (s, 1H; NH), 7.60 (d, J = 6.8 Hz, 2H), 7.31 (ddd, J = 9.9, 8.9, 2.5 Hz, 1H), 4.89, 3.97 (2x br. s, 1H, ratio=1:1.6, mixture of rotamers), 3.05 (p, J = 6.8 Hz, 2H), 2.91 (br. s, 3H),
20 2.07 – 1.52 (m, 6H), 1.00 (t, J = 7.1 Hz, 3H);

4-benzoxazol-2-yl-N-[(1R,3S)-3-(2-hydroxy-1,1-dimethyl-ethylcarbamoyl)-cyclopentyl]-N-methyl-benzamide ("A99")



LC/MS: M+H 436;

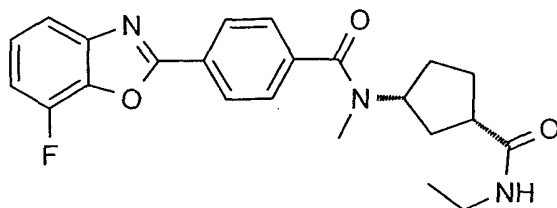
30 ^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.27 (d, J = 8.4 Hz, 2H), 7.90 – 7.78 (m, 2H), 7.61 (d, J = 7.7 Hz, 2H), 7.54 – 7.40 (m, 2H), 7.20 (s, 1H; NH), 4.83
35

(s, 1H; OH), 4.86, 3.97 (2x m, 1H, ratio=1:1.7, mixture of rotamers), 3.38 (d, $J = 5.7$ Hz, 2H), 2.91 (br. s, 3H), 2.12 – 1.46 (m, 6H), 1.17 (s, 6H);

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N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-4-(7-fluoro-benzoxazol-2-yl)-N-methyl-benzamide ("A100")

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LC/MS: M+H 410;

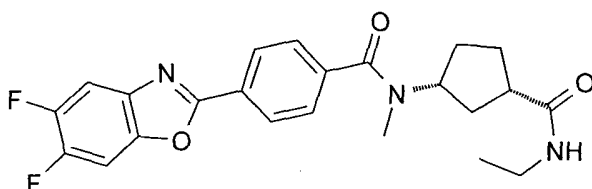
15

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.27 (d, $J = 8.3$ Hz, 2H), 7.73 (s, 1H; NH), 7.69 (d, $J = 7.8$ Hz, 1H), 7.61 (d, $J = 6.8$ Hz, 2H), 7.48 – 7.34 (m, 2H), 4.89, 3.98 (2x br. s, 1H, ratio=1:1.7, mixture of rotamers), 3.06 (p, $J = 6.6$ Hz, 2H), 2.91 (br. s, 3H), 2.42 (br. s, 1H), 2.07 – 1.52 (m, 6H), 1.00 (t, $J = 7.1$ Hz, 3H);

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4-(5,6-difluoro-benzoxazol-2-yl)-N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-N-methyl-benzamide ("A101")

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LC/MS: M+H 428;

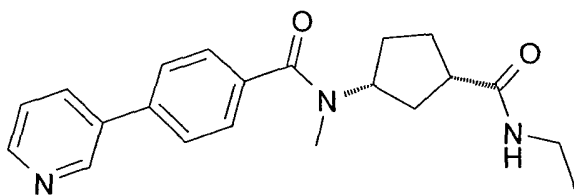
30

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.22 (d, $J = 8.2$ Hz, 2H), 8.14 (dd, $J = 9.8, 6.9$ Hz, 1H), 8.02 (dd, $J = 10.2, 7.6$ Hz, 1H), 7.74 (s, 1H; NH), 7.60 (d, $J = 7.1$ Hz, 2H), 4.89, 3.97 (2x br. s, 1H, ratio=1:1.5, mixture of rotamers), 3.05 (p, $J = 6.9$ Hz, 2H), 2.91 (br. s, 3H), 2.42 (br. s, 1H), 2.12 – 1.46 (m, 6H), 1.00 (t, $J = 7.1$ Hz, 3H);

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N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-N-methyl-4-pyridin-3-yl-benzamide ("A102")

- 94 -



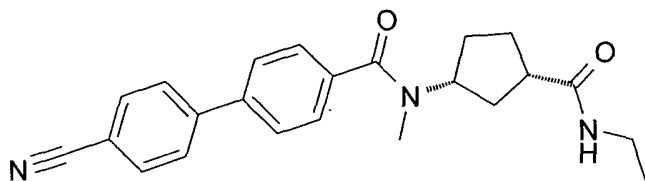
LC/MS: M+H 352;

5

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.93 (d, J = 1.9 Hz, 1H), 8.60 (dd, J = 4.8, 1.6 Hz, 1H), 8.12 (dt, J = 8.0, 2.0 Hz, 1H), 7.80 (d, J = 8.3 Hz, 2H), 7.74 (s, 1H; NH), 7.54 – 7.44 (m, 3H), 4.84, 4.07 (2x br. s, 1H, ratio=1:2.0, mixture of rotamers), 3.06 (p, J = 7.2 Hz, 2H), 2.89 (b. s, 3H), 2.00 – 1.55 (m, 6H), 1.00 (t, J = 7.2 Hz, 3H);

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4'-cyano-biphenyl-4-carboxylic acid ((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-methyl-amide ("A103")



LC/MS: M+H 376;

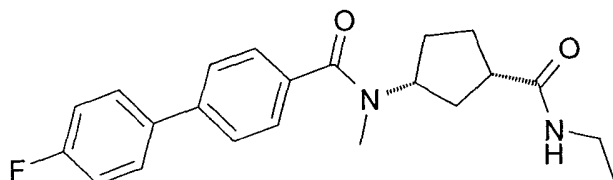
15

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^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 7.99 – 7.91 (m, 4H), 7.83 (d, J = 8.4 Hz, 2H), 7.76 (s, 1H; NH), 7.51 (d, J = 7.9 Hz, 2H), 4.87, 4.05 (2x br. s, 1H, ratio=1:1.6, mixture of rotamers), 3.07 (p, J = 7.1 Hz, 2H), 2.90 (br. s, 3H), 2.01 – 1.59 (m, 6H), 1.01 (t, J = 7.2 Hz, 3H);

25

4'-fluoro-biphenyl-4-carboxylic acid ((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-methyl-amide ("A104")



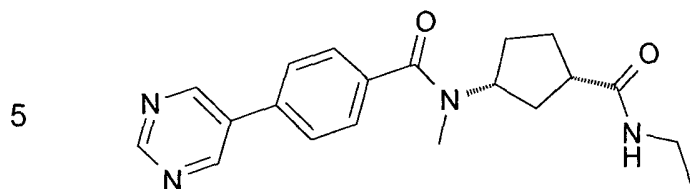
LC/MS: M+H 369;

30

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^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 7.85 – 7.67 (m, 5H), 7.46 (d, J = 7.9 Hz, 2H), 7.32 (t, J = 8.9 Hz, 2H), 4.82, 4.07 (2x br. s, 1H, ratio=1:1.6, mixture of rotamers), 3.07 (p, J = 7.1 Hz, 2H), 2.89 (br. s, 3H), 1.98 – 1.51 (m, 6H), 1.01 (t, J = 7.2 Hz, 3H);

N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-N-methyl-4-pyrimidin-5-yl-benzamide ("A105")



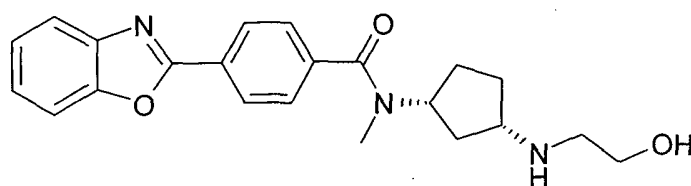
LC/MS: M+H 353;

¹H NMR (400 MHz, DMSO-d₆) δ [ppm] 9.21 (s, 1H), 9.19 (s, 2H), 7.88 (d, J = 8.4 Hz, 2H), 7.75 (s, 1H; NH), 7.52 (d, J = 7.8 Hz, 2H), 4.85, 4.03 (2x br. s, 1H, ratio=1:1.7, mixture of rotamers), 3.18 – 2.97 (m, 2H), 2.89 (br. s, 3H), 1.99 – 1.52 (m, 6H), 1.11 – 0.89 (m, 3H);

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4-benzoxazol-2-yl-N-[(1R,3S)-3-(2-hydroxy-ethylcarbamoyl)-cyclopentyl]-N-methyl-benzamide ("A106")

15



LC/MS: M+H 408;

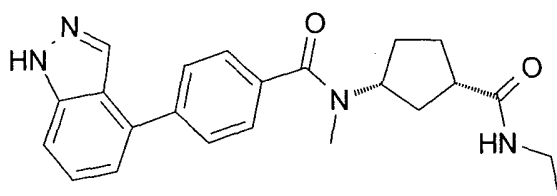
¹H NMR (400 MHz, DMSO-d₆) δ [ppm] 8.27 (d, J = 8.4 Hz, 2H), 7.88 – 7.81 (m, 2H), 7.78 (s, 1H; NH), 7.61 (d, J = 7.4 Hz, 2H), 7.51 – 7.40 (m, 2H), 4.89, 4.00 (2x br. s, 1H, ratio=1:1.8, mixture of rotamers), 4.63 (t, J = 5.4 Hz, 1H; OH), 3.39 (q, J = 5.7 Hz, 2H), 3.12 (q, J = 5.8 Hz, 2H), 2.92 (br. s, 3H), 2.11 – 1.50 (m, 6H);

20

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N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-4-(1H-indazol-4-yl)-N-methyl-benzamide ("A107")

30



LC/MS: M+H 391;

¹H NMR (400 MHz, DMSO-d₆) δ [ppm] 13.25 (s, 1H; NH), 8.21 (s, 1H), 7.80 (d, J = 8.2 Hz, 2H), 7.74 (s, 1H; NH), 7.58 (d, J = 8.3 Hz, 1H), 7.52 (d, J = 7.8

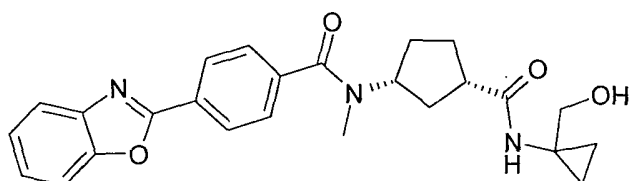
35

Hz, 2H), 7.48 – 7.43 (m, 1H), 7.28 (d, $J = 6.9$ Hz, 1H), 4.85, 4.16 (2x br. s, 1H, ratio=1:2.4, mixture of rotamers), 3.06 (p, $J = 7.2$ Hz, 2H), 2.91 (s, 3H), 2.04 – 1.58 (m, 6H), 1.00 (t, $J = 7.2$ Hz, 3H);

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4-benzoxazol-2-yl-N-[(1R,3S)-3-(1-hydroxymethyl-cyclopropylcarbamoyl)-cyclopentyl]-N-methyl-benzamide ("A108")

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LC/MS: M+H 434;

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^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.26 (d, $J = 8.4$ Hz, 2H), 8.04 (s, 1H; NH), 7.88 – 7.79 (m, 2H), 7.59 (d, $J = 7.1$ Hz, 2H), 7.50 – 7.41 (m, 2H), 4.86, 3.96 (2x br. s, 1H, ratio=1:1.6, mixture of rotamers) 4.66 (t, $J = 5.6$ Hz, 1H; OH), 3.40 (d, $J = 5.6$ Hz, 2H), 2.90 (br. s, 3H), 2.42 (br. s, 1H), 2.11 – 1.47 (m, 6H), 0.65 (s, 2H), 0.52 (s, 2H).

20

Pharmacological data

Table 2 Inhibition of FASN

of some representative compounds of the formula I

25

Compound No.	IC ₅₀ FASN (enzyme assay)	Compound No.	IC ₅₀ FASN (enzyme assay)
"A1"	A	"A61"	A
"A2"	A	"A62"	A
"A3"		"A63"	A
"A4"	B	"A64"	A
"A5"	A	"A65"	A
"A6"	A	"A66"	
"A7"	A	"A67"	A
"A8"		"A68"	A
"A9"		"A69"	A

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5	"A11"	A	"A70"	A
	"A44"	A	"A71"	A
	"A45"	A	"A72"	A
	"A46"	A	"A73"	B
	"A47"	B	"A74"	A
10	"A48"	B	"A75"	A
	"A49"	A	"A76"	A
	"A50"	A	"A77"	A
	"A51"	A	"A78"	A
	"A52"	C	"A79"	B
15	"A53"	A	"A80"	A
	"A54"	A	"A81"	A
	"A55"	A	"A82"	B
	"A56"	A	"A83"	A
	"A57"	A	"A84"	A
20	"A58"	A	"A85"	A
	"A59"	A	"A86"	B
	"A60"	C	"A87"	B
	"A88"	C	"A101"	A
	"A90"	B	"A102"	A
25	"A91"	A	"A103"	A
	"A92"	B	"A104"	A
	"A93"	C	"A106"	A
	"A96"	A	"A107"	A
	"A97"	A	"A108"	B
30	"A98"	A		
	"A99"	B		
	"A100"	A		

35 IC₅₀: < 0.3 μ M = A 0.3 - 3 μ M = B 3-50 μ M = C

The compounds shown in Table 2 are particularly preferred compounds according to the invention.

The following examples relate to medicaments:

5

Example A: Injection vials

A solution of 100 g of an active ingredient of the formula I and 5 g of disodium hydrogenphosphate in 3 l of bidistilled water is adjusted to pH 6.5 using 2 N hydrochloric acid, sterile filtered, transferred into injection vials, lyophilised under sterile conditions and sealed under sterile conditions. Each injection vial contains 5 mg of active ingredient.

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Example B: Suppositories

A mixture of 20 g of an active ingredient of the formula I with 100 g of soya lecithin and 1400 g of cocoa butter is melted, poured into moulds and allowed to cool. Each suppository contains 20 mg of active ingredient.

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Example C: Solution

A solution is prepared from 1 g of an active ingredient of the formula I, 9.38 g of $\text{NaH}_2\text{PO}_4 \cdot 2 \text{H}_2\text{O}$, 28.48 g of $\text{Na}_2\text{HPO}_4 \cdot 12 \text{H}_2\text{O}$ and 0.1 g of benzalkonium chloride in 940 ml of bidistilled water. The pH is adjusted to 6.8, and the solution is made up to 1 l and sterilised by irradiation. This solution can be used in the form of eye drops.

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Example D: Ointment

500 mg of an active ingredient of the formula I are mixed with 99.5 g of Vaseline under aseptic conditions.

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Example E: Tablets

A mixture of 1 kg of active ingredient of the formula I, 4 kg of lactose, 1.2 kg of potato starch, 0.2 kg of talc and 0.1 kg of magnesium stearate is

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pressed in a conventional manner to give tablets in such a way that each tablet contains 10 mg of active ingredient.

Example F: Dragees

5 Tablets are pressed analogously to Example E and subsequently coated in a conventional manner with a coating of sucrose, potato starch, talc, tragacanth and dye.

10 **Example G: Capsules**

2 kg of active ingredient of the formula I are introduced into hard gelatine capsules in a conventional manner in such a way that each capsule con-
15 tains 20 mg of the active ingredient.

Example H: Ampoules

A solution of 1 kg of active ingredient of the formula I in 60 l of bidistilled water is sterile filtered, transferred into ampoules, lyophilised under sterile
20 conditions and sealed under sterile conditions. Each ampoule contains 10 mg of active ingredient.

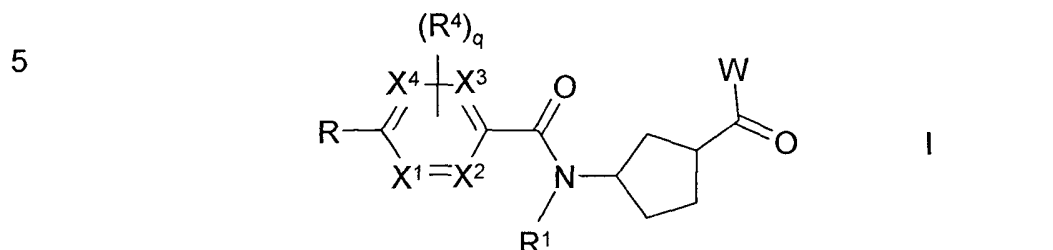
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Patent Claims

1. Compounds of the formula I



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in which

R denotes Ar, Het, $-\text{C}\equiv\text{C}-\text{Ar}$ or $-\text{C}\equiv\text{C}-\text{Het}$,

W denotes $\text{NR}^2\text{R}^{2'}$ or Het^1 ,

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R^1 denotes A, $[\text{C}(\text{R}^3)_2]_n\text{Ar}^1$ or $[\text{C}(\text{R}^3)_2]_n\text{Cyc}$,

$\text{R}^2, \text{R}^{2'}$ each, independently of one another, denote H, A or $[\text{C}(\text{R}^3)_2]_n\text{Cyc}$,

R^4 denotes H, F, Cl, Br, OH, CN, NO_2 , A', OA', SA', SO_2Me , COA', CONH_2 , CONHA' or CONA'_2 ,

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$\text{X}^1, \text{X}^2, \text{X}^3, \text{X}^4$ each, independently of one another, denote CH or N,

A denotes unbranched or branched alkyl with 1-10 C-atoms, wherein two adjacent carbon atoms may form a double bond and/or one or two non-adjacent CH- and/or CH_2 -groups may be replaced by N-, O- and/or S-atoms and wherein 1-7 H-atoms may be replaced by R^5 ,

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Cyc denotes cycloalkyl with 3-7 C-atoms, which is unsubstituted or monosubstituted by OH, Hal or A,

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A' denotes unbranched or branched alkyl with 1-6 C-atoms, wherein 1-5 H-atoms may be replaced by F,

R^5 denotes F, Cl or OH,

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Ar denotes phenyl, which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by Hal, A, $\text{O}[\text{C}(\text{R}^3)_2]_n\text{Het}^1$, Ar^1 , $[\text{C}(\text{R}^3)_2]_p\text{OR}^3$,

- $[C(R^3)_2]_p N(R^3)_2$, NO_2 , CN , $[C(R^3)_2]_p COOR^3$, $CON(R^3)_2$,
 $[C(R^3)_2]_p N(R^3)_2$, $N(R^3)_2 COA$, $NR^3 SO_2 A$, $[C(R^3)_2]_p SO_2 N(R^3)_2$,
 $S(O)_n A$, $O[C(R^3)_2]_m N(R^3)_2$, $NHCOOA$, $NHCON(R^3)_2$ and/or COA ,
- 5 Ar^1 denotes phenyl or naphthyl, which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by Hal, A, $[C(R^3)_2]_p OR^3$, $[C(R^3)_2]_p N(R^3)_2$, NO_2 , CN , $[C(R^3)_2]_p COOR^3$, $[C(R^3)_2]_p N(R^3)_2$, $N(R^3)_2 COA$, $NR^3 SO_2 A$, $[C(R^3)_2]_p SO_2 N(R^3)_2$, $S(O)_n A$, $O[C(R^3)_2]_m N(R^3)_2$, $NHCOOA$, $NHCON(R^3)_2$ and/or COA ,
- 10 R^3 denotes H or unbranched or branched alkyl with 1-6 C-atoms,
- Het denotes a mono- or bicyclic saturated, unsaturated or aromatic heterocycle having 1 to 4 N, O and/or S atoms, which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by Hal, A, $[C(R^3)_2]_n OA'$, $[C(R^3)_2]_n N(R^3)_2$, SR^3 , NO_2 , CN , $COOR^3$, $CON(R^3)_2$, $COHet^1$, $NR^3 COA$, $NR^3 SO_2 A$, $SO_2 N(R^3)_2$, $S(O)_n A$, $O[C(R^3)_2]_m N(R^3)_2$, $NHCOOA$, $NHCON(R^3)_2$, CHO , COA , $=S$, $=NH$, $=NA$ and/or $=O$ (carbonyl oxygen),
- 15 Het^1 denotes a mono- or bicyclic saturated, unsaturated or aromatic heterocycle having 1 to 4 N, O and/or S atoms, which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by Hal, A, $[C(R^3)_2]_n OR^3$, $[C(R^3)_2]_n N(R^3)_2$, SR^3 , NO_2 , CN , $COOR^3$, $CON(R^3)_2$, $NR^3 COA$, $NR^3 SO_2 A$, $SO_2 N(R^3)_2$, $S(O)_n A$, $O[C(R^3)_2]_m N(R^3)_2$, $NHCOOA$, $NHCON(R^3)_2$, CHO , COA , $=S$, $=NH$, $=NA$ and/or $=O$ (carbonyl oxygen),
- 20 Hal denotes F, Cl, Br or I,
- 30 m denotes 1, 2 or 3,
- n denotes 0, 1 or 2,
- p denotes 0, 1, 2, 3 or 4,
- 35 q 0, 1, 2 or 3,
- with the proviso that only one or two of X^1 , X^2 , X^3 , X^4 denote N,

and pharmaceutically acceptable salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios.

- 5 2. Compounds according to Claim 1 in which
 R^4 denotes H, F, Cl, OA' or A' ,
 and pharmaceutically acceptable salts, tautomers and stereoisomers
 thereof, including mixtures thereof in all ratios.
- 10 3. Compounds according to Claim 1 or 2, in which
 A denotes unbranched or branched alkyl with 1-10 C-atoms,
 wherein one or two non-adjacent CH- and/or CH_2 -groups may
 be replaced by N- and/or O-atoms and 1-7 H-atoms may be
15 replaced by R^5 ,
 and pharmaceutically acceptable salts, tautomers and stereoisomers
 thereof, including mixtures thereof in all ratios.
- 20 4. Compounds according to one or more of Claims 1-3, in which
 Ar denotes phenyl, which is unsubstituted or mono-, di-, tri-,
 tetra- or pentasubstituted by $O[C(R^3)_2]_nHet^1$, Ar^1 , A, CN
 and/or $[C(R^3)_2]_pOR^3$,
 and pharmaceutically acceptable salts, tautomers and stereoisomers
25 thereof, including mixtures thereof in all ratios.
5. Compounds according to one or more of Claims 1-4, in which
 Ar^1 denotes phenyl or naphthyl,
30 and pharmaceutically acceptable salts, tautomers and stereoisomers
 thereof, including mixtures thereof in all ratios.
6. Compounds according to one or more of Claims 1-5, in which
35 Het denotes a mono- or bicyclic aromatic heterocycle having 1 to
 4 N, O and/or S atoms, which is unsubstituted or mono- or

disubstituted by Hal, A, $[C(R^3)_2]_nOA'$, $S(O)_nA$, CN, $SO_2N(R^3)_2$ and/or COHet¹,

and pharmaceutically acceptable salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios.

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7. Compounds according to one or more of Claims 1-6, in which Het¹ denotes a monocyclic saturated heterocycle having 1 to 4 N, O and/or S atoms, which is unsubstituted or mono- or disubstituted by A,
- and pharmaceutically acceptable salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios.

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8. Compounds according to one or more of Claims 1-7, in which Het denotes furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, pyridazinyl, pyrazinyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, benzotriazolyl, indolyl, benzo-1,3-dioxolyl, benzodioxanyl, benzothiadiazolyl, indazolyl, benzofuranyl, quinolyl, isoquinolyl, oxazolo[5,4-b]-pyridyl, imidazo[1,2-a]pyridinyl or oxazolo[5,4-c]pyridyl, each of which is unsubstituted or mono- or disubstituted by Hal, A, $[C(R^3)_2]_nOA'$, $S(O)_nA$, CN, $SO_2N(R^3)_2$ and/or COHet¹,
- and pharmaceutically acceptable salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios.

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9. Compounds according to one or more of Claims 1-8, in which Het¹ denotes pyrrolidinyl, azetidiny, oxetanyl, tetrahydroimidazolyl, tetrahydropyrazolyl, tetrahydrofuranyl, piperidinyl, piperazinyl, morpholinyl, hexahydropyridazinyl, hexahydropyrimidinyl, [1,3]dioxolanyl or tetrahydropyranyl, each of which is unsubstituted or mono- or disubstituted by A,

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and pharmaceutically acceptable salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios.

- 5 10. Compounds according to one or more of Claims 1-9, in which
- R denotes Ar, Het, $-C\equiv C-Ar$ or $-C\equiv C-Het$,
- W denotes $NR^2R^{2'}$ or Het^1 ,
- 10 R^1 denotes A, $[C(R^3)_2]_nAr^1$ or $[C(R^3)_2]_nCyc$,
- $R^2, R^{2'}$ each, independently of one another, denote H, A or $[C(R^3)_2]_nCyc$,
- R^4 denotes H, F, Cl, OA' or A' ,
- 15 X^1, X^2, X^3, X^4 each, independently of one another, denote CH or N,
- A denotes unbranched or branched alkyl with 1-10 C-atoms,
wherein one or two non-adjacent CH- and/or CH_2 -groups may
be replaced by N- and/or O-atoms and 1-7 H-atoms may be
replaced by R^5 ,
- 20 Cyc denotes cycloalkyl with 3-7 C-atoms, which is unsubstituted or
monosubstituted by OH or A,
- A' denotes unbranched or branched alkyl with 1-6 C-atoms,
wherein 1-5 H-atoms may be replaced by F,
- 25 R^5 denotes F, Cl or OH,
- Ar denotes phenyl, which is unsubstituted or mono-, di-, tri-, tetra- or
pentasubstituted by $O[C(R^3)_2]_nHet^1$, Ar^1 , A, CN and/or
 $[C(R^3)_2]_pOR^3$,
- 30 Ar^1 denotes phenyl or naphthyl,
- R^3 denotes H or unbranched or branched alkyl with 1-6 C-atoms,
- Het denotes furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl,
35 isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, triazolyl,
tetrazolyl, oxadiazolyl, thiadiazolyl, pyridazinyl, pyrazinyl,

benzoxazolyl, benzothiazolyl, benzimidazolyl, benzotriazolyl, indolyl, benzo-1,3-dioxolyl, benzodioxanyl, benzothiadiazolyl, indazolyl, benzofuranyl, quinolyl, isoquinolyl, oxazolo[5,4-b]-pyridyl, imidazo[1,2-a]pyridinyl or oxazolo[5,4-c]pyridyl, each of which is unsubstituted or mono- or disubstituted by Hal, A, $[C(R^3)_2]_nOA'$, $S(O)_nA$, CN, $SO_2N(R^3)_2$ and/or $COHet^1$,

Het¹ denotes pyrrolidinyl, azetidiny, oxetanyl, tetrahydroimidazolyl, tetrahydropyrazolyl, tetrahydrofuranyl, piperidinyl, piperazinyl, morpholinyl, hexahydropyridazinyl, hexahydropyrimidinyl, [1,3]dioxolanyl or tetrahydropyranyl, each of which is unsubstituted or mono- or disubstituted by A,

Hal denotes F, Cl, Br or I,

n denotes 0, 1 or 2,

p denotes 0, 1, 2, 3 or 4,

q 0, 1, 2 or 3,

with the proviso that only one or two of X^1 , X^2 , X^3 , X^4 denote N, and pharmaceutically acceptable salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios.

11. Compounds according to Claim 1, selected from the group

No.	Name
"A1"	4-(1,3-benzoxazol-2-yl)-N-[(1R,3S)-3-(ethylcarbamoyl)cyclopentyl]-N-methyl-benzamide
"A2"	N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-N-methyl-4-(1-methyl-1H-benzoimidazol-2-yl)-benzamide
"A3"	4-benzothiazol-2-yl-N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-N-methyl-benzamide
"A4"	4'-[(R)-(tetrahydro-furan-3-yl)oxy]-biphenyl-4-carboxylic acid ((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-methyl-amide

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"A5"	4-benzoxazol-2-yl-N-((1R,3S)-3-isopropylcarbamoyl-cyclopentyl)-N-methyl-benzamide
"A6"	4-benzoxazol-2-yl-N-((1R,3S)-3-cyclopropylcarbamoyl-cyclopentyl)-N-methyl-benzamide
"A7"	4-benzoxazol-2-yl-N-((1R,3S)-3-cyclopentylcarbamoyl-cyclopentyl)-N-methyl-benzamide
"A8"	4-benzoxazol-2-yl-N-[(1R,3S)-3-(cyclohexylmethylcarbamoyl)-cyclopentyl]-N-methyl-benzamide
"A9"	4-benzoxazol-2-yl-N-methyl-N-[(1R,3S)-3-(pyrrolidine-1-carbonyl)-cyclopentyl]-benzamide
"A10"	4-(1,3-benzoxazol-2-yl)-N-[(1S,3R)-3-(ethylcarbamoyl)cyclopentyl]-N-methyl-benzamide
"A11"	4-(1H-benzimidazol-2-yl)-N-[(1R,3S)-3-(ethylcarbamoyl)cyclopentyl]-N-methyl-benzamide
"A12"	4-benzoxazol-2-yl-N-ethyl-N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-benzamide
"A13"	4-benzoxazol-2-yl-N-benzyl-N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-benzamide
"A14"	N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-N-methyl-4-oxazolo[5,4-b]pyridin-2-yl-benzamide
"A15"	N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-N-methyl-4-oxazolo[5,4-c]pyridin-2-yl-benzamide
"A16"	4'-methoxy-biphenyl-4-carboxylic acid ((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-methyl-amide
"A17"	4'-[(S)-(tetrahydro-furan-3-yl)oxy]-biphenyl-4-carboxylic acid ((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-methyl-amide
"A18"	4-benzoxazol-2-yl-N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-2-fluoro-N-methyl-benzamide
"A19"	N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-4-(5-fluoro-benzoxazol-2-yl)-N-methyl-benzamide

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"A20"	4-benzoxazol-2-yl-N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-2,6-difluoro-N-methyl-benzamide
"A21"	N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-N-methyl-4-(5-trifluoromethoxy-benzoxazol-2-yl)-benzamide
"A22"	4-benzoxazol-2-yl-N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-N-methyl-3-trifluoromethyl-benzamide
"A23"	4-(6-chloro-benzoxazol-2-yl)-N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-N-methyl-benzamide
"A24"	N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-N-methyl-4-naphthalen-2-yl-benzamide
"A25"	N-((1R,3S)-3-Ethylcarbamoyl-cyclopentyl)-4-isoquinolin-6-yl-N-methyl-benzamide
"A26"	4-benzofuran-5-yl-N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-N-methyl-benzamide
"A27"	N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-N-methyl-4-(1-methyl-1H-benzoimidazol-5-yl)-benzamide
"A28"	4-benzoxazol-2-yl-N-[(1R,3S)-3-(4-ethyl-piperazine-1-carbonyl)-cyclopentyl]-N-methyl-benzamide
"A29"	4-benzoxazol-2-yl-N-cyclopropylmethyl-N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-benzamide
"A30"	N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-4-(1H-indol-2-yl)-N-methyl-benzamide
"A31"	N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-N-methyl-4-[5-(pyrrolidine-1-carbonyl)-benzoxazol-2-yl]-benzamide
"A32"	4-benzoxazol-2-yl-N-[(1R,3S)-3-(cyclopentylmethyl-carbamoyl)-cyclopentyl]-N-methyl-benzamide
"A33"	4-benzoxazol-2-yl-N-methyl-N-[(1R,3S)-3-(oxetan-3-ylcarbamoyl)-cyclopentyl]-benzamide
"A34"	4-benzoxazol-2-yl-N-methyl-N-((1R,3S)-3-[(S)-1-(tetrahydro-furan-2-yl)methyl]-carbamoyl)-cyclopentyl)-benzamide

	"A35"	4-benzoxazol-2-yl-N-methyl-N-((1R,3S)-3-[(R)-1-(tetrahydro-furan-2-yl)methyl]-carbamoyl)-cyclopentyl)-benzamide
5	"A36"	4-benzoxazol-2-yl-N-[(1R,3S)-3-(2-methoxy-ethylcarbamoyl)-cyclopentyl]-N-methyl-benzamide
	"A37"	4-benzoxazol-2-yl-N-methyl-N-((1R,3S)-3-[(R)-(tetrahydro-furan-3-yl)carbamoyl]-cyclopentyl)-benzamide
10	"A38"	4-benzoxazol-2-yl-N-methyl-N-((1R,3S)-3-[(S)-(tetrahydro-furan-3-yl)carbamoyl]-cyclopentyl)-benzamide
	"A39"	6-benzoxazol-2-yl-N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-N-methyl-nicotinamide
15	"A40"	5-benzoxazol-2-yl-pyridine-2-carboxylic acid ((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-methyl-amide
	"A41"	N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-4-(5-methoxy-benzoxazol-2-yl)-N-methyl-benzamide
	"A42"	4-(5-chloro-benzoxazol-2-yl)-N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-N-methyl-benzamide
20	"A43"	N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-N-methyl-4-(5-trifluoromethyl-benzoxazol-2-yl)-benzamide
	"A44"	4-(1,3-benzoxazol-2-yl)-N-[(1R,3R)-3-(ethylcarbamoyl)cyclopentyl]-N-methyl-benzamide
25	"A45"	4-benzoxazol-2-yl-N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-3-methoxy-N-methyl-benzamide
	"A46"	4-benzoxazol-2-yl-N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-2-methoxy-N-methyl-benzamide
30	"A47"	4-benzoxazol-2-yl-N-[(1R,3S)-3-(ethyl-methyl-carbamoyl)-cyclopentyl]-N-methyl-benzamide
	"A48"	4-benzoxazol-2-yl-N-((1R,3S)-3-diethylcarbamoyl-cyclopentyl)-N-methyl-benzamide
35	"A49"	4'-methyl-biphenyl-4-carboxylic acid ((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-methyl-amide

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"A50"	biphenyl-4-carboxylic acid ((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-methyl-amide
"A51"	3-chloro-biphenyl-4-carboxylic acid ((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-methyl-amide
"A52"	N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-4-(6-methoxy-4-methyl-pyridazin-3-yl)-N-methyl-benzamide
"A53"	5-phenyl-pyridine-2-carboxylic acid ((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-methyl-amide
"A54"	4-(4-chloro-phenylethynyl)-N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-N-methyl-benzamide
"A55"	N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-4-(4-fluoro-phenylethynyl)-N-methyl-benzamide
"A56"	N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-N-methyl-4-pyridin-4-yl-benzamide
"A57"	N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-2-fluoro-N-methyl-4-pyridin-4-yl-benzamide
"A58"	4'-ethyl-3,5-difluoro-biphenyl-4-carboxylic acid ((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-methyl-amide
"A59"	2'-methanesulfonyl-biphenyl-4-carboxylic acid ((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-methyl-amide
"A60"	2'-tert-butylsulfamoyl-biphenyl-4-carboxylic acid ((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-methyl-amide
"A61"	2'-sulfamoyl-biphenyl-4-carboxylic acid ((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-methyl-amide
"A62"	4'-chloro-biphenyl-4-carboxylic acid ((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-methyl-amide
"A63"	2',4'-difluoro-biphenyl-4-carboxylic acid ((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-methyl-amide
"A64"	2'-trifluoromethyl-biphenyl-4-carboxylic acid ((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-methyl-amide

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"A65"	2,2'-dimethyl-biphenyl-4-carboxylic acid ((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-methyl-amide
"A66"	4'-(bis-trifluoromethyl-amino)-biphenyl-4-carboxylic acid ((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-methyl-amide
"A67"	biphenyl-4-carboxylic acid methyl-[(1R,3S)-3-(1-methyl-cyclopropylcarbamoyl)-cyclopentyl]-amide
"A68"	4-benzoxazol-2-yl-N-methyl-N-[(1R,3S)-3-(1-methyl-cyclopropylcarbamoyl)-cyclopentyl]-benzamide
"A69"	N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-4-(4-methoxy-phenylethynyl)-N-methyl-benzamide
"A70"	N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-N-methyl-4-pyridin-4-ylethynyl-benzamide
"A71"	4-benzothiazol-2-yl-N-methyl-N-[(1R,3S)-3-(1-methyl-cyclopropylcarbamoyl)-cyclopentyl]-benzamide
"A72"	4-(4-fluoro-phenylethynyl)-N-methyl-N-[(1R,3S)-3-(1-methyl-cyclopropylcarbamoyl)-cyclopentyl]-benzamide
"A73"	4-benzoxazol-2-yl-N-methyl-N-[(1R,3S)-3-(1-propyl-cyclopropylcarbamoyl)-cyclopentyl]-benzamide
"A74"	4-(1,3-benzoxazol-2-yl)-N-methyl-N-[(1R,3S)-3-[(1S)-1-methylpropyl]carbamoyl]cyclopentyl]benzamide
"A75"	4-(1,3-benzoxazol-2-yl)-N-methyl-N-[(1R,3S)-3-[(1R)-1-methylpropyl]carbamoyl]cyclopentyl]benzamide
"A76"	4-(1,3-benzoxazol-2-yl)-N-[(1R,3S)-3-(cyclobutylcarbamoyl)cyclopentyl]-N-methyl-benzamide
"A77"	4-(1,3-benzoxazol-2-yl)-N-[(1R,3S)-3-[(trans-3-hydroxycyclobutyl)carbamoyl]cyclopentyl]-N-methyl-benzamide
"A78"	4-(1,3-benzoxazol-2-yl)-N-[(1R,3S)-3-[(cis-3-hydroxycyclobutyl)carbamoyl]cyclopentyl]-N-methyl-benzamide

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"A79"	4-(1,3-benzoxazol-2-yl)-2-methoxy-N-methyl-N-[(1R,3S)-3-[(1-methylcyclopropyl)carbamoyl]cyclopentyl]benzamide
"A80"	N-methyl-N-[(1R,3S)-3-[(1-methylcyclopropyl)carbamoyl]cyclopentyl]-4-(4-pyridyl)benzamide
"A81"	4-(4-cyanophenyl)-N-methyl-N-[(1R,3S)-3-[(1-methylcyclopropyl)carbamoyl]cyclopentyl]benzamide
"A82"	4-benzoxazol-2-yl-N-((1R,3S)-3-dimethylcarbamoyl-cyclopentyl)-N-methyl-benzamide
"A83"	N-methyl-N-[(1R,3S)-3-(1-methyl-cyclopropylcarbamoyl)-cyclopentyl]-4-pyridin-3-yl-benzamide
"A84"	4-benzoxazol-2-yl-N-methyl-N-[(1R,3S)-3-(1-methyl-cyclobutylcarbamoyl)-cyclopentyl]-benzamide
"A85"	4-benzoxazol-2-yl-3-methoxy-N-methyl-N-[(1R,3S)-3-(1-methyl-cyclopropylcarbamoyl)-cyclopentyl]-benzamide
"A86"	4-benzoxazol-2-yl-N-((1R,3S)-3-carbamoyl-cyclopentyl)-N-methyl-benzamide
"A87"	4-(7-cyano-imidazo[1,2-a]pyridin-2-yl)-N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-N-methyl-benzamide
"A88"	N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-N-methyl-4-(5-methyl-[1,2,4]oxadiazol-3-yl)-benzamide
"A89"	4-benzoxazol-2-yl-N-[(1R,3S)-3-(2-dimethylamino-1-methyl-ethylcarbamoyl)-cyclopentyl]-N-methyl-benzamide
"A90"	4-benzoxazol-2-yl-N-[(1R,3S)-3-((S)-2-hydroxy-1-methyl-ethylcarbamoyl)-cyclopentyl]-N-methyl-benzamide
"A91"	4-benzoxazol-2-yl-N-[(1R,3S)-3-((R)-2-hydroxy-1-methyl-ethylcarbamoyl)-cyclopentyl]-N-methyl-benzamide
"A92"	4-benzoxazol-2-yl-N-[(1R,3S)-3-((S)-2-methoxy-1-methyl-ethylcarbamoyl)-cyclopentyl]-N-methyl-benzamide
"A93"	N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-N-methyl-4-(5-sulfamoyl-benzoxazol-2-yl)-benzamide

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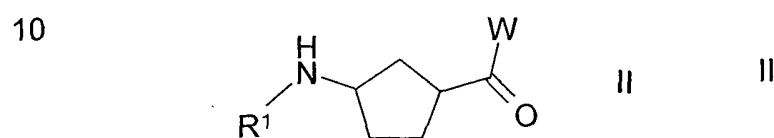
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"A94"	4-(5-ethanesulfonyl-benzoxazol-2-yl)-N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-N-methyl-benzamide
"A95"	N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-4-(1H-imidazol-2-yl)-N-methyl-benzamide
"A96"	4-(5,7-difluoro-benzoxazol-2-yl)-N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-N-methyl-benzamide
"A97"	4-benzoxazol-2-yl-N-[(1R,3S)-3-(2-hydroxy-ethylcarbamoyl)-cyclopentyl]-N-methyl-benzamide
"A98"	N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-4-(6-fluoro-benzoxazol-2-yl)-N-methyl-benzamide
"A99"	4-benzoxazol-2-yl-N-[(1R,3S)-3-(2-hydroxy-1,1-dimethyl-ethylcarbamoyl)-cyclopentyl]-N-methyl-benzamide
"A100"	N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-4-(7-fluoro-benzoxazol-2-yl)-N-methyl-benzamide
"A101"	4-(5,6-difluoro-benzoxazol-2-yl)-N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-N-methyl-benzamide
"A102"	N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-N-methyl-4-pyridin-3-yl-benzamide
"A103"	4'-cyano-biphenyl-4-carboxylic acid ((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-methyl-amide
"A104"	4'-fluoro-biphenyl-4-carboxylic acid ((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-methyl-amide
"A105"	N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-N-methyl-4-pyrimidin-5-yl-benzamide
"A106"	4-benzoxazol-2-yl-N-[(1R,3S)-3-(2-hydroxy-ethylcarbamoyl)-cyclopentyl]-N-methyl-benzamide
"A107"	N-((1R,3S)-3-ethylcarbamoyl-cyclopentyl)-4-(1H-indazol-4-yl)-N-methyl-benzamide
"A108"	4-benzoxazol-2-yl-N-[(1R,3S)-3-(1-hydroxymethyl-cyclopropylcarbamoyl)-cyclopentyl]-N-methyl-benzamide

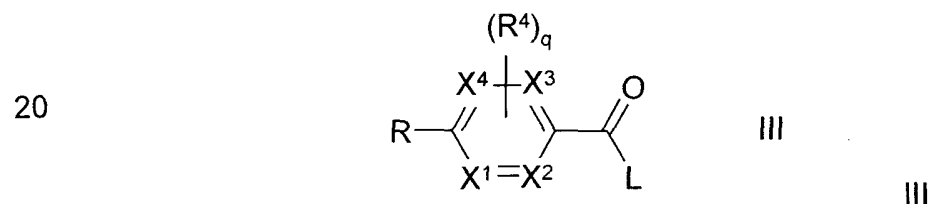
and pharmaceutically acceptable salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios.

