Eur J Med Chem (1997) 32, 351–356

Short communication

The affinity to the brain dopamine D_1 receptor in vitro of triprenyl phenols isolated from the fruit bodies of *Albatrellus ovinus*

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(Received 28 May 1996; accepted 4 November 1996)

Summary — Six triprenyl phenols that inhibit the in vitro binding of ^{3}H-SCH 23390 to the dopamine D_1 receptor subfamily in rat striatal brain membranes were isolated from extracts of the edible mushroom *Albatrellus ovinus*. The compounds, of which scutigeral **1a**, ilicicolin B **3**, neogrifolin **5a** and grifolin **6** are known while ovinal **2** and ovinol **4a** are new, were isolated by chromatography and their structures were determined by spectroscopic techniques. The IC_{50} values of the most potent compound, scutigeral **2a**, is 2.6 μM and it was shown that it decreases the binding affinity of ^{3}H-SCH 23390 in a competitive manner. Compounds **1–5** showed no inhibition on the binding of ^{3}H-spiperone to the dopamine D_2 receptor subfamily, indicating that these compounds interact selectively with the dopamine D_1 receptor subfamily.

CNS / dopamine D_1 receptor / *Albatrellus ovinus* / triprenyl phenol

Introduction

Recombinant DNA cloning techniques have shown that the central nervous system (CNS) dopamine receptor family consists of five different receptor subtypes, designated the D_1, D_2 (short- and long-spliced variants), D_3, D_4 and D_5 receptor subtypes [1]. The D_1-like subfamily (D_1 and D_5 receptor subtypes) stimulates adenylate cyclase, thus increasing intracellular levels of cAMP, while the D_2-like subfamily (D_2, D_3 and D_4 receptor subtypes) inhibits or has no effect on cAMP concentrations [2]. The dopamine receptors are the primary targets for the pharmacological treatment of schizophrenia, Parkinson's disease and Huntington's chorea. The importance of finding new and selective dopamine receptor ligands is obvious and the recent development of cloned dopamine receptors expressed in various cell systems has facilitated the search and discovery of more selective antipsychotic and anti-Parkinson drugs [3]. Several compounds with affinity to the dopamine receptors in vitro have been isolated from natural sources [4–8]. During a screening of fungal extracts for compounds interacting with mammalian CNS receptors, the ethyl acetate extract of the edible mushroom *Albatrellus ovinus* was found to displace the binding of ^{3}H-SCH 23390 (*R*-(+)-7 chloro-8 hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydrol-1*H*-3-benzazepin-7-ol), a dopamine D_1 receptor subfamily selective ligand [9], in rat striatal brain membrane homogenates. The active compounds were isolated by bioassay-guided fractionation of the crude extracts and identified by spectroscopic techniques. Furthermore, their ability to interact with the in vitro binding of the ligands ^{3}H-spiperone, ^{3}H-muscimol, ^{3}H-flunitrazepam, ^{35}S-TBPS and ^{3}H-kainic acid was studied.

Results and discussion

In total, six compounds that inhibit the binding of ^{3}H-SCH 23390 to the dopamine D_1 receptor in vitro were isolated from the extracts of *A ovinus* (see fig 1 for chemical structures). Scutigeral **1a**, neogrifolin **5a** and grifolin **6** have previously been isolated from various *Albatrellus* species [10] and ilicicolin B **3** has been isolated from *Netria* and *Fusarium* species [11]. Compounds **2** and **4a** are new compounds for which we suggest the names ovinal and ovinol, respectively. The structures of the compounds were elucidated by 2D NMR heteronuclear spectroscopy and mass spectrometry (MS). The latter technique revealed the molecular weights of ovinal **2** and ovinol **4a** to be 356 and 344, respectively, and high resolution MS meas-

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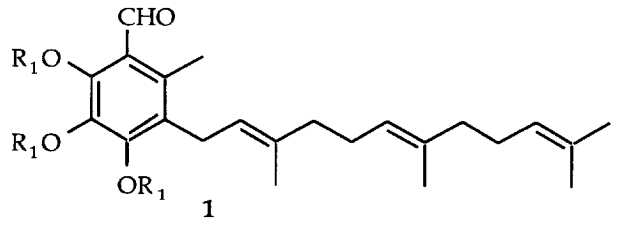

