INTERNATIONAL RESEARCH JOURNAL OF PHARMACY
www.irjponline.com
ISSN 2230 – 8407

Research Article

SCAFFOLD BASED DESIGNING OF NOVEL 1, 3-DIOXOL DERIVATIVES AS MONOAMINE OXIDASE INHIBITOR: IN SILICO APPROACH

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Article Received on: 14/03/19 Approved for publication: 17/04/19

DOI: 10.7897/2230-8407.1005182

ABSTRACT

Monoamine oxidase (MAO) catalyzes the oxidative deamination of monoamine neurotransmitters such as serotonin, dopamine, norepinephrine, and appears to play important role in many psychiatric and neurological disorders. MAO-A metabolizes serotonin and nor adrenaline and is inhibited by the low concentration of clorgyline. MAO-A inhibitors are useful in the therapy of mental disorders as antidepressants and anxiety. Therefore, this makes it a potential target for the development of novel therapies. In the present study, a series of seventy novel 1, 3-dioxol derivatives were designed as MAO-A inhibitors by using in silico approaches and nine best compounds were synthesized from the designed series. We assume the significance of computational methods in designing of novel derivatives for desired pharmacological activity. QSAR, pharmacophore, ADME methods, Auto dock techniques were used to design MAO-A inhibitors. A Ligand-based drug design was employed to optimize SP-149 and SP-150 as efficacious and potent MAO-A inhibitors. The best compound, SP-149, showed 10.42 ± 1.78 nmol/mg MAO-A inhibitory activity with -5.37 Kcal/mol binding energy.

Keywords: in silico, 1, 3-dioxol, drug design, monoamine oxidase, QSAR

INTRODUCTION

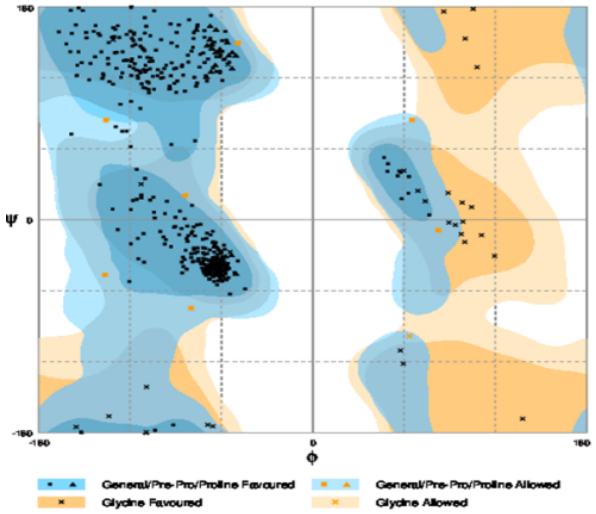
Monoamine oxidase (MAO) is a flavoenzyme containing iron which occurs within cells and bound to the membrane surface of mitochondria. MAO involved in the degradation of biogenic amines[1]. MAO-A and MAO-B are two subtypes of monoamine oxidase. MAO-A metabolizes serotonin and nor adrenaline and is inhibited by the low concentration of clorgyline whereas MAO-B acts on 2-phenylethylamine and benzylamine and is inhibited by selegiline and mofegiline[2]. MAO-A inhibitors are useful in the therapy of mental disorders as antidepressants and anxiety. Nitrogen-containing heterocyclic compounds are biologically important and the presence of structure diversity made them a striking target for synthesis by many scientists and researchers[3]. Many drugs as barbiturates, pesticides, benzodiazepines, diazepam possessing nitrogen heterocyclic are of synthetic origin. The structural subunit of these synthetic drugs is present in many natural drugs like quinine, emetine, papaverine, theobromine, etc. hence; these drugs are of more significance to life[4]. Synthesis of hydrazine derivatives originally was the starting era of MAO inhibitors which have been introduced as anti-tubercular agents. Iproniazid was the first modern antidepressant under this category[5]. Piperine an alkaloid from *Piper longum* L., *Piper nigrum* L also found to have nitrogen heterocyclic and display an ample spectrum of pharmacologic activities like antifungal[6], antimicrobial[7], anticancer[8], antidepressant[9], anti-inflammatory[10], antiasthmatic[11], anxiolytic[12], antiproliferative[13], trypanocidal[14], insecticidal[15], antileishmanial[16], antihyperlipidemic[17], antioxidant[18], analgesic[19] and UV protective agent[20] and as a bioenhancer[21]. The conjugate of natural and synthetic molecules emerged to a new approach towards the development of novel bioactive molecules. Drug discovery is the process of discovering and designing of drugs. The drug discovery process involves the identification of candidates, synthesis, characterization, screening and assays for therapeutic efficacy. The new in silico approach is being tried to understand how disease and infection are controlled the molecular and target specific entities based on this knowledge[22]. Therefore, in the present work, we applied computational methods for lead generation and lead optimization in the drug discovery process. Moreover, based on all literature and present study evidence including in silico studies, it might be suggested that piperine could be useful for the control of CNS related conditions. We have designed seventy novel 1, 3-dioxol analogues with the help of QSAR and docking studies and best compounds were synthesized on basis of their affinity towards selected proteins, 2BXR (MAO-A). We also investigated the MAO-A inhibitory activity of our synthesized compounds.

