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Research Article

Synthesis and characterization of new piperazine-dithiocarbamate compounds as potent MAO-A inhibitors

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ABSTRACT

Monoamine oxidase (MAO) enzymes have an important place in neurodegenerative diseases. While MAO-A inhibitors are used in depression; MAO-B enzyme has an important place in Parkinson's disease. Within the scope of this study, 7 new piperazine-dithiocarbamate derivative compounds were synthesized. Structure determinations of the compounds were performed using ^{1}H-NMR, ^{13}C-NMR and HRMS spectroscopic methods. The MAO inhibitory activities of the compounds were determined by *in vitro* fluorometric methods. According to the obtained results, compound **2d** with IC_{50}=0.108±0.004 µM; compound **2e** exhibited inhibitory activity with an IC_{50}=0.074±0.003 µM.

Keywords: Dithiocarbamate, HRMS, Monoamine oxidase, NMR, Piperazine

1. INTRODUCTION

Monoamine oxidase (MAO), an intracellular flavoenzyme in the outer mitochondrial membrane, is responsible for the oxidative deamination of dietary amines, monoamine neurotransmitters and hormones [1,2]. Inhibitors of monoamine oxidases (MAOIs), a member of a protein family of flavin-containing amine oxidoreductases that play an important role in the regulation and metabolism of various neurotransmitters, may be useful in the treatment of psychiatric and neurological diseases [3]. Two MAO isoforms encoded by separate genes and localized to the outer membranes of the mitochondria are termed MAO-A and MAO-B [4]. These isoforms have highly conserved structures. However, the two isozymes have different substrate and inhibitor specificities due to the difference in inhibitor specificities of a pair of gating residues due to a difference in a pair of gating residues [5]. The two isoforms of MAO are dependent on substrate specificity and inhibitor selectivity based on their amino acid sequences, their three-dimensional structure. MAO-A and MAO-B have similar amino acid residues and orientations in their active sites, with only six of the sixteen active site residues differing between the two isozymes. In reality, structural analyses have revealed that MAO-A has a single Å3 550 cavity, but MAO-B has a tighter and longer dipartite cleft known as the entrance and substrate cavities. These two pockets can Å3 unite into a single ~700 cavity [6-8]. Both the MAO-A and -B are present in the majority areas of brain [9]. The MAO-A isoform's substrate specificity includes larger endogenous amines such as norepinephrine, serotonin, and epinephrine, whereas the MAO-B isoform's substrate specificity includes small amines such as β -phenyl ethylamine and benzylamine [10].

There are two types of MAOIs that are used for medicinal purposes nowadays. MAO-A inhibitors are mostly used to treat mental illnesses such as depression and anxiety, whereas MAO-B inhibitors are used to treat Parkinson's and Alzheimer's disease

[11]. Monoaminoxidase inhibitors can reduce peroxide production, which increases neuronal damage and causes nervous system diseases such as Alzheimer's and Parkinson's disease. Monoaminoxidase inhibitors have been used in the treatment of nervous disease [12]. Because central serotonin deficiency and to a lesser extent norepinephrine play a role in depressive illness, MAO-A inhibitors are used as antidepressant agents [13]. WHO predicts that by 2020, depression will be the second most disabling condition in the world, after stress and cardiovascular system [9,14].

Although some MAO-A inhibitors, including phenelzine, isocarboxazid, tranylcypromine, iproniazid, moclobemide and toloxatone, tranylcypromine, iproniazid, moclobemide and toloxatone have made significant contributions to the treatment of depression, their clinical use has been limited due to potential adverse effects, food and medication combinations, and the emergence of other pharmacological classes [15]. In reality, MAO-A inhibitors, especially irreversible inhibitors, are used with caution in the clinic due to their potential to produce a possibly fatal hypertensive crisis when taken with tyramine-containing foods [16]. The development of reversible MAO-A inhibitors, on the other hand, eliminates this difficulty because the reversible inhibitor is displaced from MAO-A when substrate concentrations rise, enabling metabolism to occur [17]. Due to a lack of affinity and selectivity for one of the isoforms, the majority of currently used MAO inhibitors cause adverse effects. As a result, more powerful, reversible, and selective MAO-A and MAO-B inhibitors must be developed [18].

