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(54) **NOVEL SALTS AS ANTI-INFLAMMATORY, IMMUNOMODULATORY AND ANTI-PROLIFERATORY AGENTS**

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C07D 413/02	(2006.01)
A61P 29/00	(2006.01)
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A61P 33/02	(2006.01)
A61P 31/12	(2006.01)
A61P 31/04	(2006.01)
A61P 27/02	(2006.01)
A61P 11/06	(2006.01)
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A61P 19/04	(2006.01)
A61P 1/00	(2006.01)
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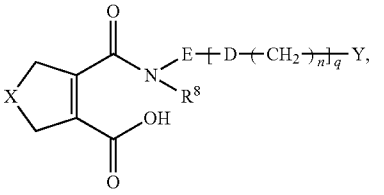
(57) **ABSTRACT**

The present invention relates to a salt selected from the group comprising the N-methyl-D-glucamine salt (NMG), the diethylamine salt (DEA) salt, the magnesium salt, the tromethamine salt, the choline salt, the L-arginine salt, the zinc salt, and the 4-(2-hydroxyethyl)morpholine (HEM) salt of compounds of the general formula (I)



wherein

X is selected from the group consisting of CH_2, S, or O;

D is O or S;

R^8 is hydrogen or alkyl;

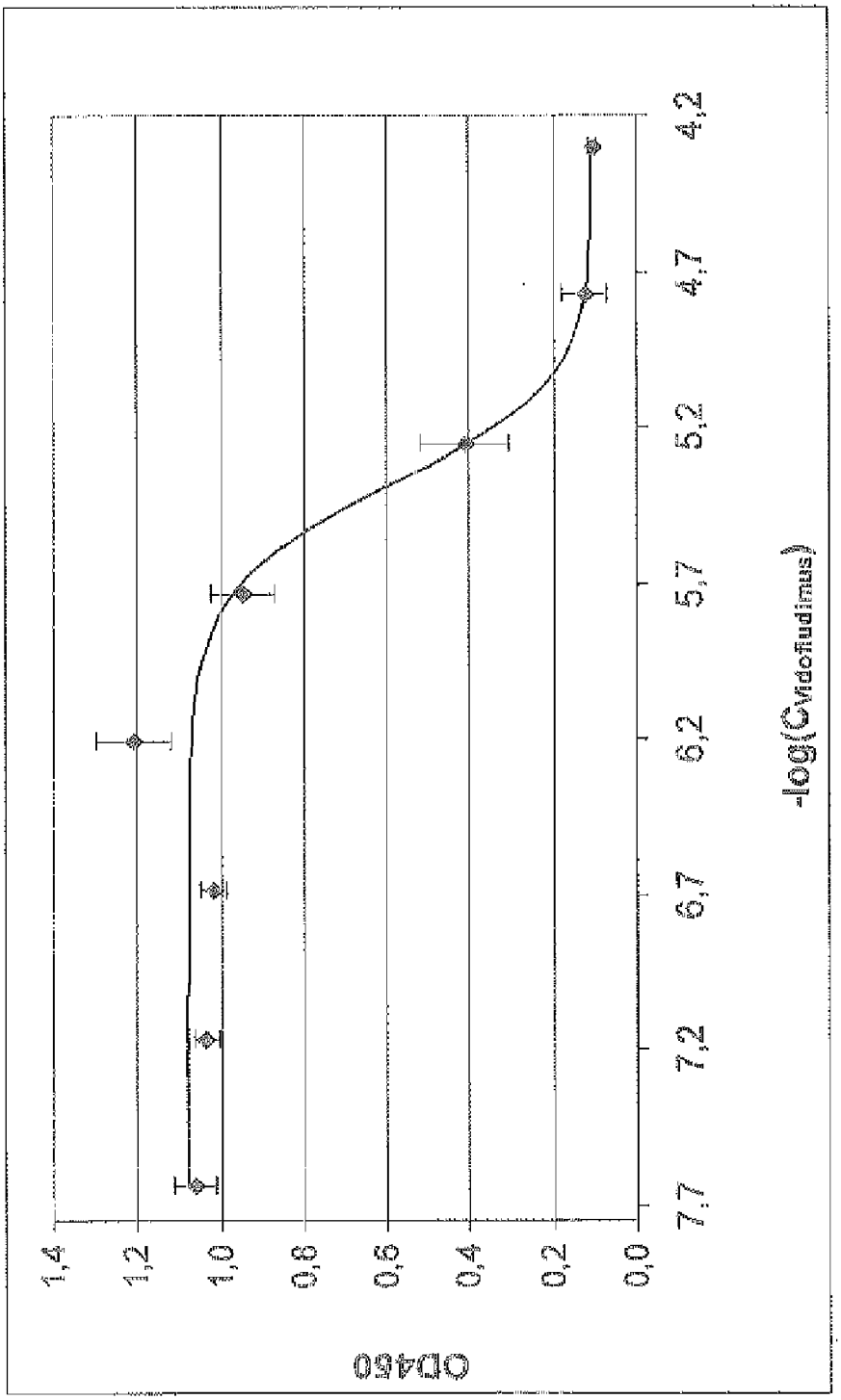
E is an optionally substituted phenylene group;

Y is a monocyclic or bicyclic substituted or unsubstituted 6-9 membered ring system which may contain one or more heteroatoms selected from N or S and which contains at least one aromatic ring;

n is 0 or 1; and

q is 0 or 1;

with the proviso that compounds wherein X=CH_2, q=0, Y=unsubstituted phenyl and E=unsubstituted phenylene are excluded; or a hydrate thereof.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0,2
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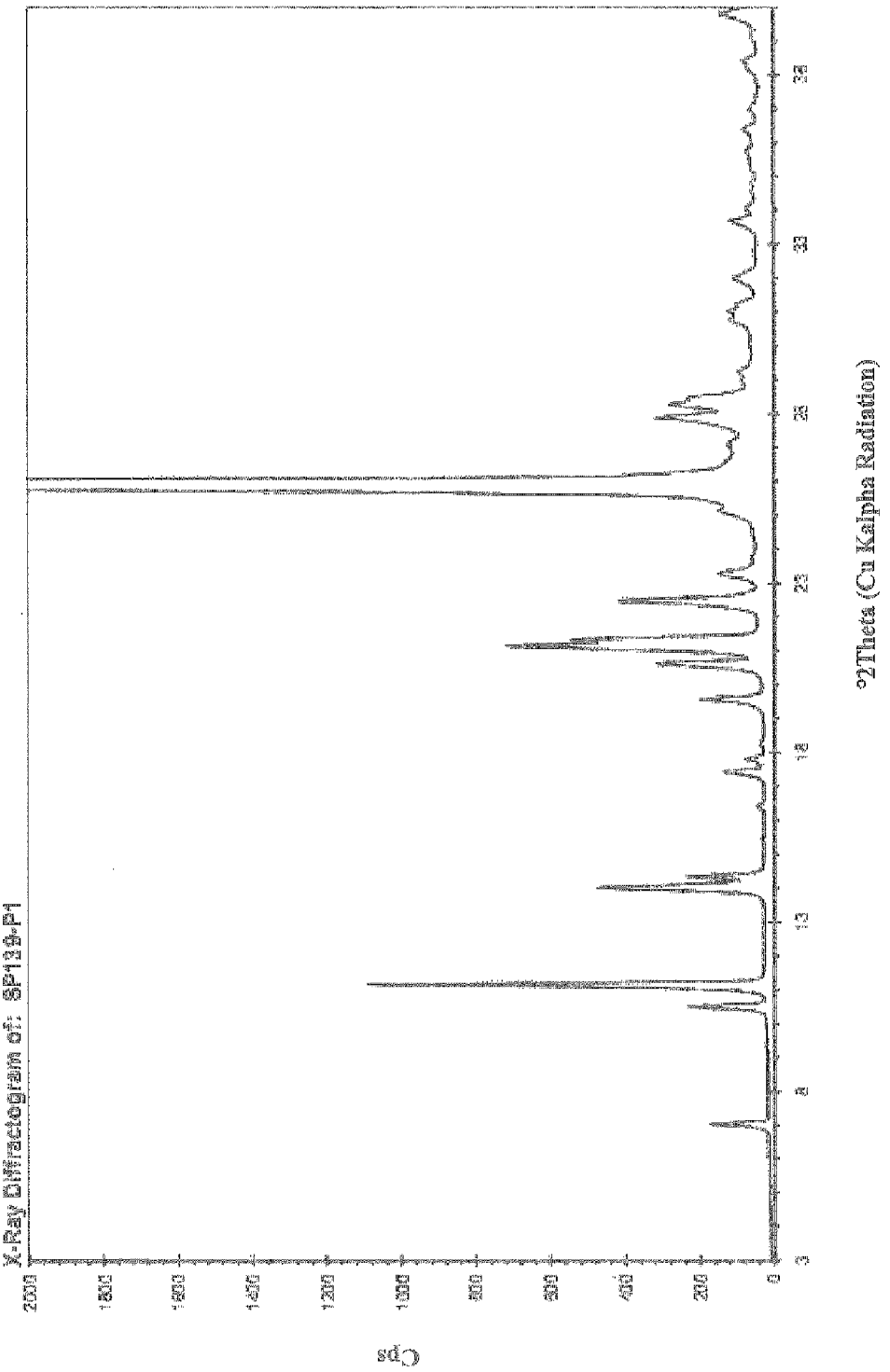
7,7
7,2
6,7
6,2
5,7
5,2
4,7
4,2
-log(Cvidofludimus)

Fig. 1:

Fig. 2: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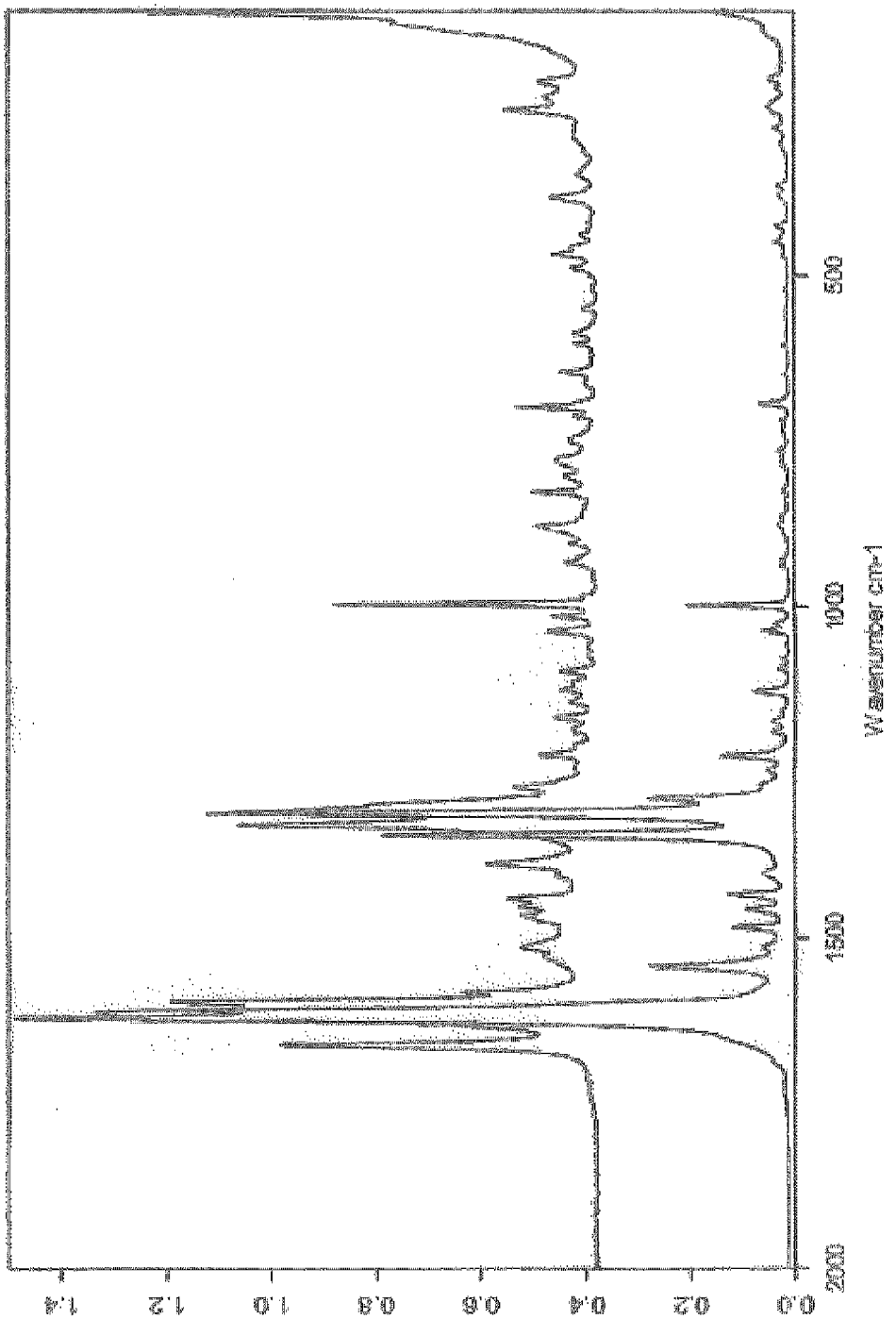
Cps
°2Theta (Cu Kalpha Radiation)


Raman intensity
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0.4
0.6
0.8
1.0
1.2
1.4
2000
1500
1000
500
Wavenumber cm-1

Fig. 3

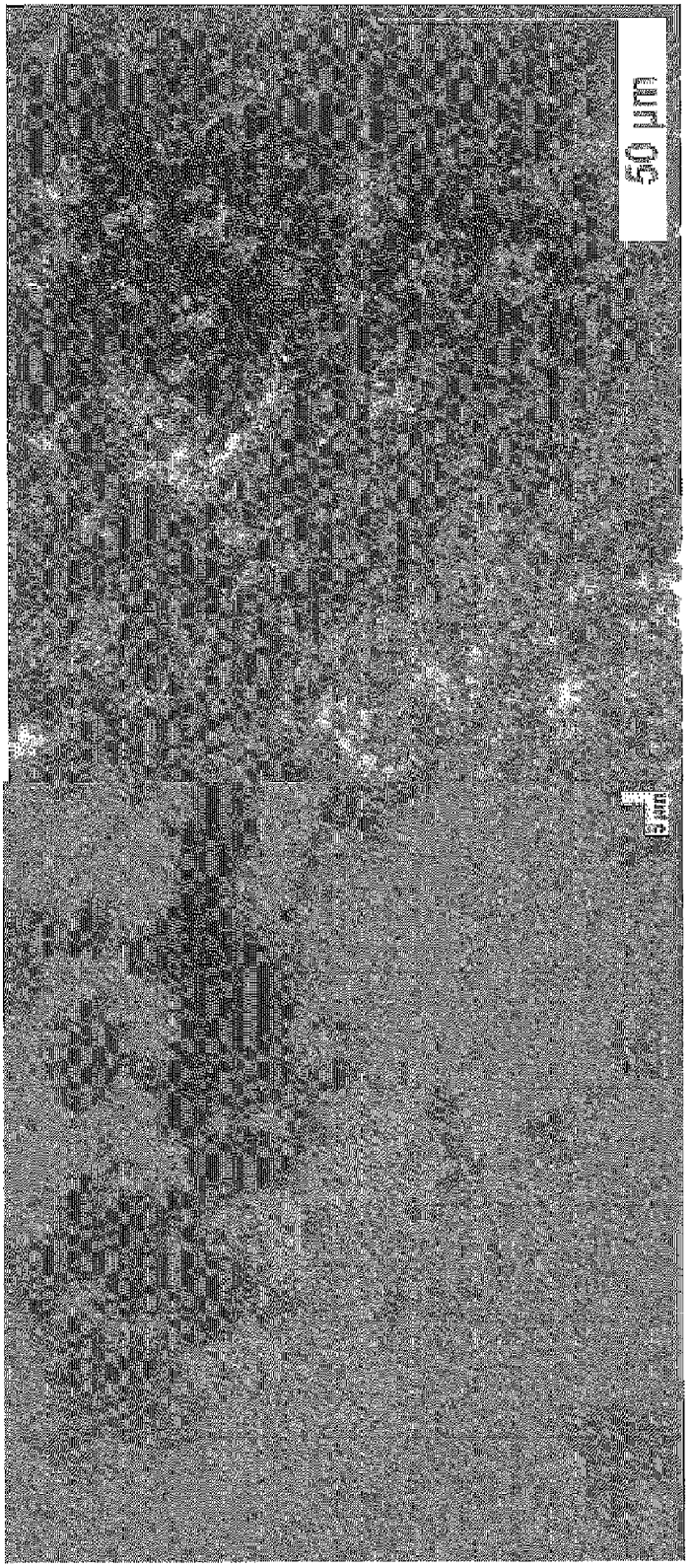
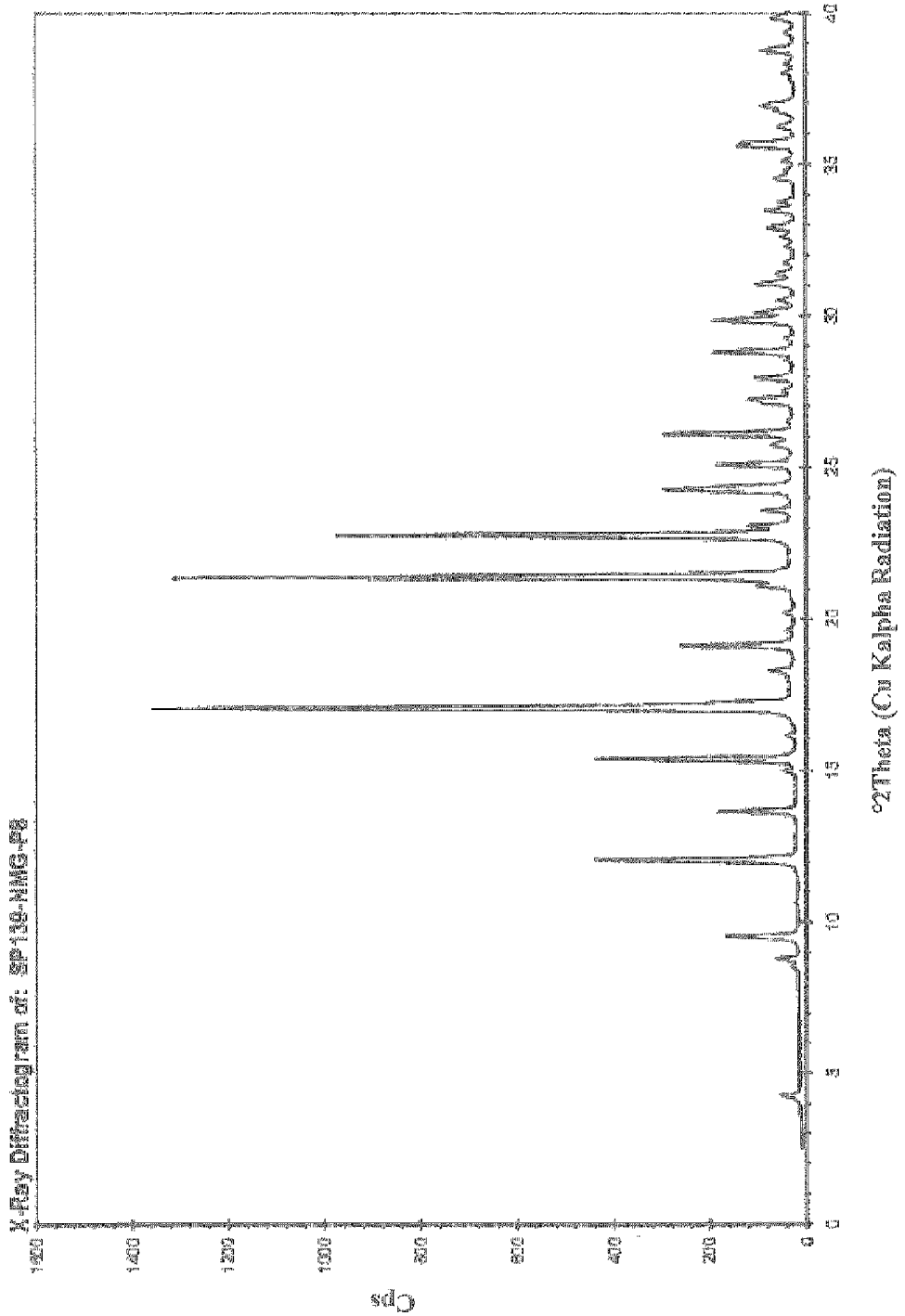


Fig. 4:

Fig. 5:


X-Ray Diffractogram of: SP139-NMG-P8
Cps
°2Theta (Cu Kalpha Radiation)
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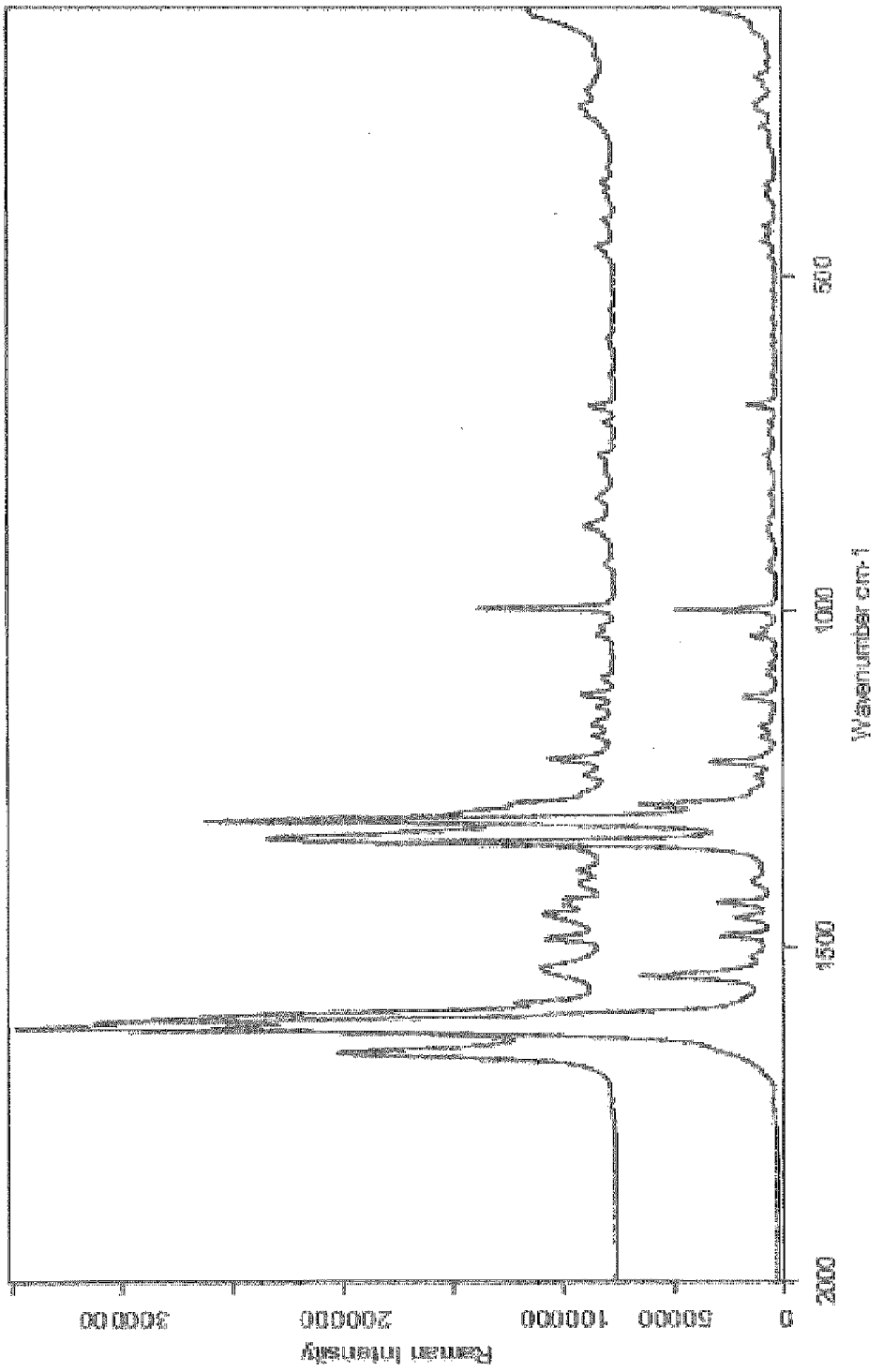
400
600
800
1000
1200
1400
1600
0
5
10
15
20
25
30
35
40


Raman Intensity
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100000
200000
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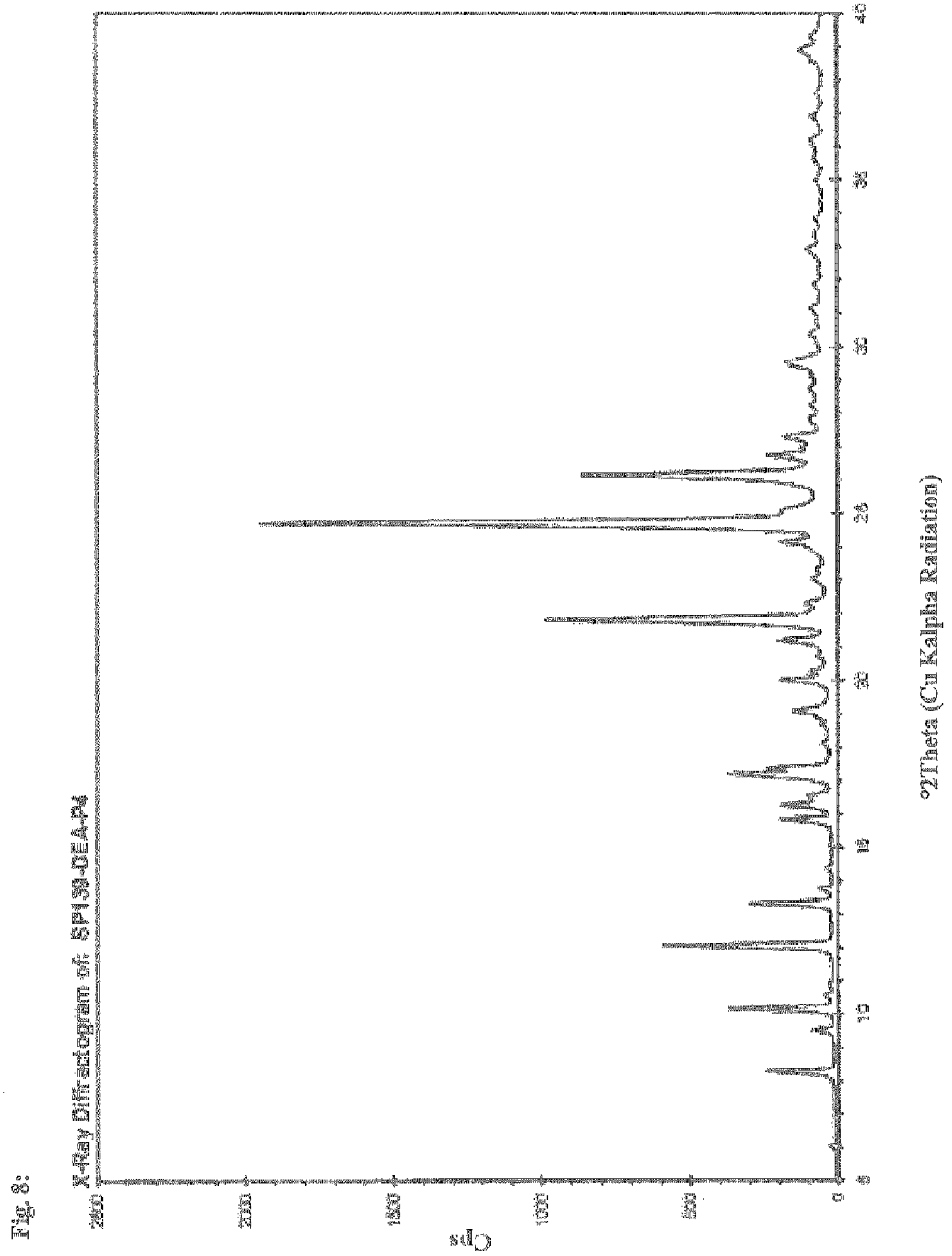
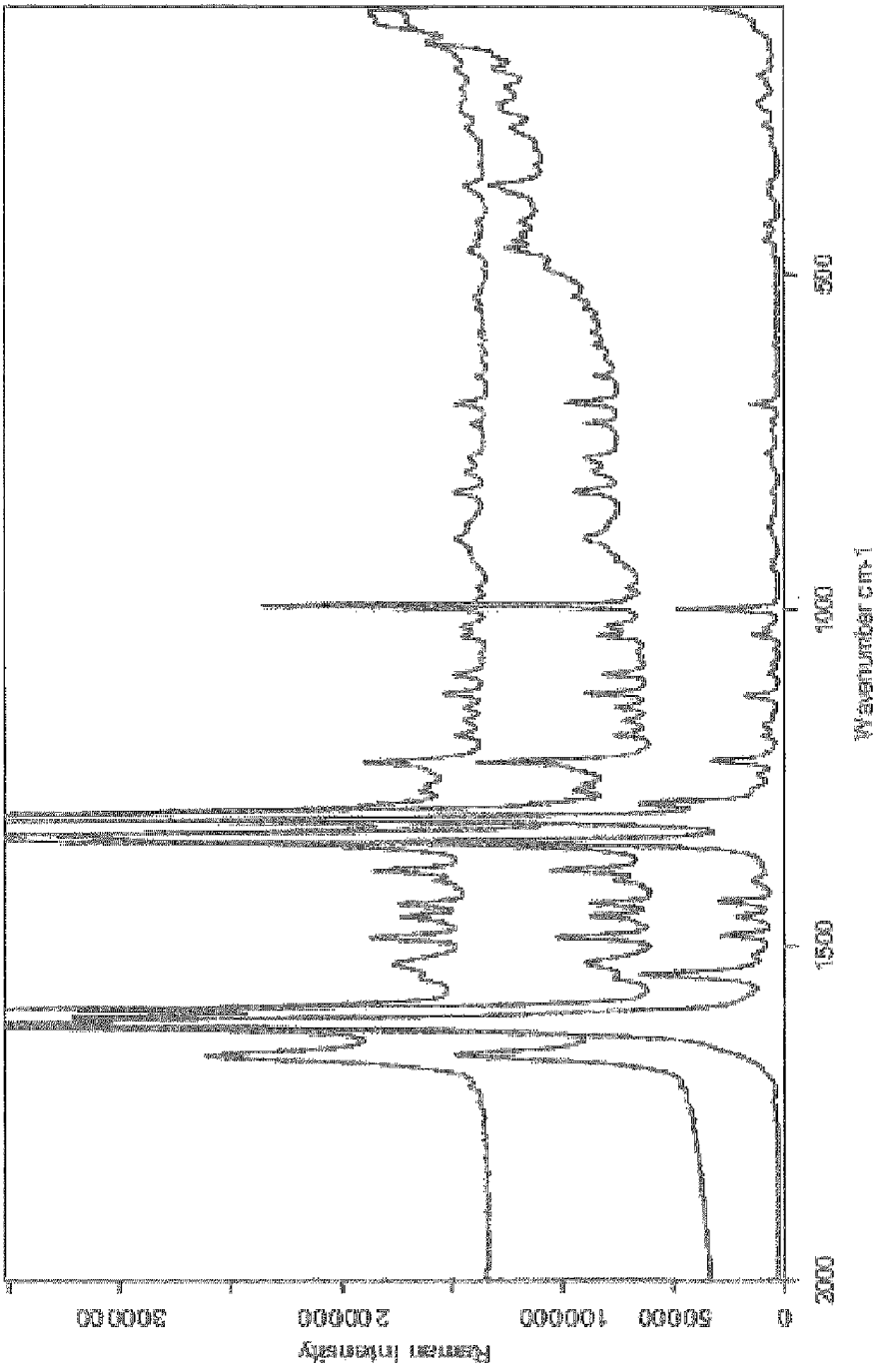
2000
1500
1000
500
Wavenumber cm-1

Fig. 6:


FIG. 8

Fig. 8:


X-Ray Diffractogram of: SP139-DEA-P4
Cps
°2Theta (Cu Kalpha Radiation)
0
500
1000
1500
2000
2500
5
10
15
20
25
30
35
40


Raman Intensity
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50000
100000
200000
300000
2000
1500
1000
500
Wavenumber cm-1

Fig. 9

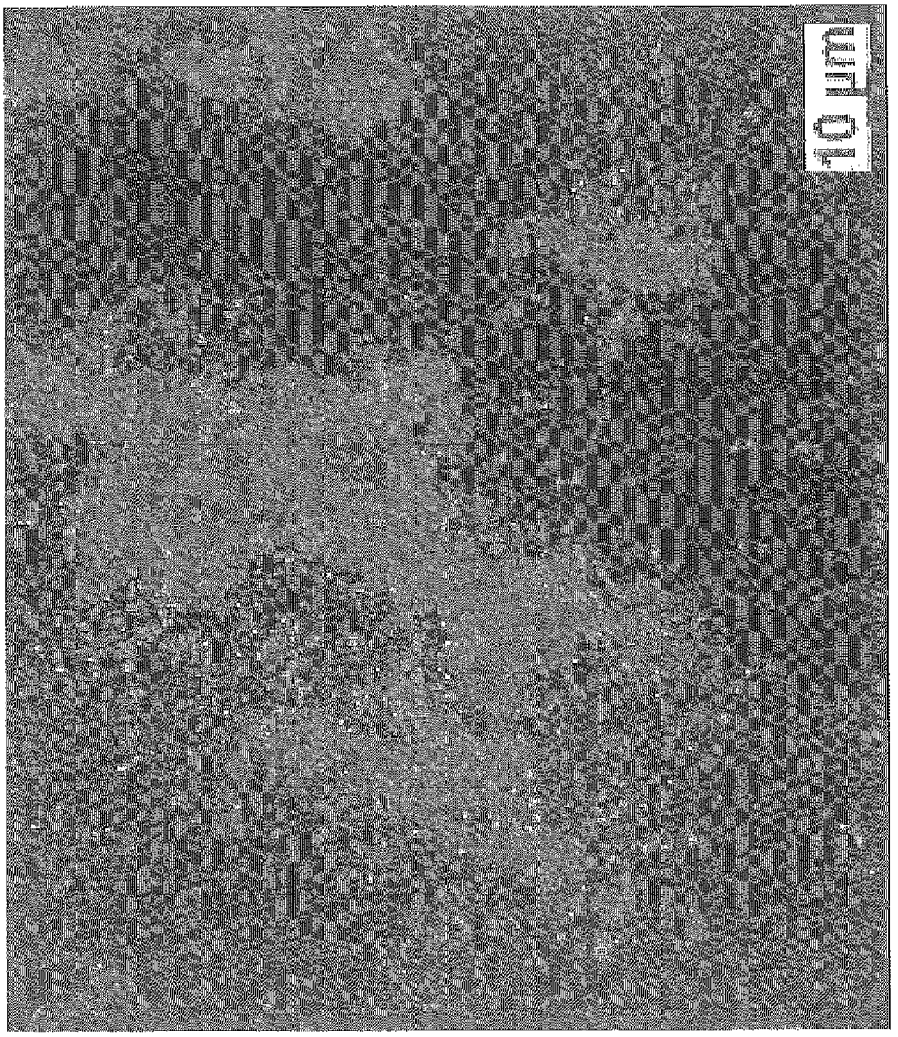
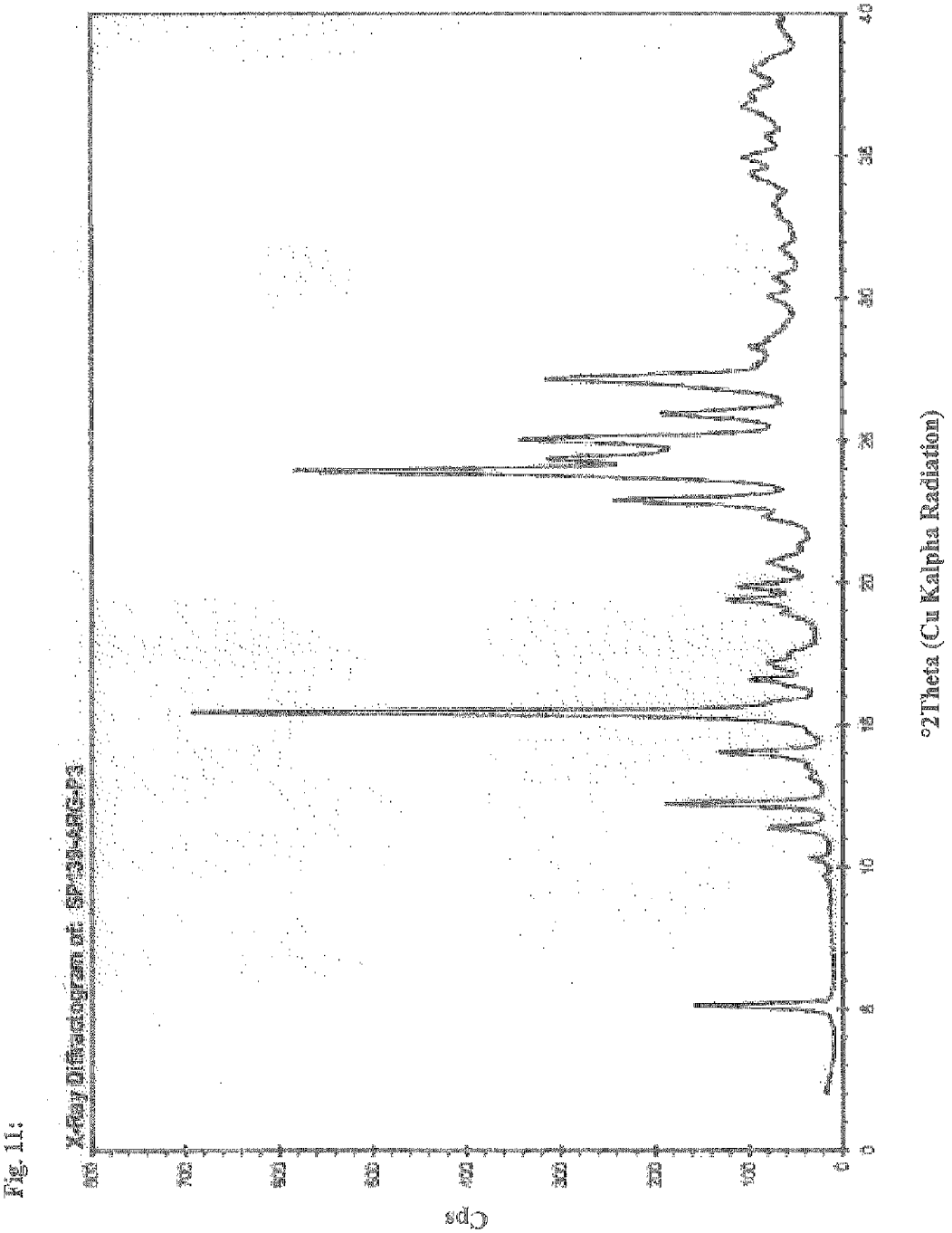


Fig. 10:

Fig. 11: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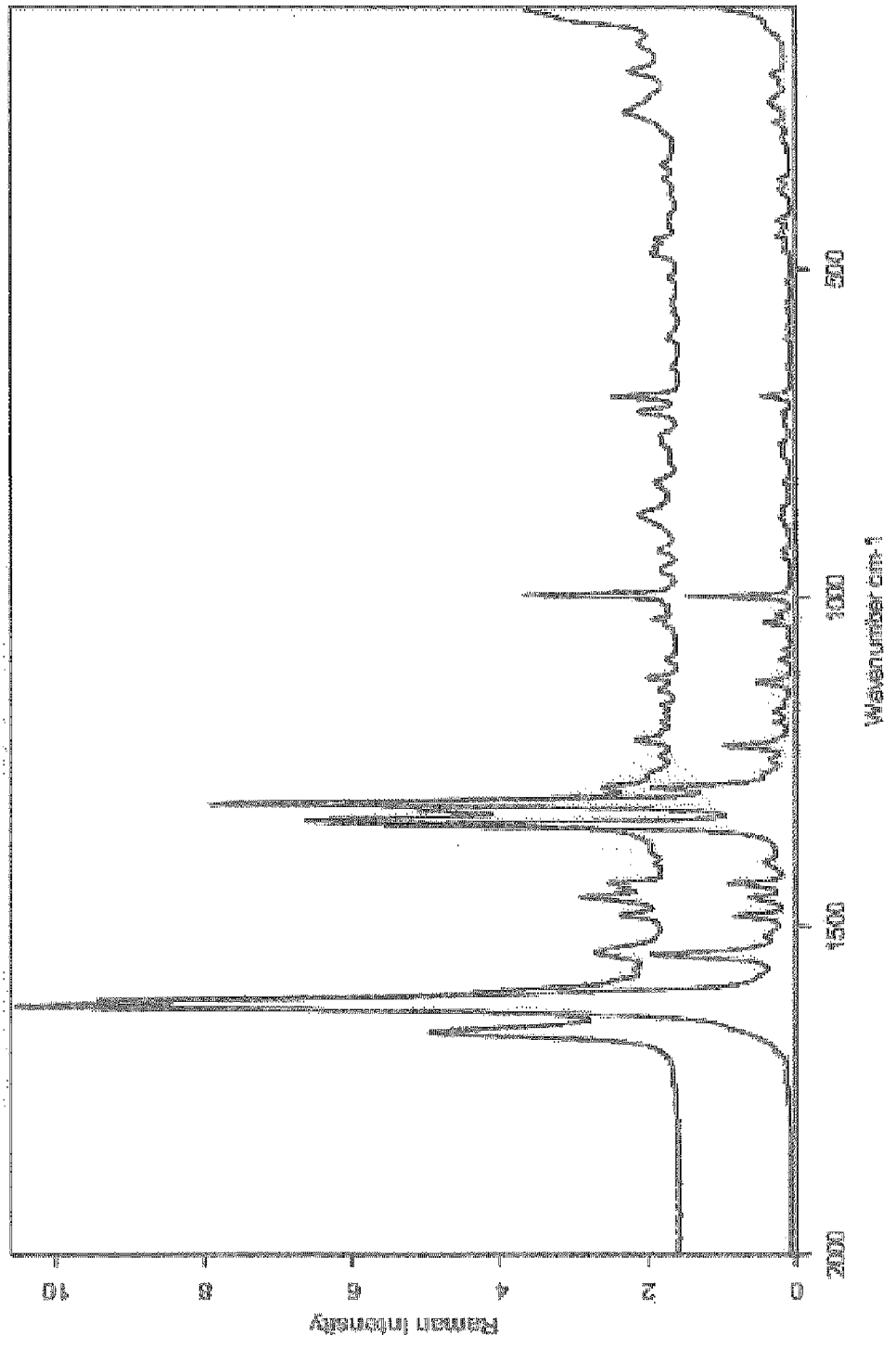
Cps
°2Theta (Cu Kalpha Radiation)


Raman Intensity
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4
6
8
10
200
450
700
950
1200
1450
Wavenumber cm-1

Fig. 12:

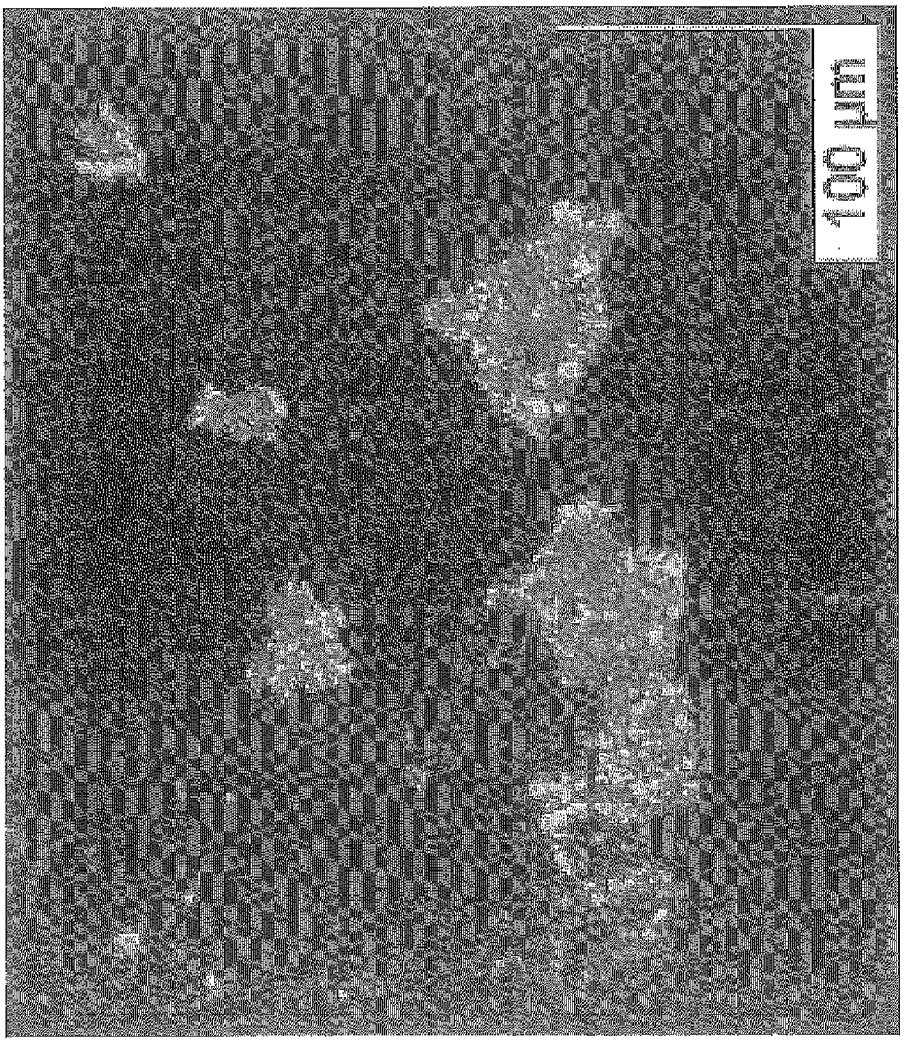


Fig. 13:

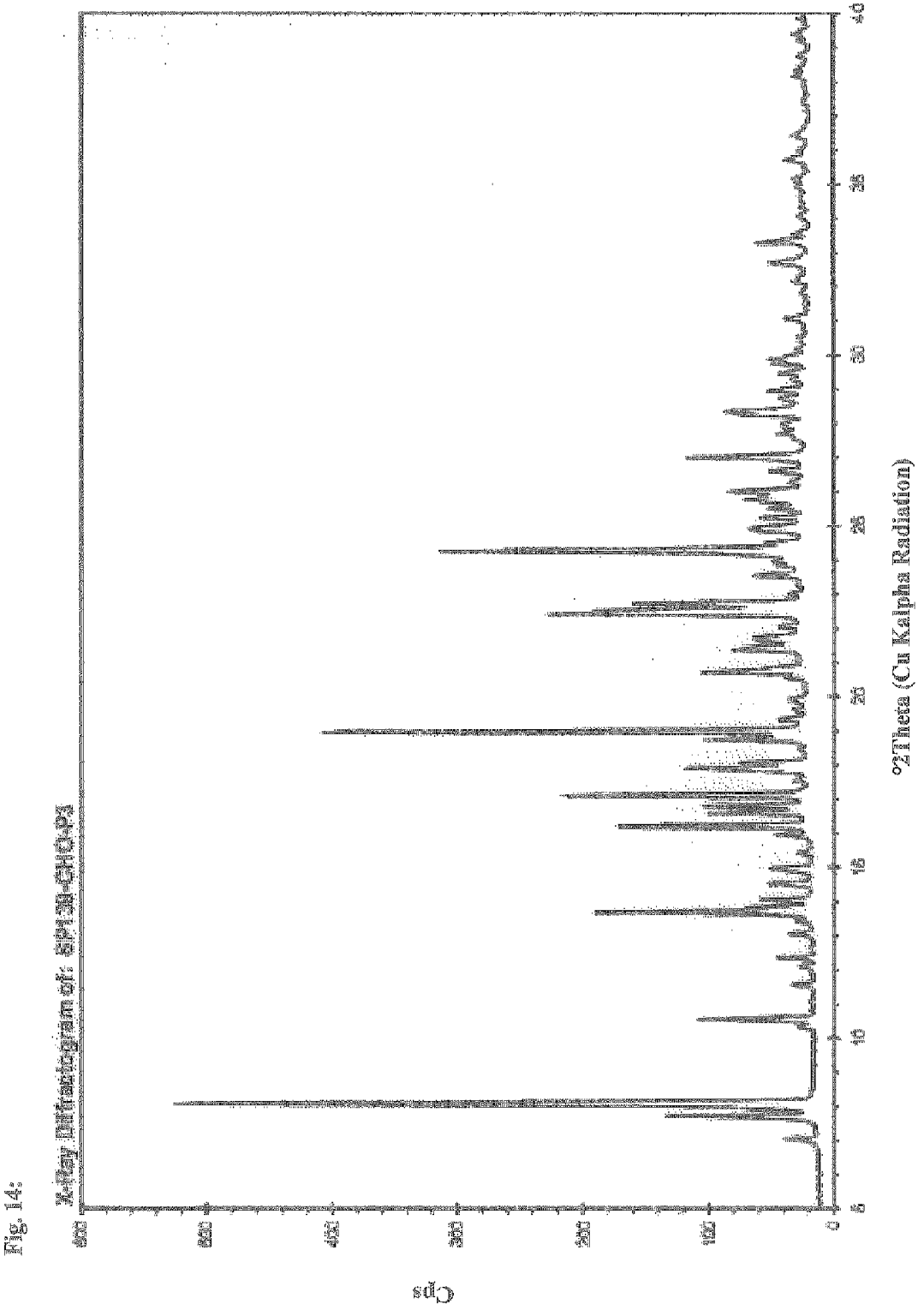

X-Ray Diffraction of: SP130-CH3-P1
Cps
°2Theta (Cu Kalpha Radiation)

Fig. 14.

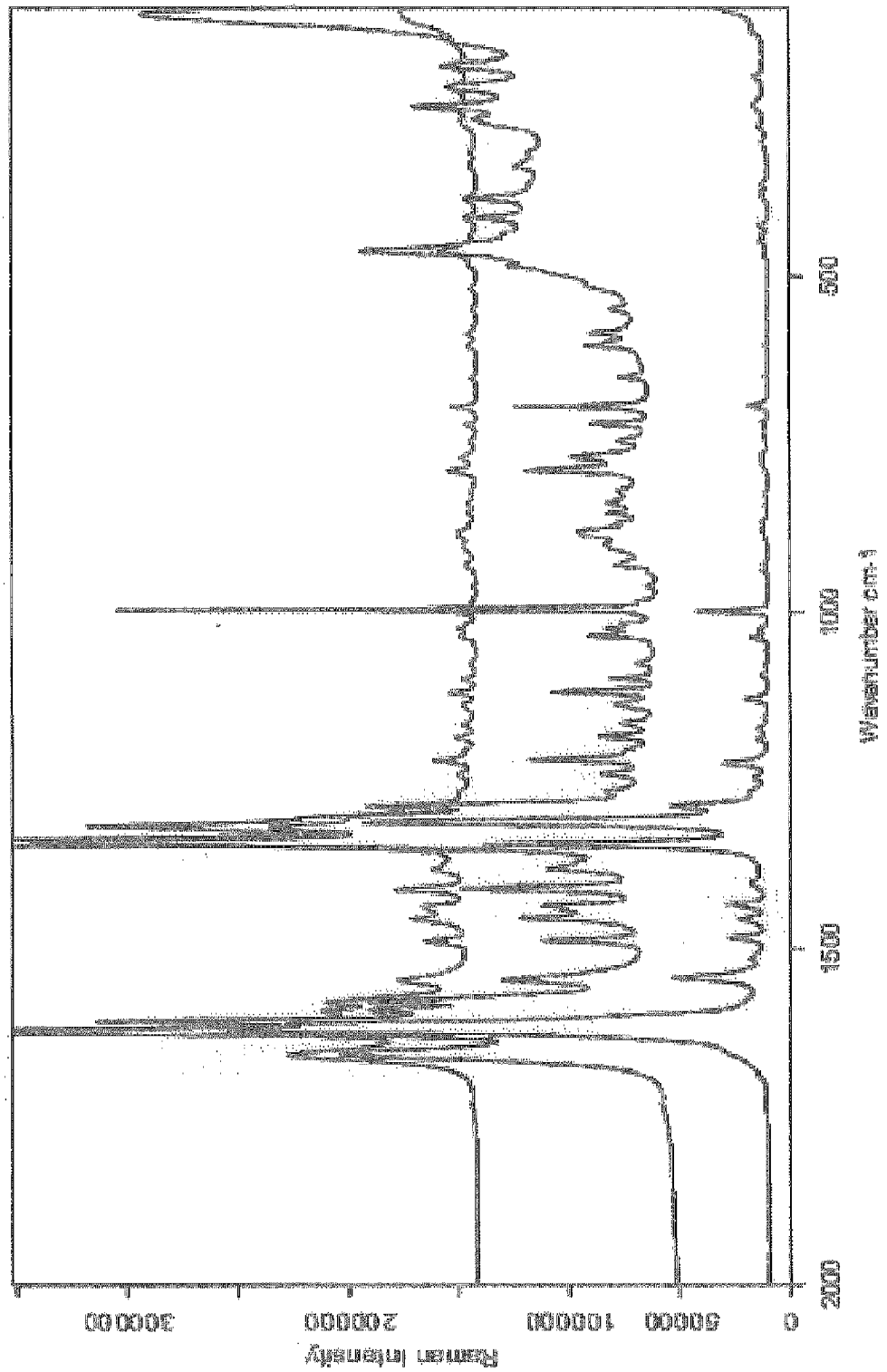

Raman Intensity
0
50000
100000
200000
300000
2000
1500
1000
500
Wavenumber cm-1

Fig. 15

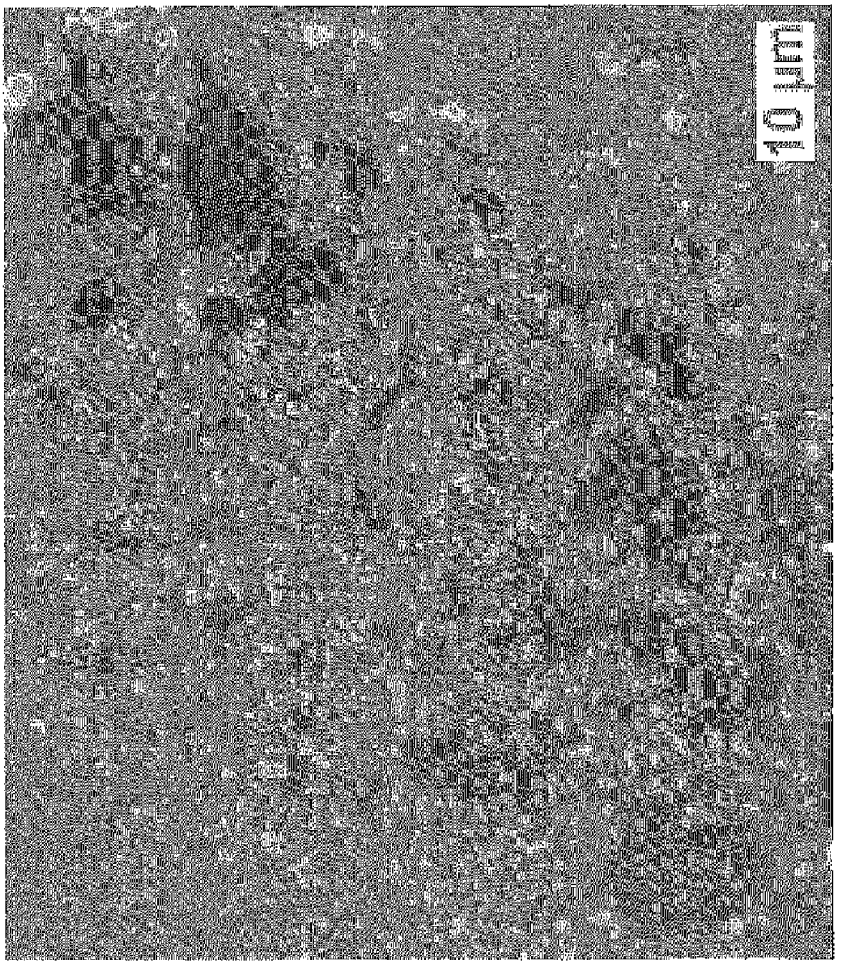
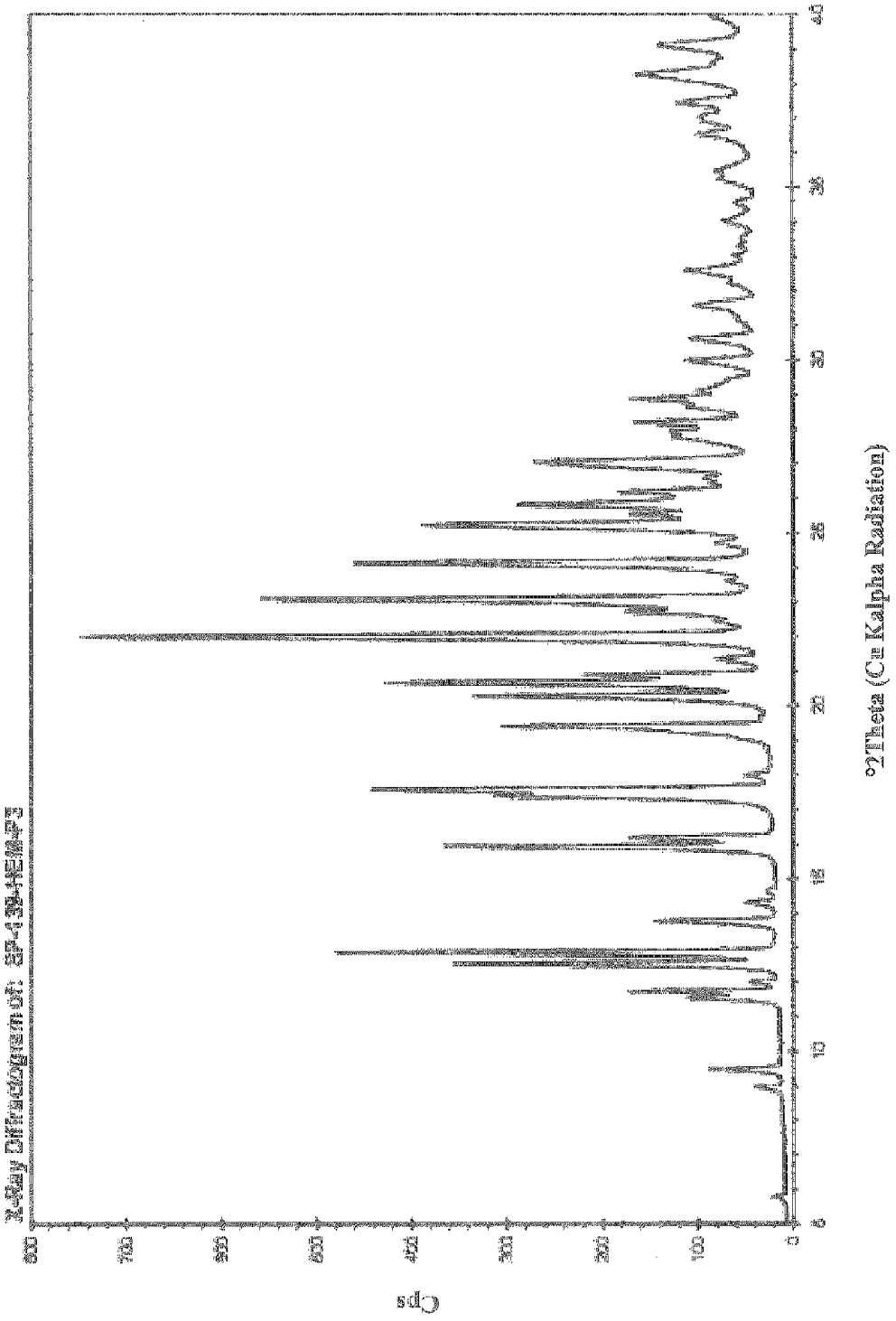


Fig. 16

Fig. 17:


X-Ray Diffractogram of: SP-139-HEM-P3
Cps
°2Theta (Cu Kalpha Radiation)

NOVEL SALTS AS ANTI-INFLAMMATORY, IMMUNOMODULATORY AND ANTI-PROLIFERATORY AGENTS

[0001] This application claims the benefit of the filing date of U.S. Provisional Application Ser. No. 61/360,670 filed Jul. 1, 2010, which is incorporated by reference herein.

[0002] The present invention relates to novel salts of compounds that can be used as anti-inflammatory, immunomodulatory and antiproliferatory agents. In particular the invention refers to new salts of compounds which inhibit dihydroorotate dehydrogenase (DHODH), a process for their manufacture, pharmaceutical compositions containing them and to their use for the treatment and prevention of diseases, in particular their use in diseases where there is an advantage in inhibiting dihydroorotate dehydrogenase (DHODH).

[0003] Rheumatoid arthritis (RA) is a disease which is quite common especially among elderly people. Its treatment with usual medications as for example non-steroid anti-inflammatory agents is not satisfactory. In view of the increasing ageing of the population, especially in the developed Western countries or in Japan the development of new medications for the treatment of RA is urgently required.

