Original Article

Design And Synthesis Of 3-Arylcoumerin Derivatives As A Selective Mao-B Inhibitor

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Abstract

Background: According to WHO Parkinson's disease affects 1-2 people 1000 of the population. Parkinson's disease increases with age and affects 1% of the population 60 years above. Parkinson's disease is a long-term degenerative disorder of the central nervous system that mainly affects the motor system.

Objectives: The present work aimed to design and synthesize of 3-arylcoumarin derivatives which may be of better pharmacological activity with lesser adverse effects. MAO-B inhibitors are used for the treatment of Parkinson's disease. Due to lack of affinity and selectivity, most of the currently used MAO inhibitors, i.e., iproniazid and tranylcypromine show various side effects such as hepatotoxicity and cheese reaction. To minimize the side effect, we try to design with fewer side effects.

Methods: A novel series of 3-arylcoumarin derivatives, molecules 3-(3-(2-hydroxypropyl)phenyl)-6-methyl-2H-chromen-2-one were synthesized and evaluated for their antiparkinson activity. The structures of the compound have been confirmed by spectral analysis. The molecular docking study was performed for finding the binding affinity of the GABAA receptor to rationalize their antiparkinson activities qualitatively. A quantitative estimate of drug likeness was also performed which calculated the molecular properties and screened the molecules based on drug-likeness rules and one compound was synthesized.

Results: Compounds 3-(3-(2-hydroxypropyl)phenyl)-6-methyl-2H-chromen-2-one are synthesis and characterized by FTIR and ^{1}H NMR spectroscopy.

Keywords: 3-ARYLCOUMERIN, QSAR, Docking, PreADMET, Parkinson's disease, Ligand-based models, MAO-B inhibitors

INTRODUCTION

Identification of new chemical entities (NCEs) has the potential to become a clinical candidate to treat any disease with innovative ideas and increased productivity is a major challenge in the field of pharmaceuticals. A large number of drugs that are in clinical use either come from scientific analysis of folk medicine or examining the biological respaces of a natural/synthetic libraries of compounds or sometimes were discovered by chance [1]. The establishment

of new tools and techniques such as combinatorial chemistry, microwave-assisted organic synthesis, and high-throughput screening enhance the drug discovery process.The development of novel drug molecules from natural/synthetic sources, followed by identification, screening for biological activity, isolation/purification structure-activity relationships (SARs), ligand-receptor interaction analysis, and synthesis of analogs of derivatives[2].

The development of new drugs is a long process that usually takes more than a decade to turn an idea into a clinical product. In a meticulous investigation of about 10,000 NCEs, only 10 ideas reach the phase of clinical development. Indeed, the low success rate is evident from the fact that only a few NCEs reach to the market, despite the steady increase in R & D, The major challenge in drug discovery is not limited to the synthesis of drug-like molecules that only interact with the target receptor, but it associates with specific pharmacokinetic and toxicological properties [3]. The concept of developing rational drug design was introduced in the 1940s and 1950s by George Hitchings and Gertrude Elion. To design a potential drug-like molecule, it is of critical importance to analyze the existing drug molecules and their biological properties and establish their quantitative structure-activity relationship (QSAR) [4,5].

Among the various approaches to drug design, the idea of bioisosteric, adding a variety of substituents, and their evaluation using bioinformatics tools or concepts of ligand and structure-based computer-aided drug design (CADD) open a new avenue for designing NCEs. MAO-B shows affinity for different substrates and is involved in different pathology and conditions such as Alzheimer's disease and Parkinson's disease. The development of selective MAO inhibitors has led to significant contributions to the therapy of several neuropsychiatric and neurological disorders [6]. The selective MAO-B inhibitors exhibit antioxidant and antiapoptotic activity in experimental models, which may potentially translate into long-term clinical neuroprotective agents [7].

Ligand-based models are very effective in the design of new compounds with improved MAO inhibitory potential [8]. However, MAO inhibitors (MAOIs) are still underexplored in CADD to reduce the effort and time to get a better result. We believe that it is the current need to further explore and design novel, reversible and selective MAO-B inhibitors, conceivably with greater potency and safety throughligand-based drug design.[9]

MATERIALS AND METHODS

Synthesis of 3-(3-(2-hydroxypropyl)phenyl)-6-methyl-2H-chromen-2-one (1E): To a round bottom flask charged with2-hydroxy-5-methylbenzaldehyde (**i**) (1088 mg, 8.0 mmol) and 2-(3-(2-hydroxypropyl)phenyl)acetic acid (**ii**) (1940 mg, 10.0 mmol), was added dimethyl sulfoxide (15 mL) And N,N'-dicyclohexylcarbodiimide (2352 mg, 11.4 mmol), and the mixture was heated in an oil bath at 110 ◦C. The reaction progress was monitored by TLC, upon reaction completion (indicated by complete consumption of2-hydroxy-5-methylbenzaldehyde), the reaction mixture was poured on ice, and was added acetic acid (10 mL) and stirred for 2 h at room temperature. Then, the mixture was extracted with ethyl acetate (3 x 30 mL) and the combined organic phase was washed with sodium bicarbonate solution (5%, 50 mL) and then water (20 mL). The solvent was evaporated under vacuum, and the crude residue was purified by column chromatography using petroleum ether/ethyl acetate (5:1).

EXPERIMENTAL

QSAR Model Development

The statistical QSAR model was developed for compounds based on the 3-arylcoumerin core as a chromophore for MAO-B inhibitory activity. The biological activity data (IC_{50} in µM) was converted into negative logarithmic for QSAR analysis. The data set of the series consists of 23 compounds based on a 3-aryl coumarin chromophore. For the molecular structure generation, Chemoffice 2002 version 7.0 or ChemBioDraw Ultra 2014 version 14.0 were used and the calculation of descriptors was done using Chemoffice 7.0. For the statistical analysis of data and generation of the QSAR model, VALSTAT was used[13].

