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Novel substituted oxadiazole - piperazine derivatives as potential MAO inhibitors: Design, synthesis, *in vitro* and *in silico* studies

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ABSTRACT: Recent studies have shown that there are many piperazine and oxadiazole derivatives with MAO-A and/or MAO-B inhibitory activity. For this reason in our recent study, a new compound series of oxadiazole - piperazine derivatives (**4a-e**) were designed, synthesized, characterized and screened their *h*MAOs inhibitory activities. When the *in silico* studies were examined, it was seen that the pharmacokinetic properties and interactions with the receptor of synthesized compounds were suitable. Compound **4e**, with a NO_2 group on the 4-position of the phenyl ring, found showing significant MAO-A inhibitory activity. Compound **4e**, was the most effective agent against MAO-A enzyme with IC_{50} value of 0.116 ± 0.004 µM. The newly synthesized oxadiazole - piperazine derivatives appears to be supported studies to design MAO inhibitors to obtain more suitable drugs, against diseases such as depression and anxiety due to MAO-A.

KEYWORDS: *h*MAOs inhibition ; oxadiazole ; piperazine ; ADME ; molecular docking.

1. INTRODUCTION

Monoamine oxidases liable for the oxidative deamination of dietary amines and neurotransmitters carry the flavin adenine dinucleotide (FAD) coenzyme [1]. There are two isoforms of MAO enzymes, MAO-A and MAO-B, which act as a catalytic agent in the oxidative deamination of various monoamines such as dopamine, serotonin, histamine, noradrenaline and adrenaline [2, 3]. Because MAOs play an significant role in the metabolism of certain neurotransmitters, there is pharmacological interest in MAO inhibitors as a result of their potential to be beneficial in the treatment of psychiatric and neurological diseases [4].

Unlike MAO-B, MAO-A does not increase with age, leading to the assumption that a completely independent mechanism regulates the expression of the two enzymatic isoforms [5]. MAO-A selective inhibitors can be used as antidepressants, while MAO-B selective inhibitors can be used to cure Parkinson's Disease (PD) and Alzheimer's Disease (AD) which neurodegenerative diseases [6]. The most common neurodegenerative diseases affecting the elderly population worldwide are stated as AD and PD. AD characterized by loss of important mental functions and memory, while PD is characterized by progressive loss of muscle control [7-9].

Compounds containing oxadiazole scaffold have become promising in recent years because they show very wide biological activity such as AD activity [10-13]. There are compounds with antianxiety-antidepressant effects such as Buspirone containing the piperazine structure approved for clinical use, and MAO activity studies on piperazine derivative compounds are still up-to-date [14-16]. Although there are many different classes of antidepressants in use, they have side effects and clinical limitations. Therefore, it is clear that there is a need for the development of effective and safer drugs in this area [17, 18].

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In this study, we explain the synthesis, *in vitro* MAO inhibition evaluation and molecular docking of a new series (**4a-e**) derived from 4-methoxyphenylpiperazine and substituted 1,3,4-oxadiazole-5-thiol. It is aimed to develop new compounds that we thought may be useful in the treatment of MAO-related diseases, and the relationship between MAO inhibitory activities and their structural properties has been tried to be revealed.

