JOTCS A
Journal of the Turkish Chemical Society
Section: A
Chemistry
TURKISH CHEMICAL SOCIETY

In Silico Exploration of Pharmacological and Molecular Descriptor Properties of Salacinol and Its Related Analogues

Yousif Taha Hussein[1*], Yousif Hussein Azeez[2], Idrees Mohammed Ahmed[1]

[1] Sulaimani Polytechnic University, Technical College of Applied Sciences/ Halabja, Medical Laboratory Science, Iraq.
[2] Department of Physics, College of Science, Halabja University, Halabja, Iraq.

Abstract: Salacinol and its related analogues have been known for their potent α-glucosidase inhibitor activity and making them interesting candidates for a new type of anti-diabetic agent. Therefore, it is essential to investigate the physicochemical properties, pharmacological parameters, and toxicity profile of these anti-diabetic agents. In this study, a comprehensive in-silico approach was used to explore the absorption, distribution, metabolism, excretion, and toxicity profiles of salacinol and its related analogues. In addition, to gain a better knowledge of structural and electrical characteristics, global and local reactivity descriptors, and molecular electrostatic potential were calculated and discussed by using DFT at the B3LYP/6−311++G (d, p) level of theory. The results explored that all the studied compounds have low GI absorption and are substrates for P-glycoprotein. None of the compounds can cross the BBB, and none of the compounds are inhibitors of cytochrome P450 isoenzymes. We also found that all compounds have various potential to interact with a wide range of biological targets, including GPCRs, enzymes, ion channels, kinases, and nuclear receptors. Additionally, all compounds have low toxicity and are unlikely to cause any major health hazards in terms of hepatotoxicity, mutagenicity, cardiotoxicity, cytotoxicity, and immunotoxicity. The molecular electrostatic potential map shows that the negative potential sites are in electronegative oxygen atoms, while the positive potential sites are around the hydrogen atoms. The present study concludes that salacinol and its analogues might be a promising safe and effective candidate for the development of therapeutic drugs derived from natural sources. However, some of their properties should be considered in the context of drug development and tissue protection strategies.

Keywords: Salacinol, Drug likeness, ADME, Toxicity profile, Density Functional Theory, Fukui Functions, Anti-diabetic.

Submitted: February 3, 2023. **Accepted:** October 16, 2023.

Cite this: Hussein YT, Azeez YH, Ahmed IM. In Silico Exploration of Pharmacological and Molecular Descriptor Properties of Salacinol and Its Related Analogues. JOTCSA. 2024;11(1):279-90.

DOI: https://doi.org/10.18596/jotcsa.1246781

***Corresponding author's E-mail:** yousif.hussein@spu.edu.iq

1. INTRODUCTION

Plants of the Salacia genus (Hippocrateaceae family) are woody climbers found in India, Sri Lanka, China, and Thailand (1). The stems and roots of Salacia species have been used for the prevention or treatment of diabetes, a common metabolic disorder seen all over the world (2). The bioactive constituent responsible for the postprandial anti-hyperglycaemic activity of these plants is a novel thiosugar sulphonium sulfate inner salt, Salacinol (1) (1). Several analogues have been isolated from Salacia species, that is, Neosalacinol (2), kotalanol (3), neokotalanol (4), Ponkoranol (5), Neoponkoranol (6), Salaprinol (7), and Neosalaprinol (8) (Fig. 1). The mechanism of the anti-diabetogenic action of these compounds was shown to be mediated by the inhibition of α-glucosidases, and their activities against maltase and sucrose were found to be as potent as the clinical inhibitors such as acarbose or voglibose (1). The results suggest that these compounds are promising leads for a new type of anti-diabetic agent (3). Therefore, the exploration of various physicochemical properties, pharmacokinetic parameters, and toxicity potential of these antidiabetic agents is and will be an important issue for investigation.

The computational methods (In-silico) have been promoted as a valid alternative to experimental procedures for the prediction of pharmacokinetic parameters such as absorption, distribution,

metabolism, excretion ("ADME"), and toxicity, principally at the initial stages when the studied compounds are numerous but the availability of compounds is scarce (4). For instance, at the initial stages of the investigations, the in-silico toxicity assessments are not only faster and inexpensive than the determination of toxic doses in animals, but can also help to decrease the number of animal experiments (5).

It is important to understand the molecular characteristics and bioactivity of the therapeutic effect of the title compound to examine them from a medical aspect. From a molecular point of view, it is believed that the bioactivity of these compounds is strongly linked to their chemical reactivity. As a result, it is essential to use computational chemistry and molecular modeling approaches to explore the chemical reactivity of natural compounds with the potential to become medicines. The Conceptual Density Functional Theory (CDFT), also known as chemical reactivity theory, is perhaps the most powerful tool available for investigating the chemical reactivity of molecular systems from the perspective of molecular modeling and computational chemistry. It uses a global and local reactivity descriptor to predict molecule interactions and understand how chemical reactions work (6). The B3LYP/6–311++G (d, p) basis set was chosen for the geometric and energetic optimization of salacinol and related analogues because it is a well-established and balanced choice for the calculation of both energies and geometries of organic molecules. The B3LYP functional is a hybrid functional that includes both exchange and correlation terms, and it is accurate for a wide range of molecules. The 6–311++G (d, p) basis set represents a triple-zeta foundation augmented with diffuse and polarization functions. This particular basis set proves advantageous in computational endeavors aimed at determining molecular properties, specifically those pertaining to dipole moments and polarizabilities. The employment of such a basis set is particularly pertinent in the context of elucidating the intricate intermolecular interactions involving salacinol and its analogous compounds with other molecular entities. Salacinol and related analogues were selected for these studies because of their potential as drug candidates. Salacinol has already been shown to be safe and effective in clinical trials for the treatment of diabetes. By understanding the reactivity and electrostatic potential of salacinol and its related analogues, we can identify new drug candidates with improved efficacy and fewer side effects.

In this study, we investigated the reactivity of salacinol and related analogues using reactivity descriptors and molecular electrostatic potential (MEP) studies. We found that neokotalanol, one of the salacinol analogues, has a small HOMO-LUMO energy gap and a high MEP, indicating that it is highly reactive. We also found that neokotalanol is more potent than salacinol in inhibiting the growth of cancer cells. These findings suggest that the high reactivity of neokotalanol is important for its bioactivity.

