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In silico study of the binding affinities of Monoamine oxidase with synthetically viable coumarin analogs

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The viability of generating synthetically feasible structures for the inhibition of the enzyme Monoamine oxidase B (MAO B), which plays a vital role in β-amyloid plaque formation, which is theorized to be one of the causes of Alzheimer's Disease, was assessed via computational studies, with the aim of investigating whether coumarin derivatives could be suitable drug candidates for the treatment of Alzheimer's disease.

Table 1. Binding Affinities of the ligands

Ligand	Binding Affinity (kJ/mol)
c13	-8.3
c10	-8.2
c3	-8.1
c4	-8.1
c18	-7.8
c12	-7.8
c11	-7.7
c16	-7.7
c8	-7.5
c17	-7.3
c19	-7.1
c5	-6.9
c9	-6.9
c14	-6.9
c15	-6.9
c7	-6.8
c20	-6.6
c1	-6.1
c6	-6
selegiline	-6
ensaculin	-5.8
c2	-5.3

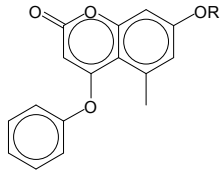

Fig 1. Parent Coumarin

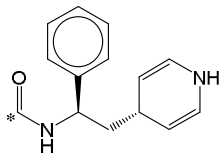

Fig 2. R group for c13

The parent structure (Fig 1) was subjected to systematic changes by introducing different moieties via simulated reactions at 'R', generating a series of coumarin analogues that were used in this study. This step was achieved by Autogrow 3.0. An asterisk (*) is used to show where the moiety connects to the parent molecule. The ligands thus generated were screened through the filters of Lipinski's Rule of Five and criteria specified by Ghose, and the ones that passed were each subjected to an energy minimization via the Spartan version 14 program, level of theory B3LYP /6-31G**. The crystal structure of MAO B, (PDB ID:1GOS), from PDB was used in this study. One chain was removed from the dimer along with water molecules and other small molecules, leaving the single chain along with its respective flavin cofactor in place. The20 coumarin derivatives and the drugs selegiline and ensaculin, were docked into the prepared receptor using Autodock Vina with the parameter of exhaustiveness set to 100. The results are shown in Table 1. Almost all derivatives showed higher binding affinity than the two reference molecules ensaculin and selegiline, commercial drugs known to have inhibitory activity against MAO B. The ligand with the best affinity, c13 (Fig.2), had a markedly high binding affinity, -8.3 kJ/mol. All the molecules would bind at the same binding site, but from the set of ligands, the drug ensaculin and ligand c13 appear to form a series of more significant hydrogen bonds which may increase the favourablity of binding to the receptor binding pocket,

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