

THIOLCHICOSIDE ANALOGUES WITH MYORELAXANT AND ANTI-INFLAMMATORY ACTIVITY

Field of the invention

The present invention relates to 3-demethoxy-3-aminothiocolchicine derivatives with myorelaxant and anti-inflammatory activity.

Technological background

5 Myorelaxant drugs share the property of reducing the muscle tone and are commonly used for alleviating pain due to tissue tension, such as muscle contractures.

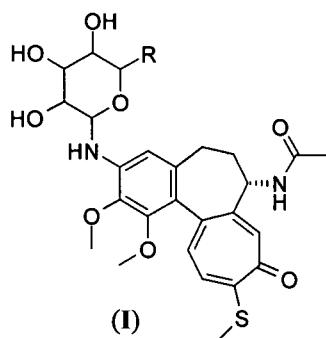
 Muscle contractures characterize several pathologies of the locomotor apparatus and are one of the main factors responsible for the persistence of the
10 pain associated to these pathologies. Muscle contractures occur also in inflammatory-rheumatic and degenerative orthopedic pathologies and when they affect the joints, they cause not only pain, but also rigidity, which limit the mutual mobility of the joint ends and consequently the functionality of the affected part. For these reasons the study of molecules endowed with
15 myorelaxant and decontracting properties still raises remarkable interest from the clinical point of view.

 As it is known, colchicine is a pseudoalkaloid widely used for a long time in therapy for the treatment of gout. Also widely used in therapy is 3- demethyl-thiocolchicine glucoside, known as thiocolchicoside (a colchicine
20 derivative in which the C₁₀ bears a thiomethyl group and the hydroxy group at the 3- position is etherified with a glucose molecule), for the treatment of contractures an inflammatory conditions of skeleton muscles (Ortopedia e Traumatologia Oggi XII, n. 4. 1992). It has recently been demonstrated that thiocolchicoside's activity can be ascribed to its ability of interacting with the
25 strychnine-sensitive glycine receptors and therefore that compounds endowed

with glycino-mimetic activity can be used in the rheumatologic-orthopedic field for their myorelaxant properties.

Disclosure of the invention

The present invention relates to 3-demethoxy-3-aminothiocolchicine
5 glycosyl derivatives of general formula (I)

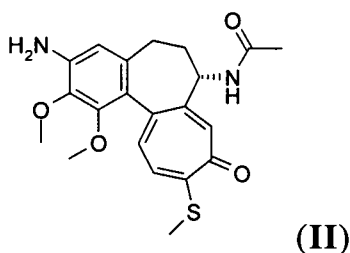


in which

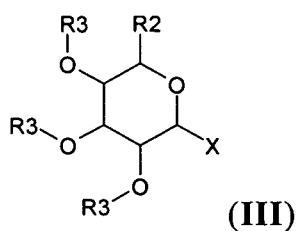
R is hydrogen, methyl or hydroxymethyl.

10 Alpha and beta anomers of pentose and hexose D- and L- glycopyranosides of 3-demethoxy-3-aminothiocolchicine are therefore comprised in the compounds of formula (I).

The compounds of the present invention are generally prepared by
15 reaction of 3-demethoxy-3-aminothiocolchicine (II)



with a protected glycopyranoside of formula (III)



20 wherein

X is OH, F, Cl, Br, I,

R₂ is hydrogen, methyl, -CH₂-O-R₃;

R₃ is hydrogen or a hydroxy-protecting group.

Among the X groups, fluorine and bromine are preferred. Among the
5 protective groups, the acetyl group is preferred.

3-Demethoxy-3-aminothiocolchicine (II) is prepared from
3-O-demethylthiocolchicine triflate, tosylate or mesylate by Buchwald
reaction as disclosed by Clark D. et al. in WO 00/35865.

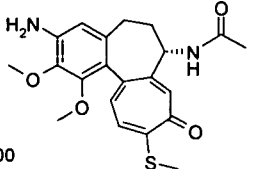
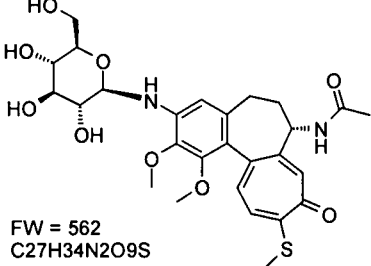
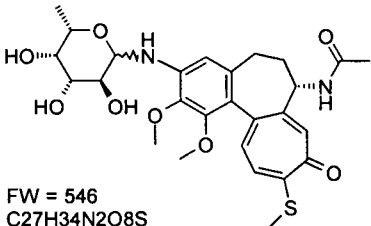
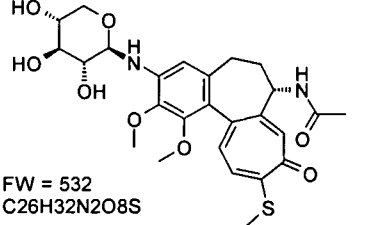
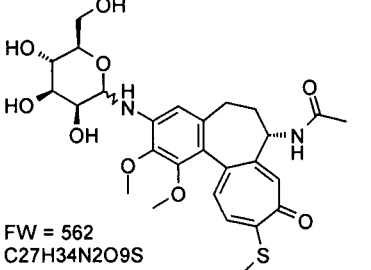
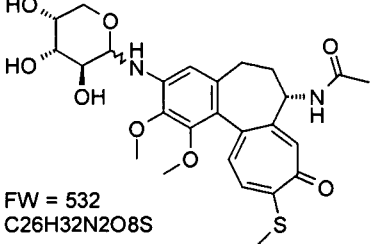
In more detail, 3-demethoxy-3-aminothiocolchicine is reacted with a
10 suitable glycoside, optionally protected at the hydroxy residues. The reaction is
carried out in polar protic solvents preferably selected from alcohols (MeOH) at
a temperature ranging from 25°C to the boiling temperature of the solvent. The
reaction is generally complete in a time ranging from 8 hours to 6 days. Where
necessary, the hydrolysis of the protecting groups can be carried out directly
15 also on the reaction crude without recovery of the intermediates.