In this study, we aim to present the new piperazine derivatives including dithiocarbamate moiety as selective MAO-A inhibitors.

2. MATERIALS AND METHODS

2.1. Chemistry

All of the chemicals were obtained from commercial sources and utilized without further purification. The uncorrected melting points (M.p.) were determined using the Mettler Toledo-MP90 Melting Point System. ^{1}H-NMR spectroscopy (nuclear magnetic resonance) FT-NMR spectrometer Bruker DPX 300; ^{13}C-NMR spectrometer Bruker DPX 75 MHz (Bruker Bioscience, Billerica, MA, USA). ESI was used to record mass spectra on an LCMS-IT-TOF (Shimadzu, Kyoto, Japan).

2.1.1. Synthesis of Sodium 4-(4-fluorobenzyl) piperazine-1-carbodithioate (1).

1-(4-Fluorobenzyl)piperazine (0.05 mol) was dissolved in EtOH (absolute) in presence of NaOH. Carbon disulfide was dissolved in absolute EtOH, and this solution placed in dropping funnel. It was added dropwise to the reaction medium in an ice bath. The precipitated product was filtered, washed with diethyl ether, and dried at the end of the process.

2.1.2. Synthesis of the target compounds (2a-2c)

Sodium 4-(4-fluorobenzyl)piperazine-1-carbodithioate (0.001 mol) and appropriate 2-bromoacetophenone (0.001 mol) was reacted in 20 ml acetone in room temperature. At the end of the reaction, acetone was evaporated under reduced pressure. The precipitated product was filtered, washed with water, dried, and crystallized from ethanol.

*2-oxo-2-phenylethyl 4-(4-fluorobenzyl)piperazine-1-carbodithioate (**2a**)*

Yield: 81 %, ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 2.47 (4H, br.s., piperazine), 3.54 (2H, s, -CH_2-), 4.00 (2H, br.s., piperazine), 4.19 (2H, br.s., piperazine), 4.96 (2H, s, -CH_2-), 7.16 (2H, t, J=8.9 Hz), 7.36 (2H, dd, J_1=5.7 Hz, J_2=8.6 Hz), 7.55 (2H, t, J=7.7 Hz), 7.64-7.67 (1H, m), 8.04 (2H, d, J=7.1 Hz). ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 44.17, 50.30, 51.76, 52.28, 60.72, 115.48 (J=21.01 Hz), 128.67, 128.68, 129.26, 131.36 (J=7.9 Hz), 133.88, 136.72, 161.87 (J=242.6 Hz), 193.25, 194.83. HRMS (m/z): $[M+H]^+$ calcd for $C_{20}H_{21}N_2OFS_2$: 389.1152; found 389.1134.

*2-oxo-2-(p-tolyl)ethyl 4-(4-fluorobenzyl)piperazine-1-carbodithioate (**2b**)*

Yield: 85 %, ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 2.39 (3H, s, -CH_3), 2.47 (4H, br.s., piperazine), 3.53 (2H, s, -CH_2-), 3.99 (2H, br.s., piperazine), 4.19 (2H, br.s., piperazine), 4.93 (2H, s, -CH_2-), 7.16

(2H, t, *J*=8.9 Hz), 7.34-7.39 (4H, m), 7.94 (2H, d, *J*=8.2 Hz). ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 21.66, 44.11, 50.36, 51.70, 52.28, 60.74, 115.47 (*J*=21.1 Hz), 128.79, 129.78, 129.79, 131.34 (*J*=7.8 Hz), 134.19, 144.33, 161.86 (*J*=242.7 Hz), 192.72, 194.87. HRMS (m/z): $[M+H]^+$ calcd for $C_{21}H_{23}N_2OFS_2$: 403.1309; found 403.1284.