Selection of Series:

The first and most crucial thing required for the QSAR study is a selection of a series of compounds. A series of 23 compounds (shown in Figure 1) of 3-arylcoumerin derivativeswere selected based on the following criteria[14].

- The entire compounds in the series have the same central nucleus (i.e. 3-arylcomerin derivatives).
- All compounds in the series must have the same mechanism of mechanism of action (i.e. MAO-B inhibitor).
- No less than 15 compounds must be present (i.e., 23 compounds present in the selected series).
- The biological activity should be identified. Biological activity given in percentage could not be considered.
- The ratio of the highest and lowest biological activity was 490 (Since the series is considered much better as this ratio was closer to 1000).

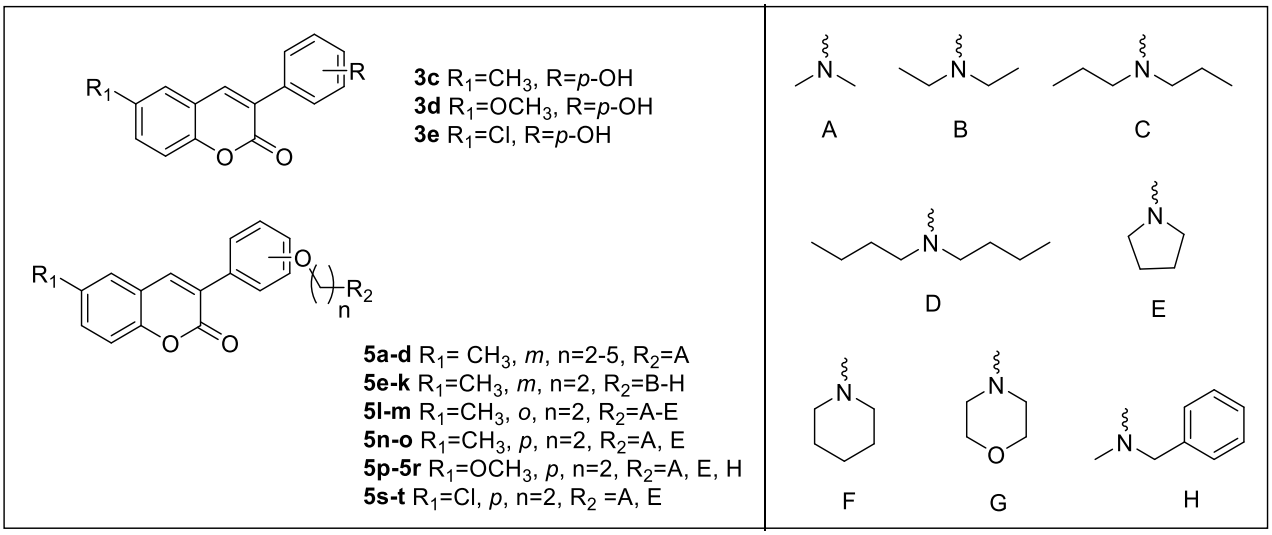


Figure 1. Selection of a series of 3-arylcoumerin derivatives

Basic ring for selection of compound moieties

The design and synthesis of 3-arylcoumarin derivatives (figure 2), which may be of better pharmacological activity with lesser adverse effects, were selected.

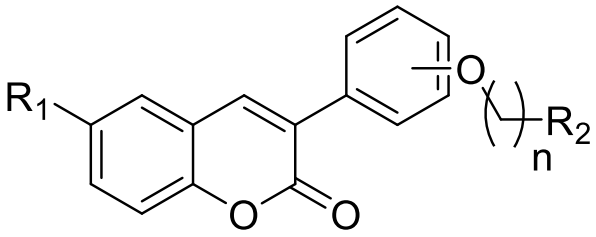


Figure 2. Basic nucleus 3-arylcoumarin

Table 1. 6-substituted 3-arylcoumerin derivatives and their IC_{50} values for human MAO-B

Compounds	**R_1**	**R_2**	**n**	**IC_{50} (µM)**
5a	CH_3	A	2	0.218 ± 0.011
5b	CH_3	A	3	0.905 ± 0.017

5c	CH_3	A	4	1.13 ± 0.04
5d	CH_3	A	5	9.87 ± 0.34
5e	CH_3	B	2	8.26 ± 0.28
5f	CH_3	C	2	10.4 ± 0.3
5g	CH_3	D	2	13.0 ± 0.5
5h	CH_3	E	2	6.75 ± 0.15
5i	CH_3	F	2	12.9 ± 0.4
5j	CH_3	G	2	3.17 ± 0.09
5k	CH_3	H	2	4.36 ± 0.12
5l	CH_3	A	2	31.1 ± 1.2
5m	CH_3	E	2	25.7 ± 0.8
5n	CH_3	A	2	0.743 ± 0.047
5o	CH_3	E	2	0.0635 ± 0.0024
5p	OCH_3	A	2	0.196 ± 0.012
5q	OCH_3	E	2	0.758 ± 0.035
5r	OCH_3	H	2	10.9 ± 1.1
5s	Cl	A	2	0.681 ± 0.082
5t	Cl	E	2	1.53 ± 0.10
3c*	CH_3	p-OH	-	0.364 ± 0.041
3d*	OCH_3	p-OH	-	0.942 ± 0.107
3e*	Cl	p-OH	-	1.26 ± 0.09
Selegiline**	-	-	-	27.8 ± 4.2
Clorgyline	-	-	-	82.0 ± 6.9

Iproniazid	-	-	-	8.12 ± 0.59

*These compounds have R Group instead of R2 **IC_{50} in Nanomolar (nM) Concentration

Data Set:

In QSAR analysis, the biological data must be accurate and precise to develop a meaningful model. The most critical aspect of the construction of the series is to warrant a great molecular diversity in this data set. The biological data used in this study was IC_{50} of a series of 3-aryl coumarin derivatives skeletons (shown in table 1) as an MAO-B inhibitor. The data were taken from the reported work of Kong et al. (2015). The biological activity data (IC_{50} in µM) was converted into negative logarithmic for QSAR analysis. The data set of the series consists of 23 compounds based on 3-aryl coumarin chromophore.[15-16]

Design of 3-arylcoumarin-Based Novel Molecules

More than 100 molecules were designed by basic molecules of 3-arylcoumarine ring. After designing all molecules; which are novel and designed by varying the different substitutions over the coumarin ring or substituted 3-aryl ring, they were subjected to 2D to 3D conversion and energy minimization using MM2 and MOPAC methods of Chemoffice 7.0.[17,18] The different kind of variations involves the lengthening of an alkyl chain or functional group alteration or change in the position of substituents. The functional groups were altered based on bio-isostere groups which have different steric or electronic properties. The descriptors which are involved in the developed QSAR model and modulate the pharmacological activity of this class of molecules (i.e., LogP, CMA, and PMI-Y) were calculated using the same software i.e. Chemoffice 7.0. and After the calculation of the desired physicochemical properties Log P, Principal momentum of Inertia – Y and Connolly Molecular Surface Area (CMA) of newly designed molecules the biological activity was predicted using the QSAR model developed [19-20]. After performing the QSAR study, a good statistical QSAR model was generated, which can be used to predict the activity of a new molecule of 3-arylcoumarin derivatives for MAO-B inhibition. Here we designed 127 novel molecules of 3-arylcoumarin derivatives as MAO-B inhibitors. Various substitutions have been made either on the 3-aryl side ring or in the coumarin core ring itself, and different kinds of substituted or nonsubstituted functional groups are placed to generate new molecules [21-25]

Docking with protein

The 47 molecules selected from the QSAR study were subjected to a molecular docking study using the Autodock module of PyRx software. Molecular docking analysis was performed for the set of 47 molecules based on 3-arylcoumarin chromophore as specific Monoamine oxidase (MAO) B inhibitors. For this, compounds were designed based on the available literature and first subjected to QSAR analysis, and 47 molecules/ligands were selected for molecular docking analysis and for viewing the molecular interaction.[26] The structure of the molecular target Mono Amino Oxidase B (MAO B) was retrieved from the PDB database (PDB ID: 4CRT). For comparative analysis, Selegiline, a well-known specific MAO B inhibitor, was taken as the standard [27-29]. The computational docking analysis was performed using PyRx AutoDock Vina option based on scoring functions. Chemoffice version 7.0 supplied by Cambridge software company, USA, was used for ligand preparation. The docking study was done by using PyRx which is a graphical user interface for AutoDock 4.2 and AutoDock Vina to perform virtual screening. It provides the binding affinity score and RMSD values for each ligand with different poses. In the present work, AutoDock Vina module was used to perform virtual screening. AutoDock Vina is a new open-source program for drug discovery, molecular docking, and virtual screening, offering multicore capability, high performance, enhanced accuracy, ease of use, and docked poses were analyzed by Discovery Studio 4.5 client.[30]

Steps Involved In Docking Study

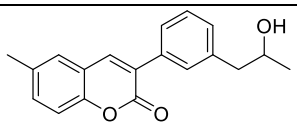
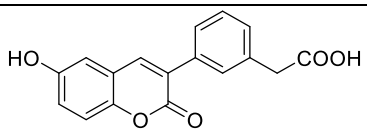
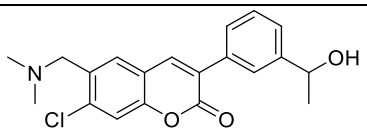
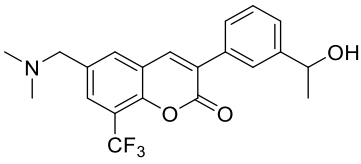
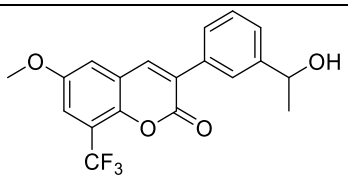
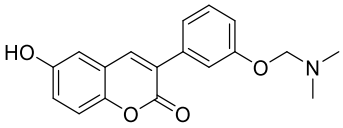
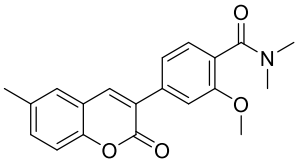
The molecular docking analysis involved the following four steps:

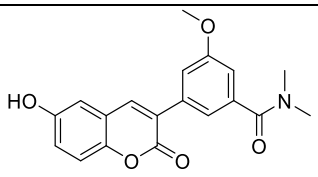
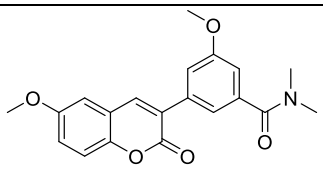
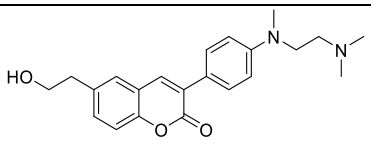
- Ligand preparations
- Protein Preparation
- Docking of ligands to the protein
- Visualization of ligand-protein interactions[31,32]

Pre-ADMET Study

In the drug discovery procedure, the analysis of the absorption, distribution, metabolism, and excretion (ADME), as well as toxicity (T) properties of drug candidates, are required to determine. Over 50% of the candidates failed due to ADME/Toxicity deficiencies during drug developments,drug predication is based on their Drug-likeness Prediction, Toxicity prediction, and ADME Prediction.[33-34]The selected ligands (**1E**, **1H**, **1L**, **1M**, **1N**, **2F**, **6F**, **7E**, **7F**, **7G** and **8A**) which are showing(shown in table 2) promising results in molecular docking study were considered for Pre-ADMET study using a web-based application called PreADMET.