This study aims to explore important information about Salacinol and its related analogues for their possibility as a potential drug originating from natural products and their pharmaceutical research. For this purpose, in silico methods are used to explore the absorption, distribution, metabolism, excretion, and toxicity profile of Salacinol and its related analogues. In addition, to gain a better knowledge of structural and electrical characteristics, molecular descriptors were calculated and discussed by using DFT at the B3LYP/6–311++G (d, p) level of theory.

2. MATERIALS AND METHODS

2.1. Bioactivity Score Prediction

The bioactivity score of the Salacinol and its related analogues was checked by calculating the bioactivity score toward G protein-coupled receptors (GPCR ligand), ion channel modulator, nuclear receptor ligand, a kinase inhibitor, protease inhibitor, and enzyme inhibitor. All of the parameters were explored by feeding the corresponding SMILES (Simplified Molecular Input Line Entry System) notation into the internet-based software Molinspiration (www.molinspiration.com), which predicts the bioactivity score of the synthesized complexes.

2.2. Drug Likeness and Pharmacokinetic Evaluation

The current industrial drug discovery paradigm includes computer-based prediction to explore absorption, distribution, metabolism, excretion, and pharmacokinetics (ADME-PK) properties of bioactive compounds in the initial stages of drug discovery projects. Drug-likeness analyses and ADME predictions were performed via the web-based tool SwissADME (4). In this part of the study, lipophilicity, water solubility, physicochemical properties, and various pharmacokinetics parameters were explored. The drug-likeness analyses were carried out with the use of Lipinski's rule of five (RO5) and Veber rule's (7, 8). Additionally, passive human gastrointestinal absorption, BBB permeation, the potential to become glycoprotein (P-gp) substrate, and inhibition of human cytochrome P450 (CYP) five isozymes—1A2, 2C9, 2C19, 2D6, and 3A4 of all studied molecules were explored.

2.3. Toxicity Potential Evaluation

In this part of the study, the toxicity profile of the studied compounds was predicted using a software-based tool, ProTox-II, a virtual lab for the prediction of toxicities of molecules (5). Also, different levels of toxicity were explored, such as organ toxicity (hepatotoxicity) and toxicological endpoints (such as mutagenicity, cardiotoxicity, cytotoxicity, and immunotoxicity), thereby providing insights into different possible adverse effects of Salacinol and its analogues on the human body.

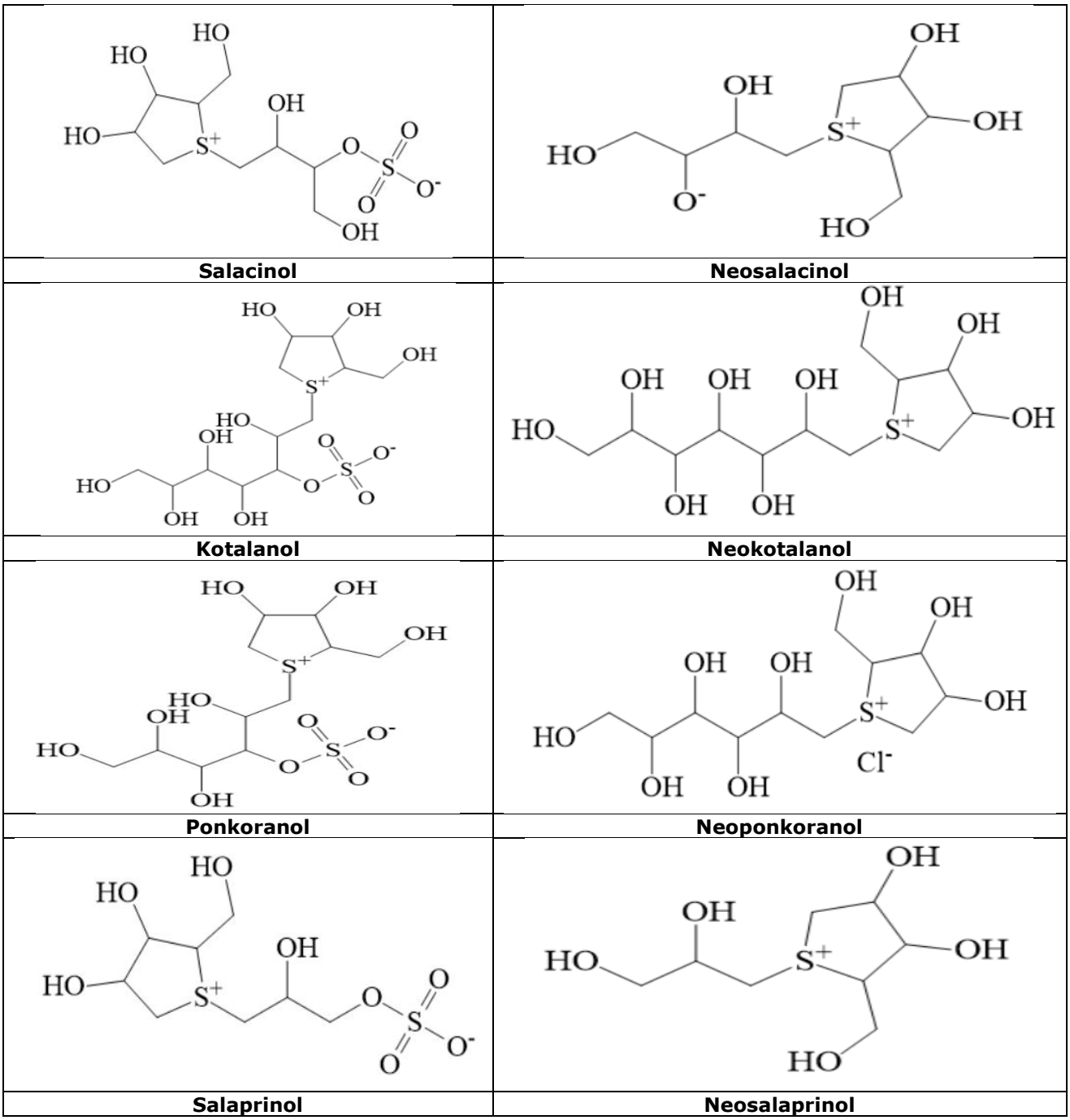

Figure 1: Chemical structure of compounds (1–8) from the plants of the Salacia genus.