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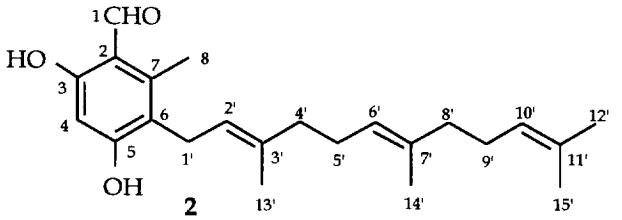

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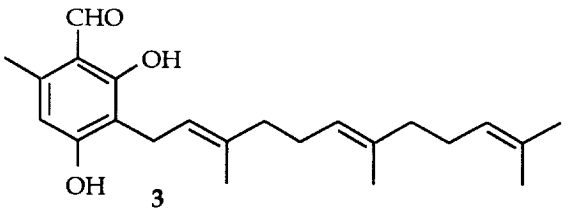

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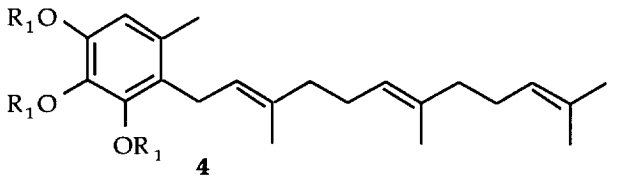

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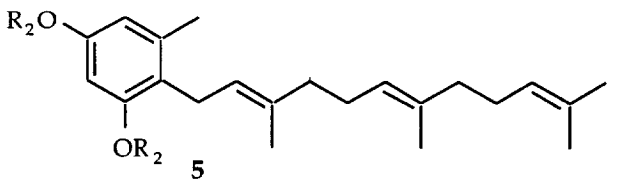

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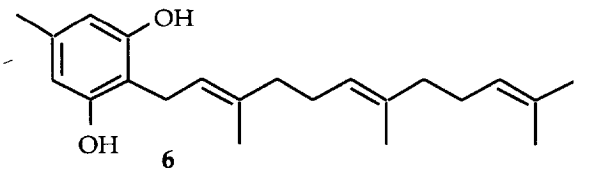

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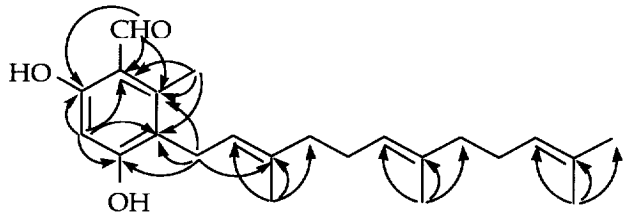
Fig 1. Chemical structures of the isolated triprenyl phenols. **a**: $R_1 = R_2 = H$; **b**: R_1 = Ac, R_2 = Me.

urements suggested that the elemental compositions of the two compounds are $C_{23}H_{32}O_3$ and $C_{22}H_{32}O_3$. The assignments of the ^1H and ^{13}C-NMR data are based on the correlations observed in the HMQC (heteronuclear multiple-quantum correlation) and the HMBC (heteronuclear multiple-bond correlation) spectra. The results of the HMBC experiments, summarised in figure 2, show that ovinal **2** is in fact a deoxyscutigeral and that ovinol **4a** is hydroxyneogrifolin. NOESY (nuclear Overhauser effect spectroscopy, see fig 3) and COSY



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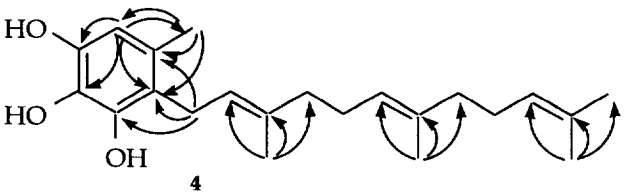

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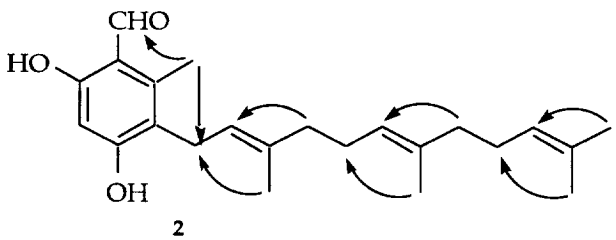
Fig 2. Significant HMBC correlations observed with ovinal **2** and ovinol **4a**.