MATERIAL AND METHODS

Target Identification

The protein target sequences of monoamine oxidase A was retrieved from NCBI which is having Uniprot Id: P21397 with PDB code: 2BXR and saved in FASTA format. Templates for homology modelling were identified using BLAST [www.ncbi.nlm.nih.gov/blast/] where the sequence similarity was checked by Psi blast as shown in Table 1. Protein model was obtained by Phyre2 and analyzed using the Ramachandran plot. 2BXR modelled structure was found to have a number of residues in the favoured region is 98.4 %, a number of residues in the allowed region 1.6 % and a number of residues in outlier region 0.0 % (Plot 1). These results clearly indicate the quality of the predicted protein structure was perfect. The obtained model was validated with the help of PROCHECK. The presence of an active site at protein structure was predicted with Castp web server. The

active sites of 2BXR comprises of amino acid residues such as GLY66, GLY110, ALA111, ARG129, ILE131, ALA174, PHE177, ASN181, VAL182, THR211, TYR264, CYS266, ILE273, ARG284, LEU287, ASP328, GLU329, ASP330, ALA331, ARG356, TYR407, ARG421, ILE423, TYR444, VAL473.



Plot 1: Ramachandran plot of 2BXR

ADME Toxicity Prediction

The QSAR properties were carried out to optimize molecular descriptors for the synthesized compounds. The structural activity relationship of synthesized compounds significantly helps to understand pharmacokinetics to derive physicochemical properties and predict biological activity as absorption, distribution, metabolism, excretion and toxicity (ADMET). The AdmetSAR[23] tool helps to evaluate biologically active compounds and eliminate biologically inactive compounds by keeping Lipinski rule as a filter. The Lipinski rule of five was calculated by using mol inspiration programme (Table 2). Blood-brain barrier penetration (QPlogBB), aqueous solubility (PlogS), intestinal absorption (log HIA), Caco-2 cell permeability (QPPCaco), hepatotoxicity also helps to understand drug metabolism for the synthesized compounds[24] (Table 3).

Molecular Docking

Molecular docking studies of protein-ligand were carried out by using Auto Dock 4.2 and Auto Dock tools from the Scripps Research Institute. The Auto Dock helps to add hydrogen to polar hydrogen those are bounded to electronegative atoms like nitrogen and oxygen. The Gasteiger charges were spread across total residue of polar and non-polar hydrogen bonds. Gasteiger charges detection was computed within the active site of amino acids. The grid of size 60x60x60 from x, y and z-axis were created on the selected ligand. Molecular simulation parameter like the Lamarckian genetic algorithm of popular size 150, the mutation rate of 0.02 and crossover rate of 0.8, these simulations were performed up to 2.5 million energy and evaluation was maximum at 27000 generations. Each simulation was carried out 10 times resulted in 10 docked conformations. The conformation having the lowest energy was selected as the best binding conformation. The resulting analysis was done based on binding energy and hydrogen bonding interaction (Table 4). The reverse validation process was done at the end to ensure the identified hits that fitted with the selected target. All the designed compounds were drawn using Chem Draw Ultra 8.0.

