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Targeting Alzheimer's disease by investigating previously unexplored chemical space surrounding the cholinesterase inhibitor donepezil

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ABSTRACT:

A series of twenty seven acetylcholinesterase inhibitors, as potential agents for the treatment of Alzheimer's disease, were designed and synthesised based upon previously unexplored chemical space surrounding the molecular skeleton of the drug donepezil, which is currently used for the management of mild to severe Alzheimer's disease. Two series of analogues were prepared, the first looking at the replacement of the piperidine ring in donepezil with different sized saturated N-containing ring systems and the second looking at the introduction of different linkers between the indanone and piperidine rings in donepezil. The most active analogue 5,6-dimethoxy-1-oxo-2,3-dihydro-1H-inden-2-yl 1-benzylpiperidine-4-carboxylate (67) afforded an in vitro IC(sub50) value of 0.03 ± 0.07 μM against acetylcholinesterase with no cytotoxicity observed (IC(sub50) of >100 μM, SH-SY5Y cell line). In comparison donepezil had an IC(sub50) of 0.05 ± 0.06 μM and an observed cytotoxicity IC(sub50) of 15.54 ± 1.12 μM. Molecular modelling showed a strong correlation between activity and in silico binding in the active site of acetylcholinesterase.