2.4. DFT with Global Chemical Reactivity Descriptors

The global reactivity indices provide information on a chemical compound's stability, reactivity, and selectivity. Global reactivity characteristics such as energy gap (E_g), global hardness (η), global softness (S), electronegativity (χ), chemical potential (μ), maximal amount of electronic charge (Q^{max}), electrophilicity (ω), electron-donating power (ω^-), electron-accepting power (ω^+), and net electrophilicity based on DFT with 6311++G (d,p) were calculated by using the energies of the frontier orbitals and Gaussian 09 software (1-11) (6, 9-12).

$$IP = -H_{HOMO} \quad \text{and} \quad EA = -E_{LUMO} \qquad (1)$$

$$E_g = E_{LUMO} - E_{HOMO} \qquad (2)$$

$$\chi = \frac{E_{HOMO} + E_{LUMO}}{2} \qquad (3)$$

$$\mu = -\frac{(E_{HOMO} + E_{LUMO})}{2} \qquad (4)$$

$$\eta = \frac{E_{LUMO} - E_{HOMO}}{2} \qquad (5)$$

$$S = \frac{1}{2\eta} \qquad (6)$$

$$\omega = \frac{\mu^2}{2\eta} \qquad (7)$$

$$(Q^{max}) = \frac{-\mu}{\eta} \qquad (8)$$

$$\omega^+ = \frac{(E_{HOMO} + 3E_{LUMO})^2}{16\,E_g} \qquad (9)$$

$$\omega^{-} = \frac{(3\,E_{HOMO} + E_{LUMO})^2}{16\,E_g} \quad (10)$$

$$\Delta\omega^{\pm} = \omega^{+} + \omega^{-} \quad (11)$$

2.5. Fukui Function (local reactivity descriptors)

The Fukui Function gives information on the reactivity indices in a given system. For the highest Fukui function values, the atom exhibits a significant degree of reactivity (13, 14). The Fukui functions from (compound 1-8) have been calculated based on the B3LYP/6-311G++(d, p) level of theory, and the results are shown in Table 6. The Fukui Functions ($f_k^-, f_k^+ f_k^0$) are computed using mulliken population analysis charges of neutral, negative, and positive ions and are given in Table 6 using equations (12-14). If (N) represents the number of electrons, then (N + 1) denotes an ion and (N − 1) denotes the system's cation.

$$f_k^+ = q(N+1) - q(N) \quad (12)$$

$$f_k^- = q(N) - q(N-1) \quad (13)$$

$$f_k^0 = \frac{q(N+1) - q(N-1)}{2} \quad (14)$$

3. RESULTS AND DISCUSSION

3.1. Bioactivity Score Prediction

The beneficial or adverse effects of a newly discovered compound on an organism are usually summarized by the term "bioactivity". On the molecular level, biological activity corresponds to the interaction between low-molecular weight compounds and the most common biological targets (receptors), usually proteins such as enzymes, ion channels, and receptors (15). In this study, the results of bioactivity prediction were analyzed as shown in Table 1, and it was explored that:

All the compounds can be considered bioactive as a GPCR ligand, the bioactivity score ranges between (0.00 to 0.30).

All the compounds are moderately active as an ion channel modulator, Kinase inhibitor, and nuclear receptor ligand; the value ranges between -0.05 to -0.27, -0.09 to -0.55, and -0.09 to -0.65, respectively.

All the compounds are active as protease inhibitors and the value ranged between 0.17 to 0.32, except 2 and 8, which has a moderately active value of -0.04 and -0.20, respectively.

All the compounds exhibit active interaction as an enzyme inhibitor, the value ranges between 0.98 to 1.20.

Table 1: Bioactivity scores of the Salacinol and eight Related Analogues based on GPCR ligand, ion channel modulator, nuclear receptor ligand, Kinase inhibitor, protease inhibitor, and Enzyme inhibitor.

Parameters	**Salacinol**	**Neosalacinol**	**Kotalanol**	**Neokotalanol**
GPCR ligand	0.30	0.07	0.27	0.29
Ion channel modulator	-0.18	-0.14	-0.13	-0.05
Kinase inhibitor	-0.09	-0.38	-0.07	-0.08
Nuclear receptor ligand	-0.13	-0.42	-0.09	-0.12
Protease inhibitor	0.25	-0.04	0.31	0.23
Enzyme inhibitor	1.19	1.04	0.98	1.03
Parameters	**Neoponkoranol**	**Ponkoranol**	**Salaprinol**	**Neosalaprinol**
GPCR ligand	0.29	0.26	0.14	0.00
Ion channel modulator	-0.14	-0.06	-0.27	-0.20
Kinase inhibitor	-0.08	-0.15	-0.28	-0.55
Nuclear receptor ligand	-0.10	-0.20	-0.30	-0.65
Protease inhibitor	0.32	0.17	0.22	-0.20
Enzyme inhibitor	1.06	1.13	1.20	1.16
>0 - active, -5.0 - 0.0 - moderately active, < -5.0 – inactive.				

3.2. Drug-Likeness Parameters

Various physicochemical features are used to evaluate the potential of a particular molecule to become a drug candidate. The RO5 is commonly used by pharmaceutical chemists in drug design and development to predict the oral bioavailability of potential leads or drug molecules (16). Lipinski's "RO5" states that a candidate molecule will likely be orally active, if: i) the molecular weight is fewer than 500, ii) the calculated partition coefficient is less than 5 (MiLog P<5), iii) there are less than 5 hydrogen bond donors (nONH<5) and, iv) there are less than 10 hydrogen bond acceptors (nON<10). If two parameters are out of range, there is a high probability that absorption or permeability problems will be encountered (7). Additional criteria such as the number of rotatable bonds, which is the measure of molecular flexibility, fewer than 10 (nrotb ≤ 10),

and topological polar surface area equal to or less than 140 Å^2 (TPSA ≤ 140 Å^2) (Veber Rule) were introduced later, (8) which are used to carry out further evaluation of the oral bioavailability of all the compounds. These physicochemical parameters are associated with acceptable aqueous solubility and intestinal permeability and comprise the initial steps in oral bioavailability (17). Good oral bioavailability implies a balance between the potential of a compound to diffuse passively across the various biological barriers and its aqueous solubility (18).