[0004] WO 2003/006425 describes certain specific compounds which are reported to be useful for treatment and prevention of diseases where there is an advantage in inhibiting dihydroorotate dehydrogenase (DHODH). However, the specific salts according to the present invention are not disclosed.

[0005] WO 99/38846 and EP 0 646 578 disclose compounds which are reported to be useful for treatment of RA.

[0006] A medicament against rheumatoid arthritis with a new mechanism of action, leflunomide, was recently put on the market by the company Aventis under the tradename ARAVA [EP 780128, WO 97/34600]. Leflunomide has immunomodulatory as well as anti-inflammatory properties [EP 217206, DE 2524929]. The mechanism of action is based upon the inhibition of dihydroorotate dehydrogenase (DHODH), an enzyme of the pyrimidine biosynthesis.

[0007] De Julian-Ortiz (J. Med. Chem. 1999, 42, 3308=3314) describes certain potential Anti-Herpes compounds with cyclopentenoic acid moieties

[0008] DE 33 46 814 A1 describes certain carbonic acid amide derivatives for the treatment, prevention and amelioration of diseases connected to cerebral dysfunction and symptoms caused thereby.

[0009] In the body, DHODH catalyzes the synthesis of pyrimidines, which are necessary for cell growth. An inhibition of DHODH inhibits the growth of (pathologically) fast proliferating cells, whereas cells which grow at normal speed may obtain their required pyrimidine bases from the normal metabolic cycle. The most important types of cells for the immuno response, the lymphocytes, use exclusively the synthesis of pyrimidines for their growth and react particularly sensitively to DHODH inhibition. Substances that inhibit the growth of lymphocytes are important medicaments for the treatment of autoimmune diseases.

[0010] The DHODH inhibitor leflunomide (ARAVA) is the first medicament of this class of compounds (leflunomides) for the treatment of rheumatoid arthritis. WO 99/45926 is a further reference that discloses compounds which act as inhibitors of DHODH.

[0011] JP-A-50-121428 discloses N-substituted cyclopentene-1,2-dicarboxylic acid monoamides as herbicides and their syntheses. For example, N-(4-chlorophenyl)-1-cyclopentene-1,2-dicarboxylic acid monoamide is produced by reacting 1-cyclopentene-1,2-dicarboxylic anhydride with 4-chloroaniline.

[0012] In the Journal of Med. Chemistry, 1999, Vol. 42, pages 3308=3314, virtual combinatorial syntheses and computational screening of new potential Anti-Herpes compounds are described. In Table 3 on page 3313 experimental results regarding IC_{50} and cytotoxicity are presented for 2-(2,3-difluorophenylcarbamoyl)-1-cyclopentene-1-carboxylic acid, 2-(2,6-difluorophenylcarbamoyl)-1-cyclopentene-1-carboxylic acid and 2-(2,3,4-trifluorophenyl-carbamoyl)-1-cyclopentene-1-carboxylic acid.

[0013] DE 3346814 and U.S. Pat. No. 4,661,630 disclose carboxylic acid amides. These compounds are useful for diseases attended with cerebral dysfunction and also have anti-ulcer, anti-asthma, anti-inflammatory and hypo-cholesterol activities.

[0014] In EP 0097056, JP 55157547, DE 2851379 and DE 2921002 tetrahydrophthalamic acid derivatives are described.

[0015] It is an object of the present invention to provide alternative effective agents, specifically certain specific salts thereof, which can be used for the treatment of diseases which require the inhibition of DHODH.

[0016] Particularly, it has previously been found that compounds of the general formula (I) shown herein below, such as 2-(3-Fluoro-3'-methoxy-biphenyl-4-ylcarbamoyl)-cyclopent-1-enecarboxylic acid (INN Vidofludimus), exhibit good anti-inflammatory activity and their usability in the oral therapy for the treatment of autoimmune diseases such as for example rheumatoid arthritis or inflammatory bowel diseases had been addressed. However, the solubility of the aforementioned compounds in aqueous media is less than 1 mg/ml at neutral pH.

[0017] The solubility of a compound is an important characteristic in drug discovery, as it serves as a starting point for formulation development. Furthermore, after oral administration, the resorption of a drug from the intestines into the circulation is at least in part dependent on its solubility. Only dissolved substances can be resorbed, so that an increase in solubility can be expected to result in a better uptake of a compound in the gastrointestinal tract, i.e. a better oral bioavailability and hence improved pharmacokinetic properties. It is desirable to provide compounds having enhanced bioavailability in order to improve their use as pharmaceutical compound for oral application.

[0018] Therefore, the present inventors have undertaken efforts to increase the solubility of the compounds in aqueous media and consequently their bioavailability. With this motivation, a study to develop a novel salt form of the compounds was performed, resulting in salts which unexpectedly exhibit significantly improved physicochemical properties.

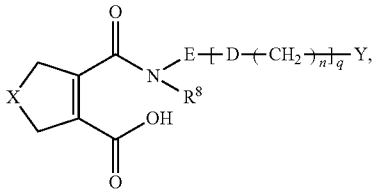
[0019] It has been found that the specific salts of compounds of formula (I) as described herein below, such as said specific salts of 2-(3-Fluoro-3'-methoxy-biphenyl-4-ylcarbamoyl)-cyclopent-1-enecarboxylic acid, exhibit favorable physicochemical properties such as improved aqueous solubility while maintaining good long-term stability. Furthermore, it was found that not all salts of the compound generally increase aqueous solubility to the same extent; in fact,

although the solubilities of the tested salts are all higher than for the free acid, they differ from each other by a factor of up to 10,000.

[0020] Accordingly, a novel class of salts of compounds with an inhibitory effect on DHODH, in particular human DHODH, was found.

[0021] The present invention is therefore directed to a salt selected from the group comprising the N-methyl-D-glucamine salt (NMG), the diethylamine salt (IDEA) salt, the magnesium salt, the tromethamine salt, the choline salt, the L-arginine salt, the zinc salt, and the 4-(2-hydroxyethyl)morpholine (HEM) salt of compounds of the general formula (I)

(I)



[0022] wherein

[0023] X is selected from the group consisting of CH_2, S, or O;

[0024] D is O or S;

[0025] R^8 is hydrogen or alkyl, preferably hydrogen or methyl;

[0026] E is an optionally substituted phenylene group;

[0027] Y is a monocyclic or bicyclic substituted or unsubstituted 6-9 membered ring system which may contain one or more heteroatoms selected from Nor S and which contains at least one aromatic ring; preferably, Y is substituted or unsubstituted phenyl;

[0028] n is 0 or 1, preferably 0; and

[0029] q is 0 or 1, preferably 0;

[0030] with the proviso that compounds wherein q=0, Y=unsubstituted phenyl and E=unsubstituted phenylene are excluded;

[0031] or a hydrate thereof.

[0032] E is preferably an unsubstituted phenylene group or a phenylene group which is substituted with one or more groups independently selected from halogen, nitro or alkoxy; more preferably E is a phenylene group which is substituted with one fluorine or chlorine atom, one methoxy group or with four fluorine atoms. Even more preferably, E is a phenylene group which is substituted with one or four fluorine atoms, yet even more preferably one fluorine atom.

[0033] Y is preferably an optionally substituted phenyl, pyridine or benzothiophene group. More preferably, Y is an unsubstituted phenyl group or a phenyl group which is substituted with one or more groups independently selected from halogen, alkyl, alkoxy, haloalkoxy, haloalkyl or CN. Even more preferably E is a phenyl group which is substituted with one or more groups independently selected from fluorine, chlorine, CN, methoxy, ethoxy, trifluoromethyl or trifluoromethoxy. Yet even more preferably, E is a phenyl group which is substituted with one or more groups independently selected from methoxy or trifluoromethoxy, yet even more preferably methoxy.

[0034] Preferably, the salts according to the present invention are selected from the N-methyl-D-glucamine salt (NMG) or the diethylamine salt (DEA) salt. Said salts, in addition to their increased solubility, show favourable characteristics with respect to their hygroscopicity, which is desirable from the viewpoint of formulating the compounds into a medicament.

[0035] An alkyl group, if not stated otherwise, is preferably a saturated linear or branched chain of 1 to 6 carbon atoms, preferably a methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isobutyl, pentyl or hexyl group, a methyl, ethyl, isopropyl or t-butyl group being more preferred, a methyl or ethyl group being even more preferred, a methyl group being yet even more preferred.

[0036] An alkoxy group denotes an O-alkyl group, the alkyl group being as defined above.

[0037] A haloalkyl group denotes an alkyl group which is substituted by one or more halogen atoms, the alkyl group being as defined above; a trifluoromethyl being preferred.

[0038] A haloalkyloxy group denotes an alkoxy group which is substituted by one or halogen atoms, the alkoxy group being as defined above; a OCF_3 being preferred.

[0039] Halogen is preferably chlorine, bromine, fluorine or iodine, fluorine, chlorine or bromine being preferred, fluorine being more preferred.

[0040] The invention also provides a pharmaceutical composition comprising the specific salts of the compounds of formula (I) as described above or, together with a pharmaceutically acceptable diluent or carrier therefore.

[0041] In another aspect, the present invention also provides a method for the treatment or prophylaxis of a condition where there is an advantage in inhibiting dihydroorotate dehydrogenase (DHODH) which comprises the administration of an effective amount of a specific salt of the compounds of formula (I) as described above or a.

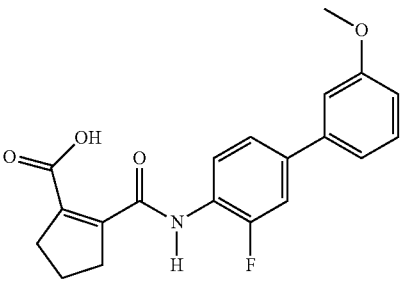
[0042] The invention is also directed to the use of a specific salt of the compounds of formula (I) as described above for the production of a medicament for the prevention and treatment of diseases, where inhibition of the pyrimidine biosynthesis is of benefit.

[0043] The present invention also encompasses hydrates of the salts according to the present invention, which specifies that crystals obtainable from said salts contain water in specific sthoichiometric or substoichiometric amounts, such as for example 0.5, 1 or 2 water molecules per molecule of the compound of formula (I) or formula (Ia) as described herein,

[0044] Further preferred aspects of the present invention are summarized in the following items [1] to [8]:

[0045] [1] A salt of the compound of the formula (Ia)

formula (Ia)



[0046] with a base selected from the group calcium (Ca), diethylamine (DEA), N-methyl-D-glucamine (NMG),

lithium (Li), zinc (Zn), L-arginine, 4-(2-hydroxyethyl) morpholine (HEM), L-lysine (LYS), choline (CHO) and ammonia (NH_3).

[0047] [2] The compound of item [1], which is a salt of 2-(3-Fluoro-3'-methoxy-biphenyl-4-ylcarbamoyl)-cyclopent-1-enecarboxylic acid with any base selected from the group consisting of calcium (Ca), diethylamine (DEA), N-methyl-D-glucamine (NMG).

[0048] [3] A pharmaceutical composition comprising a compound as defined in any of items [1] to [2] together with pharmaceutically acceptable diluents or carriers.

[0049] [4] A compound according to items [1] to [2] for the use as a medicament,

[0050] [5] The use of the compound of the formula (Ia) as defined in any of items [1] to [2] in the manufacture of a medicament for use in treatment of a disease or a therapeutic indication in which inhibition of dihydrooratate dehydrogenase and/or Interleukin-17 (IL-17) is beneficial.

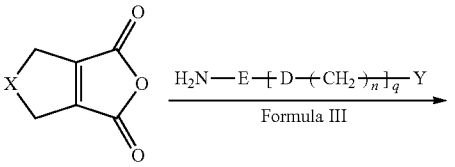
[0051] [6] The use of item [5], wherein the disease or indication is an autoimmune disease.

[0052] [7] The use of item [6], wherein the said autoimmune diseases are selected from the group consisting of ankylosing spondylitis, autoimmune thyroiditis, coeliac disease, Grave's disease, inflammatory bowel disease (Crohn's disease, ulcerative colitis), diabetes mellitus type 1, systemic lupus erythematosus, multiple sclerosis, vitiligo, osteoarthritis, psoriasis, psoriatic arthritis or rheumatoid arthritis.

[0053] [8] The use of the compound of the formula (Ia) as defined in any of items [1] to [2] in the manufacture of a medicament for use in treatment of any forms of neoplasms.

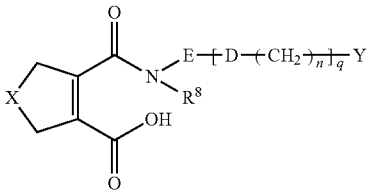
[0054] In addition, the present invention provides methods for preparing the compounds of the invention such as desired amides of the formula (I), as well as for the specific salts thereof as described above.

[0055] A first method for synthesis of amides of formula (I) comprises the step of reacting an acid anhydride of formula (II) with an amine of the formula (III).



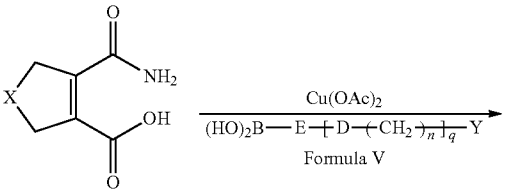
Formula II

Formula III



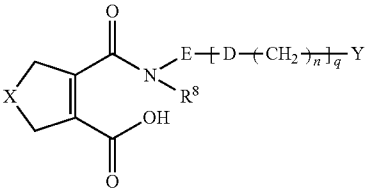
Formula I

[0056] A second method of the invention for preparing the compounds of formula (I) comprises the step of reacting an amine of the formula (IV) with an aryl-boronic acid of the general formula (V) $(HO)_2B\text{-}E[D\text{-}(CHR^3)_n]_q\text{—}Y$ [M. P. Winters, Tetrahedron Lett, 39, (1998), 2933-2936].



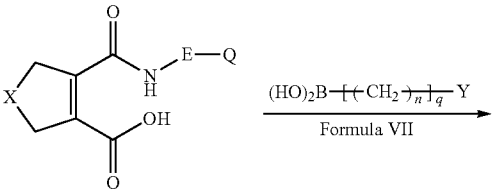
Formula IV

Formula V



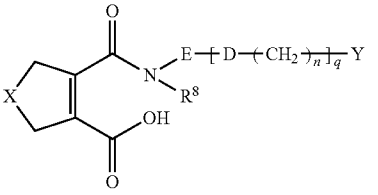
Formula I

[0057] A third method of the invention for preparing the compounds of formula (I) comprises the step of reacting an halogen derivative of the formula (VI) with an arylboronic acid of the general formula (VII) [N. E. Leadbeater, S. M. Resouly, Tetrahedron, 55, 1999, 11889-11894]. Q is a halogen group such as chlorine, bromine, fluorine or iodine, bromine being preferred.



Formula VI

Formula VII



Formula I

[0058] In the structures of formulae II to VII as depicted herein, the residues X, E, D, Y, R_8, as well as the variables n and q have the meaning as defined herein for formula I.

[0059] Preferably, the salts of the present invention are the abovementioned salts derived from a compound selected from the group comprising the compounds 1 to 76 below:

[0060] 1. 2-((4-(benzyloxy)phenyl)carbamoyl)cyclopent-1-enecarboxylic acid

[0061] 13. 2-((2'-fluoro-[1,1'-biphenyl]-4-yl)carbamoyl) cyclopent-1-enecarboxylic acid

[0062] 14. 2-((2'-chloro-[1,1'-biphenyl]-4-yl)carbamoyl) cyclopent-1-enecarboxylic acid

[0063] 15. 2-((2'-methoxy-[1,1'-biphenyl]-4-yl)carbamoyl)cyclopent-1-enecarboxylic acid

[0064] 16. 2-((4-((2,6-difluorobenzyl)oxy)phenyl)carbamoyl)cyclopent-1-enecarboxylic acid

[0065] 17. 2-((2'-ethoxy-3-fluoro-[1,1'-biphenyl]-4-yl)carbamoyl)cyclopent-1-enecarboxylic acid

[0066] 18. 2-((2-chloro-3'-cyano-[1,1'-biphenyl]-4-yl)carbamoyl)cyclopent-1-enecarboxylic acid

[0067] 19. 2-((2-chloro-4'-methoxy-[1,1'-biphenyl]-4-yl)carbamoyl)cyclopent-1-enecarboxylic acid

[0068] 22. 2-((3-chloro-4-(6-methoxypyridin-3-yl)phenyl)carbamoyl)cyclopent-1-enecarboxylic acid

[0069] 23. 2-((4'-methoxy-2-methyl-[1,1'-biphenyl]-4-yl)carbamoyl)cyclopent-1-enecarboxylic acid

[0070] 24. 2-((3,5-dibromo-4-((2,5-difluorobenzyl)oxy)phenyl)carbamoyl)cyclopent-1-enecarboxylic acid

[0071] 25. 2-((3,5-dibromo-4-((3,4-difluorobenzyl)oxy)phenyl)carbamoyl)cyclopent-1-enecarboxylic acid

[0072] 26. 2-((3-fluoro-3'-methoxy-[1,1'-biphenyl]-4-yl)carbamoyl)cyclopent-1-enecarboxylic acid

[0073] 27. 2-((3,3'-difluoro-[1,1'-biphenyl]-4-yl)carbamoyl)cyclopent-1-enecarboxylic acid

[0074] 29. 4-((4-(benzyloxy)-3,5-dibromophenyl)carbamoyl)-2,5-dihydrothiophene-3-carboxylic acid

[0075] 30. 2-((3,4',5-trifluoro-3'-methyl-[1,1'-biphenyl]-4-yl)carbamoyl)cyclopent-1-enecarboxylic acid

[0076] 31. 2-((3,5-difluoro-2'-methoxy-[1,1'-biphenyl]-4-yl)carbamoyl)cyclopent-1-enecarboxylic acid

[0077] 32. 2-((2'-methoxy-3-nitro-[1,1'-biphenyl]-4-yl)carbamoyl)cyclopent-1-enecarboxylic acid

[0078] 33. 2-((3-methoxy-[1,1'-biphenyl]-4-yl)carbamoyl)cyclopent-1-enecarboxylic acid

[0079] 34. 2-((2'-chloro-3-methoxy-[1,1'-biphenyl]-4-yl)carbamoyl)cyclopent-1-enecarboxylic acid

[0080] 35. 2-((3-methoxy-3'-(trifluoromethoxy)-[1,1'-biphenyl]-4-yl)carbamoyl)cyclopent-1-enecarboxylic acid

[0081] 36. 2-(2'-fluoro-3-methoxy-[1,1'-biphenyl]-4-yl)carbamoyl)cyclopent-1-enecarboxylic acid

[0082] 37. 2-((2',3,4'-trimethoxy-[1,1'-biphenyl]-4-yl)carbamoyl)cyclopent-1-enecarboxylic acid

[0083] 38. 2-((3'-ethoxy-3-methoxy-[1,1'-biphenyl]-4-yl)carbamoyl)cyclopent-1-enecarboxylic acid

[0084] 39. 2-((3,3'-dimethoxy-[1,1'-biphenyl]-4-yl)carbamoyl)cyclopent-1-enecarboxylic acid

[0085] 40. 2-((3,5-dibromo-4-((2-chloro-6-fluorobenzyl)oxy)phenyl)carbamoyl)cyclopent-1-enecarboxylic acid

[0086] 41. 4-((2'-chloro-[1,1'-biphenyl]-4-yl)carbamoyl)-2,5-dihydrothiophene-3-carboxylic acid

[0087] 42. 2-((4-(m-tolylthio)phenyl)carbamoyl)cyclopent-1-enecarboxylic acid

[0088] 43. 2-((3'-(trifluoromethoxy)-[1,1'-biphenyl]-4-yl)carbamoyl)cyclopent-1-enecarboxylic acid

[0089] 44. 2-((4-(benzo[b]thiophen-2-yl)phenyl)carbamoyl)cyclopent-1-enecarboxylic acid

[0090] 45. 2-((4-(benzo[b]thiophen-2-yl)-2-fluorophenyl)carbamoyl)cyclopent-1-enecarboxylic acid

[0091] 46. 2-((3'-ethoxy-3-fluoro-[1,1'-biphenyl]-4-yl)carbamoyl)cyclopent-1-enecarboxylic acid

[0092] 47. 4-((3,5-difluoro-2'-methoxy-[1,1'-biphenyl]-4-yl)carbamoyl)-2,5-dihydrofuran-3-carboxylic acid

