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SYNTHESIS OF COUMARINS AS SUBTYPE-SELECTIVE INHIBITORS OF MONOAMINE OXIDASE

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Abstract: A series of coumarin derivatives was synthesized and evaluated as inhibitors of Monoamine Oxidase (MAO). Ether derivatives demonstrate MAO-B selectivity, sulfonic acid esters MAO-A selectivity.

Monoamine Oxidase (MAO, EC 1.4.3.4) catalyses the oxidative deamination of aromatic amines. The enzyme occurs in two subtypes, MAO-A and MAO-B, which have different substrate specificities[1]. MAO-A predominantly deaminates 5-HT, MAO-B 2-phenylethylamine. Noradrenaline, dopamine and tyramine are substrates of both MAO-A and MAO-B, differing however in their selectivities.

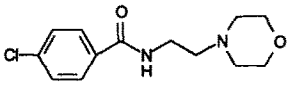
Irreversible and unspecific inhibitors of MAO like iproniazid were the first antidepressants[2]. Their success however was limited due to the occurence of side effects. These included hepatotoxicity as well as hypertensive crises ("cheese effect")[3].

Interest in MAO-inhibitors has been revived by the finding of reversible, subtype-selective MAO-inhibitors (Scheme 1). Inhibitors of MAO-A are developped as antidepressants, inhibitors of MAO-B as antiparkinsonian drugs.

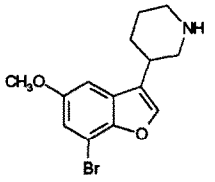
Scheme 1

Inhibitors of

MAO-A

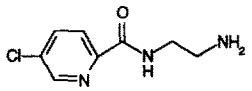


Moclobemide (Aurorix®), **1**

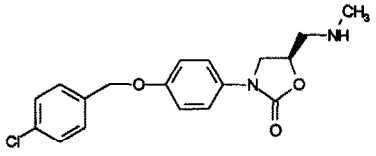


Brofaromine, **3**

MAO-B



RO 19-6327, **2**

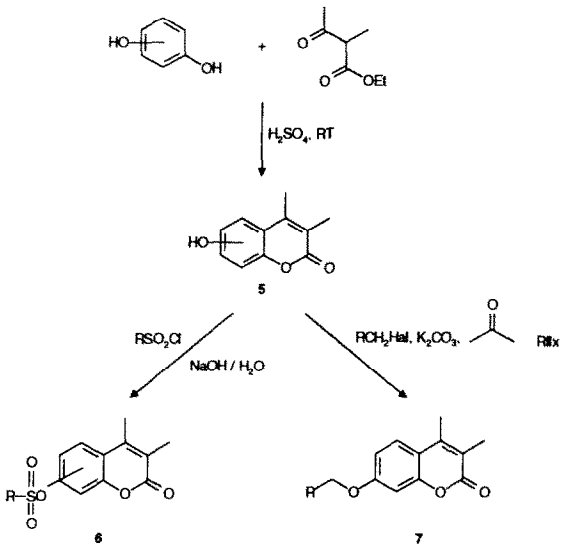


Almoxatone, **4**

In this paper we describe our work on derivatives of hydroxycoumarins, resulting in selective reversible inhibitors of MAO-A and MAO-B respectively.

The compounds were prepared in a straightforward two-step synthesis (Scheme 2). Condensation of dihydroxybenzenes with ethyl-2-methylacetoacetate in sulfuric acid provided hydroxycoumarins **5** which were reacted with sulfonyl halides in the presence of base to give sulfonates **6**. Reaction of **5** with alkylhalides under basic conditions yielded phenolethers **7**.

Scheme 2

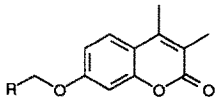


The compounds were evaluated for MAO-inhibition according to the method of Wurtmann and Axelrod[4] as modified by Traut et al[6] in rat brain homogenate in vitro. ^{14}C-Tryptamine and ^{14}C-phenylethylamine were used as substrate for MAO-A and MAO-B respectively.

Hydroxycoumarins **5** themselves as shown for 7-hydroxy-3,4-dimethylcoumarin (**5a**, table 1) do not inhibit MAO. Benzylation, however, results in highly active but rather unselective inhibitors of MAO-B. Alkylsubstitution of the phenylring has little effect on MAO-B affinity but reduces MAO-A affinity resulting in highly selective and potent inhibitors of MAO-B. Halogenation of the phenylring, however, does not attenuate MAO-A affinity. Exchange of the phenylring by a wide range of heterocycles diminishes MAO-A affinity without influencing MAO-B affinity (table 1).