Remarkable decrease in reaction times and increase in yields are
observed when the reaction is carried out with microwaves. In more detail,
3-demethoxy-3-aminothiocolchicine is reacted with a suitable glycoside in a
polar protic solvent preferably selected from alcohols, such as MeOH, at 110°C,
20 and with 150 watt power. The reaction is generally completed after 3 hours.

The resulting products were tested *in vitro* by displacement tests to
verify their affinity to strychnine-sensitive binding sites of rat spinal cord
using [³H]strychnine as ligand. The results suggest that the derivatives behave
as allosteric compounds on the strychnine-sensitive glycine receptors of the
25 spinal cord. This interaction is an indication of the myorelaxant activity of the
compounds of the invention (Cimino M. et al., Eur. J. Pharmacol. 1996, 318.
201-204; Balduini W. et al., Neuropharmacol. 2001, 40. 1044-1049).

The compound of formula II proved to be active and therefore the

invention relates also to the use of this compound for the preparation of medicaments with myorelaxant activity.

<u>COMPOUND N</u>	<u>FORMULA</u>	<u>STRY</u>
1	 FW = 400 C₂₁H₂₄N₂O₄S	39.91 ± 0.54
2	 FW = 562 C₂₇H₃₄N₂O₉S	10.55 ± 0.35
3	 FW = 546 C₂₇H₃₄N₂O₈S	4.22 ± 0.44
4	 FW = 532 C₂₆H₃₂N₂O₈S	3.25 ± 0.57
5	 FW = 562 C₂₇H₃₄N₂O₉S	13.12 ± 0.77
6	 FW = 532 C₂₆H₃₂N₂O₈S	8.61 ± 1.25

The compounds of the invention can be formulated as pharmaceutical formulations intended for the oral, intravenous, intramuscular, transdermal and topical administration, with excipients and conventional methods, such as those reported in Remington's Pharmaceutical Sciences Handbook, XVII Ed., Mack Pub., N.Y., U.S.A.. Among the excipients useful for the preparation of liposomal forms for the parenteral or topical administration, particularly preferred are natural and synthetic phospholipids. The doses can range from 5 to 50 mg a day depending on the disease and on the administration route.

The invention will be now illustrated in more detail by means of some examples.

EXPERIMENTAL SECTION

The melting points were measured using a Buchi 510 apparatus. The NMR spectra were obtained with a Bruker AC 500 instrumentation. The IR spectra were obtained with a Jasco IR Report 100 spectrophotometer. The reactions were carried out in a Milstone Micro SYNTH microwave oven. $[\alpha]_{25}^D$ values were measured with a 343- PLUS Perkin-Helmer polarimeter.

Example 1. 3-O-Trifluoromethanesulfonyl-3-O-demethylthiocolchicine

Triflic anhydride (1.24 ml, 7.40 mmoles) was added under nitrogen atmosphere at 0°C to a solution of 3-O-demethylthiocolchicine (2 g, 4.98 mmoles) and *p*-DMAP (1.77 g, 15.78 mmoles) in anhydrous CH₂Cl₂ (50 mL).

Stirring was continued at 0°C for 20 hours and then at room temperature for 3 hours. The reaction was monitored by TLC analysis (10:1 CH₂Cl₂/MeOH, R_f: starting = 0.27, product = 0.38). After evaporation of the solvent, the residue was purified by column chromatography on a alumina using a CH₂Cl₂/MeOH mixture (increasing polarity gradient). The product (1.84 g, 70%) was obtained as yellow solid after crystallization from ethanol:

mp 140-142°C; IR (Nujol) $\nu_{\max}$ 1667, 1620 cm^{-1} ; $[\alpha]_{25}^D$ - 60° (c 0.9, CHCl_3),
 ^1H NMR (CDCl_3): δ 7.94 (d, J = 7 Hz, 1H), 7.44 (s, 1H), 7.28. 7.09 (AB
system, J = 10.4 Hz, 1H), 6.84 (s, 1H), 4.65-4.55 (m, 1H), 4.05 (s, 3H), 3.68
(s, 3H), 2.63-2.54 (m, 1H), 2.45 (s, 3H), 2.39-2.25 (m, 2H), 1.98 (s, 3H),
5 1.90-1.80 (m, 2H); ^{13}C NMR (CDCl_3): δ 181.8. 170.4. 160.3, 151.9, 151.0.
145.6, 142.4. 136.9, 135.3, 134.8. 134.7, 128.7, 126.6, 121.2, 116.9, 62.2,
62.0. 36.4. 29.7, 23.3, 15.6; MS m/z 533 (MH^+).