In this study, the drug-likeness properties of Salacinol and the seven related analogues are shown in Table 2. The lipophilicity of all compounds is less than 5 as shown in Table 2. All the values range from -5.64 to -4.92. The molecular weight (MW) of all compounds is less than 500 Da. However, the minimum value is 225.29 and the maximum value is 424.45, this allows them to be easily absorbed, diffused, and transported. The number of hydrogen bond acceptors of the compounds is less than 10, and the values range from 5 to 9, except 3 and 5 which have nON 12 and 11, respectively. The number of hydrogen bond donors of the 1, 2, 7, and 8 were shown to have four or five. The other compounds, 3, 4, 5, and 6, have more than five nOHNH, ranging from 7-9. Overall, 1, 2, 7, and 8 have no violations of Lipinski's rule. 4 and 6 only have one violation of RO5. The remaining compounds, 5 and 3, have two violations of RO5.

According to veber rules, compounds that meet only two criteria of nrotb ≤ 10 and TPSA ≤ 140 Å^2 will have a high probability of good oral bioavailability in the rat. In addition, reduced polar surface area correlates better with increased permeation rate than does lipophilicity (C log P), and increased rotatable bond count harms the permeation rate (8). In this study, all compounds are flexible molecules because their number of rotatable bonds ranges between 4-10. The TPSA of compounds is more than acceptable value ((TPSA ≤ 140 Å^2), ranging between (147.34 to 228.26), indicating poor bioavailability of the compounds, except for 2 and 8, which have TPSA of 124.20 and 101.14, respectively, which suggests that they have better bioavailability than other studied compounds.

Table 2: Molecular properties of the salacinol and related analogues calculated to verify Lipinski's RO5 and Veber's rule.

Molecules	**Lipinski's RO5**				**Veber's rule**
	miLogP	**MW**	**nON**	**nOHNH**	**TPSA (A^2)**
Rule	≤ 5	< 500	< 10	< 5	≤ 140
Salacinol	-5.30	334.37	9	5	167.57
Neosalacinol	-5.10	254.30	6	5	124.20
Kotalanol	-5.64	424.45	12	8	228.26
Neokotalanol	-5.49	345.39	9	9	182.05
Ponkoranol	-5.55	394.42	11	7	208.03
Neoponkoranol	-5.38	315.36	8	8	161.82
Salaprinol	-5.10	304.34	8	4	147.34
Neosalaprinol	-4.92	225.29	5	5	101.14

Predictions for passive GI absorption and blood-brain barrier permeation are shown in Table 3. It was predicted that gastrointestinal absorption of all studied compounds is low and none of the compounds can cross the BBB. The substrate of P-glycoprotein means that the drug will efflux from the cell by P-glycoprotein and limits the bioavailability by pumping back into the lumen of the digestive tract and may promote the elimination of that drug into the bile and urine (19). Knowledge about compounds being substrate or non-substrate of the P-gp is significant because its major role is to promote drug elimination into bile and urine and protect various tissues (e.g. brain, testis, liver, and fetus) from xenobiotics (20). Additionally, it has been experimentally demonstrated that P-glycoprotein restricts the oral bioavailability and brain penetration of drugs that are its substrates. In P-glycoprotein-deficient mice, oral administration of these drugs increased plasma concentrations by 2 to 5 fold, and intravenous administration increased brain concentrations by 7 to 36 fold (21). In this study, it can be seen that all compounds are substrates for P-glycoprotein, as shown in Table 3. These results suggest that low GI absorption and no BBB permeability of all the compounds might be partly attributed to the P-glycoprotein efflux.

Knowledge of the interaction of potential therapeutic drugs with cytochromes P450 (CYP) is essential because this group of isoenzymes (CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4) plays a major role in drug elimination through metabolic biotransformation (4). It is also suggested that inhibition of these isoenzymes leads to toxic or other unwanted adverse effects due to the lower clearance and accumulation of the drug or its metabolites (22). It also suggests that CYP and P-gp can process small molecules synergistically to improve the protection of tissues and organisms (23). A non-inhibitor of cytochrome P450 means that the molecule will not hinder the biotransformation of the compound (drug) metabolized by cytochrome P450 (24). In the present study, the explored results showed that none of the studied compounds act as an inhibiter of the cytochrome P450 isoenzymes, CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, and CYP2D6, as shown in Table 3. These results suggest that the studied compounds will not hinder the biotransformation by cytochrome P450 isoenzymes.

Table 3: In silico toxicity prediction of the salacinol and related analogues.

Parameters	**Salacinol**	**Neosalacinol**	**Kotalanol**	**Neokotalanol**
GI absorption	Low	Low	Low	Low
BBB permeant	No	No	No	No
P-gp substrate	Yes	Yes	Yes	Yes
CYP1A2 inhibitor	No	No	No	No
CYP2C19 inhibitor	No	No	No	No
CYP2C9 inhibitor	No	No	No	No
CYP2D6 inhibitor	No	No	No	No
CYP3A4 inhibitor	No	No	No	No
Parameters	**Neoponkoranol**	**Ponkoranol**	**Salaprinol**	**Neosalaprinol**
GI absorption	Low	Low	Low	Low
BBB permeant	No	No	No	No
P-gp substrate	Yes	Yes	Yes	Yes
CYP1A2 inhibitor	No	No	No	No
CYP2C19 inhibitor	No	No	No	No
CYP2C9 inhibitor	No	No	No	No
CYP2D6 inhibitor	No	No	No	No
CYP3A4 inhibitor	No	No	No	No

3.3. Toxicity Prediction

The prediction of compound toxicities, along with drug-likeness and other pharmacokinetics evaluations, is an important part of the drug design and development process (5). As shown in Table 4, All the studied compounds belong to toxicity class 5 for acute oral toxicity with a median lethal dose (LD_{50}) value of 5000mg/kg, except compounds 3 and 5, which have an LD_{50} value of 2750 mg/kg. None of the molecules studied has a toxicity hazard in terms of hepatotoxicity, mutagenicity, cardiotoxicity, cytotoxicity, and immunotoxicity. Our data is consistent with the experimentally reported results where powder of Salacia plant extract was experimentally tested in various safety studies, including acute toxicity, mutagenicity, reproductive outcome, hepatotoxicity, and other toxicity studies (25-30).

