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Design and Synthesis of 4-amino-1H-indole-6-carboxamide derivatives as targeting molecules of Cholinesterase Enzymes

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ABSTRACT: Alzheimer's disease, being a neurodegenerative disorder that progresses over time, is one of such diseases that needs immediate and serious attention. As inhibitors of acetylcholinesterase and butyrylcholinesterase for the treatment of Alzheimer's disease, a new series of 4-amino-1H-indole-6-carboxamides has been designed, and 15 such molecules have been synthesized from 3,5-dinitrobenzoic acid via a multicomponent reaction. These synthesized compounds were characterized by spectral data and evaluated for inhibitory activity against acetylcholinesterase and butyrylcholinesterase. Among the series compound 9o with indole carboxamide fused with trimethoxy benzaldehyde with methylene-2-(thiazol-4-yl) aceto hydrazide linker showed potent inhibitory activity with IC_{50} of 0.94±0.10 and 1.10 ±0.05 µM compared to standard drug rivastigmine 0.47 ±0.2 & 0.65 ±0.02 µM against AChE and BuChE, respectively. 9o was further studied for brain cholinesterase inhibitory activity and exhibited potent activity with IC_{50} values of 25.32±0.25 and 28.24±0.18µM, respectively. Docking studies revealed that the designed molecules interacted with the nicotinic receptor through at least two hydrogen-bond interactions, except for a few compounds.

KEYWORDS: Tacrine, Alzheimer's disease, cholinesterase inhibitors, Hydrazine.

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Introduction

The most prevalent type of dementia in the elderly population is caused by Alzheimer's disease (AD), a gradual and deadly degenerative illness of the central nervous system. [1]. According to the 2015 Alzheimer's Disease International Association Report, dementia affects over 46 million individuals worldwide. This figure is predicted to rise sharply in the future due to the spread of the AD epidemic, reaching 131.5 million cases by 2050 [2]. The amyloid beta cascade hypothesis is the most widely recognized idea about the cause of AD. When hyperphosphorylated Tau builds up in AD, it separates from microtubules, causing instability, a disruption in neuronal transport, and brain atrophy [4]. According to the cholinergic theory of AD, cognitive and memory impairments result from a decrease in acetylcholine (ACh) levels, and medications that raise ACh levels have been shown to improve the disease's behavioral, functional, and cognitive symptoms. Therefore, maintaining or regaining cholinergic function is thought to be clinically advantageous [5]. It has been discovered that oxidative stress is present in the brain tissue of AD patients. Therefore, treatments for AD that disrupt the vicious cycles of oxidative stress and neurodegeneration present new possibilities [6].

Research Aim and Research Questions

Currently, there is no cure for Alzheimer's disease, and therapeutic therapies only provide palliative care. The primary method of treating Alzheimer's disease has been to increase ACh levels in the brain using acetyl cholinesterase inhibitors (AChEIs) such as tacrine, donepezil, galantamine, or rivastigmine, as well as the NMDA receptor antagonist memantine [7, 8]. The hybrid-based approach has been growing and has become a central point in the field of medicinal chemistry. So, in the design of multitarget-directed novel 4-amino-1H-indole-6-carboxamides derivatives, the indole group could be modified by binding other functional fragments, which is still of great interest [9]. With respect to designing hybrid structures, some multi-target compounds were designed by connecting 4-amino-1H-indole-6-carboxamides with another fragment through a proper linker in order to develop potent ChEIs with additional activities [10]. After that, several molecules with similar structures were synthesized by other groups that showed anti-Aβ activities [11-13].

Research Results

Baswaraju Macha et al. (2022) [14] reported A new series of acetylcholinesterase and butyrylcholinesterase inhibitors designed based on the structure. Bingul et al. (2020 [15] reported that the Methyl 7-[(E)-(2-benzoylhydrazinylidene)-methyl]-4,6-dimethoxy-1H-indole-2-carboxylates were evaluated for anti-cholinesterase activity, with the highest inhibition determined with the values of 83.31% and 73.55 % for AChE and BChE, respectively. Baswaraju Macha et al., 2020 [16] reported a series of new phenyl-containing benzo chromo pyridine compounds were designed, synthesized, characterized by spectral data and evaluated for cholinesterase inhibitory activity to be useful in Alzheimer's disease. Shoaib Khan et al. (2025 [17] reported synthesizing and evaluating a series of

thiazole-derived thiadiazole-based Schiff base derivatives for their potential anti-Alzheimer and antioxidant activities, with a focus on identifying promising drug-like candidates.