Example 2. 3-Demethoxy-3-aminothiocolchicine

Cs_2CO_3 (685 mg, 2.09 mmoles), $\text{Pd}(\text{OAc})_2$ (68 mg, 0.29 mmoles),
10 ($\pm$)BINAP (290 mg, 0.44 mmoles) and the compound obtained in example I
(800 mg, 1.48 mmoles) were loaded into a Schlenk round-bottom flask under
nitrogen atmosphere. The mixture was heated at 40°C for 2 h under vacuum.
After cooling, suitably degassed anhydrous toluene (3 ml) and then
benzophenone imine (0.25 ml, 1.49 mmoles) were added. The round-bottom
15 flask was sealed with a rubber stopper and saturated with nitrogen. The
reaction mixture was stirred for 45 minutes at room temperature, then heated
at 120°C for 16 hours and monitored by TLC analysis (20:1 $\text{CH}_2\text{Cl}_2/\text{MeOH}$).
The mixture was cooled to room temperature, diluted with AcOEt , filtered and
concentrated under reduced pressure. The crude product containing the desired
20 imino adduct was dissolved in MeOH (15 ml) at room temperature. The
solution was added with AcONa (509 mg, 6.21 mmoles) and $\text{NH}_2\text{OH}\cdot\text{HCl}$
(323 mg, 4.65 mmoles). After 30 minutes, the mixture was diluted with
 CH_2Cl_2 (5 ml) and acidified to pH 2 with 2N HCl . The organic phase was
separated, the aqueous phase was alkalized with a 25% NaOH solution and
25 extracted with CH_2Cl_2 (3x20 ml). The organic phase was dried over Na_2SO_4
and concentrated under pressure to give the desired product (TLC 10:1.5
 $\text{CH}_2\text{Cl}_2/\text{MeOH}$ R_f 0.43) which was then crystallized from EtOH (373 mg,
60%): mp 280-282°C. $[\alpha]_{25}^D$ - 292° (c 0.5, CHCl_3); IR (Nujol) $\nu_{\max}$ 3340,

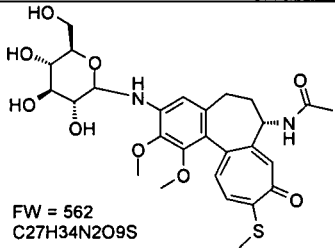
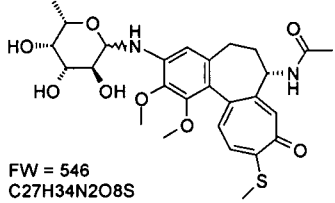
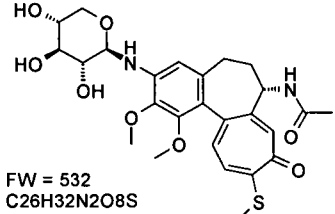
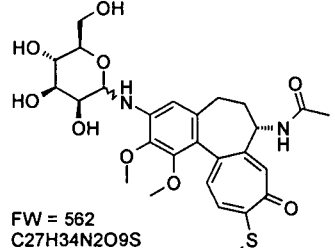
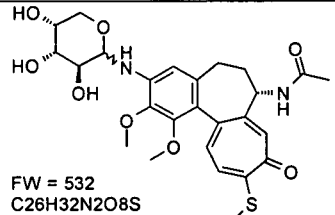
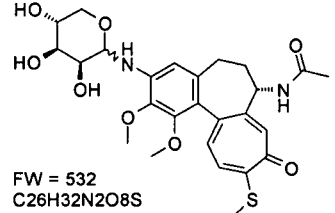
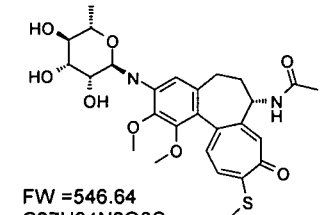
1667, 1620 cm^{-1} ; ^1H NMR (CDCl_3): δ 7.38 (s, 1H), 7.33, 7.09 (AB system, J = 10.2 Hz, 1H), 6.37 (s, 1H), 3.95 (s, 3H), 3.65 (s, 3H), 2.45 (s, 3H), 2.40-2.24 (m, 2H), 2.00 (s, 3H), 1.89-1.81 (m, 2H); ^{13}C NMR (CDCl_3): δ 182.7, 170.2, 157.9, 152.4, 150.9, 141.0, 139.7, 139.5, 135.2, 134.8, 128.7, 127.1, 123.6, 110.8, 61.5, 61.0, 52.6, 36.7, 29.8, 23.1, 15.3; MS m/z 400.1 (MH^+).