2. RESULTS AND DISCUSSIONS

2.1. Chemistry

In this study, we synthesized Oxadiazole - Piperazine derivatives (**4a-e**) in four steps. The synthetic route of the synthesized target compounds was described in **Figure 1**. Ethyl 2-(4-(4-methoxyphenyl)piperazin-1-yl)acetate (**1**) was synthesized by the reactions of 1-(4-methoxyphenyl)piperazin and ethyl 2-chloroacetate. 2-(4-(4-methoxyphenyl)piperazin-1-yl)aceto hydrazide (**2**) was synthesized by the reactions of Compound **1** and excess of hydrazine hydrate. 5-[(4-(4-methoxyphenyl)piperazin-1-yl)-1-yl)methyl]-1,3,4-oxadiazole-2-thiol (**3**) was synthesized by the reaction of Compound **2** and potassium hydroxide and then carbon disulfide. Compound **3** and the some 2-bromoacetophenone derivatives were then reacted in order to obtain the target compounds **4a-e**. The chemical structures of the all compounds (**4a-e**) were confirmed by ^{1}H-NMR, ^{13}C-NMR, HRMS. In the ^{1}H-NMR spectra, all aromatic and aliphatic protons were observed in agreement with the predicted areas. In the ^{1}H-NMR spectra, we clearly observed the presence of N-CH_2 and S-CH_2 protons at 3.83-3.84 and 5.09-5.17 ppm, respectively. In the ^{13}C-NMR spectra, the carbons of the piperazine and oxadiazole rings were recorded between 51.30-52.51 ppm and 163.85-165.25 ppm, respectively. M^{+1} peaks in HRMS spectra agreed well with the calculated molecular weight of the all compounds.

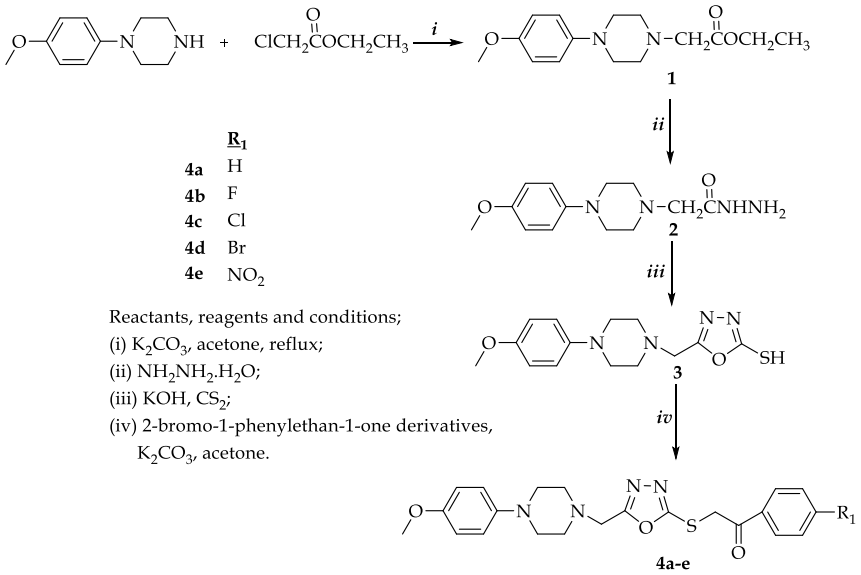

Figure 1. Synthetic pathway and the substituents for the compounds **4a-e.**

2.2. *In vitro* MAO inhibition

The *in vitro* fluorometric method previously described by our research group was used to evaluate the MAO inhibitory potencies of the synthesized compounds [19-24]. While MAO inhibitions of all compounds and reference drugs were given in **Table 1**, the IC_{50} value of the most effective Compound **4e** and Moclobemide, whose solutions were prepared by serial dilution, was calculated against MAO-A in **Table 2**.

Compound **4e** showed a significant inhibitory potency on the MAO-A enzyme at concentration of 10^{-3} M and 10^{-4} M but none of the synthesized compounds exhibited significant MAO-B enzyme inhibition. Compound **4e** was determined as the most active derivative in the series with IC_{50} value of 0.116±0.004 µM. It was very remarkable that **4e**, which was found as most effective compound among the newly synthesized compounds, performed an inhibition profile approximately 52 times more effective than used as the reference drug Moclobemide. For the compound **4e** bearing NO_2, the presence of electron withdrawing group has a positive effect on MAO enzyme inhibitory activity, especially on MAO-A.

Table 1. %Inhibition of the synthesized compounds, Selegiline and Moclobemide against MAO-A and MAO-B.

