



Research Article

Virtual Screening and Pharmacokinetic Studies of Potential MAO-B Inhibitors from Traditional Chinese Medicine

Babatomiwa Kikiowo^{1*}, Joseph A. Ogunleye², Damilohun S. Metibemu¹, Olaposi I. Omotuyi¹, Niyi S. Adelakun¹

¹Department of Biochemistry, Adekunle Ajasin University, Akungba-Akoko, Ondo State, Nigeria.

²BIOTRUST Scientific, Nigeria

*Corresponding author. E-mail: 45719155fa@aaua.edu.ng (B Kikiowo)

ARTICLE INFO:

Article History:

Received: 22/03/2020
Revised: 10/04/2020
Accepted: 09/05/2020
Available Online: 21/05/2020

Keywords:

MAO-B; Molecular docking; Parkinson's disease; QPLD; Rule of Five; SwissADME; TCM compounds

Copyright: © 2020 Kikiowo B et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License [CC BY 4.0](https://creativecommons.org/licenses/by/4.0/).

Citation: Kikiowo B, Ogunleye JA, Metibemu DS, Omotuyi OI, Adelakun NS. Virtual Screening and Pharmacokinetic Studies of Potential MAO-B Inhibitors from Traditional Chinese Medicine. Journal of Biological Engineering Research and Review. 2020, 7(1), 08-15

Abstract: Parkinson's disease (PD) is a chronic neurological disorder of the nervous system, initiated by lessened production of dopamine (DA) in the substantia nigra, it affects circa 50 percent more men than women. Theories reveal that age, genetic and environmental factors are involved in PD etiology but age seems to be the most prominent risk factor. Monoamine oxidase B (MAO-B) play prominent role in the oxidative deamination of DA in the striatum. Inhibition of MAO-B in the brain may decrease the exhaustion of DA stores and increase endogenous DA level. Glide-XP docking, Quantum-mechanics Polarized Ligand Docking (QPLD), pharmacokinetic studies and biological activity prediction studies were utilized to explain the binding mode, molecular interaction, inhibitory potential and pharmacokinetic properties of Traditional Chinese Medicine (TCM) compounds on MAO-B and compared to standard drugs used for treatment of PD, selegiline and rasagiline. Molecular docking results showed Rutaecarpine and Chrysophanol to have relatively better inhibitory activities than selegiline and rasagiline. Pharmacokinetic studies revealed that Rutaecarpine and Chrysophanol show comparative result with selegiline and rasagiline. Also, Rutaecarpine and Chrysophanol PASS prediction for their monoamine inhibitory activity showed greater P_a than P_i value. Our results have shown that Rutaecarpine and Chrysophanol can be a better therapeutic candidate in the treatment of PD.

Introduction

Parkinson's disease (PD) is the second most common neurological disease in the world, it was initially coined by Dr. James Parkinson as a "shaking palsy" in year 1817 [1]. PD is a chronic and persistent neurological disorder of the nervous system, initiated by lessened production of dopamine (DA) in the substantia nigra that results in the cardinal motor and non-motor symptoms of PD [2]. The cardinal motor symptoms include postural instability, bradykinesia, rigidity, and resting tremor. Examples of non-motor symptoms are sleep disturbance, depression and diminished sense of smell. PD affects circa 50 percent more men than women [3]. Theories reveal that age, genetic and environmental factors are involved in PD etiology [4]. Age seems to be the most prominent risk factor in the development of PD, it usually begins at around age 60, although it can start before this age. Approximately 5 to 10 percent of people suffering from PD have "early onset" disease which begins before age of 50. Early onset forms of PD can be inherited or caused by mutations in some specific genes [3].

Monoamine oxidase B (MAO-B) is a flavoenzyme that play prominent role in the oxidative deamination of DA in the striatum. Inhibition of MAO-B in the brain may

decrease the exhaustion of DA stores and increase endogenous DA level, as well as DA produced from exogenously administered levodopa [5]. Also, MAO-B inhibitors may also possess antiparkinsonian effect by reducing the production of prospective harmful byproducts of dopamine catabolism in the brain [6]. There are two most commonly used MAO-B inhibitors in the treatment of PD, which are selegiline and rasagiline. They are selective and irreversible inhibitor of MAO-B [7]. Each has its own side effects, selegiline may cause cardiovascular side effects, dizziness, nausea, hallucinations, confusion, insomnia and orthostatic hypotension [8, 9, 10]. Rasagiline may cause vomiting, rash, anxiety, nausea, sleepiness, hallucinations, impaired liver function, hypertension, orthostatic hypotension, malaise, syncope, dizziness, weight loss and headache [11, 12]. Hence, it is essential to develop a novel, more effective and selective inhibitors of MAO-B.

Contemporary method to develop new therapeutic leads for receptors is computer aided drug design (CADD) method, which is a time saving, cost-effective, rapid and automatic process [13]. Molecular docking study is very important in numerous applications of CADD, it predicts the preferred position of ligands or small molecule compounds (SMCs) inside the catalytic site of their respective target protein [14]. It is mostly used to identify different binding

modes and bio-affinities of small molecules in an enzyme active site, in order to find the best fit at the active site. At present, it has been widely used to virtual screening for the optimization of small molecules. Therefore, the current study uses Glide (Grid-base Ligand Docking with Energetics) docking and Quantum-mechanics Polarized Ligand Docking (QPLD) to determine the interaction between SMCs from TCM and MAO-B. Using TCM computational resources, several novel lead compounds with application potential have been successfully discovered for different diseases [15]. In addition, prediction of pharmacokinetic properties and Biological activity spectrum (BAS) was employed to calculate the effects of these compounds on human body.

Methodology

Protein preparation

The three-dimensional crystal structure of MAO-B (Figure 1) was downloaded from protein data bank (PDB), with PDB id: 4A7A and prepared for calculations using the protein preparation wizard of Schrödinger Maestro 11.5 [14]. Tautomeric states of heteroatom groups were generated at a pH of 7.0 ± 2 using Epik, then optimized at neutral pH. Via OPLS3 force field, restrained minimization was completed by setting heavy atom root mean square deviation to 0.30\AA .