Introduction of a sulfonic ester linkage instead of the ether bridge dramatically changes the activity profile of the compounds. Affinity for the MAO-A isozyme prevails, halogen substituents in the phenylring lead to highly selective MAO-A inhibitors (table 2). Selectivity for MAO-A is demonstrated also by alkylsulfonic acid esters. Steric requirements for the alkyl chain are not very stringent as is shown by the still high potency of the n-octyl derivative **6h** (table 2).

table 1



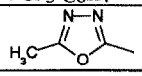
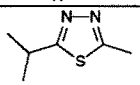
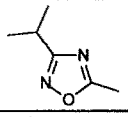
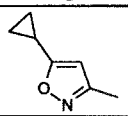
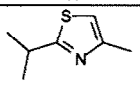
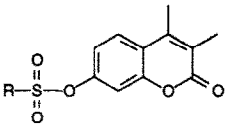
No.	R	Inhibition of	
		MAO-A IC_{50} (nM) [5]	MAO-B IC_{50} (nM) [5]
7a	H	71	0,5
7b	4-CH_3-C_6H_4	560	0,9
7c	4-i-C_3H_7-C_6H_4	> 10 000	7
7d	4-F-C_6H_4	13	0,4
7e	4-Cl-C_6H_4	12	0,6
7f	4-CF_3-C_6H_4	> 10 000	2
7g		5 600	15
7h		1 800	9
7i		> 10 000	0,9
7k		> 10 000	1,3
7l		7 000	0,8
7m		10 000	1,4
5a		~ 10 000	> 10 000
2		> 10 000	22
3		5	> 1 000

table 2

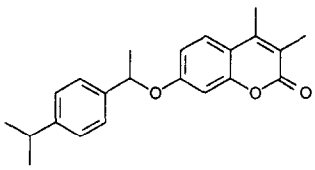
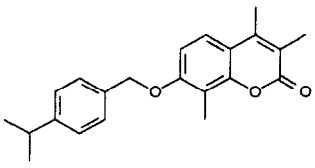
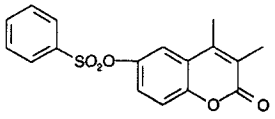


No.	R	Inhibition of	
		MAO-A IC_{50} (nM) [5]	MAO-B IC_{50} (nM) [5]
6a	C_6H_5	24	1 100
6b	4-Cl-C_6H_4	5	4 000
6c	4-CN-C_6H_4	8	> 10 000
6d	4-Br-C_6H_4	6	> 10 000
6e	CH_3	110	> 10 000
6f	C_2H_5	8	5 000
6g	n-C_5H_{11}	16	2 200
6h	n-C_8H_{17}	34	> 10 000

Taken together our results show that appropriate substitution of hydroxycoumarins provides both selective and potent inhibitors of MAO-A and MAO-B respectively. Selectivity is determined mainly by the nature of the linkage between the coumarin template and the substituent in position 7. Ethers yield inhibitors of MAO-B, sulfonic acid esters inhibitors of MAO-A. Variation of the substituent modulates activity but does not reverse selectivity.

These results suggest that the linkage gets in close contact with the enzyme during binding. This assumption is corroborated by the inactivity of compounds **7n** and **7o** whose additional methylsubstituents hinder contact of the linkage with the enzyme, as well as by the reduced activity of the regioisomer **6i** (table 3).

table 3

No.		Inhibition of	
		MAO-A IC_{50} (nM) [5]	MAO-B IC_{50} (nM) [5]
7n		> 10 000	10 000
7o		> 10 000	> 10 000
6i		190	> 10 000

Based on these results and additional pharmacological data **6f** (INN name: esuprone) and **7i** were selected for development as antidepressant and antiparkinsonian drugs respectively.

References and Notes

1. Johnston, J.P.; Biochem. Pharmacol. **1968**, 17, 1285 - 1297
2. Kline, N.S.; Clin. Psychopath, **1958**, 19 (Suppl.), 78 - 79
3. Rabkin, J.G.; J. Clin. Psychopharmacol. **1985**, 5, 2 - 9
4. Wurtmann, R.; Axelrod, J.; Biochem. Pharmacol. **1963**, 12, 1493
5. Standard deviations are within 10 % of mean values
6. Traut, M.; Brode, E.; Hoffmann, H. D.; Arzneimittelforsch. 1981, 31, 1566 - 1574

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