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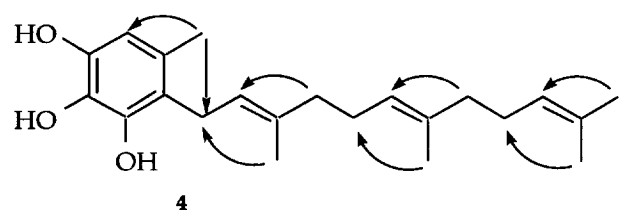

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Fig 3. Significant NOESY correlations observed with ovinal **2** and ovinol **4a**.

(correlated spectroscopy) experiments confirmed the structures, eg, the position of the C-7 methyl group between the aldehyde and the triprenyl chain in ovinal **2** and the position of the C-7 methyl group between the triprenyl chain and 2-H in ovinol **4a**. The NOESY spectra also established that the 2'/3' and 6'/7' double bonds of both ovinal **2** and ovinol **4a** are *E*.

Table I shows the inhibitory activity (as IC_{50} values) of the six fungal triprenyl phenols isolated from *A ovinus*, as well as of the three derivatives triacetylscutigeral **1b**, triacetylovinol **4b** and dimethylneogrifolin **5b**, on the specific binding of ^{3}H-SCH 23390. (No derivatives of ovinal **2**, grifolin **6** and ilicicolin B **3** were prepared due to the limited amounts of these metabolites available.) In addition, the inhibitory activity on the binding of the dopamine D_2 receptor subfamily selective ligand ^{3}H-spiperone (8-(3-(4-fluorobenzoyl)propyl)-1-phenyl-1,3,8-triazospiro[4.5]decan-4-one) [12] is also given in table I. Scutigeral **1a**, ovinal **2** and ovinol **4a** are relatively potent (< 5 μM) inhibitors of the binding of ^{3}H-SCH 23390 but do not affect the binding of ^{3}H-spiperone, neogrifolin **5a** is less potent but still selective for the dopamine D_1 receptor subtype while ilicicolin B **3** is only weakly active. Grifolin **6** differs from the others by not being selective. Interestingly, the acetates **1b** and **4b** are almost as active as their parent compounds scutigeral **1a** and ovinol **4a**, while methylation of neogrifolin (to form derivative **5b**) results in an inactive compound. Chromatographic analyses of the mixtures of the acetates **1b** and **4b** and the rat striatal brain membrane homogenate used in the assay showed that the acetates are stable during the assay, and the activity of the acetates is therefore not due to their enzymatic hydrolysis to scutigeral **1a** and ovinol **4a** by esterases. In order to investigate whether any of the compounds interacts with the main inhibitory or excitatory amino-acid receptors of the CNS we tested them on radioligand binding on various site of the $GABA_A$ receptor and on the kainic acid subtype of the glutamate receptors. None of the six natural products inhibited the binding of the following ligands to rat striatal brain membrane homogenate at concentrations up to 100 μM: ^{3}H-muscimol ($GABA_A$-benzodiazepine receptor, GABA site), ^{3}H-flunitrazepam ($GABA_A$-benzodiazepine receptor, benzodiazepine site), ^{35}S-TBPS ($GABA_A$-benzodiazepine receptor, chloride channel site) and ^{3}H-kainic acid (kainic acid subtype of the glutamate receptors) (data not shown). With the exception of grifolin **5** and possibly also of ilicicolin B **3**, the triprenyl phenols investigated here show a high degree of specificity for the binding to the dopamine D_1 receptor. In addition, a Scatchard plot analysis showed that scutigeral **1a** shows that it decreases the binding affinity of ^{3}H-SCH 23390 in a competitive manner (see fig 4).

Table I. Comparative IC_{50} values of triprenyl phenols metabolites on the specific ^{3}H-SCH 23390 and ^{3}H-spiperone binding to rat striatal membranes[a].