The designed compounds were synthesized as outlined [scheme-1]. The physical data of the synthesized compounds, results of biochemical evaluation (in vitro AChE and BuChE inhibitory activity and in vitro brain AChE and BuChE inhibitory activity of the compounds), and docking results have been tabulated below after scheme 1 in [Table-1], [Table-2] and [Table-3], respectively.

Scheme 1:

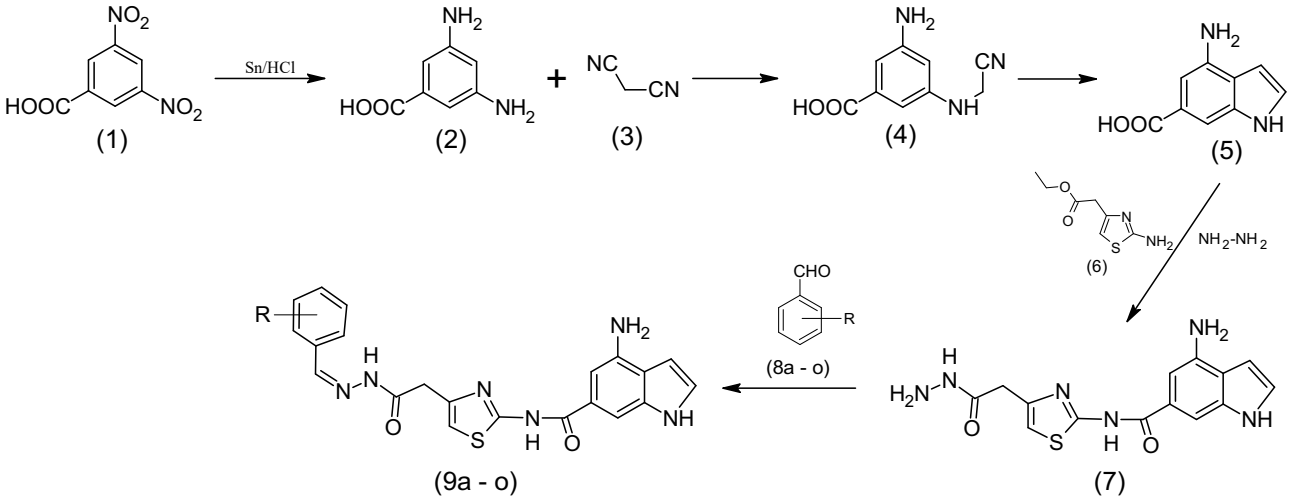

Table 1

Physical data of the 4-amino-N-(4-(2-(Substituted-2-benzylidenehydrazineyl)-2-oxoethyl)thiazol-2-yl)-1H-indole-6-carboxamide (9a-o).

Com	R	M. Form	M.Wt	M.P	Rf*	% Yield
9a	H	$C_{21}H_{18}N_6O_2S$	418	160-162	0.9	27
9b	4-Cl	$C_{22}H_{19}ClN_6O_3S$	482	175-177	0.5	30
9c	4-Br	$C_{22}H_{19}BrN_6O_3S$	527	160-162	0.6	54
9d	4-F	$C_{15}H_{12}FN_3O$	466	212-214	0.8	68
9e	4-NO_2	$C_{22}H_{19}N_7O_5S$	493	178-180	0.7	72
9f	4-CH_3	$C_{23}H_{22}N_6O_3S$	462	158-160	0.8	45
9g	3-Cl	$C_{22}H_{19}ClN_6O_3S$	482	180-182	0.5	70
9h	2,4 Di chloro	$C_{22}H_{18}Cl_2N_6O_3S$	517	158-160	0.8	47
9i	3,4,5 tri chloro	$C_{15}H_{10}Cl_3N_3O$	355	160-162	0.9	45
9j	2,4 Di bromo	$C_{22}H_{18}Br_2N_6O_3S$	603	174-176	0.8	68
9k	2,4 Di flouro	$C_{22}H_{18}F_2N_6O_3S$	484	199-201	0.7	55
9l	2,4 Di nitro	$C_{22}H_{18}N_8O_7S$	538	169-171	0.8	50

9m	2,4 Di methyl	$C_{24}H_{24}N_6O_3S$	476	180-182	0.6	65
9n	2,4 dihydroxy	$C_{22}H_{20}N_6O_5S$	480	190-192	0.4	81
9o	3,4,5 tri methoxy	$C_{25}H_{26}N_6O_6S$	538	194-196	0.5	70

Table 2

In vitro AChE/BuChE inhibitory activity and in vitro Brain AChE/BuChE inhibitory activity