Example 3. General procedure for the synthesis of 3--demethoxy-3-aminothiocolchicine glycosides

Method A. A solution of 3-demethoxy-3-aminothiocolchicine (404 mg, 1 mmole) in MeOH (8.5 ml) was added with commercial glycopyranoside (1 mmole) and the mixture was heated in a sealed tube at 80°C for 6 days. The reaction was monitored by TLC analysis (10:1.5 $\text{CH}_2\text{Cl}_2/\text{MeOH}$). The solvent was evaporated under pressure and TLC analysis of the reaction crude revealed the presence of the starting reagent (8-10%) and of an isomeric mixture of aminoglycosides which was separated through column chromatography on silica gel (100:1 to 100:5 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) then crystallised from MeOH/ $i\text{Pr}_2\text{O}$ to obtain the desired compounds.

Method B. A solution of 3-*O*-demethoxy-3-aminothiocolchicine (404 mg, 1 mmole) in MeOH (8.5 ml), was added with commercial glycopyranoside (1 mmole) and the mixture was heated in a microwave oven for 4 hours at 110°C and 150 watt. The reaction was monitored by TLC analysis (10:1.5 $\text{CH}_2\text{Cl}_2/\text{MeOH}$). The solvent was removed under pressure and TLC analysis of the reaction crude revealed the presence of traces of the starting reagent and of an isomeric mixture of aminoglycosides which was separated by column chromatography on silica gel (100:1 to 100:5 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) and recrystallized from MeOH/ $i\text{Pr}_2\text{O}$ to obtain the desired compounds.

The following table reports the yields and diastereoselection of the processes.

Name	FORMULA	Method A		Method B	
		Yield	α/β	Yield	α/β
3- <i>N</i> -D-glucopyranosyl-3- <i>O</i> -demethoxy-3-aminothiocolchicine	 FW = 562 C₂₇H₃₄N₂O₉S	34	20:80	58	20:80
3- <i>N</i> -L-fucopyranosyl-3- <i>O</i> -demethoxy-3-aminothiocolchicine	 FW = 546 C₂₇H₃₄N₂O₈S	35	1:99	58	1:99
3- <i>N</i> -D-xylopyranosyl-3- <i>O</i> -demethoxy-3-aminothiocolchicine	 FW = 532 C₂₆H₃₂N₂O₈S	34	30:70	55	30:70
3- <i>N</i> -D-mannopyranosyl-3- <i>O</i> -demethoxy-3-aminothiocolchicine	 FW = 562 C₂₇H₃₄N₂O₉S	36	1:99	60	1:99
3- <i>N</i> -D-arabinopyranosyl-3- <i>O</i> -demethoxy-3-aminothiocolchicine	 FW = 532 C₂₆H₃₂N₂O₈S	38	45:55	60	45:55
3- <i>N</i> -D-lyxopyranosyl-3- <i>O</i> -demethoxy-3-aminothiocolchicine	 FW = 532 C₂₆H₃₂N₂O₈S	37	40:60	60	40:60
3- <i>N</i> -L-ramnopyranosyl-3- <i>O</i> -demethoxy-3-aminothiocolchicine	 FW = 546.64 C₂₇H₃₄N₂O₈S	35	99:1	60	99:1

Example 4. 3-*N*- α -D-Glucopyranosyl-3-*O*-demethoxy-3-aminothiocolchicine

TLC R_f 0.30 (5:1 CH₂Cl₂/MeOH). IR (Nujol) $\nu_{\max}$ 1667, 1620 cm⁻¹; ¹H NMR (DMSO): δ 8.63 (d, J = 7.6 Hz, 1H, exch), 7.25, 7.18 (AB system, J = 10.3 Hz, 2H), 7.01 (s, 1H), 6.76 (s, 1H), 5.58 (d, J = 3.8 Hz, 1H, exch), 5.36 (bs, 1H, exch), 5.22 (bs, 1H, exch), 4.91 (dd, J = 5.0, 3.8 Hz, 1H), 4.41-4.35 (m, 1H), 3.83 (s, 3H), 3.73-3.64 (m, 1H), 3.64-3.57 (m, 1H), 3.51 (s, 3H), 3.50-3.40 (m, 1H), 3.19-3.10 (m, 2H), 2.55-2.45 (m, 1H), 2.41 (s, 3H), 2.23-2.15 (m, 1H), 2.07-1.95 (m, 1H), 1.87-1.78 (m, 1H), 1.81 (s, 3H); ¹³C NMR (DMSO): δ 181.6, 169.0, 157.0, 152.0, 150.1, 141.7, 138.9, 138.6, 135.2, 134.2, 128.4, 127.2, 122.3, 108.1, 85.5, 78.1, 77.9, 73.3, 70.8, 61.5, 60.9, 60.9, 51.9, 36.3, 29.9, 22.9, 14.8; MS m/z 563.2 (MH⁺).

