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(54) Title: NEW USE OF GLYCONJUGATES OF GLUCOCORTICOSTEROIDS AS A TARGETING TO THE COLON

(57) Abstract: The present invention relates to the use of glycoconjugates of glucocorticosteroids (GC) as a targeting to the colon, for example to colon of patients with irritable bowel syndrome (IBS), and pharmaceutical compositions containing said glycoconjugates.

NEW USE OF GLYCONJUGATES OF GLUCOCORTICOSTEROIDS AS A TARGETING TO THE COLON

Field of the Invention

The present invention relates to the use of glycoconjugates of glucocorticosteroids (GC) as a targeting to the colon, for example to colon of patients with irritable bowel syndrome (IBS), and pharmaceutical compositions containing said glycoconjugates.

Background to the Invention

IBS is an abdominal syndrome affecting 20% of the population, causing patients much discomfort and society large healthy care costs. Current treatment of IBS is mainly antispasmodics, laxatives, loperamide and antidepressants. The IBS symptoms arise from altered gastrointestinal motility, increased visceral sensitivity and/or altered brain-bowel modulation. Even if the symptoms may vary, the common ground is a neuromuscular dysfunction, including increased visceral sensitivity with pain and altered bowel habits. Up to 30% of patients hit by bacterial gastro-enteritis (Salmonella, Campylobacter etc) develop IBS, suggesting that these infections provoke longstanding or chronic alterations of the colonic neuromuscular function.

Irritable bowel syndrome (IBS) is a common disorder of the intestines that leads to crampy pain, gassiness, bloating, and changes in bowel habits. Some people with IBS have constipation (difficult or infrequent bowel movements); others have diarrhoea (frequent loose stools, often with an urgent need to move the bowels); and some people experience both. Sometimes the person with IBS has a crampy urge to move the bowels but cannot do so.

Researchers have found that the colon muscle of a person with IBS begins to spasm after only mild stimulation. The person with IBS seems to permanently have a colon that is more sensitive and reactive than usual, so it responds strongly to stimuli that would not bother most people.

The IBS dysfunction is distinct from IBD (Ulcerative colitis and Morbus Crohn) in that the IBS bowel lacks morphological signs of inflammation. The only change reported is an enhanced number of mucosal mast cells in the colon and cecum (O´Sullivan M et al Neurogastroenterology &Motility 2000;12:449-457; Yang Y et al. Chinese Journal of Internal Medicine 1997;36(4):231-233. The IBD-diseases, on the other hand, are immune-mediated illnesses characterized by a broad inflammation comprising most types of inflammatory and immune cells, and they lead to a marked remodelling of bowel tissue.

Summary of the invention

In bowel mucosa there is a close association between mast cells and nerves belonging to the enteric nervous (EN) system (Stead RH et al. Pros Natl Acad Sci USA 1987;84:2975-2979). This system contributes to the local reflexes between bowel mucosa and deeper muscle layer in the bowel wall and by that the control of peristalsis. These reflexes are modulated by the amount and type of luminal food, and by higher nervous centra, including the spinal cord and brain. The mucosal mast cells and the peripheral endings of EN can trigger each other mutually. Released mast cell mediators may trigger nerve reflexes, inducing contractions of the deeper located circular and longitudinal muscle layers and with a possibility to signal pain/discomfort to CNS. Contrary can a stressed brain trigger neuropeptide discharge (e.g. Substance P and other peptides) from the mucosal EN-nerve endings, which may degranulate adjacent mast cells and by that trigger plasma leakage and pain signals. Other mucosal cells like enterochromaffine cells, containing tachykinins and CRF (Corticotrophin Releasing Factor) may contribute to these cellular-neural interactions.