Chemistry

On basis of computational results, designed ligands were synthesised with the help of scheme 1. Here, we were prepared 2-(1,3-benzodioxol-5-yl)-5-(benzylsulfonyl)-1,3,4-thiadiazole and 2-(1,3-benzodioxol-5-yl)-5-(benzylsulfinyl)-1,3,4-thiadiazole derivatives by condensation of the compound (1) with thiosemicarbazide refluxed in ethanol to get thiosemicarbazone (2), compound (3) was prepared by oxidative cyclization of (2). On diazotization of (3) in hydrochloric acid in the presence of copper powder gave compound (4). Then compound (4) with thiourea refluxed in presence of ethanol to afford 2-mercapto-1,3,4-thiadiazoles, (5). Further on the treatment of compound (5) with different benzyl chloride in presence of an ethanolic solution of NaOH gave (6) (SP-147). To a stirring mixture of (6) (1 mmol) in glacial acetic acid (3 ml) was added 3 ml of 30 % H_2O_2 and the mixture was stirred at 60ºC for 20 minutes. After cooling, water was added; the precipitate was filtered and re-crystallized from ethanol to get compounds (7) (SP-148 to SP-151). Then to a stirring mixture of 6 (1 mmol) in glacial acetic acid (3 ml) was added 30 % H_2O_2 (3 ml) and the mixture was stirred at 2-8 ºC for 48 hours. Water was then added and the precipitate was filtered and purified by column chromatography eluting with 5 % EtOH-$CHCl_3$ to get compounds (8) (SP-152 to SP-155),

TLC was performed to monitor the reactions and determine the purity of the products. The products were further purified using re-crystallization with suitable solvents. The synthesized compounds were characterized by melting point, IR, NMR, MASS spectral analysis. The melting points of the compounds were determined using Veego VMP-1 Apparatus expressed in °C and are uncorrected. The IR spectra of the compounds were recorded on FT-IR spectrometer (Perkin Elmer Infrared-283) using KBr pellet technique. ^{1}H NMR spectra were recorded on AV-III (400 MHz FT-NMR) using DMSO-d6 as solvent and TMS as an internal standard. The chemicals used for synthesis were that of analytical grade. Melting points were determined by the capillary method. The structural details of all the synthesized compounds are given in Table 4.

Spectral Data

2-(1,3-benzodioxol-5-yl)-5-[(2-methylbenzyl)sulfanyl]-1,3,4-thiadiazole,(SP147): IR(KBr, cm^{-1}): 1451 (N-N stretch), 1352 (C-N stretch), 1517 (S-C), 1255 (C-O), 1540, 1628 (C=N), 1810 (C=O stretch), 3010 (aromatic C=C stretch), 1249, 2920 (O-CH_2-O), 3425 (N-H stretch); H1 NMR (δ ppm, DMSO-d6): δ 2.21 (s, 3H, CH_3), 4.38 (s, 2H, CH_2), 6.09 (d, 2H, CH_2), 6.99-7.16 (dd, 5H, CH), 7.32 (dd, 1H, CH), 7.56 (dd, 1H, CH)

2-(1,3-benzodioxol-5-yl)-5-(benzylsulfonyl)-1,3,4-thiadiazole,(SP148): IR(KBr, cm^{-1}): 1451 (N-N stretch), 1352 (C-N stretch), 1517 (S-C), 1255 (C-O), 1540, 1628 (C=N), 1810 (C=O stretch), 1310, 1142 (S=O), 3010 (aromatic C=C stretch), 1249, 2920 (O-CH_2-O), 3425 (N-H stretch); H1 NMR (δ ppm, DMSO-d6): δ 4.93 (s, 2H, CH_2), 6.42 (s, 2H, CH_2), 7.16-7.35 (dd, 4H, CH), 7.37 (dddd, 2H, CH), 7.51 (dd, 1H, CH), 7.67 (dd, 1H, CH)

2-(1,3-benzodioxol-5-yl)-5-[(2-methylbenzyl)sulfonyl]-1,3,4-thiadiazole,(SP149): IR(KBr, cm^{-1}): 1452 (N-N stretch), 1352 (C-N stretch), 1517 (S-C), 1255 (C-O), 1540, 1628 (C=N), 1810 (C=O stretch), 1310, 1142 (S=O), 3010 (aromatic C=C stretch), 1249, 2920 (O-CH_2-O), 3425 (N-H stretch); H1 NMR (δ ppm, DMSO-d6): δ 2.23 (s, 3H, CH_3), 4.92 (s, 2H, CH_2), 6.42 (s, 2H, CH_2), 6.83 (dd, 1H, CH), 7.01-7.13 (dd, 3H, CH), 7.23 (dd, 1H, CH), 7.51 (dd, 1H, CH), 7.67 (dd, 1H, CH)