- 5 12. Process for the preparation of compounds of the formula I according to Claims 1-11 and pharmaceutically acceptable salts, tautomers and stereoisomers thereof, characterised in that
a compound of the formula II



in which R¹ and W have the meanings indicated in Claim 1,

- 15 is reacted with a compound of the formula III



- 25 in which R, R⁴, X¹, X², X³, X⁴ and q have the meanings indicated in Claim 1,
and L denotes Cl, Br, I or a free or reactively functionally modified OH group,

- 30 and/or
a base or acid of the formula I is converted into one of its salts.

- 35 13. Medicaments comprising at least one compound of the formula I and/or pharmaceutically acceptable salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios, and

optionally an pharmaceutically acceptable carrier, excipient or vehicle.

- 5 14. Compounds of the formula I and pharmaceutically acceptable salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios, for the use for the treatment and/or prevention of cancer, multiple sclerosis, cardiovascular diseases, central nervous system injury and different forms of inflammation.
- 10 15. Compounds according to claim 14 for the use for the treatment and/or prevention of diseases selected from the group cancer of head, neck, eye, mouth, throat, esophagus, bronchus, larynx, pharynx, chest, bone, lung, colon, rectum, stomach, prostate, urinary bladder, uterine, cervix, 15 breast, ovaries, testicles or other reproductive organs, skin, thyroid, blood, lymph nodes, kidney, liver, pancreas, brain, central nervous system, solid tumors and blood-borne tumors.
- 20 16. Medicaments comprising at least one compound of the formula I and/or pharmaceutically acceptable salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios, and at least one further medicament active ingredient.
- 25 17. Set (kit) consisting of separate packs of
- (a) an effective amount of a compound of the formula I and/or pharmaceutically acceptable salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios, 30 and
- (b) an effective amount of a further medicament active ingredient.
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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2013/003128

A. CLASSIFICATION OF SUBJECT MATTER
 INV. C07C255/57 C07D213/81 C07D215/14 C07D231/56 C07D233/64
 C07C311/16 C07D235/08 C07D235/18 C07D237/14 C07D239/26
 C07C317/44 C07D413/02 C07D413/04 A61K31/166 A61P35/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07C C07D A61K

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2011/048018 A1 (BOEHRINGER INGELHEIM INT [DE]; KLEY JOERG [DE]; HAMILTON BRADFORD S [D] 28 April 2011 (2011-04-28) cited in the application claims; examples -----	1-17



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

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Date of mailing of the international search report

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Name and mailing address of the ISA/

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Authorized officer

Ginoux, Claude

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2013/003128

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2011048018 A1	28-04-2011	EP 2491009 A1	29-08-2012
		JP 2013508327 A	07-03-2013
		US 2013053412 A1	28-02-2013
		WO 2011048018 A1	28-04-2011



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(43) 申请公布日 2015. 07. 22

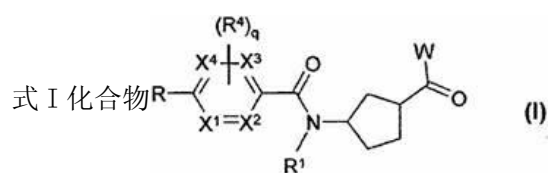
(21) 申请号 201380059746. 3	(51) Int. Cl.
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(87) PCT国际申请的公布数据	C07D 235/18(2006. 01)
W02014/075754 EN 2014. 05. 22	C07D 237/14(2006. 01)
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B. 吕特纳 P. 乔德罗夫斯基	C07D 413/04(2006. 01)
(74) 专利代理机构 中国专利代理(香港)有限公	A61K 31/166(2006. 01)
司 72001	A61P 35/00(2006. 01)
代理人 邹雪梅 彭昶	

权利要求书6页 说明书68页

(54) 发明名称

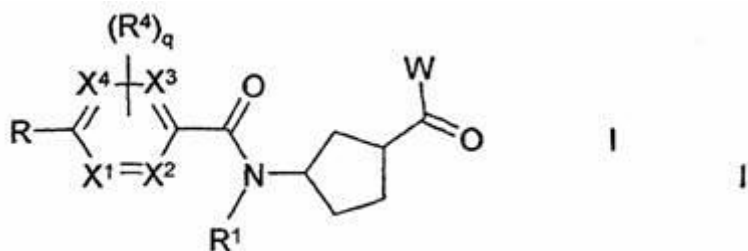
3-氨基环戊烷甲酰胺衍生物

(57) 摘要



其中 R^1 , R^4 , R , X^1 , X^2 , X^3 , X^4 , q 和 W 具有权利要求 1 中所示的含义, 为脂肪酸合酶抑制剂, 并可以尤其用于治疗疾病例如癌症、心血管疾病、中枢神经系统损伤和不同形式的炎症。

1. 式 I 化合物



其中

R 代表 Ar, Het, $-C \equiv C-Ar$ 或 $-C \equiv C-Het$,

W 代表 $NR^2R^{2'}$ 或 Het^1 ,

R^1 代表 A, $[C(R^3)_2]_nAr^1$ 或 $[C(R^3)_2]_nCyc$,

R^2 , $R^{2'}$ 彼此独立地各自代表 H, A 或 $[C(R^3)_2]_nCyc$,

R^4 代表 H, F, Cl, Br, OH, CN, NO_2 , A' , OA' , SA' , SO_2Me , COA' , $CONH_2$, $CONHA'$ 或 $CONA'_2$,

X^1 , X^2 , X^3 , X^4 彼此独立地各自代表 CH 或 N,

A 代表具有 1-10 个 C-原子的非支链或支链烷基, 其中两个相邻的碳原子可以形成双键和 / 或一个或两个不相邻 $CH-$ 和 / 或 CH_2- 基团可以被 N-、O- 和 / 或 S- 原子替代并且其中 1-7 个 H- 原子可以被 R^5 替代,

Cyc 代表具有 3-7 个 C-原子的环烷基, 其未被取代或被 OH, Ha 或 A 单取代,

A' 代表具有 1-6 个 C-原子的非支链或支链烷基, 其中 1-5 个 H- 原子可以被 F 替代,

R^5 代表 F, Cl 或 OH,

Ar 代表苯基, 其未被取代或被 Hal, A, $O[C(R^3)_2]_nHet^1$, Ar^1 , $[C(R^3)_2]_pOR^3$, $[C(R^3)_2]_pN(R^3)_2$, NO_2 , CN, $[C(R^3)_2]_pCOOR^3$, $CON(R^3)_2$, $[C(R^3)_2]_pN(R^3)_2$, $N(R^3)_2COA$, NR^3SO_2A , $[C(R^3)_2]_pSO_2N(R^3)_2$, $S(O)_nA$, $O[C(R^3)_2]_mN(R^3)_2$, $NHCOOA$, $NHCON(R^3)_2$ 和 / 或 COA 单-、二-、三-、四-或五取代,

Ar^1 代表苯基或萘基, 其未被取代或被 Hal, A, $[C(R^3)_2]_pOR^3$, $[C(R^3)_2]_pN(R^3)_2$, NO_2 , CN, $[C(R^3)_2]_pCOOR^3$, $[C(R^3)_2]_pN(R^3)_2$, $N(R^3)_2COA$, NR^3SO_2A , $[C(R^3)_2]_pSO_2N(R^3)_2$, $S(O)_nA$, $O[C(R^3)_2]_mN(R^3)_2$, $NHCOOA$, $NHCON(R^3)_2$ 和 / 或 COA 单-、二-、三-、四-或五取代,

R^3 代表 H 或具有 1-6 个 C-原子的非支链或支链烷基,

Het 代表具有 1 至 4 个 N, O 和 / 或 S 原子的单-或双环饱和、不饱和或芳族杂环, 其未被取代或被 Hal, A, $[C(R^3)_2]_nOA'$, $[C(R^3)_2]_nN(R^3)_2$, SR^3 , NO_2 , CN, $COOR^3$, $CON(R^3)_2$, $COHet^1$, NR^3COA , NR^3SO_2A , $SO_2N(R^3)_2$, $S(O)_nA$, $O[C(R^3)_2]_mN(R^3)_2$, $NHCOOA$, $NHCON(R^3)_2$, CHO , COA , $=S$, $=NH$, $=NA$ 和 / 或 $=O$ (羰基氧) 单-、二-、三-、四-或五取代,

Het^1 代表具有 1 至 4 个 N, O 和 / 或 S 原子的单-或双环饱和、不饱和或芳族杂环, 其未被取代或被 Hal, A, $[C(R^3)_2]_nOR^3$, $[C(R^3)_2]_nN(R^3)_2$, SR^3 , NO_2 , CN, $COOR^3$, $CON(R^3)_2$, NR^3COA , NR^3SO_2A , $SO_2N(R^3)_2$, $S(O)_nA$, $O[C(R^3)_2]_mN(R^3)_2$, $NHCOOA$, $NHCON(R^3)_2$, CHO , COA , $=S$, $=NH$, $=NA$ 和 / 或 $=O$ (羰基氧) 单-、二-、三-、四-或五取代,

Hal 代表 F, Cl, Br 或 I,

m 代表 1, 2 或 3,

n 代表 0, 1 或 2,

p 代表 0, 1, 2, 3 或 4,

q0, 1, 2 或 3,

条件是 X^1 , X^2 , X^3 , X^4 中的只一个或两个代表 N,

和其药学上可接受的盐、互变异构体和立体异构体, 包括其全部比率的混合物。

2. 根据权利要求 1 的化合物, 其中

R^4 代表 H, F, Cl, OA' 或 A' ,

和其药学上可接受的盐、互变异构体和立体异构体, 包括其全部比率的混合物。

3. 根据权利要求 1 或 2 的化合物, 其中

A 代表具有 1-10 个 C- 原子的非支链或支链烷基, 其中一个或两个不相邻的 $CH-$ 和 / 或 CH_2- 基团可以被 N- 和 / 或 O- 原子替代和 1-7 个 H- 原子可以被 R^5 替代,

和其药学上可接受的盐、互变异构体和立体异构体, 包括其全部比率的混合物。

4. 根据权利要求 1 至 3 的一项或多项的化合物, 其中

Ar 代表苯基, 其未被取代或被 $O[C(R^3)_2]_nHet^1$, Ar^1 , A, CN 和 / 或 $[C(R^3)_2]_pOR^3$ 单 -、二 -、三 -、四 -、或五取代,

和其药学上可接受的盐、互变异构体和立体异构体, 包括其全部比率的混合物。

5. 根据权利要求 1 至 4 的一项或多项的化合物, 其中

Ar^1 代表苯基或萘基,

和其药学上可接受的盐、互变异构体和立体异构体, 包括其全部比率的混合物。

6. 根据权利要求 1 至 5 的一项或多项的化合物, 其中

Het 代表具有 1 至 4 个 N, O 和 / 或 S 原子的单 - 或双环芳族杂环, 其未被取代或被 Hal, A, $[C(R^3)_2]_nOA'$, $S(O)_nA$, CN, $SO_2N(R^3)_2$ 和 / 或 $COHet^1$ 单 - 或二取代,

和其药学上可接受的盐、互变异构体和立体异构体, 包括其全部比率的混合物。

7. 根据权利要求 1 至 6 的一项或多项的化合物, 其中

Het^1 代表具有 1 至 4 个 N, O 和 / 或 S 原子的单环饱和杂环, 其未被取代或被 A 单 - 或二取代,

和其药学上可接受的盐、互变异构体和立体异构体, 包括其全部比率的混合物。

8. 根据权利要求 1 至 7 的一项或多项的化合物, 其中

Het 代表呋喃基, 噻吩基, 吡咯基, 咪唑基, 吡唑基, 噁唑基, 异噁唑基, 噻唑基, 异噻唑基, 吡啶基, 嘧啶基, 三唑基, 四唑基, 噁二唑基, 噻二唑基, 哒嗪基, 吡嗪基, 苯并噁唑基, 苯并噻唑基, 苯并咪唑基, 苯并三唑基, 吲哚基, 苯并-1,3-二氧杂环戊烯基, 苯并二噁烷基, 苯并噻二唑基, 吲唑基, 苯并呋喃基, 喹啉基, 异喹啉基, 噁唑并 [5,4-b] 吡啶基, 咪唑并 [1,2-a] 吡啶基 或噁唑并 [5,4-c] 吡啶基, 其各自未被取代或被 Hal, A, $[C(R^3)_2]_nOA'$, $S(O)_nA$, CN, $SO_2N(R^3)_2$ 和 / 或 $COHet^1$ 单 - 或二取代,

和其药学上可接受的盐、互变异构体和立体异构体, 包括其全部比率的混合物。

9. 根据权利要求 1 至 8 的一项或多项的化合物, 其中

Het^1 代表吡咯烷基, 氮杂环丁烷基, 氧杂环丁烷基, 四氢咪唑基, 四氢吡唑基, 四氢呋喃基, 哌啶基, 哌嗪基, 吗啉基, 六氢哒嗪基, 六氢嘧啶基, [1,3] 二氧杂环戊烷

基或四氢吡喃基，其各自未被取代或被 A 单-或二取代，

和其药学上可接受的盐、互变异构体和立体异构体，包括其全部比率的混合物。

10. 根据权利要求 1 至 9 的一项或多项的化合物，其中

R 代表 Ar, Het, $-C \equiv C-Ar$ 或 $-C \equiv C-Het$,

W 代表 $NR^2R^{2'}$ 或 Het^1 ,

R^1 代表 A, $[C(R^3)_2]_nAr^1$ 或 $[C(R^3)_2]_nCyc$,

R^2 , $R^{2'}$ 彼此独立地各自代表 H, A 或 $[C(R^3)_2]_nCyc$,

R^4 代表 H, F, Cl, OA' 或 A' ,

X^1 , X^2 , X^3 , X^4 彼此独立地各自代表 CH 或 N,

A 代表具有 1-10 个 C-原子的非支链或支链烷基，其中一个或两个不相邻的 CH- 和 / 或 CH_2 -基团可以被 N- 和 / 或 O- 原子替代和 1-7 个 H- 原子可以被 R^5 替代，

Cyc 代表具有 3-7 个 C-原子的环烷基，其未被取代或被 OH 或 A 单取代，

A' 代表具有 1-6 个 C-原子的非支链或支链烷基，其中 1-5 个 H- 原子可以被 F 替代，

R^5 代表 F, Cl 或 OH,

Ar 代表苯基，其未被取代或被 $O[C(R^3)_2]_nHet^1$, Ar^1 , A, CN 和 / 或 $[C(R^3)_2]_pOR^3$ 单-、二-、三-、四-或五取代，

Ar^1 代表苯基或萘基，

R^3 代表 H 或具有 1-6 个 C-原子的非支链或支链烷基，

Het 代表呋喃基，噻吩基，吡咯基，咪唑基，吡唑基，噁唑基，异噁唑基，噻唑基，异噻唑基，吡啶基，嘧啶基，三唑基，四唑基，噁二唑基，噻二唑基，哒嗪基，吡嗪基，苯并噁唑基，苯并噻唑基，苯并咪唑基，苯并三唑基，吲哚基，苯并-1,3-二氧杂环戊烯基，苯并二噁烷基，苯并噻二唑基，吲唑基，苯并呋喃基，喹啉基，异喹啉基，噁唑并 [5,4-b] 吡啶基，咪唑并 [1,2-a] 吡啶基或噁唑并 [5,4-c] 吡啶基，其各自未被取代或被 Hal, A, $[C(R^3)_2]_nOA'$, $S(O)_nA$, CN, $SO_2N(R^3)_2$ 和 / 或 $COHet^1$ 单或二取代，

Het^1 代表吡咯烷基，氮杂环丁烷基，氧杂环丁烷基，四氢咪唑基，四氢吡唑基，四氢呋喃基，哌啶基，哌嗪基，吗啉基，六氢哒嗪基，六氢嘧啶基，[1,3] 二氧杂环戊烷基或四氢吡喃基，其各自未被取代或被 A 单-或二取代，

Hal 代表 F, Cl, Br 或 I,

n 代表 0, 1 或 2,

p 代表 0, 1, 2, 3 或 4,

q0, 1, 2 或 3,

条件是 X^1 , X^2 , X^3 , X^4 中的只一个或两个代表 N,

和其药学上可接受的盐、互变异构体和立体异构体，包括其全部比率的混合物。

11. 根据权利要求 1 的化合物，其选自

编号	名称
"A1"	4-(1,3-苯并噁唑-2-基)-N-[(1R,3S)-3-(乙基氨基甲酰基)环戊基]-N-甲基-苯甲酰胺
"A2"	N-((1R,3S)-3-乙基氨基甲酰基-环戊基)-N-甲基-4-(1-甲基-1H-苯并咪唑-2-基)-苯甲酰胺
"A3"	4-苯并噻唑-2-基-N-((1R,3S)-3-乙基氨基甲酰基-环戊基)-N-甲基-苯甲酰胺
"A4"	4'-[(R)-(四氢-呋喃-3-基)氧基]-联苯-4-甲酸 ((1R,3S)-3-乙基氨基甲酰基-环戊基)-甲基-酰胺
"A5"	4-苯并噁唑-2-基-N-((1R,3S)-3-异丙基氨基甲酰基-环戊基)-N-甲基-苯甲酰胺
"A6"	4-苯并噁唑-2-基-N-((1R,3S)-3-环丙基氨基甲酰基-环戊基)-N-甲基-苯甲酰胺

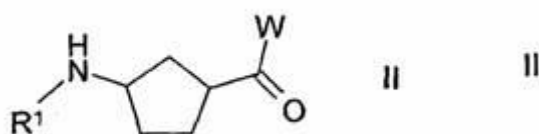
"A7"	4- 苯并噁唑-2- 基 -N- ((1R, 3S)-3- 环戊基氨基甲酰基- 环戊基)-N- 甲基- 苯甲酰胺
"A8"	4- 苯并噁唑-2- 基 -N- [(1R, 3S)-3- (环己基甲基- 氨基甲酰基)- 环戊基]-N- 甲基- 苯甲酰胺
"A9"	4- 苯并噁唑-2- 基 -N- 甲基 -N- [(1R, 3S)-3- (吡咯烷-1- 羰基)- 环戊基]- 苯甲酰胺
"A10"	4- (1, 3- 苯并噁唑-2- 基)-N- [(1S, 3R)-3- (乙基氨基甲酰基) 环戊基]-N- 甲基- 苯甲酰胺
"A11"	4- (1H- 苯并咪唑-2- 基)-N- [(1R, 3S)-3- (乙基氨基甲酰基) 环戊基]-N- 甲基- 苯甲酰胺
"A12"	4- 苯并噁唑-2- 基 -N- 乙基 -N- ((1R, 3S)-3- 乙基氨基甲酰基- 环戊基)- 苯甲酰胺
"A13"	4- 苯并噁唑-2- 基 -N- 苄基 -N- ((1R, 3S)-3- 乙基氨基甲酰基- 环戊基)- 苯甲酰胺
"A14"	N- ((1R, 3S)-3- 乙基氨基甲酰基- 环戊基)-N- 甲基-4- 噁唑并 [5, 4-b] 吡啶-2- 基- 苯甲酰胺
"A15"	N- ((1R, 3S)-3- 乙基氨基甲酰基- 环戊基)-N- 甲基-4- 噁唑并 [5, 4-c] 吡啶-2- 基- 苯甲酰胺
"A16"	4'- 甲氧基- 联苯-4- 甲酸 ((1R, 3S)-3- 乙基氨基甲酰基- 环戊基)- 甲基- 酰胺
"A17"	4'- [(S)- (四氢- 呋喃-3- 基) 氧基]- 联苯-4- 甲酸 ((1R, 3S)-3- 乙基氨基甲酰基- 环戊基)- 甲基- 酰胺
"A18"	4- 苯并噁唑-2- 基 -N- ((1R, 3S)-3- 乙基氨基甲酰基- 环戊基)-2- 氟 -N- 甲基- 苯甲酰胺
"A19"	N- ((1R, 3S)-3- 乙基氨基甲酰基- 环戊基)-4- (5- 氟- 苯并噁唑-2- 基)-N- 甲基- 苯甲酰胺
"A20"	4- 苯并噁唑-2- 基 -N- ((1R, 3S)-3- 乙基氨基甲酰基- 环戊基)-2, 6- 二氟 -N- 甲基- 苯甲酰胺
"A21"	N- ((1R, 3S)-3- 乙基氨基甲酰基- 环戊基)-N- 甲基-4- (5- 三氟甲氧基- 苯并噁唑-2- 基)- 苯甲酰胺
"A22"	4- 苯并噁唑-2- 基 -N- ((1R, 3S)-3- 乙基氨基甲酰基- 环戊基)-N- 甲基-3- 三氟甲基- 苯甲酰胺
"A23"	4- (6- 氯- 苯并噁唑-2- 基)-N- ((1R, 3S)-3- 乙基氨基甲酰基- 环戊基)-N- 甲基- 苯甲酰胺
"A24"	N- ((1R, 3S)-3- 乙基氨基甲酰基- 环戊基)-N- 甲基-4- 萘-2- 基- 苯甲酰胺
"A25"	N- ((1R, 3S)-3- 乙基氨基甲酰基- 环戊基)-4- 异喹啉-6- 基 -N- 甲基- 苯甲酰胺
"A26"	4- 苯并呋喃-5- 基 -N- ((1R, 3S)-3- 乙基氨基甲酰基- 环戊基)-N- 甲基- 苯甲酰胺
"A27"	N- ((1R, 3S)-3- 乙基氨基甲酰基- 环戊基)-N- 甲基-4- (1- 甲基-1H- 苯并咪唑-5- 基)- 苯甲酰胺
"A28"	4- 苯并噁唑-2- 基 -N- [(1R, 3S)-3- (4- 乙基- 哌嗪-1- 羰基)- 环戊基]-N- 甲基- 苯甲酰胺
"A29"	4- 苯并噁唑-2- 基 -N- 环丙基甲基 -N- ((1R, 3S)-3- 乙基氨基甲酰基- 环戊基)- 苯甲酰胺
"A30"	N- ((1R, 3S)-3- 乙基氨基甲酰基- 环戊基)-4- (1H- 吡唑-2- 基)-N- 甲基- 苯甲酰胺
"A31"	N- ((1R, 3S)-3- 乙基氨基甲酰基- 环戊基)-N- 甲基-4- [5- (吡咯烷-1- 羰基)- 苯并噁唑-2- 基]- 苯甲酰胺
"A32"	4- 苯并噁唑-2- 基 -N- [(1R, 3S)-3- (环戊基甲基- 氨基甲酰基)- 环戊基]-N- 甲基- 苯甲酰胺
"A33"	4- 苯并噁唑-2- 基 -N- 甲基 -N- [(1R, 3S)-3- (氧杂环丁烷-3- 基氨基甲酰基)- 环戊基]- 苯甲酰胺
"A34"	4- 苯并噁唑-2- 基 -N- 甲基 -N- ((1R, 3S)-3- [(S)-1- (四氢- 呋喃-2- 基) 甲基]- 氨基甲酰基)- 环戊基)- 苯甲酰胺
"A35"	4- 苯并噁唑-2- 基 -N- 甲基 -N- ((1R, 3S)-3- [(R)-1- (四氢- 呋喃-2- 基) 甲基]- 氨基甲酰基)- 环戊基)- 苯甲酰胺
"A36"	4- 苯并噁唑-2- 基 -N- [(1R, 3S)-3- (2- 甲氧基- 乙基氨基甲酰基)- 环戊基]-N- 甲基- 苯甲酰胺
"A37"	4- 苯并噁唑-2- 基 -N- 甲基 -N- ((1R, 3S)-3- [(R)- (四氢- 呋喃-3- 基) 氨基甲酰基]- 环戊基)- 苯甲酰胺
"A38"	4- 苯并噁唑-2- 基 -N- 甲基 -N- ((1R, 3S)-3- [(S)- (四氢- 呋喃-3- 基) 氨基甲酰基]- 环戊基)- 苯甲酰胺
"A39"	6- 苯并噁唑-2- 基 -N- ((1R, 3S)-3- 乙基氨基甲酰基- 环戊基)-N- 甲基- 烟酰胺
"A40"	5- 苯并噁唑-2- 基 -吡啶-2- 甲酸 ((1R, 3S)-3- 乙基氨基甲酰基- 环戊基)- 甲基- 酰胺
"A41"	N- ((1R, 3S)-3- 乙基氨基甲酰基- 环戊基)-4- (5- 甲氧基- 苯并噁唑-2- 基)-N- 甲基- 苯甲酰胺
"A42"	4- (5- 氯- 苯并噁唑-2- 基)-N- ((1R, 3S)-3- 乙基氨基甲酰基- 环戊基)-N- 甲基- 苯甲酰胺
"A43"	N- ((1R, 3S)-3- 乙基氨基甲酰基- 环戊基)-N- 甲基-4- (5- 三氟甲基- 苯并噁唑-2- 基)- 苯甲酰胺
"A44"	4- (1, 3- 苯并噁唑-2- 基)-N- [(1R, 3R)-3- (乙基氨基甲酰基) 环戊基]-N- 甲基- 苯甲酰胺
"A45"	4- 苯并噁唑-2- 基 -N- ((1R, 3S)-3- 乙基氨基甲酰基- 环戊基)-3- 甲氧基 -N- 甲基- 苯甲酰胺
"A46"	4- 苯并噁唑-2- 基 -N- ((1R, 3S)-3- 乙基氨基甲酰基- 环戊基)-2- 甲氧基 -N- 甲基- 苯甲酰胺
"A47"	4- 苯并噁唑-2- 基 -N- [(1R, 3S)-3- (乙基- 甲基- 氨基甲酰基)- 环戊基]-N- 甲基- 苯甲酰胺
"A48"	4- 苯并噁唑-2- 基 -N- ((1R, 3S)-3- 二乙基氨基甲酰基- 环戊基)-N- 甲基- 苯甲酰胺
"A49"	4'- 甲基- 联苯-4- 甲酸 ((1R, 3S)-3- 乙基氨基甲酰基- 环戊基)- 甲基- 酰胺
"A50"	联苯-4- 甲酸 ((1R, 3S)-3- 乙基氨基甲酰基- 环戊基)- 甲基- 酰胺
"A51"	3- 氯- 联苯-4- 甲酸 ((1R, 3S)-3- 乙基氨基甲酰基- 环戊基)- 甲基- 酰胺
"A52"	N- ((1R, 3S)-3- 乙基氨基甲酰基- 环戊基)-4- (6- 甲氧基-4- 甲基- 哒嗪-3- 基)-N- 甲基- 苯甲酰胺
"A53"	5- 苯基- 吡啶-2- 甲酸 ((1R, 3S)-3- 乙基氨基甲酰基- 环戊基)- 甲基- 酰胺
"A54"	4- (4- 氯- 苯基乙炔基)-N- ((1R, 3S)-3- 乙基氨基甲酰基- 环戊基)-N- 甲基- 苯甲酰胺
"A55"	N- ((1R, 3S)-3- 乙基氨基甲酰基- 环戊基)-4- (4- 氟- 苯基乙炔基)-N- 甲基- 苯甲酰胺
"A56"	N- ((1R, 3S)-3- 乙基氨基甲酰基- 环戊基)-N- 甲基-4- 吡啶-4- 基- 苯甲酰胺
"A57"	N- ((1R, 3S)-3- 乙基氨基甲酰基- 环戊基)-2- 氟 -N- 甲基-4- 吡啶-4- 基- 苯甲酰胺
"A58"	4'- 乙基-3, 5- 二氟- 联苯-4- 甲酸 ((1R, 3S)-3- 乙基氨基甲酰基- 环戊基)- 甲基- 酰胺
"A59"	2'- 甲磺酰基- 联苯-4- 甲酸 ((1R, 3S)-3- 乙基氨基甲酰基- 环戊基)- 甲基- 酰胺
"A60"	2'- 叔丁基磺酰基- 联苯-4- 甲酸 ((1R, 3S)-3- 乙基氨基甲酰基- 环戊基)- 甲基- 酰胺
"A61"	2'- 氮磺酰基- 联苯-4- 甲酸 ((1R, 3S)-3- 乙基氨基甲酰基- 环戊基)- 甲基- 酰胺
"A62"	4'- 氯- 联苯-4- 甲酸 ((1R, 3S)-3- 乙基氨基甲酰基- 环戊基)- 甲基- 酰胺
"A63"	2', 4'- 二氟- 联苯-4- 甲酸 ((1R, 3S)-3- 乙基氨基甲酰基- 环戊基)- 甲基- 酰胺
"A64"	2'- 三氟甲基- 联苯-4- 甲酸 ((1R, 3S)-3- 乙基氨基甲酰基- 环戊基)- 甲基- 酰胺
"A65"	2, 2'- 二甲基- 联苯-4- 甲酸 ((1R, 3S)-3- 乙基氨基甲酰基- 环戊基)- 甲基- 酰胺
"A66"	4'- (双- 三氟甲基- 氨基)- 联苯-4- 甲酸 ((1R, 3S)-3- 乙基氨基甲酰基- 环戊基)- 甲基- 酰胺
"A67"	联苯-4- 甲酸 甲基- [(1R, 3S)-3- (1- 甲基- 环丙基氨基甲酰基)- 环戊基]- 酰胺
"A68"	4- 苯并噁唑-2- 基 -N- 甲基 -N- [(1R, 3S)-3- (1- 甲基- 环丙基氨基甲酰基)- 环戊基]- 苯甲酰胺
"A69"	N- ((1R, 3S)-3- 乙基氨基甲酰基- 环戊基)-4- (4- 甲氧基- 苯基乙炔基)-N- 甲基- 苯甲酰胺
"A70"	N- ((1R, 3S)-3- 乙基氨基甲酰基- 环戊基)-N- 甲基-4- 吡啶-4- 基乙炔基- 苯甲酰胺
"A71"	4- 苯并噁唑-2- 基 -N- 甲基 -N- [(1R, 3S)-3- (1- 甲基- 环丙基氨基甲酰基)- 环戊基]- 苯甲酰胺
"A72"	4- (4- 氟- 苯基乙炔基)-N- 甲基 -N- [(1R, 3S)-3- (1- 甲基- 环丙基氨基甲酰基)- 环戊基]- 苯甲酰胺
"A73"	4- 苯并噁唑-2- 基 -N- 甲基 -N- [(1R, 3S)-3- (1- 丙基- 环丙基氨基甲酰基)- 环戊基]- 苯甲酰胺

"A74"	4-(1,3-苯并噁唑-2-基)-N-甲基-N-[(1R,3S)-3-[[[(1S)-1-甲基丙基]氨基甲酰基]环戊基]苯甲酰胺
"A75"	4-(1,3-苯并噁唑-2-基)-N-甲基-N-[(1R,3S)-3-[[[(1R)-1-甲基丙基]氨基甲酰基]环戊基]苯甲酰胺
"A76"	4-(1,3-苯并噁唑-2-基)-N-[(1R,3S)-3-(环丁基氨基甲酰基)环戊基]-N-甲基-苯甲酰胺
"A77"	4-(1,3-苯并噁唑-2-基)-N-[(1R,3S)-3-[(反式-3-羟基环丁基)氨基甲酰基]环戊基]-N-甲基-苯甲酰胺
"A78"	4-(1,3-苯并噁唑-2-基)-N-[(1R,3S)-3-[(顺式-3-羟基环丁基)氨基甲酰基]环戊基]-N-甲基-苯甲酰胺
"A79"	4-(1,3-苯并噁唑-2-基)-2-甲氧基-N-甲基-N-[(1R,3S)-3-[(1-甲基环丙基)氨基甲酰基]环戊基]苯甲酰胺
"A80"	N-甲基-N-[(1R,3S)-3-[(1-甲基环丙基)氨基甲酰基]环戊基]-4-(4-吡啶基)苯甲酰胺
"A81"	4-(4-氰基苯基)-N-甲基-N-[(1R,3S)-3-[(1-甲基环丙基)氨基甲酰基]环戊基]苯甲酰胺
"A82"	4-苯并噁唑-2-基-N-[(1R,3S)-3-二甲氨基甲酰基-环戊基]-N-甲基-苯甲酰胺
"A83"	N-甲基-N-[(1R,3S)-3-(1-甲基-环丙基氨基甲酰基)-环戊基]-4-吡啶-3-基-苯甲酰胺
"A84"	4-苯并噁唑-2-基-N-甲基-N-[(1R,3S)-3-(1-甲基-环丁基氨基甲酰基)-环戊基]-苯甲酰胺
"A85"	4-苯并噁唑-2-基-3-甲氧基-N-甲基-N-[(1R,3S)-3-(1-甲基-环丙基氨基甲酰基)-环戊基]-苯甲酰胺
"A86"	4-苯并噁唑-2-基-N-[(1R,3S)-3-氨基甲酰基-环戊基]-N-甲基-苯甲酰胺
"A87"	4-(7-氰基-咪唑并[1,2-a]吡啶-2-基)-N-[(1R,3S)-3-乙基氨基甲酰基-环戊基]-N-甲基-苯甲酰胺
"A88"	N-[(1R,3S)-3-乙基氨基甲酰基-环戊基]-N-甲基-4-(5-甲基-[1,2,4]噁二唑-3-基)苯甲酰胺
"A89"	4-苯并噁唑-2-基-N-[(1R,3S)-3-(2-二甲氨基-1-甲基-乙基氨基甲酰基)-环戊基]-N-甲基-苯甲酰胺
"A90"	4-苯并噁唑-2-基-N-[(1R,3S)-3-((S)-2-羟基-1-甲基-乙基氨基甲酰基)-环戊基]-N-甲基-苯甲酰胺
"A91"	4-苯并噁唑-2-基-N-[(1R,3S)-3-((R)-2-羟基-1-甲基-乙基氨基甲酰基)-环戊基]-N-甲基-苯甲酰胺
"A92"	4-苯并噁唑-2-基-N-[(1R,3S)-3-((S)-2-甲氧基-1-甲基-乙基氨基甲酰基)-环戊基]-N-甲基-苯甲酰胺
"A93"	N-[(1R,3S)-3-乙基氨基甲酰基-环戊基]-N-甲基-4-(5-氯磺酰基-苯并噁唑-2-基)-苯甲酰胺
"A94"	4-(5-乙磺酰基-苯并噁唑-2-基)-N-[(1R,3S)-3-乙基氨基甲酰基-环戊基]-N-甲基-苯甲酰胺
"A95"	N-[(1R,3S)-3-乙基氨基甲酰基-环戊基]-4-(1H-咪唑-2-基)-N-甲基-苯甲酰胺
"A96"	4-(5,7-二氟-苯并噁唑-2-基)-N-[(1R,3S)-3-乙基氨基甲酰基-环戊基]-N-甲基-苯甲酰胺
"A97"	4-苯并噁唑-2-基-N-[(1R,3S)-3-(2-羟基-乙基氨基甲酰基)-环戊基]-N-甲基-苯甲酰胺
"A98"	N-[(1R,3S)-3-乙基氨基甲酰基-环戊基]-4-(6-氟-苯并噁唑-2-基)-N-甲基-苯甲酰胺
"A99"	4-苯并噁唑-2-基-N-[(1R,3S)-3-(2-羟基-1,1-二甲基-乙基氨基甲酰基)-环戊基]-N-甲基-苯甲酰胺
"A100"	N-[(1R,3S)-3-乙基氨基甲酰基-环戊基]-4-(7-氟-苯并噁唑-2-基)-N-甲基-苯甲酰胺
"A101"	4-(5,6-二氟-苯并噁唑-2-基)-N-[(1R,3S)-3-乙基氨基甲酰基-环戊基]-N-甲基-苯甲酰胺
"A102"	N-[(1R,3S)-3-乙基氨基甲酰基-环戊基]-N-甲基-4-吡啶-3-基-苯甲酰胺
"A103"	4'-氰基-联苯-4-甲酸((1R,3S)-3-乙基氨基甲酰基-环戊基)-甲基-酰胺
"A104"	4'-氟-联苯-4-甲酸((1R,3S)-3-乙基氨基甲酰基-环戊基)-甲基-酰胺
"A105"	N-[(1R,3S)-3-乙基氨基甲酰基-环戊基]-N-甲基-4-噻唑-5-基-苯甲酰胺
"A106"	4-苯并噁唑-2-基-N-[(1R,3S)-3-(2-羟基-乙基氨基甲酰基)-环戊基]-N-甲基-苯甲酰胺
"A107"	N-[(1R,3S)-3-乙基氨基甲酰基-环戊基]-4-(1H-吡唑-4-基)-N-甲基-苯甲酰胺
"A108"	4-苯并噁唑-2-基-N-[(1R,3S)-3-(1-羟基甲基-环丙基氨基甲酰基)-环戊基]-N-甲基-苯甲酰胺

和其药学上可接受的盐、互变异构体和立体异构体,包括其全部比率的混合物。

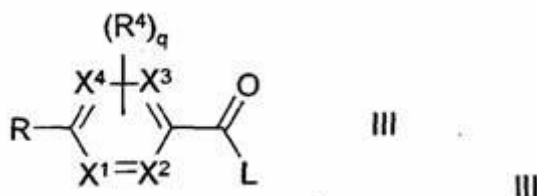
12. 制备根据权利要求 1-11 的式 I 化合物和其药学上可接受的盐、互变异构体和立体异构体的方法,其特征在于

式 II 化合物



其中 R¹和 W 具有权利要求 1 中所示的含义,

与式 III 的化合物反应



其中 R, R⁴, X¹, X², X³, X⁴和 q 具有权利要求 1 中所示的含义,

和 L 代表 Cl, Br, I 或游离的或反应性官能改性的 OH 基团,

和 / 或

式 I 的碱或酸转化成其盐的一种。

13. 包含至少一种式 I 化合物和 / 或其药学上可接受的盐、互变异构体和立体异构体, 包括其全部比率的混合物, 和任选的药学上可接受的载体、赋形剂或媒介物的药物。

14. 式 I 化合物和其药学上可接受的盐、互变异构体和立体异构体, 包括其全部比率的混合物, 其用于治疗 and / 或预防癌症、多发性硬化、心血管疾病、中枢神经系统损伤和不同形式的炎症。

15. 根据权利要求 14 的化合物, 其用于治疗 and / 或预防选自如下的疾病: 头、颈、眼、口、咽喉、食道、支气管、喉、咽、胸、骨、肺、结肠、直肠、胃、前列腺、膀胱、子宫、宫颈、乳房、卵巢、睾丸或其他生殖器官、皮肤、甲状腺、血液、淋巴节、肾脏、肝脏、胰腺、脑、中枢神经系统的癌症, 实体瘤和血源性肿瘤。

16. 包含至少一种式 I 化合物和 / 或其药学上可接受的盐、互变异构体和立体异构体, 包括其全部比例的混合物, 和至少一种其他药物活性成分的药物。

17. 由如下独立包装组成的套盒(药盒)