Ligand preparation

The first 2,000 SMCs downloaded from TCM Database [16] were prepared using LigPrep of Schrödinger Maestro 11.5 via OPLS3 force field. All possible ionization states were generated at pH 7.0 ± 2.0 using Epik. Up to 32 possible stereoisomers per ligand were retained.

Molecular docking procedure

Using Glide in Schrödinger Maestro 11.5, the prepared compounds were docked into the active site of MAO-B as defined by receptor grid generation tool in Schrödinger Maestro 11.5. The three docking precision options of Glide tool were used videlicet, High throughput virtual screening (HTVS), Standard precision (SP) and Extra precision (XP) docking, respectively. The van der Waals (vdW) radius scaling factor as well as partial charge cut-off was chosen to be at 0.80 and 0.15, respectively for ligand atoms.

Ultimately, QPLD which incorporates Quantum Mechanics/Molecular Mechanics (QM/MM) calculations to replace fixed atomic charges of force fields with quantum mechanically recalculated ones at a given docking pose was performed by the Schrödinger QPLD protocol [17] to determine the accurate electronic charges of only the top

two hit compounds and standard compounds (Selegiline and Rasagiline) due to large numbers of ligands. Calculations of QM charges were carried out by using the 6-31G*/LACVP* basis sets and B3LYP for density functional theory calculation while Glide was done by selecting XP precision for both Initial docking and redocking steps, generating maximum of 10 poses per ligand while poses are ranked using Glide score quantity. QPLD employs QSite in QM/MM calculations. QM/MM energy calculated via QSite can be define as follows [18]:

$$E = E_{QM} + E_{MM} + E_{QM/MM},$$

where,

$$E_{QM/MM} = E_{Coulomb} + E_{vdW} + E_{QM/MM}^{\text{int.coor}}$$

Molecular docking validation

The molecular docking method validation was performed by redocking method using the co-crystallized ligand (**Rosiglitazone**) of MAO-B (4A7A). The co-crystallized ligand was docked within the binding pocket of MAO-B, and the docked pose was compared with the crystal structure pose by calculating the root-mean-square deviation (RMSD) value (0.359\AA). As a general rule, a docking method can be declared valid if the RMSD value is $\leq 2.0\text{\AA}$ [19].

Drug-likeness and Pharmacokinetic studies

SwissADME, a free online software developed by Diana *et al.* [20] was adopted through the website <http://SwissADME.ch/> to determine the physicochemical and pharmacokinetic properties of our novel MAO-B inhibitors. The chemical structure of each ligand was submitted to SwissADME server in form of canonical simplified molecular-input line-entry system (SMILES). Upon calculation submission by clicking the "Run" button, the SMILES of each compound is canonicalised by OpenBabel (version 2.3.0, 2012) and processed [20].

Biological activity spectrum

PASS (prediction of activity spectra for substances), an online web server was used through <http://www.pharmaexpert.ru/passonline> [21] to predict the mechanisms of action, pharmacological effects and specific toxicity (carcinogenicity, teratogenicity, embryotoxicity and mutagenicity) that may be exhibited by our hit compounds in their respective interaction with living organisms and it is termed the "BAS" of the compounds [22].

Table 1: Docking scores calculated by glide-XP and QPLD. QPLD was calculated for the hit compounds and standard compounds (Selegiline and Rasagiline) only

Ligand ID	Molecular Formula	Glide-XP docking Score (kcal/mol)	QPLD	
			Score (kcal/mol)	Interacting amino acid
Rutaecarpine	C ₁₈ H ₁₃ N ₃ O	-11.520	-11.543	Try326, Phe343
Chrysophanol	C ₁₅ H ₁₀ O ₄	-10.904	-11.138	Try326, Cys172
Selegiline	C ₁₃ H ₁₇ N	-7.597	-8.051	-
Rasagiline	C ₁₂ H ₁₃ N	-6.926	-7.758	Ile199

RESULTS AND DISCUSSION

The current study utilizes CADD method to explain the binding mode, molecular interaction, inhibitory potential and pharmacokinetic properties of TCM compounds on MAO-B.

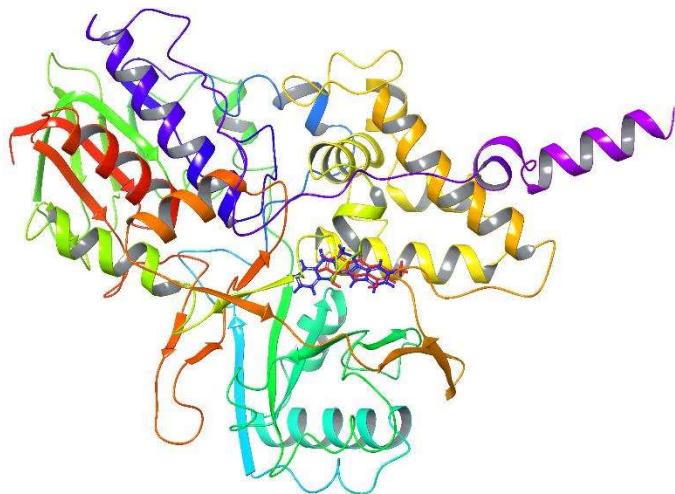


Figure 1: Three-dimensional crystal structure of MAO-B complexed with Rutaecarpine (blue) and Chrysophanol (red).