2-(1,3-benzodioxol-5-yl)-5-[(3-methylbenzyl)sulfonyl]-1,3,4-thiadiazole,(SP150): IR(KBr, cm^{-1}): 1452 (N-N stretch), 1352 (C-N stretch), 1517 (S-C), 1255 (C-O), 1540, 1628 (C=N), 1810 (C=O stretch), 1310, 1142 (S=O), 3010 (aromatic C=C stretch), 1249, 2920 (O-CH_2-O), 3425 (N-H stretch); H1 NMR (δ ppm, DMSO-d6): δ 2.25 (s, 3H, CH_3), 4.89 (s, 2H, CH_2), 6.42 (s, 2H, CH_2), 6.97-7.04 (dd, 2H, CH), 7.01-7.13 (dd, 3H, CH), 7.14-7.30 (dd, 3H, CH), 7.51 (dd, 1H, CH), 7.67 (dd, 1H, CH)

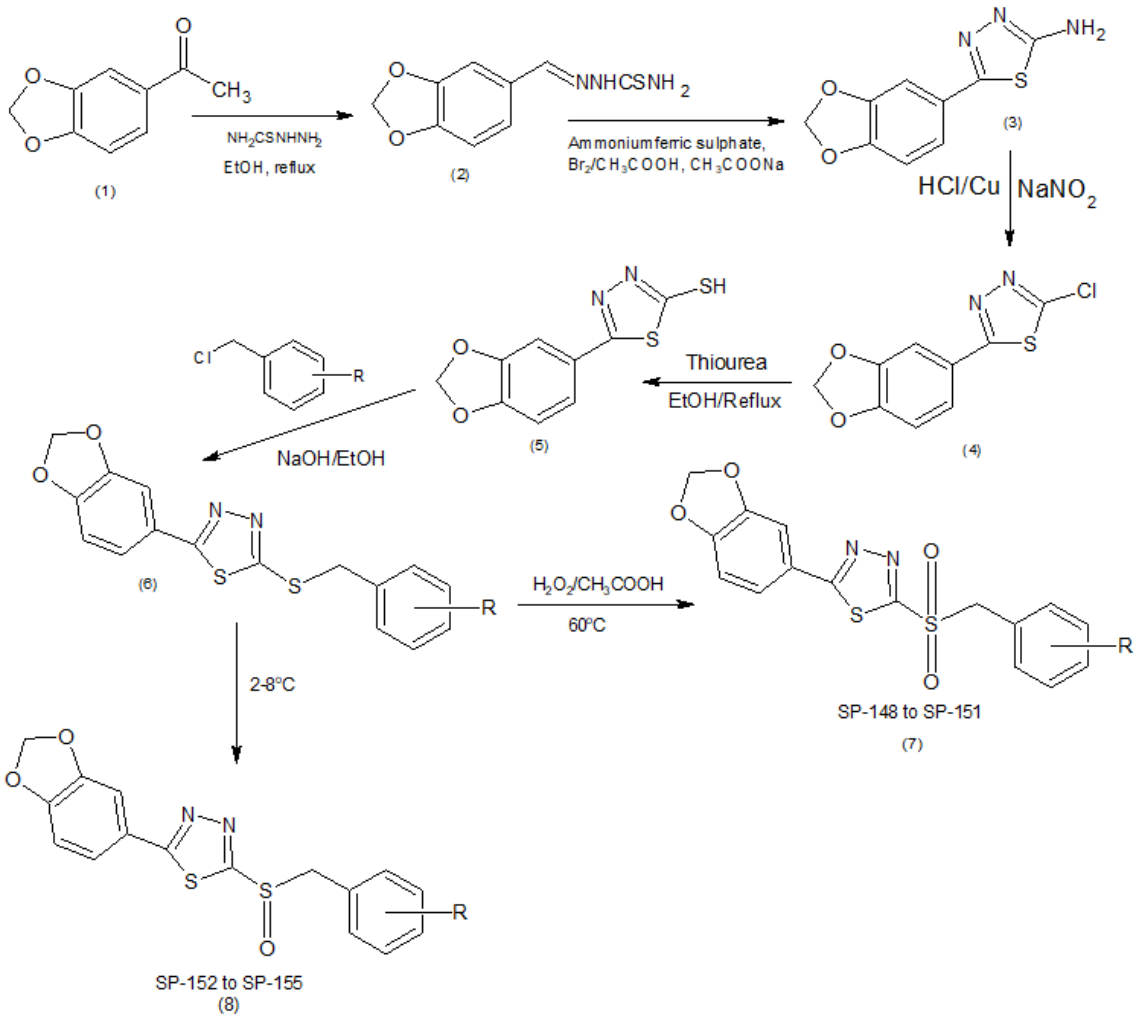
2-(1,3-benzodioxol-5-yl)-5-[(4-methylbenzyl)sulfonyl]-1,3,4-thiadiazole,(SP151): IR(KBr, cm^{-1}): 1451 (N-N stretch), 1350 (C-N stretch), 1518 (S-C), 1255 (C-O), 1540, 1629 (C=N), 1810 (C=O stretch), 1310, 1142 (S=O), 3011 (aromatic C=C stretch), 1249, 2920 (O-CH_2-O), 3425 (N-H stretch); H1 NMR (δ ppm, DMSO-d6): δ 2.26 (s, 3H, CH_3), 4.91 (s, 2H, CH_2), 6.42 (s, 2H, CH_2), 6.83 (dd, 2H, CH), 7.11 (ddd, 2H, CH), 7.23 (dd, 1H, CH), 7.51 (dd, 1H, CH), 7.67 (dd, 1H, CH)