(a) 有效量的式 I 化合物和 / 或其药学上可接受的盐、互变异构体和立体异构体, 包括其全部比率的混合物,

和

(b) 有效量的其他药物活性成分。

3- 氨基环戊烷甲酰胺衍生物

[0001] 发明技术领域

本发明涉及抑制脂肪酸合酶 (FASN; 也缩写成 FAS) 活性的新型氢化吡咯并吡咯 (hydropyrrolopyrrole) 衍生物, 涉及包含它们的药物组合物, 涉及它们的制备方法, 还涉及它们在治疗癌症的疗法中的用途。

[0002] 发明背景

脂肪酸合酶 (FAS) 是用于内生脂肪生成的重要的酶, 在调制脂质和碳水化合物细胞代谢的重要中间体中起重要作用。FAS 在具有高代谢活性的组织 (例如肝脏、脂肪组织和脑) 中高度表达并有好的理由相信 FAS 抑制剂会导致外周组织中有益的代谢效果。另外, FAS 在下丘脑中的抑制可能导致食物摄取的降低。在文献中报道非特异性不可逆 FAS 抑制剂浅蓝菌素和 C-75 降低促进食欲神经肽的脑水平并降低食物摄取。

[0003] FAS 在人类皮脂腺细胞—产生皮脂腺细胞的脂质—中也高度表达。痤疮是涉及皮脂腺的最常见疾病。痤疮的发病机理涉及由皮脂腺 (过度) 产生脂质, 并且据报道哺乳动物的抑制剂 FAS 在皮脂腺细胞中抑制皮脂产生 (US 2005/0053631)。痤疮不能在没有皮脂腺脂质的情况下产生。对于降低皮脂产生的试剂, 在治疗痤疮中存在未满足的药物需要。

[0004] 由于在细菌中的脂肪酸合成对于细胞存活是至关重要的, 因此细菌 FAS (II 型合酶) 已经发展成为抗细菌治疗的潜在目标。与大多数其他原核生物不同, 在分支杆菌中的脂肪酸合酶活性通过与哺乳动物 FAS 相关的单一高分子量、多功能肽链 (I 型合酶) 进行。已经将 I 型分支杆菌 FAS 描述成抗分支杆菌治疗, 例如结核的治疗的潜在目标。在世界上三分之一的人口受到结核杆菌感染并且分支杆菌结核的抗多药菌株发展的情况下, 存在对新型结核治疗的高度药物需要 (Silvana C. Ngo 等: Inhibition of isolated Mycobacterium tuberculosis Fatty Acid Synthase I by Pyrazinamide Analogs; Antimicrobial agents and Chemotherapy 51, 7 (2007) 2430-2435)。

[0005] 最近, 已经认为富含鞘磷脂和胆固醇的细胞器膜的微畴 (称为“脂质筏”) 充当丙型肝炎病毒 (HCV) 复制复合物的支架 (F. Amemiya 等人: Targeting Lipid Metabolism in the Treatment of Hepatitis C Virus Infection. The Journal of Infectious Diseases 197 (2008) 361 -70)。因此, 膜脂质组合物的改变和 / 或分配可以影响病毒复制。确实, 与脂质代谢相关的试剂如聚不饱和脂肪酸或 HMG-CoA 还原酶抑制剂 (他汀类) 已经显示出影响基因型 1 HCV (dto) 的复制。这些试剂可以根据它们的药理作用通过破坏脂质筏减弱 HCV 复制。能够负责抑制 HCV 复制的替代的分子机制为通过改变脂质锚定而改变宿主蛋白的定位 (S. M. Sagan 等人: The influence of cholesterol and lipid metabolism on host cell structure and hepatitis C virus replication. Biochem. Cell Biol. 84 (2006) 67-79)。与聚不饱和脂肪酸不同, 添加不饱和脂肪酸或油酸至培养的 Sfil 细胞会促进 HCV RNA 复制 (S. B. Kapadia, F. V. Chisari: Hepatitis C virus RNA replication is regulated by host geranylgeranylation and fatty acids. PNAS 102 (2005) 2561 -66)。与此一致, 已经报道在 HCV 感染之后, 在人肝癌细胞系中提高脂肪酸合酶的表达 (W. Yang 等人: Fatty acid synthase is up-regulated during hepatitis C

virus infection and regulates hepatitis C virus entry. *Hepatology* 48,5 (2008) 1396– 1403)。此外,通过 TOFA(乙酰基 -CoA 碳酸酐酶的抑制剂)或脂肪酸合酶的抑制剂(浅蓝菌素, C75)抑制脂肪酸生物合成,导致 HCV 产生的减少(dto)。

[0006] 脂肪酸合酶(FAS)活性对病毒复制或感染的影响示出并非限于 HCV,还对 HIV(D. H. Nguyen, D. D. Taub: Targeting Lipids to Prevent HIV infection. *Molecular Interventions* 4,6 (2004) 318-320), 脊髓灰质炎病毒(R. Guinea, L. Carrasco: Effects of Fatty Acids on Lipid Synthesis and Viral RNA Replication in Poliovirus-Infected Cells. *Virology* 185 (1991) 473-476), Epstein-Barr 病毒(Y. Li 等人: Fatty acid synthase expression is induced by the Epstein-Barr virus immediate-early protein BRLF1 and is required for lytic viral gene expression. *Journal of Virology* 78,8 (2004) 4197-4206), 人乳头瘤病毒(L. Louw 等人: HPV-induced recurrent laryngeal papillomatosis: fatty acid role- players. *Asia Pac J Clin Nutr* 17 (S1) (2008) 208-211), 柯萨基病毒 B3(A. Rassmann 等人: The human fatty acid synthase: A new therapeutic target for coxsackievirus B3-induced diseases? *Antiviral Research* 76 (2007) 150-158), 劳斯氏肉瘤病毒(H. Goldfine 等人: Effects of inhibitors of lipid synthesis on the replication of Rous Sarcoma Virus. A specific effect of cerulenin on the processing of major non-glycosylated viral structural proteins. *Biochimica et Biophysica Acta* 512 (1978) 229-240), 以及人巨细胞病毒(HCMV), 和甲型流感病毒(J. Munger 等人: Systems-level metabolic flux profiling identifies fatty acid synthesis as a target for antiviral therapy. *Nature Biotechnology* 26 (2008) 1 179-1 186) 进行报道。

[0007] 存在越来越多的证据证实宿主的 FAS 活性合起来在病毒性感染和病毒性复制中起重要作用,提出 FAS 作为抗病毒治疗的目标。FAS 的表达在很多癌症治疗中剧烈提高,并且存在证据证实肿瘤细胞存活需要有效的脂肪酸合成。因此,提出 FAS 的抑制作为肿瘤学的新方向(*Expert Opin. Investig. Drugs* 16,1 (2007) 1817-1829)。

[0008] 脂肪酸在各种细胞过程包括构建膜块、靶向膜蛋白的锚、合成脂质第二信使中的前体和作为储存能量的介质中起到重要作用, Menendez JS and Lupu R, Fatty acid synthase and the lipogenic phenotype in cancer pathogenesis, *Nature Reviews Cancer*, 7: 763-777 (2007)。脂肪酸可以获自饮食或可以从碳水化合物前体重新合成。后者的生物合成通过多功能同型二聚体 FAS 催化。FAS 通过使用乙酰基 -CoA 作为引物和使用丙二酰 Co-A 作为 2 碳供体和使用 NADPH 作为还原等价物合成了长链脂肪酸(Wakil SJ, Lipids, Structure and function of animal fatty acid synthase, 39: 1045-1053 (2004), Asturias FJ 等人, Structure and molecular organization of mammalian fatty acid synthase, *Nature Struct. Mol. Biol.* 12:225-232 (2005), Maier T 等人, Architecture of Mammalian Fatty Acid Synthase at 4.5 Å Resolution, *Science* 311 : 1258-1262 (2006)。

[0009] 重新脂肪酸合成在胚胎形成期间和胎儿肺(其中脂肪酸用于产生肺表面活性剂)中是活性的。在成年人中,大部分普通人组织优先从饮食中获取脂肪酸。因此,脂质重新

合成的水平和脂肪生成酶的表达是低的, Weiss L 等人, Fatty-acid biosynthesis in man, a pathway of minor importance. Purification, optimal assay conditions, and organ distribution of fatty-acid synthase. Biological Chemistry Hoppe-Seyler 367(9):905-912 (1986)。相比之下,很多肿瘤具有高速率的重新合成脂肪酸, Medes G 等人, Metabolism of Neoplastic Tissue. IV. A Study of Lipid Synthesis in Neoplastic Tissue Slices in Vitro, Can Res, 13:27-29, (1953)。FAS 已经示出在许多癌症类型(包括前列腺、卵巢、结肠、子宫内膜、肺、膀胱、胃和肾脏)中过度表达, Kuhajda FP, Fatty-acid synthase and human cancer: new perspectives on its role in tumor biology, Nutrition; 16:202-208 (2000)。在肿瘤和正常细胞中的 FAS 的这种差异表达和功能为癌症治疗提供可能的大量治疗窗口。

[0010] 药理学和小干扰 RNA 调制的 FAS 抑制已经证实癌细胞增殖的优先抑制。另外,这些抑制剂在体外在癌细胞中诱导细胞凋亡并在鼠科异种移植物模型中在体内延迟人肿瘤生长, Menendez JS and Lupu R, Nature Reviews Cancer, 7: 763-777 (2007)。基于这些发现,认为 FAS 为抗肿瘤干预的主要潜在目标。

[0011] 本发明的目的是发现具有有价值性质的新型化合物,特别是能够用于制备药物的那些。

[0012] 已经发现根据本发明的化合物和其盐具有非常有价值的药理性质,同时被良好地耐受。

[0013] 本发明具体涉及抑制 FASN 的式 I 化合物,涉及包含这些化合物的组合物,涉及其用于治疗 FASN 诱导的疾病和病症的方法。

[0014] 此外,式 I 的化合物可以用于分离和研究 FASN 的活性或表达。此外,它们尤其适合用于与未调节的或紊乱的 FASN 活性有关的疾病的诊断方法。

[0015] 宿主或患者可以属于任何哺乳动物物种,例如,灵长类物种,特别是人;啮齿类,包括小鼠、大鼠和仓鼠;兔;马,牛,狗,猫,等等。动物模型对于实验研究是有益的,能够提供治疗人疾病的模型。

[0016] 可以通过体外试验来测定具体细胞对用根据本发明化合物的治疗的敏感性。典型地,将细胞的培养物与各种浓度的根据本发明的化合物结合一段时间,该结合时间足以使活性剂(诸如抗 IgM)诱导细胞响应,诸如表面标志物的表达,通常在大约一小时和一周之间。可以使用来自血液或活检样品培养的细胞来进行体外试验。使用能够识别标志物的特异性抗体,通过流式细胞术评价表达的表面标志物的数量。

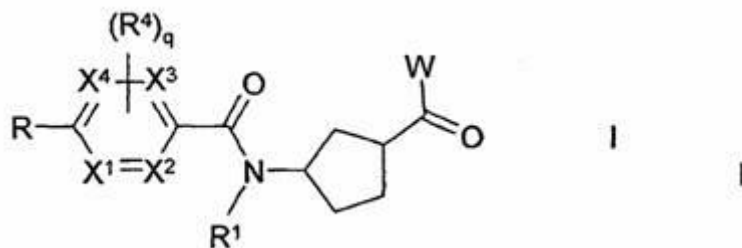
[0017] 剂量根据使用的具体化合物、具体疾病、患者状态等等而变化。治疗剂量典型地足以显著地减少靶组织中的不希望的细胞群体,同时保持患者的生存能力。治疗通常持续直到细胞载荷(cell burden)出现相当大的减少,例如,减少至少约 50%,并且可以持续直到身体内基本上不能检出更多不希望的细胞。

现有技术

[0018] 在 WO 2011/048018 A1 中记载了环戊烷甲酰胺衍生物作为治疗肥胖症和糖尿病的 FAS 抑制剂。

[0019] 发明概述

本发明涉及式 I 化合物



其中

R 代表 Ar, Het, $-C \equiv C-Ar$ 或 $-C \equiv C-Het$,

W 代表 $NR^2R^{2'}$ 或 Het¹,

R¹代表 A, $[C(R^3)_2]_nAr^1$ 或 $[C(R^3)_2]_nCyc$,

R², R^{2'}彼此独立地各自代表 H, A 或 $[C(R^3)_2]_nCyc$,

R⁴代表 H, F, Cl, Br, OH, CN, NO₂, A', OA', SA', SO₂Me, COA', CONH₂, CONHA' 或 CONA'₂,

X¹, X², X³, X⁴彼此独立地各自代表 CH 或 N,

A 代表具有 1-10 个 C-原子的非支链或支链烷基,其中两个相邻的碳原子可以形成双键和 / 或一个或两个不相邻 CH- 和 / 或 CH₂- 基团可以被 N-, O- 和 / 或 S- 原子替代并且其中 1-7 个 H- 原子可以被 R⁵替代,

Cyc 代表具有 3-7 个 C-原子的环烷基,其未被取代或被 OH, Ha 或 A 单取代,

A' 代表具有 1-6 个 C-原子的非支链或支链烷基,其中 1-5 个 H- 原子可以被 F 替代,

R⁵代表 F, Cl 或 OH,

Ar 代表苯基,其未被取代或被 Hal, A, $O[C(R^3)_2]_nHet^1$, Ar¹, $[C(R^3)_2]_pOR^3$, $[C(R^3)_2]_pN(R^3)_2$, NO₂, CN, $[C(R^3)_2]_pCOOR^3$, $CON(R^3)_2$, $[C(R^3)_2]_pN(R^3)_2$, $N(R^3)_2COA$, NR^3SO_2A , $[C(R^3)_2]_pSO_2N(R^3)_2$, S(O)_nA, $O[C(R^3)_2]_mN(R^3)_2$, NHCOOA, NHCON(R³)₂ 和 / 或 COA 单-、二-、三-、四-或五取代,

Ar¹代表苯基或萘基,其未被取代或被 Hal, A, $[C(R^3)_2]_pOR^3$, $[C(R^3)_2]_pN(R^3)_2$, NO₂, CN, $[C(R^3)_2]_pCOOR^3$, $[C(R^3)_2]_pN(R^3)_2$, $N(R^3)_2COA$, NR^3SO_2A , $[C(R^3)_2]_pSO_2N(R^3)_2$, S(O)_nA, $O[C(R^3)_2]_mN(R^3)_2$, NHCOOA, NHCON(R³)₂ 和 / 或 COA 单-、二-、三-、四-或五取代,

R³代表 H 或具有 1-6 个 C-原子的非支链或支链烷基,

Het 代表具有 1 至 4 个 N, O 和 / 或 S 原子的单-或双环饱和、不饱和或芳族杂环,其未被取代或被 Hal, A, $[C(R^3)_2]_nOA'$, $[C(R^3)_2]_nN(R^3)_2$, SR³, NO₂, CN, COOR³, $CON(R^3)_2$, COHet¹, NR^3COA , NR^3SO_2A , $SO_2N(R^3)_2$, S(O)_nA, $O[C(R^3)_2]_mN(R^3)_2$, NHCOOA, NHCON(R³)₂, CHO, COA, =S, =NH, =NA 和 / 或 =O (羰基氧) 单-、二-、三-、四-或五取代,

Het¹代表具有 1 至 4 个 N, O 和 / 或 S 原子的单-或双环饱和、不饱和或芳族杂环,其未被取代或被 Hal, A, $[C(R^3)_2]_nOR^3$, $[C(R^3)_2]_nN(R^3)_2$, SR³, NO₂, CN, COOR³, $CON(R^3)_2$, NR^3COA , NR^3SO_2A , $SO_2N(R^3)_2$, S(O)_nA,

$O[C(R^3)_2]_mN(R^3)_2$, NHCOOA, NHCON(R³)₂, CHO, COA, =S, =NH, =NA 和 / 或 =O (羰基氧) 单-、二-、三-、四-或五取代,

Hal 代表 F, Cl, Br 或 I,

m 代表 1, 2 或 3,

n 代表 0, 1 或 2,

p 代表 0, 1, 2, 3 或 4,

q0, 1, 2 或 3,

条件是 X^1 , X^2 , X^3 , X^4 中的只一个或两个代表 N,

和其药学上可接受的盐、互变异构体和立体异构体, 包括其全部比率的混合物。

[0020] 本发明还涉及这些化合物的光学活性形式 (立体异构体)、对映体、外消旋体、非对映体和水合物和溶剂化物。

[0021] 此外, 本发明涉及式 I 化合物的药学可接受的衍生物。

[0022] 术语化合物的溶剂化物是指惰性溶剂分子加合在化合物上, 其是由于它们相互的引力而形成的。溶剂化物, 例如, 是单或二水合物或醇盐。理解为本发明还涉及盐的溶剂化物。术语药学可接受的衍生物是指, 例如, 根据本发明的化合物以及所谓的前药化合物的盐。

[0023] 如本文所用, 除非另有说明, 否则, 术语“前药”是指式 I 化合物的衍生物, 其在生物条件 (体外或体内) 下可以水解、氧化或反应, 提供活性化合物, 特别是式 I 的化合物。前药的实例包括但不限于: 式 I 化合物的衍生物和代谢物, 其包含生物可水解的部分, 诸如生物可水解的酰胺, 生物可水解的酯, 生物可水解的氨基甲酸酯, 生物可水解的碳酸酯, 生物可水解的脲和生物可水解的磷酸酯类似物。在某些实施方案中, 具有羧基官能团的化合物的前药是羧酸的低级烷基酯。羧酸酯方便地由存在于分子上的任何羧酸部分的酯化而形成。前药可以典型地使用众所周知的方法制备, 诸如, 下列所描述的那些方法: Burger's Medicinal Chemistry and Drug Discovery 第 6 版 (Donald J. Abraham 编, 2001, Wiley) 和 Design and Application of Prodrugs (H. Bundgaard 编, 1985, Harwood Academic Publishers Gmfh)。

[0024] 表述“有效量”代表药物或药学活性组分的量, 该量在组织、系统、动物或人中引起例如研究人员或医生所探求或希望的生物或医学响应。

[0025] 此外, 表述“治疗有效量”代表量, 与没有接受该量的相应受试者相比, 其产生下列后果:

改善治疗, 治愈、预防或消除疾病、综合症、状况、不适、病症或副作用, 或还降低疾病、不适或病症的进展。

[0026] 表述“治疗有效量”还包括可有效提高正常生理功能的量。

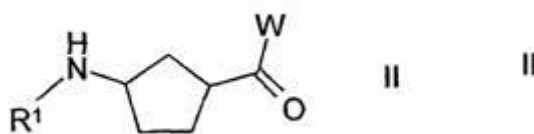
[0027] 本发明还涉及式 I 化合物的混合物的用途, 例如, 两种非对映体的混合物, 例如, 比例为 1:1、1:2、1:3、1:4、1:5、1:10、1:100 或 1:1000 的混合物。

[0028] 尤其优选立体异构化化合物的混合物。

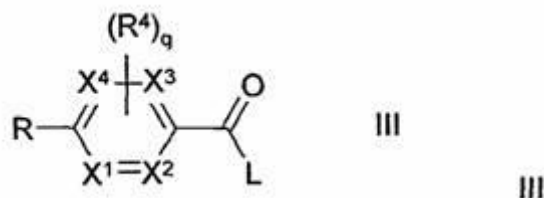
[0029] “互变异构体”是指互相平衡的化合物的异构形式。异构形式的浓度取决于发现化合物的环境, 并且可以根据 (例如) 化合物是否是固体或是否在有机或水溶液中而不同。

[0030] 本发明涉及式 I 的化合物和其盐, 以及制备式 I 化合物和其药学可接受的盐、溶剂化物、互变异构体和立体异构体的方法, 其特征在于

式 II 化合物



其中 R^1 和 W 具有权利要求 1 中所示的含义，
与式 III 化合物反应



其中 R , R^4 , X^1 , X^2 , X^3 , X^4 和 q 具有权利要求 1 中所示的含义，
且 L 代表 Cl , Br , I 或游离或反应性官能改性的 OH 基团，
和 / 或

式 I 的碱或酸转化成其盐之一。

[0031] 在上文和下文中，基团 R^1 , R^4 , R , X^1 , X^2 , X^3 , X^4 , q 和 W 具有对式 I 所示的含义，除非另外明确地指出。

[0032] A 代表烷基，其是非支链（直链）或支链烷基，并且具有 1、2、3、4、5、6、7、8、9 或 10 个 C 原子。优选地， A 代表甲基，此外，代表乙基，丙基，异丙基，丁基，异丁基，仲丁基或叔丁基，此外，还代表戊基，1-、2- 或 3- 甲基丁基，1, 1-、1, 2- 或 2, 2- 二甲基丙基，1- 乙基丙基，己基，1-、2-、3- 或 4- 甲基戊基，1, 1-、1, 2-、1, 3-、2, 2-、2, 3- 或 3, 3- 二甲基丁基，1- 或 2- 乙基丁基，1- 乙基 -1- 甲基丙基，1- 乙基 -2- 甲基丙基，1, 1, 2- 或 1, 2, 2- 三甲基丙基，此外优选地，例如，三氟甲基。

[0033] 非常特别优选地， A 代表具有 1、2、3、4、5 或 6 个 C 原子的烷基，优选甲基，乙基，丙基，异丙基，丁基，异丁基，仲丁基，叔丁基，戊基，己基，三氟甲基，五氟乙基或 1, 1, 1- 三氟乙基。

[0034] 此外， A 优选代表 CH_2OCH_3 , $\text{CH}_2\text{CH}_2\text{OH}$ 或 $\text{CH}_2\text{CH}_2\text{OCH}_3$ 。

[0035] Cyc 代表环丙基，环丁基，环戊基，环己基或环庚基，优选未被取代或被 OH , Hal 或 A 单取代。

[0036] A' 代表烷基，其是非支链（直链）或支链的，并具有 1, 2, 3, 4, 5 或 6 个 C 原子。 A 优选代表甲基，此外乙基，丙基，异丙基，丁基，异丁基，仲丁基或叔丁基，此外还戊基，1-、2- 或 3- 甲基丁基，1, 1-、1, 2- 或 2, 2- 二甲基丙基，1- 乙基丙基，己基，1-、2-、3- 或 4- 甲基戊基，1, 1-、1, 2-、1, 3-、2, 2-、2, 3- 或 3, 3- 二甲基丁基，1- 或 2- 乙基丁基，1- 乙基 -1- 甲基丙基，1- 乙基 -2- 甲基丙基，1, 1, 2- 或 1, 2, 2- 三甲基丙基，此外优选，例如，三氟甲基。

[0037] R^2 优选代表 H 。

[0038] $\text{R}^{2'}$ 优选代表 A 或 $[\text{C}(\text{R}^3)]_n\text{Cyc}$ 。

[0039] R^3 优选代表 H , 甲基，乙基，丙基，异丙基，丁基，戊基或己基，特别优选 H 或甲基。

[0040] R^4 优选代表 H, F, Cl, OA' 或 A' 。

[0041] R^5 优选代表 F 或 Cl。

[0042] Ar 代表, 优选地, 邻、间或对甲基苯基, 邻、间或对乙基苯基, 邻、间或对丙基苯基, 邻、间或对异丙基苯基, 邻、间或对叔丁基苯基, 邻、间或对羟基苯基, 邻、间或对硝基苯基, 邻、间或对氨基苯基, 邻、间或对 (N-甲基氨基) 苯基, 邻、间或对 (N-甲基氨基羰基) 苯基, 邻、间或对甲氧基苯基, 邻、间或对乙氧基苯基, 邻、间或对乙氧基羰基苯基, 邻、间或对 (N,N-二甲基氨基) 苯基, 邻、间或对 (N,N-二甲基氨基羰基) 苯基, 邻、间或对 (N-乙基氨基) 苯基, 邻、间或对 (N,N-二乙基氨基) 苯基, 邻、间或对氟苯基, 邻、间或对溴苯基, 邻、间或对氯苯基, 邻、间或对 (甲基磺酰胺基) 苯基, 邻、间或对 (甲磺酰基) 苯基, 邻、间或对氰基苯基, 邻、间或对羧基苯基, 邻、间或对甲氧基羰基苯基, 邻、间或对乙酰基苯基, 邻、间或对氨基磺酰基苯基, 邻、间或对 [2-(吗啉-4-基) 乙氧基] 苯基, 邻、间或对 [3-(N,N-二乙基氨基) 丙氧基] 苯基, 此外优选 2,3-、2,4-、2,5-、2,6-、3,4- 或 3,5- 二氟苯基, 2,3-、2,4-、2,5-、2,6-、3,4- 或 3,5- 二氯苯基, 2,3-、2,4-、2,5-、2,6-、3,4- 或 3,5- 二溴苯基, 2,4- 或 2,5- 二硝基苯基, 2,5- 或 3,4- 二甲氧基苯基, 3-硝基-4-氯苯基, 3-氨基-4-氯-, 2-氨基-3-氯-, 2-氨基-4-氯-, 2-氨基-5-氯- 或 2-氨基-6-氯苯基, 2-硝基-4-N,N-二甲基氨基- 或 3-硝基-4-N,N-二甲基氨基苯基, 2,3-二氨基苯基, 2,3,4-、2,3,5-、2,3,6-、2,4,6- 或 3,4,5- 三氯苯基, 2,4,6- 三甲氧基苯基, 2-羟基-3,5-二氯苯基, 对碘代苯基, 3,6-二氯-4-氨基苯基, 4-氟-3-氯苯基, 2-氟-4-溴苯基, 2,5-二氟-4-溴苯基, 3-溴-6-甲氧基苯基, 3-氯-6-甲氧基苯基, 3-氯-4-乙酰胺基苯基, 3-氟-4-甲氧基苯基, 3-氨基-6-甲基苯基, 3-氯-4-乙酰胺基苯基或 2,5-二甲基-4-氯苯基。

[0043] Ar 此外优选代表苯基, 其未被取代或被 $O[C(R^3)_2]_nHet^1$, Ar^1 , A, CN 和 / 或 $[C(R^3)_2]_pOR^3$ 单-、二-、三-、四- 或五取代。

[0044] Ar^1 优选代表苯基或萘基。

[0045] 不考虑进一步取代, Het 代表例如 2- 或 3- 呋喃基, 2- 或 3- 噻吩基, 1-, 2- 或 3- 吡咯基, 1-, 2, 4- 或 5- 咪唑基, 1-, 3-, 4- 或 5- 吡唑基, 2-, 4- 或 5- 噁唑基, 3-, 4- 或 5- 异噁唑基, 2-, 4- 或 5- 噻唑基, 3-, 4- 或 5- 异噻唑基, 2-, 3- 或 4- 吡啶基, 2-, 4-, 5- 或 6- 嘧啶基, 此外优选 1,2,3- 三唑-1-, -4- 或 -5- 基, 1,2,4- 三唑-1-, -3- 或 -5- 基, 1- 或 5- 四唑基, 1,2,3- 噁二唑-4- 或 -5- 基, 1,2,4- 噁二唑-3- 或 -5- 基, 1,3,4- 噻二唑-2- 或 -5- 基, 1,2,4- 噻二唑-3- 或 -5- 基, 1,2,3- 噻二唑-4- 或 -5- 基, 3- 或 4- 哒嗪基, 吡嗪基, 1-, 2-, 3-, 4-, 5-, 6- 或 7- 吡啶基, 4- 或 5- 异吡啶基, 吡啶基, 1-, 2-, 4- 或 5- 苯并咪唑基, 1-, 3-, 4-, 5-, 6- 或 7- 苯并吡唑基, 2-, 4-, 5-, 6- 或 7- 苯并噁唑基, 3-, 4-, 5-, 6- 或 7- 苯并异噁唑基, 2-, 4-, 5-, 6- 或 7- 苯并噻唑基, 2-, 4-, 5-, 6- 或 7- 苯并异噻唑基, 4-, 5-, 6- 或 7- 苯并-2,1,3- 噁二唑基, 2-, 3-, 4-, 5-, 6-, 7- 或 8- 喹啉基, 1-, 3-, 4-, 5-, 6-, 7- 或 8- 异喹啉基, 3-, 4-, 5-, 6-, 7- 或 8- 噌啉基, 2-, 4-, 5-, 6-, 7- 或 8- 喹唑啉基, 5- 或 6- 喹喔啉基, 2-, 3-, 5-, 6-, 7- 或 8-2H- 苯并-1,4- 噁嗪基, 此外优选 1,3- 苯并二氧杂环戊烯-5- 基, 1,4- 苯并二噁烷-6- 基, 2,1,3- 苯并噻二唑-4-, -5- 基或 2,1,3- 苯并噁二唑-5- 基, 氮杂二环 [3.2.1] 辛基或二苯并呋喃基。

[0046] 杂环基也可以为部分或完全氢化的。

[0047] 无论是否进一步取代, Het 可以因此还代表例如 2, 3-二氢-2-, -3-, -4- 或-5- 呋喃基, 2, 5-二氢-2-, -3-, -4- 或-5- 呋喃基, 四氢-2- 或-3- 呋喃基, 1, 3-二氧杂环戊烷-4-基, 四氢-2- 或-3- 噻吩基, 2, 3-二氢-1-, -2-, -3-, -4- 或-5- 吡咯基, 2, 5-二氢-1-, -2-, -3-, -4- 或-5- 吡咯基, 1-, 2- 或-3- 吡咯烷基, 四氢-1-, -2- 或-4- 咪唑基, 2, 3-二氢-1-, -2-, -3-, -4- 或-5- 吡唑基, 四氢-1-, -3- 或-4- 吡唑基, 1, 4-二氢-1-, -2-, -3- 或-4- 吡啶基, 1, 2, 3, 4-四氢-1-, -2-, -3-, -4-, -5- 或-6- 吡啶基, 1-, 2-, 3- 或-4- 哌啶基, 2-, 3- 或-4- 吗啉基, 四氢-2-, -3- 或-4- 吡喃基, 1, 4-二噁烷基, 1, 3-二噁烷-2-, -4- 或-5- 基, 六氢-1-, -3- 或-4- 哒嗪基, 六氢-1-, -2-, -4- 或-5- 嘧啶基, 1-, 2- 或-3- 哌嗪基, 1, 2, 3, 4-四氢-1-, -2-, -3-, -4-, -5-, -6-, -7- 或-8- 喹啉基, 1, 2, 3, 4-四氢-1-, -2-, -3-, -4-, -5-, -6-, -7- 或-8- 异喹啉基, 2-, 3-, 5-, 6-, 7- 或-8- 3, 4-二氢-2H- 苯并-1, 4-噁嗪基, 此外优选 2, 3-亚甲基二氧基苯基, 3, 4-亚甲基二氧基苯基, 2, 3-亚乙基二氧基苯基, 3, 4-亚乙基二氧基苯基, 3, 4-(二氟亚甲基二氧基) 苯基, 2, 3-二氢苯并呋喃-5- 或-6- 基, 2, 3-(2-氧代亚甲基二氧基) 苯基或此外 3, 4-二氢-2H-1, 5- 苯并二氧杂环庚二烯-6- 或-7- 基, 此外优选 2, 3-二氢苯并呋喃基, 2, 3-二氢-2- 氧代呋喃基, 3, 4-二氢-2- 氧代-1H- 喹唑啉基, 2, 3-二氢苯并噁唑基, 2- 氧代-2, 3-二氢苯并噁唑基, 2, 3-二氢苯并咪唑基, 1, 3-二氢吡啶, 2- 氧代-1, 3-二氢吡啶或 2- 氧代-2, 3-二氢苯并咪唑基。

[0048] Het 优选代表具有 1 至 4 个 N, O 和 / 或 S 原子的单- 或双环芳族杂环, 其未被取代或被 Hal, A, $[C(R^3)_2]_nOA'$, $S(O)_nA$, CN, $SO_2N(R^3)_2$ 和 / 或 COHet¹ 单- 或二取代。

[0049] Het 此外优选代表呋喃基, 噻吩基, 吡咯基, 咪唑基, 吡唑基, 噁唑基, 异噁唑基, 噻唑基, 异噻唑基, 吡啶基, 嘧啶基, 三唑基, 四唑基, 噁二唑基, 噻二唑基, 哒嗪基, 吡嗪基, 苯并噁唑基, 苯并噻唑基, 苯并咪唑基, 苯并三唑基, 吡啶基, 苯并-1, 3-二氧杂环戊烯基, 苯并二噁烷基, 苯并噻二唑基, 吡啶基, 苯并呋喃基, 喹啉基, 异喹啉基, 噁唑并 [5, 4-b] 吡啶基, 咪唑并 [1, 2-a] 吡啶基或噁唑并 [5, 4-c] 吡啶基, 其各自未被取代或被 Hal, A, $[C(R^3)_2]_nOA'$, $S(O)_nA$, CN, $SO_2N(R^3)_2$ 和 / 或 COHet¹ 单或二取代。

[0050] 无论是否进一步取代, Het¹ 代表例如 2- 或-3- 呋喃基, 2- 或-3- 噻吩基, 1-, 2- 或-3- 吡咯基, 1-, 2, 4- 或-5- 咪唑基, 1-, 3-, 4- 或-5- 吡唑基, 2-, 4- 或-5- 噁唑基, 3-, 4- 或-5- 异噁唑基, 2-, 4- 或-5- 噻唑基, 3-, 4- 或-5- 异噻唑基, 2-, 3- 或-4- 吡啶基, 2-, 4-, 5- 或-6- 嘧啶基, 此外优选 1, 2, 3- 三唑-1-, -4- 或-5- 基, 1, 2, 4- 三唑-1-, -3- 或-5- 基, 1- 或-5- 四唑基, 1, 2, 3- 噁二唑-4- 或-5- 基, 1, 2, 4- 噁二唑-3- 或-5- 基, 1, 3, 4- 噻二唑-2- 或-5- 基, 1, 2, 4- 噻二唑-3- 或-5- 基, 1, 2, 3- 噻二唑-4- 或-5- 基, 3- 或-4- 哒嗪基, 吡嗪基, 1-, 2-, 3-, 4-, 5-, 6- 或-7- 吡啶基, 4- 或-5- 异吡啶基, 吡啶基, 1-, 2-, 4- 或-5- 苯并咪唑基, 1-, 3-, 4-, 5-, 6- 或-7- 苯并吡唑基, 2-, 4-, 5-, 6- 或-7- 苯并噁唑基, 3-, 4-, 5-, 6- 或-7- 苯并异噁唑基, 2-, 4-, 5-, 6- 或-7- 苯并噻唑基, 2-, 4-, 5-, 6- 或-7- 苯并异噻唑基, 4-, 5-, 6- 或-7- 苯并-2, 1, 3- 噁二唑基, 2-, 3-, 4-, 5-, 6-, 7- 或-8- 喹啉基, 1-, 3-, 4-, 5-, 6-, 7- 或-8- 异喹啉基, 3-, 4-, 5-, 6-, 7- 或-8- 噌啉基, 2-, 4-, 5-, 6-, 7- 或-8- 喹唑啉基, 5- 或-6- 喹啉基, 2-, 3-, 5-, 6-, 7- 或-8-2H- 苯并-1, 4-噁嗪基, 此

外优选 1,3- 苯并二氧杂环戊烯-5- 基, 1,4- 苯并二噁烷-6- 基, 2,1,3- 苯并噻二唑-4-, -5- 基或 2,1,3- 苯并噻二唑-5- 基, 氮杂二环 [3.2.1] 辛基或二苯并呋喃基。

[0051] 杂环基也可以被部分或完全氢化。

[0052] 无论是否进一步取代, Het 可以因此还代表例如 2,3- 二氢-2-, -3-, -4- 或-5- 呋喃基, 2,5- 二氢-2-, -3-, -4- 或-5- 呋喃基, 四氢-2- 或-3- 呋喃基, 1,3- 二氧杂环戊烷-4- 基, 四氢-2- 或-3- 噻吩基, 2,3- 二氢-1-, -2-, -3-, -4- 或-5- 吡咯基, 2,5- 二氢-1-, -2-, -3-, -4- 或-5- 吡咯基, 1-, 2- 或-3- 吡咯烷基, 四氢-1-, -2- 或-4- 咪唑基, 2,3- 二氢-1-, -2-, -3-, -4- 或-5- 吡唑基, 四氢-1-, -3- 或-4- 吡唑基, 1,4- 二氢-1-, -2-, -3- 或-4- 吡啶基, 1,2,3,4- 四氢-1-, -2-, -3-, -4-, -5- 或-6- 吡啶基, 1-, 2-, 3- 或-4- 哌啶基, 2-, 3- 或-4- 吗啉基, 四氢-2-, -3- 或-4- 吡喃基, 1,4- 二噁烷基, 1,3- 二噁烷-2-, -4- 或-5- 基, 六氢-1-, -3- 或-4- 哒嗪基, 六氢-1-, -2-, -4- 或-5- 嘧啶基, 1-, 2- 或-3- 哌嗪基, 1,2,3,4- 四氢-1-, -2-, -3-, -4-, -5-, -6-, -7- 或-8- 喹啉基, 1,2,3,4- 四氢-1-, -2-, -3-, -4-, -5-, -6-, -7- 或-8- 异喹啉基, 2-, 3-, 5-, 6-, 7- 或-8- 3,4- 二氢-2H- 苯并-1,4- 噁嗪基, 此外优选 2,3- 亚甲基二氧基苯基, 3,4- 亚甲基二氧基苯基, 2,3- 亚乙基二氧基苯基, 3,4- 亚乙基二氧基苯基, 3,4-(二氟亚甲基二氧基) 苯基, 2,3- 二氢苯并呋喃-5- 或-6- 基, 2,3-(2- 氧代亚甲基二氧基) 苯基或此外 3,4- 二氢-2H-1,5- 苯并二氧杂环庚二烯-6- 或-7- 基, 此外优选 2,3- 二氢苯并呋喃基, 2,3- 二氢-2- 氧代呋喃基, 3,4- 二氢-2- 氧代-1H- 喹唑啉基, 2,3- 二氢苯并噻唑基, 2- 氧代-2,3- 二氢苯并噻唑基, 2,3- 二氢苯并咪唑基, 1,3- 二氢吡啶, 2- 氧代-1,3- 二氢吡啶或 2- 氧代-2,3- 二氢苯并咪唑基。

[0053] Het¹ 优选代表具有 1 至 4 个 N, O 和 / 或 S 原子的单环饱和杂环, 其未被取代或被 A 单- 或二取代。Het¹ 此外优选代表吡咯烷基, 氮杂环丁烷基, 氧杂环丁烷基, 四氢咪唑基, 四氢吡唑基, 四氢呋喃基, 哌啶基, 哌嗪基, 吗啉基, 六氢哒嗪基, 六氢嘧啶基, [1,3] 二氧杂环戊烷基或四氢吡喃基, 其各自未被取代或被 A 单- 或二取代。

[0054] Hal 优选代表 F, Cl 或 Br, 和 I, 特别优选 F 或 Cl。

[0055] 贯穿本发明, 出现多于一次的全部基团都可以相同或不同, 即彼此独立。式 I 化合物可以具有一个或多个手性中心并因此可以各种立体异构形式出现。式 I 包括全部这些形式。

[0056] 因此, 本发明特别涉及式 I 化合物, 其中所述基团中的至少一种具有上述的一种优选含义。一些优选的化合物组可以有下文的子式 Ia 至 Ik 表示, 其符合式 I, 其中没有更详细定义的基团具有对式 I 指出的含义, 但其中

在 Ia 中 X¹, X³ 代表 CH,

X², X⁴ 代表 N;

在 Ib 中 X¹, X², X³, X⁴ 代表 CH,

在 Ic 中 X¹, X³, X⁴ 代表 CH,

X² 代表 N;

在 Id 中 X¹, X², X³ 代表 CH,

X⁴ 代表 N;

在 Ie 中 X¹, X² 代表 CH,

X^3, X^4 代表 N;

在 If 中 X^3, X^4 代表 CH,

X^1, X^2 代表 N;

在 Ig 中 R^2 代表 H;

在 Ih 中 $R^{2'}$ 代表 A 或 $[C(R^3)_2]_n\text{Cyc}$;

在 Ii 中 R^4 代表 H, F, Cl, OA' 或 A' ;

在 Ij 中 R^3 代表 H 或甲基;

在 Ik 中 A 代表具有 1-10 个 C- 原子的非支链或支链烷基, 其中一个或两个不相邻的 $CH-$ 和 / 或 CH_2- 基团可以被 N- 和 / 或 O- 原子替代和 1-7 个 H- 原子可以被 R^5 替代;

在 Il 中 Ar 代表苯基, 其未被取代或被 $O[C(R^3)_2]_n\text{Het}^1$, Ar^1 , A, CN 和 / 或 $[C(R^3)_2]_pOR^3$ 单-、二-、三-、四- 或五取代;

在 Im 中 Het 代表具有 1 至 4 个 N, O 和 / 或 S 原子的单-或二环芳族杂环, 其未被取代或被 Hal, A, $[C(R^3)_2]_nOA'$, $S(O)_nA$, CN, $SO_2N(R^3)_2$ 和 / 或 $COHet^1$ 单-或二取代;

