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Design, synthesis, and evaluation of 2-phenoxy-indan-1-one derivatives as acetylcholinesterase inhibitors

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Abstract—A series of 2-phenoxy-indan-1-one derivatives have been designed, synthesized, and tested as acetylcholinesterase inhibitors. The most potent compound exhibited high AChE inhibitory activity (IC_{50} = 50 nM), and the molecular docking study indicated that it was nicely accommodated by AChE.

Alzheimer's disease (AD) is one of the most severe health problems of the aged. Acetylcholinesterase (AChE) inhibitors are the first and the most developed group of drugs approved for AD symptomatic treatment, such as tacrine, donepezil, rivastigmine, huperzine, and galanthamine. Among them, donepezil (**1**) and rivastigmine (**2**) exhibit excellent effects in the early to moderate stages of AD patients with few side effects.[1] The crystallographic structure of donepezil–TcAChE complex reveals that the dimethoxy-indanone and benzylpiperidine moieties of donepezil interact with the peripheral and central binding site of AChE separately.[2] Rivastigmine was presumed as central site binding inhibitor.[3] Recently, it has been pointed out that AChE may be involved in several noncatalytic actions[4] such as accelerating β-amyloid peptide deposition and promoting the formation of β-amyloid fibril.[5] It has been speculated that the peripheral binding site may be responsible for this aggregation-promoting action of AChE.[6] Therefore, molecules that are able to interact with both central and peripheral binding sites may prevent the catalytic and noncatalytic actions of AChE. Following this reasoning, 5,6-dimethoxy-indan-1-one from donepezil and dialkyl-benzylamine from rivastigmine were chosen as the two pharmacophoric moieties to interact with the two binding sites of AChE separately, and they were linked with oxygen. With the changing of the position (para or meta) and the sort of aminoalkyl group on the benzene ring, a series of 2-phenoxy-indan-1-one derivatives **3a**–**x** were designed, synthesized, and tested for their AChE inhibitory activity (Fig. 1).

Target compounds **3a**–**x** were synthesized as shown in Scheme 1. Reaction of 3-(or 4-)(1-chloro-ethyl)anisole **4** with a secondary amine (dimethylamine, diethylamine, pyrrolidine, and so on) provided **5a**–**l**, followed by O-demethylation with 47% HBr to give phenols **6a**–**l**.[7] Other phenols, **8a**–**l**, could be prepared by reductive amination of 3-(or 4-)hydroxyl benzaldehyde **7** with the corresponding secondary amine and $NaBH_4$.[8] Reaction of 5,6-dimethoxy-indan-1-one **9** with $CuBr_2$ in refluxing ethyl acetate yielded 2-bromo-5,6-dimethoxy-indan-1-one, **10**. Finally, the final products **3a**–**x** were achieved by refluxing phenols **6a**–**l** or **8a**–**l** with **10** in acetone nitrile in the presence of K_2CO_3.

To determine AChE and BChE inhibitory activities, compounds **3a**–**x** were measured in vitro according to the modified Ellman method using rat cortex homogenate (AChE) and rat serum (BChE).[9]

As shown in Table 1, most of the compounds showed high activity of AChE inhibition, while all the compounds were almost inactive against BChE. The activity of AChE inhibition was influenced by the position and the sort of aminoalkyl group on benzene ring. In the trial, the para-position substituted compounds (i.e., **3g**, **k**, **o**) were more potent than the meta-position substituted compounds (i.e., **3e**, **i**, **m**), and compounds having mor-