Compound	*IC_{50} (μM) value*		*Ratio*[b]
	^{3}H-SCH 23390	*^{3}H-Spiperone*	
Scutigeral **1a**	2.6 ± 0.02	> 100	> 38.5
Ovinol **4a**	3.0 ± 0.7	> 100	> 33.3
Ovinol-Ac **4b**	4.4 ± 0.1	> 100	> 22.7
Scutigeral-Ac **1b**	4.7 ± 0.6	> 100	> 21.3
Ovinal **2**	5.1 ± 0.3	> 100	> 19.6
Grifolin **6**	8.8 ± 0.4	20.2 ± 2.1	2.3
Neogrifolin **5a**	13.5 ± 1.1	> 100	> 7.4
Ilicicolin B **3**	> 50[c]	> 100	> 2
Neogrifolin-Me **5b**	> 100	> 100	–

[a]Values are as mean ± SD (n = 3); [b]ratio is IC_{50} of ^{3}H-SCH 23390 binding/IC_{50} of ^{3}H-spiperone binding; [c]due to limited amounts of ilicicolin B **3** the IC_{50} is an approximate value.

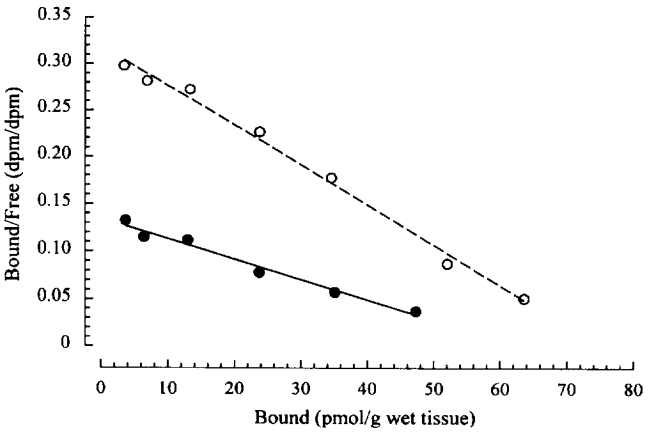

Fig 4. Representative Scatchard plot of ^{3}H-SCH 23390 binding to rat striatal membrane homogenates in vitro. (O) Specific control binding: K_D = 0.24 ± 0.01 nM; B_{max} = 68.0 ± 7.9 pmol/g wet tissue. (●) In the presence of 3 μM scutigeral **1a**: K_D = 0.44 ± 0.12 nM: B_{max} = 58.0 ± 8.2 pmol/g wet tissue. Values are mean ± SD (n = 3).

As the triprenyl chain attached to C-6 is identical in all compounds, the nature and position of the aromatic substituents must determine the potency with which the compounds bind to the dopamine D_1 receptors. Unexpectedly, the aldehyde group of compounds **1a**, **2** and **3** is not a necessity for the activity, as ovinol **4a** is approximately as potent as scutigeral **1a**, neogrifolin **5** is only two or three times less potent compared to ovinal **2** and grifolin **6** is approximately five times more potent compared to ilicicolin B **3**. The presence of a C-4 hydroxyl group appears to enhance the ability of the compounds to interact with the D_1 receptor, as scutigeral **1a** and ovinol **4a** are more active compared to the 4-deoxy analogues ovinal **2** and neogrifolin **5a**, although the effect is not dramatic. Ilicicolin B **3** and grifolin **6** differ chemically from the other four metabolites, in that the aromatic methyl group is positioned at C-3 instead of C-7 and both C-5 and C-7 are hydroxylated. This gives them slightly different chemical properties, but it is impossible to determine whether these differences explain the lower potency of ilicicolin B **3** (which is approximately ten times less potent compared to its isomer ovinal **2**) and the poorer selectivity of grifolin **6** compared to neogrifolin **5** for the dopamine D_1 receptor.

In conclusion, the potency and selectivity towards the dopamine D_1 receptor subfamily of naturally occurring triprenyl phenols has been demonstrated. In addition, two new bioactive fungal metabolites, ovinal **2** and ovinol **4a**, have been isolated, and the elucidation of their structures is reported. At present nothing is known about whether the triprenyl phenols have any in vivo CNS activity, but we are currently trying to obtain larger amounts for studies in rodents.

The results presented emphasise the potential of natural products as a source of new compounds with activity on CNS receptor subtypes, which may aid the development of new neurobiological tools and pharmacological drugs for the future.