*2-(4-methoxyphenyl)-2-oxoethyl 4-(4-fluorobenzyl) piperazine-1-carbodithioate (**2c**)*

Yield: 75 %, ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 2.48 (4H, br.s., piperazine), 3.54 (2H, s, -CH_2-), 3.85 (3H, s, -OCH_3), 3.99 (2H, br.s., piperazine), 4.20 (2H, br.s., piperazine), 4.91 (2H, s, -CH_2-), 7.07 (2H, d, *J*=8.9 Hz), 7.16 (2H, t, *J*=8.9 Hz), 7.37 (2H, dd, J_1=5.8 Hz, J_2=8.4 Hz), 8.02 (2H, d, *J*=8.9 Hz). ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 43.98, 50.22, 51.78, 52.25, 56.08, 60.71, 114.46, 115.49 (*J*=21.1 Hz), 129.50, 131.06, 131.07, 131.39 (*J*=6.7 Hz), 161.88 (*J*=242.9 Hz), 163.78, 191.53, 194.96. HRMS (m/z): $[M+H]^+$ calcd for $C_{21}H_{23}N_2O_2FS_2$: 419.1258; found 419.1238.

*2-(4-cyanophenyl)-2-oxoethyl 4-(4-fluorobenzyl) piperazine-1-carbodithioate (**2d**)*

Yield: 89 %, ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 2.46 (4H, br.s., piperazine), 3.52 (2H, s, -CH_2-), 3.98 (2H, br.s., piperazine), 4.18 (2H, br.s., piperazine), 4.93 (2H, s, -CH_2-), 7.16 (2H, t, *J*=8.9 Hz), 7.36 (2H, dd, J_1=5.7 Hz, J_2=8.6 Hz), 7.62 (2H, d, *J*=8.6 Hz), 8.65 (2H, d, *J*=8.6 Hz). ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 44.02, 50.33, 51.70, 52.18, 60.65, 115.50 (*J*=21.1 Hz), 115.69, 118.62, 129.24, 129.56, 131.43 (*J*=5.3 Hz), 133.31, 140.11, 161.91 (*J*=241.5 Hz), 163.78, 193.05, 194.59. HRMS (m/z): $[M+H]^+$ calcd for $C_{21}H_{20}N_3OFS_2$: 414.1105; found 414.1119.

*2-(4-nitrophenyl)-2-oxoethyl 4-(4-fluorobenzyl) piperazine-1-carbodithioate (**2e**)*

Yield: 80 %, ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 2.46 (4H, br.s., piperazine), 3.52 (2H, s, -CH_2-), 3.98 (2H, br.s., piperazine), 4.17 (2H, br.s., piperazine), 4.97 (2H, s, -CH_2-), 7.16 (2H, T, *J*=8.8 Hz), 7.35 (2H, dd, J_1=6.0 Hz, J_2=8.1 Hz), 8.26 (2H, d, *J*=8.9 Hz), 8.37 (2H, d, *J*=8.9 Hz). ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 44.13, 51.57, 51.91, 52.30, 60.77, 115.45 (*J*=21.1 Hz), 124.37, 130.02, 131.28 (*J*=7.9 Hz), 134.15, 134.20, 141.62, 150.37, 161.83 (*J*=242.7 Hz), 192.93, 194.47. HRMS (m/z): $[M+H]^+$ calcd for $C_{20}H_{20}N_3O_3FS_2$: 434.1003; found 434.1006.

*2-(4-fluorophenyl)-2-oxoethyl 4-(4-fluorobenzyl) piperazine-1-carbodithioate (**2f**)*

Yield: 70 %, ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 2.48 (4H, br.s., piperazine), 3.54 (2H, s, -CH_2-), 3.99 (2H, br.s., piperazine), 4.19 (2H, br.s., piperazine), 4.94 (2H, s, -CH_2-), 7.16 (2H, t, *J*=8.9 Hz), 7.34-7.42 (4H, m), 8.13 (2H, dd, J_1=5.5 Hz, J_2=8.9 Hz). ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 44.03, 50.34, 51.77, 52.26, 60.71, 115.48 (*J*=21.1 Hz), 116.29 (*J*=21.9 Hz), 131.37 (*J*=7.7 Hz), 131.69 (*J*=9.5 Hz), 133.47, 133.50, 161.87 (*J*=242.78 Hz), 165.55 (*J*=251.9 Hz), 191.94, 194.77. HRMS (m/z): $[M+H]^+$ calcd for $C_{20}H_{20}N_2OF_2S_2$: 407.1058; found 407.1039.