Table 2.- Selected compounds after Pre-ADMET Study

CODE	STRUCTURE	IUPAC NAME
1E		3-[3-(2-Hydroxy-propyl)-phenyl]-6-methyl-chromen-2-one
1H		[3-(6-Hydroxy-2-oxo-2H-chromen-3-yl)-phenyl]-acetic acid
1L		7-Chloro-6-dimethylaminomethyl-3-[3-(1-hydroxy-ethyl)-phenyl]-chromen-2-one
1M		6-Dimethylaminomethyl-3-[3-(1-hydroxy-ethyl)-phenyl]-8-trifluoromethyl-chromen-2-one
1N		3-[3-(1-Hydroxy-ethyl)-phenyl]-6-methoxy-8-trifluoromethyl-chromen-2-one
2F		3-(3-Dimethylaminomethoxy-phenyl)-6-hydroxy-chromen-2-one
7E		2-Methoxy-N,N-dimethyl-4-(6-methyl-2-oxo-2H-chromen-3-yl)-benzamide

7F		3-(6-Hydroxy-2-oxo-2H-chromen-3-yl)-5-methoxy-N,N-dimethyl-benzamide
7G		3-Methoxy-5-(6-methoxy-2-oxo-2H-chromen-3-yl)-N,N-dimethyl-benzamide
8A		3-[4-{(2-Dimethylamino-ethyl)-methyl-amino}-phenyl]-6-(2-hydroxy-ethyl)-chromen-2-one

RESULTS AND DISCUSSION

QSAR Analysis and Designing of Novel Molecules

All the data set (23 molecules) were divided into two sets,first one training set having 17 molecules for generation of QSAR models and second test set having 6 molecules for validation of generated QSAR models. VALSTAT software was used to generate QSAR models by multiple linear regression analysis. The inter-correlation between the parameters was less than 0.5 which show inter-pair correlations among the selected descriptors are very low.Multiple linear regression analysis and other statistical analysis were carried out on all the compounds of the training set. The set of descriptors selected on the basis of intercorrelation coefficient below 0.5. For multiple linear regression analysis biological activity (-log IC_{50}) values were used as dependent variables and calculated parameters (descriptors) used as independent variables.Internal and external validation was performed to validate the QSAR model.For the validation of QSAR models, statistical external validation was used and the molecules were rationally divided into training and test set. The test set should represent a balanced number of both active and inactive compounds for uniform sampling of data, as shown in table 3.The test set molecules captured structural features of training set molecules, thus their activities could be well predicted the size of the training set was aimed to be about two-third of the whole set. Before the final model development outliers detected in the training set were moved to the test set. The size of final training set therefore became 17 compounds.The outputs of cross-validation are q^2 = cross- validated r^2. The initial regression analysis was performed on all the 17 molecules of training set which resulted in the regression model (Figure 3). The best model has the characters of large F, low P- value, r^2 andq^2 values close to 1, as well as $p<0.001$.

The best QSAR model obtained was: "**BA = [8.69492(± 0.594853)] +log P [-0.482112(± 0.110801)] +CMA [-0.0872747(± 0.0690698)] +PMI-Y [-3.69959e-005(± 8.58177e-006)]**" where, n = 17, r = 0.877032, r^2 = 0.769186, r^2_{adj} = 0.715921, variance = 0.130921, std = 0.36183, QF = 2.42388, PE = 0.0373205, F = 14.4408, FIT = 1.66624, LOF = 4.9187, AIC = 0.211488, standard F_{max} value at 95% confidence = 12.6871. This statistical QSAR model can explain that 77% of the total variance.

Table 3. Experimental and predicted biological activity of test set compounds

Compounds	Exp BA	Pred BA	Exp - Pred
3e	5.8996	6.1907	-0.2911
5d	5.0057	5.7683	-0.7626

5j	6.4989	6.1336	0.3654
5k	6.3605	5.9517	0.4088
5m	4.5901	5.1365	-0.5464
5o	7.1972	6.2865	0.9107

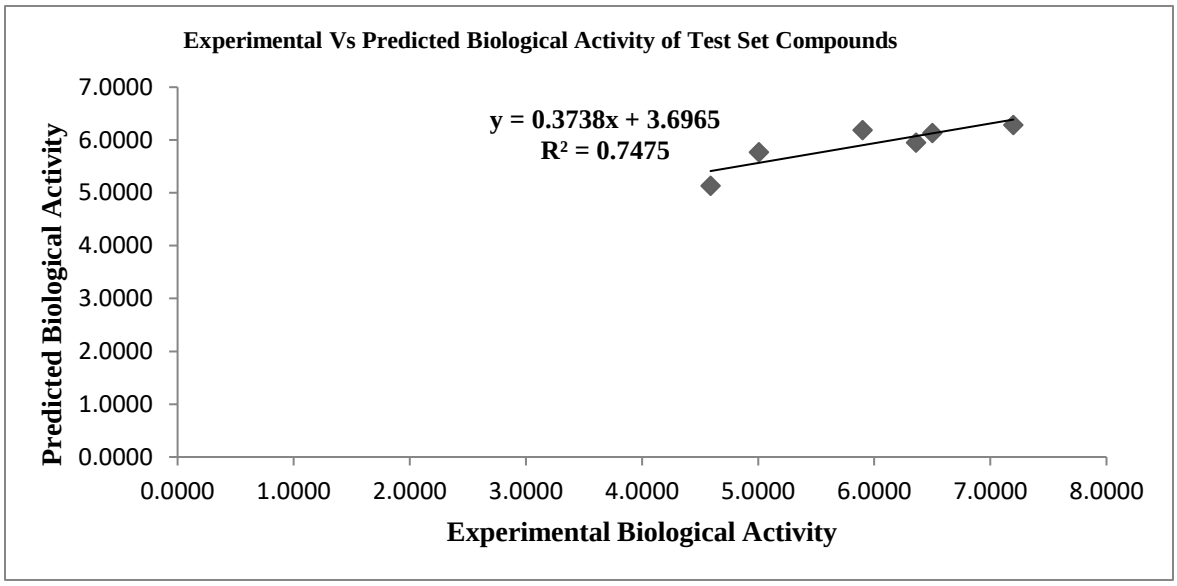


Figure 3. The plot of observed/experimental vs. predicted/calculated biological activity for test set molecules displays the actual activity against the activity predicted by a QSAR equation.