[0093] 50. 2-((4-phenoxyphenyl)carbamoyl)cyclopent-1-enecarboxylic acid

[0094] 52. 4-((3,5-dibromo-4-((2-chloro-6-fluorobenzyl)oxy)phenyl)carbamoyl)-2,5-dihydrothiophene-3-carboxylic acid

[0095] 53. 2-((3-chloro-2'-methoxy-[1,1'-biphenyl]-4-yl)carbamoyl)cyclopent-1-enecarboxylic acid

[0096] 54. 2-((2-chloro-2'-methoxy-[1,1'-biphenyl]-4-yl)carbamoyl)cyclopent-1-enecarboxylic acid

[0097] 56. 2-((2,3,5,6-tetrafluoro-2'-methoxy-[1,1'-biphenyl]-4-yl)carbamoyl)cyclopent-1-enecarboxylic acid

[0098] 57. 2-((2'-methoxy-3-methyl-[1,1'-biphenyl]-4-yl)carbamoyl)cyclopent-1-enecarboxylic acid

[0099] 58. 2-((3,5-dichloro-2'-methoxy-[1,1'-biphenyl]-4-yl)carbamoyl)cyclopent-1-enecarboxylic acid

[0100] 62. 2-((2'-ethoxy-3,5-difluoro-[1,1'-biphenyl]-4-yl)carbamoyl)cyclopent-1-enecarboxylic acid

[0101] 63. 2-((3'-ethoxy-3,5-difluoro-[1,1'-biphenyl]-4-yl)carbamoyl)cyclopent-1-enecarboxylic acid

[0102] 64. 2-((3,5-difluoro-3'-(trifluoromethoxy)-[1,1'-biphenyl]-4-yl)carbamoyl)cyclopent-1-enecarboxylic acid

[0103] 65. 2-((2'-chloro-3,5-difluoro-[1,1'-biphenyl]-4-yl)carbamoyl)cyclopent-1-enecarboxylic acid

[0104] 66. 2-((2',3,5-trifluoro-[1,1'-biphenyl]-4-yl)carbamoyl)cyclopent-1-enecarboxylic acid

[0105] 67. 2-((3,5-difluoro-2',4'-dimethoxy-[1,1'-biphenyl]-4-yl)carbamoyl)cyclopent-1-enecarboxylic acid

[0106] 68. 2-((3-chloro-4-((2-(trifluoromethyl)benzyl)oxy)phenyl)carbamoyl)cyclopent-1-enecarboxylic acid

[0107] 69. 2-((3-chloro-4-((2-chloro-6-fluorobenzyl)oxy)phenyl)carbamoyl)cyclopent-1-enecarboxylic acid

[0108] 72. 2-((4-(benzyloxy)-3-chlorophenyl)carbamoyl)cyclopent-1-enecarboxylic acid

[0109] 74. 2-((3-chloro-4-((2-fluorobenzyl)oxy)phenyl)carbamoyl)cyclopent-1-enecarboxylic acid

[0110] 76. 2-((3-fluoro-2'-methoxy-[1,1'-biphenyl]-4-yl)oxy)carbonyl)cyclopent-1-enecarboxylic acid

[0111] Preferably, the salts of the present invention are the abovementioned specific salts wherein the compound of formula (I) is selected from the group comprising the compounds shown below in table 1:

TABLE 1

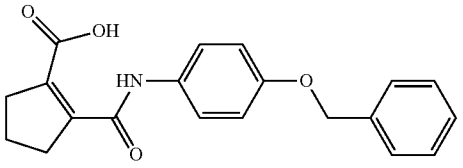
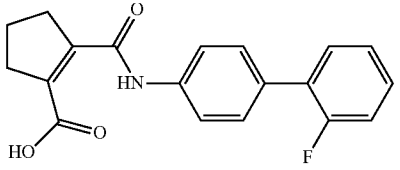
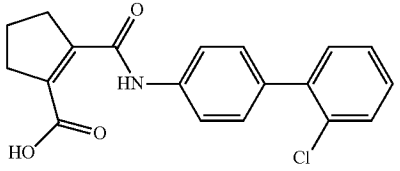
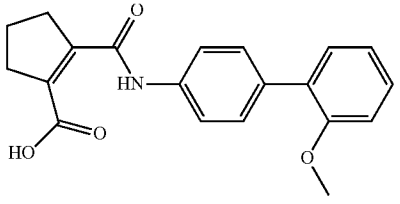
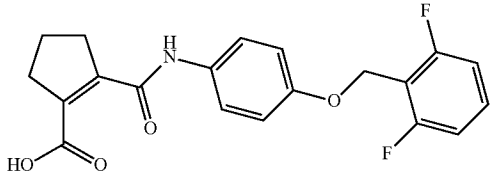
N	Structure	^{1}H-NMR	Molecule-Mass [g/mol]	HPLC/MS (ESI)	human IC_{50}-Value [µM]	murine IC_{50}-Value [µM]	rate IC_{50}-Value [µM]
01		N.D.	337.37	338 $[M + H]^+$	0.350	8.2	N.D.
13		δ = 1.91 (m_C, 2H, CH_2), 2.65 (m_C, 2H, CH_2), 2.78 (m_C, 2H, CH_2), 7.27-7.51 (m, 6H), CH_{Ar}), 7.72 (d, 2H, CH_{Ar}), 10.40 (s, 1H, NH), 12.67 (s, 1H, OH).	325	326 $[M + H]^+$	A	C	C
14		δ = 1.95 (m_C, 2H, CH_2), 2.65 (m_C, 2H, CH_2), 2.78 (m_C, 2H, CH_2), 7.35-7.72 (m, 8H, CH_{Ar}), 10.36 (s, 1H, NH), 12.66 (s, 1H, OH).	341	342 $[M + H]^+$	A	C	C
15		δ = 1.94 (m_C, 2H, CH_2), 2.66 (m_C, 2H, CH_2), 2.79 (m_C, 2H, CH_2), 3.76 (s, 3H, O—CH_3), 7.01-7.67 (m, 8H, CH_{Ar}), 10.30 (s, 1H, NH).	337	338 $[M + H]^+$	A	N.D.	N.D.
16		δ = 1.90 (m_C, 2H, CH_2), 2.57 (m_e, 2H, CH_2), 2.76 (m_C, 2H, CH_2), 5.08 (s, 2H, CH_2—O), 6.95-7.57 (m, 7H, CH_{Ar}), 10.11 (s, 1H, NH), 11.33 (s, 1H, OH).	373	374 $[M + H]^+$	A	N.D.	N.D.

TABLE 1-continued

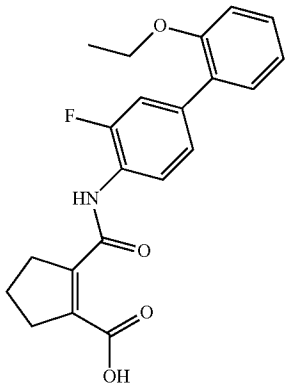
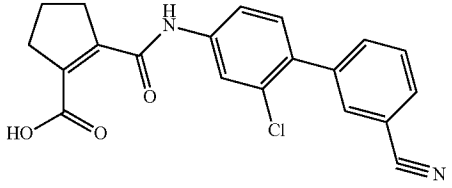
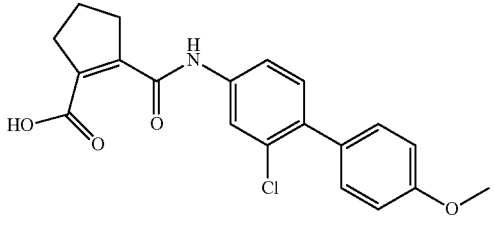
N	Structure	^{1}H-NMR	Molecule-Mass [g/mol]	HPLC/MS (ESI)	human IC_{50}-Value [µM]	murine IC_{50}-Value [µM]	rate IC_{50}-Value [µM]
17		δ = 1.04 (m_C, 3H, O—CH_2—CH_3), 1.65 (m_C, 2H, CH_2), 2.45 (m_C, 2H, CH_2), 2.55 (m_C, 2H, CH_2), 3.82 (m_C, 2H, O—CH_2—CH_3), 6.75-6.87 (m, 2H, CH_{Ar}), 7.06-7.28 (m, 4H, CH_{Ar}), 7.71-7.77 (m, 1H, CH_{Ar}), 10.23 (s, 1H, NH), 12.83 (s, 1H, OH).	369	370 $[M + H]^+$	A	N.D.	N.D.
18		δ = 1.7 (m_C, 2H, CH_2), 2.60 (m_C, 2H, CH_2), 2.73 (m_C, 2H, CH_2), 7.36-7.91 (m, 7H, CH_{Ar}), 10.61 (s, 1H, NH), 12.61 (s, 1H, OH).	366	367 $[M + H]^+$	A	N.D.	N.D.
19		δ = 2.16 (m_C, 2H, CH_2), 2.89 (m_C, 2H, CH_2), 3.01 (m_C, 2H, CH_2), 4.03 (s, 3H, O—CH_3), 7.23-8.15 (m, 7H, CH_{Ar}), 10.66 (s, 1H, NH), 13.00 (s, 1H, OH).	371	372 $[M + H]^+$	A	A	A

TABLE 1-continued

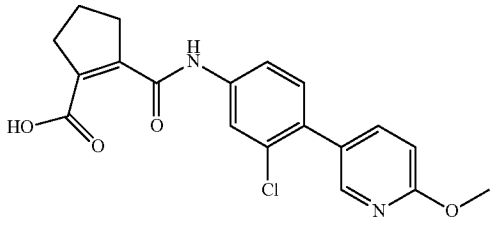
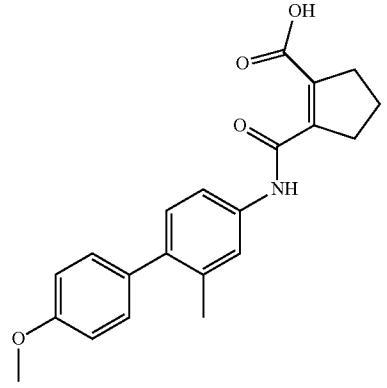
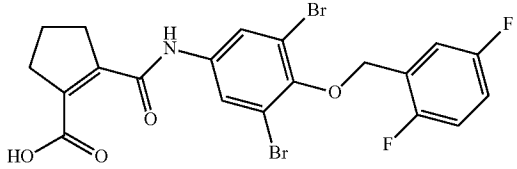
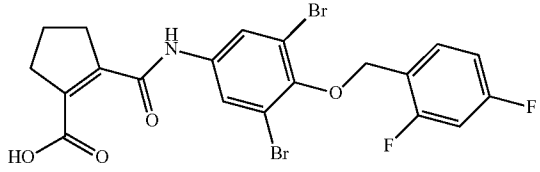
N	Structure	^{1}H-NMR	Molecule-Mass [g/mol]	HPLC/MS (ESI)	human IC_{50}-Value [µM]	murine IC_{50}-Value [µM]	rate IC_{50}-Value [µM]
22		δ = 1.74 (m_C, 2H, CH_2), 2.48 (m_C, 2H, CH_2), 3.71 (s, 3H, O—CH_3), 6.70-8.02 (m, 6H, CH_{Ar}), 10.28 (s, 1H, NH), 12.48 (s, 1H, OH).	372	373 $[M + H]^+$	A	N.D.	N.D.
23		δ = 1.92 (m_C, 2H, CH_2), 2.50 (s, 3H, CH_3), 2.66 (m_C, 2H, CH_2), 2.79 (m_C, 2H, CH_2), 3.79 (s, 3H, O—CH_3), 6.97-7.54 (m, 7H, CH_{Ar}), 10.20 (s, 1H, NH), 12.00 (s, 1H, OH).	351	352 $[M + H]^+$	A	N.D.	N.D.
24		δ = 1.92 (m_C, 2H, CH_2), 2.64 (m_C, 2H, CH_2), 2.74 (m_C, 2H, CH_2), 5.02 (s, 2H, O—CH_2), 7.28-7.93 (m, 5H, CH_{Ar}), 10.41 (s, 1H, NH), 12.68 (s, 1H, OH).	529	530 $[M + H]^+$	A	B	C
25		δ = 1.83 (m_C, 2H, CH_2), 2.55 (m_C, 2H, CH_2), 2.65 (m_C, 2H, CH_2), 4.86 (s, 2H, O—CH_2), 7.28-7.85 (m, 5H, CH_{Ar}), 10.34 (s, 1H, NH), 12.56 (s, 1H, OH).	529	530 $[M + H]^+$	A	N.D.	N.D.

TABLE 1-continued

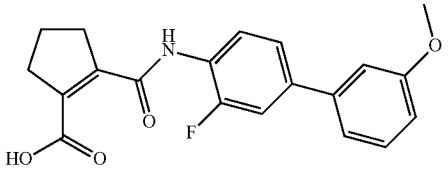
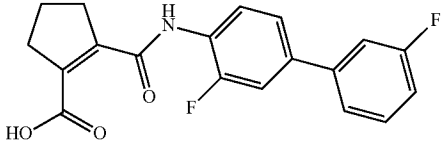
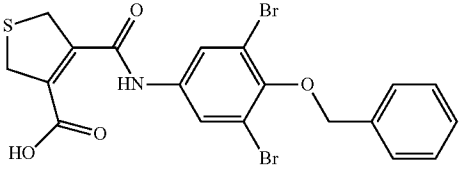
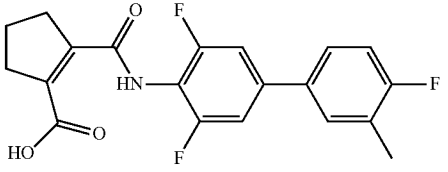
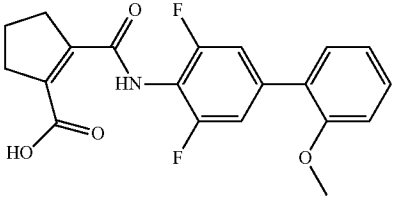
N	Structure	^{1}H-NMR	Molecule-Mass [g/mol]	HPLC/MS (ESI)	human IC_{50}-Value [µM]	murine IC_{50}-Value [µM]	rate IC_{50}-Value [µM]
26		δ = 1.89 (m_C, 2H, CH_2), 2.69 (m_C, 2H, CH_2), 2.80 (m_C, 2H, CH_2), 3.83 (s, 3H, O—CH_3), 6.92-8.09 (m, 7H, CH_{Ar}), 10.57 (s, 1H, NH).	355	356 $[M + H]^+$	A	C	C
27		δ = 1.67 (m_C, 2H, CH_2), 2.47 (m_C, 2H, CH_2), 2.58 (m_C, 2H, CH_2), 6.94-7.91 (m, 7H, CH_{Ar}), 10.40 (s, 1H, NH), 12.81 (s, 1H, OH).	343	344 $[M + H]^+$	A	C	N.D.
29		δ = 3.93 (m_C, 2H, CH_2), 4.03 (m_C, 2H, CH_2), 4.87 (s, 2H, O—CH_3), 7.30-7.83 (m, 7H, CH_{Ar}), 10.49 (s, 1H, OH).	511	512 $[M + H]^+$	A	C	B
30		δ (CD3OD) = 1.91 (mC, 2H, CH2), 2.32 (s, 3H, CH3), 2.84 (mC, 2H, CH2), 2.93 (mC, 2H, CH2), 7.11 (mC, 1H, CHAr), 7.29 (s, 1H, CHAr), 7.32 (s, 1H, CHAr), 7.43-7.56 (m, 2H, CHAr).	375	376 [M + H]+	A	N.D.	N.D.
31		δ (CD3OD) = 2.00 (mC, 2H, CH2), 2.84 (mC, 2H, CH2), 2.94 (mC, 2H, CH2), 3.83 (s, 3H, O—CH3), 7.00-7.10 (m, 2H, CHAr), 7.18 (s, 1H, CHAr), 7.21 (s, 1H, CHAr), 7.31-7.39 (m, 2H, CHAr).	373	374 [M + H]+	A	N.D.	N.D.

TABLE 1-continued

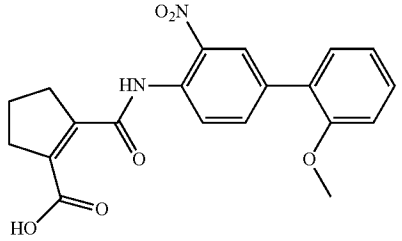
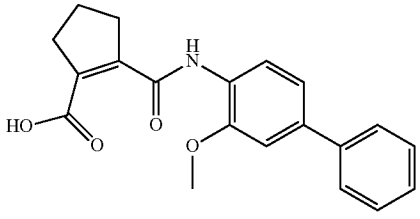
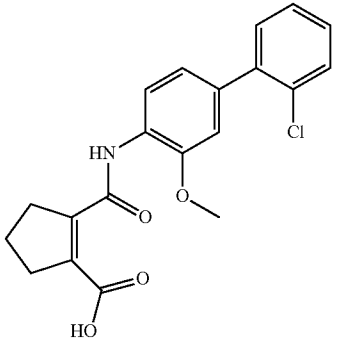
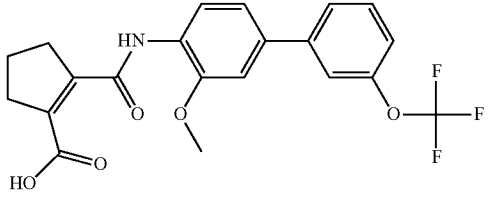
N	Structure	^{1}H-NMR	Molecule-Mass [g/mol]	HPLC/MS (ESI)	human IC_{50}-Value [μM]	murine IC_{50}-Value [μM]	rate IC_{50}-Value [μM]
32		δ = 1.90 (mC, 2H, CH2), 2.64 (mC, 2H, CH2), 2.74 (mC, 2H, CH2), 3.76 (s, 3H, O—CH3), 7.03 (mC, 1H, CHAr), 7.11 (mC, 1H, CHAr), 7.34 (s, 1H, CHAr), 7.36 (s, 1H, CHAr), 7.72-7.82 (m, 2H, CHAr), 8.02 (s, 1H, CHAr), 10.59 (s, 1H, NH), 12.85 (s, 1H, OH).	382	383 [M + H]+	A	N.D.	N.D.
33		δ = 1.85 (mC, 2H, CH2), 2.71 (mC, 2H, CH2), 2.80 (mC, 2H, CH2), 3.92 (s, 3H, O—CH3), 7.22 (mC, 1H, CHAr), 7.29-7.36 (m, 2H, CHAr), 7.45 (mC, 2H, CHAr), 7.67-7.71 (m, 2H, CHAr), 8.18 (mC, 1H, CHAr), 10.17 (s, 1H, NH).	337	338 [M + H]+	A	N.D.	N.D.
34		δ = 1.85 (mC, 2H, CH2), 2.71 (mC, 2H, CH2), 2.80 (mC, 2H, CH2), 3.85 (s, 3H, O—CH3), 6.98 (mC, 1H, CHAr), 7.10 (mC, 1H, CHAr), 7.37-7.46 (m, 3H, CHAr), 7.55 (mC, 1H, CHAr), 8.17 (mC, 1H, CHAr), 10.19 (s, 1H, NH).	371	372 [M + H]+	A	N.D.	N.D.
35		δ = 1.84 (mC, 2H, CH2), 2.71 (mC, 2H, CH2), 2.80 (mC, 2H, CH2), 3.93 (s, 3H, O—CH3), 7.26-7.35 (m, 3H, CHAr), 7.57 (mC, 1H, CHAr), 7.67 (s, 1H, CHAr), 7.74 (mC, 1H, CHAr), 8.23 (mC, 1H, CHAr), 10.33 (s, 1H, NH).	421	422 [M + H]+	A	N.D.	N.D.