Microscopic investigations have now revealed a raised number of mast cells in cecum and colon of IBS patients. Important parts of the IBS-symptoms are believed to originate from augmented or altered interactions between mucosal cells and peripheral nerve endings of EN, and these changes are sensitive to topical treatment with anti-inflammatory glucocorticoids (GC). A therapeutic aim would thus be to dampen the activity of the mast cell-EN system in colon of IBS patients. As demonstrated in other tissues or with high steroid doses given intraperitoneally, GC can affect this or similar systems. Thus, steroids

have been shown to: a/ strongly deplete the number of jejunal mucosal mast cells in rats (Soda K, et al. Gastroenterology 1991;100:929-937); b/ reduce tachykinins (Substance P), tachykinin receptors (NK1)) and neurotensin; c/ diminish the expression of the pro-inflammatory enzymes COX-2 (and by that the prostaglandin production) and INOS (and by that the proinflammatory part of the NO system); and d/ inhibit the production of CRF. As a functional proof of steroid efficacy on bowel hyperresponsiveness, Barbara G and Collins S (Gastroenterology 2001, in press) report that a high steroid dose (dexamethasone 0.5 mg/kg given intraperitoneally) blunted nearly fully the neuromuscular hyperresponsiveness of rat jejunum, persisting after parasite infestation.

This shows that steroids have a capacity to normalise an exaggerated bowel neuromuscular function. However, current steroids cannot be therapeutically used for that purpose in IBS-patients, as these compounds provoke too much adverse steroid actions for this benign and longstanding condition. Furthermore, a conventional colonic targeting via time delayed and /or osmotically controlled pharmaceutical formulations is difficult to achieve in IBS-patients, due to their irregular bowel transit times. According to the invention a new and better mode to selectively deliver steroid to colon mucosa of IBS-patients is the administration of glycoconjugates of selected steroids. These steroidal prodrugs are inactive at the GC-receptor, they are very hydrophilic and are by that poorly absorbed by the small intestine. Bacterial glycosidases will then gradually release the active steroid when the prodrugs reach and dwell in colon lumen over a number of hours. To achieve the required colonic targeting and high local steroid activity, a preferred glycoconjugate needs the following combination of properties:

* The glycoconjugate should be slowly hydrolysed by the colon microbial flora, and mucosal glycosidases may also contribute.
* The released, active steroid should have
  - a combination of some water solubility for its distribution within bowel lumen, and a high lipophilicity for its efficient uptake by colon mucosa
  - a high affinity for the GC-receptor, to induce strong and longstanding GC- effects within colon mucosa

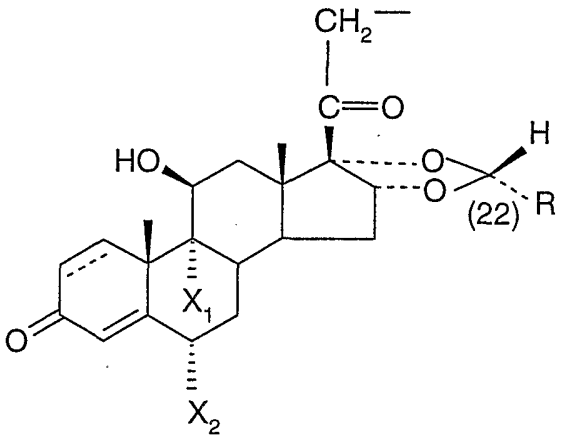
- a hepatic first pass inactivation rate (90% or more) into metabolites of negligible GC-activity, to ensure the necessary excellent systemic tolerance.