2-(1,3-benzodioxol-5-yl)-5-(benzylsulfinyl)-1,3,4-thiadiazole,(SP152): IR(KBr, cm^{-1}): 1451 (N-N stretch), 1350 (C-N stretch), 1518 (S-C), 1255 (C-O), 1540, 1629 (C=N), 1810 (C=O stretch), 1052 (S=O), 3011 (aromatic C=C stretch), 1249, 2920 (O-CH_2-O), 3425 (N-H stretch); H1 NMR (δ ppm, DMSO-d6): δ 5.17 (s, 2H, CH_2), 6.23 (s, 2H, CH_2), 6.42 (s, 2H, CH_2), 6.83 (dd, 2H, CH), 7.09-7.18 (dd, 3H, CH), 7.21-7.30 (3H, ddd, CH), 7.45 (dd, 1H, CH), 7.62 (dd, 1H, CH)

2-(1,3-benzodioxol-5-yl)-5-[(2-methylbenzyl)sulfinyl]-1,3,4-thiadiazole,(SP153): IR(KBr, cm^{-1}): 1451 (N-N stretch), 1350 (C-N stretch), 1518 (S-C), 1255 (C-O), 1540, 1629 (C=N), 1810 (C=O stretch), 1052 (S=O), 3011 (aromatic C=C stretch), 1249, 2920 (O-CH_2-O), 3425 (N-H stretch); H1 NMR (δ ppm, DMSO-d6): δ 2.21 (s, 3H, CH_3), 5.16 (s, 2H, CH_2), 6.21-6.32 (d, 2H, CH), 7.06 (ddd, 1H, CH), 7.45 (dd, 1H, CH), 7.62 (dd, 1H, CH)

2-(1,3-benzodioxol-5-yl)-5-[(3-methylbenzyl)sulfinyl]-1,3,4-thiadiazole,(SP154): IR(KBr, cm^{-1}): 1451 (N-N stretch), 1350 (C-N stretch), 1518 (S-C), 1255 (C-O), 1540, 1629 (C=N), 1810 (C=O stretch), 1052 (S=O), 3011 (aromatic C=C stretch), 1249, 2920 (O-CH_2-O), 3425 (N-H stretch); H1 NMR (δ ppm, DMSO-d6): δ 2.21 (s, 3H, CH_3), 5.16 (s, 2H, CH_2), 6.21-6.32 (d, 2H, CH), 7.06 (ddd, 1H, CH), 7.45 (dd, 1H, CH), 7.62 (dd, 1H, CH)