Table 4: Prediction of ADME descriptors of the salacinol and related analogues.

Parameters	**Salacinol**	**Neosalacinol**	**Kotalanol**	**Neokotalanol**
Hepatotoxicity	Inactive	Inactive	Inactive	Inactive
Carcinogenicity	Inactive	Inactive	Inactive	Inactive
Immunotoxicity	Inactive	Inactive	Inactive	Inactive
Mutagenicity	Inactive	Inactive	Inactive	Inactive
Mutagenicity	Inactive	Inactive	Inactive	Inactive
Cytotoxicity	Inactive	Inactive	Inactive	Inactive
Predicted LD50 (mg/kg)	5000	5000	2750	5000
Toxicity class	5	5	5	5
Parameters	**Neoponkoranol**	**Ponkoranol**	**Salaprinol**	**Neosalaprinol**
Hepatotoxicity	Inactive	Inactive	Inactive	Inactive
Carcinogenicity	Inactive	Inactive	Inactive	Inactive
Immunotoxicity	Inactive	Inactive	Inactive	Inactive
Mutagenicity	Inactive	Inactive	Inactive	Inactive
Mutagenicity	Inactive	Inactive	Inactive	Inactive
Cytotoxicity	Inactive	Inactive	Inactive	Inactive
Predicted LD50 (mg/kg)	2750	5000	5000	5000
Toxicity class	5	5	5	5

3.4. Frontier Molecular Orbitals (FMOs) and Global Reactivity Descriptors

Understanding the structural behavior of bioactive compounds is crucial to investigating how structural orientation affects biological activity and what factors are responsible for a molecule's biological activity. Thus, the frontier molecular orbitals (FMO) and electronic parameters were estimated and examined. The frontier molecular orbital (FMO) (HOMO-LUMO) can be used to analyze chemical properties including chemical reactivity kinetic stability, and biological properties (31, 32). The FMOs and their energy difference Eg are computed to predict salacinol's energetic properties and reactivity. In addition, the energy gap between HOMO-LUMO explains molecule stability and reactivity. Moreover, the energy gap (HOMO-LUMO) is highly significant for the bio (active/ inactive), and chemical structure. By using the B3LYP/6- 311G ++ (d, p) level of theory, it is possible to determine the HOMO–LUMO values. Table 5 shows the different physical characteristics derived from HOMO–LUMO. The electron affinity (EA) and ionization potential (IP) are linked to LUMO and HOMO energy, according to Koopman's established theorem. Furthermore, the HOMO has an electron-rich capacity that allows it to give electrons. Whereas the LUMO is deficient in electrons, it is always capable of accepting them.

Table 5 shows that neokotalanol has the highest HOMO energy (EHOMO = -0.53 eV). Due to the higher energy, it is the most efficient electron donor. Salaprinol has the lowest LUMO energy (ELUMO = -2.95 eV), indicating that it may be the best electron acceptor.

The lower value of the energy gap indicates that the molecule is more active, polarized, and with small kinetic bioactivity. Neokotalanol and Ponkoranol have smaller energy gaps (Eg = 0.345 eV and 0.64 eV, respectively) than all other compounds as seen in Table 5.

Hardness and softness parameters are important in a chemical system. Molecules with high HOMO-LUMO gaps are referred to as hard molecules, while molecules with small HOMO-LUMO gaps are referred to as soft molecules and are consequently more favorable for reaction. This explanation also supports that Neokotalanol and Ponkoranol are chemically reactive.

The electronegativity refers to the molecule’s capacity to attract electrons. According to the values in Table 5, Salacinol has greater electronegativity among all the compounds, making it the best acceptor of electrons.

The term “Chemical Potential” quantifies an electron's propensity to escape and is related to molecule electronegativity. With decreasing chemical potential, it becomes more difficult to lose an electron but easier to get one. As can be seen in Table 5, neokotalanol (-4.381 eV) has a smaller electronic chemical potential than the rest of the molecules. As a consequence of this finding, neokotalanol is more stable and less reactive than the other results.

The maximal charge transfer (Qmax) signifies the system's tendency to acquire more electrical charge from its surroundings. As presented in Table 5, salaprinol is more susceptible to receiving an additional electronic charge than other compounds. The electrophilicity index measures the reduction in energy due to maximum electron flow between donor (HOMO) and acceptor (LUMO). Salaprinol (14.90 eV) has a greater value than the rest of the molecules, making it the strongest electrophile.

Electrodonating power is related to charge donation, while electroaccepting power is connected to charge acceptance. In contrast, having a higher electron-accepting power shows a high capacity to accept an electron, while having a lower electron-donating power suggests a high ability to donate an electron. Based on the data in Table 5, salaprinol has a greater capacity to accept electrons, whereas neokotalanol has a higher ability to donate electrons.

The net electrophilicity index is related to the values of electron-donating and electron-accepting power. As shown in Table 5, salaprinol has a higher net electrophilicity index. As a result, neokotalanol and ponkoranol have the greatest chemical reactivity and bioactivity compared to the other compounds.

3.6. Local Reactivity Descriptors

Depending on the local reactivity descriptors (Fukui Functions), the electron density is utilized to identify the positive reactive locations of the molecule that are essential for the biological substance. The Fukui function (FF) may be used to investigate the reactivity of a molecule. They are among the most helpful reactivity indices derived from the most helpful DFT. Furthermore, it helps in determining the most reactive electrophilic and nucleophilic attack sites on a molecule. when the number of electrons is changed. The study in Fukui shows that the more reactive locations in a molecule contribute to chemical consequences (33). From Table 6, 2S, 9C, and 6C (reactive sites) are locations for a nucleophilic attack for salacinol, neosalacionol, and neokotalanol, respectively. Whereas 44Cl, 46H, and 19O (reactive sites) are locations for an electrophilic attack for neoponkoranol, neokotalanol, and ponkoranol respectively. Moreover, the most reactive sites in radical attacks are 44Cl and 46H (reactive sites), for neoponkoranol, and neokotalanol, respectively.

Table 5: Global chemical reactivity descriptors for all compounds.