Among all 47 ligands/molecules which were docked, 11 hits were recognized as promising MAO-B inhibitors according to their docking scores (better than the standard ligands) and selected for further study of interaction and visualization. All 11 hit ligands showed an optimum binding affinity and stable complex with a molecular target MAO B with the lower binding energy. The study of molecular interactions and findings of different modifications in 3-arylcoumarin derivatives may produce more potent and specific MAO-B inhibitors to treat different CNS disorders including Parkinson's and Alzheimer with lesser side effects.

Table 4, Major interactions of ligands having good docking scores

		Major Interactions with 4CRT	
Ligands	**Scores**	**Electrostatic**	**Hydrophobic**

1E	-6.8	H-Bonding (LYS149); Pi-interaction (ALA325 LYS348)	ASP318, GLN16, ASN170 and THR177
1H	-6.5	H-Bonding (GLN163); Pi-interaction (ASP318 LYS348)	GLU176, LEU345, ASN170 and GLY319
1L	-6.5	Pi-interaction (GLU176 HIS347)	ASN145*, HIS178, GLU179, GLN409* and GLU141*
1M	-6.8	H-Bonding (THR166, LYS149 and ASN145*); Pi-interaction (LYS162)	GLN163, HIS178 and GLU141*
1N	-6.6	H-Bonding (THR166 LYS149); Pi-interaction (LYS162 THR166)	GLN163, ASP318, HIS347, GLU176, ASN145* and GLU141*
2F	-7.0	H-bonding (GLU176); Pi-interaction (LYS348 and ASP318)	ASN170, ALA346 and LEU345
6F	-6.7	H-Bonding (GLU176); Pi-interaction (ASP318)	ASN170, ALA346 and HIS347,
7E	-7.1	H-Bonding (ARG36* and ARG38*) Pi-interaction (ARG36*)	ASP37*, THE274, TYR393* and GLU391*
7F	-7.7	H-Bonding (GLU176 and THR166); Pi-interaction (ASP318)	LYS162, GLN163, ASN170, HIS347 and ALA346
7G	-6.9	H-Bonding (ASN145*, LYS149 and THR177); Pi-interaction (LYS348)	LAP318 and ALA325
8A	-6.5	H-Bonding (THE274, TYR395* and ASP37*); Pi-interaction (TYR395*)	ALA35*, HIS373 and GLU391*

*Amino acid residues belong to the B-chain of the protein while others belong to A-chain of proteins.The docking scores and results are (shown in Table 4), and ligands with the best docking score (free energy of ligand binding, ΔG binding, kcal/mol),and low value of RMSD were considered as "HIT" and selected for visualization. 2d and 3D ligand-protein interaction images(Figure 4).

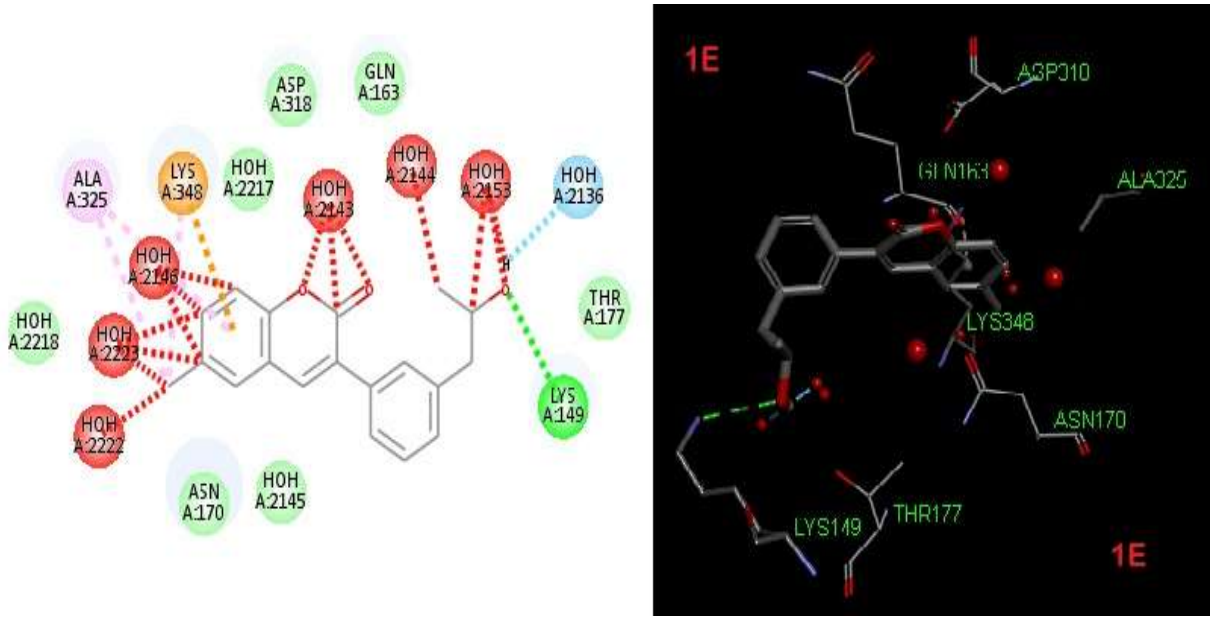


Figure 4. Ligand 1E **interaction with the target protein 4CRT**

Pre-ADMET Study

The pre-ADMET study is based on Lipinski's rule of five which helps to distinguish between drug-like and non-drug-like molecules. It helps in predicting the high probability of success of a molecule to become a drug candidate due to the drug-likeness rules applied to select the best molecules. Lipinski's rule of five comprises(shown in table 5)of the following considerations:

Table 5, Physicochemical parameters for good oral bioavailability of selected ligands

Ligands	**MW[#]**	**Log P**	**HBD[a]**	**HBA[b]**	**MR[##]**	**Lipinski's Violation**
1E	294.352	3.8736	1	3	87.0306	0
1H	296.281	2.4746	1	5	79.0024	0
1L	357.838	3.6072	2	3	100.582	0
1M	391.392	3.9701	2	3	101.751	0
1N	364.323	3.9015	1	4	89.6717	0
6F	365.431	3.5792	2	4	102.391	0
7E	337.377	3.1014	0	5	95.8791	0
7F	339.35	2.2248	1	6	92.532	0
7G	353.377	2.4879	0	6	97.3011	0
8A	366.462	3.3526	2	4	110.019	0
2F	311.339	3.1227	2	4	86.9866	0

[a]No of hydrogen bond donor; [b]No of hydrogen bond acceptor; [#]Molecular Weight; [##] Molar Refractivity; *Standard

Along with the pharmacokinetic properties prediction, some of the pharmacological parameters were also considered during the study to predict the toxicological profile of the molecules(shown in table 6). The various toxicological parameters included AMES, Mutagenicity, Carcino_Mouse, Carcino_Rat, and hER_inhibition; the results of toxicological parameters.

Table 6 predicts ADME profiles of selected ligands

Ligands	BBB score	Human intestinal absorption level	Aq. Solubility (mg/L)	Caco-2 cell[d] permeability assay	CYP2D6 inhibition	Plasma protein binding
1E	0.866458	95.79851	10.5444	28.9688	No	91.33218
1H	0.011778	96.12655	226.387	21.1139	No	88.778655
1L	0.658081	96.32616	9.14311	33.9277	Inhibitor	74.566162
1M	0.946511	95.99328	15.3882	26.6448	No	86.883879
1N	0.449337	95.79355	5.11262	22.8833	No	90.091182
6F	0.317336	95.94977	31.1474	45.4093	No	82.975271
7E	0.056103	97.68984	12.8636	33.7675	No	90.035704
7F	0.014241	96.58615	99.2485	16.9591	No	81.363275
7G	0.018908	98.34778	23.4425	33.5308	No	81.550056
8A	0.131961	96.1164	163.446	37.5216	Inhibitor	53.058071
2F	0.025119	94.19112	160.55	19.8988	Inhibitor	43.660251

[d] Caco2-cell - heterogeneous human epithelial colorectal adenocarcinoma cell line

Table 7 Toxicity profiles of selected ligands

Ligand Code	AMES Mutagenicity	Carcino_Mouse	Carcino_Rat	hERG_inhibition
1E	Non-Mutagen	Negative	Negative	Medium-risk
1H	Mutagen	Positive	Negative	Medium-risk
1L	Non-Mutagen	Negative	Negative	Medium-risk
1M	Non-Mutagen	Negative	Negative	Medium-risk
1N	Non-Mutagen	Positive	Negative	Medium-risk
6F	Mutagen	Negative	Negative	Medium-risk
7E	Mutagen	Negative	Positive	Medium-risk
7F	Mutagen	Negative	Positive	Medium-risk
7G	Mutagen	Negative	Positive	Medium-risk
8A	Non-Mutagen	Negative	Negative	Medium-risk
2F	Non-Mutagen	Negative	Negative	Medium-risk

Although all ligands considered for Pre-ADMET study obeyed the Lipinski's rule of five and doesn't show any Lipinski's violation of drug-likeness study. Ligands **1E**, **1M**, **1N,** and **6F** were showing the best pharmacokinetics profile out of all these 4 ligands, **1E** and **1M** also have a good non-toxicological profile(shown in table 7) and while **1N** was carcinogenic to the mouse and **6F** was a mutagenic molecule.

Synthesis of One of Selected Molecule "1E":

To evaluate the efficacy and biological potency, the molecule shows the most promising results in the different computational analysis (QSAR Analysis, Molecular Docking Analysis, and ADMET Prediction) was finally attempted

for its synthesis(Figure 5) using the previously reported strategy. In consequence, the molecule 3-(3-(2-hydroxypropyl)phenyl)-6-methyl-2H-chromen-2-one (**1E**) was prepared by a cyclization reaction between 2-hydroxy-5-methyl benzaldehyde (**i**) and 2-(3-(2-hydroxypropyl)phenyl)acetic acid (**ii**) using N,N'-dicyclohexyldicarbodiimide (DCC) as coupling agent and dimethylsulphoxide (DMSO) as solvent at 110 ◦C.

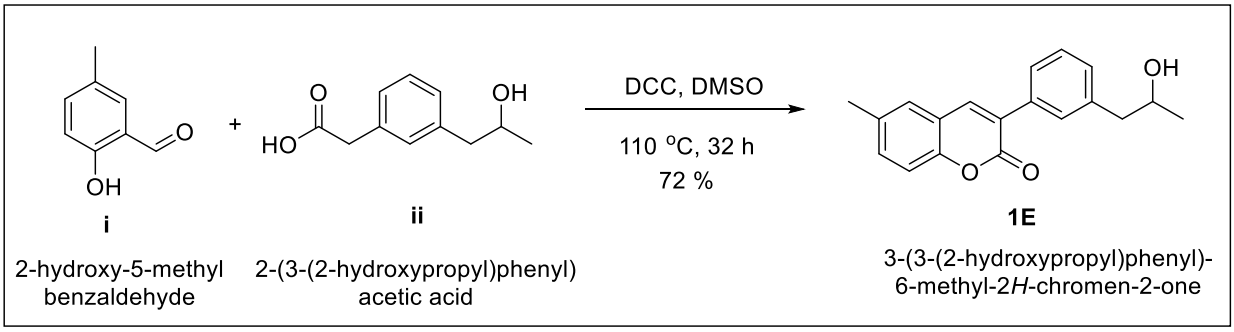


Figure 5. Synthetic scheme of the designed molecule **1E**

The reaction progress was monitored by TLC and the reaction was completed in 32 h. The compound **1E** was isolated as a white crystalline solid with a yield of 72%. The synthesized compound **1E** was characterized by using physical parameters (white solid crystal, m. p. 210 ◦C) and spectroscopic techniques (FTIR and ^{1}H NMR).(shown in table 8)