在 In 中 Het 代表呋喃基, 噻吩基, 吡咯基, 咪唑基, 吡唑基, 噁唑基, 异噁唑基, 噻唑基, 异噻唑基, 吡啶基, 嘧啶基, 三唑基, 四唑基, 噁二唑基, 噻二唑基, 哒嗪基, 吡嗪基, 苯并噁唑基, 苯并噻唑基, 苯并咪唑基, 苯并三唑基, 吲哚基, 苯并-1,3-二氧杂环戊烯基, 苯并二噁烷基, 苯并噻二唑基, 吲唑基, 苯并呋喃基, 喹啉基, 异喹啉基, 噁唑并 [5,4-b] 吡啶基, 咪唑并 [1,2-a] 吡啶基或噁唑并 [5,4-c] 吡啶基, 其各自未被取代或被 Hal, A, $[C(R^3)_2]_nOA'$, $S(O)_nA$, CN, $SO_2N(R^3)_2$ 和 / 或 $COHet^1$ 单-或二取代;

在 In 中 Het^1 代表具有 1 至 4 个 N, O 和 / 或 S 原子的单环饱和杂环, 其未被取代或被 A 单-或二取代;

在 Io 中 Het^1 代表吡咯烷基, 氮杂环丁烷基, 氧杂环丁烷基, 四氢咪唑基, 四氢吡唑基, 四氢呋喃基, 哌啶基, 哌嗪基, 吗啉基, 六氢哒嗪基, 六氢嘧啶基, [1,3] 二氧杂环戊烷基或四氢吡喃基, 其各自未被取代或被 A 单-或二取代;

在 Ip 中 R 代表 Ar, Het, $-C \equiv C-Ar$ 或 $-C \equiv C-Het$,,

W 代表 $NR^2R^{2'}$ 或 Het^1 ,

R^1 代表 A, $[C(R^3)_2]_nAr^1$ 或 $[C(R^3)_2]_n\text{Cyc}$,

$R^2, R^{2'}$ 彼此独立地各自代表 H, A 或 $[C(R^3)_2]_n\text{Cyc}$,

R^4 代表 H, F, Cl, OA' 或 A' ,

X^1, X^2, X^3, X^4 彼此独立地各自代表 CH 或 N,

A 代表具有 1-10 个 C- 原子的非支链或支链烷基, 其中一个或两个不相邻的 $CH-$ 和 / 或 CH_2- 基团可以被 N- 和 / 或 O- 原子替代或 1-7 个 H- 原子可以被 R^5 替代,

Cyc 代表具有 3-7 个 C- 原子的环烷基, 其未被取代或被 OH 或 A 单取代,

A' 代表具有 1-6 个 C- 原子的非支链或支链烷基, 其中 1-5 个 H- 原子可以被 F 替代,

R^5 代表 F, Cl 或 OH,

Ar 代表苯基, 其未被取代或被 $O[C(R^3)_2]_n\text{Het}^1$, Ar^1 , A, CN 和 / 或 $[C(R^3)_2]_pOR^3$ 单-、二-、三-、四- 或五取代,

Ar^1 代表苯基或萘基,

R^3 代表 H 或具有 1-6 个 C- 原子的非支链或支链烷基,

Het 代表呋喃基, 噻吩基, 吡咯基, 咪唑基, 吡唑基, 噁唑基, 异噁唑基, 噻唑基, 异噻唑基, 吡啶基, 嘧啶基, 三唑基, 四唑基, 噁二唑基, 噻二唑基, 哒嗪基, 吡嗪基, 苯并噁唑基, 苯并噻唑基, 苯并咪唑基, 苯并三唑基, 吲哚基, 苯并-1,3- 二氧杂环戊烯基, 苯并二噁烷基, 苯并噻二唑基, 吲唑基, 苯并呋喃基, 喹啉基, 异喹啉基, 噁唑并 [5,4-b] 吡啶基, 咪唑并 [1,2-a] 吡啶基或噁唑并 [5,4-c] 吡啶基, 其各自未被取代或被 Hal, A, $[C(R^3)_2]_nOA'$, $S(O)_nA$, CN, $SO_2N(R^3)_2$ 和 / 或 COHet¹单 - 或二取代,

Het¹代表吡咯烷基, 氮杂环丁烷基, 氧杂环丁烷基, 四氢咪唑基, 四氢吡唑基, 四氢呋喃基, 哌啶基, 哌嗪基, 吗啉基, 六氢哒嗪基, 六氢嘧啶基, [1,3] 二氧杂环戊烷基或四氢吡喃基, 其各自未被取代或被 A 单 - 或二取代,

Hal 代表 F, Cl, Br 或 I,

n 代表 0, 1 或 2,

p 代表 0, 1, 2, 3 或 4,

q0, 1, 2 或 3,

条件是 X^1 , X^2 , X^3 , X^4 中的只一个或两个代表 N,

和其药学上可接受的盐、互变异构体和立体异构体, 包括其全部比例的混合物。

[0057] 此外, 式 I 化合物和用于它们的制备的起始原料通过本身已知的方法制备, 如文献 (例如在标准文献, 例如 Houben-Weyl, Methoden der organischen Chemie [Methods of Organic Chemistry], Georg-Thieme-Verlag, Stuttgart) 中, 确切地说在已知的并适合所述反应的反应条件下记载的。此处用途也可以由本身已知的变体构成, 其在此处没有更具体地提及。

[0058] 式 II 和 III 的起始化合物通常是已知的。如果它们是新型的, 它们可以通过本身已知的方法制备。

[0059] 式 I 化合物可以优选通过式 II 化合物与式 III 化合物反应获得。

[0060] 在式 III 化合物中, L 优选代表 Cl, Br, I 或游离或反应性改性的 OH 基团, 例如活性酯、咪唑烷 (imidazolidine) 或具有 1-6 个 C 原子的烷基磺酰基氧基 (优选甲基磺酰基氧基或三氟甲基磺酰基氧基) 或具有 1-6 个 C 原子的芳基磺酰基氧基 (优选苯基 - 或对甲苯基磺酰基氧基)。

[0061] 该反应通常在酸结合剂, 优选有机碱例如 DIPEA, 三乙胺, 二甲基苯胺, 吡啶或喹啉的存在下进行。

[0062] 添加碱金属或碱土金属氢氧化物、碳酸盐或碳酸氢盐或碱金属或碱土金属的弱酸的其他盐, 优选钾盐、钠盐、钙盐或铯盐也可以是有利的。取决于所使用的条件, 反应时间为几分钟至 14 天, 反应温度为约 -30° 至 140° , 通常 -10° 至 90° , 特别是约 0° 至约 70° 。

[0063] 合适惰性溶剂的实例是烃类, 诸如己烷, 石油醚, 苯, 甲苯或二甲苯; 氯化烃, 诸如三氯乙烯, 1,2- 二氯乙烷, 四氯化碳, 氯仿或二氯甲烷; 醇, 诸如甲醇, 乙醇, 异丙醇, 正丙醇, 正丁醇或叔丁醇; 醚, 诸如二乙醚, 二异丙醚, 四氢呋喃 (THF) 或二噁烷; 二醇醚, 诸如乙二醇单甲醚或单乙醚, 乙二醇二甲醚 (二甘醇二甲醚); 酮, 诸如丙酮或丁酮; 酰胺, 诸如乙酰胺, 二甲基乙酰胺或二甲基甲酰胺 (DMF); 腈, 诸如乙腈; 亚砜, 诸如二甲亚砜 (DMSO); 二

硫化碳；羧酸，诸如甲酸或乙酸；硝基化合物，诸如硝基甲烷或硝基苯；酯，诸如乙酸乙酯，或所述溶剂的混合物。

[0064] 特别优选的是提供乙腈、二氯甲烷和 / 或 DMF。

[0065] 药盐及其它形式

所述根据本发明的化合物可以使用它们的最终非盐形式。另一方面，本发明还包括使用其药学可接受的盐形式的这些化合物，它们可以利用本领域已知的方法、由各种有机和无机酸和碱来获得。式 I 化合物的药学可接受的盐形式大部分是通过常规方法制备的。如果式 I 的化合物包含羧基，它的一种合适盐可以如下形成：该化合物与合适碱反应，得到相应的碱加成盐。这种碱是，例如，碱金属氢氧化物，包括氢氧化钾、氢氧化钠和氢氧化锂；碱土金属氢氧化物，诸如氢氧化钡和氢氧化钙；碱金属醇盐，例如乙醇钾和丙醇钠；和各种有机碱，诸如吡啶、二乙醇胺和 N- 甲基谷氨酰胺。同样包括式 I 化合物的铝盐。在某些式 I 化合物的情况下，酸加成盐可以通过用药学可接受的有机和无机酸，例如氢卤酸，诸如盐酸、氢溴酸或氢碘酸，其它矿物酸和其相应的盐，诸如硫酸盐、硝酸盐或磷酸盐等等，和烷基-和单芳基磺酸盐，诸如乙磺酸盐、甲苯磺酸盐和苯磺酸盐，及其它有机酸和其相应的盐，诸如乙酸盐，三氟乙酸盐，酒石酸盐，马来酸盐，琥珀酸盐，柠檬酸盐，苯甲酸盐，水杨酸盐，抗坏血酸盐等等处理这些化合物来形成。相应地，式 I 化合物的药学可接受的酸加成盐包括下列：乙酸盐，己二酸盐，海藻酸盐，精氨酸盐，天冬氨酸盐，苯甲酸盐，苯磺酸盐 (benzenesulfonate) (苯磺酸盐 (besylate))，硫酸氢盐，亚硫酸氢盐，溴化物，丁酸盐，樟脑酸盐，樟脑磺酸盐，辛酸盐，氯化物，氯苯甲酸盐，柠檬酸盐，环戊烷丙酸盐，二葡萄糖酸盐，磷酸二氢盐，二硝基苯甲酸盐，十二烷基硫酸盐，乙磺酸盐，延胡索酸盐，粘酸盐 (galactate) (得自于粘酸)，半乳糖醛酸盐，葡庚糖酸盐，葡萄糖酸盐，谷氨酸盐，甘油磷酸盐，半琥珀酸盐，半硫酸盐，庚酸盐，己酸盐，马尿酸盐，盐酸盐，氢溴酸盐，氢碘酸盐，2- 羟基乙磺酸盐，碘化物，羟乙基磺酸盐，异丁酸盐，乳酸盐，乳糖酸盐，苹果酸盐，马来酸盐，丙二酸盐，苦杏仁酸盐，偏磷酸盐，甲磺酸盐，甲基苯甲酸盐，磷酸一氢盐，2- 萘磺酸盐，烟酸盐，硝酸盐，草酸盐，油酸盐，棕榈酸盐，果冻酸盐，过硫酸盐，苯乙酸盐，3- 苯丙酸盐，磷酸盐，麟酸盐，邻苯二甲酸盐，但不限于这些。

[0066] 此外，根据本发明化合物的碱盐包括铝、铵、钙、铜、铁 (III)、铁 (II)、锂、镁、锰 (III)、锰 (II)、钾、钠和锌盐，但不意在限于这些。上述盐之中，优选铵盐；碱金属盐钠和钾盐，碱土金属盐钙和镁盐。衍生自药学可接受的有机无毒碱的式 I 化合物的盐包括下述的盐：伯、仲和叔胺，取代的胺，还包括天然存在的取代的胺，环胺和碱离子交换树脂，例如精氨酸，甜菜碱，咖啡因，氯普鲁卡因，胆碱，N, N'- 二苄基乙二胺 (苯乍生)，二环己基胺，二乙醇胺，二乙胺，2- 二乙基氨基乙醇，2- 二甲基氨基乙醇，乙醇胺，乙二胺，N- 乙基吗啉，N- 乙基吡啶，葡萄糖胺，氨基葡萄糖，组氨酸，哈胺，异丙胺，利多卡因，赖氨酸，葡甲胺，N- 甲基-D- 葡萄糖胺，吗啉，哌嗪，哌啶，多胺树脂，普鲁卡因，嘌呤，可可碱，三乙醇胺，三乙胺，三甲胺，三丙胺和三 (羟甲基) 甲胺 (氨基丁三醇)，但不限于这些。

[0067] 可以使用试剂诸如 (C₁-C₄) 烷基卤化物，例如甲基、乙基、异丙基和叔丁基的氯化物、溴化物和碘化物；二 (C₁-C₄) 烷基硫酸酯，例如硫酸二甲基、二乙基和二戊基酯；(C₁₀-C₁₈) 烷基卤化物，例如癸基、十二烷基、月桂基、十四烷基和硬脂基的氯化物、溴化物和碘化物；和芳基 (C₁-C₄) 烷基卤化物，例如苄基氯和苄基溴，将包含碱性含氮基团的本发

明化合物季化。根据本发明的水和油溶性两类化合物可以使用这种盐来制备。

[0068] 优选地,上述药学盐包括乙酸盐,三氟乙酸盐,苯磺酸盐,柠檬酸盐,延胡索酸盐,葡糖酸盐,半琥珀酸盐,马尿酸盐,盐酸盐,氢溴酸盐,羟乙基磺酸盐,苦杏仁酸盐,葡甲胺,硝酸盐,油酸盐,膦酸盐,新戊酸盐,磷酸钠,硬脂酸盐,硫酸盐,磺基水杨酸盐,酒石酸盐,硫代苹果酸盐,甲苯磺酸盐和氨基丁三醇,但不限于这些。

[0069] 特别优选盐酸盐,二盐酸盐,氢溴酸盐,马来酸盐,甲磺酸盐,磷酸盐,硫酸盐和琥珀酸盐。

[0070] 如下制备式 I 的碱性化合物的酸加成盐:利用常规方式,使游离碱形式与足够量的期望酸接触,引起盐的形成。利用常规方式,使盐形式接触碱,并分离游离碱,可以再生游离碱。在某些方面,游离碱形式在某些物理性能(诸如,在极性溶剂中的溶解度)方面与其相应的盐形式不同;然而,对于本发明的目的来说,盐在其它方面相当于其相应的游离碱形式。

[0071] 如提到的,与金属或胺(诸如碱金属和碱土金属或有机胺)一起形成式 I 化合物的药学可接受的碱加成盐。优选的金属是钠、钾、镁和钙。优选的有机胺是 N,N'-二苄基乙二胺,氯普鲁卡因,胆碱,二乙醇胺,乙二胺,N-甲基-D-葡糖胺和普鲁卡因。

[0072] 如下制备根据本发明的酸式化合物的碱加成盐:利用常规方式,使游离酸形式与足够量的目标碱接触,引起盐的形成。利用常规方式,使盐形式接触酸,并分离游离酸,可以再生游离酸。在某些方面,游离酸形式在某些物理性能(诸如,在极性溶剂中的溶解度)方面与其相应的盐形式不同;然而,对于本发明的目的来说,盐在其它方面相当于其相应的游离酸形式。

[0073] 如果根据本发明的化合物包含多于一个能够形成这种类型的药学可接受的盐的基团,则本发明还包括多重盐(multiple salts)。典型的多重盐形式包括,例如,二酒石酸盐,双乙酸盐,二富马酸盐,二葡甲胺,二磷酸盐,二钠和三盐酸盐,但不限于这些。

[0074] 关于上述,能够看出,本发明中的表述“药学可接受的盐”是指活性组分,其包括其盐之一形式的式 I 化合物,特别是当这种盐形式赋予提高的活性组分药代动力学特性的时候(与先前使用的活性组分的游离形式或活性组分的任何其它盐形式相比)。活性组分的药学可接受的盐形式还可以第一次为这种活性组分提供先前不具有的期望的药代动力学特性,并且甚至在体内治疗效能方面可以对这种活性组分的药效学具有积极影响。

[0075] 同位素

此外,式 I 化合物意在包括其同位素标记的形式。式 I 化合物的同位素标记形式与该化合物相同,除了该化合物的一个或多个原子被具有与天然常规存在的原子的原子量或原子质量不同的原子量或原子质量的一个或多个原子代替的事实。容易商购和能够通过熟知方法并入式 I 化合物的同位素的实例包括氢、碳、氮、氧、磷、氟、和氯的同位素,例如分别为 ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F 和 ^{36}Cl 。含有一种或多种上述同位素和/或其他原子的其他同位素的式 I 化合物、其前药或药学上可接受的盐意在为本发明的一部分。同位素标记的式 I 化合物可以很多有益方式使用。例如,其中例如引入放射性同位素例如 ^3H 或 ^{14}C 的同位素标记的式 I 化合物适合药物和/或底物组织分配分析。这些放射性同位素,即氚(^3H)和碳-14(^{14}C),由于简单制备和优异的检测能力是特别优选的。较重的同位素例如氘(^2H)引入式 I 化合物由于该同位素标记化合物的较高的代谢稳定性而具有

治疗优势。较高的代谢稳定性直接转化成体内增加的半衰期或较低的剂量,其在大多数环境下代表本发明优选的实施方案。同位素标记的式 I 化合物通常可以通过进行在合成方案和相关描述中、在本文中的实施例部分中和制备部分中公开的程序,通过容易获得的同位素标记的反应物代替非同位素标记的反应物制备。

[0076] 为了通过基本动力学同位素效应控制该化合物的氧化代谢,氘 (^2H) 也可以引入式 I 化合物中。所述基本动力学同位素效应是由同位素核交换产生的化学反应的速率变化,其通过在同位素交换之后的共价键形成所需的基态能量中的变化产生。较重的同位素的交换通常导致化学键的基态能量的降低并因此导致速率限制的键裂解的速率降低。如果随着多产物反应的配合,在鞍点区域中或附近发生键断裂,则大体上可以改变产物分配比率。为了解释:如果氘在不可交换的位置键合至碳原子, $k_{\text{H}}/k_{\text{D}} = 2-7$ 的速率差异是典型的。如果速率差异成功地适用于容易氧化的式 I 化合物,则该化合物在体内的特征可以显著地改变并导致改善的药代动力学性质。

[0077] 当发现和开发治疗剂时,本领域技术人员试图优化药代动力学参数,同时维持需要的体外性质。有理由认为很多具有差药代动力学特征的化合物容易发生氧化代谢。当下可以进行的体外肝脏线粒体分析在这种类型的氧化代谢过程中提供有价值的信息,其反过来允许通过对此类氧化代谢具有耐受性的改善的稳定性的氘化的式 I 化合物的合理设计。从而获得式 I 化合物的药代动力学特征中的明显改善,并可以体内半衰期 ($t/2$)、最高治疗效果下的浓度 (C_{max})、在剂量响应曲线 (AUC) 的面积和 F 下中的提高的形式;和以降低的清除率、剂量和材料成本的形式定量表达。

[0078] 下文意在示例上述内容:具有对于氧化代谢具有攻击性的多个潜在位点例如苺型氢原子和与氮原子键合的氢原子的式 I 化合物制备成一系列类似物,其中氢原子的各种组合被氘原子代替,从而使这些氢原子中的一些、大部分或全部被氘原子代替。半衰期测定是有利的并且精确测定对氧化代谢的耐受性改善的改善程度。以此方式,由于这种类型的氘-氢交换,测定母体化合物的半衰期可以扩展到最多 100%。

[0079] 式 I 化合物中的氘-氢交换也可以用于实现起始化合物的代谢物谱的有利修饰从而减少或消除不期望的有毒代谢物。例如,如果有毒代谢物通过氧化碳-氢 (C-H) 键断裂出现,则可以合理地认为氘代类似物会大幅度减少或消除不期望的代谢物的产生,即使特定的氧化不是速率决定的步骤。可以找到现有技术中关于氘-氢交换的其他信息,例如在 Hanzlik 等人, J. Org. Chem. 55, 3992-3997, 1990, Reider 等人, J. Org. Chem. 52, 3326-3334, 1987, Foster, Adv. Drug Res. 14, 1-40, 1985, Gillette 等人, Biochemistry 33(10) 2927-2937, 1994, and Jarman 等人. Carcinogenesis 16(4), 683-688, 1993。

[0080] 此外,本发明涉及药物,其包含至少一种式 I 的化合物和 / 或其药学可接受的盐、互变异构体和立体异构体,包括其所有比例的混合物,和任选的赋形剂和 / 或助剂。

[0081] 药物制剂可以以剂量单位形式给予,每个剂量单位含有预定量的活性组分。根据所治疗的病症、给药方法和患者的年龄、体重和状态,这种单位可以包含例如 0.5 mg 至 1 g, 优选 1 mg 至 700 mg, 尤其优选 5 mg 至 100 mg 的根据本发明的化合物,或可以以剂量单位形式给予药物制剂,每个剂量单位包含预定量的活性组分。优选的剂量单位制剂是包含活性组分的上述日剂量或部分剂量或其相应分数的那些制剂。此外,可以使用药物领域通常

已知的方法来制备这种类型的药物制剂。

[0082] 药物制剂可以适合于经过任何目标合适方法给药,例如口服(包括口腔或舌下)、直肠、鼻部、局部(包括口腔、舌下或透皮)、阴道或肠胃外(包括皮下、肌内、静脉内或皮内)方法。这种制剂可以使用药物领域已知的所有方法来制备,例如,将活性组分与赋形剂或助剂混合。

[0083] 适合于口服给药的药物制剂可以以离散单位形式给药,诸如例如,胶囊或片剂;粉剂或粒剂;在水或非水液体中的溶液剂或混悬剂;可食用泡沫体或泡沫食物;或水包油型液体乳剂或油包水型液体乳剂。

[0084] 因此,例如,在口服给予片剂或胶囊剂形式的情况下,可以将活性成分组分与口服无毒的药学可接受的惰性赋形剂诸如例如乙醇、丙三醇、水等等结合。粉剂是如下制备的:将化合物磨碎至合适大小的细粉,与以类似方法磨碎的药物赋形剂(诸如例如食用碳水化合物,诸如例如淀粉或甘露糖醇)混合。也可以存在调味剂、防腐剂、分散剂和染料。

[0085] 胶囊剂可以如下产生:制备如上所述的粉末混合物,并将其填充到成型的明胶壳中。可以将助流剂和润滑剂,诸如例如高度分散的硅酸、滑石、硬脂酸镁、硬脂酸钙或固体形式的聚乙二醇添加到粉末混合物中,而后进行填充。为了在已经获取胶囊剂之后提高药物的利用率,也可以添加崩解剂或增溶剂,诸如例如,琼脂、碳酸钙或碳酸钠。

[0086] 此外,如果希望或需要,还可以将合适的粘合剂、润滑剂和崩解剂以及染料引入混合物中。合适的粘合剂包括淀粉,明胶,天然糖诸如例如葡萄糖或 β -乳糖,由玉米制得的甜味剂,天然和合成胶诸如例如阿拉伯胶、黄芪胶或海藻酸钠,羧甲基纤维素,聚乙二醇,蜡等等。用于这些剂型中的润滑剂包括油酸钠、硬脂酸钠、硬脂酸镁、苯甲酸钠、乙酸钠、氯化钠等等。崩解剂包括但不限于:淀粉,甲基纤维素,琼脂,膨润土,黄原胶等等。如下配制片剂:例如,制备粉末混合物,将该混合物造粒或干压,添加润滑剂和崩解剂,并挤压整个混合物,得到片剂。如下制备粉末混合物:如上所述,将以合适方式粉碎的化合物与稀释剂或基料混合,任选与粘合剂(诸如例如,羧甲基纤维素,海藻酸盐,明胶或聚乙烯吡咯烷酮)、溶解阻滞剂(诸如例如,链烷烃)、吸收促进剂(诸如例如,季盐)和/或吸收剂(诸如例如,膨润土,高岭土或磷酸氢钙)混合。可以将粉末混合物如下进行造粒:用粘合剂诸如例如糖浆、淀粉糊、阿卡迪亚胶浆或纤维素或聚合物材料的溶液将其湿润,并将其挤压通过筛网。作为造粒的替代性方法,可以使粉末混物流过压片机,得到不均匀形状的块,将其破碎,形成颗粒。为了防止粘住片剂造型模,可以添加硬脂酸、硬脂酸盐、滑石粉或矿物油,将颗粒润滑。然后将润滑的混合物压缩,得到片剂。根据本发明的化合物还可以与自由流动的惰性赋形剂结合,而后直接压制,得到片剂,不用进行造粒或干压步骤。可以存在由虫胶密封层、糖或聚合物材料层和石蜡光泽层组成的透明或不透明保护层。可以将染料添加到这些涂层中,以便能够区别不同的剂量单位。

[0087] 可以制备剂量单位形式的口服液体,诸如例如溶液剂、糖浆剂和酏剂,使得给定量包含预定量的化合物。可以通过将化合物溶解在含有合适调味剂的水溶液中来制备糖浆剂,而酏剂是通过使用无毒的醇媒介物来制备的。可以通过将化合物分散在无毒的媒介物中来配制混悬剂。也可以添加增溶剂和乳化剂,诸如例如,乙氧基化的异十八烷醇和聚氧乙烯山梨糖醇醚,防腐剂,调味添加剂,诸如例如,薄荷油或天然甜味料或糖精,或其它人工甜味料等等。

[0088] 如果需要,可以将口服给药的剂量单位制剂包封在微囊中。还可以制备延长或延迟方式释放的该制剂,诸如例如,在聚合物、蜡等等中涂覆或包埋颗粒材料。

[0089] 还可以给予脂质体递送系统形式的式 I 的化合物和其药学上可接受的盐、互变异构体和立体异构体,诸如例如,小单层囊泡、大单层囊泡和多层囊泡。脂质体可以由各种磷脂诸如例如胆固醇、硬脂胺或磷脂酰胆碱形成。

[0090] 式 I 的化合物和其药学上可接受的盐、互变异构体和生理学上官能衍生物也可以利用作为化合物分子与其结合的个别载体的单克隆抗体来递送。该化合物也可以与作为靶向药物载体的可溶性聚合物类结合。这种聚合物可以包括聚乙烯吡咯烷酮,吡喃共聚物,聚羟丙基甲基丙烯酰胺基苯酚,聚羟乙基天冬酰胺基苯酚或被棕榈酰基团取代的聚氧化乙烯-聚赖氨酸。此外,该化合物可以与适合于实现药物的控制释放的能够生物降解的聚合物类结合,例如聚乳酸、聚 ϵ -己内酯、聚羟基丁酸、聚原酸酯类 (polyorthoesters)、聚缩醛类、聚二羟基吡喃类、聚氰基丙烯酸酯类和水凝胶的交联的或两亲性的嵌段共聚物。

[0091] 适合于透皮给药的药物制剂,可以用能够与受体的表皮长时间紧密接触的独立硬膏剂形式给药。因此,例如,利用在 *Pharmaceutical Research*, 3(6), 318(1986) 中以通用形式描述的离子电渗疗法,活性组分可以从硬膏剂中递送。

[0092] 可以将适合于局部给药的药物化合物配制为软膏剂、乳膏剂、混悬剂、洗剂、粉剂、溶液剂、糊剂、凝胶剂、喷雾剂、气雾剂或油剂。

[0093] 对于治疗眼睛或其它外部组织,例如口腔和皮肤,优选地,以局部软膏剂或乳膏剂的形式给予制剂。在配制得到软膏剂的情况下,活性组分可以与石蜡或水可混溶的乳膏基料一起使用。或者,可以将活性组分与水包油型乳膏基料或油包水型基料一起配制,得到乳膏剂。

[0094] 适合于局部给予眼睛的药物制剂包括滴眼剂,其中活性组分溶解或悬浮在合适载体中,特别是水溶剂中。

[0095] 适合于局部给予口中的药物制剂包括锭剂、软锭剂和嗽口水。

[0096] 适合于直肠给药的药物制剂可以以栓剂或灌肠剂形式给予。

[0097] 适合于鼻部给药的药物制剂(其中载体物质是固体)包括具有例如 20 至 500 微米范围粒径的粗粉剂,其是采用鼻吸的方式给药的,即从保持接近鼻子的承装粉剂的容器中通过鼻腔快速吸入。以鼻喷雾或滴鼻剂形式给药的合适制剂(液体作为载体物质),包括活性组分的水或油溶液。

[0098] 适合于吸入给药的药物制剂包括细粒喷粉或雾剂,其可以利用各种类型的加压分配器(具有喷雾器(aerosols)、雾化器或吹入器)来产生。

[0099] 适合于阴道给药的药物制剂可以以阴道栓、塞、乳膏剂、凝胶剂、糊剂、泡沫体或喷雾剂的形式给药。

[0100] 适合于肠胃外给药的药物制剂包括水和非水无菌注射溶液剂,其含有抗氧化剂、缓冲剂、抑菌剂和溶质,借助于它们使制剂与所治疗的受体的血液等渗压;和可以包含悬浮介质和增稠剂的水和非水无菌混悬剂。制剂还可以用单剂量或多剂量容器给药,例如密封的安瓿和小瓶,并且保存在冷冻干燥(冻干)状态,从而只需要在使用之前不久,添加无菌的载液,例如注射用水。根据配方制备的注射溶液剂和混悬剂可以用无菌粉剂、颗粒剂和片剂制备。

[0101] 不言而喻,除了上面特别提到的组分之外,制剂还可以包含本领域中关于具体类型制剂常用的其它试剂;因此,例如,适合于口服给药的制剂可以包含调味剂。

[0102] 式 I 化合物的治疗有效量取决于各种因素,包括,例如,动物的年龄和体重,需要治疗的确切病症和它的严重程度,制剂的特性和给药方法,并且最终由治疗的医生或兽医来决定。然而,根据本发明化合物的有效量通常在每天 0.1 至 100 mg/kg 受体(哺乳动物)体重的范围,尤其典型地在每天 1 至 10 mg/kg 体重的范围。因此,对于重量 70 kg 的成年哺乳动物来说,每天的实际量通常在 70 和 700 mg 之间,其中可以以每天单剂量的形式或通常以每天一系列部分剂量(诸如例如,二剂量、三剂量、四剂量、五剂量或六剂量)的形式给予该量,使得总的日剂量相同。其盐、或溶剂化物、或生理学上官能衍生物的有效量,可以根据本发明化合物本身的有效量的分数来确定。可以假定的是,类似的剂量适合于治疗上面所提及的其它病症。

[0103] 这种类型的联合治疗可以借助于同时、顺序或分别分配治疗的个别组分来实现。这种类型的联合产品使用根据本发明的化合物。

[0104] 此外,本发明涉及药物,其包含至少一种式 I 的化合物和/或其药学可接受的盐、互变异构体和立体异构体,包括其所有比例的混合物,和至少一种其它药物活性组分。

[0105] 本发明还涉及由下列的独立包装组成的套件(药盒):

(a) 有效量的式 I 化合物和/或其药学可接受的盐、互变异构体和立体异构体,包括其所有比例的混合物,

和

(b) 有效量的其它药物活性组分。

[0106] 该套件包括合适的容器,诸如盒子,独立的瓶、袋或安瓿。该套件例如可以包括独立的安瓿,每个包含溶解或冻干形式的有效量的式 I 化合物和/或其药学可接受的盐、溶剂化物和立体异构体,包括其所有比例的混合物,和有效量的其它药物活性组分。

[0107] 如本文所用,“治疗”是指完全或部分地减轻与病症或疾病相关的症状,或减缓或中止那些症状的进一步发展或恶化,或预防或防止处于形成疾病或病症的危险之中的患者的疾病或病症。

[0108] 与式 (I) 化合物有关的术语“有效量”是指能够完全或部分地减轻与病症或疾病相关的症状的量,或能够减缓或中止那些症状的进一步发展或恶化的量,或能够使患有本文所公开疾病或处于形成本文所公开疾病的危险之中的患者预防或防止疾病或病症,诸如,炎症性状况、免疫状况、癌症、或代谢状况的量。

[0109] 在一个实施方案中,式 (I) 化合物的有效量是能够在细胞中抑制端锚聚合酶的量,诸如例如,体外或体内抑制。在一些实施方案中,相比于未经处理的细胞中的端锚聚合酶活性,式 (I) 化合物的有效量能够在细胞中抑制端锚聚合酶的 10%、20%、30%、40%、50%、60%、70%、80%、90% 或 99% 的活性。式 (I) 化合物的有效量,例如,在药物组合物中,可以处于产生预期效果的水平;例如,在口服和肠胃外两者给药的单位剂量中,约为 0.005 mg/kg 患者体重至约 10 mg/kg 患者体重。

[0110] 用途

本发明式 I 化合物可用于治疗或预防心血管障碍和/或病症。采用本发明化合物的治疗由于它们的抗血脂异常和抗炎症被预期降低与动脉粥样硬化相关的心血管发病率和死

亡率。心血管疾病包括导致心肌梗死、充血心力衰竭、脑血管疾病和下肢的外周动脉不足的各种内脏的宏观血管病变。由于它们的胰岛素致敏效应,式 I 化合物也被预期防止或延迟 2 型糖尿病发展以免代谢综合症和妊娠糖尿病。因此,与糖尿病中的慢性高血糖症,例如导致肾脏疾病、视网膜损伤和下肢的周围血管病变的微观血管病变相关的长期并发症的发展被预期延迟。

[0111] 另外,本发明的式 I 化合物可用于治疗或预防炎症和 / 或神经退行性疾病和 / 或病症。此类疾病或病症的实例为多囊卵巢综合症和炎性疾病包括神经退行性疾病例如轻度认知功能障碍、阿尔茨海默病、帕金森氏病和多发性硬化的状况。

[0112] 本发明化合物还可以用于在全身性或局部性给药之后降低皮肤的皮脂腺中皮脂产生。皮脂腺的疾病为痤疮、皮脂溢出、皮脂腺瘤和皮脂腺癌。痤疮的发病机理涉及通过皮脂腺导致的脂质(过度)产生,因此本发明化合物特别可以用于治疗痤疮。此外,式 I 化合物可以在治疗分支杆菌感染例如结核中用作抗分支杆菌试剂。本发明化合物可以用于治疗与病毒性感染例如丙型肝炎、AIDS、小儿麻痹症、流行性感、疣相关的病症。

[0113] 炎症疾病的实例包括类风湿性关节炎、牛皮癣、接触性皮炎、迟发过敏反应等。

[0114] 还包括式 I 化合物和 / 或其药学上可接受的盐、互变异构体和立体异构体用于制备治疗或预防哺乳动物中 FASN 诱导的疾病或 FASN 诱导的病症的药物的用途,其中对于该方法,对此治疗需要的患病哺乳动物给予治疗有效量的根据本发明的化合物。治疗量根据特定疾病变化并可以通过本领域技术人员确定而无需过度的努力。

[0115] 表达“FASN- 诱导的疾病或病症”涉及取决于 FASN 活性的病理学条件。与 FASN 活性相关的疾病包括癌症、多发性硬化、心血管疾病、中枢神经系统损伤和不同形式的炎症。

[0116] 本发明具体涉及式 I 化合物和其药学上可接受的盐、互变异构体和立体异构体,包括其全部比率的混合物,其用于治疗其中 FASN 的抑制、调节和 / 或调制起作用的疾病。

[0117] 本发明具体涉及式 I 化合物和其药学上可接受的盐、互变异构体和立体异构体,包括其全部比率的混合物,其用于抑制 FASN。

[0118] 本发明具体涉及式 I 化合物和其药学上可接受的盐、互变异构体和立体异构体,包括其全部比率的混合物,其用于治疗癌症、多发性硬化、心血管疾病、中枢神经系统损伤和不同形式的炎症。

[0119] 本发明具体涉及治疗或预防癌症、多发性硬化、心血管疾病、中枢神经系统损伤和不同形式的炎症的方法,其包括对此需要的对象给予有效量的式 I 化合物或其药学上可接受的盐、互变异构体、立体异构体或溶剂化物。

[0120] 式 I 化合物可用于治疗或预防的代表性的癌症包括但不限于:头,颈,眼睛,口,咽喉(throat),食道,支气管,喉(larynx),咽(pharynx),胸,骨,肺,结肠,直肠,胃,前列腺,膀胱,子宫,宫颈,乳房,卵巢,睾丸或其它生殖器官,皮肤,甲状腺,血液,淋巴结,肾脏,肝,胰腺,脑,中枢神经系统的癌症,实体瘤和血源性肿瘤(blood-borne tumors)。

[0121] 此外,式 I 化合物可用于治疗或预防的代表性癌症包括脑癌(神经胶质瘤)、恶性胶质瘤、白血病、Bannayan-Zonana 综合症、Cowden 病、Lhermitte-Duclos 病、乳腺癌、炎性乳腺癌、Wilm 氏肿瘤、Ewing 氏肉瘤、横纹肌肉瘤、室管膜瘤、成神经管细胞瘤、结肠癌、头颈癌、肾癌、肺癌、肝癌、黑素瘤、卵巢癌、胰腺癌、前列腺癌、肉瘤、骨肉瘤、骨和甲状腺的骨巨细胞瘤。

[0122] 式 I 化合物可用于治疗或预防的代表性的心血管疾病包括但不限于：再狭窄，动脉粥样硬化和它的后遗症，诸如中风，心肌梗塞，对心脏、肺、肠管、肾脏、肝、胰腺、脾脏或脑的缺血性损伤。

[0123] 本发明涉及治疗增殖、自身免疫、抗炎或传染病的方法，其包括对有此需要的对象给予治疗有效量的式 I 化合物。

[0124] 优选地，本发明涉及其中疾病为癌症的方法。

[0125] 特别优选地，本发明涉及其中疾病为癌症的方法，其中与给予至少一种其他活性药物试剂同时、相继或交替给药。

[0126] 公开的式 I 化合物可以与其它已知的治疗剂（包括抗癌剂）组合给药。如本文所用，术语“抗癌剂”涉及出于治疗癌症目的给予患有癌症的患者的任何试剂。

[0127] 本文中定义的抗癌治疗可以作为单一疗法应用，或者除了本发明的化合物以外，可以包括常规外科手术或放疗或化疗。此类化疗可以包括以下类别的抗肿瘤剂中的一种或多种：

(i) 肿瘤内科中所用的抗增殖药 / 抗肿瘤药 / DNA- 损伤剂及其组合，诸如烷化剂（例如顺铂、卡铂、环磷酰胺、氮芥、美法仑、苯丁酸氮芥、白消安和亚硝基脲）；抗代谢药（例如抗叶酸药诸如氟嘧啶如 5- 氟尿嘧啶和替加氟、雷替曲塞、甲氨蝶呤、阿糖胞苷、羟基脲和吉西他滨）；抗肿瘤抗生素（例如蒽环类抗生素如阿霉素、博来霉素、多柔比星、道诺霉素、表柔比星、伊达比星、丝裂霉素 C、放线菌素 D 和光神霉素）；抗有丝分裂药（例如长春花属类生物碱如长春新碱、长春花碱、长春地辛和长春瑞滨以及紫杉类生物碱如紫杉醇和泰索帝）；拓扑异构酶抑制剂（例如表鬼臼毒素如依托泊苷和替尼泊苷、安吡啶、托泊替康、伊立替康和喜树碱）以及细胞分化剂（例如，全反式维甲酸，13- 顺 - 维甲酸和维甲酸酰胺）；

(ii) 细胞抑制剂诸如抗雌激素药（例如他莫昔芬、托瑞米芬、雷洛昔芬、屈洛昔芬和 iodoxyfene）、雌激素受体减量调节药（例如氟维司群）、抗雄激素药（例如比卡鲁胺、氟他胺、尼鲁米特和醋酸环丙孕酮）、LHRH 拮抗剂或 LHRH 激动剂（例如戈舍瑞林、亮丙瑞林和布舍瑞林）、孕酮（例如醋酸甲地孕酮）、芳香酶抑制剂（例如阿那曲唑、来曲唑、vorazole 和依西美坦）和 5 α 还原酶抑制剂诸如非那雄胺；

(iii) 抑制癌细胞侵袭的药物（例如金属蛋白酶抑制剂如马立马司他和尿激酶纤溶酶原激活受体功能的抑制剂）；

(iv) 生长因子功能的抑制剂，例如这样的抑制剂包括生长因子抗体、生长因子受体抗体（例如抗 erbb2 抗体曲妥单抗 [Herceptin™] 和抗 erbb1 抗体西曲妥单抗 [C225]）、法呢基转移酶抑制剂、酪氨酸激酶抑制剂和丝氨酸 / 苏氨酸激酶抑制剂例如表皮生长因子家族抑制剂（例如 EGFR 家族酪氨酸激酶抑制剂，诸如 N-(3- 氯 -4- 氟苯基)-7- 甲氧基 -6-(3- 吗啉代丙氧基) 喹唑啉 -4- 胺（吉非替尼 (gefitinib), AZD1839）、N-(3- 乙炔基苯基)-6, 7- 双 (2- 甲氧基乙氧基) 喹唑啉 -4- 胺（埃罗替尼 (erlotinib), OSI-774) 和 6- 丙烯酰胺基 -N-(3- 氯 -4- 氟苯基)-7-(3- 吗啉代丙氧基) 喹唑啉 -4- 胺 (CI 1033))、例如血小板衍生长因子家族抑制剂和例如肝细胞生长因子家族抑制剂；

