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Synthesis of Novel Piperidine Compounds As Anticholinesterase Agents

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Abstract : *Donepezil is a piperidine based agent that is used for treatment of Alzheimer's diseases. This agent acts as acetylcholine esterase inhibitor and therefore, synthesis of piperidine compounds to evaluate anticholinesterase activity is very popular field in medicinal chemistry. Thus, in this study some novel piperidine derivatives were synthesized in order to observe their probable anticholinesterase effects. Structures of obtained compounds were confirmed by IR, NMR and Mass spectroscopic methods. Anticholinesterase activity of the synthesized compounds were tested by using Ellman's method. Some of the compounds in the series indicated good enzyme inhibitory activity.*

Keywords–*Acetylcholine, AChE, Donepezil, Ellman's Method.*

I. Introduction

Alzheimer's disease (AD) is the most common reason of progressive dementia in the old population. In recent years, many studies have been alleged to find out the complex pathophysiology of AD, but its ethology remains obscure [1]. Cholinergic hypothesis asserts one of the classical hypothesis related to AD which suggests that the substantial decrease in the levels of acetylcholine (ACh) result in cognitive and memory deficits relevant in AD patients [2]. Acetylcholinesterase (AChE) is the main enzyme responsible for the hydrolysis of the ACh at the cholinergic synapses, while butyrylcholinesterase (BuChE) acts as a co-regulator of the activity of AChE. Therapeutic agents that function as inhibitors of both enzymes can ensure additional benefits in AD. Present therapies for AD mainly focus on the use of FDA accepted acetylcholinesterase inhibitors (AChEIs), i.e. donepezil, rivastigmine, galantamine, tacrine. These medications are counted as solely symptomatic. Thus there is a need to find more efficient agents to stop the disease progression [3].

Piperidine ring possesses a tertiary nitrogen element that act as proton acceptor. Thus, nitrogen element converts to quaternary form and can interact with anionic site of AChE by electrostatic attraction. Due to this property of piperidine it is usually sited into chemical structure of new inhibitor candidates of AChE [4, 5].In recent studies, the importance of piperidine ring system has been emphasized. For instance, it was found out that the existence of benzyl piperidine moiety in the compounds provide inhibitor effect thanks to interaction with AChE's catalytic site [6]. In another assay, it was indicated that piperidine derivatives were more effective than other heterocyclic compounds on AChE activity [7].

II. Experimental

Synthesis of 4-Piperidin-1-yl-acetophenone (1)

4-Fluoroacetophenone (10 mmol, 1,214 mL), K_2CO_3 (10 mmol, 1,38 g), piperidine (20 mmol, 2.5 mll and DMF (5 mL) were added into a vial (30 mL) of microwave synthesis reactor (Anton-Paar, Monowave 300). The reaction mixture was heated under conditions of 200 ◦C and 10 bars for 15 min. After the control of reaction by TLC, the mixture was poured into iced-water, precipitated product was washed with water, dried, and recrystallized from ethanol.

Synthesis of 2-Bromo-(4'-Piperidin-1-yl)-acetophenone (2)

4-Piperidin-1-yl-acetophenone (1) (0.04, 10.12 g mol) was brominated in 30 mL acetic acid with the presence of 0.05 mol (2.58 mL) bromine and 0.5 mL HBr to give 2-Bromo-(4'-Piperidin-1-yl)-acetophenone (2) in 86% yield.

Synthesis of 4-[4-(Piperidin-1-yl)phenyl]-2-aminothiazole (3)

2-Bromo-(4'-Piperidin-1-yl)-acetophenone (2) (0.03 mol, 8.43 g) and thiourea (0.03 mol, 2.25g) were stirred in ethanol at room temperature for 48 h. The precipitated solid was filtered, dried and recrystallized from ethanol to afford title compound in 78% yield.

General synthesis method of N-[4-[4-(Piperidin-1-yl)pheniy]-thiazol-2-yl]-substituted benzamide derivatives (4a-4e)

Corresponding benzoyl chloride (0.025 mol) was added dropwise over 15 min to a magnetically stirred solution of the 4-[4-(Piperidin-1-yl)phenyl]-2-aminothiazole (0.022 mol, 5.70. g) (3) and triethylamine (0.025 mol, 3.48 mL) in dry THF (15 mL). The reaction was monitored by TLC. After the reaction was completed, the

solvent was evaporated under reduced pressure. Water was added to wash the resulting solid, the mixture was filtered, dried and recrystallized from ethanol to afford compound 4.