*2-(4-chlorophenyl)-2-oxoethyl 4-(4-fluorobenzyl) piperazine-1-carbodithioate (**2g**)*

Yield: 80 %, ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 2.46 (4H, br.s., piperazine), 3.52 (2H, s, -CH_2-), 3.98 (2H, br.s., piperazine), 4.18 (2H, br.s., piperazine), 4.93 (2H, s, -CH_2-), 7.16 (2H, t, *J*=8.9 Hz), 7.33-7.38 (2H, m), 7.63 (2H, d, *J*=8.6 Hz), 8.06 (2H, d, *J*=8.6 Hz). ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 43.98, 50.49, 51.88, 52.31, 60.78, 115.46 (*J*=21.1 Hz), 129.37, 130.58, 131.29 (*J*=8.1 Hz), 134.17, 134.21, 135.47, 138.75, 161.83 (*J*=242.7 Hz), 192.46, 194.65. HRMS (m/z): $[M+H]^+$ calcd for $C_{20}H_{20}N_2OFS_2Cl$: 423.0762; found 423.0746.

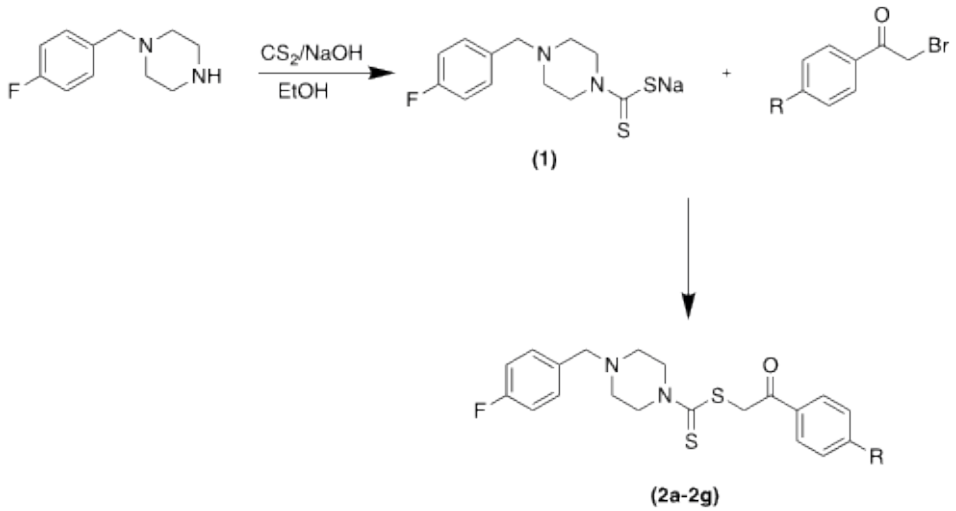
2.2. MAO Enzymes Inhibition Assay

The in vitro MAO inhibition test was carried out using the standard fluorometric method, and the percentages and IC_{50} values of the compounds obtained were reported as described by our research group already [19-25].

3. RESULTS AND DISCUSSION

3.1. Chemistry

The compounds **2a**-**2g** were obtained as presented in **Scheme 1**. Initially, a sodium 4-(4-fluorobenzyl) piperazine-1-carbodithioate (**1**) was obtained by means of the reaction between 1-(4-fluorobenzyl)



Compounds	R
2a	-H
2b	-CH_3
2c	-OCH_3
2d	-CN
2e	-NO_2
2f	-F
2g	-Cl

Scheme 1. Synthesis pathway for obtained compounds (**2a-2g**)

piperazine and carbon disulfide using NaOH. Secondly, the resulting products were obtained by reacting the sodium 4-(4-fluorobenzyl) piperazine-1-carbodithioate with appropriate 2-bromoacetophenone derivatives. The structures of the compounds obtained were established by spectroscopic methods, namely ^{1}H-NMR, ^{13}C-NMR, and HRMS.