Example 5. 3-*N*- β -D-Glucopyranosyl-3-*O*-demethoxy-3-aminothiocolchicine

TLC R_f 0.37 (5:1 CH₂Cl₂/MeOH). IR (Nujol) $\nu_{\max}$ 1667, 1620 cm⁻¹; ¹H NMR (DMSO): δ 8.63 (d, J = 7.6 Hz, 1H, exch), 7.26, 7.15 (AB system, J = 10.3 Hz, 2H), 7.01 (s, 1H), 6.48 (s, 1H), 5.78 (d, J = 6.5 Hz, 1H, exch), 5.19 (d, J = 10.2 Hz, 1H, exch), 5.18 (d, J = 4.6 Hz, 1H, exch), 5.04 (d, J = 3.8 Hz, 1H, exch), 4.41-4.35 (m, 1H), 4.34 (dd, J = 8.1, 6.5 Hz, 1H), 3.79 (s, 3H), 3.73-3.64 (m, 1H), 3.64-3.57 (m, 1H), 3.52 (s, 3H), 3.50-3.40 (m, 1H), 3.32-3.23 (m, 2H), 2.55-2.45 (m, 1H), 2.41 (s, 3H), 2.23-2.15 (m, 1H), 2.07-1.95 (m, 1H), 1.87-1.78 (m, 1H), 1.81 (s, 3H); ¹³C NMR (DMSO) 181.6, 169.0, 157.0, 152.0, 150.1, 141.7, 138.9, 138.6, 135.2, 134.2, 128.4, 127.2, 122.3, 108.1, 85.5, 78.1, 77.9, 73.3, 70.8, 61.5, 60.9, 60.9, 51.9, 36.3, 29.9, 23.3, 14.8; MS m/z 563.2 (MH⁺).

Example 6. 3-*N*- α -D-Arabinopyranosyl-3-*O*-demethoxy-3-aminothiocolchicine

TLC R_f 0.37 (5:1 CH₂Cl₂/MeOH). IR (Nujol) $\nu_{\max}$ 1667, 1620 cm⁻¹; ¹H

NMR (DMSO): δ 8.59 (d, J = 8.7 Hz, 1H exch), 7.25, 7.18 (AB system, J = 10.4 Hz, 1H), 7.01 (s, 1H), 6.49 (s, 1H), 6.01 (d, J = 9.8 Hz, 1H exch), 5.77 (d, J = 6.1 Hz, 1H exch), 5.48 (d, J = 4.2 Hz, 1H exch), 5.29 (d, J = 4.4 Hz, 1H exch), 4.93 (dd, J = 9.8, 3.5 Hz, 1H), 4.41-4.32 (m, 1H), 3.78 (m, 3H), 3.68-3.64 (m, 1H), 3.62-3.57 (m, 3H), 3.52 (s, 3H), 3.46-3.37 (m, 1H), 2.55-2.48 (m, 1H), 2.41 (s, 3H), 2.21-2.16 (m, 1H), 2.05-1.98 (m, 1H), 1.86-1.78 (m, 1H), 1.85 (s, 3H); ^{13}C NMR (DMSO) δ 181.6, 168.9, 157.2, 152.2, 150.4, 141.9, 141.0, 138.7, 135.4, 134.2, 128.3, 127.2, 122.4, 107.4, 81.6, 73.5, 70.5, 68.2, 65.7, 61.1, 60.9, 51.9, 36.3, 29.9, 23.3, 22.7, 14.8; MS m/z 533.3 (MH^+).

Example 7. 3-*N*- β -D-Arabinopyranosyl-3-*O*-demethoxy-3-aminothiocolchicine

TLC R_f 0.30 (5:1 $\text{CH}_2\text{Cl}_2/\text{MeOH}$). IR (Nujol) ν_{max} 1667, 1620 cm^{-1} ; ^1H NMR (DMSO): δ 8.56 (d, J = 7.7 Hz, 1H exch), 7.26, 7.18 (AB system, J = 10.5 Hz, 1H), 7.01 (s, 1H), 6.45 (s, 1H), 6.21 (d, J = 8.3 Hz, 1H exch), 5.57 (d, J = 9.2 Hz, 1H exch), 5.51 (d, J = 5.6 Hz, 1H exch), 4.61 (dd, J = 8.3, 4.8 Hz, 1H), 4.57 (d, J = 6.1 Hz, 1H exch), 4.41-4.32 (m, 1H), 3.80 (s, 3H), 3.68-3.64 (m, 1H), 3.62-3.57 (m, 3H), 3.52 (s, 3H), 3.46-3.37 (m, 1H), 2.55-2.48 (m, 1H), 2.41 (s, 3H), 2.21-2.16 (m, 1H), 2.05-1.98 (m, 1H), 1.86-1.78 (m, 1H), 1.84 (s, 3H); ^{13}C NMR (DMSO) δ 181.6, 168.9, 157.2, 152.2, 150.4, 141.9, 141.0, 138.7, 135.4, 134.2, 128.3, 127.2, 122.4, 107.4, 81.6, 73.5, 70.5, 68.2, 65.7, 61.1, 60.9, 51.9, 36.3, 29.9, 23.3, 22.7, 14.8; MS m/z 533.3 (MH^+).