Molecular docking studies

In order to understand the binding modes and bio-affinities of the TCM compounds with MAO-B, they were docked into the active site of MAO-B, using the three docking precision options of Glide tool, although only the XP docking results are reported as HTVS and SP docking results may give some false positives. The top two compounds with better XP-Glide docking scores were selected for QPLD calculations for guaranteeing a better prediction of their binding modes with MAO-B [23]. QPLD provides a better accurate treatment of electrostatic interactions, which leads to an increase in docking accuracy. QPLD achieve docking accuracy by improving the description of partial charges on the ligand atoms [24]. Three-dimensional chemical structure of Rutaecarpine and Chrysophanol is shown in figure 3. As reported in Table 1, Rutaecarpine and Chrysophanol showed Glide-XP docking score of -11.520 kcal/mol and -10.904 kcal/mol, respectively; with a good QPLD score of -11.543 kcal/mol for Rutaecarpine and -11.138 kcal/mol for Chrysophanol. It has been reported that more negative E-total value indicates stronger interaction between SMCs and protein, which leads to inhibition of protein activity [25, 26], therefore this result proves that Rutaecarpine and Chrysophanol have relatively better inhibitory activities and may pose lesser side effects than selegiline and rasagiline which recorded a QPLD score of -8.051 and -7.758 kcal/mol, respectively. To validate the accuracy of our docking method, the co-crystallized ligand was docked within the binding pocket of MAO-B, and the docked pose was compared with the crystal structure pose by calculating the RMSD value (0.359 Å). Figure 2 shows that the docked pose almost overlapped completely with the experimental orientation of MAO-B, this indicates that our docking method is valid, therefore all docking scores obtained are correct. The docking results denote that Rutaecarpine and Chrysophanol bind to the active site of MAO-B, the active site is a hydrophobic pocket surrounded by aliphatic and aromatic residues. The active site comprises of an entrance

cavity and substrate cavity, based on the nature of the binding ligand, the two cavities can be joined or separated. TYR326 and ILE199 form a “gate” between the entrance cavity and substrate cavity, the gate readily opened by movement of these amino acid residues, in order to accommodate SMCs at the active site flavin ring [27].

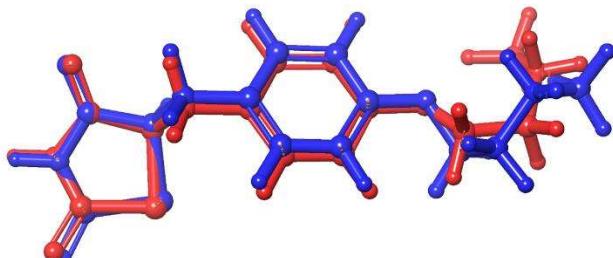


Figure 2: Validation of the molecular docking protocol employed using the before docking (red) and after Glide XP-docking (blue) pose of co-crystallized ligand (Rosiglitazone). Rosiglitazone overlaps almost perfectly with an RMSD of 0.359 Å indicating that our docking method is valid, therefore all docking scores obtained are correct.

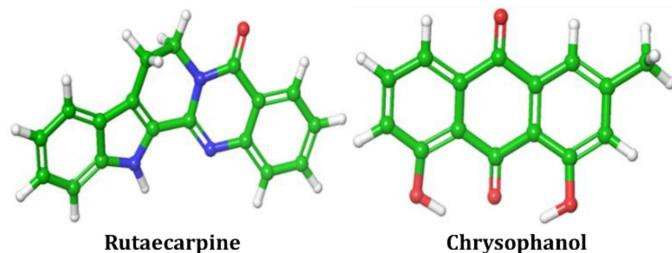


Figure 3: Three-dimensional chemical structure of Rutaecarpine and Chrysophanol

It was interesting to note that Rutaecarpine and Chrysophanol shared maximum interaction with one of these gate residues by forming π-π stacking with hydrophobic TYR326, and PHE343 in case of Rutaecarpine. Hydrogen (H)-bonds are ubiquitous in nature and play key role in enzyme catalysis and protein-ligand interaction [28]. Interestingly, our result shows that Chrysophanol form key H-bond interaction with the carbonyl group attached to its heterocyclic with hydrophobic CYS172 (a main residue at the active site), whereas none of the active site amino residues was found to interact with selegiline neither in hydrophobic nor hydrophilic interactions, which is similar to the report of Ogidiog et al., [29] as shown in Figure 4-7.

Drug-likeness

The eminent Rule of Five (RO5) by Lipinski and co-workers helps to evaluate the drug-likeness of a chemical compound or determine if a compound has the properties that would make it a potential orally active drug for humans [30]. As reported by Lipinski [30], an orally active drug should not breach more than one of the following rules: hydrogen bond acceptor ≤ 10, octanol-water partition coefficient < 5, hydrogen bond donor ≤ 5 and molecular weight < 500Da. The results of the Lipinski's RO5 calculations using SwissADME online software are presented in Table 2. Rutaecarpine and Chrysophanol have shown good result and are in agreement with this rule. Hence, it can be predicted that they have passable absorptivity for oral medications.

Table 2: Physicochemical properties of the hit compounds and standard compounds (Selegiline and Rasagiline) as predicted by SwissADME

Ligand ID	Molecular weight	Number H-bond donors	Num. of H-bond acceptors	MlogP	TPSA	Rotatable bonds
Rutaecarpine	287.32	1	2	3.15	50.68	0
Chrysophanol	254.24	2	4	0.92	74.60	0
Selegiline	187.28	0	1	3.25	3.24	4
Rasagiline	171.24	1	1	2.58	12.03	2

Table 3: Pharmacokinetics properties of the hit compounds and standard compounds (Selegiline and Rasagiline) as predicted by SwissADME.