Experimental results have earlier been presented for glycoconjugates of steroids (Friend DR. In "Oral Colon-Specific Drug Delivery"; Friend, DR, ed; CRC: Boca Raton, FL, 1992, pp 153-187; Cui N et al. Gut; Vol 35 (1994):1439-1446; Nolen III H. J Pharmaceutic Sci 1995; 84(6): 677-681; Fedorak RN et al. Gastroenterology, Vol 108, A924, 1995). One patent (US 5,908,833) claims the use of glycoconjugates (including two glycoconjugates specified below in current use application). However, these publications and the patent discuss and claim only the use of steroid glycoconjugates for treating colitis or Morbus Crohn (the latter located in the ileocecal region). In fact the pathophysiology and the symptoms of IBD and IBS are quite different. The IBDs are immune-mediated severe illnesses, provoking marked morphologic and functional changes of the bowel wall. Due to their immunologic basis, the main steroid targets in IBD are mononuclear immune cells (lymphocytes and macrophages) located in the *submucosa (*in *Morbus Crohn also granulomas even deeper in the bowel wall).* Neuromuscular changes are not primary and major symptoms in IBD. Due to the severe character of IBD, steroid adverse actions can be better accepted than for IBS that has a very good long-term prognosis. The microscopic picture of IBS bowel is normal, except some increase of the number of mucosal mast cells, and the symptoms are just neuromuscular. Therefore, it is not obvious from prior art that selected topical steroids should be of value in the treatment of IBS. Current invention is based on above hypothesis of a changed neuromuscular condition in IBS, and that this condition is sensitive to GC modulation.

The present invention relates to the use of a compound of the general formula

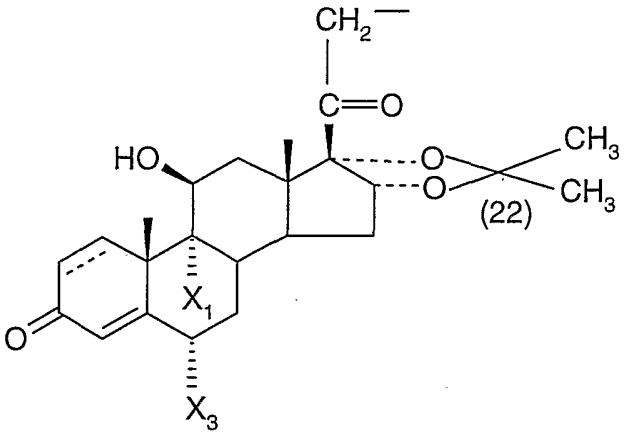
$$GCS^1\text{-}O\text{-}Sugar^1$$

wherein GCS^1 is a glucocorticosteroid (GCS^1-OH) with a hepatic first pass metabolism of at least 95%, selected from the group of formula I



I

as the pure 22R-epimer, or of formula II



II

in which formulas X_1 and X_2 being the same or different selected from the group consisting of hydrogen, fluoro, chloro or bromo, X_3 being a fluoro, chloro or bromo

substituent, R being a hydrocarbon chain with 1-9 carbon atoms and in which formulas the 1,2-position is saturated or unsaturated, the $Sugar^1$ being the moiety of a monosaccharide, a disaccharide or an oligosaccharide, the GCS being linked in 21-position to the sugar via a glycosidic bond as well as a pharmaceutically acceptable salt and/or solvate thereof in the manufacture of a medicament for dampening the neuromuscular hyperresponsiveness of bowel.

The compound according to the invention is preferably used for dampening the activity of the mast cells and nerves belonging to the enteric nervous (EN) system. The most preferred use is for the prevention and/or treatment of irritable bowel syndrome (IBS), particularly post-infectious IBS.

According to the invention there is further provided a method for dampening the neuromuscular hyperresponsiveness of bowel, by administering to a mammal including man in need of such a treatment a therapeutically effective amount of a compound of the general formula GCS^1-O-$Sugar^1$ as described above.

According to the invention there is further provided a pharmaceutical formulation for use in dampening the neuromuscular hyperresponsiveness of bowel wherein a compound of the general formula GCS^1-O-$Sugar^1$ as described above is used as active ingredient.

According to above pharmacological prerequisites, the sugar conjugated via a glycosidic bond to the steroid can be D-glucose, D-glucuronic acid, D-galactose, D-galacturonic acid, D-cellobiose, or D-lactose.