Compounds	MAO-A % Inhibition		MAO-B % Inhibition	
	10^{-3} M	10^{-4} M	10^{-3} M	10^{-4} M
4a	58.916±1.106	44.268±0.859	39.551±0.895	28.357±0.742
4b	59.204±1.001	41.035±0.788	38.340±0.986	26.312±0.836
4c	63.578±1.129	40.654±0.736	42.735±0.852	25.769±0.722
4d	55.388±0.975	43.774±0.897	40.528±0.855	20.645±0.628
4e	**90.354±1.654**	**79.659±1.248**	44.799±0.997	23.498±0.709
Moclobemide	**94.121±2.760**	**82.143±2.691**	-	-
Selegiline	-	-	**98.258±1.052**	**96.107±1.165**

Table 2. %Inhibition and IC_{50} values of 4e and Moclobemide against MAO-A.

Compound	MAO-A % Inhibition							IC_{50} (μM)
	10^{-3} M	10^{-4} M	10^{-5} M	10^{-6} M	10^{-7} M	10^{-8} M	10^{-9} M	
4e	90.354 ±1.654	79.659 ±1.248	71.146 ±1.108	69.647 ±1.007	48.695 ±0.894	24.726 ±0.716	18.337 ±0.593	0.116 ±0.004
Moclobemide	94.121 ±2.760	82.143 ±2.691	60.458 ±2.559	36.151 ±1.984	22.135 ±1.337	18.166 ±0.812	14.128 ±0.725	6.061 ±0.262

2.3. *In silico* ADME prediction

The computational approach that provides information for drug design greatly helps to reduce cost and time. In this study, Schrödinger QikProp software [25] was used to obtain ADME predictions of all synthesized compounds, further details were given in **Table 3**. The "Rule of Five" by Lipinski and the "Rule of Three" by Jorgensen enounce the structural properties found in a candidate compound that could be a pharmaceutical compound [26, 27]. It was defined that the parameters of the all compounds were in the standard ranges in general and there was not much violation in terms of rules in **Table 3**. Since the molecules are expected to show activity in the central nervous system (CNS) for antidepressant effect, when the results were analyzed in this respect, it was seen that the predicted CNS activity values of the compounds were between 1 and 2. The value of 1 on this scale represents positive activity in the CNS. In addition, the log P and log BB values, which are the guides for the compounds to cross the blood brain barrier, were in the range of 2.613 to 3.368 and (-1.780) to (-0.175), respectively, and were within the recommended limits. Therefore, it can be considered that the synthesized compounds can exceed the blood-brain barrier (BBB), which is very important for CNS-related drugs. Considering the results of the ADME and BBB permeability studies, the synthesized compounds **4a-e** were determined to possess pharmacokinetic profiles that may be appropriate for clinical use.

2.4. Molecular docking studies

When the results of the MAO inhibition assay were examined, Compound **4e** was found as the most active derivative (with IC_{50} value of 0.116±0.004 μM) in the series against *h*MAO-A enzyme. Therefore, molecular docking studies were carried out to evaluate inhibition capability of Compounds **4e**. By using 2.2Å resolution X-ray crystal structure of *h*MAO-A (PDB ID: 2Z5X) [28] molecular docking studies were performed, and binding modes of Compound **4e** were defined. The docking poses of Compound **4e** were presented in **Figures 2** and **3.**

Compound **4e** was found to bind sufficiently to amino acid residues lining the cavity and was found to be very close to the FAD cofactor (**Figure 2**). When the molecular docking study of this compound was examined, it was clearly seen that there were three types of interaction including π-π, cation-π interactions and formation of hydrogen bond. The π-π interaction was detected between the p-nitrophenyl and the phenyl of Tyr407. Also, there was a cation-π interaction between the nitrogen atom of nitro group and the phenyl of Try444 (**Figure 3**). The last interaction was observed in the carbonyl moiety. The carbonyl of Compound **4e** formed a hydrogen bond with the amino of Gln215. All these interactions detected explained why Compound **4e** exhibited a stronger inhibition profile the other synthesized compounds.