Table 8. Peaks were observed in the FTIR spectrum of the synthesized compound

Peaks	**Functional Group**
3435 cm^{-1}	-OH Stretching
2969 cm^{-1}	-Aromatic C-H Stretching
2921 cm^{-1}	-Alkyl C-H Stretching
1670 cm^{-1}	-C=O Stretching
1584 cm^{-1}	-C=C Stretching
1462 cm^{-1}	-C-H Bending
1368 cm^{-1}	-O-H Bending
1234 cm^{-1}	-C-O Aromatic Stretching
1009 cm^{-1}	-C-O Aliphatic Alcohol Stretching
678 cm^{-1}	-O-H Bending (Out of Plane)
786 cm^{-1}	-C-H Bending (Out of Plane)

The 1H NMR spectrums also shows presence of following desired peaks: 1H NMR (200 MHz, DMSO): δ 1.01-1.03 (d, J = 6.2 Hz, 3H); 1.81 (s, 1H); 2.32 (s, 3H); 2.72-2.74 (d, J = 2.7 Hz, 2H); 3.91-3.99 (q, J = 6.2, 2.7 Hz, 1H); 7.20-7.22 (d, J = 4.0 Hz, 3H); 7.39-7.42 (d, J = 6.0 Hz, 2H); 7.76-7.98 (q, J = 4.0 Hz, 3H).

CONCLUSION

A new series of 3-arylcoumarin derivatives has been designed, synthesis of one selected compound by the computational study of derivatives as MAO-B inhibitors. A series of 23 compounds based on 3-arylcoumerin derivatives were selected for the 2D-QSAR study. The QSAR model was generated using ChemOffice 2002 and VALSTAT 6.0. The model was validated based on various statistical parameters and it significantly predicted the biological activity of compounds from the "Test set" and "Training set". The reported experimental IC_{50} value was used as the biological data set in the QSAR model development. A total of 127 new molecules were designed by

varying the different substituents on 3-arylcoumarin scaffolds. All designed molecules were subjected to molecular descriptor calculations which were involved in the QSAR model generated (LogP, CMA, and PMI-Y), followed by the prediction of biological activity for each of them. Out of a total of 127 designed molecules; 47 molecules have comparable predicted biological activity even better than the compounds that are already reported for some of the ligands. All those 47 molecules which are having better predicted biological activity were further subjected to the molecular docking analysis along with one of the standard ligands (selegiline) using the AutoDock module of PyRx software to see their bonding efficacy and interaction with the target protein i. e. MAO-B (PDB ID 4CRT). Out of all 47 ligands which were docked, a total of 11 ligands showed good electrostatic and hydrophobic interaction with the active site residues of MAO-B protein (4CRT) and they have a better docking score in comparison to the standard ligand docked (selegiline). Furthermore, PreADMET study was performed for all 11 ligands which were having promising results in docking analysis using the online web-based application Pre-ADMET. PreADMET study directly correlated the pharmacokinetic and toxicological characteristics of molecules. Out of the 11 ligands considered for the Pre-ADMET study, ligand "**1E** and **1M**" were showing the best pharmacokinetic profile including BBB crossing capability and it shows negative results in terms of toxicity to the rat and mouse. Based on this predicated, ligand **1E** was synthesized in good yield using the previously reported cyclization reaction between substituted benzaldehyde and phenylacetic acid and characterized by FTIR and ^{1}H NMR spectroscopy. Pharmacological activity can be performed on this synthesized compound in the coming future.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No animals/humans were used for studies that are basis of this research.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The data supporting the findings of the article is available within the article.

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CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

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REFERENCES

1. Povl, KL; Tommy, L; and Ulfa, H; "Text Book of Drug Design and Discovery", Taylor and Franchis, New York, **2004**, pp. 16-20.
2. John Smith, H; "Introduction to the Principles of Drug Design and Action" 4th edition, CRC Press, New York, **2006**, pp. 78-80.
3. Eggenweile, H. M; Int. J. Immunopharmacol. **1985**, 7, 655-660.
4. Tipton, K F; "Enzymology of monoamine oxidase" Cell. Biochem. Funct., **1986**, 4, 79-87.
5. Rang, HP; Dale, MM; Ritter, J M; Flower, RJ; Pharmacology; Churchill Vingstone Elsevier, London, **2008**, pp 174.
6. Bortolato, M; Chen, K; Shih, JC; "Monoamine oxidase inactivation: from pathophysiology to therapeutics" Adv. Drug Deliv. Rev.**2008**, 60, 1527-1533.