Preferably, the sugar is β-linked D-glucuronic acid or D-glucose.

A preferred embodiment of the invention is the use of the compound according to claim 1 wherein the glucocorticosteroid (GCS^1-OH) has a hepatic first pass metabolism of at least 97%.

Preferred steroids to be linked at the 21-OH position with a sugar are (22R)-16α,17α-butylidenedioxy-11β,21-dihydroxypregna-1,4-diene-3,20 dione; (22R)-16α,17α-butylidenedioxy-6α,9α-difluoro-11β,21-dihydroxy-4-pregnene-3,20-dione; or (22R)-16α,17α-butylidenedioxy-6α,9α-difluoro-11β,21-dihydroxy-1,4-pregnadiene-3,20 .

The compounds to be used according to the present invention may be prepared according to the methods described in WO 94/15947.

When the glycoconjugate is administered orally, it is administered oesophageally, generally administered in the form of tablets, pills, capsules, syrups, powders, or granules and when it is administered rectally, is in the form of suppositories or enemas.

The glycoconjugates as well as a pharmaceutically acceptable salt and/or solvate thereof may be administered on its own or as a pharmaceutical formulation in combination with pharmaceutical acceptable diluent, adjuvant or carrier.

The glycoconjugate as well as a pharmaceutically acceptable salt and/or solvate thereof is preferably administered at a dosage of from 0.1 to 50 mg, more preferably from 0.5 to 25 mg, either as a single dose or in divided doses from to 2-4 times per day.

* These glycoconjugates have a very high water solubility.

* They have a high stability against spontaneous hydrolysis. The high water solubility of the stable conjugates impairs their absorption at the small bowel level.

* They lack completely own glucocorticoid activity at 10^{-7} M in an in vitro assay with colon epithelial cells, while their active steroid components have been shown to exert strong activity at a 10-100 lower concentration (Zareie et al. J Exptl Pharm Ther 1999).

* They are hydrolysed by the colonic flora.

These data support the use of glycoconjugate prodrugs for a targeted GC-therapy of colon mucosa in IBS patients. The very high hepatic first pass inactivation rate of the active steroids enables a good systemic tolerance of the glycoconjugates.

A potential animal model is nematode-infested mice, which after expulsion of the parasites develop a persistent enteric muscle dysfunction with similarities to human postinfectious IBS and which has been described in Barbara G et al. Role of immunological factors and cyclooxygenase-2 in persistent post infective enteric muscle dysfunction in mice. Gastroenterology 2001; 120:1729-1736.

Examples of formulations

Example 1. Tablet

Tablets are prepared by conventional compression methods with the following composition

Budesonide 22R-epimer ß-D-glucoside, budesonide 22R-epimer β-D-glucosiduronate, GCS[1] IV 22R-epimer ß-D-glucoside or GCS[1]IV 22R-epimer β-D-glucosiduronate	5 mg
Lactose	80 mg
Microcrystalline cellulose	20 mg
Crosspovidone	5 mg
Polyvinylpyrrolidone	5 mg
Magnesium stearate	2 mg

Example 2. Enteric tablet

The tablet from Example 1 is coated with

Eudragit L30D	3.7 mg
PEG 6000	0.4 mg
Talc	0.9 mg

Example 3. Delayed release capsule

Budesonide 22R-epimer ß-D-glucoside, budesonide 22R-epimer β-D-glucosiduronate, GCS[1] IV 22R-epimer ß-D-glucoside or GCS[1]IV 22R-epimer β-D-glucosiduronate (7.1 g) is mixed with 300 g lactose, 128 g microcrystalline cellulose, 75 g crosslinked polyvinylpyrrolidone and 25 g polyvinylpyrrolidone. The mixture is granulated with water and the wet mass is extruded and spheronized giving cores with approximate size of 1 mm. The cores are dried and sieved. The cores are coated with a mixture of 255 g Eudragit NE30D, 77 g magnesium stearate and 250 g water in a fluid bed apparatus. Finally an enteric coating consisting of 11 g Eudragit L30D dispersion, 3 g triethylcitrate and 15 g talc is sprayed on the spheres. The pellets are dried in the fluid bed apparatus, sieved and filled in hard gelatine capsules.