(v) 抗血管生成药，诸如抑制血管内皮生长因子作用的那些抗血管生成药（例如抗血管内皮细胞生长因子抗体贝伐单抗 [Avastin™]、以下公开的国际专利申请公开的那些化合物：WO 97/22596、WO 97/30035、WO 97/32856 和 WO 98/13354) 和以其它机制起作用的化

合物（例如利诺胺、整联蛋白 $\alpha v \beta 3$ 功能抑制剂和血管生长抑素）；

(vi) 血管损伤药，诸如康普瑞汀 A4 和以下国际专利申请公开的化合物：WO 99/02166、WO 00/40529、WO 00/41669、WO 01/92224、WO 02/04434 和 WO 02/08213；

(vii) 反义疗法，例如针对上述靶的那些疗法，诸如 ISIS 2503、抗 Ras 反义疗法；

(viii) 基因疗法，包括例如替代异常基因的疗法，诸如异常 p53 或异常 BRCA1 或 BRCA2、GDEPT（基因指导的酶前药疗法）疗法，诸如使用胞嘧啶脱氨酶、胸苷激酶或细菌硝基还原酶的那些和增加患者对化疗或放疗耐受性的疗法，诸如多药抗性基因疗法；和

(ix) 免疫疗法，包括例如增加患者肿瘤细胞免疫原性的体外和体内疗法，诸如用细胞因子诸如白介素 2、白介素 4 或粒细胞 - 巨噬细胞集落刺激因子转染，减少 T 细胞无反应性的疗法，使用转染免疫细胞的疗法，诸如细胞因子转染的树突细胞，使用细胞因子转染的肿瘤细胞系的疗法和使用抗独特型抗体的疗法。

[0128] 来自下表 1 的药物优选，但非排他地，与式 I 的化合物联用。

表1.		
烷化剂	环磷酰胺 白消安 异环磷酰胺 美法仑 六甲蜜胺 塞替派 瘤可宁 达卡巴嗪 卡莫司汀	洛莫司汀 甲基苄肼 六甲蜜胺 磷酸雌莫司汀 二氯甲基二乙胺 链脲菌素 替莫唑胺 司莫司汀
铂类药物	顺铂 奥沙利铂 螺铂 Carboxyphthalatoplatinum Tetraplatin Ormiplatin 异丙铂	卡铂 ZD-0473 (AnorMED) 洛铂(Aetema) 沙铂(Johnson Matthey) BBR-3464 (Hoffmann-La Roche) SM-11355 (Sumitomo) AP-5280 (Access)
抗代谢药	氮杂胞苷 吉西他滨 卡培他滨 5-氟尿嘧啶 氟尿苷 2-氯脱氧腺苷 6-巯基嘌呤 6-硫鸟嘌呤 阿糖胞苷 2-氟脱氧胞苷 氨甲喋呤 Idatrexate	雷替曲塞 三甲曲沙 脱氧柯福霉素 氟达拉滨 喷司他丁 雷替曲塞 羟基脲 地西他滨(SuperGen) 氯法拉滨(Bioenvision) 伊洛福芬(MGI Pharrna) DMDC (Hoffmann-La Roche) 乙炔基胞苷(Taiho)
拓扑异构酶抑制剂	安吡啶 表柔比星 依托泊苷 替尼泊苷或米托蒽醌 伊立替康(CPT-11) 7-乙基-10-羟基喜树碱 拓扑替康 Dexrazoxanet (TopoTarget)	鲁比特康(SuperGen) 甲磺酸依喜替康(Daiichi) Quinamed (ChemGenex) 吉马替康(Sigma- Tau) Diflomotecan (Beaufour-Ipsen) TAS-103 (Taiho) 依沙芦星(Spectrum) J-107088 (Merck & Co)

	匹克生琼(Novuspharrna) 蝶霉素类似物(Exelixis) BBR-3576 (Novuspharrna)	BNP-1350 (BioNumerik) CKD-602 (Chong Kun Dang) KW-2170 (Kyowa Hakko)
抗肿瘤抗生素	更生霉素(放线菌素D) 多柔比星(阿霉素) Deoxyrubicin 戊柔比星 道诺霉素(柔红霉素) 表柔比星 Therarubicin 伊达比星 Rubidazon Plicamycinp 泊非霉素 Cyanomorpholinodoxo- rubicin 米托蒽醌(Novantron)	氨萘非特 Azonafide Anthrapyrazole Oxantrazole 洛索蒽醌 硫酸博莱霉素(Blenoxan) Bleomycinic acid 博莱霉素A 博莱霉素B 丝裂霉素C MEN-10755 (Menarini) GPX-100 (Gem Pharmaceuticals)
抗有丝分裂剂	紫杉醇 多西他赛 秋水仙碱 长春碱 长春新碱 长春瑞滨 长春地辛 多拉司他汀10 (NCI) 根瘤菌素(Fujisawa) Mivobulin (Warner-Lambert) 西马多丁(BASF) RPR 109881A (Aventis) TXD 258 (Aventis) 埃博霉素B (Novartis) T 900607 (Tularik) T 138067 (Tularik) Cryptophycin 52 (Eli Lilly) 长春氟宁(Fabre) 阿里他汀 PE (Teikoku Hormone) BMS 247550 (BMS) BMS 184476 (BMS) BMS 188797 (BMS)	SB 408075 (GlaxoSmithKline) E7010 (Abbott) PG-TXL (Cell Therapeutics) IDN 5109 (Bayer) A 105972 (Abbott) A 204197 (Abbott) LU 223651 (BASF) D 24851 (ASTA Medica) ER-86526 (Eisai) 康普瑞丁A4 (BMS) Isohomohalichondrin-B (PharmaMar) ZD 6126 (AstraZeneca) PEG-Paclitaxel (Enzon) AZ10992 (Asahi) !DN-5109 (Indena) AVLB (Prescient NeuroPharma) Azaepothilon B (BMS) BNP- 7787 (BioNumerik) CA-4-前药(OXiGENE) 多拉司他汀-10 (NrH) CA-4 (OXiGENE)

	Taxoprexin (Protarga)	
芳香化酶抑制剂	氨鲁米特 来曲唑 阿那曲唑 Formestan	依西美坦 Atamestan (BioMedicines) YM-511 (Yamanouchi)
胸苷酸合成酶抑制剂	培美曲塞(Eli Lilly) ZD-9331 (BTG)	洛拉曲塞(Eximias) CoFactor™ (BioKeys)
DNA拮抗剂	曲贝替定 (PharmaMar) 葡 磷 酰 胺 (Baxter International) 白 蛋 白 + 32P (Isotope Solutions) Thymectacin (NewBiotics) Edotreotid (Novartis)	马 磷 酰 胺 (Baxter International) Apaziquone (Spectrum Pharmaceuticals) O6-苄基鸟嘌呤(Paligent)
法尼基转移酶抑制剂	Arglabin (NuOncology Labs) 洛那法尼(Schering-Plough) BAY-43-9006 (Bayer)	替 吡 法 尼 (Johnson & Johnson) 紫苏醇(DOR BioPharma)
泵抑制剂	CBT-1 (CBA Pharma) Tariquidar (Xenova) MS-209 (Schering AG)	Zosuquidar 三 盐 酸 盐 (Eli Lilly) 比 立 考 达 二 柠 檬 酸 炎 (Vertex)
组蛋白乙酰转移酶抑制剂	Tacedinaline (Pfizer) SAHA (Aton Pharma) MS-275 (Schering AG)	丁 酸 新 戊 酰 氧 基 甲 酯 (Titan) 缩 酚 酸 肽 (Fujisawa)
金属蛋白酶抑制剂 核糖核苷还原酶抑制剂	Neovastat (Aeterna Laboratories) 马 立 马 司 他 (British Biotech) Gallium maltolate (Titan) Triapin (Vion)	CMT -3 (CollaGenex) BMS-275291 (Celltech) 替扎他滨(Aventis) Didox (Molecules for Health)
TNF-α激动剂/拮抗剂	维如利金(Lorus Therapeutics) CDC-394 (Celgene)	Revimid (Celgene)

内皮素-A受体拮抗剂	阿曲生坦(Abbot) ZD-4054 (AstraZeneca)	YM-598 (Yamanouchi)
视黄酸受体激动剂	维 甲 酰 酚 胺 (Johnson & Johnson) LGD-1550 (Ligand)	阿利维A酸(Ligand)
免疫调节剂	干扰素 Oncophage (Antigenics) GMK (Progenics) 腺癌疫苗(Biomira) CTP-37 (AVI BioPharma) JRX-2 (Immuno-Rx) PEP-005 (Peplin Biotech) Synchrovax 疫 苗 (CTL Immuno) 黑 色 素 瘤 疫 苗 (CTL Immuno) p21-RAS疫苗(GemVax)	Dexosome疗法(Anosys) Pentrix (Australian Cancer Technology) JSF-154 (Tragen) 癌症疫苗(Intercell) Norelin (Biostar) BLP-25 (Biomira) MGV (Progenics) !3-Alethin (Dovetail) CLL-Thera (Vasogen)
激素和抗激素药	雌激素 缀合雌激素 乙炔雌二醇 三对甲氧苯氯乙烯 Idenestrol 己酸羟孕酮 甲羟孕酮 睾酮 丙酸睾丸酮 氟甲睾酮 甲睾酮 己烯雌酚 甲地孕酮 他莫昔芬 Toremofin 地塞米松	泼尼松 甲泼尼龙 泼尼松龙 氨鲁米特 亮丙瑞林 戈舍瑞林 Leuporelin 比卡鲁胺 氟他胺 奥曲肽 尼鲁米特 米托坦 P-04 (Novogen) 2-甲氧基雌二醇(EntreMed) Arzoxifen (Eli Lilly)
光动力药	他拉泊芬(Light Sciences) Theralux (Theratechnologies) 莫 特 沙 芬 - 钆 (Pharmacyclics)	Pd-Bacteriopheophorbid (Yeda) Lutetium-Texaphyrin (Pharmacyclics) 金丝桃素

酪氨酸激酶抑制剂	伊马替尼(Novartis) 来氟米特 (Sugen/Pharmacia) ZD1839 (AstraZeneca) 厄洛替尼 (Oncogene Science) Canertinib (Pfizer) 角鲨胺(Genaera) SU5416 (Pharmacia) SU6668 (Pharmacia) ZD4190 (AstraZeneca) ZD6474 (AstraZeneca) 瓦他拉尼(Novartis) PKI166 (Novartis) GW2016 (GlaxoSmithKline) EKB-509 (Wyeth) EKB-569 (Wyeth)	Kahalide F (PharmaMar) CEP- 701 (Cephalon) CEP-751 (Cephalon) MLN518 (Millenium) PKC412 (Novartis) Phenoxodiol O 曲妥珠单抗(Genentech) C225 (ImClone) rhu-Mab (Genentech) MDX-H210 (Medarex) 2C4 (Genentech) MDX-447 (Medarex) ABX-EGF (Abgenix) IMC-1C11 (ImClone)
各种药剂	SR-27897 (CCK-A抑制剂, Sanofi-Synthelabo) Tocladesine (环AMP激动剂, Ribapharm) Alvocidib (CDK抑制剂, Aventis) CV-247 (COX-2抑制剂, Ivy Medical) P54 (COX-2抑制剂, Phytopharm) CapCell™ (CYP450刺激剂, Bavarian Nordic) GCS-100 (gal3拮抗剂, GlycoGenesys) G17DT免疫原(胃泌素抑制剂, Aphton) 乙丙昔罗(氧合物, Allos Therapeutics) PI-88 (乙酰肝素酶抑制剂, Progen) Tesmilifen (组胺拮抗剂, YM BioSciences) 组胺(组胺H2受体激动剂, Maxim) 噻唑呋林(IMPDH抑制剂, Ribapharm) 西仑吉肽(整合素拮抗剂,	BCX-1777 (PNP抑制剂, BioCryst) 豹蛙酶(核糖核酸酶刺激剂, Alfacell) Galarubicin (RNA合成抑制剂, Dong-A) 替拉扎明(还原剂, SRI International) N-乙酰半胱氨酸(还原剂, Zambon) R-氟比洛芬(NF-κB抑制剂, Encore) 3CPA (NF-κB抑制剂, Active Biotech) 西奥骨化醇(维生素D受体激动剂, Leo) 131-I-TM-601 (DNA拮抗剂, TransMolecular) Eflornithin (ODC抑制剂, ILEX Oncology) 米诺膦酸(破骨细胞抑制剂, Yamanouchi) Indisulam (p53刺激剂, Eisai) Aplidin (PPT抑制剂, PharmaMar) 利妥昔单抗(CD20抗体,

Merck KGaA) SR-31747 (IL-1 拮抗剂, Sanofi-Synthelabo) CCI-779 (mTOR 激酶抑制剂, Wyeth) 依昔舒林 (PDE-V 抑制剂, Cell Pathways) CP-461 (PDE-V 抑制剂, Cell Pathways) AG-2037 (GART 抑制剂, Pfizer) WX-UK1 (纤溶酶原激活物抑制剂, Wilex) PBI-1402 (PMN 刺激剂, ProMetic LifeSciences) 硼替佐米(蛋白酶体抑制剂, Millennium) SRL-172 (T-细胞刺激剂, SR Pharma) TLK-286 (谷胱甘肽-S转移酶抑制剂, Telik) PT-100 (生长因子激动剂, Point Therapeutics) 米哚妥林 (PKC 抑制剂, Novartis) 苔藓抑素-1 (PKC 刺激剂, GPC Biotech) CDA-II (凋亡促进剂, Everlife) SDX-101 (凋亡促进剂, Salmedix) Ceflatonin (凋亡促进剂, ChemGenex)	Genentech) 吉妥单抗 (CD33 抗体, Wyeth Ayerst) PG2 (造血促进剂, Pharmagenesis) Immunol™ (三氯生漱口水, Endo) 三乙酰尿苷 (尿苷前药, Wellstat) SN-4071 (肉瘤药, Signature BioScience) TransMID-107™ (免疫毒素, KS Biomedix) PCK-3145 (凋亡促进剂, Procyon) Doranidazole (凋亡促进剂, Pola) CHS-828 (细胞毒性剂, Leo) 反式视黄酸(分化剂, NIH) MX6 (凋亡促进剂, MAXIA) Apomine (凋亡促进剂, ILEX Oncology) Urocidin (凋亡促进剂, Bioniche) Ro-31-7453 (凋亡促进剂, La Roche) Brostallicin (凋亡促进剂, Pharmacia)
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[0129] 下列缩写分别指示下面的定义：

aq(含水的), h(小时), g(克), L(升), mg(毫克), MHz(兆赫), min.(分钟), mm(毫米), mmol(毫摩尔), mM(毫摩尔浓度), m. p.(熔点), eq(当量), mL(毫升), μ L(微升), ACN(乙腈), AcOH(乙酸), CDCl_3 (氘代氯仿), CD_3OD (氘代甲醇), CH_3CN (乙腈), c-hex(环己烷), DCC(二环己基碳二亚胺), DCM(二氯甲烷), DIC(二异丙基碳二亚胺), DIEA(二异丙基乙基-胺), DMF(二甲基甲酰胺), DMSO(二甲亚砜), DMSO-d_6 (氘化二甲亚砜), EDC(1-(3-二甲基-氨基-丙基)-3-乙基碳二亚胺), ESI(电喷雾电离), EtOAc(乙酸乙酯), Et_2O (二乙醚), EtOH(乙醇), HATU(二甲基氨基-([1, 2, 3]三唑并[4, 5-b]吡啶-3-基氧基)-亚甲基]-二甲基铵六氟磷酸盐), HPLC(高效液相色谱), i-PrOH(2-丙醇), K_2CO_3 (碳酸钾), LC(液相色谱), MeOH(甲醇), MgSO_4 (硫酸镁), MS(质谱), MTBE(甲基叔丁基醚), NaHCO_3 (碳酸氢钠), NaBH_4 (硼氢化钠), NMM(N-甲基吗啉), NMR(核磁共振),

PyBOP(苯并三唑 -1- 基 - 氧基 - 三 - 吡咯烷子基 - 磷六氟磷酸盐), RT(室温), Rt(保留时间), SPE(固相提取), TBTU(2-(1-H- 苯并三唑 -1- 基)-1, 1, 3, 3- 四甲基脒鎓四氟硼酸盐), TEA(三乙胺), TFA(三氟乙酸), THF(四氢呋喃), TLC(薄层层析), UV(紫外线)。

[0130] 体外测定的说明

缩写 :

GST = 谷胱甘肽 -S- 转移酶

FRET= 荧光共振能量转移

HTRF® = (均相时间分辨荧光)

HEPES =4-(2- 羟基乙基)-1- 哌嗪乙磺酸缓冲剂

DTT = 二硫苏糖醇

BSA = 牛血清白蛋白

CHAPS = 清洁剂 ;

CHAPS = 3-[(3- 胆固醇氨基丙基) 二甲基铵]-1- 丙磺酸盐。

[0131] 人脂肪酸合酶 FASN 的生物化合物活性测试

脂肪酸合酶 FASN 为具有七种催化活性的多功能酶,从而在起始于底物乙酰基 - CoA 和丙二酰 -CoA 的辅助因子 NADPH 存在下合成长链脂肪酸尤其是棕榈酰 -CoA。还原合成通过氧化 NADPH 成 NADP 实现。由于在 340 nm 下激发在 460 nm 下发射的情况下 NADPH 相比于 NADP 具有高荧光强度量子产率,该反应可以通过荧光强度降低被监控。

[0132] 生物化学 FASN 活性测试在 Greiner 低体积介质结合 384- 孔空白微量滴定板中在 8 μ l 的总分析体积中作为 384 孔二时间点动力学荧光强度分析模式进行并用于高通量筛选。在各孔中,将 3 μ l 40 nM 人重组全长脂肪酸合酶(在内部在 SF9 细胞中产生)分配在随后的分析缓冲剂中:50 mM 磷酸钾缓冲剂 pH 7.0, 0.005 % (w/v) BSA, 2 mM 谷胱甘肽, 0.02 % Tween-20。然后,添加分析缓冲剂的 2 μ l 的 200 μ M NADPH,然后添加采用 30 μ M(最终浓度)起始的 10 种稀释浓度的测试化合物以获得最终 1 % (v/v) 的 DMSO 含量。在室温下孵育该混合物至少 15 分钟。在预孵育之后,通过添加 2 μ l 底物溶液(80 μ M 乙酰基 -CoA, 240 μ M 丙二酰 -CoA) 开始酶反应。在 340 nm 波长下激发(灯模式)和在 460 nm 波长下发射的情况下,采用 Envision 多模式读数器(Perkin Elmer LAS Germany GmbH)进行第一荧光强度测试(一个时间点)。在室温下孵育该反应 30 分钟。之后,在 Envision 中使用与上述相同的参数再次测试荧光强度(第二个时间点测试)。通过从第二时间点测量值减去第一时间点测量值分析数据(在酶反应之后)。测定发射信号的差。这些直接反映 NADPH 的转化率。所使用的满分数值是无抑制剂反应。如 GSK837149A(Sigma-Aldrich),在 5-10 μ M 的最终浓度下使用药理学零值。使用来自 GeneData 的程序 Symyx Assay Explorer® 或 Condosseo® 测定抑制值 (IC50)。

[0133] 在上面和下面,所有温度都是以℃表示。在下面的实施例中,“常规处理”是指:根据最终产物的组成,如果需要,添加水,如果需要,将 pH 值调节至 2 和 10 之间,用乙酸乙酯或二氯甲烷萃取混合物,分离各相,用硫酸钠干燥有机相,蒸发,并将残余物用硅胶层析纯化,和 / 或结晶纯化。在硅胶上的 Rf 值;洗脱液:乙酸乙酯 / 甲醇 9:1。

[0134] LCMS:

方法 A

方法：A-0.1 % HCOOH 在 H₂O 中，B-0.1 % HCOOH 在 CAN 中：流量 - 2.4 mL/min。

柱：Chromolith SpeedRod RP-18e (50x4.6mm)

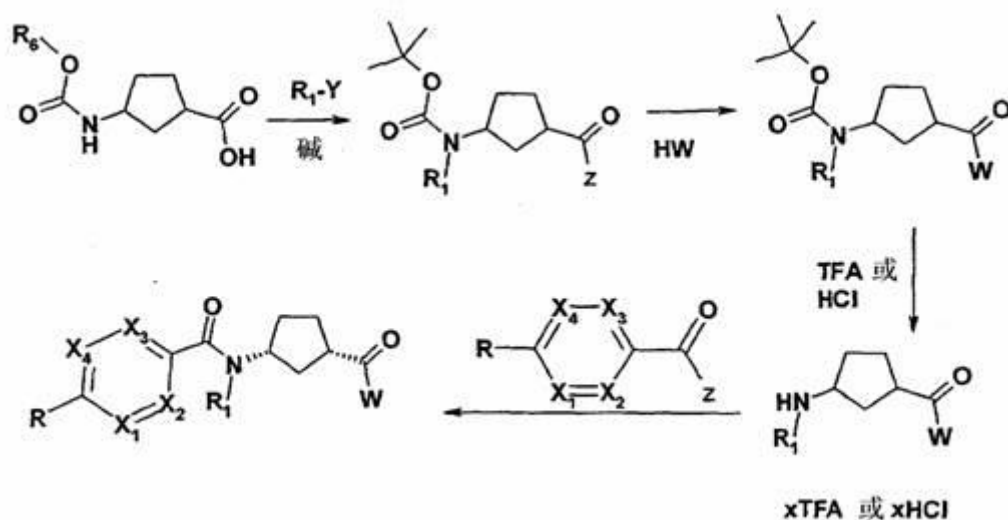
方法 B

方法：A-0.1 % TFA 在 H₂O 中，B-0.1 % TFA 在 CAN 中：流量 - 2.4 mL/min。

柱：Chromolith SpeedRod RP-18e (50x4.6mm) (50 x 4.6mm)。

[0135] 在 Bruker DPX-300, DRX-400 或 AVII-400 分光仪上使用氘代溶剂的残余信号作为内标记录 ¹H NMR。以 ppm 相对于残余溶剂信号记录化学位移 (δ) (δ = 2.49 ppm 对于 ¹H NMR 在 DMSO-d₆ 中)。¹H NMR 数据报道如下：化学位移 (重数, 耦合常数, 和氢数)。重数缩写如下：s (单峰), d (双峰), t (三峰), q (四峰), m (多峰), br (宽峰)。

[0136] 一般合成



R₆ : 甲基, 叔丁基, 苄基, 烯丙基

Y : Cl, Br, I 或 -OSO₂-R₇

R₇ : 甲基, 三氟甲基, 苯基, 甲苯酰基

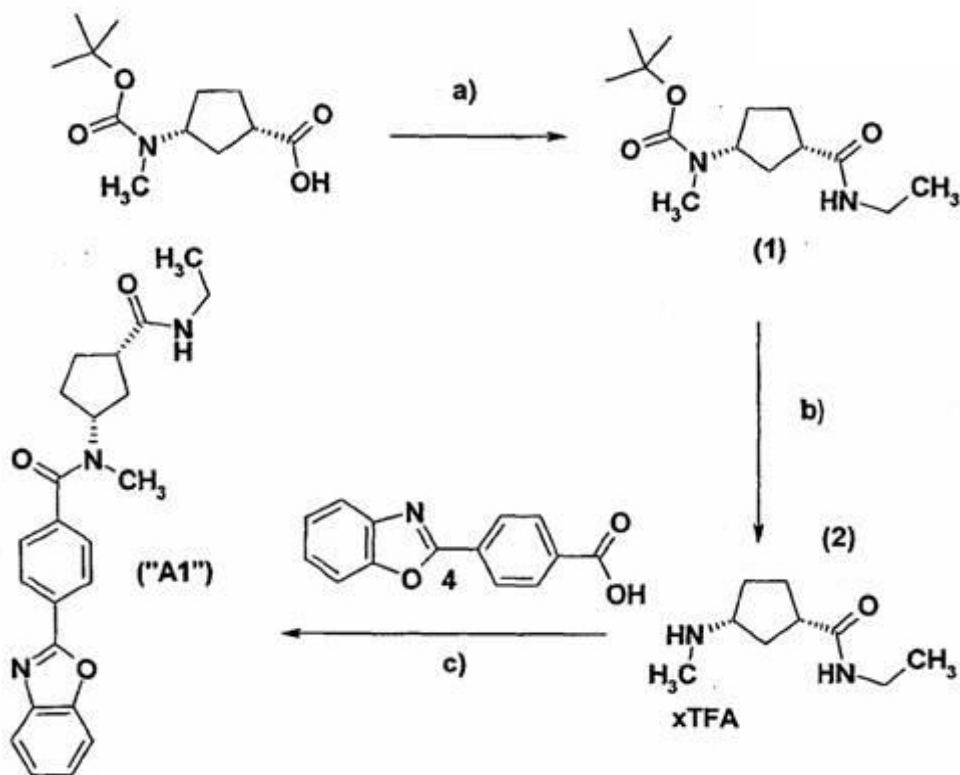
Base : NaH, KH, LiN(i-丙基)₂, LiN((CH₃)₃Si)₂, Na₂CO₃, K₂CO₃, Cs₂CO₃, NaOH, KOH

Z = -Cl, Br, OH 或活化甲酸酯 -O-CO-CH₃或

-OCO-C₂H₅。

[0137] 实施例 1

4-(1,3-苯并噁唑-2-基)-N-[(1R,3S)-3-(乙基氨基甲酰基)环戊基]-N-甲基-苯甲酰胺 ("A1")



1.1 将 (1S, 3R)-3-(叔丁氧基羰基-甲基-氨基)-环戊烷甲酸 (Roberto J. Brea Angew. Chem. Int. Ed. 2005, 44, 5710 - 5713) (90 mg; 0,37 mmol), 乙胺 (2.0 M 溶液, 在四氢呋喃中) (555 μ l; 1,11 mmol), N-(3-二甲基氨基丙基)-N'-乙基碳二亚胺盐酸盐 (142 mg; 0,74 mmol) 和 1-羟基苯并三唑水合物 (56,65 mg; 0,37 mmol) 溶解于 5 ml N,N-二甲基甲酰胺中。添加 4-甲基吗啉 (0,122 ml; 1,11 mmol) 并在室温下搅拌该混合物 14 小时。用水 (10 ml) 稀释该反应溶液并用 2 x 10 ml 的乙酸乙酯萃取。用 3 x 10 ml 的水和 1 x 10 ml 的盐水洗涤合并的有机层,经 Na_2SO_4 干燥,过滤并蒸发至干以获得 100 mg (100%) N-[(1R, 3S)-3-(乙基氨基甲酰基)环戊基]-N-甲基-氨基甲酸叔丁酯 (1); LC/MS : 271 (M+H)。

[0138] 1.2 向 N-[(1R, 3S)-3-(乙基氨基甲酰基)环戊基]-N-甲基-氨基甲酸叔丁酯 (1) (100 mg; 0,37 mmol) 在 15 ml 二氯甲烷中的溶液中加入三氟乙酸 (1 ml; 13 mmol)。在室温下搅拌该溶液 14 小时,然后在真空下减压干燥以获得 105 mg (100%) TFA 盐形式的 (1S, 3R)-N-乙基-3-(甲基氨基)环戊烷甲酰胺 (2); LC/MS : 171 (M+H)。

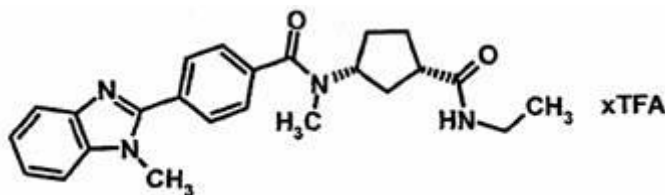
[0139] 1.3 将 4-苯并噁唑-2-基-苯甲酸 (4) (Dinesh Kumar Aust. J. Chem. 2008 (61) 881 - 887) (50 mg; 0,21 mmol), (1S, 3R)-N-乙基-3-(甲基氨基)环戊烷甲酰胺三氟乙酸盐 (2) (59,42 mg; 0,21 mmol), N-(3-二甲基氨基丙基)-N'-乙基碳二亚胺盐酸盐(用于合成) (60,1 mg; 0,314 mmol), 和 1-羟基苯并三唑 (32 mg; 0,21 mmol) 溶解于 3 ml 的 N,N-二甲基甲酰胺中,然后添加 4-甲基吗啉(用于合成) (91,9 μ l; 0,84 mmol)。在室温下搅拌该反应混合物 14 小时。采用 10 ml 的水稀释反应溶液并用 3 x 10 ml 的乙酸乙酯萃取。用 3 x 水和 1 x 盐水洗涤合并的有机层并经 Na_2SO_4 干燥,过滤,蒸发至干,并通过快速层析法(二氯甲烷:甲醇 95:5)纯化残余物以获得 65 mg 白色固体形式的 (78. /%) 4-(1,3-苯并噁唑-2-基)-N-[(1R, 3S)-3-(乙基氨基甲酰基)环戊基]-N-甲

基-苯甲酰胺 ("A1");

LC/MS : 392 (M+H); ^1H NMR (500 MHz, DMSO- d_6) δ [ppm] 8.26 (d, J = 8.3 Hz, 2H), 7.86-7.80 (m, 2H), 7.72 (br. s, 1H; NH), 7.65-7.55 (m, 2H), 7.45 (pd, J = 7.4, 1.3 Hz, 2H), 4.89, 4.00 (2x br. s, 1H, 比率=1:1.8 旋转异构体混合物), 3.06 (q, J = 6.6 Hz, 2H, NCH₂), 2.91 (br. s, 3H, CH₃), 2.67, 2.49 (2x br.s, 1H, ,比率=1:1.8 旋转异构体混合物), 2.20 – 1.52 (m, 6H), 1.00 (t, J = 7.1 Hz, 3H, CH₃)。

[0140] 实施例 2

N-((1R, 3S)-3-乙基氨基甲酰基-环戊基)-N-甲基-4-(1-甲基-1H-苯并咪唑-2-基)-苯甲酰胺 ("A2")



采用胺 (2) (实施例 1.2) 和离子形式 4-(1-甲基-1H-苯并咪唑-2-基)-苯甲酸以类似于上述方法 (实施例 1.3) 合成该化合物;

LC/MS: M+H = 405; ^1H NMR (500 MHz, DMSO- d_6) δ [ppm] 7.97 (d, J = 8.3 Hz, 2H), 7.88 (d, J = 7.6 Hz, 1H), 7.80 (d, J = 7.8 Hz, 1H), 7.73 (s, 1H; NH), 7.70 – 7.60 (m, 2H), 7.51 (dq, J = 15.0, 7.0 Hz, 2H), 4.90, 4.00 (2x br. s, 1H, 比率=1.6:1, 旋转异构体混合物), 4.00 (s, 3H), 3.06 (q, J = 7.0 Hz, 2H), 2.92 (s, 3H), 2.64, 2.44 (2x br. s, 1H, 比率=1.6:1 旋转异构体混合物), 2.08 – 1.51 (m, 6H), 1.00 (t, J = 7.1 Hz, 3H)。

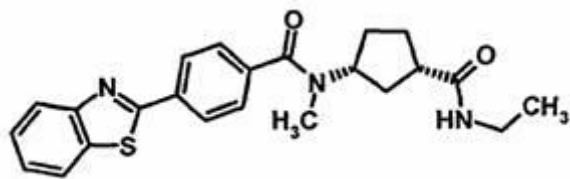
[0141] 4-(1-甲基-1H-苯并咪唑-2-基)-苯甲酸的合成:

0, 50 g (4, 1 mmol) N-甲基-1, 2-亚苯基二胺和 (0, 67 g; 4, 1 mmol) 4-甲酰基苯甲酸甲酯(用于合成)溶解于 20 ml 干甲醇 (最大 0, 005% H₂O) 中。在添加 1.17 ml 乙酸 (冰 100%) 之后, 在室温下搅拌该混合物 14 小时。将该反应溶液蒸发至干, 将残余物溶解于 10 ml 的 5% NaHCO₃-溶液中并用 2x 10 ml 乙酸乙酯萃取。用盐水洗涤合并的有机层, 经 Na₂SO₄ 干燥, 过滤并蒸发至干燥。通过硅胶柱层析法采用 CombiFlash. 洗脱液: 100% 二氯甲烷至 65:35 二氯甲烷: 乙酸乙酯纯化残余物 1, 15 g 以获得 367 mg (33.7%) 浅褐色固体形式的 4-(1-甲基-1H-苯并咪唑-2-基)-苯甲酸甲酯; LC/MS: M+H 267。将该固体溶解于 15 ml 四氢呋喃和 5 ml 水中。在添加 99.02 mg 氢氧化锂之后, 在室温下搅拌该反应混合物 2 小时并在减压下浓缩。采用 5 ml 稀释该残余物, 使用 1 N HCl 酸化 (pH~3) 并用抽吸过滤所得沉淀物, 用水洗涤, 并在真空干燥箱中在 50°C 下干燥以获得 280 mg (80.5%) 浅褐色形式的 4-(1-甲基-1H-苯并咪唑-2-基)-苯甲酸; LC/MS: M+H 253。

[0142] 实施例 3

4-苯并咪唑-2-基-N-((1R, 3S)-3-乙基氨基甲酰基-环戊基)-N-甲基-苯甲酰胺

("A3")

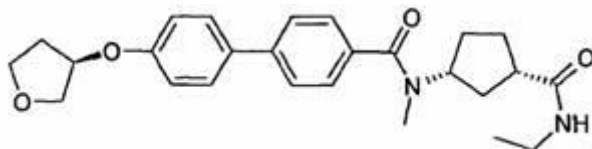


采用胺 (2) (实施例 1.2) 和离析物形式的 4- 苯并噻唑 -2- 基 - 苯甲酸 (Lloyd J. Nadeau, Chem. Commun., 2006, 564 - 565) 以类似于上述方法 (实施例 1.3) 合成该化合物。

LC/MS: M+H = 408; ^1H NMR (500 MHz, DMSO- d_6) δ [ppm] 8.17 (dd, J = 12.1, 7.9 Hz, 3H), 8.09 (d, J = 8.0 Hz, 1H), 7.73 (s, 1H; NH), 7.63 - 7.52 (m, 3H), 7.49 (t, J = 7.6 Hz, 1H), 4.88, 4.02 (2x br. s, 1H, 比率=1:2 旋转异构体混合物) 3.06 (q, J = 7.0 Hz, 2H), 2.90 (s, 3H), 2.90, 2.44 (2x br.s, 1H, 比率=1:2 旋转异构体混合物), 2.20 - 1.63 (m, 6H), 1.00 (t, J = 7.2 Hz, 3H)。

[0143] 实施例 4

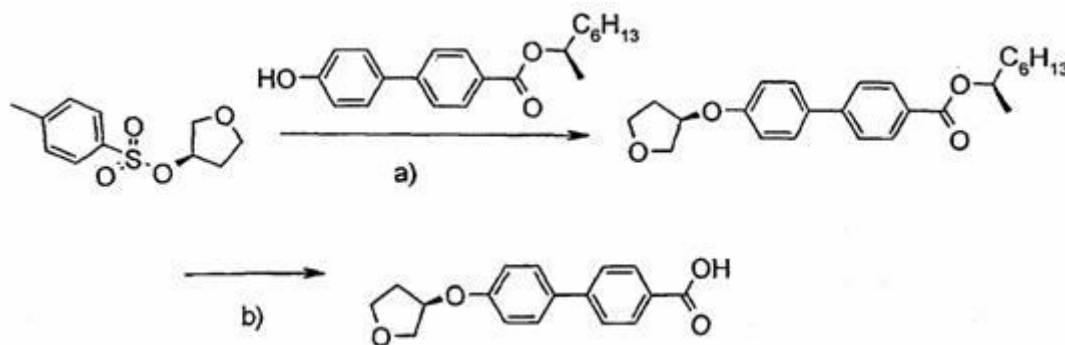
4'-[(R)-(四氢-呋喃-3-基)氧基]-联苯-4-甲酸 ((1R, 3S)-3-乙基氨基甲酰基-环戊基)-甲基-酰胺



采用胺 (2) (实施例 1.2) 和以离析物形式的 4'-[(R)-(四氢-呋喃-3-基)氧基]-联苯-4-甲酸类似于上述方法 (实施例 1.3) 合成该化合物。

LC/MS: M+H = 437; ^1H NMR (500 MHz, DMSO- d_6) δ [ppm] 7.73 (s, 1H; NH), 7.70 - 7.61 (m, 4H), 7.41 (d, J = 7.9 Hz, 2H), 7.02 (d, J = 8.8 Hz, 2H), 5.11 - 5.05 (m, 1H), 4.83, 4.12 (2x br. s, 1H, 比率=1:1.6 旋转异构体混合物) 3.92 (dd, J = 10.1, 4.6 Hz, 1H), 3.86 (q, J = 8.1 Hz, 1H), 3.81 (d, J = 10.1 Hz, 1H), 3.77 (td, J = 8.3, 4.6 Hz, 1H), 3.05 (q, J = 7.2 Hz, 2H), 2.88 (s, 3H), 2.31 - 2.18 (m, 1H), 1.99 (dt, J = 12.6, 5.8 Hz, 1H), 1.95 - 1.58 (m, 6H), 1.00 (t, J = 7.2 Hz, 3H)。

[0144] 4'-[(R)-(四氢-呋喃-3-基)氧基]-联苯-4-甲酸的合成

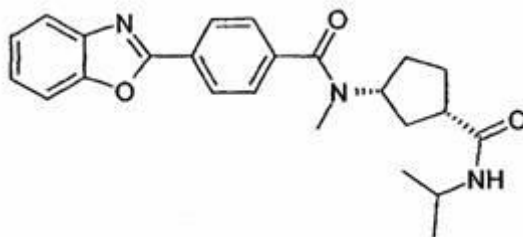


a) 4'-羟基-联苯-4-甲酸 (R)-1-甲基-庚酯 (269.5 mg; 0.825 mmol), 甲苯-4-磺酸 (R)-(四氢-呋喃-3-基) 酯 (200 mg; 0.825 mmol) 和碳酸铯 (350 mg; 1.07 mmol) 在 N,N-二甲基甲酰胺 (5 mL) 中的混合物加热至 60 °C 持续 4 小时。采用 10 mL 水稀释该反应混合物并用 3x 10 mL 乙酸乙酯萃取。有机层经 Na₂SO₄ 干燥、过滤并在真空下除去溶剂。残余物采用甲醇结晶, 用抽吸过滤, 用冷甲醇洗涤并在 40 °C 下在真空下干燥以提供 300 mg (91.7%) 白色粉末形式的 4'-[(R)-(四氢-呋喃-3-基) 氧基]-联苯-4-甲酸 (R)-1-甲基-庚酯; LC/MS: M+Na = 419。

[0145] b) 将 4'-[(R)-(四氢-呋喃-3-基) 氧基]-联苯-4-甲酸 (R)-1-甲基-庚酯 (300 mg) 溶解于 15 mL 四氢呋喃和 3 mL 水中。在添加 54.36 mg 氢氧化锂之后, 在 70 °C 下搅拌该反应混合物 14 小时, 并在减压下浓缩。用 5 mL 水稀释残余物, 使用 1 N HCl 酸化 (pH~3), 并用抽吸过滤所得沉淀物, 用水洗涤并在 50 °C 下在真空干燥箱中干燥以获得 210 mg (97.6%) 浅褐色固体形式的 4'-[(R)-(四氢-呋喃-3-基) 氧基]-联苯-4-甲酸; LC/MS: M+H 285。

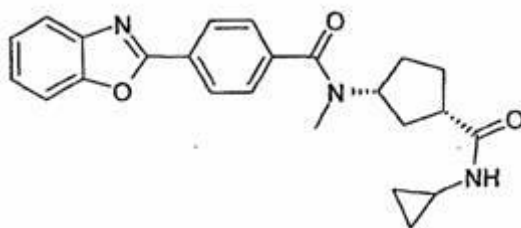
[0146] 以类似于方法 1.1 至 1.3 (实施例 1) 合成以下化合物:

4-苯并噁唑-2-基-N-((1R, 3S)-3-异丙基氨基甲酰基-环戊基)-N-甲基-苯甲酰胺 ("A5")



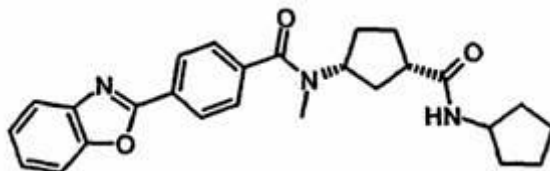
LC/MS: M+H 406; ¹H NMR (500 MHz, DMSO-d₆) δ [ppm] 8.26 (d, J = 8.3 Hz, 2H), 7.83 (dd, J = 14.3, 7.3 Hz, 2H), 7.60 (m, 3H; 2xCH+NH), 7.53 – 7.37 (m, 2H), 4.89, 3.98 (2x br. s, 1H, 比率=1:1.6 旋转异构体混合物), 3.82 (dq, J = 13.2, 6.6 Hz, 1H), 2.91 (br. s, 3H, CH₃), 2.63, 2.41 (2x br. s, 1H, 比率=1:1.6 mixture of rotamers) 2.00 – 1.61 (m, 6H), 1.03 (d, J = 6.3 Hz, 6H);