Parameters	Rutaecarpine	Chrysophanol	Selegiline	Rasagiline
GI Absorption	High	High	High	High
BBB permeant	Yes	Yes	Yes	Yes
P-gp substrate	Yes	No	No	No
CYP1A2 inhibitor	Yes	Yes	Yes	No
CYP2C19 inhibitor	No	No	No	No
CYP2C9 inhibitor	No	No	No	No
CYP2D6 inhibitor	No	No	Yes	Yes
CYP3A4 inhibitor	Yes	Yes	No	No
Log K _p (Skin permeation)	-5.90	-5.34	-5.38	-6.05

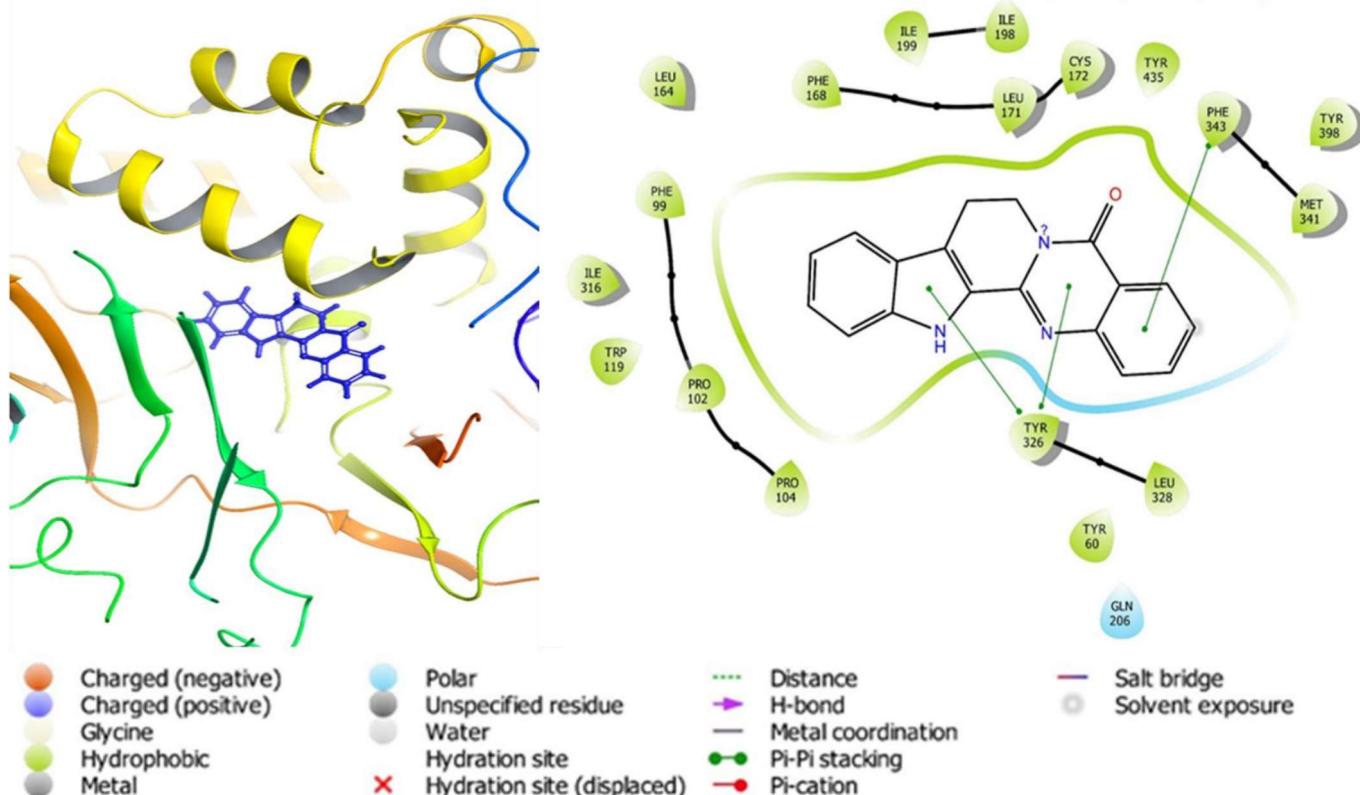


Figure 4: 2D interaction view of Rutaecarpine with amino acid residues at the active site of MAO-B upon QM/MM assisted docking

Additionally, other significant properties such as total polar surface area (TPSA) and the number of rotatable bonds were also calculated (Table 2). PSA has been used by several researcher as a predictor for blood brain barrier (BBB) penetration. In general, drugs aimed at the central nervous system (CNS) tend to possess lower PSA than other classes of therapeutic drugs [31, 32, 33]. Similar conclusion was made by Feng [34], who reported that PSA value for CNS penetration is $\leq 90 \text{ \AA}^2$ compared to other classes which is $< 140 \text{ \AA}^2$. Also, the number of rotatable bonds is now a

broadly used filter following the findings that rotatable bonds greater than ten decreases oral bioavailability. Most CNS drugs also have fewer rotatable bonds value (≤ 5) than other drug classes [35]. Studies has also revealed that a high PSA ($> 150 \text{ \AA}^2$) or number of rotatable bond above 10 leads to lessened oral bioavailability and permeability [30, 36]. The findings of this study shows Rutaecarpine and Chrysophanol have a good TPSA of $< 90 \text{ \AA}^2$ and number of rotatable bond < 5 .