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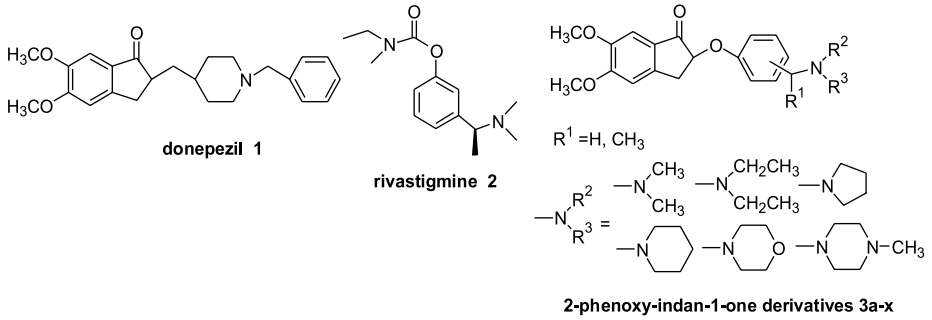
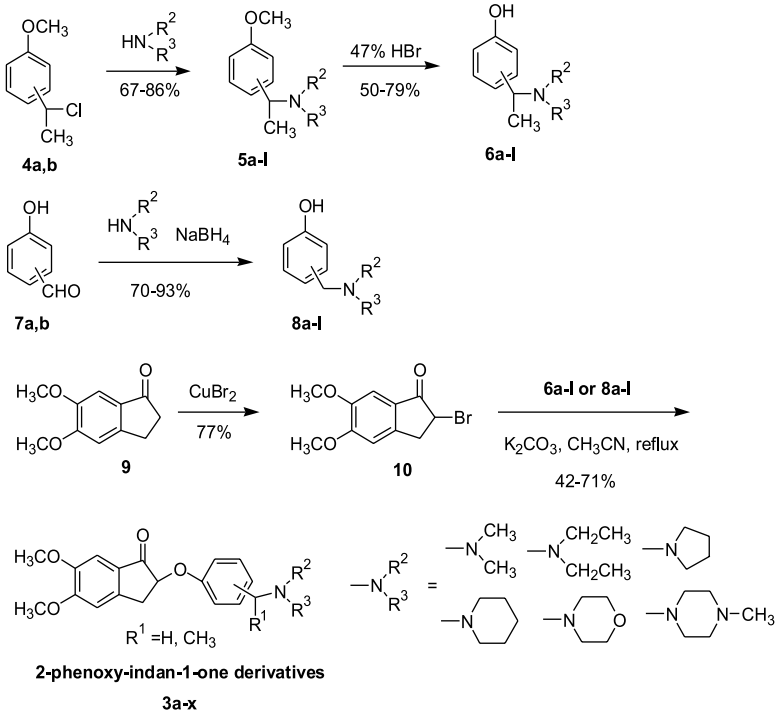


Figure 1. Structures of donepezil **1**, rivastigmine **2**, and 2-phenoxy-indan-1-one derivatives **3a**–**x**.



Scheme 1. Synthesis of 2-phenoxy-indan-1-one derivatives **3a**–**x**.

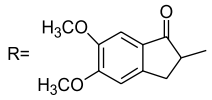
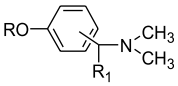
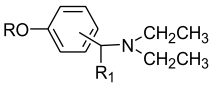
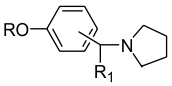
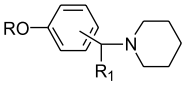
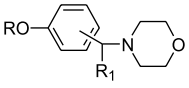
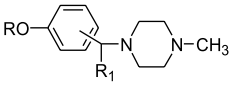
pholine (i.e., **3q**, **r**) and piperazine group (i.e., **3w**, **x**) showed less activity than those having other aminoalkyl groups (i.e., **3a**, **b**, **g**, **h**). We also found that the change of R_1 from H (i.e., **3a**, **c**, **m**, **o**) to CH_3 (i.e., **3b**, **d**, **n**, **p**) contributed little toward the AChE inhibitory activity.

The high AChE inhibitory activity of compound **3k** prompted us to perform molecular docking study to understand the ligand–protein interactions in detail. Compound **3k** is a long chain molecule and we supposed that its binding mode with AChE shares some of features of donepezil–AChE complexes. Therefore, the crystallographic structure of AChE–donepezil complexes was selected from PDB, and the Flexidock program in SYBYL6.8 software was used for the docking study. The most stable docking model was selected according to the best scored conformation predicted by the Flexidock scoring function.

As seen in Figure 2, compound **3k** interacts principally along the active-site gorge of AChE through four major functional groups: the phenyl and oxygen of indan-1-one moiety, the phenyl of phenoxy group, and the pyrrolidine nitrogen. Near the bottom of the gorge, the charged nitrogen of pyrrolidine makes a cation–π interaction with the pyrrole ring of Trp84, with the distance of 4.7 Å. In the middle of the gorge, one face of the phenyl ring of the phenoxy group displays classic parallel π–π stacking with the phenyl ring of Tyr334, with the ring-to-ring distance being 4.83 Å. At the top of the gorge, the phenyl ring of indan-1-one stacks against the indole of Trp279 through π–π interaction with the distance of 3.61 Å, and the oxygen of indan-1-one makes a hydrogen bond with the nitrogen of the Phe288; the distance is 3.17 Å.