Example 8. 3-*N*- α -D-Lyxopyranosyl-3-*O*-demethoxy-3-aminothiocolchicine

TLC R_f 0.37 (5:1 $\text{CH}_2\text{Cl}_2/\text{MeOH}$). IR (Nujol) ν_{max} 1667, 1620 cm^{-1} ; ^1H NMR (DMSO): δ 8.58 (d, J = 7.6 Hz, 1H, exch), 7.26, 7.17 (AB system, J = 10.7 Hz, 2H), 7.03 (s, 1H), 6.45 (s, 1H), 5.68 (d, J = 7.1 Hz, 1H exch), 5.18 (d, J = 4.5 Hz, 1H exch), 4.95 (d, J = 3.9 Hz, 1H exch), 4.83 (d, J = 7.1 Hz,

1H exch), 4.72 (dd, $J = 8.4, 7.1$ Hz, 1H), 4.40-4.36 (m, 1H), 3.81 (s, 3H), 3.75-3.72 (m, 2H), 3.52 (s, 3H), 3.55-3.51 (m, 1H), 2.0-3.16 (m, 1H), 3.18-3.15 (m, 1H), 2.56-2.48 (m, 1H), 2.41 (s, 3H), 2.24-2.15 (m, 1H), 2.07-1.95 (m, 2H), 1.86-1.78 (m, 1H), 1.84 (s, 3H); ^{13}C NMR (DMSO) δ 181.6, 168.9, 157.1, 151.9, 150.2, 141.7, 141.0, 138.7, 135.2, 134.2, 128.4, 127.2, 122.1, 106.4, 82.1, 71.2, 70.1, 67.8, 63.6, 60.8, 60.7, 51.9, 36.3, 29.9, 23.3, 22.9, 14.8; MS m/z 533.3 (MH^+).

Example 9. 3-*N*- β -D-Lyxopyranosyl-3-*O*-demethoxy-3-aminothiocolchicine

10 TLC R_f 0.30 (5:1 $\text{CH}_2\text{Cl}_2/\text{MeOH}$). IR (Nujol) ν_{max} 1667, 1620 cm^{-1} ; ^1H NMR (DMSO): δ 8.59 (d, $J = 7.3$ Hz, 1H, exch), 7.25, 7.15 (AB system, $J = 10.4$ Hz, 2H), 7.03 (s, 1H), 6.48 (s, 1H), 6.13 (d, $J = 8.9$ Hz, 1H, exch), 5.06 (d, $J = 5.5$ Hz, 1H exch), 4.90 (dd, $J = 8.9, 2.7$ Hz, 1H), 4.86 (d, $J = 4.5$ Hz, 1H exch), 4.40-4.36 (m, 1H), 3.82-3.79 (m, 2H), 3.79 (s, 3H), 3.62-3.58 (m, 1H), 3.52 (s, 3H), 3.55-3.51 (m, 1H), 3.49-3.46 (m, 1H), 3.18-3.15 (m, 1H), 2.56-2.48 (m, 1H), 2.41 (s, 3H), 2.24-2.15 (m, 1H), 2.07-1.95 (m, 2H), 1.86-1.78 (m, 1H), 1.84 (s, 3H); ^{13}C NMR (DMSO) δ : 181.6, 169.0, 157.1, 152.0, 150.3, 141.7, 141.0, 138.9, 135.2, 134.3, 128.4, 127.2, 122.2, 107.4, 81.6, 73.6, 71.5, 68.0, 65.5, 61.0, 60.9, 51.9, 36.2, 29.8, 23.3, 22.9, 14.8; MS m/z 533.3 (MH^+).

20 **Example 10. 3-*N*- α -D-Xylopyranosyl-3-*O*-demethoxy-3-aminothiocolchicine**

TLC R_f 0.30 (5:1 $\text{CH}_2\text{Cl}_2/\text{MeOH}$). IR (Nujol) ν_{max} 1667, 1620 cm^{-1} ; ^1H NMR (DMSO): δ 8.65-8.56 (m, 1H exch), 7.25, 7.17 (AB system, $J = 10.6$ Hz, 2H), 7.02 (s, 1H), 6.55 (s, 1H), 5.46 (d, $J = 5.9$ Hz, 1H exch), 5.32 (d, $J = 5.6$ Hz, 1H exch), 5.21 (bs, 1H exch), 5.05 (d, $J = 5.4$ Hz, 1H exch), 4.88 (dd, $J = 5.9, 3.8$ Hz, 1H), 4.42-4.35 (m, 1H), 3.82 (s, 3H), 3.70-3.50 (m, 2H), 3.51 (s, 3H), 3.40-3.30 (m, 1H), 3.30-3.20 (m, 2H), 2.57-2.50 (m, 1H), 2.50 (s, 3H), 2.21-2.12 (m, 1H), 2.07-1.97 (m, 1H), 1.86-1.78 (m, 1H), 1.85 (s, 3H), ^{13}C

NMR (DMSO) δ 181.6, 168.9, 157.2, 151.8, 150.1, 141.5, 138.8, 135.4, 134.4, 128.3, 127.2, 123.1, 108.0, 81.7, 77.2, 71.1, 67.8, 66.1, 60.9, 51.9, 36.3, 29.8, 23.3, 14.8; MS m/z 533.3 (MH^+).