TABLE 1-continued

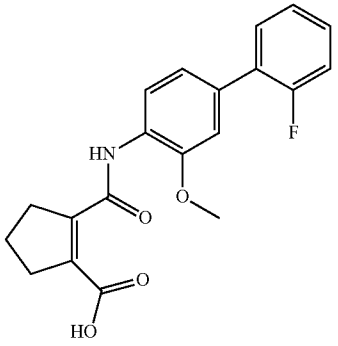
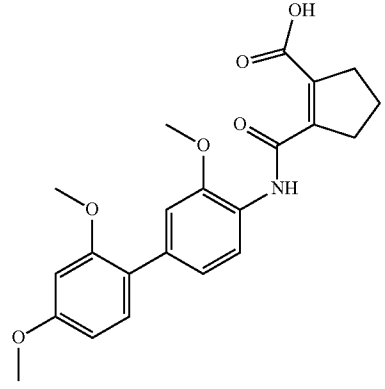
N	Structure	^{1}H-NMR	Molecule-Mass [g/mol]	HPLC/MS (ESI)	human IC_{50}-Value [μM]	murine IC_{50}-Value [μM]	rate IC_{50}-Value [μM]
36		δ = 1.85 (mC, 2H, CH2), 2.71 (mC, 2H, CH2), 2.80 (mC, 2H, CH2), 3.88 (s, 3H, O—CH3), 7.11 (mC, 1H, CHAr), 7.19 (s, 1H, CHAr), 7.25-7.42 (mC, 3H, CHAr), 7.56 (mC, 1H, CHAr), 8.20 (mC, 1H, CHAr), 10.23 (s, 1H, NH).	355	356 [M + H]+	A	N.D.	N.D.
37		δ = 1.84 (mC, 2H, CH2), 2.71 (mC, 2H, CH2), 2.79 (mC, 2H, CH2), 3.76 (s, 3H, O—CH3), 3.79 (s, 3H, O—CH3), 3.83 (s, 3H, O—CH3), 6.60 (mC, 1H, CHAr), 6.64 (mC, 1H, CHAr), 7.98 (mC, 1H, CHAr), 7.08 (mC, 1H, CHAr), 7.24 (mC, 1H, CHAr), 8.04 (mC, 1H, CHAr), 10.24 (s, 1H, NH).	397	398 [M + H]+	A	N.D.	N.D.

TABLE 1-continued

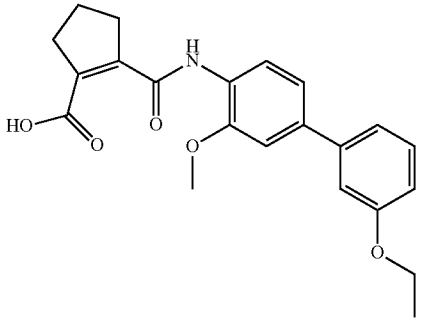
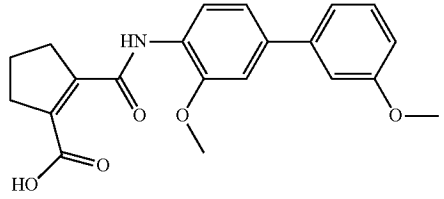
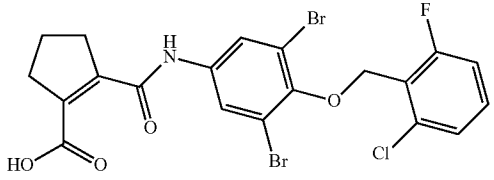
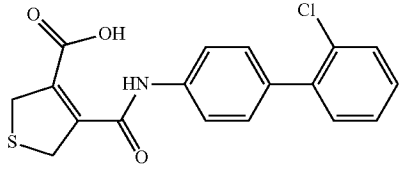
N	Structure	^{1}H-NMR	Molecule-Mass [g/mol]	HPLC/MS (ESI)	human IC_{50}-Value [μM]	murine IC_{50}-Value [μM]	rate IC_{50}-Value [μM]
38		δ = 1.34 (mC, 3H, O—CH2HC3), 1.84 (mC, 2H, CH2), 2.71 (mC, 2H, CH2), 2.80 (mC, 2H, CH2), 3.92 (s, 3H, O—CH3), 4.09 (mC, 2H, O—CH2CH3), 6.90 (mC, 1H, CHAr), 7.18-7.24 (mC, 3H, CHAr), 7.28 (mC, 1H, CHAr), 7.34 (mC, 1H, CHAr), 8.17 (mC, 1H, CHAr), 10.20 (s, 1H, NH).	381	382 [M + H]+	A	N.D.	N.D.
39		δ = 1.84 (mC, 2H, CH2), 2.71 (mC, 2H, CH2), 2.80 (mC, 2H, CH2), 3.82 (s, 3H, O—CH3), 3.92 (s, 3H, O—CH3), 6.92 (mC, 1H, CHAr), 7.20-7.26 (m, 3H, CHAr), 7.28 (mC, 1H, CHAr), 7.36 (mC, 1H, CHAr), 8.19 (mC, 1H, CHAr), 10.24 (s, 1H, NH).	367	368 [M + H]+	A	N.D.	N.D.
40		δ = 1.91 (mC, 2H, CH2), 2.63 (mC, 2H, CH2), 2.74 (mC, 2H, CH2), 5.21 (s, 2H, O—CH2), 7.22-7.89 (m, 5H, CHAr), 10.38 (s, 1H, nH), 12.65 (s, 1H, OH).	545	546 [M + H]+	A	C	C
41		δ = 4.22 (mC, 2H, CH2), 4.34 (mC, 2H, CH2), 7.57-7.90 (m, 8H, CHAr), 10.65 (s, 1H, OH).	359	360 [M + H]+	A	C	C

TABLE 1-continued

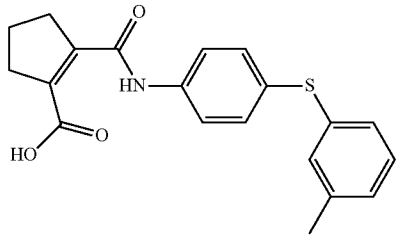
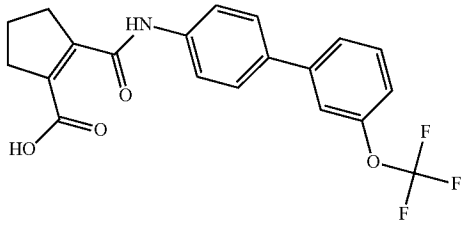
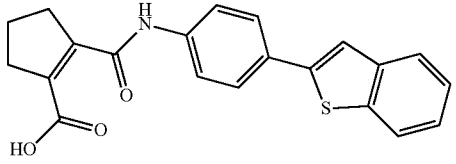
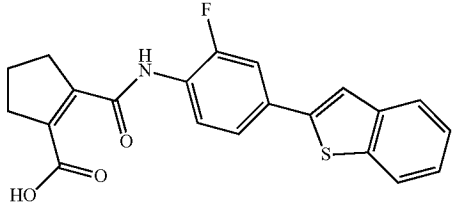
N	Structure	^{1}H-NMR	Molecule-Mass [g/mol]	HPLC/MS (ESI)	human IC_{50}-Value [μM]	murine IC_{50}-Value [μM]	rate IC_{50}-Value [μM]
42		δ = 1.85 (mC, 2H, CH2), 2.17 (s, 2H, CH3), 2.56 (mC, 2H, CH2), 2.65-2.70 (m, 2H, CH2), 6.89-7.59 (m, 8H, CHAr), 10.29 (s, 1H, NH), 12.55 (s, 1H, OH).	353	354 [M + H]+	A	A	A
43		δ = 1.94 (mC, 2H, CH2), 2.66 (mC, 2H, CH2), 2.79 (mC, 2H, CH2), 7.25-7.76 (m, 8H, CHAr), 10.36 (s, 1H, NH).	391	392 [M + H]+	A	N.D.	N.D.
44		δ = 2.03 (mC, 2H, CH2), 2.77 (mC, 2H, CH2), 2.88 (mC, 2H, CH2), 7.41-8.07 (m, 9H, CHAr), 10.55 (s, 1H, NH), 12.83 (s, 1H, OH).	363	364 [M + H]+	A	N.D.	N.D.
45		δ = 1.74 (mC, 2H, CH2), 2.55 (mC, 2H, CH2), 2.64 (mC, 2H, CH2), 7.18-8.02 (m, 8H, CHAr), 10.55 (s, 1H, NH), 12.91 (s, 1H, OH).	381	382 [M + H]+	A	N.D.	N.D.

TABLE 1-continued

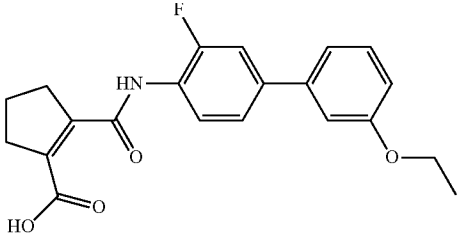
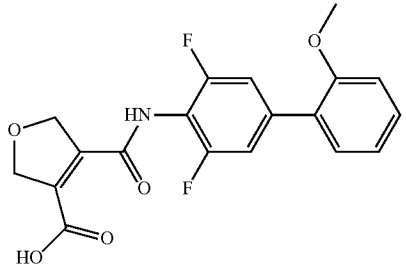
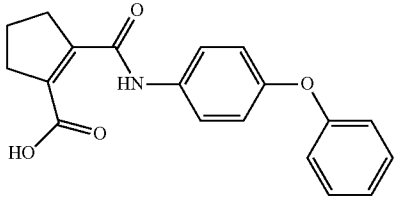
N	Structure	^{1}H-NMR	Molecule-Mass [g/mol]	HPLC/MS (ESI)	human IC_{50}-Value [µM]	murine IC_{50}-Value [µM]	rate IC_{50}-Value [µM]
46		δ = 1.19 (s, 3H, O—CH2—CH3), 1.74 (mC, 2H, CH2), 2.54 (mC, 2H, CH2), 2.65 (mC, 2H, CH2), 3.95 (mC, 2H, O—CH2—CH3), 6.75-6.78 (m, 1H, CHAr), 7.04-7.38 (m, 3H, CHAr), 7.43-7.48 (m, 2H, CHAr), 7.87-7.93 (m, 1H, CHAr), 10.41 (s, 1H, NH), 12.90 (s, 1H, OH).	369	370 [M + H]+	A	C	C
47		δ = 4.00 (s, 3H, O—CH3), 5.10-5.17 (m, 4H, CH2), 7.25-7.60 (m, 6H, CHAr), 10.55 (s, 1H, NH).	375	376 [M + H]+	A	C	A
50		δ = 1.90 (mC, 2H, CH2), 2.64 (mC, 2H, CH2), 2.76 (mC, 2H, CH2), 6.94-7.64 (m, 9H, CHAr), 10.25 (s, 1H, NH), 12.73 (s, 1H, OH).	323	324 [M + H]+	A	A	A

TABLE 1-continued

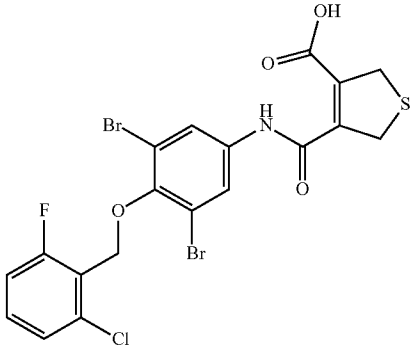
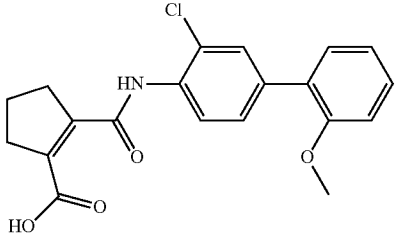
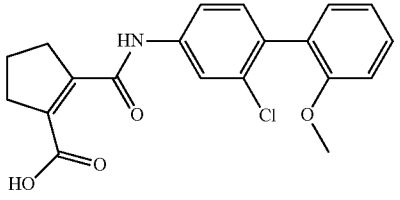
N	Structure	^{1}H-NMR	Molecule-Mass [g/mol]	HPLC/MS (ESI)	human IC_{50}-Value [µM]	murine IC_{50}-Value [µM]	rate IC_{50}-Value [µM]
52		δ = 4.08 (mC, 4H, CH2), 5.21 (mC, 2H, CH2), 6.61-7.63 (m, 9H, CHAr), 11.24 (s, 1H, NH).	563	564 [M + H]+	A	B	A
53		δ (CDCl3) = 2.03 (mC, 2H, CH2), 3.01-3.09 (m, 4H, CH2), 3.81 (s, 3H, O—CH3), 6.96-7.05 (m, 2H, CHAr), 7.25-7.37 (m, 2H, CHAr), 7.50 (mC, 1H, CHAr), 7.63 (s, 1H, CHAr), 8.36-8.39 (m, 2H, NH and CHAr).	371	372 [M + H]+	A	B	B
54		δ (CD3OD) = 2.00 (mC, 2H, CH2), 2.81 (mC, 2H, CH2), 2.9 (mC, 2H, CH2), 3.76 (s, 3H, O—CH3), 6.97-7.07 (m, 2H, CHAr), 7.14 (mC, 1H, CHAr), 7.22 (mC, 1H, CHAr), 7.37 (mC, 1H, CHAr), 7.50 (mC, 1H, CHAr), 7.85 (mC, 1H, CHAr).	371	372 [M + H]+	A	B	A

TABLE 1-continued

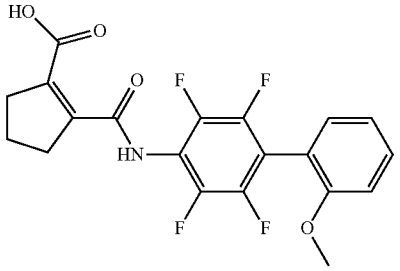
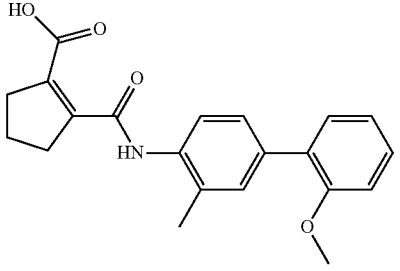
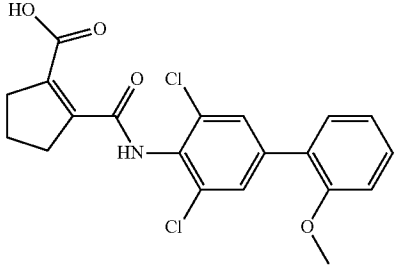
N	Structure	^{1}H-NMR	Molecule-Mass [g/mol]	HPLC/MS (ESI)	human IC_{50}-Value [μM]	murine IC_{50}-Value [μM]	rate IC_{50}-Value [μM]
56		δ (DMSO-d6) = 1.93 (mC, 2H, CH2), 2.67 (mC, 2H, CH2), 2.79 (mC, 2H, CH2), 3.79 (s, 3H, O—CH3), 7.09 (mC, 1H, CHAr), 7.20 (mC, 1H, CHAr), 7.37 (mC, 1H, CHAr), 7.51 (mC, 1H, CHAr).	409	410 [M + H]+	A	A	A
57		δ (CD3OD) = 1.97 (mC, 2H, CH2), 2.33 (s, 3H, CH3), 2.84 (mC, 2H, CH2), 2.94 (mC, 2H, CH2), 3.78 (s, 3H, O—CH3), 6.96-7.06 (m, 2H, CHAr), 7.25-7.35 (m, 4H, CHAr), 7.50 (mC, 1H, CHAr).	351	352 [M + H]+	A	B	B
58		δ (CD3OD) = 1.93 (mC, 2H, CH2), 2.87-2.95 (m, 4H, CH2), 3.83 (s, 3H, O—CH3), 7.01-7.10 (m, 2H, CHAr), 7.29-7.37 (m, 2H, CHAr), 7.56 (s, 2H, CHAr).	405	406 [M + H]+	A	B	B

TABLE 1-continued

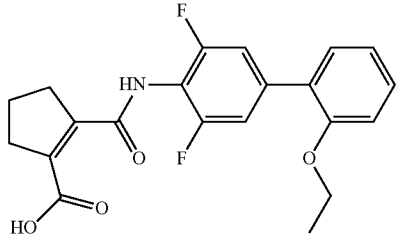
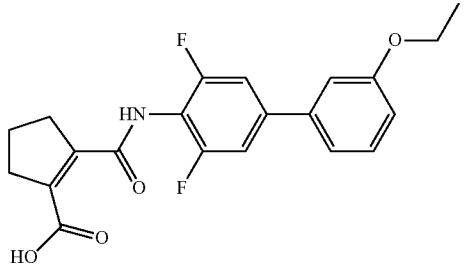
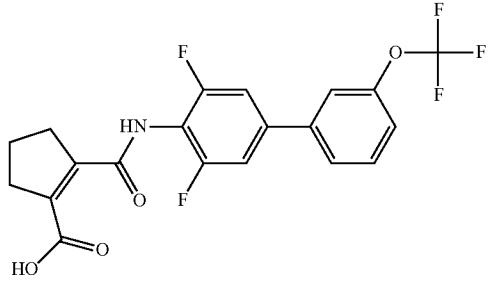
N	Structure	^{1}H-NMR	Molecule-Mass [g/mol]	HPLC/MS (ESI)	human IC_{50}-Value [µM]	murine IC_{50}-Value [µM]	rate IC_{50}-Value [µM]
62		δ (CD3OD) = 1.35 (mC, 3H, OCH2CH3), 2.00 (mC, 2H, CH2), 2.84 (mC, 2H, CH2), 2.94 (mC, 2H, CH2), 4.07 (mC, 2H, OCH2CH3), 6.98-7.08 (m, 2H, CHAr), 7.23 (mC, 2H, CHAr), 7.30-7.37 (m, 2H, CHAr).	387	388 [M + H]+	A	B	A
63		δ (CD3OD) = 1.40 (mC, 3H, OCH2CH3), 1.99 (mC, 2H, CH2), 2.84 (mC, 2H, CH2), 2.93 (t, J = 7.5 Hz, 2H, CH2), 4.09 (mC, 2H, OCH2CH3), 6.94 (mC, 1H, CHAr), 7.13-7.20 (m, 2H, CHAr), 7.30-7.38 (m, 3H, CHAr).	387	388 [M + H]+	A	B	A
64		δ (CD3OD) = 1.99 (mC, 2H, CH2), 2.85 (mC, 2H, CH2), 2.91 (mC, 2H, CH2), 7.31-7.39 (m, 3H, CHAr), 7.54-7.59 (m, 2H, CHAr), 7.66 (mC, 2H, CHAr).	427	428 [M + H]+	A	C	N.D.