In summary, a series of 2-phenoxy-indan-1-one derivatives were designed, synthesized, and evaluated as AChE inhibitors.[10] Structure–activity studies showed that the AChE inhibitory activity of compounds was influenced by the position and the type of the aminoalkyl group on the benzene ring. The modeling study of the most

Table 1. Physical properties and ChE inhibition activity of 2-phenoxy-indan-1-one derivatives **3a–x**

Compound	Structure	Position of aminoalkyl group	R^1	Melting point (°C)	IC_{50} for AChE (μM)[a]	IC_{50} for BChE (μM)[b]
	R= 					
Donepezil					0.016	7.6
Rivastigmine					1.82	0.35
Huperzine A					0.053	56.2
3a		meta	H	96–98	1.10	207
3b			CH_3	92–94	0.82	288
3c		para	H	112–114	0.21	1980
3d			CH_3	107–109	0.15	1370
3e		meta	H	98–100	2.28	190
3f			CH_3	94–96	1.36	199
3g		para	H	123–124	0.10	251
3h			CH_3	100–102	0.22	234
3i		meta	H	99–101	2.66	39.5
3j			CH_3	105–107	1.96	212
3k		para	H	116–118	0.050	84.3
3l			CH_3	106–108	0.14	130
3m		meta	H	127–129	3.18	55.5
3n			CH_3	115–117	3.58	158
3o		para	H	136–138	0.15	262
3p			CH_3	120–122	0.13	176
3q		meta	H	168–170	14.6	219
3r			CH_3	138–140	22.1	247
3s		para	H	155–157	1.30	384
3t			CH_3	129–131	3.14	346
3u		meta	H	118–120	6.41	209
3v			CH_3	134–136	17.6	252
3w		para	H	100–102	1.42	347
3x			CH_3	88–90	2.98	393

[a] Assay performed by the modified Ellman method[9] using rat cortex homogenate. Values are means of three different experiments.
[b] Assay performed using rat serum.

potent compound, **3k**, indicated that it was nicely accommodated by AChE. Further studies on this series of derivatives are in progress and will be reported in due course.

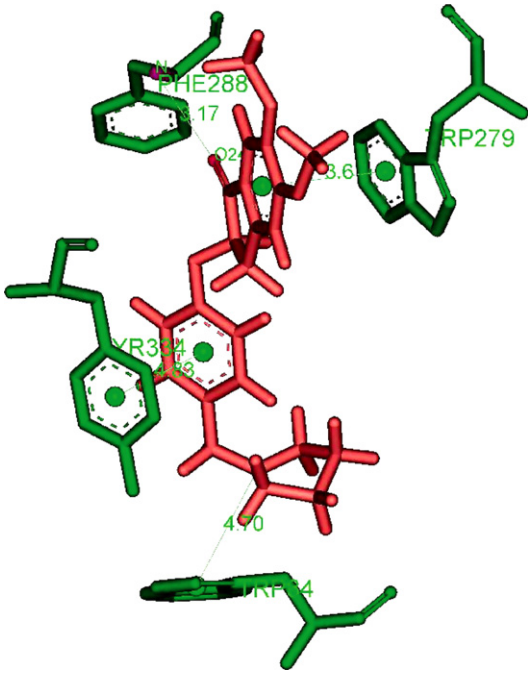


Figure 2. Docking model of **3k** within the AChE gorge.

Acknowledgments

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10. All new compounds showed satisfactory spectroscopic data. Selected analytical data: **3k**: ^{1}H NMR (400 MHz,

$CDCl_3$) δ: 7.23–7.27 (m, 3H), 6.98 (d, 2H, J = 8.0 Hz), 6.85 (s, 1H), 5.00 (dd, 1H,J = 7.8, and 3.6 Hz), 3.97 (s, 3H), 3.92 (s, 3H), 3.56–3.63 (m, 3H), 3.02 (dd, 1H, J = 16.8 and 3.6 Hz), 2.49 (m, 4H), 1.78 (m, 4H); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 200.1, 156.9, 156.4, 149.8, 146.19, 132.4, 130.0, 127.3, 115.3, 107.4, 104.7, 77.9, 59.9, 56.3, 56.1, 54.0, 34.0, 23.3; IR (KBr) v (cm^{-1}): 3083, 2962, 1703, 1604, 1589, 1453, 1270, 820; EI-MS MS (*m*/*z*): 367 (M^+), 297, 191 (100), 107; Anal. Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 71.56; H, 6.79; N, 3.76.