Experimental protocols

General

The HPLC system and reversed-phase columns were from Millipore Waters, all solvents for HPLC separations were 'HPLC grade' from Rathburn Chemicals (UK). Column chromatography was performed on silica-gel 60 eluted with mixtures of ethyl acetate and heptane, and thin-layer chromatography was carried out on 0.25 μm silica-gel-coated glass plates (Merck 60 F_{254}) using UV and/or 10% H_2SO_4 and heat as the developing agents.

Extraction and isolation of the active compounds

Fruit bodies of *A ovinus* (Schff per Fr) Kotl et Pouz were collected in the vicinity of Kaiserslautern, Germany, in the autumns of 1994 and 1995, and extracted with ethyl acetate. The six compounds were isolated following an initial fractionation of the extract (dissolved in methanol) on a PrepPak C_{18} Nova-Pak reverse phase column (250 x 10 mm) eluted with a linear gradient (from water/acetonitrile 75:25 to 100% acetonitrile over 60 min). Fifty milligrams of the extract (dissolved in methanol) was injected on to the HPLC column, the flow was 7 mL/min and UV detection at 210 nm was used. Fractions were collected and aliquots were tested for the inhibition of the specific binding of ^{3}H-SCH 23390 in rat striatal brain membrane homogenates. The activity was found in fractions eluting with the retention times 44–46 min (fraction A), 49–51 min (fraction B) and 54–56 min (fraction C). These fractions were further purified on an analytical C_{18} Nova-Pak reverse-phase (300 x 3.9 mm) column eluted with water/acetonitrile 27:73 (flow 1 mL/min). From fraction A, grifolin **6**, ovinol **4a** and neogrifolin **5a** was purified (retention times of 10.1, 12.3 and 14.0 min, respectively). Scutigeral **1a** was obtained from fraction B (retention time 19.6 min), while fraction C yielded ovinal **2** and ilicicolin B **3** (retention times 22.7 and 24.2 min, respectively).

Spectroscopy

^{1}H-NMR (500 MHz) and ^{13}C-NMR (125 MHz) were recorded at room temperature using a Bruker ARX 500 spectrometer with an inverse 5 mm probe equipped with a shielded gradient coil. COSY, HMQC and HMBC experiments were done with gradient enhancements using sine-shaped gradient pulses and for the 2D heteronuclear correlation spectroscopy the refocusing delays were optimised for $^1J_{CH}$ = 145 Hz and $^2J_{CH}$ = 10 Hz. The raw data were transformed and the spectra were evaluated

with the standard Bruker UXNMR software (rev 950901). The chemical shifts are given in ppm (with the chloroform peaks at 7.26 and 77.0 ppm, respectively, serving as reference) and the coupling constants J in Hz. EI mass spectra were recorded by a JEOL SX102 spectrometer at 70 eV. UV spectra were recorded with a Cary 219 spectrophotometer in methanol, and the melting points, which are uncorrected, were determined using a Reichert microscope.

Characterisation of new compounds

Triacetylscutigeral **1b** was prepared by acetylating scutigeral **1a** (5 mg) with acetic anhydride (0.5 mL) in pyridine (1 mL) at room temperature overnight. Evaporation of the volatiles and chromatography of the residues on silica gel eluted with ethyl acetate/heptane 1:1 yielded 4 mg of pure **1b** as a yellow oil. ^{1}H-NMR (δ, multiplicity, J in Hz): 10.31, s, 1-H; 5.07, m, 6'-H_2 and 10'-H_2; 4.94, tq, $J_{1'-2'}$ = 6.4, $J_{2'-13'}$ = 1.1, 2'-H_2; 3.29, d, $J_{1'-2'}$ = 6.4, 1'-H_2; 2.53, s, 8-H_3; 2.32, 2.30 and 2.28, 3s, 3-OAc, 4-OAc and 5-OAc; 2.07–1.93, m, 4'-H_2, 5'-H_2, 8'-H_2 and 9'-H_2; 1.73, s, 13'-H_3; 1.66, s, 12'-H_3; 1.58, 2s, 14'-H_3 and 15'-H_3. MS: *m/z*: 498.2633 (M^+, 9%, $C_{29}H_{38}O_7$ requires 498.2617), 455 (6%), 413 (8%), 371 (10%), 345 (14%), 303 (20%), 277 (25%), 235 (57%), 181 (92%), 136 (49%), 69 (100%).