Table 3. Parameters of ADME predictions.

Parameters	Compounds				
	4a	4b	4c	4d	4e
RB	7	7	7	7	8
CNS	1	1	1	1	-2
MW	424.517	442.507	458.962	503.413	469.514
DM	6.483	4.547	4.618	5.006	5.362
MV	1285.76	1300.116	1321.743	1329.202	1424.007
DHB	0	0	0	0	0
AHB	8.25	8.25	8.25	8.25	9.25
logP	2.92	3.125	3.305	3.368	2.613
logS	-2.571	-2.872	-3.015	-3.094	-4.29
Pcaco	268.557	268.522	268.535	268.541	28.536
logBB	-0.313	-0.222	-0.183	-0.175	-1.78
PMDCK	221.559	362.546	425.044	447.961	19.437
PM	5	5	5	5	6
%HOA	87.520	88.720	89.769	77.182	68.292
PSA	87.456	87.460	87.459	87.459	131.490
VRF	0	0	0	1	0
VRT	0	0	0	0	0

MW: Molecular weight, **DM:** Computed dipole moment (recommended value: 1-12.5), **RB:** Number of rotatable bonds (recommended value: 0-15), **MV:** Total solvent-accessible volume (recommended value: 500-2000), **AHB:** Estimated number of hydrogen bond acceptors (recommended value: 2-20), **DHB:** Estimated number of hydrogen bond donors (recommended value: 0-6), **PSA:** Van der Waals surface area of polar nitrogen and oxygen atoms and carbonyl carbon atoms (recommended value: 7-200), **PMDCK:** Predicted apparent MDCK cell permeability (recommended value: <25 poor, >500 great), **PM:** Number of likely metabolic reactions (recommended value: 1-8) **CNS:** Predicted central nervous system activity (recommended value: −2 (inactive), +2 (active)), **%HOA:** Predicted human oral absorption percent (recommended value: >80% is high, <25% is poor), **logS:** Predicted aqueous solubility (recommended value: -6.5-0.5), **logP:** Predicted octanol/water partition coefficient (recommended value: -2-6.5), **PCaco:** Predicted apparent Caco-2 cell permeability (recommended value: <25 poor, >500 great), **logBB:** Predicted brain/blood partition coefficient (recommended value: -3-1.2), **VRT:** Number of violations of Jorgensen's rule of three. The three rules are: logS > -5.7, PCaco > 22 nm/s, PM < 7, **VRF:** Number of violations of Lipinski's rule of five. The rules are: MW < 500, logP < 5, DHB ≤ 5, AHB≤ 10, Positive PSA value.