Indices	**Salacinol**	**Neosalacinol**	**Kotalanol**	**Neokotalanol**	**Ponkoranol**	**Neoponkoranol**	**Salaprinol**	**Neosalaprinol**
E_{HOMO} (eV)	-7.130	-3.65	-5.62	-0.53	-2.16	-6.98	-3.69	-3.36
E_{LUMO} (eV)	-1.633	-2.62	-2.08	-0.185	-1.52	-0.48	-2.95	-1.94
IP (eV)	7.130	3.65	5.62	0.53	2.16	6.98	3.69	3.36
EA (eV)	1.633	2.62	2.08	0.185	1.52	0.48	2.95	1.94
Eg (eV)	5.497	1.03	3.54	0.345	0.64	6.5	0.74	1.42
η(eV)	2.749	0.52	1.77	0.173	0.32	3.25	0.37	0.71
S $(eV)^{-1}$	0.182	0.971	0.283	2.899	1.563	0.154	1.351	0.704
χ(eV)	4.381	3.14	3.85	0.358	1.84	3.73	3.32	2.65
μ (eV)	-4.381	-3.14	-3.85	-0.358	-1.84	-3.73	-3.32	-2.65
ω (eV)	3.493	9.56	7.41	0.371	5.29	2.14	14.90	4.95
Q^{max}	1.568	6.04	2.18	2.05	2.88	1.15	8.97	3.73
ω^{+}(eV)	1.645	8.04	6.33	0.57	12.5	4.41	16.60	12.72
ω^{-} (eV)	6.027	11.17	4.10	0.213	8.18	0.68	11.44	7.42
$\omega^{\pm}$ (eV)	7.672	19.21	10.43	0.78	20.68	5.09	28.04	20.14

Table 6: Order of the reactive sites on all compounds.

	Salacinol		**Neosalacinol**	
Sites	2 S	7 O	9 C	8 C
F_k^+	0.57	0.40	0.63	0.10
Sites	11 O	2 S	27 H	15 C
F_k^-	0.97	0.02	0.65	0.15
Sites	11 O	2 S	27 H	9 C
F_k^0	0.49	0.29	0.34	0.32
	Kotalanol		**Neokotalanol**	
Sites	15 C	1 S	6 C	5 O
F_k^+	0.53	0.45	0.513	0.449
Sites	13 O	2S	46 H	3 C
F_k^-	0.98	0.02	0.99	0.0007
Sites	13 O	15 C	46 H	6 C
F_k^0	0.49	0.27	0.502	0.256
	Ponkoranol		**Neoponkoranol**	
Sites	1 C	5 S	6 C	5 S
F_k^+	0.520	0.459	0.529	0.445
Sites	19 O	16 S	44 Cl	5 S
F_k^-	0.99	0.008	1.00	0.002
Sites	19 O	5 S	44 Cl	6 C
F_k^0	0.495	0.229	0.500	0.265
	Salaprinol		**Neosalaprinol**	
Sites	16 C	1 S	10 C	1 S
F_k^+	0.490	0.482	0.524	0.455
Sites	31 H	18 C	21 H	27 H
F_k^-	0.659	0.051	0.694	0.209
Sites	31 H	1 S	21 H	10 C
F_k^0	0.329	0.242	0.347	0.262

3.7. Molecular Electrostatic Potential (MEP) Map

Molecular electrostatic potential (MEP) analysis is a valuable method for determining electrophilic and nucleophilic sites of molecular systems, hydrogen bond interactions, and chemical reactivities, such as biomolecules and drugs, in three dimensions. It enables us to compare a molecule's most reactive nucleophilic and electrophilic sites to its reactive biological potentials.