Ovinal ***2***

Colourless crystals, mp 93–95 °C (ethanol). UV (methanol) λ_{max} (ε): 238 nm (11 100), 290 nm (13 700), 334 (5300). ^{1}H-NMR (δ, multiplicity, J in Hz): 10.16, s, 1-H; 6.23, s, 4-H; 5.05, m, 2'-H_2, 6'-H_2 and 10'-H_2; 3.33, d, $J_{2'-3'}$ = 6.8, 1'-H_2; 2.48, s, 8-H_3; 2.12–1.92, m, 4'-H_2, 5'-H_2, 8'-H_2 and 9'-H_2; 1.78, s, 13'-H_3; 1.66, s, 12'-H_3; 1.58, 2s, 14'-H_3 and 15'-H_3. ^{13}C-NMR (δ): 193.6 C-1, 164.3 C-3, 162.4 C-5, 142.0 C-7, 137.6 C-3', 135.4 C-7', 131.4 C-11', 124.3 C-10', 123.7 C-6', 121.5 C-2', 119.4 C-6, 113.8 C-2, 101.3 C-4, 39.7 C-8', 39.6 C-4', 26.7 C-9', 26.4 C-5', 25.7 C-12', 24.6 C-1', 17.7 C-15', 16.3 C-13', 16.1 C-14', 13.8 C-8. MS: *m/z*: 356.2366 (M^+, 23%, $C_{23}H_{32}O_3$ requires 356.2351), 219 (41%), 205 (25%), 203 (22%), 191 (33%), 177 (24%), 165 (100%), 136 (30%), 81 (45%), 69 (83%), 41 (39%).

Ovinol ***4a***

Yellowish oil. UV (methanol) λ_{max} (ε): 275 nm (1000). ^{1}H-NMR (δ, multiplicity, J in Hz): 6.33, s, 2-H; 5.17, tq, $J_{1'-2'}$ = 7.0, $J_{2'-13'}$ = 1.2, 2'-H_2; 5.07, m, 6'-H_2 and 10'-H_2; 3.29, d, $J_{1'-2'}$ = 7.0, 1'-H_2; 2.17, s, 8-H_3; 2.11, dt, $J_{4'-5'}$ = $J_{5'-6'}$ = 7, 5'-H_2; 2.05, m, 4'-H_2 and 9'-H_2; 1.96, m, 8'-H_2; 1.79, s, 13'-H_3; 1.67, s, 12'-H_3; 1.58, s, 14'-H_3 and 15'-H_3. ^{13}C-NMR (δ): 142.6 C-5, 141.5 C-4, 137.9 C-3', 135.6 C-7', 131.4 C-11', 130.0 C-3, 127.7 C-7, 124.3 C-10', 123.6 C-6', 122.1 C-2', 118.0 C-6, 109.2 C-2, 39.7 and 39.6 C-4' and C-8', 26.6 C-9', 26.3 C-5', 25.7 C-1', 25.7 C-12', 19.4 C-8, 17.7 C-15', 16.2 C-13', 16.0 C-14'. MS: *m/z*: 344.2347 (M^+, 15%, $C_{22}H_{32}O_3$ requires 344.2351), 207 (11%), 191 (32%), 153 (100%), 152 (41%), 81 (12%), 69 (37%), 41 (12%).

Triacetylovinol ***4b***

Triacetylovinol **4b** was prepared by acetylating ovinol **4a** (4 mg) with acetic anhydride (0.5 mL) in pyridine (1 mL) at room temperature overnight. Evaporation of the volatiles and chromatography of the residues on silica gel eluted with ethyl acetate/heptane 1:1 yielded 3 mg of pure **4b** as a colourless oil. ^{1}H-NMR (δ, multiplicity, J in Hz): 6.93, s, 2-H; 5.07, m, 6'-H_2 and 10'-H_2; 4.97, tq, $J_{1'-2'}$ = 6.6, $J_{2'-13'}$ = 1.1, 2'-H_2; 3.22, d, $J_{1'-2'}$ = 6.6, 1'-H_2; 2.27, s, 8-H_3; 2.27, 2.25 and 2.24, 3s, 3-OAc, 4-OAc and 5-OAc; 2.08–1.93, m, 4'-H_2, 5'-H_2, 8'-H_2 and 9'-H_2; 1.72, s, 13'-H_3; 1.67, s, 12'-H_3; 1.58, 2s, 14'-H_3 and 15'-H_3. MS: *m/z*: 470.2677 (M^+, 13%, $C_{28}H_{38}O_6$ requires 470.2668), 428 (10%), 406 (9%), 386 (11%), 364 (20%), 344 (14%), 322 (28%), 207 (53%), 195 (60%), 191 (69%), 153 (100%).