N-(4-(4-(piperidin-1-yl)phenyl)thiazol-2-yl)benzamide (4a)

FTIR (ATR, cm^{-1}): 3223 (N-H), 1668 (C=O), 1537, 1236, 692. ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 1.58-1.64 (6H, m, piperidine $–CH_2$), 3.24-3.28 (4H, m, piperidine $–CH_2$-), 6.93-6.95 (1H, m, aromatic –CH-), 7.55 (2H, d, *J*=8.50 Hz, aromatic -CH-), 7.65-7.74 (5H, s, aromatic –CH-), 8.14 (2H, d, *J*=8.50 Hz, aromatic -CH-), 12.70 (1H, s,–NH-). HRMS (m/z): $[M+H]^+$ calcd for$C_{21}H_{21}N_3OS$: 364.1484; found 364.1487

4-fluoro-N-(4-(4-(piperidin-1-yl)phenyl)thiazol-2-yl)benzamide (4b)

FTIR (ATR, cm^{-1}): 3231 (N-H), 1668 (C=O), 1508, 1234, 848. ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 1.56-1.63 (6H, m, piperidine $–CH_2$), 3.21 (4H, t, *J*=5.00 Hz, piperidine $–CH_2$-), 6.94 (1H, s, aromatic –CH-), 7.54 (2H, d, *J*=8.20 Hz, aromatic -CH-), 7.77-7.89 (4H, s, aromatic –CH-), 8.08 (2H, d, *J*=8.00 Hz, aromatic -CH-), 12.47 (1H, s,–NH-). HRMS (m/z): $[M+H]^+$ calcd for$C_{21}H_{20}N_3FOS$: 382.1389; found 382.1388.

4-chloro-N-(4-(4-(piperidin-1-yl)phenyl)thiazol-2-yl)benzamide (4c)

FTIR (ATR, cm^{-1}): 3414 (N-H), 1669 (C=O), 1537, 1236, 742. ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 1.59-1.65 (6H, m, piperidine $–CH_2$), 3.23-3.27 (4H, m, piperidine $–CH_2$-), 6.94 (1H, s, aromatic –CH-), 7.58 (2H, d, *J*=8.00 Hz, aromatic -CH-), 7.64 (2H, d, *J*=7.40 Hz, aromatic –CH-), 7.94 (2H, d, *J*=7.40 Hz, aromatic –CH-), 8.15 (2H, d, *J*=8.00 Hz, aromatic -CH-), 12.81 (1H, s,–NH-). HRMS (m/z): $[M+H]^+$ calcd for$C_{21}H_{20}N_3ClOS$: 398.1094; found 398.1101

3,4-dichloro-N-(4-(4-(piperidin-1-yl)phenyl)thiazol-2-yl)benzamide (4d)

FTIR (ATR, cm^{-1}): 3314 (N-H), 1663 (C=O), 1537, 1236, 745. ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 1.59-1.63 (6H, m, piperidine $–CH_2$), 3.21 (4H, t, *J*=5.00 Hz, piperidine $–CH_2$-), 6.95 (1H, s, aromatic –CH-), 7.45 (1H, s, aromatic -CH-), 7.77 (2H, d, *J*=7.90 Hz, aromatic –CH-), 7.94-8.03 (2H, m, aromatic –CH-), 8.41 (2H, d, *J*=7.90 Hz, aromatic -CH-), 12.88 (1H, s,–NH). HRMS (m/z): $[M+H]^+$ calcd for$C_{21}H_{19}N_3Cl_2OS$: 432.0704; found 432.0710

4-methoxy-N-(4-(4-(piperidin-1-yl)phenyl)thiazol-2-yl)benzamide (4e)

FTIR (ATR, cm^{-1}): 3230 (N-H), 1661 (C=O), 1539, 1236, 760. ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 1.59-1.63 (6H, m, piperidine $–CH_2$), 3.07-3.10 (4H, m, piperidine $–CH_2$-), 3.87 (3H, s, $–OCH_3$), 6.93 (1H, s, aromatic –CH-), 7.02 (2H, d, *J*=7.60 Hz, aromatic -CH-), 7.09 (2H, d, *J*=7.60 Hz, aromatic –CH-), 7.78 (2H, d, *J*=8.20 Hz, aromatic –CH-), 8.14 (2H, d, *J*=8.20 Hz, aromatic -CH-), 12.53 (1H, s,–NH). HRMS (m/z): $[M+H]^+$ calcd for$C_{22}H_{23}N_3O_2S$: 394.1589; found 394.1595

