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The Inhibitory Effect of Sesquiterpenoid Unsaturated Dialdehydes on the Dopamine D1 Receptor, a Quantitative Structure-Activity Relationships Study

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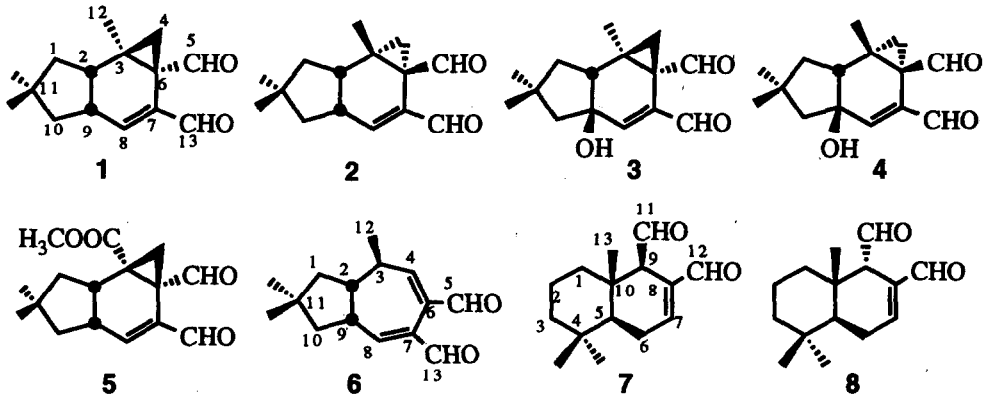
Abstract: The ability of 8 sesquiterpenoid unsaturated dialdehydes to inhibit the binding of the ligand ^{3}H SCH 23390 to the dopamine D1 receptor has been correlated with chemical and molecular features of the compounds by the multivariate PLS method. A good correlation was obtained, and the most important descriptors were found to be the dipole moment, the atomic charge on the α-carbon in the unsaturated aldehyde, and geometrical properties of the unsaturated dialdehyde functionality.

Sesquiterpenoids containing an unsaturated dialdehyde functionality, isolated from various organisms such as plants, fungi, molluscs, etc., possess a number of biological activities. They generally have very pungent taste,[1] many of them are potent antibiotics[2] and antifeedants,[3] and some have been shown to possess mutagenic activity.[4] Some of their biological activities are believed to be linked to the reactivity of the unsaturated dialdehyde functionality, which at least in the case of polygodial 7 may react with primary amino groups in enzymes and DNA forming pyrrole derivatives.[5] However, large quantitative and qualitative activity differences between the unsaturated dialdehydes have been reported, and other molecular mechanisms have been suggested besides the formation of pyrroles.[6]

In view of the ability of these compounds to induce membrane leakage in neuroblastoma cells,[7] and their strong taste (which could be due to the stimulation of sensory neurons), the effect of eight unsaturated dialdehydes (shown in Scheme 1) to inhibit the binding of radioactive labelled ligands to a number of CNS receptors was assayed.[8] Interestingly, the compounds specifically inhibit the binding of ^{3}H SCH 23390 [(R)-(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1H-3-benzazepin-7-ol] to the dopamine D1 receptor in a rat striatal membrane preparation *in vitro*, and were inactive in binding assays performed on the following CNS receptors *in vitro* (radioactive ligands given in brackets): $GABA_A$ receptors (^{3}H-muscimol), benzodiazepine receptors (^{3}H-diazepam), dopamine D2 receptors (^{3}H-spiroperidol), opiate-μ receptor subtype (^{3}H-naloxone), chloride ionophore of the GABA/benzodiazepine receptor complex (^{35}S-TBPS), muscarinic acetylcholine receptors (^{3}H-QNB) and kainic acid binding sites (^{3}H-kainic acid). Scatchard Plot analysis showed that the inhibition of ^{3}H-SCH 23390 binding was due to a reduction of the number of binding sites (B_{max} effect). The compounds that showed the



Scheme 1

highest activity in the binding study, isovelleral **1**, methyl marasmate **5** and velleral **6**, are potent and have IC_{50}-values between 0.2 and 0.3 μM. The isovelleral derivatives **3** and **4** on the other hand, which in other assays may be more potent than isovelleral **1**, were found to be considerably less active (the IC_{50}-values for the 8 compounds are given in Table 1). These differences in activity and specificity suggest that the ability of the unsaturated dialdehydes to inhibit ^3H SCH 23390 binding to the D1 receptor depends on their specific interaction with a crucial part of the receptor, and not on a general reactivity towards nucleophilic groups.

As part of an effort to demonstrate quantitative structure-activity relationships for unsaturated dialdehydes, 22 chemical and molecular features (descriptors) of the compounds **1-8** have been correlated with their IC_{50}-values for the inhibition of ^3H SCH 23390 binding to the D1 receptor by the multivariate PLS method[9] (Partial Least Squares in latent variables). PLS will calculate components of the descriptors that are maximally correlated with the activity, and informs for each component how much of the variance it explains as well as the importance (as the loading value) of each descriptor for that component. Most of the 22 descriptors are theoretical (intraatomic distances and dihedral angles, and atomic charges), obtained from MM (Molecular Mechanichs) and CNDO (Complete Neglect of Differential Overlap) calculations of the conformers with the lowest steric energy as described earlier.[7,10] In this case, the first component calculated explains not less than 96 % of the variance in the activity, and no more components were calculated. The most important descriptors, with loading values exceeding ±0.30, are given in Table 1.

