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Original article

In silico design of novel 2*H*-chromen-2-one derivatives as potent and selective MAO-B inhibitors

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ABSTRACT

Inhibition data on rat monoamine oxidase B isoform of a large number of 7-*meta*halobenzyloxy-2*H*-chromen-2-one derivatives (67 compounds) carrying at position 4 a variety of substituents differing in steric, electrostatic, lipophilic and H-bonding properties, were modeled by Gaussian field-based 3D-QSAR and docking simulations carried out on rat MAO-B homology model. The computational study combining two different approaches provided easily interpretable binding modes, highlighting the dominant role of the steric effects at position 4, and guided the design of new, potent and selective MAO-B inhibitors. The 4-hydroxyethyl-, 4-chloroethyl-, 4-carboxamidoethyl-coumarin derivatives **70**, **71**, and **76**, respectively, were endowed with high MAO-B inhibitory potency (pIC_{50} = 8.13, 7.89 and 7.82, respectively) and good selectivity over MAO-A (pIC_{50} = 5.33, 3% inhibition at 10 μM, and pIC_{50} = 5.37, respectively). New compounds with moderate to low MAO-B inhibitory activity were also designed and prepared to challenge the predictive power of our docking-based 3D-QSAR model. The good match between predicted and experimental pIC_{50} values for all the newly designed compounds confirmed the robustness of our model (r^2 = 0.856, RMSE = 0.421) and its transparent rationale in unveiling the main molecular determinants for high potency towards MAO-B.

1. Introduction

Monoamine oxidases (MAOs, EC 1.4.3.4) are flavoenzymes that catalyze the Cα-H oxidation of unhindered arylalkylamines [1] The MAO-driven oxidative deamination leads to the inactivation of many exogenous as well as endogenous aminic substrates, including dietary components (e.g., tyramine) and neurotransmitters (e.g., serotonin, histamine and catecholamines), and to the bioactivation of the Parkinson-inducing neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). The two known and fully characterized enzymatic isoforms of MAO, named MAO-A and MAO–B [2], share 70% sequence identity [3] but differ for substrates and inhibitors sensitivity, tissue distribution [4] and three-dimensional structural motifs [5–7]. In the catecholaminergic system the prevalent isoform is MAO-A, whereas MAO-B predominates in cerebral districts under serotonin regulation. MAO-A degrades preferentially serotonin and is selectively inhibited by clorgyline. On the other side, MAO–B isoform is blocked by selegiline and deaminates preferentially 2-phenylethylamine. Both isoenzymes are able to catabolize catecholamines with similar rates [8].

Since MAOs play a major role in controlling the levels of several neurotransmitters, mainly in the CNS, their therapeutic potential has been clearly related to the treatment of neuropathies [9]. The earliest inhibitors developed as antidepressant (e.g., tranylcypromine) showed no isoform selectivity and an irreversible mechanism (suicide-type inhibitors). Therefore, many of them have been discontinued because of severe side effects (i.e., hepatotoxicity and hypertensive crisis) and tedious dietary restrictions. Propargylamine-bearing derivatives clorgyline, a selective MAO-A inhibitor, and selegiline and rasagiline, two selective MAO-B inhibitors, showed improved safety because of their enhanced

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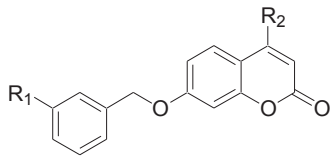
Table 1
Chemical structure and MAO inhibition data of coumarin training and test set for 3D-QSAR Model.