Example 4. Gut microflora controlled release capsule

Budesonide 22R-epimer ß-D-glucoside or budesonide 22R-epimer β-D-glucosiduronate (6.6 g) is suspended in a solution of 1 g of hydroxypropylmethylcellulose in 50 ml of water. The mixture is sprayed on to 510 g sugar spheres in a fluid bed apparatus. Thereafter a mixture of 85 g guar gum, 30 g (solid content) Eudragit RL30D and 15 g talc in totally 900 g of a 1:1 mixture of water and isopropanol is sprayed on the spheres. Finally an enteric coating consisting of 100 g Eudragit L30D dispersion, 3 g triethylcitrate and 15 g talc is sprayed on the spheres. The pellets are dried in the fluid bed apparatus, sieved and filled into hard gelatine capsules.

Example 5. Gut microflora controlled release capsule

GCS[1] IV 22R-epimer ß-D-glucoside or GCS[1]IV 22R-epimer β-D-glucosiduronate (6.8 g) is suspended in a mixture of 15 g locust bean gum, 5 g (solid content) Eudragit RL30D and 2 g talc in totally 220 g of a 1:1 mixture of water and isopropanol. This mixture is sprayed on to 510 g of sugar spheres in a fluid bed apparatus. Then a mixture of 80 g locust bean gum, 40 g (solid content) Eudragit RL30D and 15 g talc in totally 900 g of a 1:1 mixture of

water and isopropanol is sprayed on the spheres. Finally an enteric coating consisting of 100 g Eudragit L30D dispersion, 3 g triethylcitrate and 15 g talc is sprayed on the spheres. The pellets are dried in the fluid bed apparatus, sieved and filled in hard gelatine capsules.

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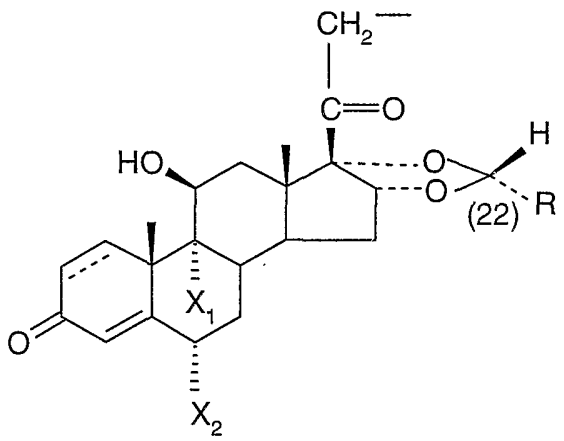
Claims

1. The use of a compound of the general formula

GCS^1-O-$Sugar^1$

wherein GCS^1 is a glucocorticosteroid (GCS^1-OH) with a hepatic first pass metabolism of at least 95%, selected from the group of formula I



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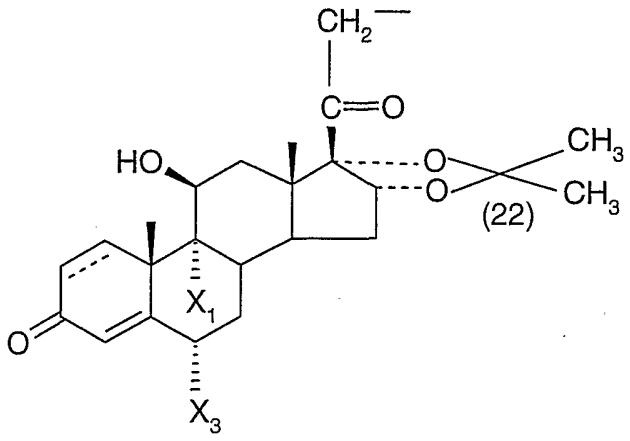
as the pure 22R-epimer,