TABLE 1-continued

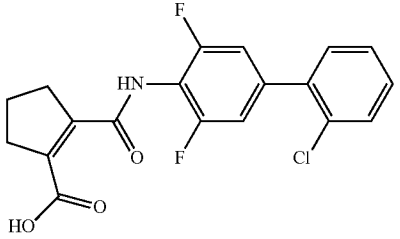
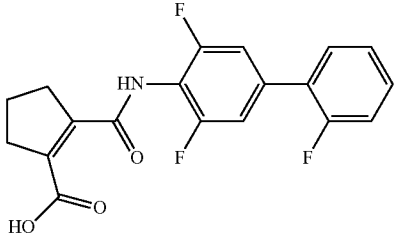
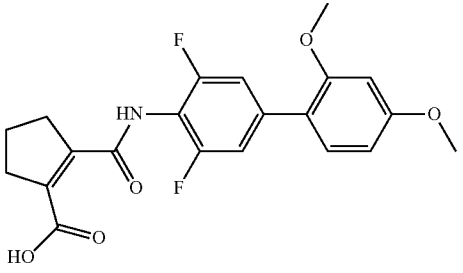
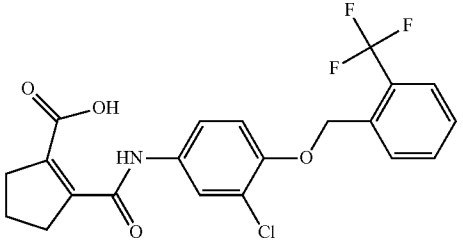
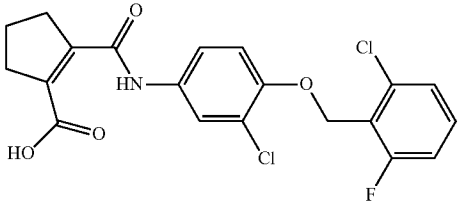
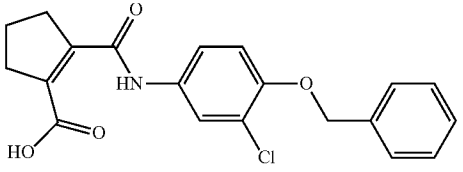
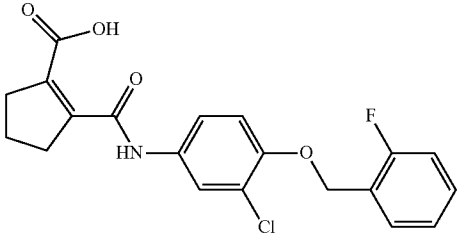
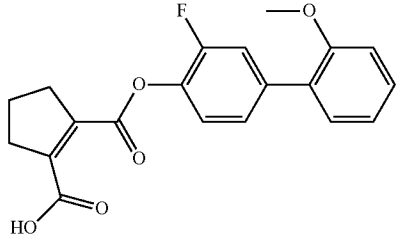
N	Structure	^{1}H-NMR	Molecule-Mass [g/mol]	HPLC/MS (ESI)	human IC_{50}-Value [µM]	murine IC_{50}-Value [µM]	rate IC_{50}-Value [µM]
65		δ (CD3OD) = 2.00 (mC, 2H, CH2), 2.84 (mC, 2H, CH2), 2.94 (mC, 2H, CH2), 7.12 (s, 1H, CHAr), 7.14 (s, 1H, CHAr), 7.37-7.42 (m, 3H, CHAr), 7.49-7.53 (m, 1H, CHAr).	377	378 [M + H]+	A	A	N.D.
66		δ (CD3OD) = 2.00 (mC, 2H, CH2), 2.84 (mC, 2H, CH2), 2.94 (t, J = 7.8 Hz, 2H, CH2), 7.18-7.30 (m, 4H, CHAr), 7.38-7.46 (m, 1H, CHAr), 7.46-7.55 (m, 1H, CHAr).	361	362 [M + H]+	A	B	N.D.
67		δ (CD3OD) = 1.94 (mC, 2H, CH2), 2.84-2.92 (m, 4H, CH2), 3.82 (s, 3H, O—CH3), 3.83 (s, 3H, O—CH3), 6.58-6.64 (m, 2H, CHAr), 7.14 (s, 1H, CHAr), 7.17 (s, 1H, CHAr), 7.26 (mC, 1H, CHAr).	403	404 [M + H]+	A	C	N.D.
68		δ = 1.90 (mC, 2H, CH2), 2.63 (mC, 2H, CH2), 2.74 (mC, 2H, CH2), 5.27 (s, 2H, O—CH2), 7.19-7.82 (m, 7H, CHAr), 10.23 (s, 1H, NH), 12.69 (s, 1H, OH).	439	440 [M + H]+	A	C	C

TABLE 1-continued

N	Structure	^{1}H-NMR	Molecule-Mass [g/mol]	HPLC/MS (ESI)	human IC_{50}-Value [μM]	murine IC_{50}-Value [μM]	rate IC_{50}-Value [μM]
69		δ = 1.89 (mC, 2H, CH2), 2.62 (mC, 2H, CH2), 2.74 (mC, 2H, CH2), 5.18 (mC, 2H, O—CH2), 7.27-7.77 (m, 6H, CHAr), 10.21 (s, 1H, NH), 12.69 (s, 1H, OH).	423	424 [M + H]+	A	A	N.D.
72		δ = 1.73 (mC, 2H, CH2), 2.46 (mC, 2H, CH2), 2.57 (mC, 2H, CH2), 4.99 (mC, 2H, O—CH2), 7.00-7.62 (m, 8H, CHAr), 10.02 (s, 1H, NH), 12.70 (s, 1H, OH).	371	372 [M + H]+	A	B	N.D.
74		δ = 1.82 (mC, 2H, CH2), 2.55 (mC, 2H, CH2), 2.67 (mC, 2H, CH2), 5.11 (mC, 2H, O—CH2), 7.14-7.72 (m, 7H, CHAr), 10.18 (s, 1H, NH), 12.53 (s, 1H, OH).	389	390 [M + H]+	A	A	N.D.
76		δ (CDCl3) = 2.01 (mC, 2H, CH2), 2.99-3.04 (m, 4H, CH2), 3.81 (s, 3H, O—CH3), 6.96-7.04 (m, 2H, CHAr), 7.27-7.41 (m, 4H, CHAr), 8.19 (s, 1H, NH), 8.28 (mC, 1H, CHAr).	355	356 [M + H]+	A	B	A

abbreviations: N.D. = not determined, m_C = multiplet center
inhibition activity is defined: A: 0-800 nM B: 800-1500 nM C: >1500 nM

[0112] The compounds of formula (I) may be obtained via various methods, including the method described in JP-A-50-121428. In preferred embodiments of the methods of the invention the two following methods of synthesis are used.

[0113] Method 1: In a first step the cycloalkene-1,2-dicarboxic acids can be obtained from the corresponding α,α'-dibromo alkanedicarboxylic acids as described by R. N. Mc Donald and R. R. Reitz, J. Org. Chem. 37, (1972) 2418-2422, Cyclopentene-1,2-dicarboxylic acid can also be obtained in large amounts from pimelic acid [D. C. Owsley and J. J. Bloomfield, Org. Prep. Proc. Int. 3, (1971) 61-70; R. Willstätter, J. Chem. Soc. (1926), 655-663].

[0114] Dicarboxylic acids substituted in or on the ring system can be synthesized in general via the cyanhydrine synthesis [Shwu-Jiüan Lee et. al., Bull. Inst. Chem. Academia Sinica Number 40, (1993), 1-10 or B. R. Baker et al., J. Org. Chem. 13, 1948, 123-133; and B. R. Baker at al., J. Org. Chem. 12, 1947, 328-332; L. A. Paquette et. al., J. Am. Chem. Soc. 97, (1975), 6124-6134].

[0115] The dicarboxylic acids can then be converted into the corresponding acid anhydrides by reacting them with acetic acid anhydride [P. Singh and S. M. Weinreb, Tetrahedron 32, (1976), 2379-2380].

[0116] Other methods for preparing different acid anhydrides of formula (II) are described in V. A. Montero at al., J. Org. Chem. 54, (1989), 3664=3667; P. ten Haken, J. Heterocycl. Chem. 7, (1970), 1211-1213; K. Alder, H. Holzrichter, J. Lieb. Annalen d. Chem. 524, (1936), 145-180; K. Alder, E. Windemuth, J. Lieb. Annalen d, Chem. 543, (1940), 56-78; and W. Flaig, J. Lieb. Annalen d. Chem. 568, (1950), 1-33.

[0117] These anhydrides may then be reacted with the corresponding amines to the desired amides of formula (I). This reaction can be carried out either by use of the reaction conditions as described in J. V. de Julian Ortiz et al., J. Med. Chem. 42, (1999), 3308 (designated route A in Example 1) or by use of 4-dimethylamino pyridine (designated route B in Example 1).

[0118] Method 2: The amides of formula (I) can also be synthesized by reacting an amine of the formula (IV) with an arylboronic-acid of the general formula (V) [M. P. Winters, Tetrahedron Lett., 39, (1998), 2933=2936].

[0119] Biarylaniline can be synthesized in general via the palladium coupling [G. W. Kabalka et al., Chem.Commun., (2001), 775; A. Demeter, Tetrahedron Lett. 38; (1997), 5219-5222; V. Snieckus, Chem.Commun. 22, (1999), 2259-2260].

[0120] Method 3: The amides of fo mula (I) can also be synthesized by reacting an halogen derivative of the formula (VI) with an arylboronic acid of the general formula (VII) [N. E. Leadbeater, S. M. Resouly, Tetrahedron, 55, 1999, 11889=11894].

[0121] The salts of the present invention can be used for a variety of human and animal diseases, preferably human diseases, where inhibition of the pyrimidine metabolism is beneficial. Such diseases are:

[0122] fibrosis, uveitis, rhinitis, asthma or athropathy, in particular, arthrosis

[0123] all forms of rheumatism

[0124] acute immunological events and disorders such as sepsis, septic shock, endotoxic shock, Gram-negative sepsis, toxic shock sydrome, acute respiratory distress syndrome, stroke, reperfusion injury, CNS injury, serious forms of allergy, graft versus host and host versus graft reactions, alzheimer's or pyresis, restenosis, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, bone resorption disease. These immunological events also include a desired modulation and suppression of the immune system;

[0125] all types of autoimmune diseases, in particular rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, multiple sclerosis, insulin dependent diabetes mellitus and non-insulin dependent diabetes, and lupus erythematosus, ulcerative colitis, Morbus Crohn, inflammatory bowel disease, as well as other chronic inflammations, chronic diarrhea;

[0126] dermatological disorders such as psoriasis

[0127] progressive retinal atrophy

[0128] all kinds of infections including opportunistic infections.

[0129] The salts according to the invention and medicaments prepared therewith are generally useful for the treatment of cell proliferation disorders, for the treatment or prophylaxis, immunological diseases and conditions (as for instance inflammatory diseases, neuroimmunological diseases, autoimmune diseases or other).

[0130] The salts of the present invention are also useful for the development of immunomodulatory and anti-inflammatory medicaments or, more generally, for the treatment of diseases where the inhibition of the pyrimidine biosynthesis is beneficial.

[0131] The salts of the present invention are also useful for the treatment of diseases which are caused by malignant cell proliferation, such as all forms of hematological and solid cancer. Therefore the compounds according to the invention and medicaments prepared therewith are generally useful for regulating cell activation, cell proliferation, cell survival, cell differentiation, cell cycle, cell maturation and cell death or to induce systemic changes in metabolism such as changes in sugar, lipid or protein metabolism. They can also be used to support cell generation poiesis, including blood cell growth and generation (prohematopoietic effect) after depletion or destruction of cells, as caused by, for example, toxic agents, radiation, immunotherapy, growth defects, malnutrition, malabsorption, immune dysregulation, anemia and the like or to provide a therapeutic control of tissue generation and degradation, and therapeutic modification of cell and tissue maintenance and blood cell homeostasis.

[0132] These diseases and conditions include but are not limited to cancer as hematological (e.g. leukemia, lymphoma, myeloma) or solid tumors (for example breast, prostate, liver, bladder, lung, esophageal, stomach, colorectal, genitourinary, gastrointestinal, skin, pancreatic, brain, uterine, colon, head and neck, and ovarian, melanoma, astrocytoma, small cell lung cancer, glioma, basal and squameous cell carcinoma, sarcomas as Kaposi's sarcoma and osteosarcoma), treatment of disorders involving T-cells such as aplastic anemia and DiGeorge syndrome, Graves' disease.

[0133] Leflunomide, was previously found to inhibit HCMV replication in cell culture. Ocular herpes is the most common couse of infectious blindness in the developed world. There are about 50,000 cases per year in the US alone, of which 90% are recurences of initial infections. Recurrences are treated with antivirals and corticosteroids. Cytomegalovirus another herpes virus is a common couse of retinal damage and blindness in patients with aids. The compounds of the present invention can be used alone or in combination with other antiviral compounds such as Ganciclovir and Foscarnet to treat such diseases.

[0134] The salts of the present invention can further be used for diseases that are caused by protozoal infestations in humans and animals. Such veterinary and human pathogenic protozoas are preferably intracellular active parasites of the phylum Apicomplexa or Sarcomastigophora, especially Trypanosoma, Plasmodia, Leishmania, Babesia and Theileria, Cryptosporidia, Sacrocystida, Amoebia, Coccidia and Trichomonadia. These active substances or corresponding drugs are especially suitable for the treatment of Malaria tropica, caused by *Plasmodium falciparum*, Malaria tertiana, caused by *Plasmodium vivax* or *Plasmodium ovale* and for the treatment of Malaria quartana, caused by *Plasmodium malariae*. They are also suitable for the treatment of Toxoplasmosis, caused by *Toxoplasma gondii*, Coccidiosis, caused for instance by *Isospora belli*, intestinal Sarcosporidiosis, caused by *Sarcocystis suihominis*, dysentery caused by *Entamoeba histolytica*, Cryptosporidiosis, caused by *Cryptosporidium parvum*, Chargas' disease, caused by *Trypanosoma cruzi*, sleeping sickness, caused by *Trypanosoma brucei rhodesiense* or *gambiense*, the cutaneous and visceral as well as other forms of Leishmaniosis. They are also suitable for the treatment of animals infected by veterinary pathogenic protozoa, like *Theileria parva*, the pathogen causing bovine East coast fever, *Trypanosoma congolense congolense* or *Trypanosoma vivax vivax, Trypanosoma brucei brucei*, pathogens causing Nagana cattle disease in Africa, *Trypanosoma brucei evansi* causing Surra, *Babesia bigemina*, the pathogen causing Texas fever in cattle and buffalos, *Babesia bovis*, the pathogen causing european bovine Babesiosis as well as Babesiosis in dogs, cats and sheep, *Sarcocystis ovicanis* and *ovifelis* pathogens causing Sarcocystiosis in sheep, cattle and pigs, Cryptosporidia, pathogens causing Cryptosporidioses in cattle and birds, Eimeria and *Isospora* species, pathogens causing Coccidiosis in rabbits, cattle, sheep, goats, pigs and birds, especially in chickens and turkeys. The use of the compounds of the present invention is preferred in particular for the treatment of Coccidiosis or Malaria infections, or for the preparation of a drug or feed stuff for the treatment of these diseases. This treatment can be prophylactic or curative. In the treatment of malaria, the compounds of the present invention may be combined with other anti-malaria agents.

[0135] The salts of the present invention can further be used for viral infections or other infections caused for instance by *Pneumocystis carinii.*

[0136] Preferably, the diseases or medical conditions to be treated or prevented by the calcium salts according to the present invention are selected from the group comprising graft versus host and host versus graft reactions, rheumatoid arthritis, multiple sclerosis, lupus erythematosus, inflammatory bowel disease, and psoriasis.

[0137] The specific salts of the compounds of the formula (I) according to the present invention can be administered to animals, preferably to mammals, and in particular to humans, dogs and chickens as therapeutics per se, as mixtures with one another or in the form of pharmaceutical preparations which allow enteral or parenteral use and which as active constituent contain an effective dose of at least one of the aforementioned specific salts of the compound of the formula (I) according to the present invention, in addition to customary pharmaceutically innocuous excipients and additives.

[0138] The therapeutics can be administered orally, e.g. in the form of pills, tablets, coated tablets, sugar coated tablets, hard and soft gelatin capsules, solutions, syrups, emulsions or suspensions or as aerosol mixtures. Administration, however, can also be carried out rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injections or infusions, or percutaneously, e.g. in the form of ointments, creams or tinctures.

[0139] In addition to the aforementioned salts of the active compounds of formula (I), the pharmaceutical composition can contain further customary, usually inert carrier materials or excipients. Thus, the pharmaceutical preparations can also contain additives, such as, for example, fillers, extenders, disintegrants, binders, glidants, wetting agents, stabilizers, emulsifiers, preservatives, sweetening agents, colorants, flavorings or aromatizers, buffer substances, and furthermore solvents or solubilizers or agents for achieving a depot effect, as well as salts for changing the osmotic pressure, coating agents or antioxidants. They can also contain the aforementioned salts of two or more compounds of the formula (I) and also other therapeutically active substances.

[0140] Thus, the salts of the present invention can be used alone or in combination with other active compounds—for example with medicaments already known for the treatment of the aforementioned diseases, whereby in the latter case a favorable additive, amplifying effect is noticed. Suitable amounts to be administered to humans range from 5 to 500 mg.

[0141] To prepare the pharmaceutical preparations, pharmaceutically inert inorganic or organic excipients can be used. To prepare pills, tablets, coated tablets and hard gelatin capsules, for example, lactose, corn starch or derivatives thereof, talc, stearic acid or its salts, etc. can be used. Excipients for soft gelatin capsules and suppositories are, for example, fats, waxes, semi-solid and liquid polyols, natural or hardened oils etc. Suitable excipients for the production of solutions and syrups are, for example, water, sucrose, invert sugar, glucose, polyols etc. Suitable excipients for the production of injection solutions are, for example, water, alcohols, glycerol, polyols or vegetable oils.

[0142] The dose can vary within wide limits and is to be suited to the individual conditions in each individual case. For the above uses the appropriate dosage will vary depending on the mode of administration, the particular condition to be treated and the effect desired. In general, however, satisfactory results are achieved at dosage rates of about 1 to 100 mg/kg animal body weight preferably 1 to 50 mg/kg. Suitable dosage rates for larger mammals, for example humans, are of the order of from about 10 mg to 3 g/day, conveniently administered once, in divided doses 2 to 4 times a day, or in sustained release faun.

[0143] In general, a daily dose of approximately 10 mg to 5000 mg, preferably 50 to 500 mg, per human individual is appropriate in the case of the oral administration which is the preferred for in of administration according to the invention. In the case of other administration forms too, the daily dose is in similar ranges.

BRIEF DESCRIPTION OF THE FIGURES

[0144] FIG. **1**: Reduction of human lymphocyte cell proliferation caused by 2-(Biphenyl-4-ylcarbamoyl)-cyclopent-1-enecarboxylic acid used in a concentration of 100 μM;

[0145] FIG. **2**: Powder Xray diffraction pattern of vidofludimus free acid.

[0146] FIG. **3**: The upper line shows the Raman spectrum of the NMG salt produced as described in example 4, the lower spectrum pertains to vidofludimus free acid. The spectra have been scaled and offset in y-direction for comparison.

[0147] FIG. **4**: Optical microscopy of the NMG salt without crossed and with crossed polarizers. The picture shows that the sample consists of very small crystalline particles.

[0148] FIG. **5**: Powder Xray diffraction pattern of the NMG salt. The sharp peaks demonstrate that crystalline material was obtained.

[0149] FIG. **6**: Raman spectrum of the DEA salt (top trace) and for comparison of the vidofludimus free acid (lower trace). The differences in the spectra support the notion that salt formation led to a new crystal structure.

[0150] FIG. **7**: Optical microscopy image of the DEA salt through crossed polarizers

[0151] FIG. **8**: XRPD of the DEA salt.

[0152] FIG. **9**: Raman spectra of two different Arg salt preparations (top and middle trace). For comparison, the Raman spectrum of vidofludimus acid is shown in the bottom trace; it differs significantly from the salt spectra.

[0153] FIG. **10**: Optical microscopy image through crossed polarizers of the arginine salt, suggesting that the material is crystalline.

[0154] FIG. **11**: PXRD of the arginine salt.

[0155] FIG. **12**: Raman spectrum of the choline salt (top trace) and vidofludimus acid (bottom).

[0156] FIG. **13**: Optical microscopy image through crossed polarizers of the choline salt, suggesting that the material is crystalline.

[0157] FIG. **14**: PXRD of the choline salt.

[0158] FIG. **15**: Raman spectrum of HEM salt (top and middle trace, two different preparations) which differs from vidofludimus acid Raman spectrum (bottom)

[0159] FIG. **16**: Optical microscopy image through crossed polarizers of the HEM salt, suggesting that the material is crystalline.

[0160] FIG. **17**: PXRD spectrum of the HEM salt, confirming its crystalline nature.

EXAMPLES

[0161] The invention is further illustrated by the following non-limiting Examples. The data shown for the specific compounds depicted in above Table 1 also relates to specific Examples of the present invention.

Experimental/Instrument Settings

[0162] ^{1}H-NMR: ^{1}H-NMR spectra were recorded using a Bruker DPX300 spectrometer with a proton frequency of 300.13 MHz, a 30° excitation pulse, and a recycle delay of 1 s. 16 scans were accumulated, D_2O; MeOD or d6-DMSO was used as the solvent.

[0163] Solubility: Solubility was determined by a stepwise addition of 0.05 mL portions of solvent to a suspension of 10 mg of sample in 0.05 mL of solvent. If the substance was not dissolved by addition of a total of 10 mL solvent, the solubility is indicated as less than 1 mg/mL.

[0164] DSC: Differential scanning calorimetry was carried out with a Perkin Elmer DSC-7 instrument (closed gold sample pan under N_2 atmosphere). The sample are heated up to the melting point at a rate of 10K/min), then cooled down (cooling rate 200K/min) and afterwards heated up again at a rate of 10K/min.

[0165] DVS (SMS): Surface Measurement Systems Ltd. DVS-1 water vapour sorption analyzer. The sample is placed on a platinum sample pan and allowed to equilibrate at a given relative humidity (r.h.), usually 50% r.h. Then, a pre-defined humidity program was started with a scanning rate of 5% r.h. change per hour. First step: from 50% r.h. to 0% r.h. (in case of a possibly hydrate as starting material 50 to 95% r.h.), second step: from 0% to 95% r.h. (in case of a possibly hydrate as starting material 95 to 0% r.h.)

[0166] FT-Raman spectroscopy: FT-Raman spectra were recorded on a Bruker RFS 100 FT-Raman system with a near infrared Nd:YAG laser operating at 1064 nm and a liquid nitrogen-cooled germanium detector. For each sample, a minimum of 64 scans with a resolution of 2 cm^{-1} were accumulated. 300 mW nominal laser power was used. The FT-Raman data are shown in the region between 3500 to 100 cm^{-1}. Below 100 cm^{-1} the data are unreliable due to the Rayleigh filter cut-off.

[0167] Optical Microscopy: Leitz Orthoplan 110680 microscope equipped with a Leica DFC280 camera and IM50 v.5 image-capturing software: Images were recorded with or without crossed polarizers and with 4×, 10×, or 25× magnification.

[0168] Powder X-ray diffraction: Bruker D8; Copper K_α radiation, 40 kV/40 mA; LynxEye detector, 0.02 °2Θ step size, 37 s step time. Sample preparation: The samples were generally measured without any special treatment other than the application of slight pressure to get a flat surface. Silicon single crystal sample holders were used (0.1, 0.5 or 1 mm deep). The samples were rotated during the measurement.