3.2. MAO Enzymes Inhibition Assay

The in vitro fluorometric approach published previously by our research group was used to

Table 1. % Inhibition and IC50 values of the synthesized compounds, moclobemide and selegiline against MAO-A and MAO-B.

Compounds	MAO-A % Inhibition		MAO-A	MAO-B % Inhibition		MAO-B
	10-3 M	10-4 M	IC_{50} (µM)	10-3 M	10-4 M	IC_{50} (µM)
2a	**65.152±1.234**	42.861±0.948	>100	45.451±0.763	24.451±0.632	>1000
2b	**72.647±1.052**	40.542±0.891	>100	41.894±0.612	20.132±0.741	>1000
2c	**68.496±1.319**	46.668±0.961	>100	36.135±0.754	28.648±0.665	>1000
2d	**90.497±1.316**	**84.433±0.868**	**0.108±0.004**	35.532±0.817	27.745±0.662	>1000
2e	**93.134±1.034**	**90.225±0.921**	**0.074±0.003**	33.177±0.793	20.647±0.765	>1000
2f	**63.320±1.263**	41.150±0.918	>100	38.736±0.806	20.349±0.621	>1000
2g	**69.033±0.958**	44.962±0.845	>100	43.940±0.730	31.033±0.733	>1000
Moclobemid	94.121±2.760	82.143±2.691	6.061±0.262	-	-	-
Selegiline	-	-	-	98.258±1.052	96.107±1.165	0.037±0.001

assess the inhibitory capability of the synthesized compounds on MAO isoenzymes [19-25]. % Inhibition and IC_{50} values of the synthesized compounds, moclobemide and selegiline against MAO-A and MAO-B were presented in **Table-1**. As seen in **Table-1**, none of the compounds showed more than 50% inhibition against MAO-B enzyme at 10^{-4} M concentration. In contrast, compounds **2d** and **2e** showed greater than 50% inhibitory activity against the MAO-A enzyme. Therefore, serial dilutions of these compounds at 10^{-3}-10^{-9} M concentrations were prepared and their inhibitory activities on MAO-A enzyme were investigated. According to the results obtained, compound **2d** with IC_{50}=0.108±0.004 µM; compound **2e** exhibited inhibitory activity with an IC_{50}=0.074±0.003 µM.

3.2.1. Statistical analysis

Percentage of % inhibitions compared to the control group and values of IC_{50} were determined. All descriptive data were expressed as the mean±standart error of mean (SEM) from 5 times repetition within the experiments. Data were calculated on Microsoft Excel software with the sigmoidal dose-response curves by using Hill equation.

4. CONCLUSION

MAO-A inhibitors are used in the treatment of depression. However, this group of drugs is not preferred because of their side-effect profiles. Therefore, there is a need for new inhibitors with a reduced side-effect profile. Within the scope of this study, 7 new piperazine-dithiocarbamate derivative compounds were synthesized. Structure determinations of the compounds were performed using ^{1}H-NMR, ^{13}C-NMR and HRMS spectroscopic methods. The MAO inhibitory activities of the compounds were determined by *in vitro* fluorimetric methods. None of the compounds showed inhibitory activity against the MAO-B enzyme. In contrast, compounds **2d** and **2e** showed greater than 50% inhibitory activity against the MAO-A enzyme. According to the obtained results, compound **2d** with IC_{50}=0.108±0.004 µM; compound **2e** exhibited inhibitory activity with an IC_{50}=0.074±0.003 µM. When the structures of the compounds are examined, compound **2d** contains CN group and compound **2e** contains NO_2 group. Both groups are active groups that can withdraw electrons. Therefore, it is thought that such substituents contribute positively to the activity.

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Ethical approval

Not applicable, because this article does not contain any studies with human or animal subjects.

Author contribution

Concept: ZAK, YO; Design: ZAK, YO; Supervision: ZAK; Materials: DO, BNS, SL; Data Collection and/or Processing: DO, BNS, SL; Analysis and/or Interpretation: DO, BNS, SL; Literature Search: DO, ZAK; Writing: DO, ZAK; Critical Reviews: YO, ZAK.

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Conflict of interest

The authors declared that there is no conflict of interest.

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