2-(1,3-benzodioxol-5-yl)-5-[(4-methylbenzyl)sulfinyl]-1,3,4-thiadiazole,(SP155): IR(KBr, cm^{-1}): 1452 (N-N stretch), 1350 (C-N stretch), 1516 (S-C), 1254 (C-O), 1540, 1629 (C=N), 1810 (C=O stretch), 1053 (S=O), 3010 (aromatic C=C stretch), 1249, 2920 (O-CH_2-O), 3424 (N-H stretch); H1 NMR (δ ppm, DMSO-d6): δ 2.26 (s, 3H, CH_3), 5.16 (s, 2H, CH_2), 6.21-6.32 (d, 2H, CH), 7.06-7.16 (dd, 3H, CH), 7.20 (ddd, 2H, CH), 7.45 (dd, 1H, CH), 7.62 (dd, 1H, CH)



Scheme 1
R=H, 2-CH_3, 3-CH_3, 4-CH_3

Monoamine Oxidase Assay

The synthesized compounds tested to determine their activity toward MAO rat brain mitochondria were isolated. The inhibitory effects of compounds on MAO were determined using fluorimetric method[25]. The samples were diluted as needed in Assay Buffer according to concentration. Aliquot 25 µL of each sample into separate wells, 25 µL of enzyme added to the sample well and 50 µL of assay buffer to the wells. A sensitive fluorometric assay for serum monoamine oxidase with kynuramine as substrate was done. p-Tyramine, HRP enzyme and Dye reagent 1 µL each added to the sample well. The solution was mixed well using a horizontal shaker or by pipetting, and incubated at room temperature for 10 minutes. For Enzyme inhibitor, add 25 µL MAO enzyme, 25 µL Inhibitor and 1 µL of each p-Tyramine, HRP enzyme and Dye reagent to the well. For Standard enzyme, add 50 µL MAO enzyme, 50 µL Assay buffer and 1 µL of each p-Tyramine, HRP enzyme and Dye reagent to the well.

RESULT AND DISCUSSION

Various 1,3-dioxol derivatives were designed by using computational methods and synthesized to explore their monoamine oxidase A inhibitory activity. The QSAR properties of synthesized compounds were calculated to relate the structural descriptors with physicochemical properties and biological activities. The Lipinski rule of five was applied on selected molecules are molecular weight; logarithm of the octanol/water partition coefficient; topological polar surface area; the number of atoms; the number of hydrogen bond donors; the number of hydrogen bond acceptors; the number of rotatable bonds; molecular volume; the number of violations. Most of the synthesised compounds have shown "drug-like" character (log P ≤ 5, molecular weight ≤ 500, number of hydrogen bond acceptors ≤ 10 and number of hydrogen bond donor's ≤ 5), but the compound SP-147 showed one violation with its molecular weight. The compound with any molecular violation shows the problem with bioavailability. The quantitative structure-activity relationship was used to characterize the properties of each functionally derived compound with calculated molecular properties to understand the properties of inhibitors. The protein target with PDB id: 2BXR was selected for the molecular docking studies to study the interactions between protein and ligands. The docking results were calculated according to binding energy. The docking scores of all the ligands in complex with protein are shown in Table 4. The compound, 2-(1,3-benzodioxol-5-yl)-5-[(2-methylbenzyl)sulfonyl]-1,3,4-thiadiazole (SP-149) was found to be the best molecule among all other compounds in the series with binding energy -5.37 kcal/mol which is an evidence for its good monoamine oxidase A inhibitory activity of 10.42 ± 1.78 nmol/mg. Other compound, 2-(1,3-benzodioxol-5-yl)-5-[(3-methylbenzyl)sulfonyl]-1,3,4-thiadiazole (SP-154), showed -5.22 kcal/mol binding energy with 11.56 ± 2.22 nmol/mg inhibitory activity. These compounds interacted with selected protein with the formation of three hydrogen bonds.

Table 1: validation of selected protein

Target Protein	Template	Description	Total Score	Identity	E-Value	Sequence Coverage
MAO-A	2BXR	Chain A Human Monoamine Oxidase A complex with Clorgyline, crystal A form A	1098	100%	0.0	100%
	2Z5X	Chain A crystal structure of Human Oxidase A with Harmine	1070	97%	0.0	97%
	2Z5Y	Chain A crystal structure of Human Oxidase A (G110a) with Harmine	1068	97%	0.0	97%