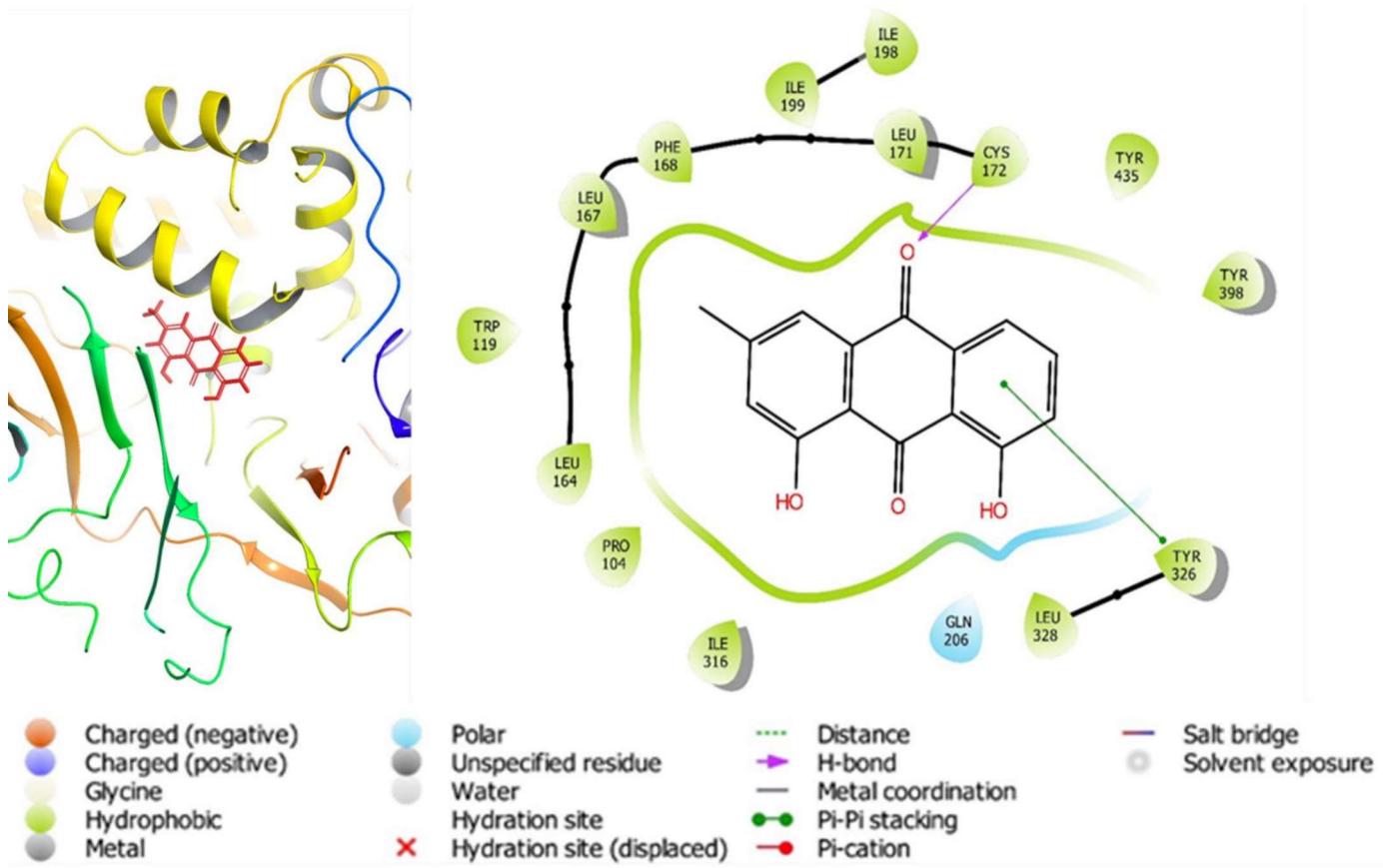


Figure 5: 2D interaction view of Chrysophanol with amino acid residues at the active site of MAO-B upon QM/MM assisted docking