4-苯并噁唑-2-基-N-((1R, 3S)-3-环丙基氨基甲酰基-环戊基)-N-甲基-苯甲酰胺 ("A6")



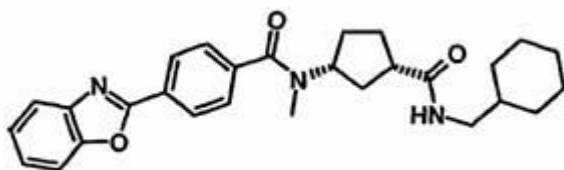
LC/MS: M+H 404; ^1H NMR (500 MHz, DMSO- d_6) δ [ppm] 8.25 (d, $J = 8.4$ Hz, 2H), 7.92 – 7.70 (m, 3H; 2xCH+NH), 7.59 (br. d, $J = 5.6$ Hz, 2H), 7.52 – 7.35 (m, 2H), 4.88, 3.98 (2x br. s, 1H, 比率=1:1.7 旋转异构体混合物), 2.91 (br. s, 3H), 2.67, 2.38 (2x br. s, 1H, 比率=1:1.7 旋转异构体混合物), 2.64 – 2.55 (m, 1H), 2.03 – 1.52 (m, 6H), 0.58 (d, $J = 5.2$ Hz, 2H), 0.36 (br. s, 2H);

4- 苯并噁唑-2-基-N-((1R,3S)-3-环戊基氨基甲酰基-环戊基)-N-甲基-苯甲酰胺 (“A7”)



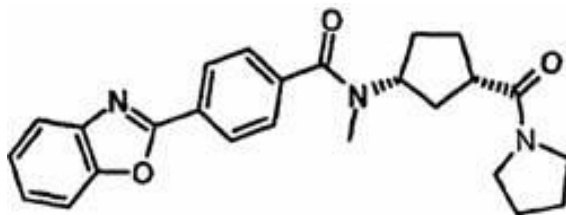
LC/MS: M+H 432; ^1H NMR (500 MHz, DMSO- d_6) δ [ppm] 8.26 (d, $J = 8.4$ Hz, 2H), 7.83 (dd, $J = 14.3, 7.3$ Hz, 2H), 7.68 (s, 1H; NH), 7.60 (d, $J = 7.0$ Hz, 2H), 7.45 (pd, $J = 7.4, 1.4$ Hz, 2H), 4.89, 3.98 (2x br. s, 1H, 比率=1:2 旋转异构体混合物), 3.97 (q, $J = 6.8$ Hz, 2H), 2.91 (br. s, 3H), 2.73, 2.43 (2x br. s, 1H, 比率=1:2 旋转异构体混合物), 2.10 – 1.54 (m, 10H), 1.53 – 1.41 (m, 2H), 1.40 – 1.24 (m, 2H);

4- 苯并噁唑-2-基-N-[(1R,3S)-3-(环己基甲基-氨基甲酰基)-环戊基]-N-甲基-苯甲酰胺 (“A8”)



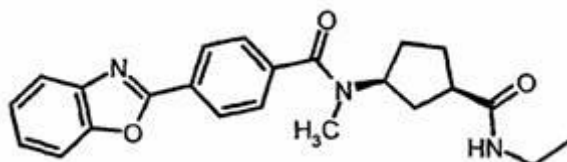
LC/MS: M+H 460;

4- 苯并噁唑-2-基-N-甲基-N-[(1R,3S)-3-(吡咯烷-1-羰基)-环戊基]-苯甲酰胺 (“A9”)



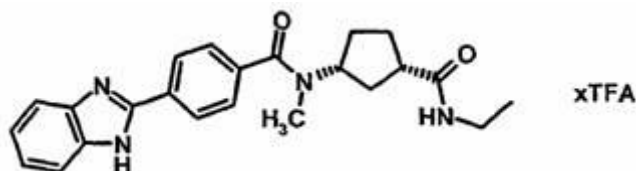
LC/MS: M+H 418; ^1H NMR (500 MHz, DMSO- d_6) δ [ppm] 8.26 (d, $J = 8.3$ Hz, 2H), 7.83 (dd, $J = 14.2, 7.3$ Hz, 2H), 7.60 (d, $J = 7.3$ Hz, 2H), 7.45 (pd, $J = 7.4, 1.4$ Hz, 2H), 4.90, 4.00 (2x br. s, 1H, 比率=1:1.8, 旋转异构体混合物), 3.51 – 3.24 (m, 4H), 2.91 (s, 3H), 3.03, 2.78 (2x br. s, 1H, 比率=1:1.8 旋转异构体混合物), 2.09 – 1.56 (m, 10H);

4-(1, 3- 苯并噁唑 -2- 基) -N-[(1S, 3R)-3-(乙基氨基甲酰基) 环戊基] -N- 甲基 - 苯甲酰胺 (“A10”)



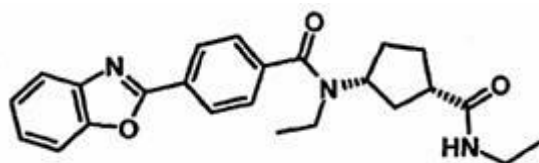
LC/MS: 392 (M+H); ^1H NMR (500 MHz, DMSO- d_6) δ [ppm] 8.26 (d, $J = 8.3$ Hz, 2H), 7.86-7.80 (m, 2H), 7.72 (br. s, 1H; NH), 7.65-7.55 (m, 2H), 7.45 (pd, $J = 7.4, 1.3$ Hz, 2H), 4.89, 4.00 (2x br. s, 1H, 比率=1:1.8 旋转异构体混合物), 3.06 (q, $J = 6.6$ Hz, 2H, NCH₂), 2.91 (br. s, 3H, CH₃), 2.67, 2.49 (2x br. s, 1H, 比率=1:1.8 旋转异构体混合物), 2.20 – 1.52 (m, 6H), 1.00 (t, $J = 7.1$ Hz, 3H, CH₃);

4-(1H- 苯并咪唑 -2- 基) -N-[(1R, 3S)-3-(乙基氨基甲酰基) 环戊基] -N- 甲基 - 苯甲酰胺 (“A11”)



LC/MS: M+H 391; ^1H NMR (500 MHz, DMSO- d_6) δ [ppm] 8.23 (d, $J = 8.4$ Hz, 2H), 7.75 (s, 1H, NH), 7.71 (dd, $J = 6.0, 3.2$ Hz, 2H), 7.69 – 7.55 (m, 2H), 7.36 (dd, $J = 5.9, 3.0$ Hz, 2H), 4.90, 4.00 (2x br. s, 1H, 比率=1:1.4, 旋转异构体混合物), 3.06 (q, $J = 7.2$ Hz, 2H), 2.90 (s, 3H), 2.71, 2.46 (2x br. s, 1H, 比率=1:1.4 旋转异构体混合物), 2.05 – 1.53 (m, 6H), 1.00 (t, $J = 7.2$ Hz, 3H);

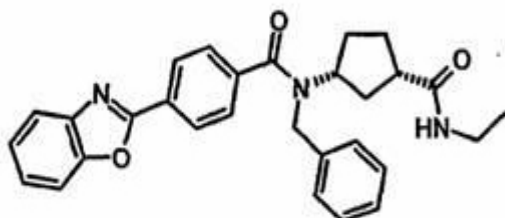
4- 苯并噁唑 -2- 基 -N- 乙基 -N-((1R, 3S)-3- 乙基氨基甲酰基 - 环戊基) - 苯甲酰胺 (“A12”)



LC/MS: M+H 406;

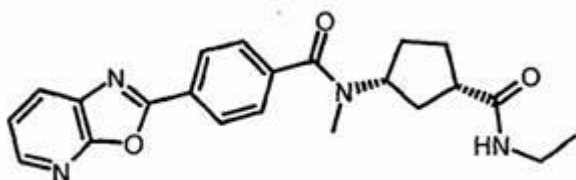
^1H NMR (500 MHz, DMSO- d_6), 旋转异构体混合物, δ [ppm] 8.26 (d, $J = 8.3$ Hz, 2H), 7.83 (ddd, $J = 12.2, 7.3, 1.9$ Hz, 2H), 7.72 (s, 1H; NH), 7.57 (d, $J = 8.3$ Hz, 2H), 7.51 – 7.39 (m, 2H), 3.38 (br. s, 2H), 3.16 – 2.98 (m, 2H), 2.16 – 1.52 (m, 6H), 1.38 – 1.06 (m, 3H), 1.07 – 0.91 (m, 3H);

4- 苯并噁唑-2-基-N-苄基-N-((1R, 3S)-3-乙基氨基甲酰基-环戊基)-苯甲酰胺 (“A13”)



LC/MS: M+H 468;

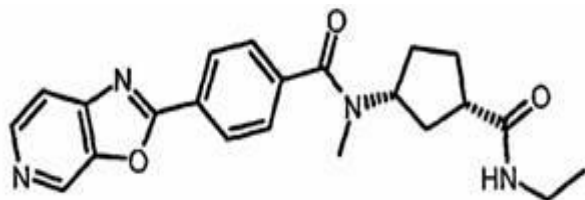
N-((1R, 3S)-3-乙基氨基甲酰基-环戊基)-N-甲基-4-噁唑并[5, 4-b]吡啶-2-基-苯甲酰胺 (“A14”)



LC/MS: M+H 393;

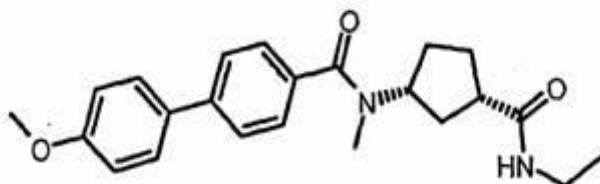
^1H NMR (500 MHz, DMSO- d_6) δ [ppm] 8.42 (dd, $J = 4.9, 1.5$ Hz, 1H), 8.31 (dd, $J = 7.9, 1.5$ Hz, 1H), 8.29 (d, $J = 8.3$ Hz, 2H), 7.72 (s, 1H; NH), 7.62 (d, $J = 6.6$ Hz, 2H), 7.53 (dd, $J = 7.8, 4.9$ Hz, 1H), 4.89, 3.97 (2x br.s, 1H, 比率=1:1.9, 旋转异构体混合物), 3.05 (q, $J = 6.0, 1.0$ Hz, 2H), 2.92 (s, 3H), 2.41 (br. s, 1H), 2.13 – 1.49 (m, 6H), 1.00 (t, $J = 7.0$ Hz, 3H);

N-((1R, 3S)-3-乙基氨基甲酰基-环戊基)-N-甲基-4-噁唑并[5, 4-c]吡啶-2-基-苯甲酰胺 (“A15”)



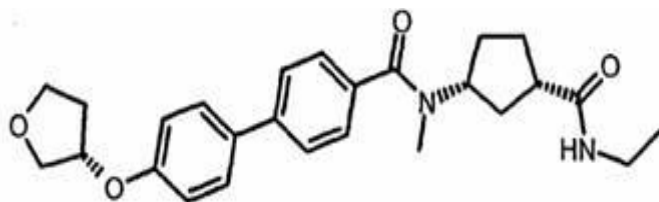
LC/MS: M+H 393;

4'-甲氧基-联苯-4-甲酸 ((1R, 3S)-3-乙基氨基甲酰基-环戊基)-甲基-酰胺 (“A16”)



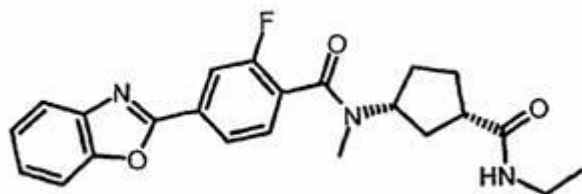
LC/MS: M+H 381; ^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 7.74 (s, 1H; NH), 7.66 (t, $J = 8.6$ Hz, 4H), 7.41 (d, $J = 8.1$ Hz, 2H), 7.04 (d, $J = 8.8$ Hz, 2H), 4.41 (br. s, 1H), 3.81 (s, 3H; CH_3O), 3.05 (dd, $J = 7.2, 5.6$ Hz, 2H), 2.88 (s, 3H; CH_3N), 1.94 – 1.58 (m, 6H), 1.00 (t, $J = 7.2$ Hz, 3H);

4'-[(S)-(四氢-呋喃-3-基)氧基]-联苯-4-甲酸 ((1R, 3S)-3-乙基氨基甲酰基-环戊基)-甲基-酰胺 ("A17")



LC/MS: M+H 437;

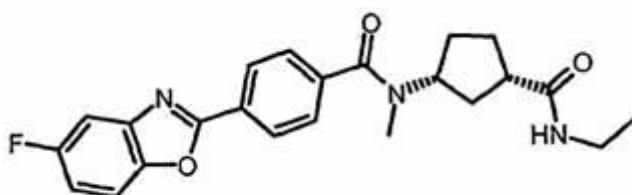
4-苯并噁唑-2-基-N-((1R, 3S)-3-乙基氨基甲酰基-环戊基)-2-氟-N-甲基-苯甲酰胺 ("A18")



LC/MS: M+H 410;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.10 (d, $J = 7.9$ Hz, 1H), 8.04 (d, $J = 9.8$ Hz, 1H), 7.85 (dd, $J = 14.2, 7.8$ Hz, 2H), 7.72 (t, $J = 5.4$ Hz, 1H; NH), 7.62 (q, $J = 8.0$ Hz, 1H), 7.47 (pd, $J = 7.4, 1.4$ Hz, 2H), 4.92, 3.91 (2x br. s, 1H, , 比率=1:7, 旋转异构体混合物), 3.06 (dp, $J = 14.3, 7.2$ Hz, 2H), 2.96, 2.79 (2x s, 比率=1:1,6, 旋转异构体混合物, 3H), 2.65, 2.43 (2x br. s, 比率=1:1,6, 旋转异构体混合物, 1H), 2.06 – 1.52 (m, 6H), 1.00 (dt, $J = 14.3, 7.2$ Hz, 3H);

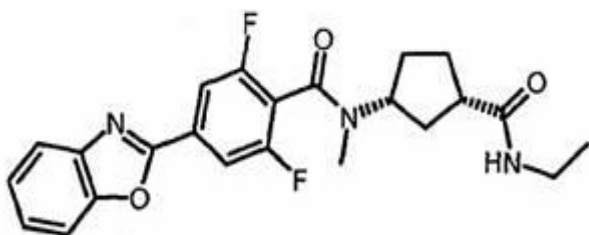
N-((1R, 3S)-3-乙基氨基甲酰基-环戊基)-4-(5-氟-苯并噁唑-2-基)-N-甲基-苯甲酰胺 ("A19")



LC/MS: M+H 410;

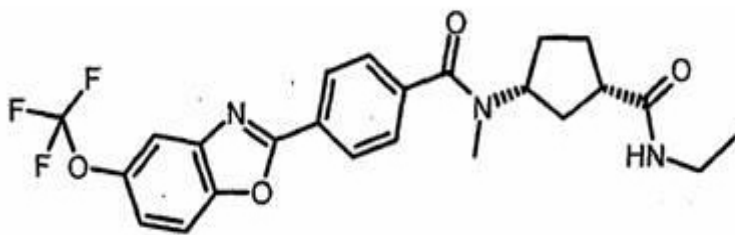
¹H NMR (500 MHz, DMSO-d₆) δ [ppm] 8.25 (d, *J* = 8.3 Hz, 2H), 7.85 (dd, *J* = 8.9, 4.4 Hz, 1H), 7.72 (dd, *J* = 8.7, 2.6 Hz, 1H+1H, NH), 7.60 (d, *J* = 6.8 Hz, 2H), 7.32 (td, *J* = 9.4, 2.6 Hz, 1H), .4.89, 3.97 (2x br.s, 1H, 比率=1:1,6, 旋转异构体混合物) 3.05 (q, *J* = 6.7 Hz, 2H), 2.91 (br. s, 3H), 2.63, 2.42 (2x br.s, 1H, 比率=1:1,6, 旋转异构体混合物) 2.05 – 1.52 (m, 6H), 1.00 (t, *J* = 7.1 Hz, 3H);

4- 苯并噁唑-2-基-N-((1R, 3S)-3- 乙基氨基甲酰基-环戊基)-2, 6- 二氟-N- 甲基- 苯甲酰胺 (“A20”)



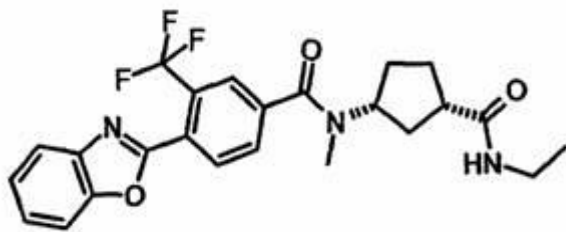
LC/MS: M+H 428;

N-((1R, 3S)-3- 乙基氨基甲酰基-环戊基)-N- 甲基-4-(5- 三氟甲氧基- 苯并噁唑-2-基)- 苯甲酰胺 (“A21”)



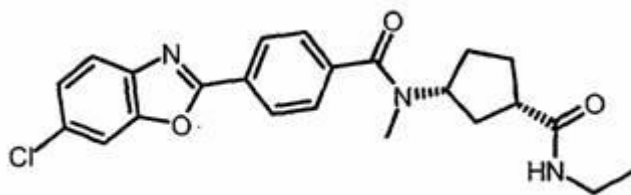
LC/MS: M+H 476;

4- 苯并噁唑-2-基-N-((1R, 3S)-3- 乙基氨基甲酰基-环戊基)-N- 甲基-3- 三氟甲基- 苯甲酰胺 (“A22”)



LC/MS: M+H 460;

4-(6- 氯- 苯并噁唑-2-基)-N-((1R, 3S)-3- 乙基氨基甲酰基-环戊基)-N- 甲基- 苯甲酰胺 (“A23”)

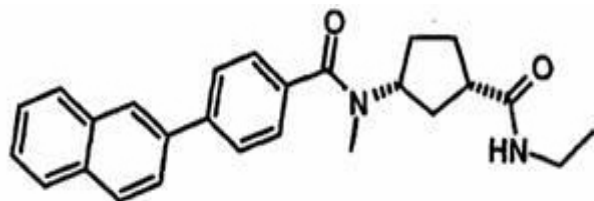


LC/MS: M+H 426;

^1H NMR (500 MHz, DMSO- d_6) δ [ppm] 8.24 (d, J = 8.3 Hz, 2H), 8.03 (d, J = 1.9 Hz, 1H), 7.86 (d, J = 8.5 Hz, 1H), 7.72 (s, 1H; NH), 7.60 (d, J = 6.8 Hz, 2H), 7.49 (dd, J = 8.5, 2.0 Hz, 1H), , 4.87, 3.96 (2x br.s, 1H, 比率=1:1,46,

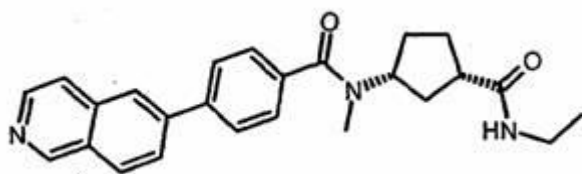
旋转异构体混合物), 3.05 (q, J = 6.6 Hz, 2H), 2.91 (br. s, 3H), 2.61, 2.43 (2x br.s, 1H, , 比率=1:1,46, 旋转异构体混合物), 2.06 – 1.49 (m, 6H), 1.00 (t, J = 7.1 Hz, 3H);

N-((1R, 3S)-3-乙基氨基甲酰基-环戊基)-N-甲基-4-萘-2-基-苯甲酰胺 (“A24”)



LC/MS: M+H 401;

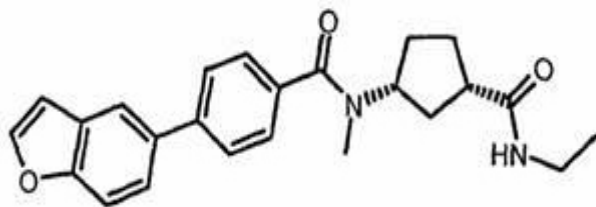
N-((1R, 3S)-3-乙基氨基甲酰基-环戊基)-4-异喹啉-6-基-N-甲基-苯甲酰胺 (“A25”)



LC/MS: M+H 402;

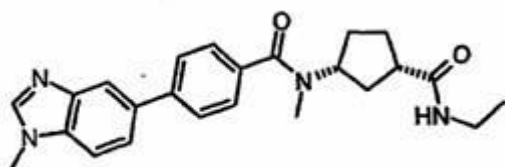
^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 9.66 (s, 1H), 8.64 (d, J = 6.2 Hz, 1H), 8.54 (s, 1H), 8.46 (d, J = 8.7 Hz, 1H), 8.33 – 8.16 (m, 2H), 7.99 (d, J = 8.3 Hz, 2H), 7.75 (s, 1H; NH), 7.57 (d, J = 7.6 Hz, 2H), 3.06 (p, J = 7.1 Hz, 2H), 2.91 (br. s, 3H), 2.09 – 1.54 (m, 6H), 1.00 (t, J = 7.2 Hz, 3H);

4-苯并呋喃-5-基-N-((1R, 3S)-3-乙基氨基甲酰基-环戊基)-N-甲基-苯甲酰胺 (“A26”)



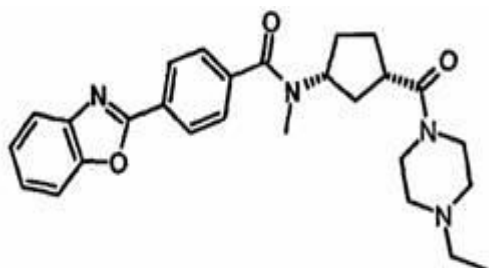
LC/MS: M+H 391;

N-((1R, 3S)-3-乙基氨基甲酰基-环戊基)-N-甲基-4-(1-甲基-1H-苯并咪唑-5-基)-苯甲酰胺 (“A27”)



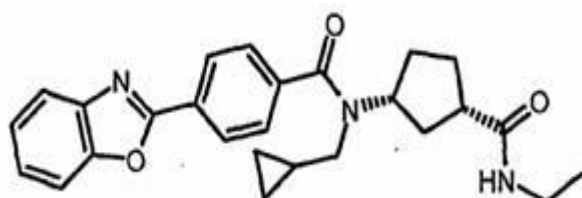
LC/MS: M+H 391;

4- 苯并噁唑 -2- 基 -N-[(1R, 3S)-3-(4- 乙基 - 哌嗪 -1- 羰基) - 环戊基] -N- 甲基 - 苯甲酰胺 (“A28”)



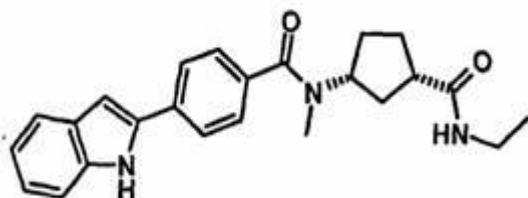
LC/MS: M+H 461;

4- 苯并噁唑 -2- 基 -N- 环丙基甲基 -N-((1R, 3S)-3- 乙基氨基甲酰基 - 环戊基) - 苯甲酰胺 (“A29”)



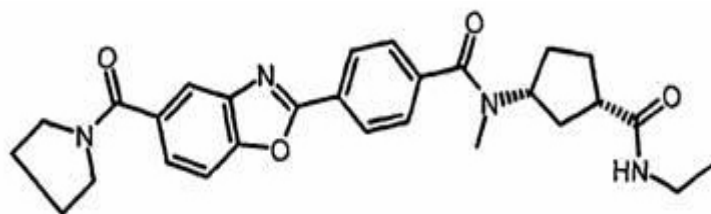
LC/MS: M+H 432;

N-((1R, 3S)-3- 乙基氨基甲酰基 - 环戊基) -4-(1H- 吲哚 -2- 基) -N- 甲基 - 苯甲酰胺 (“A30”)



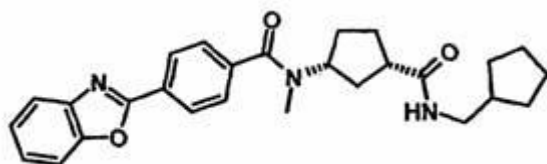
LC/MS: M+H 390;

N-((1R, 3S)-3- 乙基氨基甲酰基 - 环戊基) -N- 甲基 -4-[5-(吡咯烷 -1- 羰基) - 苯并噁唑 -2- 基] - 苯甲酰胺 (“A31”)



LC/MS: M+H 489;

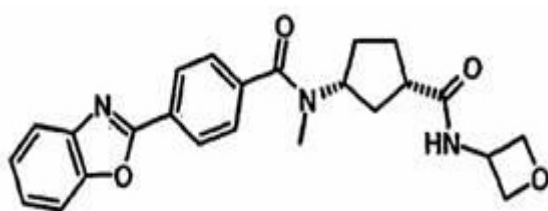
4- 苯并噁唑 -2- 基 -N-[(1R, 3S)-3-(环戊基甲基 - 氨基甲酰基) - 环戊基] -N- 甲基 - 苯甲酰胺 (“A32”)



LC/MS: M+H 446;

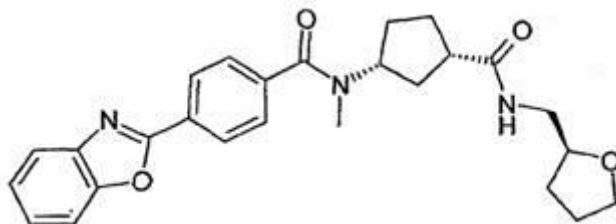
^1H NMR (500 MHz, DMSO- d_6) δ [ppm] 8.26 (d, J = 8.4 Hz, 2H), 7.83 (dd, J = 13.4, 8.0 Hz, 2H), 7.73 (s, 1H; NH), 7.60 (d, J = 7.1 Hz, 2H), 7.49 – 7.37 (m, 2H), 4.89, 3.99 (2x br.s, 1H, 比率=1:1.7, 旋转异构体混合物) 3.11 – 2.72 (m, 5H), 2.10 – 1.34 (m, 13H), 1.23 – 0.97 (m, 2H);

4- 苯并噁唑-2-基 -N- 甲基 -N-[(1R, 3S)-3-(氧杂环丁烷-3-基氨基甲酰基)-环戊基]-苯甲酰胺 (“A33”)



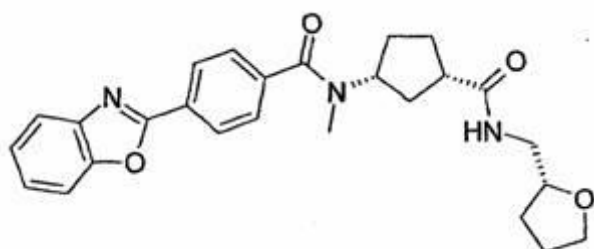
LC/MS: M+H 420;

4- 苯并噁唑-2-基 -N- 甲基 -N-((1R, 3S)-3-[(S)-1-(四氢-呋喃-2-基)甲基]-氨基甲酰基)-环戊基)-苯甲酰胺 (“A34”)



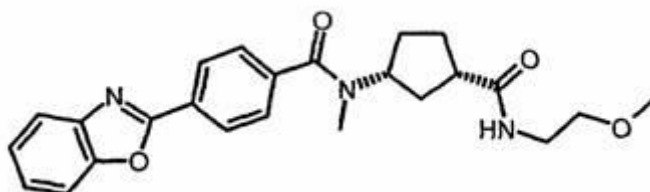
LC/MS: M+H 448; ^1H NMR (500 MHz, DMSO- d_6) δ [ppm] 8.27 (d, J = 8.3 Hz, 2H), 7.98 – 7.72 (m, 3H), 7.61 (d, J = 6.9 Hz, 2H), 7.46 (pd, J = 7.4, 1.4 Hz, 2H), 4.91, 4.00 (2x br. s, 1H, 比率=1:1.8 旋转异构体混合物) 3.89 – 3.78 (m, 1H), 3.75 (q, J = 6.9 Hz, 1H), 3.61 (q, J = 7.2 Hz, 1H), 3.16 - 3.06 (m, 2H), 2.92 (s, 3H), 2.90 (s, 3H), 2.72, 2.55 (2x br.s, 1H, , 比率=1:1.8 旋转异构体混合物), 2.03 - 1.58 m, 9H), 1.49 (dq, J = 14.4, 7.2 Hz, 1H).

4- 苯并噁唑-2-基 -N- 甲基 -N-((1R, 3S)-3-[(R)-1-(四氢-呋喃-2-基)甲基]-氨基甲酰基)-环戊基)-苯甲酰胺 (“A35”)



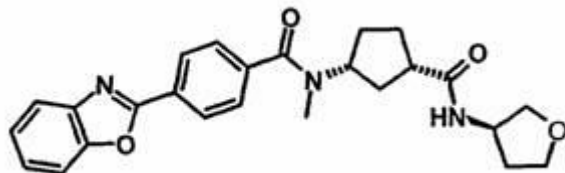
LC/MS: M+H 448; ^1H NMR (500 MHz, DMSO- d_6) δ [ppm] 8.27 (d, $J = 8.3$ Hz, 2H), 7.98 – 7.72 (m, 3H), 7.61 (d, $J = 6.9$ Hz, 2H), 7.46 (pd, $J = 7.4, 1.4$ Hz, 2H), 4.91, 4.00 (2x br. s, 1H, 比率=1:1.8 旋转异构体混合物) 3.89 – 3.78 (m, 1H), 3.75 (q, $J = 6.9$ Hz, 1H), 3.61 (q, $J = 7.2$ Hz, 1H), 3.16 - 3.06 (m, 2H), 2.92 (s, 3H), 2.90 (s, 3H), 2.72, 2.55 (2x br.s, 1H, , 比率=1:1.8 旋转异构体混合物), 2.03 - 1.58 m, 9H), 1.49 (dq, $J = 14.4, 7.2$ Hz, 1H);

4- 苯并噁唑-2-基 -N-[(1R, 3S)-3-(2- 甲氧基 - 乙基氨基甲酰基)- 环戊基]-N- 甲基 - 苯甲酰胺 (“A36”)



LC/MS: M+H 422; ^1H NMR (500 MHz, DMSO- d_6) δ [ppm] 8.27 (d, $J = 8.3$ Hz, 2H), 7.89 – 7.79 (m, 3H), 7.61 (d, $J = 6.7$ Hz, 2H), 7.46 (pd, $J = 7.4, 1.4$ Hz, 2H), 4.90, 4.00 (2x br. s, 1H, 比率=1:2 旋转异构体混合物) 3.34 (t, $J = 5.6$ Hz, 2H), 3.31 (s, 3H; OCH_3), 3.24 – 3.18 (m, 2H), 2.92 (s, 3H), 2.08 – 1.52 (m, 6H);

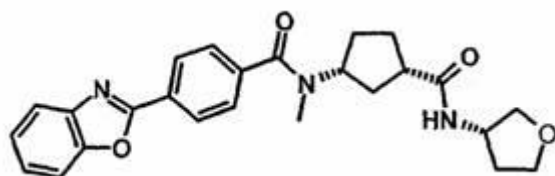
4- 苯并噁唑-2-基 -N- 甲基 -N-[(1R, 3S)-3-[(R)-(四氢 - 呋喃 -3- 基) 氨基甲酰基]- 环戊基]- 苯甲酰胺 (“A37”)



LC/MS: M+H 434;

^1H NMR (500 MHz, DMSO- d_6) δ [ppm] 8.26 (d, $J = 8.3$ Hz, 2H), 7.98 (s, 1H; NH), 7.83 (ddd, $J = 12.7, 7.3, 1.8$ Hz, 2H), 7.60 (d, $J = 6.9$ Hz, 2H), 7.50 – 7.40 (m, 2H), 4.90, 3.99 (2x br.s, 1H, 比率=1:1.5, 旋转异构体混合物) 4.25 – 4.17 (m, 1H), 3.83 – 3.70 (m, 2H), 3.65 (q, $J = 8.1$ Hz, 1H), 3.41 (dd, $J = 8.6, 3.3$ Hz, 1H), 2.91 (br. s, 3H), 2.12 – 1.99 (m, 1H), 2.00 – 1.54 (m, 7H);

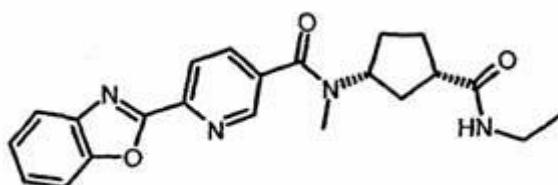
4- 苯并噁唑-2-基 -N- 甲基 -N-[(1R, 3S)-3-[(S)-(四氢 - 呋喃 -3- 基) 氨基甲酰基]- 环戊基]- 苯甲酰胺 (“A38”)



LC/MS: M+H 434;

^1H NMR (500 MHz, DMSO- d_6) δ [ppm] 8.26 (d, $J = 8.3$ Hz, 2H), 7.98 (s, 1H; NH), 7.83 (ddd, $J = 12.7, 7.3, 1.8$ Hz, 2H), 7.60 (d, $J = 6.9$ Hz, 2H), 7.50 – 7.40 (m, 2H), 4.90, 3.99 (2x br.s, 1H, 比率=1:1.5, 旋转异构体混合物) 4.25 – 4.17 (m, 1H), 3.83 – 3.70 (m, 2H), 3.65 (q, $J = 8.1$ Hz, 1H), 3.41 (dd, $J = 8.6, 3.3$ Hz, 1H), 2.91 (br. s, 3H), 2.12 – 1.99 (m, 1H), 2.00 – 1.54 (m, 7H);

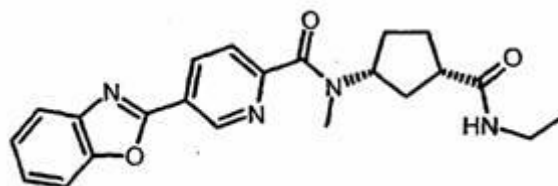
6- 苯并噁唑 -2- 基 -N-((1R, 3S)-3- 乙基氨基甲酰基 - 环戊基)-N- 甲基 - 烟酰胺 (“A39”)



LC/MS: M+H 393;

^1H NMR (500 MHz, DMSO- d_6) δ [ppm] 8.79 (s, 1H), 8.39 (d, $J = 8.1$ Hz, 1H), 8.07 (s, 1H), 7.90 (d, $J = 7.6$ Hz, 1H), 7.86 (d, $J = 7.7$ Hz, 1H), 7.73 (s, 1H; NH), 7.52 (td, $J = 7.8, 1.4$ Hz, 1H), 7.47 (td, $J = 7.7, 1.2$ Hz, 1H), 4.91, 3.99 (2x br.s, 1H, 比率=1:1.5, 旋转异构体混合物), 3.14 – 3.00 (m, 2H), 2.95 (s, 3H), 2.44 (br. s, 1H), 2.11 – 1.52 (m, 6H), 1.13 – 0.89 (m, 3H);

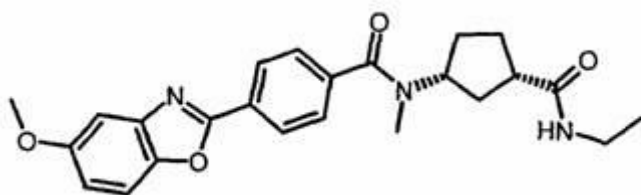
5- 苯并噁唑 -2- 基 -吡啶 -2- 甲酸 ((1R, 3S)-3- 乙基氨基甲酰基 - 环戊基)- 甲基 - 酰胺 (“A40”)



LC/MS: M+H 393;

^1H NMR (500 MHz, DMSO- d_6) 旋转异构体混合物: δ [ppm] 9.35 (s, 1H), 8.63 (d, $J = 8.1$ Hz, 1H), 7.87 (dd, $J = 16.0, 7.1$ Hz, 2H), 7.83 – 7.62 (m, 2H), 7.60 – 7.32 (m, 2H), 4.93, 4.00 (m, 1H), 3.11- 3.01 (m, 2H), 2.96, 2.85 (s, 3H), 2.65, 2.44 (m, 1H), 2.08 – 1.53 (m, 6H), 1.10 – 0.93 (m, 3H);

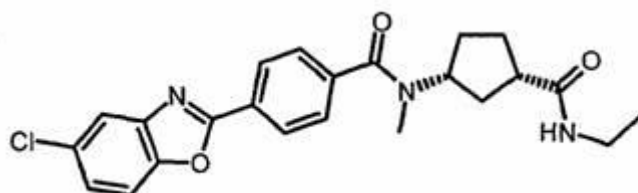
N-((1R, 3S)-3- 乙基氨基甲酰基 - 环戊基)-4-(5- 甲氧基 - 苯并噁唑 -2- 基)-N- 甲基 - 苯甲酰胺 (“A41”)



LC/MS: M+H 422;

^1H NMR (500 MHz, DMSO- d_6) δ [ppm] 8.22 (d, $J = 8.1$ Hz, 2H), 7.73 (br. s, 1H; NH), 7.70 (d, $J = 8.9$ Hz, 1H), 7.58 (d, $J = 6.5$ Hz, 2H), 7.38 (d, $J = 2.4$ Hz, 1H), 7.03 (dd, $J = 8.9, 2.5$ Hz, 1H), 4.89, 3.97 (2x br.s, 1H, 比率=1:2, 旋转异构体混合物), 3.84 (s, 3H), 3.14 – 2.99 (m, 2H), 2.90 (br. s, 3H), 2.33 (br. s, 1H), 2.07 – 1.49 (m, 6H), 1.00 (t, $J = 7.0$ Hz, 3H);

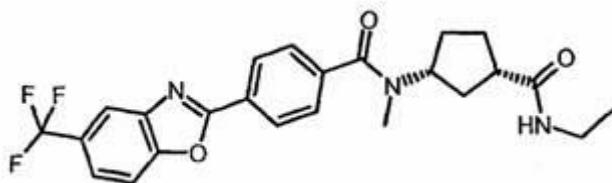
4-(5-氯-苯并噁唑-2-基)-N-((1R,3S)-3-乙基氨基甲酰基-环戊基)-N-甲基-苯甲酰胺 (“A42”)



LC/MS: M+H 426

^1H NMR (500 MHz, DMSO- d_6) δ [ppm] 8.25 (d, $J = 8.3$ Hz, 2H), 7.95 (d, $J = 2.1$ Hz, 1H), 7.86 (d, $J = 8.7$ Hz, 1H), 7.72 (s, 1H; NH), 7.60 (d, $J = 6.4$ Hz, 2H), 7.50 (dd, $J = 8.7, 2.1$ Hz, 1H), 4.89, 3.97 (2x br.s, 1H, 比率=1:1.9, 旋转异构体混合物) 3.05 (q, $J = 6.7$ Hz, 2H), 2.91 (br. s, 3H), 2.42 (br. s, 1H), 2.10 – 1.50 (m, 6H), 1.00 (t, $J = 7.1$ Hz, 3H);

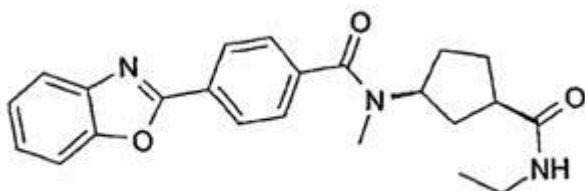
N-((1R,3S)-3-乙基氨基甲酰基-环戊基)-N-甲基-4-(5-三氟甲基-苯并噁唑-2-基)-苯甲酰胺 (“A43”)



LC/MS: M+H 460;

^1H NMR (500 MHz, DMSO- d_6) δ [ppm] 8.34 – 8.24 (m, 3H), 8.06 (d, $J = 8.5$ Hz, 1H), 7.87 – 7.80 (m, 1H), 7.74 (s, 1H; NH), 7.63 (s, 2H), 4.90, 3.96 (2x br.s, 1H, 比率=1:1.7, 旋转异构体混合物) 3.05 (q, $J = 6.7, 5.8$ Hz, 2H), 2.93 (br. s, 3H), 2.15 – 1.50 (m, 6H), 0.99 (t, $J = 6.4$ Hz, 3H);

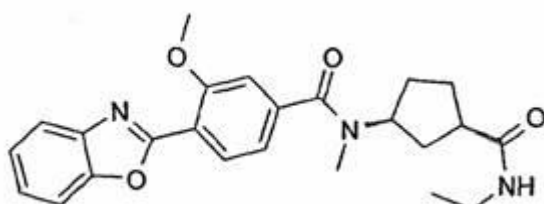
4-(1,3-苯并噁唑-2-基)-N-[(1R,3R)-3-(乙基氨基甲酰基)环戊基]-N-甲基-苯甲酰胺 (“A44”)