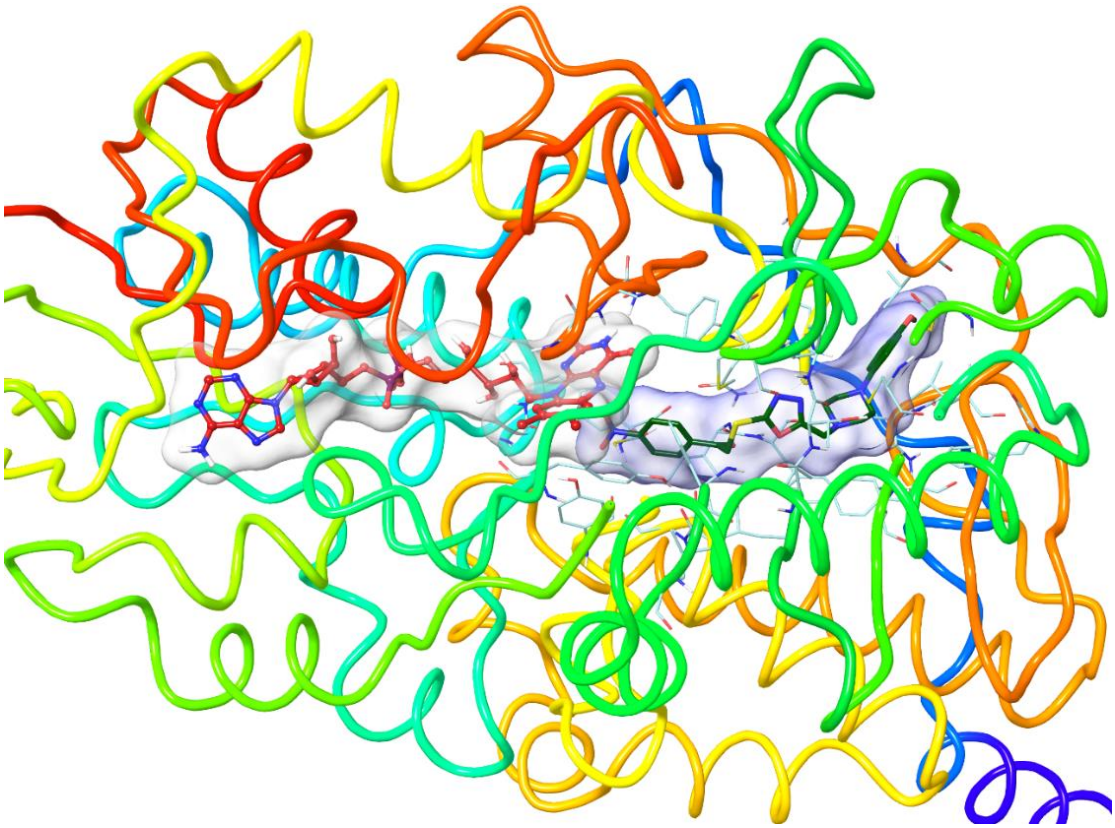

Figure 2. 3D pose of Compound **4e** in the active region of *h*MAO-A (PDB ID: 2Z5X). The significant residues (colored with turquoise) in the active site as tube model and Compound 4e (colored with dark green) are presented.

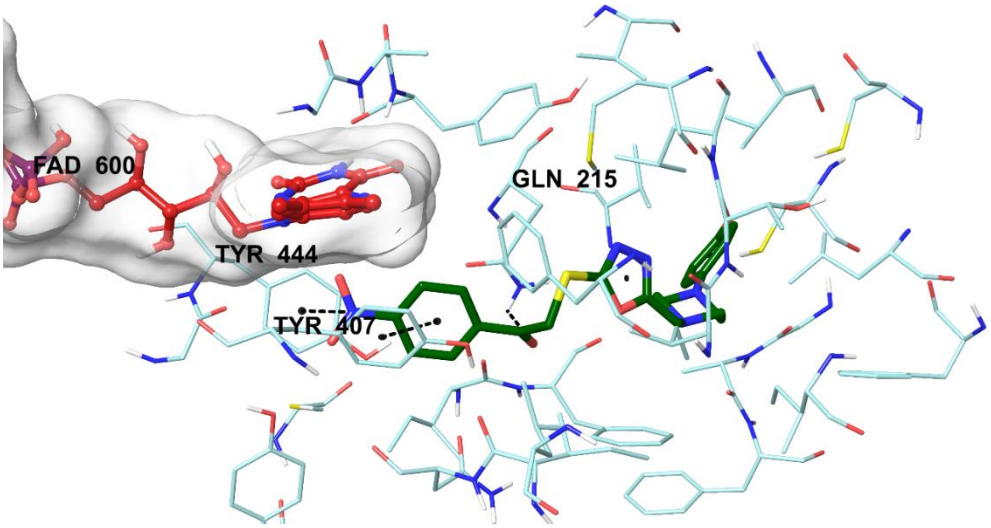

Figure 3. 3D interacting mode of Compound **4e** in the active region of *h*MAO-A. The inhibitor and the significant residues in the active site of the *h*MAO-A are presented by tube model. The FAD molecule (colored with red) is presented by ball and stick model.