or of formula II



II

in which formulas X_1 and X_2 being the same or different selected from the group consisting of hydrogen, fluoro, chloro or bromo, X_3 being a fluoro, chloro or bromo substituent, R being a hydrocarbon chain with 1-9 carbon atoms and in which formulas the 1,2-position is saturated or unsaturated, the Sugar[1] being the moiety of a monosaccharide, a disaccharide or an oligosaccharide, the GCS being linked in 21-position to the sugar via a glycosidic bond as well as a pharmaceutically acceptable salt and/or solvate thereof in the manufacture of a medicament for dampening the neuromuscular hyperresponsiveness of bowel.

2. The use of the compound according to claim 1, wherein the GCS[1] is (22R)-16α,17α-butylidenedioxy-11β,21-dihydroxypregna-1,4-diene-3,20-dione.

3. The use of the compound according to claim 1, wherein the GCS[1] is (22R)-16α,17α-butylidenedioxy-6α,9α-difluoro-11β,21-dihydroxy-4-pregnene-3,20-dione or (22R)-16α,17α-butylidenedioxy-6α,9α-difluoro-11β,21-dihydroxy-1,4-pregnadiene-3,20-dione.

4. The use of the compound according to any of claims 1-3, wherein Sugar[1]-OH is D-glucose, D-galactose, D-cellobiose or D-lactose.

5. The use of the compound according to any of claims 1-3, wherein Sugar^1-OH is D-glucuronic acid or D-galacturonic acid.

6. The use of the compound according to claim 1, wherein Sugar^1-OH is ß-linked D-glucose.

7. The use of the compound according to claim 1, wherein Sugar^1-OH is ß-linked D-glucuronic acid.

8. The use of the compound according to claim 2, wherein Sugar^1-OH is ß-linked D-glucose.

9. The use of the compound according to claim 2, wherein Sugar^1-OH is ß-linked D-glucuronic acid.

10. The use of the compound according to claim 3, wherein Sugar^1-OH is ß-linked D-glucose.

11. The use of the compound according to claim 3, wherein Sugar^1-OH is ß-linked D-glucuronic acid.

12. The use of the compound according to claim 3, which is (22R)-16α,17α-butylidenedioxy-6α-9α-difluoro-11β-hydroxy-4-pregnene-3,20-dione-21-yl β-D-glucopyranoside.

13. The use of the compound according to claim 2, which is (22R)-16α,17α-butylidenedioxy-11β-hydroxypregna-1,4-diene-3,20 dione-21-yl β-D-glucopyranoside.

14. The use of the compound according to claim 3, which is sodium[(22R)-16α,17α-butylidenedioxy-6α,9α-difluoro-11β-hydroxy-4-pregnene-3,20 dione-21-yl β-D-glucopyranoside]uronate.

15. The use of the compound according to claim 2, which is sodium[(22R)-16α,17α-butylidenedioxy-11β-hydroxypregna-1,4-diene-3,20 dione-21-yl β-D-glucopyranoside]uronate.

16. The use of the compound according to claim 1 wherein the glucocorticosteroid (GCS^1-OH) has a hepatic first pass metabolism of at least 97%.

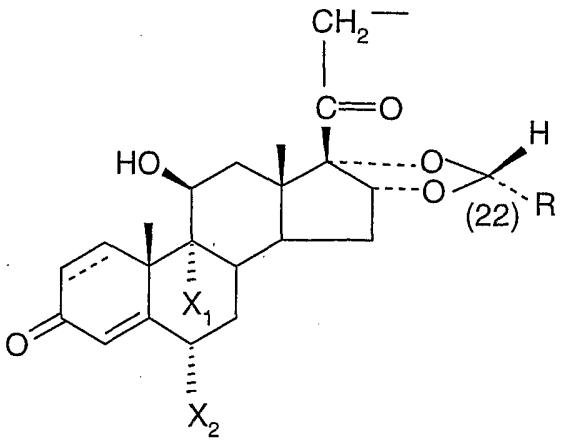
17. The use according to claim 1 in the manufacture of a medicament for dampening the activity of the mast cells and nerves belonging to the enteric nervous (EN) system.