LC/MS: M+H 392;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.26 (d, $J = 8.3$ Hz, 2H), 7.88 – 7.78 (m, 2H), 7.74 (s, 1H; NH), 7.58 (d, $J = 7.3$ Hz, 2H), 7.51 – 7.39 (m, 2H), 4.94, 4.17 (2x br.s, 1H, 比率=1:2.2, 旋转异构体混合物), 3.01 (br. s, 2H), 2.86 (br. s, 3H), 2.80 – 2.64 (m, 1H), 2.15 – 1.53 (m, 6H), 0.96 (br. s, 3H);

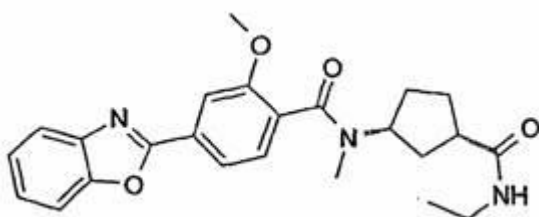
4-苯并噁唑-2-基-N-((1R,3S)-3-乙基氨基甲酰基-环戊基)-3-甲氧基-N-甲基-苯甲酰胺 (“A45”)



LC/MS: M+H 422;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.09 (d, $J = 7.9$ Hz, 1H), 7.85 (d, $J = 8.8$ Hz, 1H), 7.80 (d, $J = 6.9$ Hz, 1H), 7.75 (s, 1H; NH), 7.49 – 7.39 (m, 2H), 7.24 (s, 1H), 7.12 (d, $J = 7.3$ Hz, 1H), 4.93, 4.07 (2x br.s, 1H, 比率=1:1.5, 旋转异构体混合物), 3.98 (s, 3H), 3.15 – 3.00 (m, 2H), 2.93 (br. s, 3H), 2.09 – 1.58 (m, 6H), 1.02 (t, $J = 7.0$ Hz, 3H);

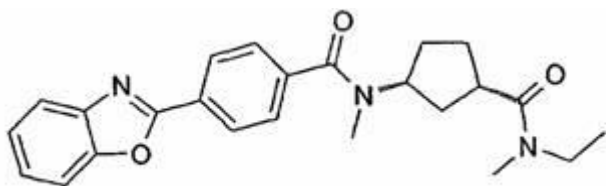
4-苯并噁唑-2-基-N-((1R,3S)-3-乙基氨基甲酰基-环戊基)-2-甲氧基-N-甲基-苯甲酰胺 (“A46”)



LC/MS: M+H 422;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 旋转异构体混合物
7.90 – 7.78 (m, 4H), 7.69 (s, 1H, NH), 7.46 (td, $J = 7.2, 1.4$ Hz, 2H), 7.39 (d, $J = 7.7$ Hz, 1H), 4.95, 3.83 (2x m, 1H, 比率=1:1.8, 旋转异构体混合物), 3.95 (s, 3H), 3.15 – 2.98 (m, 2H), 2.92, 2.70 (2xs, 3H), 2.04 – 1.44 (m, 6H), 1.08 – 0.92 (m, 3H);

4-苯并噁唑-2-基-N-[(1R,3S)-3-(乙基-甲基-氨基甲酰基)-环戊基]-N-甲基-苯甲酰胺 (“A47”)

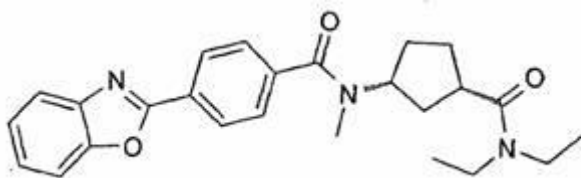


LC/MS: M+H 406;

¹H NMR (400 MHz, DMSO-d₆) δ [ppm] 旋转异构体混合物

8.26 (d, *J* = 8.3 Hz, 2H), 7.83 (dd, *J* = 13.7, 6.9 Hz, 2H), 7.60 (d, *J* = 7.2 Hz, 2H), 7.45 (pd, *J* = 7.4, 1.4 Hz, 2H), 4.93, 4.04 (2x s, 1H, 比率=1:1.7, 旋转异构体混合物), 3.29 – 3.16 (m, 2H), 3.10 – 2.70 (m, 6H), 2.13 – 1.57 (m, 6H), 1.19 – 0.84 (m, 3H);

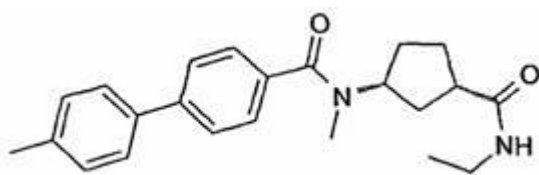
4- 苯并噁唑 -2- 基 -N-((1R, 3S)-3- 二乙基氨基甲酰基 - 环戊基)-N- 甲基 - 苯甲酰胺 (“A48”)



LC/MS: M+H 420;

¹H NMR (400 MHz, DMSO-d₆) δ [ppm] 8.26 (d, *J* = 8.4 Hz, 2H), 7.87 – 7.78 (m, 2H), 7.60 (d, *J* = 7.1 Hz, 2H), 7.45 (td, *J* = 7.5, 1.5 Hz, 2H), 4.95, 4.04 (2x s, 1H, 比率=1:1.7, 旋转异构体混合物), 3.30 – 3.11 (m, 2H), 2.91 (br. s, 3H), 2.09 – 1.53 (m, 6H), 1.21 – 0.84 (m, 6H);

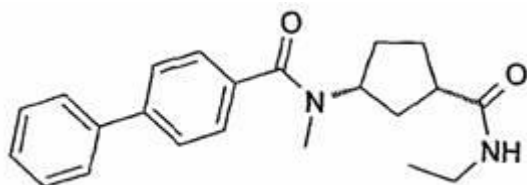
4'- 甲基 - 联苯 -4- 甲酸 ((1R, 3S)-3- 乙基氨基甲酰基 - 环戊基)- 甲基 - 酰胺 (“A49”)



LC/MS: M+H 365;

¹H NMR (400 MHz, DMSO-d₆) δ [ppm] 7.73 (s, 1H; NH), 7.70 (d, *J* = 8.3 Hz, 2H), 7.60 (d, *J* = 8.1 Hz, 2H), 7.43 (d, *J* = 7.9 Hz, 2H), 7.29 (d, *J* = 7.9 Hz, 2H), 4.83, 4.09 (2x s, 1H, 比率=1:1.8, 旋转异构体混合物), 3.05 (p, *J* = 7.2 Hz, 2H), 2.88 (s, 3H), 2.35 (s, 3H), 2.05 – 1.54 (m, 6H), 1.00 (t, *J* = 7.2 Hz, 3H);

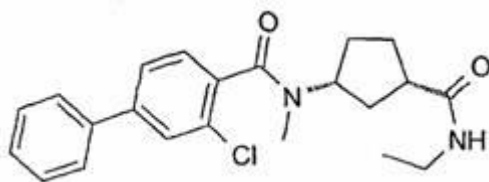
联苯 -4- 甲酸 ((1R, 3S)-3- 乙基氨基甲酰基 - 环戊基)- 甲基 - 酰胺 (“A50”)



LC/MS: M+H 351;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 7.81 – 7.63 (m, 5H), 7.49 (t, $J = 7.7$ Hz, 2H), 7.45 (d, $J = 7.9$ Hz, 2H), 7.40 (t, $J = 7.4$ Hz, 1H), , 4.84, 4.08 (2x s, 1H, 比率=1:1.8, 旋转异构体混合物), 3.06 (p, $J = 7.2$ Hz, 2H), 2.88 (br. s, 3H), 2.05 – 1.54 (m, 6H), 1.00 (t, $J = 7.2$ Hz, 3H);

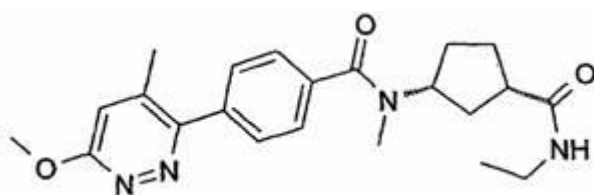
3-氯-联苯-4-甲酸 ((1R,3S)-3-乙基氨基甲酰基-环戊基)-甲基-酰胺 ("A51")



LC/MS: M+H 385;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 7.81 (d, $J = 6.9$ Hz, 1H), 7.77 – 7.65 (m, 4H), 7.50 (t, $J = 7.6$ Hz, 2H), 7.41 (q, $J = 7.4, 6.8$ Hz, 2H), Hz, 2H), 7.40 (t, $J = 7.4$ Hz, 1H), , 4.95, 3.82 (2x m, 1H, 比率=1:1.6, 旋转异构体混合物), 3.15 – 2.98 (m, 2H), 2.94, 2.72 (2x s, 3H, 比率=1:1.6, 旋转异构体混合物), 2.65, 2.41 (2x m, 1H ratio=1:1.6, 旋转异构体混合物), 2.02 – 1.50 (m, 6H), 1.07 – 0.91 (m, 3H);

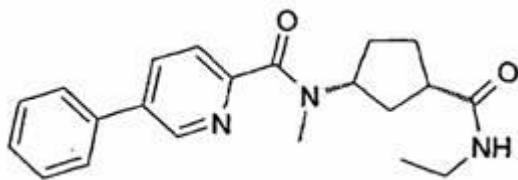
N-((1R,3S)-3-乙基氨基甲酰基-环戊基)-4-(6-甲氧基-4-甲基-吡嗪-3-基)-N-甲基-苯甲酰胺 ("A52")



LC/MS: M+H 397;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 7.74 (s, 1H; NH), 7.62 (d, $J = 8.2$ Hz, 2H), 7.48 (d, $J = 7.7$ Hz, 2H), 7.20 (s, 1H), 4.87, 4.04 (2x s, 1H, 比率=1:1.2, 旋转异构体混合物), 4.06 (s, 3H), 3.06 (p, $J = 7.1$ Hz, 2H), 2.90 (br. s, 3H), 2.29 (s, 3H), 2.04 – 1.55 (m, 6H), 1.00 (t, $J = 7.2$ Hz, 3H);

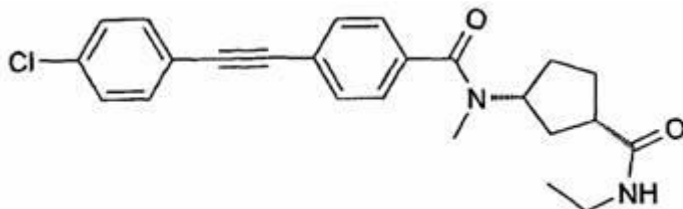
5-苯基-吡啶-2-甲酸 ((1R,3S)-3-乙基氨基甲酰基-环戊基)-甲基-酰胺 ("A53")



LC/MS: M+H 352;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.89 (s, 1H), 8.19 (dd, $J = 8.1, 2.3$ Hz, 1H), 7.78 (d, $J = 7.5$ Hz, 2H), 7.69 (t, $J = 4.2$ Hz, 1H; NH), 7.66 – 7.57 (m, 1H), 7.53 (t, $J = 7.5$ Hz, 2H), 7.45 (t, $J = 7.4$ Hz, 1H), 4.93, 4.132 (2x m, 1H, 比率=1:1.5, 旋转异构体混合物), 3.17 – 2.97 (m, 2H), 2.94, 2.86 (2x s, 3H, 比率=1:1.5, 旋转异构体混合物; N-CH₃), 2.64, 2.41 (2x m, 1H 比率=1:1.5, 旋转异构体混合物), 2.10 – 1.49 (m, 6H), 1.08 – 0.90 (m, 3H);

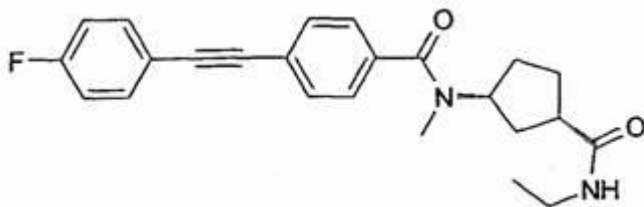
4-(4-氯-苯基乙炔基)-N-((1R, 3S)-3-乙基氨基甲酰基-环戊基)-N-甲基-苯甲酰胺 (“A54”)



LC/MS: M+H 409;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 7.73 (br. s, 1H; NH), 7.61 (t, $J = 8.2$ Hz, 4H), 7.51 (d, $J = 8.6$ Hz, 2H), 7.41 (d, $J = 7.4$ Hz, 2H), 4.86, 3.95 (2x br. s, 1H, 比率=1:1.8, 旋转异构体混合物), 3.05 (p, $J = 7.1$ Hz, 2H), 2.86 (br. s, 3H), 2.56, 2.43 (2x br. s, 1H, 比率=1:1.8, 旋转异构体混合物), 2.08 – 1.46 (m, 6H), 1.00 (t, $J = 7.2$ Hz, 3H);

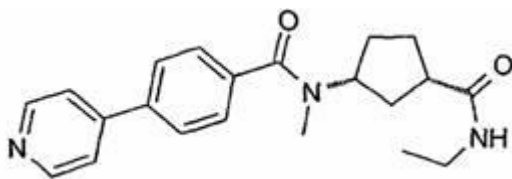
N-((1R, 3S)-3-乙基氨基甲酰基-环戊基)-4-(4-氟-苯基乙炔基)-N-甲基-苯甲酰胺 (“A55”)



LC/MS: M+H 393;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 7.73 (br. s, 1H; NH), 7.64 (dd, $J = 8.9, 5.5$ Hz, 2H), 7.60 (d, $J = 8.3$ Hz, 2H), 7.41 (d, $J = 8.3$ Hz, 2H), 7.29 (t, $J = 8.9$ Hz, 2H), 4.87, 3.94 (2x br. s, 1H, 比率=1:1.8, 旋转异构体混合物), 3.05 (p, $J = 7.1$ Hz, 2H), 2.86 (br. s, 3H), 2.56, 2.43 (2x br. s, 1H, 比率=1:1.8, 旋转异构体混合物), 2.11 – 1.50 (m, 6H), 1.00 (t, $J = 7.2$ Hz, 3H);

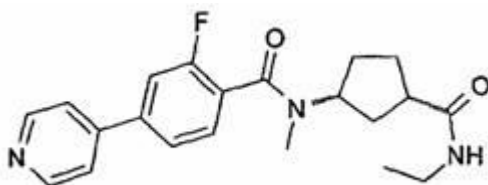
N-((1R, 3S)-3-乙基氨基甲酰基-环戊基)-N-甲基-4-吡啶-4-基-苯甲酰胺 ("A56")



LC/MS: M+H 352;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.66 (d, J = 6.1 Hz, 2H), 7.87 (d, J = 8.3 Hz, 2H), 7.82 – 7.61 (m, 3H), 7.50 (d, J = 7.6 Hz, 2H), 4.87, 4.04 (2x s, 1H, 比率=1:1.9, 旋转异构体混合物), 3.05 (p, J = 7.1 Hz, 2H), 2.89 (br. s, 3H), 2.13 – 1.52 (m, 6H), 1.00 (t, J = 7.2 Hz, 3H);

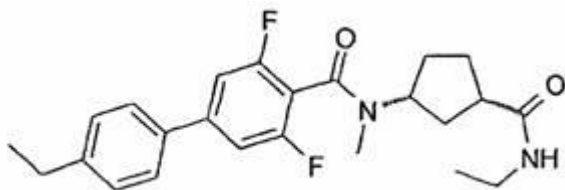
N-((1R, 3S)-3-乙基氨基甲酰基-环戊基)-2-氟-N-甲基-4-吡啶-4-基-苯甲酰胺 ("A57")



LC/MS: M+H 370;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.67 (d, J = 4.6 Hz, 2H), 7.84 – 7.76 (m, 3H), 7.74 (dd, J = 7.9, 1.6 Hz, 1H), 7.70 (t, J = 5.2 Hz, 1H; NH), 7.50 (q, J = 7.6 Hz, 1H), 4.93, 3.92 (2x p, J = 8.2 Hz, 1H, 比率=1:1.8, 旋转异构体混合物), 3.17 – 2.97 (m, 2H), 2.94, 2.78 (2x s, 3H), 2.65, 2.40 (2x m, 1H, 比率=1:1.8, 旋转异构体混合物), 2.09 – 1.51 (m, 6H), 1.07 – 0.91 (m, 3H);

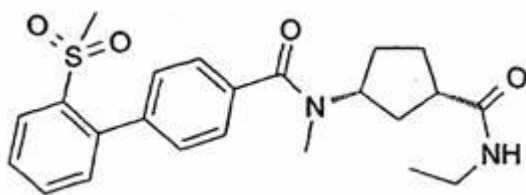
4'-乙基-3,5-二氟-联苯-4-甲酸 ((1R, 3S)-3-乙基氨基甲酰基-环戊基)-N-甲基-酰胺 ("A58")



LC/MS: M+H 415;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 7.84 – 7.66 (m, 3H), 7.54 (dd, J = 9.3, 2.9 Hz, 2H), 7.34 (d, J = 8.3 Hz, 2H), 4.93, 3.99 (2x m, 1H, 比率=1:1.7, 旋转异构体混合物), 3.14 – 2.99 (m, 2H), 2.96, 2.81 (2x s, 3H, 比率=1:1.7, 旋转异构体混合物), 2.66 (q, J = 7.6 Hz, 2H), 2.04 – 1.54 (m, 6H), 1.28 – 1.17 (m, 3H), 1.07 – 0.91 (m, 3H);

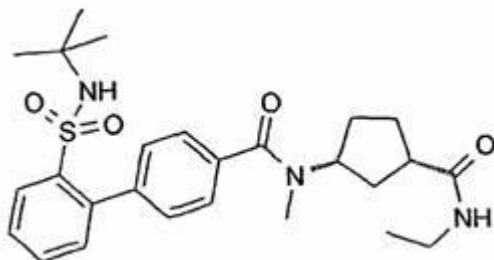
2'-甲磺酰基-联苯-4-甲酸 ((1R, 3S)-3-乙基氨基甲酰基-环戊基)-甲基-酰胺 ("A59")



LC/MS: M+H 429;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.11 (dd, $J = 8.0, 1.3$ Hz, 1H), 7.82 – 7.72 (m, 2H), 7.70 (td, $J = 7.7, 1.4$ Hz, 1H), 7.54 – 7.31 (m, 5H), 3.06 (p, $J = 7.1$ Hz, 2H), 4.87, 4.02 (2x br. s, 1H, 比率=1:1.4, 旋转异构体混合物), 2.94 – 2.78 (m, 6H), 2.09 – 1.54 (m, 6H), 1.00 (t, $J = 7.2$ Hz, 3H);

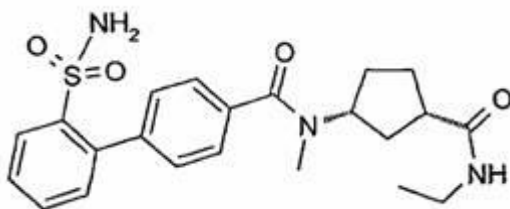
2'-叔丁基氨磺酰基-联苯-4-甲酸 ((1R, 3S)-3-乙基氨基甲酰基-环戊基)-甲基-酰胺 ("A60")



LC/MS: M+H 486;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.11 – 7.98 (m, 1H), 7.75 (s, 1H; NH), 7.65 (td, $J = 7.5, 1.3$ Hz, 1H), 7.58 (td, $J = 7.7, 1.4$ Hz, 1H), 7.46 (d, $J = 8.1$ Hz, 2H), 7.38 (d, $J = 7.5$ Hz, 2H), 7.34 (dd, $J = 7.5, 1.1$ Hz, 1H), 6.67 (s, 1H; NH), 4.82, 4.13 (2x br. s, 1H, 比率=1:1.7, 旋转异构体混合物), 3.06 (p, $J = 7.2$ Hz, 2H), 2.90 (s, 3H), 2.04 – 1.48 (m, 6H), 1.05 – 0.92 (m, 12H);

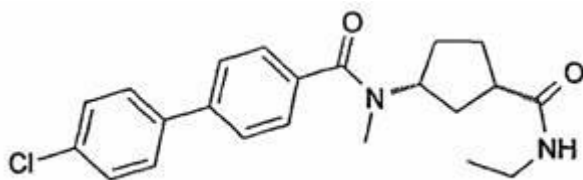
2'-氨磺酰基-联苯-4-甲酸 ((1R, 3S)-3-乙基氨基甲酰基-环戊基)-甲基-酰胺 ("A61")



LC/MS: M+H 430;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.05 (dd, $J = 7.8, 1.3$ Hz, 1H), 7.76 (s, 1H; NH), 7.67 – 7.55 (m, 2H), 7.44 (d, $J = 8.2$ Hz, 2H), 7.37 (d, $J = 7.8$ Hz, 2H), 7.34 (dd, $J = 7.4, 1.3$ Hz, 1H), 7.27 (s, 2H), 4.87, 4.13 (2x br. s, 1H, 比率=1:1.8, 旋转异构体混合物), 3.06 (p, $J = 7.1$ Hz, 2H), 2.89 (s, 3H), 2.02 – 1.55 (m, 6H), 1.00 (t, $J = 7.2$ Hz, 3H);

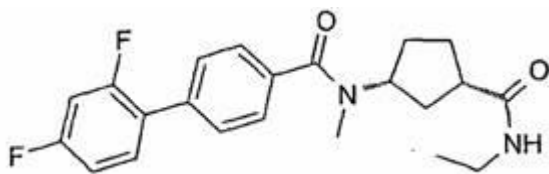
4'-氯-联苯-4-甲酸 ((1R, 3S)-3-乙基氨基甲酰基-环戊基)-甲基-酰胺 ("A62")



LC/MS: M+H 385;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 7.80 – 7.69 (m, 5H), 7.55 (d, $J = 8.6$ Hz, 2H), 7.47 (d, $J = 7.8$ Hz, 2H), 4.84, 4.08 (2x br. s, 1H, 比率=1:2.1, 旋转异构体混合物), 3.07 (p, $J = 7.1$ Hz, 2H), 2.89 (s, 3H), 2.09 – 1.50 (m, 6H), 1.01 (t, $J = 7.2$ Hz, 3H);

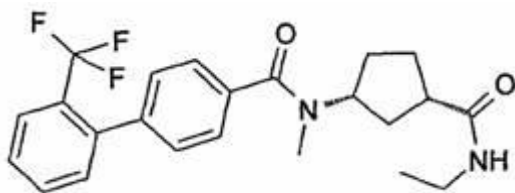
2', 4'-二氟-联苯-4-甲酸 ((1R, 3S)-3-乙基氨基甲酰基-环戊基)-甲基-酰胺 ("A63")



LC/MS: M+H 387;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 7.75 (s, 1H; NH), 7.65 (td, $J = 8.9, 6.6$ Hz, 1H), 7.60 (d, $J = 6.8$ Hz, 2H), 7.48 (d, $J = 7.8$ Hz, 2H), 7.40 (ddd, $J = 11.6, 9.3, 2.6$ Hz, 1H), 7.23 (td, $J = 8.8, 2.3$ Hz, 1H), 4.84, 4.08 (2x br. s, 1H, 比率=1:1.7, 旋转异构体混合物), 3.07 (p, $J = 7.1$ Hz, 2H), 2.89 (s, 3H), 2.04 – 1.57 (m, 6H), 1.01 (t, $J = 7.2$ Hz, 3H);

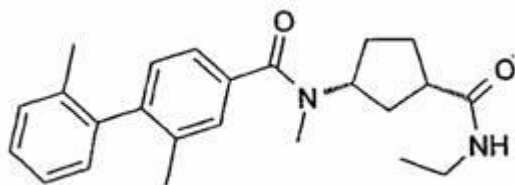
2'-三氟甲基-联苯-4-甲酸 ((1R, 3S)-3-乙基氨基甲酰基-环戊基)-甲基-酰胺 ("A64")



LC/MS: M+H 419;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 7.86 (d, $J = 7.7$ Hz, 1H), 7.82 – 7.69 (m, 2H), 7.65 (t, $J = 7.7$ Hz, 1H), 7.49 – 7.42 (m, 3H), 7.38 (d, $J = 8.0$ Hz, 2H), 4.88, 4.05 (2x br. s, 1H, 比率=1:1.5, 旋转异构体混合物), 3.07 (p, $J = 7.1$ Hz, 2H), 2.90 (s, 3H), 2.02 – 1.56 (m, 6H), 1.01 (t, $J = 7.2$ Hz, 3H);

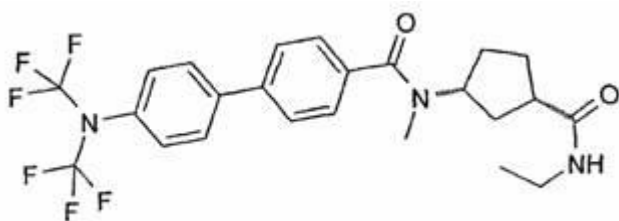
2, 2'-二甲基-联苯-4-甲酸 ((1R, 3S)-3-乙基氨基甲酰基-环戊基)-甲基-酰胺 ("A65")



LC/MS: M+H 379;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 7.77 (s, 1H; NH), 7.39 – 7.16 (m, 5H), 7.16 – 7.03 (m, 2H), 4.87, 4.14 (2x br. s, 1H, 比率=1:1.5, 旋转异构体混合物), 3.07 (p, $J = 7.2$ Hz, 2H), 2.89 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H), 2.00 – 1.58 (m, 6H), 1.01 (t, $J = 7.2$ Hz, 3H);

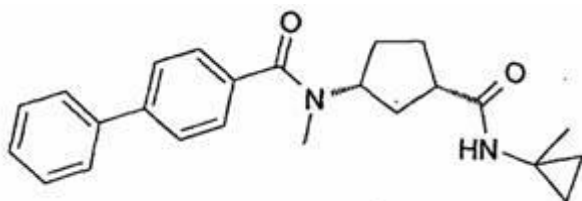
4'-(双-三氟甲基-氨基)-联苯-4-甲酸 ((1R, 3S)-3-乙基氨基甲酰基-环戊基)-甲基-酰胺 ("A66")



LC/MS: M+H 502;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 7.90 (d, $J = 8.6$ Hz, 2H), 7.79 (d, $J = 8.3$ Hz, 2H), 7.73 (s, 1H; NH), 7.63 (d, $J = 8.4$ Hz, 2H), 7.49 (d, $J = 7.8$ Hz, 2H), 4.82, 4.04 (2x br. s, 1H, 比率=1:1.8, 旋转异构体混合物), 3.06 (p, $J = 7.1$ Hz, 2H), 2.89 (s, 3H), 2.07 – 1.54 (m, 6H), 1.00 (t, $J = 7.2$ Hz, 3H);

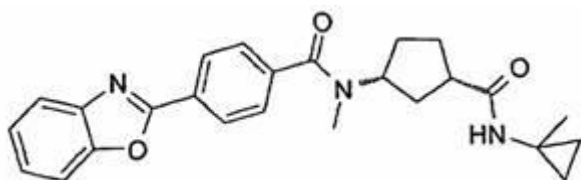
联苯-4-甲酸 甲基-[(1R, 3S)-3-(1-甲基-环丙基氨基甲酰基)-环戊基]-酰胺 ("A67")



LC/MS: M+H 377;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 7.95 (s, 1H; NH), 7.75 – 7.67 (m, 4H), 7.49 (t, J = 7.6 Hz, 2H), 7.45 (d, J = 7.8 Hz, 2H), 7.40 (t, J = 7.4 Hz, 1H), 4.83, 4.05 (2x br. s, 1H, 比率=1:1.8, 旋转异构体混合物), 2.88 (s, 3H), 2.47 – 2.23 (m, 1H), 2.11 – 1.45 (m, 6H), 1.25 (s, 3H), 0.64 – 0.41 (m, 4H);

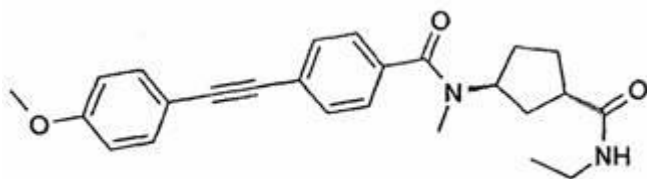
4- 苯并噁唑 -2- 基 -N- 甲基 -N-[(1R, 3S)-3-(1- 甲基 - 环丙基氨基甲酰基) - 环戊基] - 苯甲酰胺 (“A68”)



LC/MS: M+H 418;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.25 (d, J = 8.4 Hz, 2H), 7.94 (s, 1H; NH), 7.88 – 7.75 (m, 2H), 7.59 (d, J = 5.8 Hz, 2H), 7.51 – 7.35 (m, 2H), 4.86, 3.96 (2x br. s, 1H, 比率=1:1.7, 旋转异构体混合物), 2.90 (s, 3H), 2.45 – 2.23 (m, 1H), 2.09 – 1.42 (m, 6H), 1.25 (s, 3H), 0.66 – 0.36 (m, 4H);

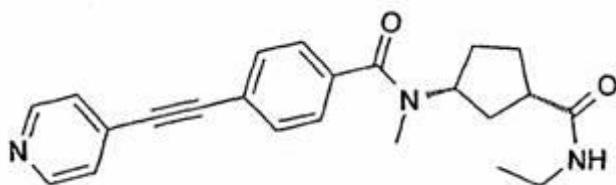
N-((1R, 3S)-3- 乙基氨基甲酰基 - 环戊基) -4-(4- 甲氧基 - 苯基乙炔基) -N- 甲基 - 苯甲酰胺 (“A69”)



LC/MS: M+H 405;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 7.73 (s, 1H; NH), 7.56 (d, J = 8.3 Hz, 2H), 7.51 (d, J = 8.9 Hz, 2H), 7.39 (d, J = 7.5 Hz, 2H), 7.00 (d, J = 8.9 Hz, 2H), 4.84, 3.97 (2x br. s, 1H, 比率=1:1.9, 旋转异构体混合物), 3.80 (s, 3H; CH_3O), 3.05 (p, J = 7.1 Hz, 2H), 2.86 (s, 3H), 2.01 – 1.49 (m, 6H), 1.00 (t, J = 7.2 Hz, 3H);

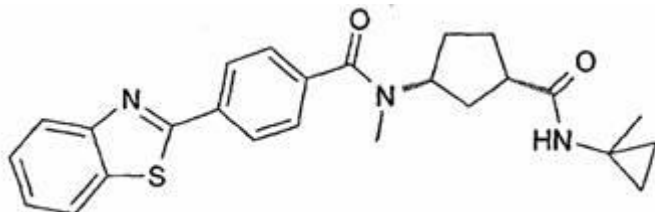
N-((1R, 3S)-3- 乙基氨基甲酰基 - 环戊基) -N- 甲基 -4- 吡啶 -4- 基乙炔基 - 苯甲酰胺 (“A70”)



LC/MS: M+H 376;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.65 (d, J = 6.0 Hz, 2H), 7.73 (s, 1H; NH), 7.67 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 6.1 Hz, 2H), 7.44 (d, J = 7.7 Hz, 2H), 4.83, 3.94 (2x br. s, 1H, 比率=1:1.9, 旋转异构体混合物), 3.11 – 3.00 (m, 2H), 2.86 (br. s, 3H), 2.10 – 1.49 (m, 6H), 1.00 (t, J = 7.2 Hz, 3H);

4- 苯并噻唑-2-基 -N- 甲基 -N-[(1R, 3S)-3-(1- 甲基 - 环丙基氨基甲酰基) - 环戊基] - 苯甲酰胺 (“A71”)

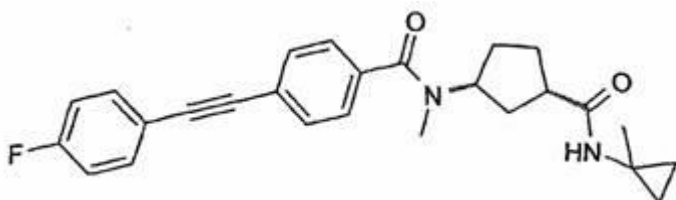


LC/MS: M+H 434;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.18 (d, J = 8.0 Hz, 1H), 8.15 (d, J = 8.4 Hz, 2H), 8.09 (d, J = 7.8 Hz, 1H), 7.94 (s, 1H; NH), 7.61 – 7.52 (m, 3H), 7.49 (t, J = 7.6 Hz, 1H), 4.84, 3.97 (2x br. s, 1H, 比率=1:1.6, 旋转异构体

混合物), 2.90 (br. s, 3H), 2.00 – 1.58 (m, 6H), 1.25 (s, 3H), 0.66 – 0.40 (m, 4H);

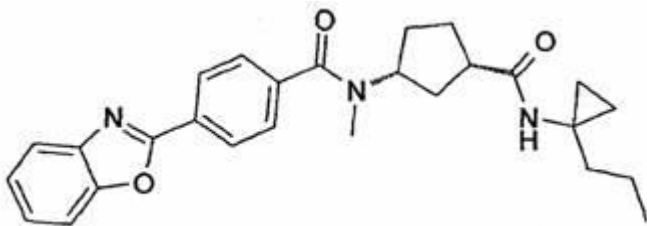
4-(4- 氟 - 苯基乙炔基) -N- 甲基 -N-[(1R, 3S)-3-(1- 甲基 - 环丙基氨基甲酰基) - 环戊基] - 苯甲酰胺 (“A72”)



LC/MS: M+H 419;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 7.94 (s, 1H; NH), 7.68 – 7.56 (m, 4H), 7.40 (d, J = 7.8 Hz, 2H), 7.28 (t, J = 8.9 Hz, 2H), 4.83, 3.92 (2x br. s, 1H, 比率=1:1.3, 旋转异构体混合物), 2.86 (s, 3H), 1.99 – 1.48 (m, 6H), 1.25 (s, 3H), 0.64 – 0.39 (m, 4H);

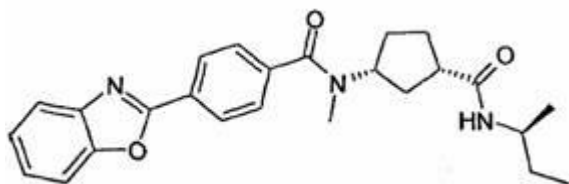
4- 苯并噁唑-2-基 -N- 甲基 -N-[(1R, 3S)-3-(1- 丙基 - 环丙基氨基甲酰基) - 环戊基] - 苯甲酰胺 (“A73”)



LC/MS: M+H 446;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.25 (d, J = 8.4 Hz, 2H), 7.89 (br. s, 1H; NH), 7.86 – 7.79 (m, 2H), 7.59 (d, J = 6.1 Hz, 2H), 7.45 (pd, J = 7.4, 1.4 Hz, 2H), 2.90 (s, 3H), 4.86, 3.95 (2x m, 1H, 比率=1:1.9, 旋转异构体混合物), 2.39 (br. s, 1H), 2.02 – 1.53 (m, 6H), 1.51 – 1.38 (m, 2H), 1.39 – 1.25 (m, 2H), 0.86 (t, J = 7.3 Hz, 3H), 0.60 – 0.39 (m, 4H);

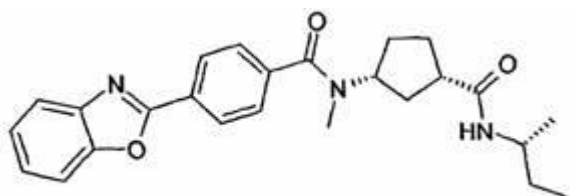
4-(1, 3- 苯并噁唑-2- 基)-N- 甲基-N-[(1R, 3S)-3-[[(1S)-1- 甲基丙基] 氨基甲酰基] 环戊基] 苯甲酰胺 (“A74”)



LC/MS: M+H 420;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.26 (d, J = 8.4 Hz, 2H), 7.83 (dd, J = 14.4, 7.3 Hz, 2H), 7.60 (d, J = 7.0 Hz, 2H), 7.50 (s, 1H; NH), 7.45 (pd, J = 7.4, 1.4 Hz, 2H), 4.85, 3.97 (2x br. s, 1H, 比率=1:1.7, 旋转异构体混合物), 3.65 (dt, J = 13.6, 6.7 Hz, 1H), 2.91 (br. s, 3H), 2.11 – 1.50 (m, 6H), 1.36 (p, J = 6.5 Hz, 2H), 1.00 (d, J = 6.2 Hz, 3H), 0.81 (t, J = 7.4 Hz, 3H);

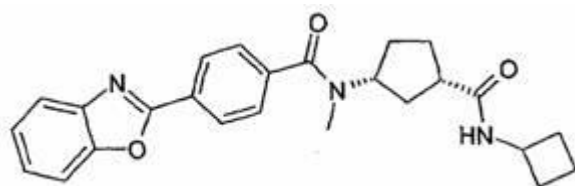
4-(1, 3- 苯并噁唑-2- 基)-N- 甲基-N-[(1R, 3S)-3-[[(1R)-1- 甲基丙基] 氨基甲酰基] 环戊基] 苯甲酰胺 (“A75”)



LC/MS: M+H 420;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.26 (d, J = 8.4 Hz, 2H), 7.83 (dd, J = 14.4, 7.3 Hz, 2H), 7.60 (d, J = 7.0 Hz, 2H), 7.50 (s, 1H; NH), 7.45 (pd, J = 7.4, 1.4 Hz, 2H), 4.85, 3.97 (2x br. s, 1H, 比率=1:1.7, 旋转异构体混合物), 3.65 (dt, J = 13.6, 6.7 Hz, 1H), 2.91 (br. s, 3H), 2.11 – 1.50 (m, 6H), 1.36 (p, J = 6.5 Hz, 2H), 1.00 (d, J = 6.2 Hz, 3H), 0.81 (t, J = 7.4 Hz, 3H);

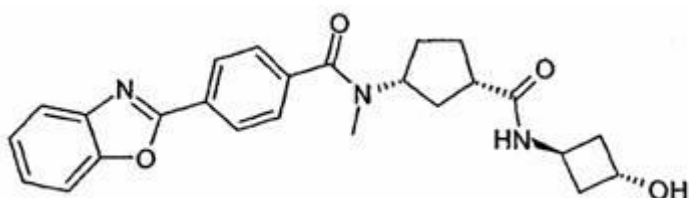
4-(1, 3- 苯并噁唑-2- 基)-N-[(1R, 3S)-3-(环丁基氨基甲酰基) 环戊基]-N- 甲基- 苯甲酰胺 (“A76”)



LC/MS: M+H 418;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.26 (d, J = 8.4 Hz, 2H), 7.99 (s, 1H; NH), 7.89 – 7.76 (m, 2H), 7.60 (d, J = 7.2 Hz, 2H), 7.45 (pd, J = 7.4, 1.4 Hz, 2H), 4.86, 3.98 (2x br. s, 1H, 比率=1:1.9, 旋转异构体混合物), 4.17 (h, J = 8.2 Hz, 1H), 2.90 (br. s, 3H), 2.22 – 2.04 (m, 2H), 2.02 – 1.48 (m, 10H);

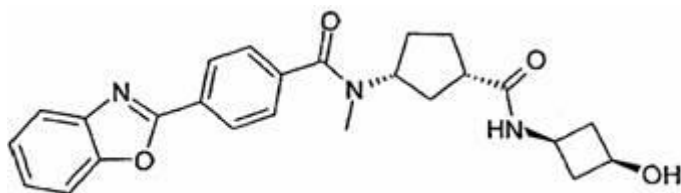
4-(1, 3- 苯并噁唑 -2- 基)-N-[(1R, 3S)-3-[(反式-3- 羟基环丁基) 氨基甲酰基] 环戊基]-N- 甲基 - 苯甲酰胺 (“A77”)



LC/MS: M+H 434;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.26 (d, J = 8.4 Hz, 2H), 7.98 (s, 1H; NH), 7.88 – 7.77 (m, 2H), 7.60 (d, J = 7.2 Hz, 2H), 7.45 (pd, J = 7.4, 1.4 Hz, 2H), 4.95 (d, J = 5.4 Hz, 1H), 4.89, 3.98 (2x br. s, 1H, 比率=1:1.7, 旋转异构体混合物), 4.22 (dt, J = 13.0, 3.8 Hz, 1H), 4.16 (q, J = 6.5 Hz, 1H), 2.90 (br. s, 3H), 2.19 – 1.95 (m, 4H), 1.99 – 1.53 (m, 6H);

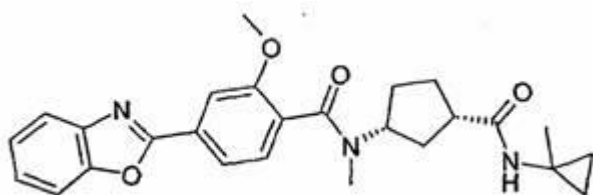
4-(1, 3- 苯并噁唑 -2- 基)-N-[(1R, 3S)-3-[(顺式-3- 羟基环丁基) 氨基甲酰基] 环戊基]-N- 甲基 - 苯甲酰胺 (“A78”)