3. CONCLUSION

It has been reported that heterocyclic structures such as piperazine and oxadiazole are important in terms of biological activity, moreover promising structures in drug design against central nervous system diseases. In this study, a new series 1-(4-substituted phenyl)-2-((5-((4-(4-methoxyphenyl)piperazin-1-yl)methyl)-1,3,4-oxadiazol-2-yl)thio)ethan-1-ones was synthesized and characterized and *h*MAOs inhibition activities were investigated. ADME predictions indicated that all newly synthesized compounds (**4a-e**) had promising pharmacokinetic properties. Molecular docking studies showed that Compound **4e** sufficiently binds to amino acid residues in the binding cavity of the macromolecule and was very close to the FAD cofactor. Compound **4e**, which carries the NO_2, has a positive effect on the MAO-A enzyme inhibitory activity compared to halogenated derivatives. In later studies, synthesizing derivatives with electron withdrawing groups such as NO_2 may lead to better results in MAO-A inhibitory activity studies. When the IC_{50} value of the most effective Compound **4e** was examined, it was approximately 52 times more active than the reference drug against MAO-A. All these data in the study may prompt pharmaceutical chemists to research similar *h*MAO-A inhibitors that could be valuable for the treatment of depression and anxiety.

4. MATERIALS AND METHODS

4.1. General information

Each chemicals used in synthesis of compounds were purchased from Sigma-Aldrich Chemicals (Sigma-Aldrich Corp., USA) and Merck Chemicals (Merck KGaA, Germany). Melting points of five synthesized compounds were determined by MP90 digital melting point apparatus (Mettler Toledo, USA) and were uncorrected. The purities of five synthesized compounds were verified by TLC on silica gel 60 F254. HRMS studies were performed on a Shimadzu 8040 LC-MS-MS spectrophotometer (Shimadzu, Japan). ^{1}H-NMR and ^{13}C-NMR spectra were recorded by a Bruker 300 MHz and 75 MHz digital FT-NMR spectrometer (Bruker Bioscience, USA) in DMSO-d^6. In the NMR spectra *J* values (coupling constants) were recorded as Hertz and splitting patterns were symbolized as m: multiplet, t: triplet, d: doublet, s: singlet.

4.2. Chemistry

Synthesis of ethyl 2-(4-(4-methoxyphenyl)piperazin-1-yl)acetate (1): 0.04 mol 1-(4-methoxyphenyl)piperazin derivative was dissolved in 250 mL acetone. 0.04 mol potassium carbonate and ethyl 2-chloroacetate was added and then the reaction mixture was refluxed for 8 hours. The solvent was evaporated with rotary evaporator. Later on the resulting solid was washed by adding water. The mixture was dried after filtration and recrystallized from ethanol to give Compound **1** [29].

Synthesis of 2-(4-(4-methoxyphenyl)piperazin -1-yl)aceto hydrazide (2): 0.03 mol ethyl 2-(4-(4-methoxyphenyl)piperazin-1-yl)acetate was dissolved in 250 mL ethanol. 0.03 mol hydrazine hydrate dissolved in ethanol, was added slowly and the mixture stirred at room temperature. After the reaction was determined

to be complete, the solvent was evaporated with a rotary evaporator. Later on the resulting solid was washed by adding water. The mixture was dried after filtration and recrystallized from ethanol to give Compound **2** [29].