Example 11. 3-*N*- β -D-Xylopyranosyl-3-*O*-demethoxy-3-aminothiocolchicine

TLC R_f 0.37 (5:1 CH_2Cl_2 /MeOH). IR (Nujol) ν_{max} 1667, 1620 cm^{-1} ; 1H NMR (DMSO) δ 8.65-8.56 (m, 1H exch), 7.25, 7.17 (AB system, $J = 10.6$ Hz, 2H), 7.02 (s, 1H), 6.46 (s, 1H), 5.81 (d, $J = 7.2$ Hz, 1H exch), 5.52 (t, $J = 5.3$ Hz, 0.06 H_{6f} exch), 5.11 (bs, 2H exch), 4.99 (d, $J = 4.8$ Hz, 1H exch), 4.42-4.35 (m, 1H), 4.41 (dd, $J = 7.8, 7.2$ Hz, 1H), 3.79 (s, 3H), 3.70-3.50 (m, 2H), 3.49 (s, 3H), 3.40-3.30 (m, 1H), 3.30-3.20 (m, 2H), 2.57-2.50 (m, 1H), 2.50 (s, 3H), 2.21-2.12 (m, 1H), 2.07-1.97 (m, 1H), 1.86-1.78 (m, 1H), 1.84 (s, 3H); ^{13}C NMR (DMSO) δ 181.6, 168.9, 157.1, 151.9, 150.2, 141.4, 138.7, 135.2, 134.2, 128.3, 127.2, 122.3, 107.5, 85.7, 77.4, 72.9, 70.2, 66.6, 61.1, 61.0, 51.9, 36.3, 29.8, 22.9, 14.8; MS m/z 533.3 (MH^+).

Example 12. 3-*N*- α -L-Rhamnopyranosyl-3-*O*-demethoxy-3-aminothiocolchicine

TLC R_f 0.30 (10:2 CH_2Cl_2 -MeOH). Mp 185-188°C; $[\alpha]_{25}^D - 299^\circ$ (c 0.4, MeOH); IR (Nujol) ν_{max} 1667, 1620 cm^{-1} ; 1H -NMR (DMSO) δ 8.58 (d, $J = 7.3$ Hz, 1H exch), 7.27, 7.14 (AB system, $J = 10.5$ Hz, 2H), 7.02 (s, 1H), 6.49 (s, 1H), 5.64 (d, $J = 9.8$ Hz, 1H exch), 5.12 (d, $J = 4.4$ Hz, 1H exch), 4.84 (d, $J = 10.2$ Hz, 1H exch), 4.79 (brs, 2H exch), 4.41-4.38 (m, 1H), 3.80 (s, 3H), 3.79-3.78 (m, 1H), 3.51 (s, 3H), 3.45-3.15 (m, 3H), 2.55-2.47 (m, 1H), 2.40 (s, 3H), 2.22-2.17 (m, 1H), 2.06-1.97 (m, 1H), 1.85 (s, 3H), 1.84-1.81 (m, 1H), 1.11 (d, $J = 5.6$ Hz, 3H); ^{13}C NMR (DMSO): δ 182.00, 169.39, 157.51, 152.33, 150.61, 140.77, 139.01, 135.59, 134.64, 128.75, 127.58, 122.62, 108.07, 94.92, 80.94, 74.94, 73.39, 72.75, 71.88, 61.37, 61.22, 36.68, 29.87, 23.31, 22.95, 18.88; MS m/z 547.2 (MH^+).