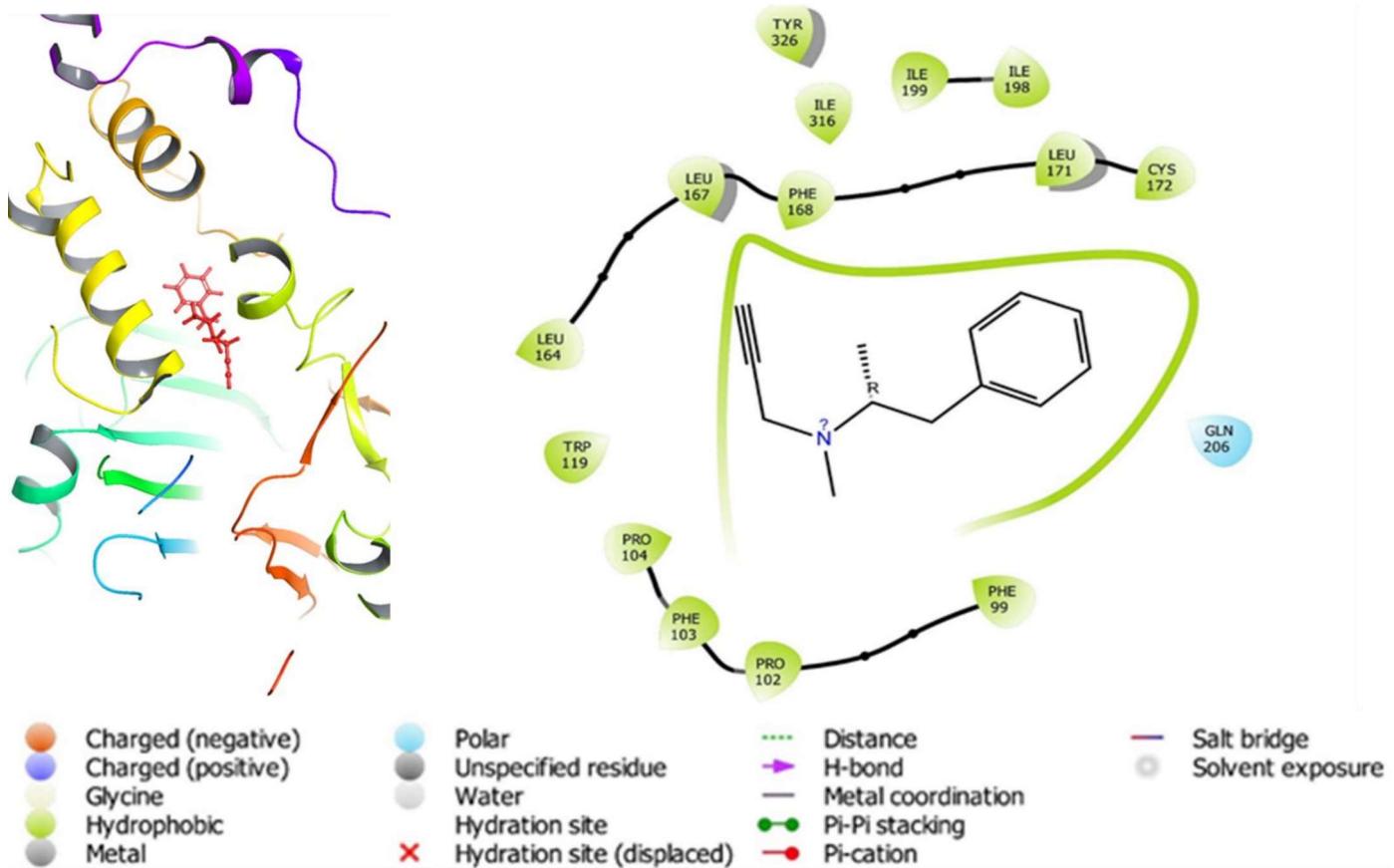
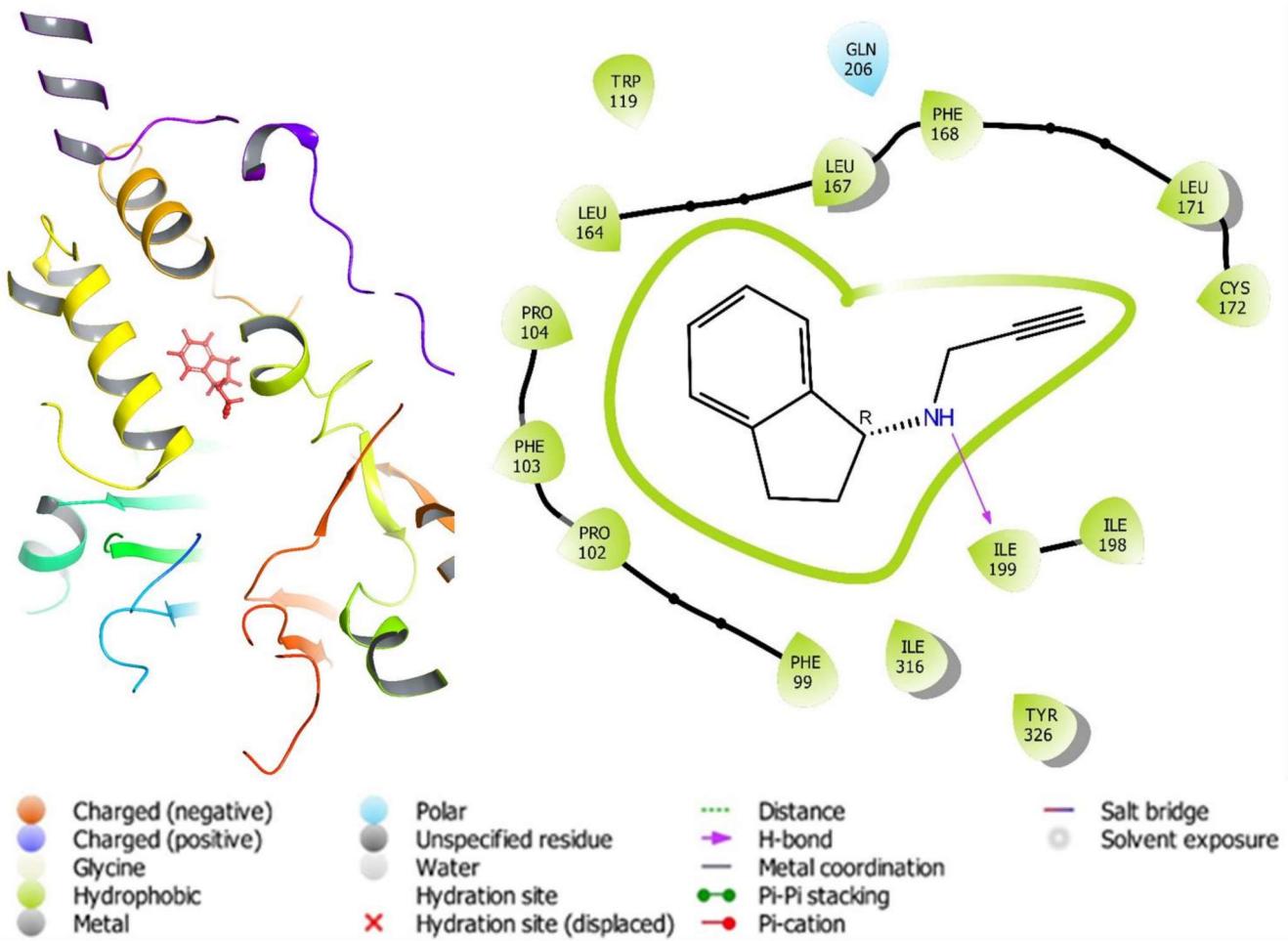


Figure 6: 2D interaction view of Selegiline with amino acid residues at the active site of MAO-B upon QM/MM assisted docking



Pharmacokinetics studies

Many letdowns during drug development are associated to poor pharmacokinetics. Monitoring the physicochemical and pharmacokinetics properties of lead compounds at early stage of drug discovery decreases the fraction of pharmacokinetics-associated failures in advanced phases of drug development. Therefore, using SwissADME online software the pharmacokinetics properties videlicet GI Absorption, BBB permeant, P-glycoprotein (P-gp) substrate, cytochrome P (CYP) 450 isoforms inhibitor and Log K_p (Skin permeation) was studied (Table 3).

The predicted pharmacokinetics properties show that Rutaecarpine and Chrysophanol could be absorbed by the human intestine. The chief interfaces separating the CNS and the blood circulation are BBB and the blood-cerebrospinal fluid barrier. BBB permeation is a prominent property in the pharmaceutical field, it helps to determine if a compound can or cannot cross the BBB and thereby exercise its therapeutic effect on the brain [37]. Consequently, the result of this study shows that Rutaecarpine and Chrysophanol have the ability to cross the BBB through passive diffusion, without upsetting the normal CNS functions.

P-gp is a transmembrane efflux pump that transport drugs away from the cytoplasm and cell membrane causing compounds to undergo farther metabolism and clearance, thereby limiting cellular uptake of drugs resulting in therapeutic failure because the drug concentration would be lower than expected [29, 38]. The result demonstrates Rutaecarpine to be a substrate of P-gp. Thus, dosage

regulation and knowledge of co-administered drugs might be considered to lessen therapeutic failures.