Synthesis of 5-[(4-(4-methoxyphenyl)piperazin-1-yl)-1-yl)methyl]-1,3,4-oxadiazole-2-thiol (3): 0.02 mol 2-(4-(4-methoxyphenyl)piperazin-1-yl)-1-yl)aceto hydrazide was dissolved in 250 mL ethanol. 0.02 mol potassium hydroxide was dissolved in 80 mL ethanol with continuous stirring. The second solution was added to first one. 0.02 mol carbon disulfide was added and then the mixture was refluxed for 5 hours. After the reaction was determined to be complete, dilute HCl was added to remove the salt form of the compound. Later on the resulting solid was washed by adding water. The mixture was dried after filtration and recrystallized from ethanol to give Compound **3** [29, 30].

General procedure for the synthesis of 1-(substituted phenyl)-2-((5-((4-(4-methoxyphenyl)piperazin-1-yl)methyl)-1,3,4-oxadiazol-2-yl)thio)ethan-1-one derivatives (4a-e): 10 mmol 5-[(4-(4-methoxyphenyl)piperazin-1-yl))methyl]-1,3,4-oxadiazole-2-thiol derivative was dissolved in 100 mL acetone. 10 mmol potassium carbonate was added. The indicated phenacyl bromide derivatives were added and stirred for 12 hours at room temperature. After TLC scanning to check the reaction completion, the solvent was evaporated with a rotary evaporator. Later on the resulting solid was washed by adding water. The mixture was dried after filtration and recrystallized from ethanol to give final compounds **4a-e** [30].

2-((5-((4-(4-methoxyphenyl)piperazin-1-yl)methyl)-1,3,4-oxadiazol-2-yl)thio)-1-phenylethan-1-one ***(4a):*** M.P.: 102.9-104.8°C, Yield: %77. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 2.56-2.59 (4H, t, piperazinyl CH_2), 2.96-2.99 (4H, t, piperazinyl CH_2), 3.67 (3H, s, O-CH_3), 3.84 (2H, s, N-CH_2), 5.12 (2H, s, S–CH_2), 6.78-6.87 (4H, q, methoxyphenyl CH), 7.54-7.59 (2H, t, phenyl CH), 7.67-7.73 (1H, m, phenyl CH), 8.03-8.06 (2H, d, J = 9 Hz, phenyl CH). ^{13}C-NMR (75 MHz, DMSO-d_6): = 49.95, 51.30, 52.51, 55.59, 55.62, 114.66, 117.96, 128.94, 129.37, 134.48, 135.47, 145.68, 153.44, 164.13, 165.06, 192.87. ESI-MS (m/z): $[M+H]^+$: 425.1649 (100%).

1-(4-fluorophenyl)-2-((5-((4-(4-methoxyphenyl)piperazin-1-yl)methyl)-1,3,4-oxadiazol-2-yl)thio)ethan-1-one ***(4b):*** M.P.: 108.3-110.4°C, Yield: %89. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 2.55-2.58 (4H, t, piperazinyl CH_2), 2.96-2.99 (4H, t, piperazinyl CH_2), 3.67 (3H, s, O-CH_3), 3.83 (2H, s, N-CH_2), 5.10 (2H, s, S–CH_2), 6.78-6.88 (4H, q, methoxyphenyl CH), 7.38-7.43 (2H, q, phenyl CH), 8.14-8.16 (2H, m, phenyl CH). ^{13}C-NMR (75 MHz, DMSO-d_6): = 49.96, 51.31, 52.51, 55.60, 55.63, 114.66, 116.31, 116.60, 117.95, 132.00, 132.12, 145.71, 153.43, 164.05, 164.22, 165.13, 167.57, 191.57. ESI-MS (m/z): $[M+H]^+$: 443.1539 (100%).