Compd	R_1	R_2	Observed MAO-B inhibitory activity[a]	Predicted MAO-B inhibitory activity[b]
1	Cl	H	7.77	7.40
2	Cl	Me	8.13	7.44
3	Cl	Et	7.54	7.45
4	Cl	CF_3	6.06	6.93
5	Cl	Cl	7.68	7.05
6	Cl	CH_2Cl	7.36	7.33
7	Br	CH_2Cl	6.68	7.47
8	H	OH	5.04	5.21
9	F	OH	5.68	5.42
10	Cl	OH	6.32	5.77
11	Br	OH	6.31	5.87
12	Cl	NH_2	7.32	7.50
13	Cl	CHO	7.28	7.64
14	Cl	$COCH_3$	7.40	7.40
15	Cl	COOH	4.00[c]	4.49
16	Cl	COOEt	6.38	6.35
17	Cl	$CONH_2$	6.63	6.60
18	Cl	CN	6.99	7.04
19	Cl	CH=NOH	6.66	6.92
20	Cl	CH_2OH	8.28	8.11
21	Br	CH_2OH	7.85	8.22
22	Cl	$CH(OH)CH_3$	7.11	7.38
23	Cl	CH_2CN	7.80	7.78
24	Cl	CH_2CONH_2	7.52	8.09
25	Cl	$CH_2CONHMe$	7.62	7.79
26	Cl	$CH_2CON(Me)_2$	7.40	7.85
27	Cl	CH_2NH_2	7.82	7.66
28	Cl	CH_2NHMe	7.89	7.70
29	Br	CH_2NHMe	7.96	7.53
30	Cl	CH_2NHnPr	6.69	6.94
31	Cl	CH_2NHnBu	6.35	6.70
32	Cl	$CH_2N(Me)_2$	5.95	6.96
33	Cl	CH_2-1′-pyrrolidinyl	5.77	6.06
34	Cl	CH_2-4′-morpholinyl	5.64	5.81
35	H	OMe	7.00	6.91
36	F	OMe	7.44	7.15
37	Cl	OMe	8.11	7.46
38	Br	OMe	8.24	7.55
39	H	OEt	6.12	6.59
40	F	OEt	6.58	6.82
41	Cl	OEt	6.94	6.86
42	Br	OEt	6.90	7.29
43	H	OnPr	6.24	6.05
44	F	OnPr	6.39	6.26
45	Cl	OnPr	7.21	6.92
46	Br	OnPr	7.13	7.08
47	Cl	OiPr	4.61	5.61
48	Cl	OCH_2OMe	7.00	7.16
49	Cl	OCH_2SMe	6.50	7.09
50	Cl	OCH_2CN	7.34	7.45
51	Cl	OPh	5.39	5.33
52	Cl	NHMe	8.06	7.37
53	Cl	NHEt	7.55	6.70
54	Cl	NHiPr	5.11	5.75
55	Cl	NHPh	5.01	5.37
56	Cl	$NHCOCH_3$	7.41	7.08
57	Cl	NHCOOEt	6.23	5.62
58	Cl	NHCONHEt	4.50[c]	4.85
59	Cl	OCH_2COCH_3	7.57	7.44
60	Cl	OCH_2COOH	4.50[c]	4.79
61	Cl	OCH_2COOEt	5.74	6.08
62	Cl	OCH_2CONH_2	8.48	8.44
63	Br	OCH_2CONH_2	8.05	8.53
64	Cl	$OCH_2CONHMe$	7.47	7.07
65	Cl	$OCH_2CON(Me)_2$	6.30	5.80
66	Cl	OCH_2CO-1′-piperidinyl	4.41	3.98
67	Cl	OCH_2CO-4′-morpholinyl	4.89	4.84

[a] MAO-B inhibitory activities are expressed as pIC_{50} (*M*). Values are the mean of two or three independent experiments. SEM of the IC_{50} values were within ±10%.
[b] pIC_{50} values predicted by our Gaussian-based 3D-QSAR model with Phase.
[c] Estimated value from the % of inhibition at 10 μM concentration.

isoform selectivity and are currently used as antidepressant and as dopamine-sparing agents against Parkinson's disease (PD), respectively [10–12].

In addition to these well-consolidated pharmacological actions, MAO inhibitors have recently been exploited as potential therapeutics to combat severe age-related neurodegenerative diseases (NDs) [13], such as Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS) and Huntington's disease (HD). Several biochemical abnormalities in neurons underlie these debilitating syndromes, spanning from protein misfolding to bio-metal dyshomeostasis and including mitochondrial impairment and oxidative stress. The catalytic cycle of MAOs produces as one of the end-products hydrogen peroxide, which is a precursor of harmful reactive oxygen species (ROS) and a toxic oxidant itself. When the physiological radical detoxification system is altered as it is in NDs, MAOs become a source of oxidative stress and their inhibition may result in a neuroprotective activity [14,15]. Moreover, the analysis of post-mortem AD patients brain tissues pointed out an increased MAO-B expression in plaques-related astrocytes [16].

For these reasons, we have performed a series of studies on the design, synthesis and biological evaluation of selective MAO inhibitors [17], and on dual acetylcholinesterase and MAO-B inhibitors as well [18], looking for potential therapeutics for NDs [19]. Within this frame we have reported the discovery of novel selective MAO B inhibitors with favorable physicochemical and pharmacokinetic profiles carrying properly selected substituents at position 4 of 7-benzyloxy-substituted coumarins [20]. More recently, a large number of new coumarin derivatives were synthesized through a fine molecular tuning at position 4 aimed at an optimization of the MAO affinity and selectivity profiles [21]. The inhibitory activity towards MAO-B together with the MAO-B over MAO-A selectivity have been carefully evaluated, but only in qualitative terms. To gain more significant insights into the pivotal physicochemical interactions governing MAO inhibition, we therefore modeled the inhibition data for a large panel of sixtyseven coumarin derivatives through Gaussian field-based 3D-QSAR method and docking simulations. These compounds carry a (3′-halo)benzyloxy group as the common substituent at position 7 and differ for the substituents placed at position 4 of the coumarin skeleton. The modeling studies provided easily interpretable binding modes and guided the design of new, potent and selective inhibitors by exploiting our expertise on coumarin-based MAO inhibitors [22,23]. New compounds with moderate or low MAO-B inhibitory activity were also designed and prepared in order to challenge the predictive power of our model. We obtained good predictions for all the newly prepared compounds, thus demonstrating the solid statistics of our model as well as its real-life potential for optimizing potency towards MAO-B. The novel molecules here reported may be considered promising hit compounds for the discovery of new neuroprotectants and for the development of multi-target directed ligands having MAO-B inhibition as the core activity.