7. Tabakman, R; Lecht, S; Lazarovici, P; "Neuroprotection by monoamine oxidase B inhibitors: A therapeutic strategy for Parkinson's disease" Bioessays. **2004**, 26, 80-90.
8. Lu, YY; Zhu, Q; "A novel fluorogenic probe for monoamine oxidase assays" Chin. Chem. Lett. **2008**, 19, 947-950.
9. Youdim, MBH; Edmondson, D; Tipton KF; "The therapeutic potential of monoamine oxidase inhibitors" Nat Rev Neurosci.**2006**, 7, 295–309.
10. Shih, JC; Chen, K; Ridd, MJ; "Monoamine oxidase: From genes to behaviour" Annu Rev Neurosci.**1999**, 22, 197–217.
11. Edmondson, DE; Mattevi, A; Binda, C; Li, M; Hubalek, F; "Structure and mechanism of monoamine oxidase" Curr Med Chem. **2004**, 11, 1983-1993.
12. Johnston, JP; "Some observations upon a new inhibitor of monoamine oxidase in brain tissue" Biochem. Pharmacol. **1968**, 17, 1285-1287.
13. Sliwoski, G; "Computational Methods in Drug Discovery" Pharmacol Rev. **2014,** 66, 334–395
14. Rarey M; Kramer B; Lengauer T; Klebe G; "A fast flexible docking methods using an incremental construction algorithm" J. Mol. Biol. **1996,**261, 470-489.
15. Colibus L, De; Li, M; Binda, C; Lustig, A; Edmondson, DE; Mattevi, A; "Three-dimensional structure of human monoamine oxidase A (MAO A): relation to the structures of rat MAO-A and human MAO-B" Proc. Natl. Acad. Sci. U.S.A., **2005**, 102, 12684-12689.
16. Zhi-Min Wang; Xue-Mei Li; Gui-Min Xue; Wei Xu; Xiao-Bing Wang; Ling-Yi Kong; "Synthesis and evaluation of 6-substituted 3-arylcoumarin derivatives as multifunctional acetylcholinesterase/monoamine oxidase B dual inhibitors for the treatment of Alzheimer's disease" RSC Adv. **2015**, 5, 104122-104137
17. Cohen N; "Guidebook on Molecular Modeling in Drug Design" San Drego, CA : Academic Press; **1996**
18. Schneider G; Bohm H J; "Virtual screening and fast automated docking methods" Drug Discov. Today, **2002**, 7, 64-70.
19. Hansch C; "A quantitative approach to biochemical structure activity relationships" Acc. Chem. Res.**1969**, 2, 232-236.
20. Leach AR; "Molecular Modelling: Principles and Applications" 2nd ed. Boston: Addison Wesley Longman, Harlow; **1996**
21. Petzer A; Grobler P; Jacobus J; Jacobus P Petzer; "Inhibition of monoamine oxidase by selected phenylalkylcaffeine analogues" Journal of Pharmacy and Pharmacology, **2013**, DOI: 10.1111/jphp.12193.
22. Kong, YK; Pan, FL; Wang, BX; Xie, SS; "Multitarget-directed resveratrol derivatives: anticholinesterases, anti-β-amyloid aggregation and monoamine oxidase inhibition properties against Alzheimer's disease" Med. Chem.Commun.**2014,** 5, 609-616.
23. Logoabe, JL; Petzer, A; Petzer, PJ; "The synthesis and evaluation of C-7-substituted α-tetralone derivatives as inhibitors of monoamine oxidase" **2014,** DOI: 10.1111/cbdd.12508.
24. Jayprakash, V; Monda, KS; Sinha, NB; Ucar, G; Badavath, NV; "Monoaminoe oxidase inhibitory activity of novel pyarazoline analogues: curcumin based design and synthesis" biological chemistry and chemical biology, **2016,** 1, 5879-5884.
25. Joubert, J; Foka, BG; Repsold, PB; Oliver, WD; Kapp, E; Malan, FS; "Synthesis and evalution of 7-substituted coumarine derivative as multimodal monoamine oxidase-B and cholinesterase inhibitor for the treatment of Alzherimer's dieases" Eur. J. Med. Chem., **2016,** DOI: 10.1016/j.ejmech.2016.09.041.
26. De Colibus L; Li M; Binda C; Lustig A; Edmondson DE; Mattevi A; "Three-dimensional structure of human monoamine oxidase A (MAO-A): relation to the structures of rat MAO A and human MAO B"PNAS**2005**, 102, 12684-12689
27. Tabakman, R; Lecht, S; Lazarovici, P; "Neuroprotection by monoamine oxidase B inhibitors: A therapeutic strategy for Parkinson's disease?" Bioessays. **2004**, 26, 80-90.
28. deMarcaida, JA; Schwid, SR; White, WB; Blindauer, K; Fahn, S; Kieburtz, K; Stern, M; Shoulson, I; "Parkinson Study: Effects of tyramine administration in Parkinson's disease patients treated with selective MAO-B inhibitor rasagiline" Mov. Disord. **2006**, 21, 1716-1721.
29. Finberg, JP; Gillman, K; "Selective inhibitors of monoamine oxidase type B and the cheese effect" Int. Rev. Neurobiol. **2011**, 100, 169-90
30. Morris GM; Goodsell DS;, Huey R;, Olson AJ; "Distributed automated docking of flexible ligands to proteins: parallel applications of AutoDock2.4" J. Comput. Aided. Mol Des. **1996,**10, 293 – 304
31. Edmondson, DE; Mattevi, A; Binda, C; Li, M; Hubalek, F; "Structure and mechanism of monoamine oxidase" Curr Med Chem. **2004**, 11, 1983-1993.
32. Johnston, JP; "Some observations upon a new inhibitor of monoamine oxidase in brain tissue" Biochem. Pharmacol. **1968**, 17, 1285-1287
33. Hong Wan; "what ADME test should be conducted for pre-clinical study" ADMET and DMPK, **2013**, 1, 19-28
34. Syed Mobasher Ali Abid; Sana Aslam; Sumera Zaib; Syeda Mahwish Bakht; Matloob Ahmad; Muhammad Makshoof Athar; John M Gardinar; Jamshed Iqbal; "Pyrazolobenzothiazine based carbothioamide as new structural leads for the inhibition of mono amino oxidase: design, synthesis, in-vitro bioevaluation and molecular docking" Med. Chem. Comm. **2017**, DOI: 10.1039/C6MD00570E.