The study on the potential of SMCs to inhibit the CYP450 is essential in determining their likely drug interactions and toxicity. CYP450 play prominent role in drug metabolism and clearance in the liver [39]. The CYP450 inhibition profile for Rutaecarpine and Chrysophanol were assessed for five most important isoforms videlicet; CYP1A2, CYP2C19, CYP2C9, CYP2D6 and CYP3A4. Inhibition of CYP450 isoforms is a major cause of pharmacokinetics related drug-drug interactions [40]. Nevertheless, Rutaecarpine and Chrysophanol were found to have inhibited some of the CYP450 isoforms.

The skin permeate is also an important parameter in the pharmaceutical industry to determine the risk of compounds in case there is accidental contact with skin. The more negative the log K_p, the less skin permeate is the molecule [38]. Hence, Rutaecarpine and Chrysophanol are found to be poorly permeable to skin and accidental contact will not have any effect on the skin.

Biological activity predictions

PASS evaluates predicted BAS of SMCs as Probable active (P_a) and Probable inactive (P_i). The biological activity prediction is centered on structure-activity relationship analysis of the training set containing over 205,000 SMCs exhibiting over 3,750 types of biological activities. P_a and P_i values ranges between 0.000 and 1.000. Biological activities with P_a greater than P_i are regarded as possible for SMCs [41]. The greater the value of P_a, the less is the probability of

false positives [42]. Rutaecarpine and Chrysophanol were analyzed by the PASS for their Monoamine oxidase inhibitory activity. Interestingly, they both showed P_a greater than P_i . Their P_a values are 0.226 and 0.301 for Rutaecarpine and Chrysophanol, respectively (Table 4). Therefore, Rutaecarpine and Chrysophanol could act as potential leads for evaluation with *in vitro* and/or *in vivo* biological assay.

Table 4: Biological activity Spectrum of the hit compounds.

Ligand ID	P_a	P_i	Biological Activity
Rutaecarpine	0.226	0.119	Monoamine inhibition
Chrysophanol	0.301	0.061	Monoamine inhibition

CONCLUSION

The results of this study has shown Rutaecarpine and Chrysophanol from TCM Database to bind and subsequently inhibit MAO-B. The compounds have relatively better inhibitory and pharmacokinetic profile than selegiline and rasagiline, thus they can be a useful therapeutic candidate in the treatment of PD. *In vivo* and or *in vitro* assay are required to further demonstrate the antiparkinsonian potential of these compounds.

ACKNOWLEDGEMENT

Authors sincerely appreciate all members of Biochemistry Department, Adekunle Ajasin University, Nigeria for their scientific guidance and support.

ETHICAL STATEMENT

No ethical issue to be declared

COMPETING INTERESTS

No conflicts of interest

REFERENCES

- DeMaagd G, Philip A. Parkinson's disease and its management: part 1: disease entity, risk factors, pathophysiology, clinical presentation, and diagnosis. P T 2015; 40: 504-10.
- Marvanova M. Introduction to Parkinson disease (PD) and its complications. Ment Health Clin 2016; 6: 229-35.
- Rewar S. A systematic review on Parkinson's disease (PD). Indian Journal of Research in Pharmacy and Biotechnology 2015; 3: 176.
- Alves G, Forsaa EB, Pedersen KF, Gjerstad MD, Larsen JP. Epidemiology of Parkinson's disease. Journal of neurology 2008; 255: 18-32.
- Azam F, Madi AM, Ali HI. Molecular Docking and Prediction of Pharmacokinetic Properties of Dual Mechanism Drugs that Block MAO-B and Adenosine A2A Receptors for the Treatment of Parkinson's Disease. J Young Pharm 2012; 4: 184-92.
- Youdim MB, Bakht YS. Monoamine oxidase: isoforms and inhibitors in Parkinson's disease and depressive illness. Br J Pharmacol 2006; 147(S1): S287-96.
- Dézsi L, Vécsei L. Monoamine oxidase B inhibitors in Parkinson's disease. CNS Neurol Disord Drug Targets 2017; 16: 425-39.
- Kamakura K, Mochizuki H, Kaida KI, Hirata A, Kanzaki M, Masaki T, et al. Therapeutic factors causing hallucination in Parkinson's disease patients, especially those given selegiline. Parkinsonism Rel Disord 2004; 10: 235-42.
- Montastruc JL, Chaumerliac O, Desboeuf K, Manika M, Bagheri H, Rascol O, et al. Adverse drug reactions to selegiline: a review of the French pharmacovigilance database. Clin Neuropharmacol 2000; 23: 271-5.
- Klein C, Kömpf D, Pulkowski U, Moser A, Vieregge P. A study of visual hallucinations in patients with Parkinson's disease. J Neurol 1997; 244: 371-7.
- Chen JJ, Berchou RC. Rasagiline, a selective second-generation irreversible inhibitor of the monoamine oxidase type B, is effective in patients older and younger than 65 years of age with early-to-advanced Parkinson's disease. Pharmacotherapy 2004; 24: 1448.
- Goetz CG, Schwid SR, Eberly SW, Oakes D, Shoulson I. Safety of rasagiline in elderly patients with Parkinson disease. Neurology 2006; 66: 1427-9.
- Surabhi S, Singh BK. Computer aided drug design: an overview. J Drug Deliv and Ther 2018; 8: 504-9.
- Kikiwo BB, Ogunleye AJ, Inyang OK, Adelakun NS, Omotuyi OI, Metibemu DS, et al. Flavones scaffold of Chromolaena odorata as a potential Xanthine oxidase inhibitor: Induced Fit Docking and ADME studies. Bioimpacts 2020; 10: 45-51.
- Tou WI, Chen CY. In silico investigation of potential SRC kinase ligands from traditional Chinese medicine. PLoS One 2012; 7: e33728.
- Joseph OA, Babatomiwa K, Niyi A, Olaposi O, Olumide I. Molecular docking and 3D Qsar Studies of C000000956 as a Potent Inhibitor of Bace-1. Drug Research 2019; 69: 451-7.
- Cho AE, Guallar V, Berne BJ, Friesner R. Importance of accurate charges in molecular docking: quantum mechanical/molecular mechanical (QM/MM) approach. J Comput Chem 2005; 26: 915-31.
- Park K, Sung NK, Cho AE. Importance of accurate charges in binding affinity calculations: a case of neuraminidase series. Bull Korean Chem Soc 2013; 34: 545-8.
- Setiawan AA, Kumala S, Dian Ratih L, Yuliana ND. In Silico Study On S-Allyl Cysteine and Quercetin From Garlic (*Allium sativum* Linn) As Xanthine Oxidase Inhibitor.
- Daina A, Michielin O, Zoete V. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Scientific reports 2017; 7: 42717.
- Ramos RD, Costa JD, Silva RC, da Costa GV, Rodrigues AB, Rabelo ÉD, Souto RN, Taft CA, Silva CH, Rosa JM, Santos CB. Identification of potential inhibitors from pyriproxyfen with insecticidal activity by virtual screening. Pharmaceuticals 2019; 12: 20.
- Tripathi SK, Selvaraj C, Singh SK, Reddy KK. Molecular docking, QPLD, and ADME prediction studies on HIV-1 integrase leads. Med Chem Res 2012; 21: 4239-51.
- Siroos H, Chemi G, Gemma S, Butini S, Debyser Z, Christ F, Saghaie L, Brogi S, Fassihi A, Campiani G, Brindisi M. Identification of novel 3-hydroxy-pyran-4-one derivatives as potent HIV-1 integrase inhibitors using in silico structure-based combinatorial library design approach. Front Chem 2019; 7:574.
- Nisha C, Kotni MK, Chetan S, Manga V, Jitander KK, Pawan KS. QM/MM docking strategy and prime/MM-GBSA calculation of celecoxib analogues as N-