1-(4-chlorophenyl)-2-((5-((4-(4-methoxyphenyl)piperazin-1-yl)methyl)-1,3,4-oxadiazol-2-yl)thio)ethan-1-one ***(4c):*** M.P.: 104.8-106.8°C, Yield: %79. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 2.55-2.58 (4H, t, piperazinyl CH_2), 2.95-2.98 (4H, t, piperazinyl CH_2), 3.67 (3H, s, O-CH_3), 3.83 (2H, s, N-CH_2), 5.09 (2H, s, S–CH_2), 6.78-6.88 (4H, m, methoxyphenyl CH), 7.63-7.66 (2H, d, J = 9 Hz, phenyl CH), 8.04-8.07 (2H, d, J = 9 Hz, phenyl CH). ^{13}C-NMR (75 MHz, DMSO-d_6): = 49.96, 51.32, 52.51, 55.63, 114.67, 117.95, 129.49, 130.86, 134.19, 139.39, 145.70, 153.43, 163.99, 165.15, 192.06. ESI-MS (m/z): $[M+H]^+$: 459.1248 (100%).

1-(4-bromophenyl)-2-((5-((4-(4-methoxyphenyl)piperazin-1-yl)methyl)-1,3,4-oxadiazol-2-yl)thio)ethan-1-one ***(4d):*** M.P.: 111.8-112.7°C, Yield: %81. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 2.55-2.58 (4H, t, piperazinyl CH_2), 2.95-2.98 (4H, t, piperazinyl CH_2), 3.67 (3H, s, O-CH_3), 3.83 (2H, s, N-CH_2), 5.09 (2H, s, S–CH_2), 6.78-6.87 (4H, m, methoxyphenyl CH), 7.77-7.80 (2H, d, J = 9 Hz, phenyl CH), 7.96,7.99 (2H, d, J = 9 Hz, phenyl CH). ^{13}C-NMR (75 MHz, DMSO-d_6): = 49.95, 51.31, 52.51, 55.59, 55.62, 114.66, 117.95, 128.66, 130.92, 132.45, 134.49, 145.70, 153.43, 163.99, 165.15, 192.28. ESI-MS (m/z): $[M+H]^+$: 503.0757 (100%).

1-(4-nitrophenyl)-2-((5-((4-(4-methoxyphenyl)piperazin-1-yl)methyl)-1,3,4-oxadiazol-2-yl)thio)ethan-1-one ***(4e):*** M.P.: 129.4-131.2°C, Yield: %82. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 2.55-2.58 (4H, t, piperazinyl CH_2), 2.95-2.98 (4H, t, piperazinyl CH_2), 3.67 (3H, s, O-CH_3), 3.84 (2H, s, N-CH_2), 5.17 (2H, s, S–CH_2), 6.77-6.87 (4H, q, methoxyphenyl CH), 8.25-8.28 (2H, d, J = 9 Hz, phenyl CH), 8.36-8.39 (2H, d, J = 9 Hz, phenyl CH). ^{13}C-NMR (75 MHz, DMSO-d_6): = 49.95, 51.31, 52.50, 55.61, 114.64, 117.93, 124.44, 130.39, 140.12, 145.69, 150.73, 153.41, 163.85, 165.25, 192.41. ESI-MS (m/z): $[M+H]^+$: 470.1495 (100%).

4.3. *In vitro* MAO inhibition assay

The MAO inhibition test was performed by our research group using the fluorometric method as previously stated, and the IC_{50} values were also calculated by our research group as previously stated [19-24].

4.4. ADME predictions

QikProp 4.8 software [25] was used to predict the pharmacokinetic properties of the all synthesized compounds (**4a-e**), physicochemical parameters were detected with *in silico* method.

4.5. Molecular docking studies

In silico procedure was applied to discover the binding modes of Compound **4e** on *h*MAO-A enzyme binding cavity. Pdb file of hMAO-A (PDB ID: 2Z5X) [28], which was crystallized with Harmine, was get from the Protein Data Bank (www.pdb.org). The docking studies was conducted according to procedure of previously published papers by our research group [13, 19-24].

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Conflict of interest statement: The authors declared no conflict of interest.

Appendix A. Supplementary Material

Supplementary material related to this article can be accessed at https://dx.doi.org/10.29228/jrp.99.

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