Dimethylneogrifolin ***5b***

Dimethylneogrifolin **5b** was obtained as a colourless oil after treatment of neogrifolin **5a** with TMS-diazomethane in methanol at room temperature for 30 min and evaporation of the volatiles. ^{1}H-NMR (δ, multiplicity, J in Hz): 6.32, m, 2-H and 4-H; 5.07, m, 6'-H_2 and 10'-H_2; 5.03, tq, $J_{1'-2'}$ = 6.8, $J_{2'-13'}$ = 1.3, 2'-H_2; 3.77 and 3.77, 2s, 3-OMe and 5-OMe; 3.28, d, $J_{1'-2'}$ = 6.8, 1'-H_2; 2.22, s, 8-H_3; 2.10–1.90, m, 1'-H_2, 4'-H_2, 5'-H_2, 8'-H_2 and 9'-H_2; 1.74, s, 13'-H_3; 1.66, s, 12'-H_3; 1.58 and 1.56, 2s, 14'-H_3 and 15'-H_3. MS: *m/z*: 356.2729 (M^+, 31%, $C_{24}H_{36}O_2$ requires 356.2715), 219 (80%), 165 (100%).

Binding assays

^{3}H-SCH 23390 ([*N*-methyl-^{3}H], 2638.1 Gbq/mmol), ^{3}H-Spiperone ([benzene ring-^{3}H], 814.0 Gbq/mmol), ^{3}H-muscimol ([methylene-^{3}H(*N*)]-3-hydroxy-5-aminomethylisoxazole, 445.9 Gbq/mmol), ^{35}S-TBPS (butyl bicyclophosphorothionate, tertiary-[^{35}S], 2.3 TBq/mmol), ^{3}H-flunitrazepam ([methyl-^{3}H], 3034.0 Gbq/mmol) and ^{3}H-kainic acid ([vinylidene-^{3}H], 2146.0 Gbq/mmol) were from New England Nuclear, Du Pont, USA.

The experimental details of the ^{3}H-muscimol, ^{35}S-TBPS, ^{3}H-flunitrazepam and ^{3}H-kainic acid binding assays have been published previously [13, 14].

The ^{3}H-SCH 23390 and ^{3}H-spiperone binding studies were performed on the same membrane preparation. Male Wistar rats (weighing 200–230 g) were decapitated and the brain removed. Striata were dissected and rapidly homogenised (Ultra Turrax, 10 s) in 50 mM KH_2PO_4 buffer pH 7.4 and centrifuged at 30 000 *g* for 10 min. The pellet was resuspended in 50 mM KH_2PO_4 at a final concentration of 1 mg original tissue/mL. All binding assays were in duplicate.

^{3}H-SCH 23390 binding

^{3}H-SCH 23390 (25 µL, final concentration 0.2 nM) was added to 1 mL aliquots of homogenate and incubated for 60 min at 30 °C. Samples were rapidly filtered through Whatman GF/C filters and washed twice with 10 mL of 50 mM KH_2PO_4 buffer. Non-specific binding was obtained in the presence of *cis*-(*Z*)-flupentixol (1 µM final concentration). For Scatchard plot analysis, eight concentrations of ^{3}H-SCH 23390 between 0.01 nM and 1.0 nM were used.

^{3}H-spiperone binding

^{3}H-spiperone (25 µL, final concentration 0.2 nM) were added to 1 mL aliquots of homogenate and incubated for 15 min at 37 °C, followed by 15 min incubation at 0–4 °C. Non-specific binding was obtained in the presence of 2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (ADTN) (final concentration 10 µM).

Acknowledgments

Financial support from the Lundbeck Foundation and the Swedish Science Research Council (NFR) is gratefully acknowledged.

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