The dipole moment is negatively correlated with the IC_{50}-values, i.e. compounds with a large dipole moment are more active. As the compounds also have a nonpolar part, they are to some extent amphiphatic. Compounds with a large dipole moment (i.e. isovelleral **1**) may therefore interact more efficiently with the membranes, with the polar part positioned at the membrane surface, compared to compounds with a small dipole moment (i.e. 9-hydroxyiso-

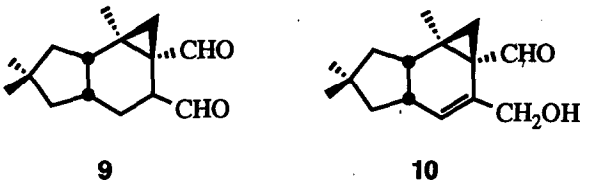
Table 1. The Potency of the Investigated Compounds to Inhibit the Binding of ^{3}H SCH 23390 to the D1 receptor, and the Important Descriptors (Loading Values > ±0.30).

Compound	IC_{50} (μM)[a]	Dipole[b] moment (D)	Charge[c] C-7/8	Dihedral angle[d] aldehydes (°)	Distance[e] aldehydes (Å)	Distance[e] 5-8/7-11 (Å)
1	0.31	5.0	-0.032	35	3.07	3.79
2	0.40	4.5	-0.026	45	3.08	3.72
3	3.7	3.5	-0.007	43	3.06	3.74
4	5.4	4.2	-0.004	61	3.18	3.59
5	0.20	5.2	-0.025	37	3.04	3.77
6	0.32	5.0	-0.026	44	3.08	3.71
7	0.46	5.2	-0.031	35	2.98	3.73
8	5.3	3.4	-0.021	72	3.16	3.40
Loading value:		-0.37	0.33	0.38	0.34	-0.35

[a] IC_{50}-values for the inhibition of ^{3}H SCH 23390 binding to D1 receptors, unpublished data.[8]
[b-e]The descriptors were obtained from CNDO and MM data of the most stable conformer of each compound.[10]
[c]Atomic charge on C-7 in compounds **1-6**, and on C-8 in compounds 7 and 8 (the α-carbon in the α,β-unsaturated aldehyde group).
[e]Distances between the two aldehyde carbons, and between carbons 5 and 8 in compounds **1-6** and carbons 7 and 11 in compounds **7** and **8**.

velleral **3**). This quality may be important for compounds that affect membrane proteins. However, the charge separation creating the dipole moment is concentrated to the unsaturated dialdehyde functionality, and depends particularily on the charge separation in the unsaturated aldehyde group (carbons 8-7-13 in compounds **1-6** and carbons 7-8-12 in compounds **7** and **8**). This also influences the electrophilic properties of the unsaturated aldehyde group, which may be more important for the activity studied here. The necessity for an intact unsaturated dialdehyde functionality for the inhibition of ^{3}H SCH 23390 binding to the D1 receptor was demonstrated for isovelleral **1**, the reduction[4] of either the double bond or of the unsaturated aldehyde carbonyl carbon gives two derivatives (**9** and **10**) which completely lack any ability to inhibit ^{3}H SCH 23390 binding to the D1 receptor.

The remaining descriptors with high loading values are all geometrical, and indicates for example that compounds with the aldehyde groups close together will be more active (both dihedral angle and distance between the aldehyde groups are positively correlated). This has previously been suggested to determine the chemical reactivity of the unsaturated dialdehyde functionality, and to explain activity differences between polygodial **7** and *epi*-polygodial **8**. The former, with a small dihedral angle and distance between the aldehyde groups, react much faster with primary amines to pyrrole derivatives than the latter, in which the aldehydes are more apart.[5]



9 10

Figure 1

EXPERIMENTAL

The compounds were isolated from natural sources (compounds **1**, **6** and **7**), or prepared from natural products, as described previously.[4] The MacMimic program for the MM calculations was obtained from InStar Software AB, Lund (Sweden). Only the conformeres with the lowest steric energy were considered. The descriptors were chosen to characterize the unsaturated dialdehyde functionality, and the following were included in the PLS correlation: (The atom numbering refer to isovelleral **1**, the corresponding atoms were chosen in the other compounds.) Molecular weight; dihedral angles C(8)-C(7)-C(13)-(13-O); C(9)-C(8)-C(7)-C(13); and C(5)-C(6)-C(7)-C(13); intraatomic distances between C(5)-C(13); and C(5)-C(8); Z coordinate of C(5) when the structure is fixed in a coordinate system as described earlier[10]; the energy differences between the lowest unoccupied molecular orbital (LUMO) and the highest occu-pied molecular orbital (HOMO); and the next lowest unoccupied molecular orbital (NLUMO) and the HOMO; atomic charges on C(8), C(7), C(13), (13-O), C(3), C(6), C(5) and (5-O); X, Y and Z components of the dipole moment when the stucture is fixed in a coordinate system[10]; the total dipole moment; and the experimental log P-value[7].

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