18. The use according to claim 1 in the manufacture of a medicament for the prevention and/or treatment of irritable bowel syndrome.

19. A method for dampening the neuromuscular hyperresponsiveness of bowel by administering to a mammal including man in need of such a treatment a therapeutically effective amount of a compound of the general formula

GCS^1-O-$Sugar^1$

wherein GCS^1 is a glucocorticosteroid (GCS^1-OH) with a hepatic first pass metabolism of at least 95%, selected from the group of formula I



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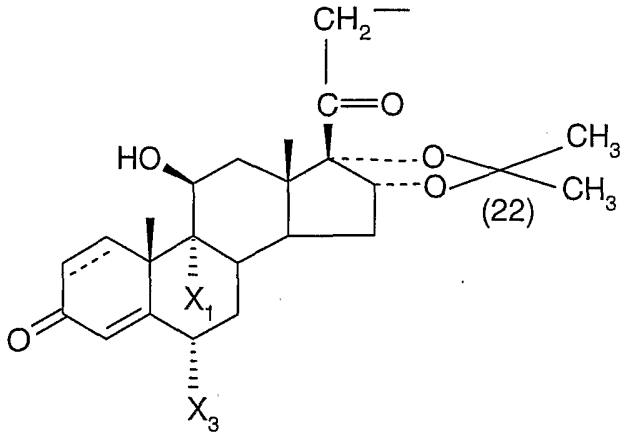
as the pure 22R-epimer,

or of formula II



II

in which formulas X_1 and X_2 being the same or different selected from the group consisting of hydrogen, fluoro, chloro or bromo, X_3 being a fluoro, chloro or bromo substituent, R being a hydrocarbon chain with 1-9 carbon atoms and in which formulas the 1,2-position is saturated or unsaturated, the Sugar[1] being the moiety of a monosaccharide, a disaccharide or an oligosaccharide, the GCS being linked in 21-position to the sugar via a glycosidic bond as well as a pharmaceutically acceptable salt and/or solvate thereof.

20. A method according claim 19 for dampening the activity of the mast cells and nerves belonging to the enteric nervous (EN) system.

21. A method according claim 19 for the prevention and/or treatment of irritable bowel syndrome.

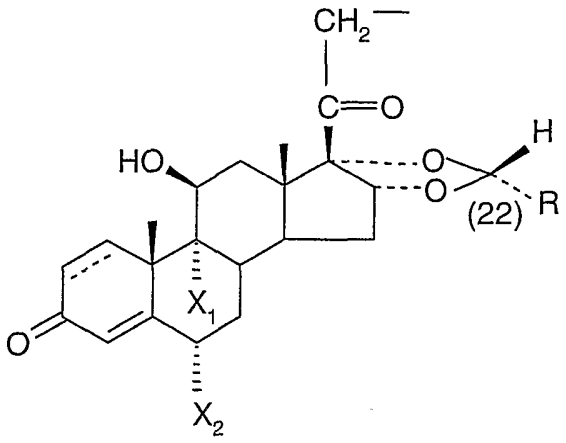
22. A method according to any one of claims 19-21 wherein (22R)-16α,17α-butylidenedioxy-6α-9α-difluoro-11β-hydroxy-4-pregnene-3,20-dione-21-yl β-D-glucopyranoside or sodium[(22R)-16α,17α-butylidenedioxy-6α,9α-difluoro-11β-hydroxy-4-pregnene-3,20 dione-21-yl β-D-glucopyranoside]uronate is administered.