Table 2: Pharmacokinetic properties for all ligands

Ligand	m Log P	TPSA	natoms	MW	nON	nOHNH	nvilations	nrotb	volume
Piperine	3.33	38.78	21	285.34	4	0	0	3	267.74
SP147	5.06	44.25	23	342.44	4	0	1	4	284.68
SP148	3.53	78.39	24	360.42	6	0	0	4	281.42
SP149	3.93	78.39	25	374.44	6	0	0	4	297.98
SP150	3.96	78.39	25	374.44	6	0	0	4	297.98
SP151	3.98	78.39	25	374.44	6	0	0	4	297.98
SP152	3.06	61.32	23	344.42	5	0	0	4	275.67
SP153	3.46	61.32	24	358.44	5	0	0	4	292.23
SP154	3.49	61.32	24	358.44	5	0	0	4	292.23
SP155	3.51	61.32	24	358.44	5	0	0	4	292.23

Log P = logarithm of the octanol/water partition coefficient; TPSA = topological polar surface area; nAtoms = number of atoms; MW = molecular weight; nON = number of hydrogen bond acceptors; nOHNH = number of hydrogen bond donors; nrotb = number of rotatable bonds; MV = molecular volume; n violations = number of violations of the Lipinski's rule of five.

Table 3: ADMET and pharmacological parameters prediction for ligands using admet SAR toolbox

Ligands	PlogBB	Log_{HIA}	PCaco	logpGI (substrate)	logpGI (non-inhibitor)	PlogS
Piperine	0.9921	0.9639	0.8147	0.9175	0.4563	-3.628
SP-147	0.9757	0.9547	0.5756	0.8436	0.5614	-4.024
SP-148	0.9734	0.9617	0.7326	0.9295	0.7120	-3.583
SP-149	0.9730	0.9725	0.5205	0.8961	0.5358	-3.651
SP-150	0.9734	0.9725	0.6199	0.8350	0.6656	-3.618
SP-151	0.9734	0.9725	0.6881	0.8921	0.5349	-3.586
SP-152	0.9735	0.9680	0.6000	0.9038	0.6544	-3.576
SP-153	0.9727	0.9777	0.5992	0.8599	0.4936	-3.668
SP-154	0.9734	0.9777	0.5077	0.8037	0.6302	-3.628
SP-155	0.9734	0.9777	0.5388	0.8585	0.4701	-3.593

Table 4: Molecular docking details of 2BXR in complex with designed 2-(1,3-benzodioxol-5-yl)-5-(benzylsulfonyl)-1,3,4-thiadiazole and 2-(1,3-benzodioxol-5-yl)-5-(benzylsulfinyl)-1,3,4-thiadiazole derivatives

S.No.	Compounds	Binding Energy with 2BXR (Kcal/mol)	Hydrogen bonds	Interacting amino acid
1	Piperine	-4.75	1	LYS280
2	SP-147	-5.05	1	GLY404
3	SP-148	-5.10	2	GLY404, MET300
4	SP-149	-5.37	3	LYS280, GLY404, MET300
5	SP-150	-5.22	3	GLY404, MET300, THR276
6	SP-151	-5.20	2	MET300, THR276
7	SP-152	-4.81	2	MET300, THR276
8	SP-153	-5.17	2	MET300, THR276
9	SP-154	-5.29	1	MET300
10	SP-155	-5.44	2	MET300, THR276
11	Clorgiline	-3.31	1	THR276
12	Mofegiline	-2.78	0	
13	Selegiline	-2.16	0	

Table 5: Data obtained from our studies

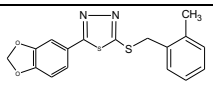
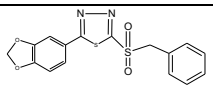
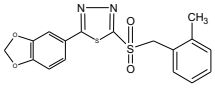
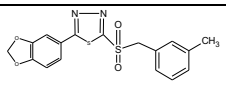
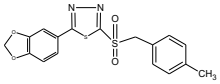
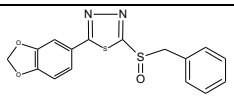
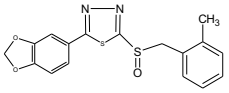
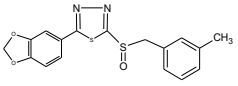
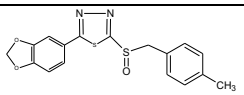
S.No.	Code	Structural	Molecular Formula	Melting Point	Yield
1.	SP-147		$C_{17}H_{14}N_2O_2S_2$	118^0C-119^0C	80%
2.	SP-148		$C_{16}H_{12}N_2O_4S_2$	126^0C -127^0C	78%
3.	SP-149		$C_{17}H_{14}N_2O_4S_2$	122^0C -123^0C	76%
4.	SP-150		$C_{17}H_{14}N_2O_4S_2$	123^0C -124^0C	77%
5.	SP-151		$C_{17}H_{14}N_2O_4S_2$	120^0C -121^0C	75%
6.	SP-152		$C_{16}H_{12}N_2O_3S_2$	113^0C -114^0C	80%
7.	SP-153		$C_{17}H_{14}N_2O_3S_2$	129^0C -130^0C	73%
8.	SP-154		$C_{17}H_{14}N_2O_3S_2$	130^0C -131^0C	73%
9.	SP-155		$C_{17}H_{14}N_2O_3S_2$	131^0C -132^0C	73%