LC/MS: M+H 434;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.26 (d, J = 8.4 Hz, 2H), 7.90 (s, 1H; NH), 7.83 (dd, J = 13.8, 8.0 Hz, 2H), 7.59 (d, J = 7.0 Hz, 2H), 7.45 (pd, J = 7.4, 1.4 Hz, 2H), 5.00 (d, J = 5.7 Hz, 1H; OH), 4.88, 3.98 (2x br. s, 1H, 比率=1:1.5, 旋转异构体混合物), 3.77 (h, J = 7.0 Hz, 1H), 3.65 (h, J = 8.5 Hz, 1H), 2.90 (br. s, 3H), 2.46 (d, J = 7.0 Hz, 2H), 2.03 – 1.49 (m, 8H);

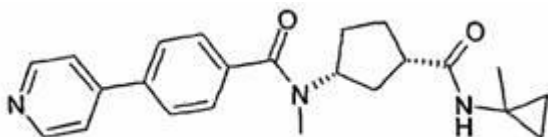
4-(1, 3- 苯并噁唑 -2- 基)-2- 甲氧基 -N- 甲基 -N-[(1R, 3S)-3-[(1- 甲基环丙基) 氨基甲酰基] 环戊基] 苯甲酰胺 (“A79”)



LC/MS: M+H 448;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 7.92, 7.89 (2x s, 1H, NH; 比率=1:1.9, 旋转异构体混合物), 7.87 – 7.75 (m, 4H), 7.45 (pd, J = 7.4, 1.4 Hz, 2H), 7.41 – 7.33 (m, 1H), 4.91, 3.80 (2x m, 1H, 比率=1:1.9, 旋转异构体混合物), 3.97 – 3.90 (m, 3H), 2.90, 2.69 (2x s, 3H, 比率=1:1.9, 旋转异构体混合物), 1.96 – 1.46 (m, 6H), 1.29 – 1.19 (m, 3H), 0.65 – 0.39 (m, 4H);

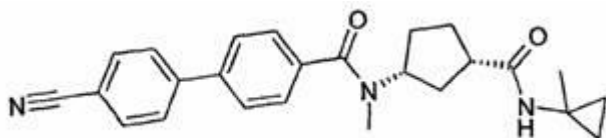
N-甲基-N-[(1R, 3S)-3-[(1-甲基环丙基)氨基甲酰基]环戊基]-4-(4-吡啶基)苯甲酰胺 (“A80”)



LC/MS: M+H 378;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.66 (d, J = 6.1 Hz, 2H), 7.94 (s, 1H; NH), 7.86 (d, J = 8.4 Hz, 2H), 7.75 (d, J = 6.2 Hz, 2H), 7.50 (d, J = 7.4 Hz, 2H), 4.85, 3.97 (2x br. s, 1H, 比率=1:1.7, 旋转异构体混合物), 2.88 (br. s, 3H), 2.08 – 1.45 (m, 6H), 1.25 (s, 3H), 0.64 – 0.41 (m, 4H);

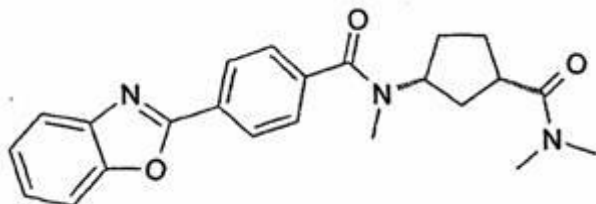
4-(4-氰基苯基)-N-甲基-N-[(1R, 3S)-3-[(1-甲基环丙基)氨基甲酰基]环戊基]苯甲酰胺 (“A81”)



LC/MS: M+H 402;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 7.97 – 7.90 (m, 5H), 7.81 (d, J = 8.4 Hz, 2H), 7.49 (d, J = 7.5 Hz, 2H), 2.88 (br. s, 3H), 4.82, 4.02 (2x br. s, 1H, 比率=1:1.8, 旋转异构体混合物), 2.08 – 1.45 (m, 6H), 1.25 (s, 3H), 0.63 – 0.40 (m, 4H);

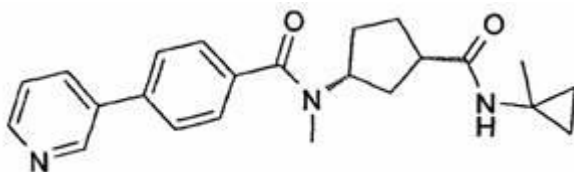
4-苯并噁唑-2-基-N-((1R, 3S)-3-二甲基氨基甲酰基-环戊基)-N-甲基-苯甲酰胺 (“A82”)



LC/MS: M+H 392;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.26 (d, $J = 8.3$ Hz, 2H), 7.83 (ddd, $J = 12.4, 7.0, 1.6$ Hz, 2H), 7.60 (d, $J = 7.3$ Hz, 2H), 7.45 (pd, $J = 7.4, 1.4$ Hz, 2H), 4.92, 4.00 (2x br. s, 1H, 比率=1:2.5, 旋转异构体混合物), 3.16 – 2.83 (m, 6H), 2.82 (s, 3H), 2.10 – 1.57 (m, 6H);

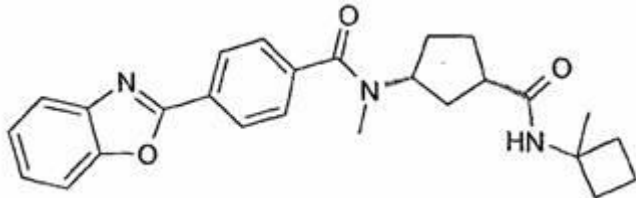
N- 甲基 -N-[(1R, 3S) -3-(1- 甲基 - 环丙基氨基甲酰基) - 环戊基]-4- 吡啶 -3- 基 - 苯甲酰胺 (“A83”)



LC/MS: M+H 378;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.93 (dd, $J = 2.4, 0.7$ Hz, 1H), 8.60 (dd, $J = 4.8, 1.6$ Hz, 1H), 8.12 (ddd, $J = 8.0, 2.4, 1.7$ Hz, 1H), 7.95 (s, 1H; NH), 7.79 (d, $J = 8.4$ Hz, 2H), 7.59 – 7.33 (m, 3H), 4.83, 4.04 (2x br. s, 1H, 比率=1:1.8, 旋转异构体混合物), 2.88 (s, 3H), 1.98 – 1.53 (m, 6H), 1.25 (s, 3H), 0.64 – 0.41 (m, 4H);

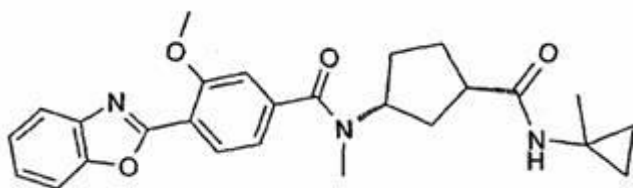
4- 苯并噁唑 -2- 基 -N- 甲基 -N-[(1R, 3S) -3-(1- 甲基 - 环丁基氨基甲酰基) - 环戊基]- 苯甲酰胺 (“A84”)



LC/MS: M+H 432;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.26 (d, $J = 8.4$ Hz, 2H), 7.87 – 7.78 (m, 2H), 7.74 (s, 1H; NH), 7.60 (d, $J = 7.8$ Hz, 2H), 7.51 – 7.37 (m, 2H), 2.90 (br. s, 3H), 4.84, 3.95 (2x br. s, 1H, 比率=1:1.5, 旋转异构体混合物), 2.26 – 2.12 (m, 2H), 2.01 – 1.60 (m, 10H), 1.34 (s, 3H);

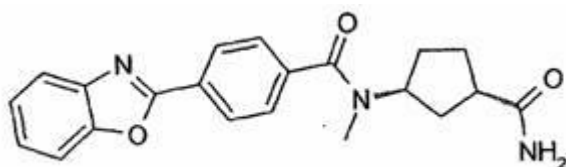
4- 苯并噁唑 -2- 基 -3- 甲氧基 -N- 甲基 -N-[(1R, 3S) -3-(1- 甲基 - 环丙基氨基甲酰基) - 环戊基]- 苯甲酰胺 (“A85”)



LC/MS: M+H 448;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.09 (d, $J = 7.9$ Hz, 1H), 7.96 (s, 1H; NH), 7.88 – 7.73 (m, 2H), 7.50 – 7.39 (m, 2H), 7.23 (s, 1H), 7.11 (d, $J = 7.9$ Hz, 1H), 3.98 (s, 3H), , 4.89, 4.02 (2x br. s, 1H, 比率=1:1.4, 旋转异构体混合物), 2.92 (br. s, 3H), 2.11 – 1.55 (m, 6H), 1.26 (s, 3H), 0.66 – 0.37 (m, 4H);

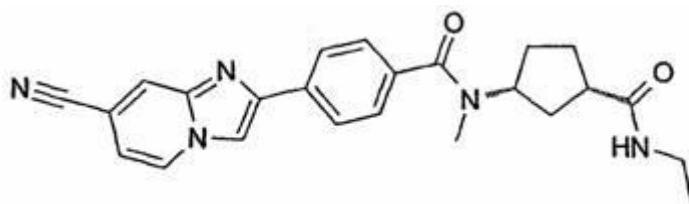
4- 苯并噁唑-2-基-N-((1R, 3S)-3-氨基甲酰基-环戊基)-N-甲基-苯甲酰胺 (“A86”)



LC/MS: M+H 364;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.26 (d, $J = 8.3$ Hz, 2H), 7.83 (ddd, $J = 13.1, 7.3, 1.7$ Hz, 2H), 7.60 (d, $J = 6.7$ Hz, 2H), 7.45 (pd, $J = 7.4, 1.3$ Hz, 2H), 7.23 (s, 1H; NH), 6.74 (s, 1H; NH), , 4.89, 3.99 (2x br. s, 1H, 比率=1:2.0, 旋转异构体混合物), 2.91 (br. s, 3H), 2.45 (br. s, 1H), 2.15 – 1.51 (m, 6H);

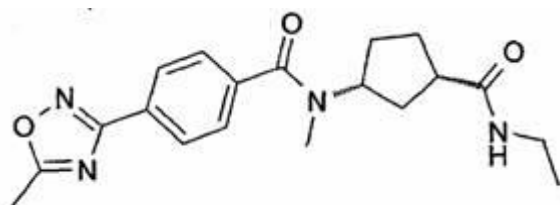
4-(7-氰基-咪唑并[1,2-a]吡啶-2-基)-N-((1R, 3S)-3-乙基氨基甲酰基-环戊基)-N-甲基-苯甲酰胺 (“A87”)



LC/MS: M+H 416;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.72 (d, $J = 7.0$ Hz, 1H), 8.69 (s, 1H), 8.36 (s, 1H), 8.06 (d, $J = 8.3$ Hz, 2H), 7.73 (s, 1H; NH), 7.47 (d, $J = 7.8$ Hz, 2H), 7.22 (dd, $J = 7.0, 1.6$ Hz, 1H), 4.85, 4.07 (2x br. s, 1H, 比率=1:2.0, 旋转异构体混合物), 3.05 (p, $J = 7.1$ Hz, 2H), 2.88 (br. s, 3H), 2.01 – 1.51 (m, 6H), 1.00 (t, $J = 7.2$ Hz, 3H);

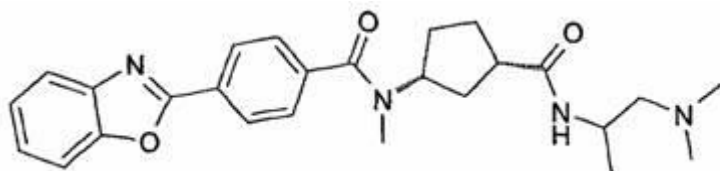
N-((1R, 3S)-3-乙基氨基甲酰基-环戊基)-N-甲基-4-(5-甲基-[1,2,4]噁二唑-3-基)-苯甲酰胺 (“A88”)



LC/MS: M+H 357;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.04 (d, J = 8.3 Hz, 2H), 7.72 (s, 1H; NH), 7.54 (d, J = 7.2 Hz, 2H), 4.88, 3.96 (2x br. s, 1H, 比率=1:1.7, 旋转异构体混合物), 3.05 (p, J = 7.1 Hz, 2H), 2.89 (br. s, 3H), 2.68 (s, 3H), 2.42 (br. s, 1H), 2.06 – 1.49 (m, 6H), 0.99 (t, J = 7.1 Hz, 3H);

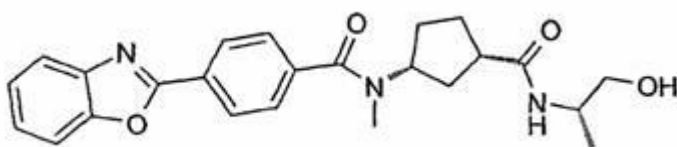
4- 苯并噁唑-2-基 -N-[(1R, 3S)-3-(2- 二甲基氨基-1- 甲基- 乙基氨基甲酰基)- 环戊基]-N- 甲基- 苯甲酰胺 (“A89”)



LC/MS: M+H 449;

^1H NMR (400 MHz, DMSO- d_6 + CF_3COOD) δ [ppm] 8.31 (d, J = 8.1 Hz, 2H), 7.84 (d, J = 7.2 Hz, 1H), 7.78 (d, J = 8.1 Hz, 1H), 7.61 (d, J = 7.4 Hz, 2H), 7.45 (p, J = 7.3 Hz, 2H), 4.95, 4.09 (2x br. s, 1H, 比率=1:1.8, 旋转异构体混合物), 4.35 – 4.17 (m, 1H), 3.13 (d, J = 4.8 Hz, 2H), 2.95 (s, 3H), 2.85 (s, 3H), 2.83 (s, 3H), 2.18 – 1.60 (m, 6H), 1.19 – 1.03 (m, 3H);

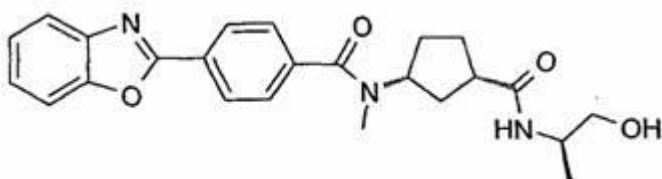
4- 苯并噁唑-2-基 -N-[(1R, 3S)-3-((S)-2- 羟基-1- 甲基- 乙基氨基甲酰基)- 环戊基]-N- 甲基- 苯甲酰胺 (“A90”)



LC/MS: M+H 422;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.26 (d, J = 8.2 Hz, 2H), 7.83 (dd, J = 14.3, 7.3 Hz, 2H), 7.60 (d, J = 6.4 Hz, 2H), 7.54 – 7.39 (m, 3H), 4.88, 3.99 (2x br. s, 1H, 比率=1:1.7, 旋转异构体混合物), 4.61 (t, J = 5.4 Hz, 1H; OH), 3.85 – 3.64 (m, 1H), 3.40 – 3.29 (m, 1H), 3.26 – 3.12 (m, 1H), 2.91 (br. s, 3H), 2.15 – 1.45 (m, 6H), 1.00 (d, J = 6.0 Hz, 3H);

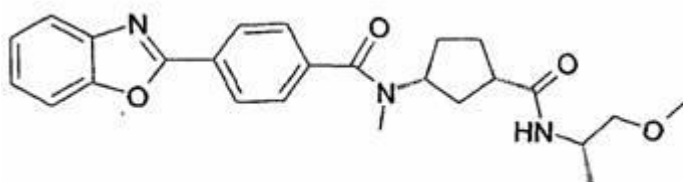
4- 苯并噁唑-2-基 -N-[(1R, 3S)-3-((R)-2- 羟基-1- 甲基- 乙基氨基甲酰基)- 环戊基]-N- 甲基- 苯甲酰胺 (“A91”)



LC/MS: M+H 422;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.26 (d, J = 8.2 Hz, 2H), 7.83 (dd, J = 14.3, 7.3 Hz, 2H), 7.60 (d, J = 6.4 Hz, 2H), 7.54 – 7.39 (m, 3H), 4.88, 3.99 (2x br. s, 1H, 比率=1:1.7, 旋转异构体混合物), 4.61 (t, J = 5.4 Hz, 1H; OH), 3.85 – 3.64 (m, 1H), 3.40 – 3.29 (m, 1H), 3.26 – 3.12 (m, 1H), 2.91 (br. s, 3H), 2.15 – 1.45 (m, 6H), 1.00 (d, J = 6.0 Hz, 3H);

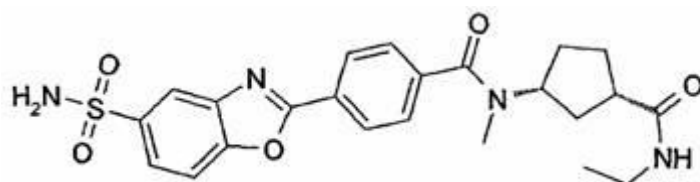
4- 苯并噁唑 -2- 基 -N-[(1R, 3S)-3-((S)-2- 甲氧基 -1- 甲基 - 乙基氨基甲酰基) - 环戊基]-N- 甲基 - 苯甲酰胺 (“A92”)



LC/MS: M+H 436;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.26 (d, J = 8.3 Hz, 2H), 7.87 – 7.78 (m, 2H), 7.71 – 7.53 (m, 3H), 7.45 (pd, J = 7.4, 1.4 Hz, 2H), 4.87, 3.98 (2x br. s, 1H, 比率=1:1.9, 旋转异构体混合物), 3.91 (p, J = 6.7 Hz, 1H), 3.27 – 3.24 (m, 1H), 3.24 (s, 3H; CH_3O), 3.15 (dd, J = 9.4, 6.1 Hz, 1H), 2.89 (br. s, 3H), 2.08 – 1.53 (m, 6H), 1.01 (d, J = 6.4 Hz, 3H);

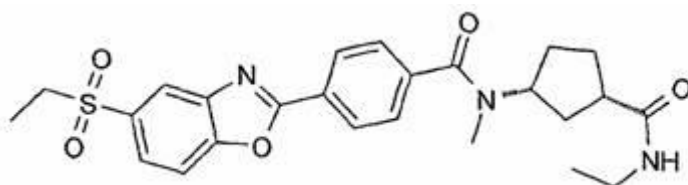
N-((1R, 3S)-3- 乙基氨基甲酰基 - 环戊基)-N- 甲基-4-(5- 氨磺酰基 - 苯并噁唑 -2- 基)- 苯甲酰胺 (“A93”)



LC/MS: M+H 471;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.29 (d, J = 8.3 Hz, 2H), 8.23 (d, J = 1.6 Hz, 1H), 8.01 (d, J = 8.6 Hz, 1H), 7.93 (dd, J = 8.6, 1.8 Hz, 1H), 7.72 (s, 1H; NH), 7.62 (d, J = 6.5 Hz, 2H), 7.47 (s, 2H; NH_2), 1H; NH), 7.63 (d, J = 6.6 Hz, 2H), 4.90, 3.97 (2x m, 1H, 比率=1:1.8, 旋转异构体混合物), 3.05 (p, J = 6.9 Hz, 2H), 2.92 (bt. s, 3H), 2.42 (br. s, 1H), 2.12 – 1.46 (m, 6H), 1.00 (t, J = 7.1 Hz, 3H);

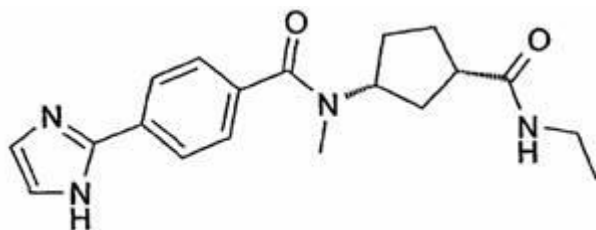
4-(5- 乙磺酰基 - 苯并噁唑 -2- 基)-N-((1R, 3S)-3- 乙基氨基甲酰基 - 环戊基)-N- 甲基 - 苯甲酰胺 (“A94”)



LC/MS: M+H 484;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.34 (d, $J = 1.7$ Hz, 1H), 8.30 (d, $J = 8.3$ Hz, 1H), 8.10 (d, $J = 8.6$ Hz, 1H), 7.98 (dd, $J = 8.6, 1.8$ Hz, 1H), 7.72 (br. s, 1H; NH), 7.63 (d, $J = 6.6$ Hz, 2H), 4.90, 3.97 (2x m, 1H, 比率=1:1.6, 旋转异构体混合物), 3.39 (q, $J = 7.3$ Hz, 2H), 3.06 (p, $J = 6.9, 6.5$ Hz, 2H), 2.92 (br. s, 3H), 2.41 (br. s, 1H), 2.07 – 1.50 (m, 6H), 1.14 (t, $J = 7.3$ Hz, 3H), 1.00 (t, $J = 7.1$ Hz, 3H);

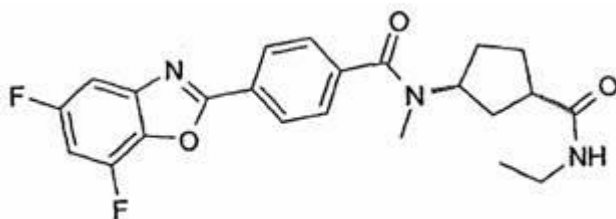
N-((1R, 3S)-3-乙基氨基甲酰基-环戊基)-4-(1H-咪唑-2-基)-N-甲基-苯甲酰胺 (“A95”)



LC/MS: M+H 341;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 12.59 (s, 1H; NH), 7.99 (d, $J = 8.3$ Hz, 2H), 7.75 (s, 1H; NH), 7.44 (d, $J = 7.7$ Hz, 2H), 7.29 (s, 1H), 7.07 (s, 1H), 4.85, 4.05 (2x br. s, 1H, 比率=1:2.0, 旋转异构体混合物), 3.07 (p, $J = 7.1$ Hz, 2H), 2.88 (br. s, 3H), 2.46 (br. s, 1H), 2.00 – 1.55 (m, 6H), 1.01 (t, $J = 7.2$ Hz, 3H);

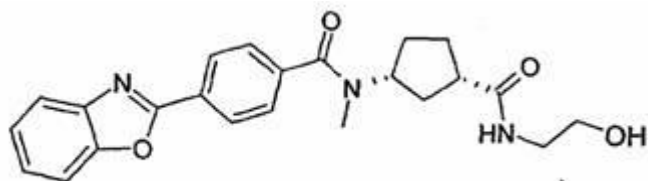
4-(5, 7-二氟-苯并噁唑-2-基)-N-((1R, 3S)-3-乙基氨基甲酰基-环戊基)-N-甲基-苯甲酰胺 (“A96”)



LC/MS: M+H 428;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.27 (d, $J = 8.4$ Hz, 2H), 7.74 (s, 1H; NH), 7.66 (dd, $J = 8.4, 2.0$ Hz, 1H), 7.61 (d, $J = 3.2$ Hz, 2H), 7.51 (td, $J = 10.3, 2.3$ Hz, 1H), 4.89, 3.96 (2x m, 1H, 比率=1:1.5, 旋转异构体混合物), 3.05 (q, $J = 7.0, 5.9$ Hz, 2H), 2.91 (br. s, 3H), 2.43 (br. s, 1H), 2.09 – 1.48 (m, 6H), 0.99 (t, $J = 7.1$ Hz, 3H);

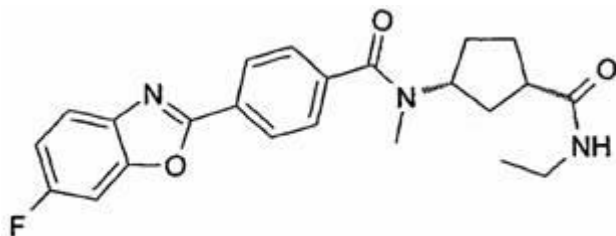
4- 苯并噁唑-2-基-N-[(1R, 3S)-3-(2-羟基-乙基氨基甲酰基)-环戊基]-N-甲基-苯甲酰胺 (“A97”)



LC/MS: M+H 407;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.27 (d, J = 8.4 Hz, 2H), 7.89 – 7.81 (m, 2H), 7.77 (s, 1H; NH), 7.61 (d, J = 7.4 Hz, 2H), 7.53 – 7.39 (m, 2H), 4.63 (t, J = 5.4 Hz, 1H; OH), 4.91, 4.00 (2x m, 1H, 比率=1:1.7, 旋转异构体混合物), 3.39 (q, J = 5.7 Hz, 2H), 3.12 (q, J = 5.8 Hz, 2H), 2.92 (br. s, 3H), 2.19 – 1.47 (m, 6H);

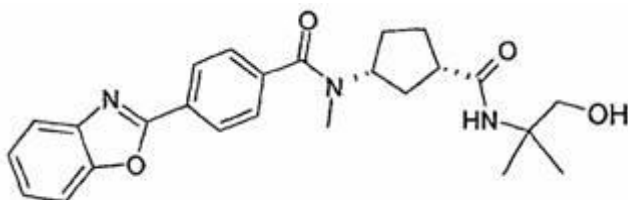
N-((1R, 3S)-3-乙基氨基甲酰基-环戊基)-4-(6-氟-苯并噁唑-2-基)-N-甲基-苯甲酰胺 (“A98”)



LC/MS: M+H 410;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.22 (d, J = 8.3 Hz, 2H), 7.86 (dd, J = 8.8, 5.0 Hz, 1H), 7.82 (dd, J = 8.4, 2.4 Hz, 1H), 7.72 (s, 1H; NH), 7.60 (d, J = 6.8 Hz, 2H), 7.31 (ddd, J = 9.9, 8.9, 2.5 Hz, 1H), 4.89, 3.97 (2x br. s, 1H, 比率=1:1.6, 旋转异构体混合物), 3.05 (p, J = 6.8 Hz, 2H), 2.91 (br. s, 3H), 2.07 – 1.52 (m, 6H), 1.00 (t, J = 7.1 Hz, 3H);

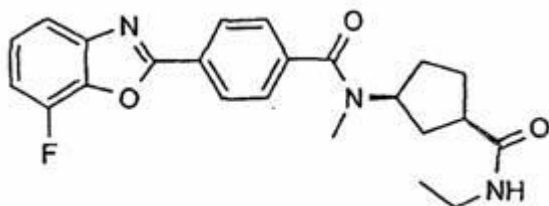
4- 苯并噁唑-2-基-N-[(1R, 3S)-3-(2-羟基-1, 1-二甲基-乙基氨基甲酰基)-环戊基]-N-甲基-苯甲酰胺 (“A99”)



LC/MS: M+H 436;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.27 (d, J = 8.4 Hz, 2H), 7.90 – 7.78 (m, 2H), 7.61 (d, J = 7.7 Hz, 2H), 7.54 – 7.40 (m, 2H), 7.20 (s, 1H; NH), 4.83 (s, 1H; OH), 4.86, 3.97 (2x m, 1H, 比率=1:1.7, 旋转异构体混合物), 3.38 (d, J = 5.7 Hz, 2H), 2.91 (br. s, 3H), 2.12 – 1.46 (m, 6H), 1.17 (s, 6H);

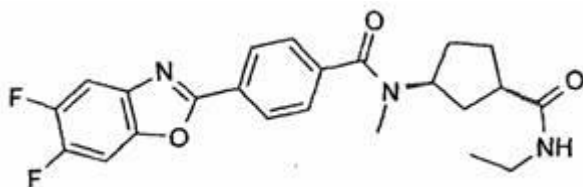
N-((1R, 3S)-3-乙基氨基甲酰基-环戊基)-4-(7-氟-苯并噁唑-2-基)-N-甲基-苯甲酰胺 ("A100")



LC/MS: M+H 410;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.27 (d, J = 8.3 Hz, 2H), 7.73 (s, 1H; NH), 7.69 (d, J = 7.8 Hz, 1H), 7.61 (d, J = 6.8 Hz, 2H), 7.48 – 7.34 (m, 2H), 4.89, 3.98 (2x br. s, 1H, 比率=1:1.7, 旋转异构体混合物), 3.06 (p, J = 6.6 Hz, 2H), 2.91 (br. s, 3H), 2.42 (br. s, 1H), 2.07 – 1.52 (m, 6H), 1.00 (t, J = 7.1 Hz, 3H);

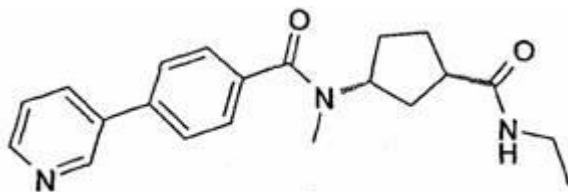
4-(5,6-二氟-苯并噁唑-2-基)-N-((1R, 3S)-3-乙基氨基甲酰基-环戊基)-N-甲基-苯甲酰胺 ("A101")



LC/MS: M+H 428;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.22 (d, J = 8.2 Hz, 2H), 8.14 (dd, J = 9.8, 6.9 Hz, 1H), 8.02 (dd, J = 10.2, 7.6 Hz, 1H), 7.74 (s, 1H; NH), 7.60 (d, J = 7.1 Hz, 2H), 4.89, 3.97 (2x br. s, 1H, 比率=1:1.5, 旋转异构体混合物), 3.05 (p, J = 6.9 Hz, 2H), 2.91 (br. s, 3H), 2.42 (br. s, 1H), 2.12 – 1.46 (m, 6H), 1.00 (t, J = 7.1 Hz, 3H);

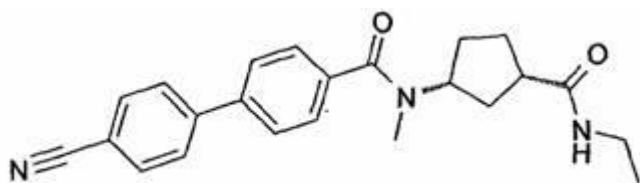
N-((1R, 3S)-3-乙基氨基甲酰基-环戊基)-N-甲基-4-吡啶-3-基-苯甲酰胺 ("A102")



LC/MS: M+H 352;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.93 (d, J = 1.9 Hz, 1H), 8.60 (dd, J = 4.8, 1.6 Hz, 1H), 8.12 (dt, J = 8.0, 2.0 Hz, 1H), 7.80 (d, J = 8.3 Hz, 2H), 7.74 (s, 1H; NH), 7.54 – 7.44 (m, 3H), 4.84, 4.07 (2x br. s, 1H, 比率=1:2.0, 旋转异构体混合物), 3.06 (p, J = 7.2 Hz, 2H), 2.89 (b. s, 3H), 2.00 – 1.55 (m, 6H), 1.00 (t, J = 7.2 Hz, 3H);

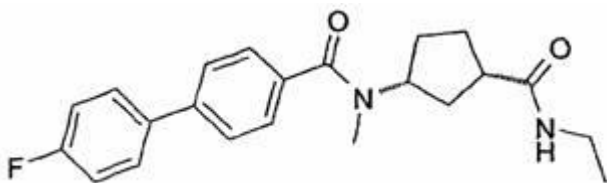
4'-氰基-联苯-4-甲酸 ((1R, 3S)-3-乙基氨基甲酰基-环戊基)-甲基-酰胺 ("A103")



LC/MS: M+H 376;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 7.99 – 7.91 (m, 4H), 7.83 (d, J = 8.4 Hz, 2H), 7.76 (s, 1H; NH), 7.51 (d, J = 7.9 Hz, 2H), 4.87, 4.05 (2x br. s, 1H, 比率=1:1.6, 旋转异构体混合物), 3.07 (p, J = 7.1 Hz, 2H), 2.90 (br. s, 3H), 2.01 – 1.59 (m, 6H), 1.01 (t, J = 7.2 Hz, 3H);

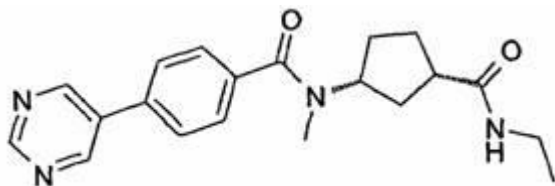
4'-氟-联苯-4-甲酸 ((1R, 3S)-3-乙基氨基甲酰基-环戊基)-甲基-酰胺 ("A104")



LC/MS: M+H 369;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 7.85 – 7.67 (m, 5H), 7.46 (d, J = 7.9 Hz, 2H), 7.32 (t, J = 8.9 Hz, 2H), 4.82, 4.07 (2x br. s, 1H, 比率=1:1.6, 旋转异构体混合物), 3.07 (p, J = 7.1 Hz, 2H), 2.89 (br. s, 3H), 1.98 – 1.51 (m, 6H), 1.01 (t, J = 7.2 Hz, 3H);

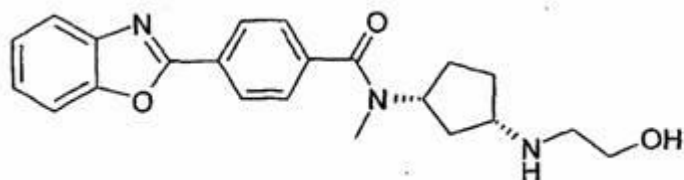
N-((1R, 3S)-3-乙基氨基甲酰基-环戊基)-N-甲基-4-嘧啶-5-基-苯甲酰胺 ("A105")



LC/MS: M+H 353;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 9.21 (s, 1H), 9.19 (s, 2H), 7.88 (d, J = 8.4 Hz, 2H), 7.75 (s, 1H; NH), 7.52 (d, J = 7.8 Hz, 2H), 4.85, 4.03 (2x br. s, 1H, 比率=1:1.7, 旋转异构体混合物), 3.18 – 2.97 (m, 2H), 2.89 (br. s, 3H), 1.99 – 1.52 (m, 6H), 1.11 – 0.89 (m, 3H);

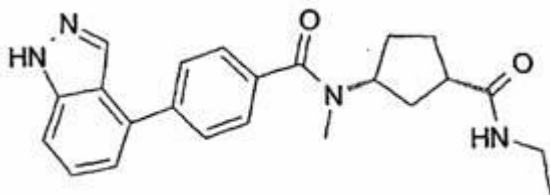
4-苯并噁唑-2-基-N-[(1R, 3S)-3-(2-羟基-乙基氨基甲酰基)-环戊基]-N-甲基-苯甲酰胺 ("A106")



LC/MS: M+H 408;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.27 (d, $J = 8.4$ Hz, 2H), 7.88 – 7.81 (m, 2H), 7.78 (s, 1H; NH), 7.61 (d, $J = 7.4$ Hz, 2H), 7.51 – 7.40 (m, 2H), 4.89, 4.00 (2x br. s, 1H, 比率=1:1.8, 旋转异构体混合物), 4.63 (t, $J = 5.4$ Hz, 1H; OH), 3.39 (q, $J = 5.7$ Hz, 2H), 3.12 (q, $J = 5.8$ Hz, 2H), 2.92 (br. s, 3H), 2.11 – 1.50 (m, 6H);

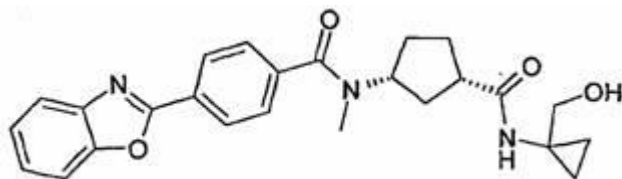
N-((1R, 3S)-3-乙基氨基甲酰基-环戊基)-4-(1H-吡唑-4-基)-N-甲基-苯甲酰胺 (“A107”)



LC/MS: M+H 391;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 13.25 (s, 1H; NH), 8.21 (s, 1H), 7.80 (d, $J = 8.2$ Hz, 2H), 7.74 (s, 1H; NH), 7.58 (d, $J = 8.3$ Hz, 1H), 7.52 (d, $J = 7.8$ Hz, 2H), 7.48 – 7.43 (m, 1H), 7.28 (d, $J = 6.9$ Hz, 1H), 4.85, 4.16 (2x br. s, 1H, 比率=1:2.4, 旋转异构体混合物), 3.06 (p, $J = 7.2$ Hz, 2H), 2.91 (s, 3H), 2.04 – 1.58 (m, 6H), 1.00 (t, $J = 7.2$ Hz, 3H);

4-苯并噁唑-2-基-N-[(1R, 3S)-3-(1-羟基甲基-环丙基氨基甲酰基)-环戊基]-N-甲基-苯甲酰胺 (“A108”)



LC/MS: M+H 434;

^1H NMR (400 MHz, DMSO- d_6) δ [ppm] 8.26 (d, $J = 8.4$ Hz, 2H), 8.04 (s, 1H; NH), 7.88 – 7.79 (m, 2H), 7.59 (d, $J = 7.1$ Hz, 2H), 7.50 – 7.41 (m, 2H), 4.86, 3.96 (2x br. s, 1H, 比率=1:1.6, 旋转异构体混合物), 4.66 (t, $J = 5.6$ Hz, 1H; OH), 3.40 (d, $J = 5.6$ Hz, 2H), 2.90 (br. s, 3H), 2.42 (br. s, 1H), 2.11 – 1.47 (m, 6H), 0.65 (s, 2H), 0.52 (s, 2H)。

[0147] 药理学数据

表 2 式 I 的一些代表性化合物的 FASN 的抑制率。

化合物 编号	IC ₅₀ FASN (酶分析)	化合物编号	IC ₅₀ FASN (酶分析)
"A1"	A	"A61"	A
"A2"	A	"A62"	A
"A3"		"A63"	A
"A4"	B	"A64"	A
"A5"	A	"A65"	A
"A6"	A	"A66"	
"A7"	A	"A67"	A
"A8"		"A68"	A
"A9"		"A69"	A

"A11"	A	"A70"	A
"A44"	A	"A71"	A
"A45"	A	"A72"	A
"A46"	A	"A73"	B
"A47"	B	"A74"	A
"A48"	B	"A75"	A
"A49"	A	"A76"	A
"A50"	A	"A77"	A
"A51"	A	"A78"	A
"A52"	C	"A79"	B
"A53"	A	"A80"	A
"A54"	A	"A81"	A
"A55"	A	"A82"	B
"A56"	A	"A83"	A
"A57"	A	"A84"	A
"A58"	A	"A85"	A
"A59"	A	"A86"	B
"A60"	C	"A87"	B
"A88"	C	"A101"	A
"A90"	B	"A102"	A
"A91"	A	"A103"	A
"A92"	B	"A104"	A
"A93"	C	"A106"	A
"A96"	A	"A107"	A
"A97"	A	"A108"	B
"A98"	A		
"A99"	B		
"A100"	A		

IC₅₀: < 0.3 μ M = A 0.3 - 3 μ M = B 3-50 μ M = C

[0148] 表 2 中示出的化合物是本发明的特别优选的化合物。

[0149] 以下实施例涉及药物：

实施例 A：注射小瓶

使用 2N 盐酸，将 3 升重蒸馏水中 100 g 式 I 的活性成分和 5 g 磷酸氢二钠的溶液调节至 pH 6.5，无菌过滤，转移到注射小瓶中，在无菌条件下冷冻干燥，并在无菌条件下密封。每

个注射小瓶包含 5 mg 活性成分。

[0150] 实施例 B :栓剂

将 20 g 式 I 的活性成分与 100 g 大豆卵磷脂和 1400 g 可可脂的混合物融化,倒入模具中,冷却。每个栓剂包含 20 mg 活性成分。

[0151] 实施例 C :溶液剂

在 940 ml 重蒸馏水中,从 1 g 式 I 的活性成分、9.38 g $\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$ 、28.48 g $\text{Na}_2\text{HPO}_4 \cdot 12 \text{H}_2\text{O}$ 和 0.1 g 苯扎氯铵制备溶液剂。将 pH 值调节至 6.8,并将溶液剂补充至 1 升,照射消毒。该溶液剂可以以滴眼剂形式使用。

[0152] 实施例 D :软膏剂

在无菌条件下,将 500 mg 式 I 的活性组分与 99.5 g 凡士林混合。

[0153] 实施例 E :片剂

将 1 kg 式 I 的活性成分、4 kg 乳糖、1.2 kg 马铃薯淀粉、0.2 kg 滑石和 0.1 kg 硬脂酸镁的混合物用常规方式压制,得到片剂,从而使得每个片剂包含 10 mg 活性成分。

[0154] 实施例 F :糖锭

类似于实施例 E,压制片剂,随后用蔗糖、马铃薯淀粉、滑石、黄芪胶和染料的包衣料,用常规方式包衣。

[0155] 实施例 G :胶囊剂

用常规方式将 2 kg 式 I 的活性成分引入硬明胶胶囊中,从而使得每个胶囊剂包含 20 mg 活性成分。

[0156] 实施例 H :安瓿剂

将 60 升重蒸馏水中 1 kg 式 I 的活性成分的溶液无菌过滤,转移到安瓿中,在无菌条件下冷冻干燥,并在无菌条件下密封。每个安瓿剂包含 10 mg 活性成分。