Example 13. 3-*N*-β-D-Mannopyranosyl-3-*O*-demethoxy-3-aminothiocolchicine

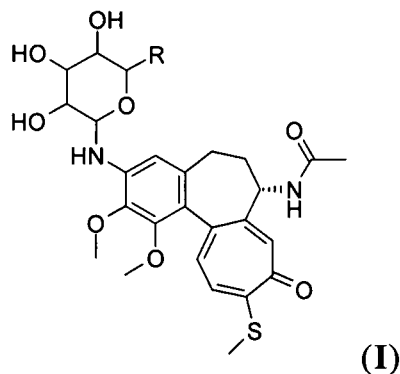
TLC R_f 0.21 (10:2 CH₂Cl₂-MeOH). M.p. 165-167°C; $[\alpha]_{25}^D$ -395° (c 0.44. MeOH); IR (Nujol) $\nu_{\max}$ 1667, 1620 cm⁻¹; ¹H NMR (DMSO) δ 8.59 (d, J = 7.5 Hz, 1H, exch), 7.25, 7.16 (AB system, J = 10.3 Hz, 2H), 7.01 (s, 1H), 6.48 (s, 1H), 5.72 (d, J = 10.0 Hz, 1H, exch), 5.13 (d, J = 5.2 Hz, 1H, exch), 4.80 (d, J = 5.4 Hz, 1H, exch), 4.82 (d, J = 10 Hz, 1H), 4.76 (d, J = 5.0 Hz, 1H, exch), 4.43 (t, J = 6.1 Hz, 1H, exch), 4.42-4.33 (m, 1H), 3.49 (s, 3H), 3.83 (s, 3H), 3.77-3.52 (m, 3H), 3.49-3.35 (m, 2H), 3.29-3.15 (m, 1H), 2.52-2.45 (m, 1H), 2.42 (s, 3H), 2.20-2.15 (m, 1H), 2.05-1.98 (m, 1H), 1.84-1.78 (m, 1H), 1.86 (s, 3H); ¹³C NMR (DMSO) δ 181.6, 169.0, 157.1, 152.0, 150.1, 140.4, 138.8, 138.6, 135.2, 134.3, 128.4, 127.2, 122.3, 108.2, 94.5, 78.5, 74.9, 71.3, 67.9, 67.6, 61.6, 60.9, 60.8, 51.9, 36.2, 29.9, 23.3, 14.8; MS m/z 563.2 (MH⁺). In admixture with 10% of the conformational isomer.

Example 14. 3-*N*-β-L-Fucopyranosyl-3-*O*-demethoxy-3-aminothiocolchicine

TLC R_f 0.30 (5:1 CH₂Cl₂/MeOH). M.p. 185-188°C; $[\alpha]_{25}^D$ -299° (c 0.4. MeOH); IR (Nujol) $\nu_{\max}$ 1667, 1620 cm⁻¹; ¹H-NMR (DMSO): δ 8.60 (d, J = 7.3 Hz, 1H exch), 7.26, 7.17 (AB system, J = 10.3 Hz, 2H), 7.02 (s, 1H), 6.46 (s, 1H), 5.65 (d, J = 6.6 Hz, 1H exch), 4.94 (d, J = 6.6 Hz, 1H exch), 4.74 (d, J = 5.5 Hz, 1H exch), 4.40 (d, J = 5.1 Hz, 1H exch), 4.40-4.35 (m, 1H), 4.36 (dd, J = 8.6, 6.6 Hz, 1H), 3.81 (s, 3H), 3.75-3.65 (m, 1H), 3.70-3.38 (m, 5H), 3.65-3.50 (m, 2H), 3.51 (s, 3H), 3.50-3.40 (m, 1H), 2.55-2.47 (m, 1H), 2.40 (s, 3H), 2.22-2.17 (m, 1H), 2.06-1.97 (m, 1H), 1.88-1.78 (m, 1H), 1.84 (s, 3H), 1.10 (d, J = 6.1 Hz, 3H); ¹³C NMR (DMSO): δ 181.62, 168.98, 157.03, 152.00, 150.18, 141.71, 138.74, 138.65, 135.21, 134.21, 128.36, 127.21, 122.06, 107.38, 85.38, 74.61, 71.91, 70.99, 70.14, 60.97, 60.91, 51.88, 36.32, 29.96, 23.29, 17.29, 14.82; MS m/z 547.2 (MH⁺).

CLAIMS

1. Compounds of general formula (I)



wherein

R is hydrogen, methyl or hydroxymethyl.

2. A compound selected from:

3-*N*-D-xylopyranosyl-3-*O*-demethoxy-3-aminothiocolchicine;

3-*N*-D-glucopyranosyl-3-*O*-demethoxy-3-aminothiocolchicine;

3-*N*-D-mannopyranosyl-3-*O*-demethoxy-3-aminothiocolchicine;

3-*N*-D-arabinopyranosyl-3-*O*-demethoxy-3-aminothiocolchicine;

3-*N*-D-lyxopyranosyl-3-*O*-demethoxy-3-aminothiocolchicine;

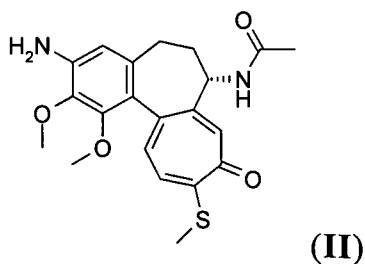
3-*N*-L-rhamnopyranosyl-3-*O*-demethoxy-3-aminothiocolchicine;

3-*N*-L-fucopyranosyl-3-*O*-demethoxy-3-aminothiocolchicine.

3. Pharmaceutical compositions comprising a compound of claim 1 or 2 in admixture with acceptable carriers and/or excipients.

4. Use of the compounds of claims 1 and 2 for the preparation of medicaments with myorelaxant and anti-inflammatory activity.

5. Use of the compound of formula (II)



for the preparation of medicaments with myorelaxant activity.