Table 6: Monoamine Oxidase inhibitory activity of the synthesized compounds

S. No.	Compounds	MAO-A activity (nmol/mg)
1	Control	23.56 ± 2.22
2	SP-147	15.45 ± 1.36
3	SP-148	14.98 ±2.34
4	**SP-149**	**10.42 ± 1.78**
5	**SP-150**	**11.56 ± 2.22**
6	SP-151	12.27 ± 2.89
7	SP-152	18.96 ± 1.39
8	SP-153	17.80 ± 1.76
9	SP-154	14.76 ± 3.21
10	SP-155	17.45± 1.45
11	Clorgiline	14.83 ± 1.29

Molecular docking study of 2BXR in complex with designed 2-(1,3-benzodioxol-5-yl)-5-(benzylsulfonyl)-1,3,4-thiadiazole and 2-(1,3-benzodioxol-5-yl)-5-(benzylsulfinyl)-1,3,4-thiadiazole derivatives

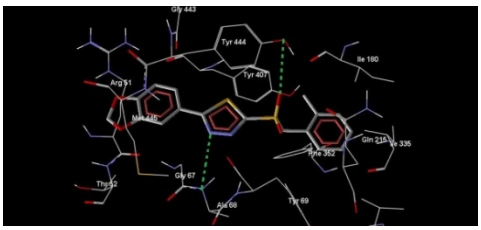


Figure 1: Docking pose of (SP-149)

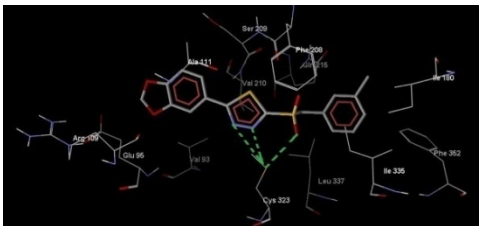


Figure 2: Docking pose of (SP-150)

CONCLUSION

In summary, the main objective of present work was to design, synthesize and biologically screening of designed derivatives as monoamine Oxidase A inhibitors. In silico predictions, QSAR, ADMET studies, pharmacophore mapping, target identification, target validation, active site predictions and docking studies were carried out. On the basis of our computational results, we have synthesized a novel series of 2-(1,3-benzodioxol-5-yl)-5-(benzylsulfonyl)-1,3,4-thiadiazole and 2-(1,3-benzodioxol-5-yl)-5-(benzylsulfinyl)-1,3,4-thiadiazole derivatives and explored them for monoamine oxidase A inhibitory activity. With the findings of our results, we have concluded that SP-149 and SP-150 are the best compounds in the series. These two compounds are benzylsulfonyl derivatives of 1,3-dioxol scaffold having a methyl group as a substitution on benzylsulfonyl ring system. The compound SP-149; having a methyl group on the second position of the ring system; whereas SP-150 having a methyl group on third position. As the compound SP-149 showed good binding affinity and significant monoamine oxidase A inhibitory activity, we concluded that ortho position methyl group which is an electron donating group makes this compound more potent than other compounds in the series.

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Cite this article as:

Sakshi Bhardwaj *et al*. Scaffold based designing of novel 1, 3-dioxol derivatives as monoamine oxidase inhibitor: In silico approach. Int. Res. J. Pharm. 2019; 10(5):150-156 http://dx.doi.org/10.7897/2230-8407.1005182

Source of support: Nil, Conflict of interest: None Declared