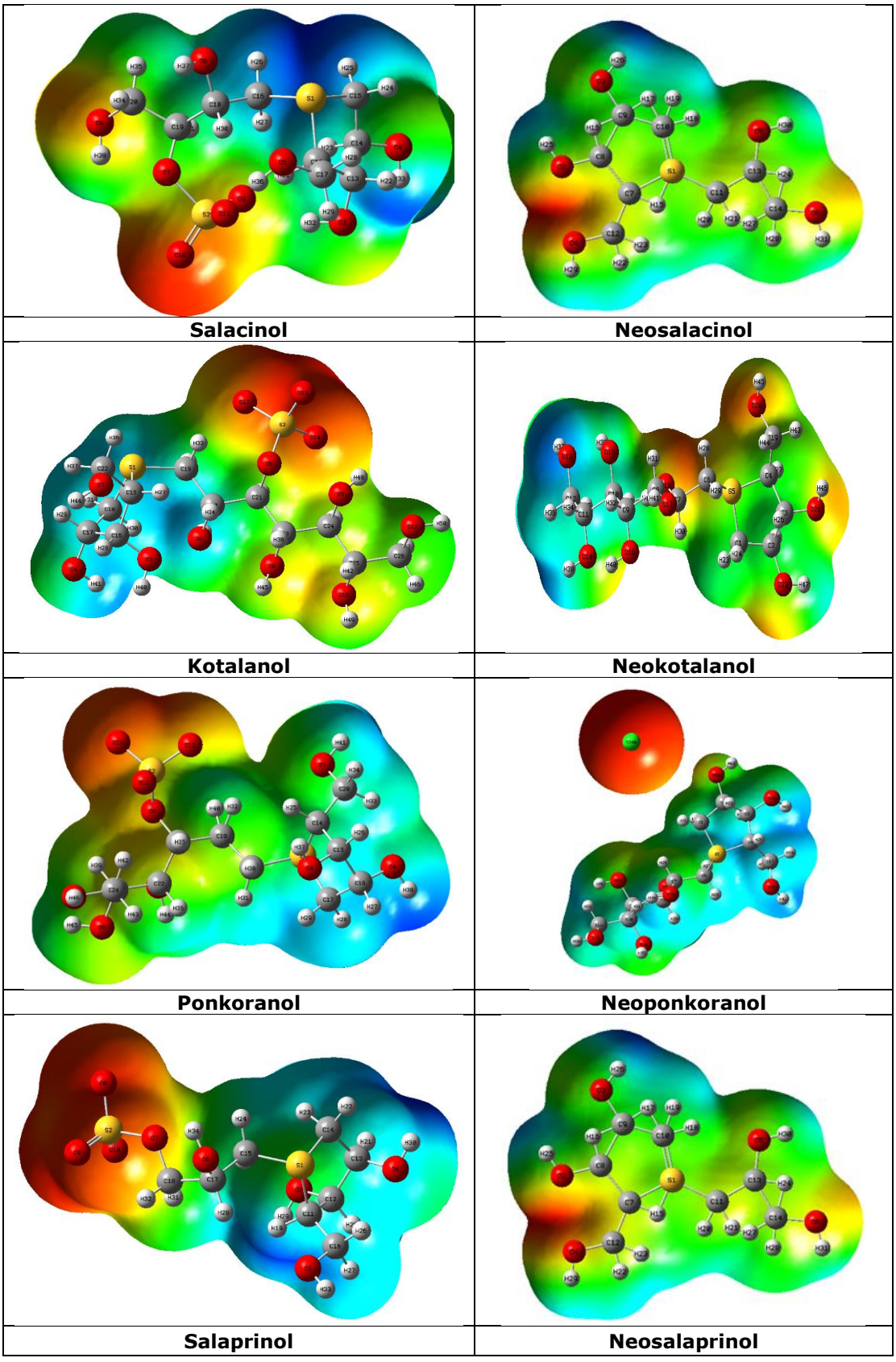

Figure 2: MEP maps for all compounds.

The molecular Electrostatic Potential (MEP) maps for the title compounds were computed by using DFT at the B3LYP/6–311++G (d, p) level. An electrophilic site shows significant attraction, whereas a nucleophilic site shows strong repulsion. The red color is the electrostatic most electronegative possibility (34-37). In this area, atoms prefer to attract electrons (electrophilic). The blue color shows the most electropositive potentials. In this region, atoms prefer to donate electrons (nucleophilic).

In addition, the green color is used to indicate regions where the potentials are equal to zero. As can be seen, the MEP map of all compounds shows that all hydrogen atoms have the greatest positive area, which indicates a potential location for electrophilic attack. As well, the O11, O5, O13, O20, O19, Cl44, O8, and O4 atoms for all compounds respectively have the greatest negative area, which specifies a potential location for nucleophilic attack. Consequently, we can conclude that the positive and area sites provide information about the region where the molecule is capable of forming intermolecular interaction.

4. CONCLUSION

In this study, we conducted a comprehensive in silico evaluation of the potential of salacinol and its related analogues as drug candidates.

Our results predicted that all compounds have various favorable druglike properties.

All the studied compounds exhibit low gastrointestinal absorption, inability to cross the blood-brain barrier and act as substrates for P-glycoprotein. Additionally, none of the compounds function as inhibitors of cytochrome P450 isoenzymes. This suggests that the limited bioavailability and brain penetration of these compounds may be influenced by P-glycoprotein-mediated efflux, limiting the significance of their interaction with this transporter in drug development and tissue protection.

We also found that all compounds have various potential to interact with a wide range of biological targets, including GPCRs, enzymes, ion channels, kinases, and nuclear receptors. This suggests that they could be used to modulate a range of physiological processes.

Additionally, all compounds have low toxicity and are unlikely to cause any major health hazards in terms of hepatotoxicity, mutagenicity, cardiotoxicity, cytotoxicity, and immunotoxicity.

the MEP, FUKUI functions, and HOMO-LUMO energy gap are useful tools for understanding the reactivity of salacinol and its derivatives. This information can be used to design new drugs that target specific biological molecules. This suggests that they are reliable for in vivo applications.

5. CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

6. ACKNOWLEDGMENTS

Not applicable.

7. FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

8. CODE AVAILABILITY

The calculations have been carried out using Gaussian 09 and GaussView version 6.0.

9. REFERENCES

1. Akaki J, Morikawa T, Miyake S, Ninomiya K, Okada M, Tanabe G, et al. Evaluation of *Salacia* Species as Anti-diabetic Natural Resources Based on Quantitative Analysis of Eight Sulphonium Constituents: A New Class of α-Glucosidase Inhibitors. Phytochem Anal [Internet]. 2014 Nov 1;25(6):544–50. Available from: <URL>.

2. Federation ID. IDF diabetes atlas ninth. Dunia Idf. 2019;9:168.

3. Morikawa T, Akaki J, Ninomiya K, Kinouchi E, Tanabe G, Pongpiriyadacha Y, et al. Salacinol and Related Analogs: New Leads for Type 2 Diabetes Therapeutic Candidates from the Thai Traditional Natural Medicine Salacia chinensis. Nutrients [Internet]. 2015 Feb 27;7(3):1480–93. Available from: <URL>.

4. Daina A, Michielin O, Zoete V. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Sci Rep [Internet]. 2017 Mar 3;7(1):42717. Available from: <URL>.

5. Banerjee P, Eckert AO, Schrey AK, Preissner R. ProTox-II: a webserver for the prediction of toxicity of chemicals. Nucleic Acids Res [Internet]. 2018 Jul 2;46(W1):W257–63. Available from: <URL>.

6. Hussein YT, Azeez YH. DFT analysis and *in silico* exploration of drug-likeness, toxicity prediction, bioactivity score, and chemical reactivity properties of the urolithins. J Biomol Struct Dyn [Internet]. 2023 Mar 4;41(4):1168–77. Available from: <URL>.

7. 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 [Internet]. 1997 Jan 15;23(1–3):3–25. Available from: <URL>.

8. Veber DF, Johnson SR, Cheng H-Y, Smith BR, Ward KW, Kopple KD. Molecular Properties That Influence the Oral Bioavailability of Drug Candidates.

J Med Chem [Internet]. 2002 Jun 1;45(12):2615–23. Available from: <URL>.

9. Rahuman MH, Muthu S, Raajaraman BR, Raja M, Umamahesvari H. Investigations on 2-(4-Cyanophenylamino) acetic acid by FT-IR,FT-Raman, NMR and UV-Vis spectroscopy, DFT (NBO, HOMO-LUMO, MEP and Fukui function) and molecular docking studies. Heliyon [Internet]. 2020 Sep 1;6(9):e04976. Available from: <URL>.

10. Gaussian 09 RA, Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, et al. Gaussian 16, Revision A. 02, Gaussian. Inc, Wallingford CT. 2016;2.

11. Gnanamozhi P, Pandiyan V, Srinivasan P, David Stephen A. Exploring the Structure, Electron Density and HOMOLUMO Studies of Tetrathiafulvalene (TTF) as Organic Superconductors: A DFT and AIM Analysis. J At Mol Condens Nano Phys. 2019;10(1):33–43.