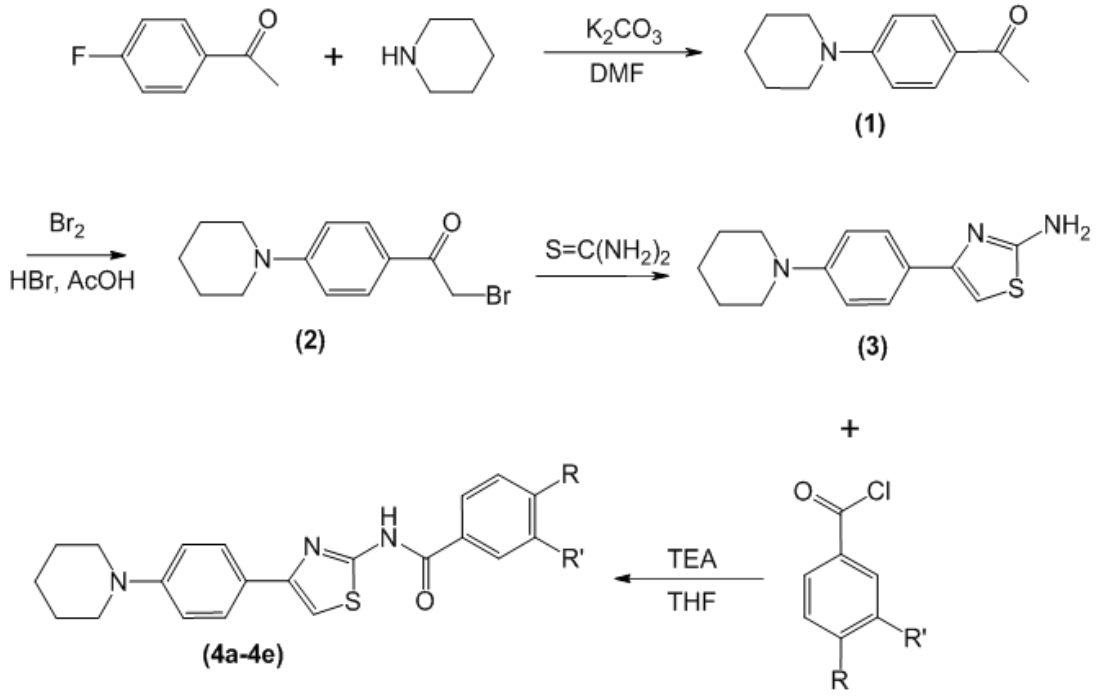
Biological Activity Studies

Anticholinesterase assay all compounds were subjected to a slightly modified method of Ellman's test [8, 9] in order to evaluate their potency to inhibit the AchE. Enzyme solutions were prepared in gelatine solution (1%), at a concentration of 2.5 units/mL.AChE and compound solution (50 µL) which is prepared in 2% DMSO at 0.1 and 1 mM concentrations were added to 3.0 mL phosphate buffer (pH 8±0.1) and incubated at 25 oC for 5 min. The reaction was started by adding DTNB) (50 µL) and ATC (10 µL) to the enzyme-inhibitor mixture. The production of the yellow anion was recorded for 10 min at 412 nm. As a control, an identical solution of the enzyme without the inhibitor is processed following the same protocol. The blank reading contained 3.0 mL buffer, 50 µL 2% DMSO, 50 µL DTNB and 10 µL substrate. All processes were assayed in triplicate. The inhibition rate (%) was calculated by the following equation:Inhibition % = [(AC-AB) – (AI-AB)] / (AC-AB) x 100Where AI is the absorbance in the presence of the inhibitor, AC is the absorbance of the control and AB is the absorbance of blank reading. Both of the values are corrected with blank-reading value. SPSS for Windows 15.0 was used for statistical analysis. Student's t- test was used for all statistical calculations. Data were expressed as Mean ± SD inactive in culture medium.

III. Results And Discussion

The chemical structures of the compounds (4a-4e) were confirmed by IR, 1H-NMR, and mass spectral data and elemental analyses. Characteristic stretching absorption of N-H and C=O groups were observed at 3122-3280 and 1660-1682 cm-1 respectively as expected. The stretching absorption at about 1388-1629 cm-1 were recorded for C=C. The stretching absorption for 1,4-disubstituted benzene bond at about 829-856 cm-1. In the 1H-NMR spectra, all of the aromatic and aliphatic protons were observed at estimated areas. M+H peaks in Mass spectra agreed well with the calculated molecular weight of the compounds. Activity tests were performed against AChE. In the series, the compound 4d was found as the most active derivative against AChE with the 73.07% and 59.26% inhibition rates at 1 µM and 0.1 µM concentrations, respectively. This result may have an impact on chemists to synthesize more active compounds.

IV. Figures And Tables



Scheme 1: Synthesis pathway of targeted compounds.

Table 1: Enzyme inhibition results and some physicochemical properties of the final compounds

Compound	R	R'	MW g/mol	Melting Point °C	% Enzyme Inhibition	
					1 µM	0.1 µM
4a	-H	-H	363.14	135	30.12	11.14
4b	-F	-H	381.13	155	26.14	9.42
4c	-Cl	-H	379.10	205	68.34	51.70
4d	-Cl	-Cl	431.06	165	73.07	59.26
4e	$-OCH_3$	-H	393.15	125	32.27	17.54
Donepezil	-	-	-	-	98.22	93.26

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