- myristoyltransferase inhibitors. *Virol Mycol* 2015; 4: 141.
25. Lokesh MR, Krishnamurthy G, Bhojyanaik HS, Shashikumar ND, Murali P. Synthesis, molecular docking, DNA binding and biological evaluation of schiff base transition metal complexes
 26. David TI, Adelakun NS, omotuyi OI, Metibemu DS, Ekun OE. Molecular docking analysis of phyto-constituents from Cannabis sativa with pfDHFR. *Bioinformation* 2018; 14: 574.
 27. Ramsay RR. Molecular aspects of monoamine oxidase B. *Prog Neuro-psychopharmacology Biol Psychiatry* 2016; 69: 81-9.
 28. Chen D, Oezguen N, Urvil P, Ferguson C, Dann SM, Savidge TC. Regulation of protein-ligand binding affinity by hydrogen bond pairing. *Sci Adv* 2016; 2: e1501240.
 29. Ogidigo JO, Anosike C, Nwodo OF, Omotuyi IO, Sani MA. In-silico molecular docking and pharmacokinetic studies of some selected phyto-constituents of bryophyllum pinnatum as a potential selective inhibitor of Monoamine oxidase-B (MAO-B).
 30. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv Drug Deliv Rev* 1997; 46: 3-26.
 31. Van de Waterbeemd H, Camenish G, Folkers G, Chretien JR, Raevsky OA. Estimation of blood-brain barrier crossing of drugs using molecular size and shape, and H-bonding characteristics. *J Drug Target* 1998; 46: 151-65.
 32. Abraham MH, Chadha HS, Martins F, Mitchell RC, Bradbury MW, Gratton JA. Hydrogen bonding part 46: a review of the correlation and prediction of transport properties by an LFER method: physicochemical properties, brain penetration and skin permeability. *Pestic Sci* 1999; 55: 78-88.
 33. Skaaeda T, Okamura N, Nagata S, Yagami T, Horinouchi M, Okumura K, Yamahita F, Hashida M. Molecular and pharmacokinetic properties of 222 commercially available oral drugs in humans. *Biol Pharm Bull* 2001; 24: 935-40.
 34. Feng RM. Assessment of blood-brain barrier penetration: in-silico, in vitro and in vivo. *Curr drug metab* 2002; 3: 647-657.
 35. Kalidasu S, Kuna Y. Validation of selected Anti-Alzheimer's drugs through Lipinski rule of five. *J Pharm Res* 2012; 5: 2174-7.
 36. Clark DE. Rapid calculation of polar molecular surface area and its application to the prediction of transport phenomena 1. Prediction of intestinal absorption. *J Pharm Sci* 2000; 88: 807-14.
 37. Ghaleb A, Aouidate A, Bouachrine M, Lakhlifi T, Sbai A. In Silico Exploration of Aryl Halides Analogues as Checkpoint Kinase 1 Inhibitors by Using 3D QSAR, Molecular Docking Study, and ADMET Screening. *Adv pharm Bull* 2019; 9: 84.
 38. Ahmed AH, Alkali YI. In silico Pharmacokinetics and Molecular Docking Studies of Lead Compounds Derived from *Diospyros Mespiliformis*. *PharmaTutor* 2019; 7: 31-7.
 39. Marital JD, Kemp CA, Roberts GCK, Paine MJI, Wolf CR, Sutcliffe MJ. Insights into drug metabolism by cytochromes P450 from modelling studies of CYP2D6-drug interactions. *Br J Pharmacology* 2008; 153(S1):S82-9.
 40. Hollenberg, PF. Characteristics and common properties of inhibitors, inducers, and activators of CYP enzymes. *Drug Metab Rev* 2002; 34: 17-35.
 41. Paul A, Kabir MS, Majumder M, Chakraborty J, Banik H, Paul R, Siddika KA, Al Gazzaly J, Sohel M. *Int J Pharm*.
 42. Mathew B, Suresh J, Anbazhagan S, Dev S. Proposed interaction of some novel antidepressant pyrazolines against monoamine oxidase isoforms. Molecular docking studies and PASS assisted in silico approach. *Biomed Aging Pathol* 2014; 4: 297-301.

About Author



Mr. Kikiowo Babatomiwa is a graduate of Biochemistry at Adekunle Ajasin University. His area of interest is biochemistry, molecular biology and bioinformatics. He is currently working in the field of drug discovery and development.