23. A method according to any one of claims 19-21 wherein (22R)-16α,17α-butylidenedioxy-11β-hydroxypregna-1,4-diene-3,20 dione-21-yl β-D-glucopyranoside or sodium[(22R)-16α,17α-butylidenedioxy-11β-hydroxypregna-1,4-diene-3,20 dione-21-yl β-D-glucopyranoside]uronate is administered.

24. A pharmaceutical formulation for use in dampening the neuromuscular hyperresponsiveness of bowel, comprising a compound of the general formula

$$GCS^1\text{-}O\text{-}Sugar^1$$

wherein GCS^1 is a glucocorticosteroid (GCS^1-OH) with a hepatic first pass metabolism of at least 95%, selected from the group of formula I



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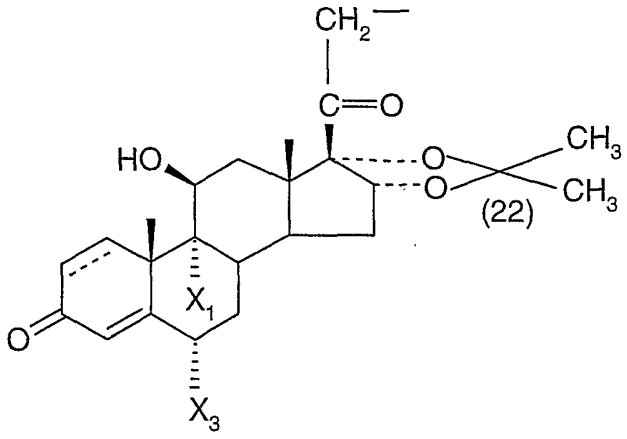

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1,2-position is saturated or unsaturated, the Sugar[1] being the moiety of a monosaccharide, a disaccharide or an oligosaccharide, the GCS being linked in 21-position to the sugar via a glycosidic bond as well as a pharmaceutically acceptable salt and/or solvate thereof as active ingredient.

25. A pharmaceutical formulation according to claim 24 for use in dampening the activity of the mast cells and nerves belonging to the enteric nervous (EN) system.

26. A pharmaceutical formulation according to claim 24 for use in the prevention and/or treatment of irritable bowel syndrome.

27 A pharmaceutical formulation according to any one of claims 24-26 wherein (22R)-16α,17α-butylidenedioxy-6α-9α-difluoro-11β-hydroxy-4-pregnene-3,20-dione-21-yl β-D-glucopyranoside or sodium[(22R)-16α,17α-butylidenedioxy-6α,9α-difluoro-11β-hydroxy-4-pregnene-3,20 dione-21-yl β-D-glucopyranoside]uronate is used.

28. A pharmaceutical formulation according to any one of claims 24-26 wherein (22R)-16α,17α-butylidenedioxy-11β-hydroxypregna-1,4-diene-3,20 dione-21-yl β-D-glucopyranoside or sodium[(22R)-16α,17α-butylidenedioxy-11β-hydroxypregna-1,4-diene-3,20 dione-21-yl β-D-glucopyranoside]uronate is used.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 02/00662

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/58, A61P 1/04
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K, A61P

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

SE,DK,FI,NO classes as above

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

EPO-INTERNAL, WPI DATA, PAJ, CHEM.ABS.DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5908833 A (BRATTSAND ET AL), 1 June 1999 (01.06.99)	1-23
X	--	24-28

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 July 2002	24-07-2002
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer ANNA SJÖLUND/BS Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE02/00662

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 19-23
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Claims 19-23 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 02/00662

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5908833 A	01/06/99	AT 183192 T	15/08/99
		AU 678803 B	12/06/97
		AU 5844794 A	15/08/94
		BR 9307746 A	14/11/95
		CA 2152374 A	21/07/94
		CZ 9501710 A	17/01/96
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		EP 0678097 A,B	25/10/95
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		EP 0625943 A,B	30/11/94
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