In vitro AChE/BuChE inhibitory activity				**In vitro Brain AChE/BuChE inhibitory activity**		
Comp.	**AChE[a]**	**BuChE[a]**	**SI[b]**	**Comp.**	**AChE[a]**	**BuChE[a]**
9a	2.82±0.25	3.08±0.03	1.09	9b	32.27±0.20	35.36±0.28
9b	1.82±0.12	2.35±0.07	2.0	9h	29.24±0.20	31.45±0.23
9c	2.43±0.21	3.86±0.05	2.69	9i	26.34±0.18	30.43±0.26
9d	3.05±0.03	4.08±0.03	1.33	9j	29.65±0.15	33.56±0.32
9e	4.35±0.02	3.89±0.02	1.52	9k	28.24±0.41	31.35±0.34
9f	3.79±0.04	4.28±0.12	2.94	9n	34.31±0.24	30.23±0.26
9g	2.30±0.02	3.65±0.15	1.06	9o	25.32±0.25	28.24±0.18
9h	1.03±0.02	1.35±0.07	1.20	Rivastigmine	23.48±0.20	29.25±0.28
9i	0.98±0.18	1.21±0.14	1.61	Control	38.25±0.52	55.20±0.22
9j	1.25±0.02	2.64±0.12	2.18			
9k	1.38±0.15	2.02±0.10	2.20			
9l	2.65±0.27	5.04±0.08	1.90			
9m	3.08±0.14	4.24±0.06	3.0			
9n	1.94±0.10	2.10±0.05	**1.17**			
9o	0.94±0.10	1.10±0.05	1.40			
Standard	**0.47±0.2**	**0.65±0.02**	**1.38**			

[a] data are expressed in IC_{50}(μM)as(mean ± SD, n=3).

[b]Selectivity index = IC_{50} (BuChE)/ IC_{50} (AChE)

Table 3

Results of Docking Studies

Comp	**B.E* (1HBJ)**	**Hydrogen bonding (1acj)**	**B.E* (7Q1P)**	**Hydrogen bonding (6ep4)**
9a	-10.07(6)	Tyr121, Ser122(2), Ser200,	-7.57(1)	Asp221
9b	-9.22(3)	Tyr121, Ser122,	-6.61(1)	Gly128
9c	-8.66(4)	Tyr70, Ser122,Ser200, Se122	-6.38(2)	Asp56(2)w

9d	-9.51 (4)	Ser122, His440, Ser122	-7.33(3)	Asp33, Glu125, Gly128
9e	-10.73(5)	Trp84, Tyr121, Ser122, Ser200, Ser122	-6.84(2)	Asp133, Gly128
9f	-10.90 (4)	Ser200, Ser81, Trp84	-7.52(4)	Tsr54, Asp56, Lys54, Asn49
9g	-11.05(4)	Ser122, Ser200, Ser122, His440	-7.46(2)	Gly128, Glu125
9h	-10.73(4)	Tyr121, Ser122, Ser122	-8.56(0)	----
9i	-11.01(5)	Ser122, Tyr121, Glu199(3)	-8.55(2)	Glu125(2)
9j	-10.97(2)	Ser200, Glu199	-7.44(2)	Gly128, Asp56
9k	-10.71(4)	Tyr121, Ser122, Tyr130, Ser122	-8.13(1)	Phe55
9l	-10.62 (4)	Trp84, Tyr121, Tyr130, Gly80	-8.51(2)	Glu96(2)
9m	-10.50(3)	Tyr130, Tyr121, Ser122	-7.59 (1)	Glu125
9n	-10.79(0)	--	-6.15(3)	Gly128
9o	**-11.38(4)**	**Asp72, Ser200(2), Trp84**	**-9.16 (1)**	**Gly128**

Conclusions

In conclusion, new compounds based on novel 4-amino-1h-indole-6-carboxamides have been designed and fifteen such molecules have been synthesized from 3, 5-dinitrobenzoic acid in multicomponent reaction. Most active compound among the series was found to be 9o with indole carboxamide fused with Trimethoxy benzaldehyde with methylene-2-(thiazol-4-yl)aceto hydrazide linker showed potent inhibitory activity with IC_{50} of 0.94±0.10 and 1.10 ±0.05 μM compared to standard drug rivastigmine 0.47 ±0.2 & 0.65 ±0.02 μM against AChE and BuChE respectively.9o was further studied for brain cholinesterase inhibitory activity and exhibited potent activity with IC_{50} of value of 25.32±0.25 and 28.24±0.18μM respectively. Docking studies revealed that the designed molecules interacted with in nicotinic receptor with at list two hydrogen bond interactions barring few compounds.

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