[0169] Raman microscopy: Renishaw in Via Reflex Raman System. Stabilized diode laser with 785 nm excitation and an NIR enhanced Peltier-cooled CCD camera as the detector. Measurements were carried out with a long working distance 20× objective. Wavenumber range 2000-100 cm^{-1}, 10 s detection time, three accumulations per spectrum.

[0170] Solvents: For all experiments, Fluka, Merck or ABCR analytical grade solvents were used.

[0171] TG-FTIR: Thermogravimetric measurements were carried out with a Netzsch Thermo-Microbalance TG 209 coupled to a Bruker FTIR Spectrometer Vector 22 or IFS 28 (sample pans with a pinhole, N2 atmosphere, heating rate 10° C./min, range 25° C. to 350° C.).

[0172] HPLC: HPLC was performed with a Dionex UltiMate® 3000 liquid chromatograph comprising a solvent Rack, a vacuum degasser, a binary pump (mikro), a static mixer (500 μl), an autosampler, a 25 μl sample loop, a 100 μl syringe, a column oven and a DAD detector (semimicro measuring cell), which was set up for UV analysis. Data analysis was done with Chromeleon® 6.80 SP3. Compounds were separated at 30° C. on a Phenomenex Onyx™ Monolithic C18 50×2 mm column. The injection volume was 2 μl and the detection wavelength was 305 nm. As mobile phase, a gradient of 0.1% formic acid in HPLC grade water/acetonitrile was used, starting at a concentration of 5% acetonitrile. The starting concentration was held for 1 minute, then the gradient was ramped linearly to 95% acetonitrile over the course of 2 min, held for 0.7 min at 95% acetonitrile, after which it was returned to 5% acetonitrile within 0.1 min and kept constant for 0.7 min to re-equilibrate the column. The mobile phase flow rate was 1.5 ml/min.

Example 1

The synthesis of compounds of formula (I) is described in detail in WO 2003/0006425, which is incorporated herein by reference

Example 2

Inhibition Assay of DHODH Activity

[0173] The standard assay mixture contained 50 μM decyclo ubichinone, 100 μM dihydroorotate, 60 μM 2,6-dichlor-

oindophenol, as well as 20 mU DHODH. The volume activity of the recombinant enzyme used was 30 U/ml. Measurements were conducted in 50 mM TrisHCl (150 mM KCl, 0.1% Triton X-100, pH 8.0) at 30° C. in a final volume of 1 ml. The components were mixed, and the reaction was started by adding dihydroorotate. The course of reaction was followed by spectrophotometrically measuring the decrease in absorption at 600 nm for 2 mM.

[0174] Inhibitory studies were conducted in a standard assay with additional variable amounts of inhibitor. For the determination of the IC_{50} values (concentration of inhibitor required for 50% inhibition) at least five different inhibitor concentrations were applied. These investigations were carried out with recombinant human as well as with recombinant murine DHODH provided by Prof. M. Löffler, Marburg, Germany [M. Löffler, Chem. Biol. Interact. 124, (2000), 61-76].

[0175] As a reference the active metabolite of leflunomide A77-1726 (Compound 12) was used [J. Jöckel et. al. Biochemical Pharmacology 56 (1998), 1053-1060].

[0176] The results of the inhibition assay are shown in the above Table 1. It is evident from the comparison of the IC_{50}-values that the compounds used for the preparation of the salts according to the present invention not only have a comparable or even better inhibitory activity on the human enzyme than the active metabolite of leflunomide but also a higher specifity for the human enzyme.

Example 3

Proliferation Assay of Human T-Cells

[0177] Human peripheral blood mononuclear cells (PBMC) were obtained from healthy volunteers and transferred to RPM11640 cell culture medium containing 10% dialyzed fetal calf serum. 80,000 cells per well were pipetted into a 96-well plate and phytohemagglutinin (PHA) was added in phosphate buffered saline to a final concentration of 20 μg/ml to stimulate T-cell proliferation. Vidofludimus was added in dimethyl sulfoxide (DMSO, final concentration: 0.1 Vol %) to final concentrations ranging from 20 nM to 50 μM. After incubation for 48 hours, cell proliferation was quantified using the "cell proliferation ELISA BrdU" (Roche) according to the manufacturer's instructions. Half maximal inhibition (IC_{50}) was calculated using a 4-parameter sigmoidal curve fit, T-cell proliferation was inhibited by Vidofludimus with an IC_{50} of 4.1 μM. (see FIG. **1**).

Example 4

Preparation of the NMG Salt

[0178] 301.2 mg of Vidofludimus free acid was dissolved in 18 mL of DCM/MeOH (3:1). 165.4 mg of N-methyl-D-glucamine (NMG) was suspended in 5 mL of DCM/MeOH (3:1). The solution of NMG was slowly added to the solution of Vidofludimus free acid. The color of the solution changed from yellow to light yellow. The solution was stirred overnight at 25° C. The solvent was evaporated under nitrogen flow at 25° C. The recovered amorphous solid was suspended in 1.0 mL DCM/MeOH (3:1). The suspension was stirred for 5 days at 25° C. The solid was recovered by filtration. The solid was dried for 15 minutes under vacuum (Sample A).

[0179] Sample B) About ⅓ of the solid produced as Sample A was suspended in 500 μL of 1,4-dioxane/TBME (tert-butylmethylether) (1:1) and stirred for 3 days at 25° C. Partially crystalline material (Sample B) was obtained.

[0180] 253.9 mg of sample A produced above was suspended in 2 mL of 1,4-dioxane/TBME and seeded with Sample B. The suspension was stirred for seven days at 25° C. The solid was recovered by vacuum filtration and washed with 1,4-dioxane/TBME, The sample was dried for 15 min under vacuum. The material was shown to be crystalline using the methods described in the following.

[0181] From elemental analysis, the ratio of nitrogen to fluorine was calculated; the elemental composition analysis is essentially consistent with a 1:1 salt.

[0182] The Raman spectrum of the newly formed compound demonstrated differences to that of the free acid (see FIG. **3** for both spectra.). (Note that a Raman spectrum that is not simply the superposition of the free acid, the salt former and the solvent spectra, e.g., a Raman spectrum where new peaks or shifted peaks are observed, may correspond to a salt. However, from the Raman spectrum alone, it cannot be determined whether crystalline salt formation has occurred. Peak shifts could also be due, in principle, to complexation of the free acid and salt former as an amorphous product, to polymorphs of either the free acid or salt former, to impurities, or to degradation products. Therefore, the integrity of the molecular structure was confirmed by ^{1}H-NMR (not shown)).

[0183] In addition, the powder X-ray diffraction shown in FIG. **5** show that crystalline material was obtained, however with a pattern different from that of the free acid (see FIG. **2**), With light microscopy the crystals were visualized (FIG. **4**), DSC (differential scanning calorimetry) demonstrated a melting point of about 143° C., TG-FTIR (thermogravimetric analyzer-coupled Fourier-Transform Infrared) indicates that probably a hydrate was formed (0.8% water) and dynamic vapor sorption yielded 0.3% water uptake at about 85% r.h. and 0.5% water uptake at 95% r.h. (reversible).

Example 5

Preparation of the DEA Salt

[0184] 201.1 mg of Vidofludimus free acid was dissolved in 23.5 mL of acetone at 50° C. 58 μL of diethyl amine was added. The solution decolorized. The solution was evaporated under nitrogen flow at 25° C. The white crystalline solid was suspended in 1.4 mL of acetone. The suspension was stirred for almost 5 h at 25° C. The solid was recovered by filter centrifugation with a 0.2-μm PTFE centrifuge filter. The crystallinity of the material was determined as described in the following.

[0185] The elemental composition analysis data is shown in the table below; the data is consistent with a 1:1 salt that contains water.

Element	% calculated	% found
C	67.0	67.0
H	6.968	6.6
N	6.5	6.7
O	15.2	15.3
F	4.4	4.4

[0186] The Raman spectrum of the newly formed compound demonstrated differences to that of the free acid (see FIG. **6** for both spectra). As noted already in the previous examples, further analysis was performed to confirm the integrity of the molecular structure (1H-NMR). PXRD also

confirmed formation of a new crystalline structure (see FIG. **8**). The salt was further characterized by light microscopy (FIG. **7**), DSC (melting point around 161° C.), TG-FTIR (probably nonsolvated form) and dynamic vapor sorption (0.2% water uptake at about 85% r.h., 0.5% water uptake at 95% r.h., reversible).

Example 6

Preparation of the Arginine Salt

[0187] 298.0 mg of vidofludimus free acid was suspended in 34 mL of acetone at 50° C. A small amount of the material was not dissolved. 146.4 mg of L-arginine was dissolved in 1.0 mL of water, and slowly added to the suspension. The vessel containing the salt former solution was rinsed with 100 μL of water; this solution was also added to the vidofludimus acid suspension. Precipitation was observed. After sonication and stirring for a few minutes at 50° C., an amorphous film at the bottom of the vessel was observed. The sample was treated for 10 min with ultrasound and afterwards stirred at 25° C. After 1 h precipitation alongside the amorphous film was observed. The suspension was stirred overnight at 25° C. The white solid was recovered by filter centrifugation with a 0.2-μm PTFE centrifuge filter and washed with 500 μL of acetone. The material was dried for a few minutes under vacuum at 25° C. The crystallinity of the material was determined as described in the following.

[0188] Elemental composition analysis is summarized in the table below and corresponds to a 1:1 salt.

Element	% calculated	% found
C	58.7	58.6
H	6.5	6.4
N	12.0	12.0
O	19.5	19.8
F	3.3	3.1

[0189] The Raman spectrum of the newly formed arginine salt demonstrated differences to that of the free acid (see FIG. **9**). As noted already in the previous examples, further analysis was performed to confirm the integrity of the molecular structure (1H-NMR). PXRD also confirmed formation of a new crystalline structure (FIG. **11**). The salt was further characterized by light microscopy (see FIG. **10**), DSC (melting point around 156° C.), TG-FTIR (probably acetone solvate) and dynamic vapor sorption (1.7% water uptake at about 85% r.h., >12% water uptake at 95% r.h., irreversible).

Example 7

Preparation of the Choline Salt

[0190] 300.7 mg of vidofludimus acid was dissolved in 18 mL of DCM/MeOH (3:1) (sonication for 3 minutes). 239 μL of choline solution (~45% in methanol) was slowly added. The color of the solution changed from yellow to light yellow. The solution was stirred overnight at 25° C. The solution was evaporated under nitrogen flow at 25° C. The yellow solid was suspended in 200 μL of DCM/MeOH (3:1). The suspension was stirred for 2 days at 25° C. The solid was recovered by filtration and washed with DCM/MeOH (3:1). The material was dried for 15 min under vacuum. The crystallinity of the material was determined as described in the following.

[0191] Elemental composition analysis is summarized in the table below and corresponds to a 1:1 salt that contains water.

Element	% calculated	% found
C	63.9	63.9
H	6.9	6.7
N	6.0	6.1
O	19.1	19.2
F	4.0	4.1

[0192] The Raman spectrum of the newly formed choline salt demonstrated differences to that of the free acid (see FIG. **12** for both spectra). As noted already in the previous examples, further analysis was performed to confirm the integrity of the molecular structure (1H-NMR). PXRD also confirmed formation of a new crystalline structure (see FIG. **14**). The salt was further characterized by light microscopy (see FIG. **13**), DSC (melting point around 138° C.), TG-FTIR (probably hemihydrate) and dynamic vapor sorption (ca. 2% water for hemi-hydrate and 0.4% water uptake at about 85% r.h., 1.2% water uptake at 95% r.h., almost reversible).

Example 8

Preparation of the 4-(2-hydroxyethyl)morpholine (HEM) Salt

[0193] 269.9 mg of vidofludimus acid was suspended in 35 mL of acetone at 50° C. A small amount of material was not dissolved. 102 μL of 4-(2-hydroxyethyl)morpholine was mixed with 1.5 mL of acetone and slowly added to the FA suspension. The suspension became a solution and its color changed from yellow to light yellow. The solution was filtered with a 0.2-μm PTFE filter. The solution was partially evaporated under nitrogen flow at 25° C. and precipitation was observed. The suspension was stirred overnight at 25° C. and afterwards partially evaporated again. The white solid was recovered by filter centrifugation with a 0.2-μm PTFE centrifuge filter and washed with 500 μL of acetone.

[0194] The material was dried for a few minutes under vacuum at 25° C. The crystallinity of the material was determined as described in the following.

[0195] Elemental composition analysis is summarized in the table below and corresponds to a 1:1 salt that contains water.

Element	% calculated	% found
C	64.0	64.0
H	6.4	6.3
N	5.7	5.9
O	19.9	19.9
F	3.9	3.9

[0196] The Raman spectrum of the newly formed HEM salt demonstrated differences to that of the free acid (see FIG. **15** for both spectra). As noted already in the previous examples, further analysis was performed to confirm the integrity of the molecular structure (1H-NMR). PXRD also confirmed formation of a new crystalline structure (see FIG. **17**) The salt was further characterized by light microscopy (see FIG. **16**), DSC (melting point around 152° C.), TG-FTIR (probably

nonsolvated form, 0.1% water) and dynamic vapor sorption (ca. 0.7% water uptake at about 85% r.h., 1.5% water uptake at 95% r.h., almost reversible).

Example 9

Investigation of the Solubility of the Compounds

[0197] The aqueous solubility of the respective compound was determined by HPLC, and the pH of the resulting saturated solution was measured. For each compound tested, a suspension was prepared and equilibrated for 24 hours at 25° C. The suspension was filtered, the filtrate was diluted and analysed by HPLC. The data illustrates that not all salts led to increase in solubility.

TABLE 2

Sample	Solubility	pH	% water uptake at 85% r.h.	% water uptake at 95% r.h.
Vidofludimus free acid	<1 mg/ml	6.5	0.03	0.1
Na salt	5-10 mg/ml	7.1	Ca. 5	Ca. 7.5
K salt	<1 mg/ml	7.9	Ca. 0.5	Ca. 1
Mg salt	<1 mg/ml	7.2	Ca. 5	Ca. 10
Tromethamine salt	<1 mg/ml	7.3	A)	A)
N-methyl-D-glutamines (NMG) salt	29 mg/ml	7.6	0.3	0.5
Choline salt	216 mg/ml	8.0	0.4[B)]	1.2
Diethylamine (DEA) salt	4.5 mg/ml	7.9	0.2	0.5
L-Arginine salt	127 mg/ml	7.9	1.7	>12
Zinc salt	0.95 mg/ml	6.3	4	5.5
4-(2-hydroxyethyl)morpholine (HEM) salt	3.2 mg/ml	7.7	0.7	1.5

A) no additional water uptake, however the salt exists already as hydrate
[B)]ca. 2% for hemi-hydrate

Example 10

Determination of the Bioavailability

[0198] Oral bioavailabilities of Vidofludimus free acid, the N-methyl-D-glucamine salt and the diethylamine salt were compared in male Wistar rats. The free acid or the aforementntioned salts were filled into gelatine capsules and the animals received a single administration at a dose level of approximately 10 mg free acid equivalents per kilogram body weight. Four male Wistar rats (body weight range: 250-275 g) per group were treated with either Vidofludimus free acid the aforementioned salts. The capsules were administered into the oesophagus of the animals using an application device. Venous blood samples were taken from the animals under isoflurane anaesthesia at the following time points after administration: 30 min; 1 h; 2 h; 4 h; 6 h; 8 h; 24 h; 28 h; 32 h and 48 h. Coagulation was inhibited using Na-heparin and plasma was generated by centrifugation of the blood samples. Plasma samples were analyzed for Vidofludimus by LC-MS/MS and pharmacokinetic parameters calculated according to the mixed log linear trapezoidal method.

[0199] Oral bioavailabilities of the salts were evaluated by comparing the areas under the plasma-concentration-time-curves (AUCs) and the maximally attained plasma concentrations (Cmax values) of Vidofludimus after administration of the salt with those observed after administration of the free acid. These ratios are shown in Table 3,

TABLE 3

Compound	In vivo AUC increase compared to free acid
Vidofludimus free acid	1
N-methyl-D-glucamine (NMG) salt	1.3
DEA salt	1.5

Example 11

Determination of the Long-Term Stability

[0200] The compounds were stored for 18 months at ambient conditions (20-25° C., 30-60% relative humidity) and subsequently analysed by HPLC for purity.

Compound	Occurrence of hydrolysis product in HPLC after 18 months storage	Peak area
Vidofludimus free acid	Below LOD*	>99%
N-methyl-D-glutamine (NMG) salt	Below LOD*	>99%
DEA salt	Below LOD*	>99%

*LOD for hydrolysis product: 0.1 μg/ml

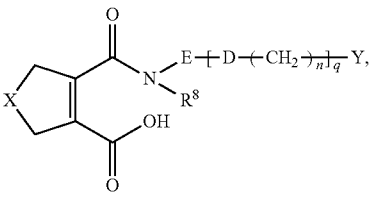
[0201] Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The preceding preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

[0202] The entire disclosures of all applications, patents and publications, cited herein and of corresponding U.S. Provisional Application Ser. No. 61/360,670, filed Jul. 1, 2010, are incorporated by reference herein.

[0203] From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention and, without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

1. A salt selected from the group consisting of N-methyl-D-glucamine salt (NMG), the diethylamine salt (DEA) salt, the magnesium salt, the tromethamine salt, the choline salt, the L-arginine salt, the zinc salt, and the 4-((2-hydroxyethyl) morpholine (HEM) salt of a compound of the general formula (I)

(I)



wherein
X is selected from the group consisting of CH_2, S, or O;
D is O or S;
R^8 is hydrogen or alkyl;
E is an optionally substituted phenylene group;

Y is a monocyclic or bicyclic substituted or unsubstituted 6-9 membered ring system which may contain one or more heteroatoms selected from N or S and which contains at least one aromatic ring;

n is 0 or 1; and

q is 0 or 1;

with the proviso that compounds wherein X═CH_2, q=0, Y=unsubstituted phenyl and E=unsubstituted phenylene are excluded;

or a hydrate thereof.

2. The salt or hydrate thereof according to claim **1**, wherein R^8 is hydrogen or methyl.

3. The salt or hydrate thereof according to claim **1**, wherein Y is substituted or unsubstituted phenyl;

4. The salt or hydrate thereof according to claim **1**, wherein q is 0.

5. The salt or hydrate thereof according to claim **1**, wherein E is an unsubstituted phenylene group or a phenylene group which is substituted with one or more groups independently selected from halogen, nitro or alkoxy.

6. The salt or hydrate thereof according to claim **1**, wherein Y is an unsubstituted phenyl group or a phenyl group which is substituted with one or more groups independently selected from halogen, alkyl, alkoxy, haloalkoxy, haloalkyl or CN.

7. The salt or hydrate thereof according to claim **1**, wherein E is a phenyl group which is substituted with one or more groups independently selected from methoxy or trifluorornethoxy, yet even more preferably methoxy.

8. The salt or hydrate thereof according to claim **1**, wherein the compound of formula 1 is 2-(3-Fluoro-3'-methoxy-biphenyl-4-ylcarbamoyl)-cyclopent-1-enecarboxylic acid.

9. The salt or hydrate thereof according to claim **1**, wherein the salt is selected from the N-methyl-D-glucamine salt (NMG) or the diethylamine salt (DEA) salt.

10. A pharmaceutical composition comprising a salt or hydrate thereof as defined in claim **1**, together with pharmaceutically acceptable diluents or carriers.

11. A salt or hydrate thereof according to claim **1** for the use as a medicament.

12. A method for treating rheumatism, acute immunological disorders, autoimmune diseases, diseases caused by malignant cell proliferation, inflammatory diseases, diseases that are caused by protozoal infestations in humans and animals, diseases that are caused by viral infections and *Pneumocystis carinii*, fibrosis, uveitis, rhinitis, asthma or athropathy, comprising administering to a subject in need thereof an effective amount of a salt or hydrate according to claim **1**.

13. The method according to claim **12**, wherein graft versus host and host versus graft reactions, rheumatoid arthritis, multiple sclerosis, lupus erythematosus, inflammatory bowel disease, or psoriasis is treated.

14. A process for the preparation of a salt or hydrate thereof as defined in claim **1** which comprises the steps of

a) dissolving a free acid of a compound of formula (I) in an organic solvent,

b) adding a suspension of N-methyl-D-glucamine in an organic solvent or adding diethyl amine,

c) at least partially evaporating the organic solvent, and

d) optionally recrystallizing the solid which is recoverable from the mixture obtained in step c).

* * * * *