12. Choudhary V, Bhatt A, Dash D, Sharma N. DFT calculations on molecular structures, HOMO–LUMO study, reactivity descriptors and spectral analyses of newly synthesized diorganotin(IV) 2-chloridophenylacetohydroxamate complexes. J Comput Chem [Internet]. 2019 Oct 15;40(27):2354–63. Available from: <URL>.

13. R D, Kumar D. Tuning the properties of truxene by successive substitution of nitrogen and sulphur heteroatoms: a DFT insight. J Mol Model [Internet]. 2022 Jan 4;28(1):27. Available from: <URL>.

14. Mu T, Xi Y, Huang M, Chen G. Search for optimal monomers for fabricating active layers in thin-film composite osmosis membranes by conceptual density functional theory. J Mol Model [Internet]. 2020 Dec 6;26(12):334. Available from: <URL>.

15. Gohlke H, Klebe G. Approaches to the Description and Prediction of the Binding Affinity of Small-Molecule Ligands to Macromolecular Receptors. Angew Chemie Int Ed [Internet]. 2002 Aug 2;41(15):2644–76. Available from: <URL>.

16. Husain A, Ahmad A, Khan SA, Asif M, Bhutani R, Al-Abbasi FA. Synthesis, molecular properties, toxicity and biological evaluation of some new substituted imidazolidine derivatives in search of potent anti-inflammatory agents. Saudi Pharm J [Internet]. 2016 Jan 1;24(1):104–14. Available from: <URL>.

17. Lipinski CA. Lead- and drug-like compounds: the rule-of-five revolution. Drug Discov Today Technol [Internet]. 2004 Dec 1;1(4):337–41. Available from: <URL>.

18. Hammoudi N-E-H, Benguerba Y, Attoui A, Hognon C, Lemaoui T, Sobhi W, et al. *In silico* drug discovery of IKK-β inhibitors from 2-amino-3-cyano-4-alkyl-6-(2-hydroxyphenyl) pyridine derivatives based on QSAR, docking, molecular dynamics and drug-likeness evaluation studies. J Biomol Struct Dyn [Internet]. 2022 Jan 22;40(2):886–902. Available from: <URL>.

19. Finch A, Pillans P. P-glycoprotein and its role in drug-drug interactions. Aust Prescr [Internet]. 2014 Aug 1;37(4):137–9. Available from: <URL>.

20. Fromm MF. Importance of P-glycoprotein at blood–tissue barriers. Trends Pharmacol Sci [Internet]. 2004 Aug 1;25(8):423–9. Available from: <URL>.

21. Kim RB, Fromm MF, Wandel C, Leake B, Wood AJ, Roden DM, et al. The drug transporter P-glycoprotein limits oral absorption and brain entry of HIV-1 protease inhibitors. J Clin Invest [Internet]. 1998 Jan 15;101(2):289–94. Available from: <URL>.

22. Kirchmair J, Göller AH, Lang D, Kunze J, Testa B, Wilson ID, et al. Predicting drug metabolism: experiment and/or computation? Nat Rev Drug Discov [Internet]. 2015 Jun 24;14(6):387–404. Available from: <URL>.

23. van Waterschoot RAB, Schinkel AH. A Critical Analysis of the Interplay between Cytochrome P450 3A and P-Glycoprotein: Recent Insights from Knockout and Transgenic Mice. Scott EE, editor. Pharmacol Rev [Internet]. 2011 Jun 1;63(2):390–410. Available from: <URL>.

24. Cheng F, Li W, Zhou Y, Shen J, Wu Z, Liu G, et al. admetSAR: A Comprehensive Source and Free Tool for Assessment of Chemical ADMET Properties. J Chem Inf Model [Internet]. 2012 Nov 26;52(11):3099–105. Available from: <URL>.

25. Kishino E, Ito T, Fujita K, Kiuchi Y. A mixture of Salacia reticulata (Kotala himbutu) aqueous extract and cyclodextrin reduces body weight gain, visceral fat accumulation, and total cholesterol and insulin increases in male Wistar fatty rats. Nutr Res [Internet]. 2009 Jan 1;29(1):55–63. Available from: <URL>.

26. Flammang AM, Cifone MA, Erexson GL, Stankowski LF. Genotoxicity testing of a fenugreek extract. Food Chem Toxicol [Internet]. 2004 Nov 1;42(11):1769–75. Available from: <URL>.

27. Im R, Mano H, Nakatani S, Shimizu J, Wada M. Safety Evaluation of the Aqueous Extract Kothala Himbutu (*Salacia reticulata*) Stem in the Hepatic Gene Expression Profile of Normal Mice Using DNA Microarrays. Biosci Biotechnol Biochem [Internet]. 2008 Dec 23;72(12):3075–83. Available from: <URL>.

28. Jihong Y, Shaozhong L, Jingfeng S, Kobayashi M, Akaki J, Yamashita K, et al. Effects of Salacia chinensis extract on reproductive outcome in rats. Food Chem Toxicol [Internet]. 2011 Jan 1;49(1):57–60. Available from: <URL>.

29. Jayawardena MHS, de Alwis NMW, Hettigoda V, Fernando DJS. A double blind randomised placebo controlled cross over study of a herbal preparation containing Salacia reticulata in the treatment of type 2 diabetes. J Ethnopharmacol [Internet]. 2005 Feb 28;97(2):215–8. Available from: <URL>.

30. Oda Y, Yuasa A, Ueda F, Kakinuma C. A subchronic oral toxicity study of Salacia reticulata extract powder in rats. Toxicol Reports [Internet]. 2015 Jan 1;2:1136–44. Available from: <URL>.

31. Ganesan M, Paranthaman S. Molecular structure, interactions, and antimicrobial properties of curcumin-PLGA Complexes—a DFT study. J Mol Model [Internet]. 2021 Nov 28;27(11):329. Available from: <URL>.

32. Suvitha A, El-Mansy MAM, Kothandan G, Steephen A. Molecular Structure, FT-RAMAN, IR, NLO, NBO, HOMO–LUMO analysis, physicochemical descriptors, adme parameters, and pharmacokinetic bioactivity of 2, 3, 5, 6-tetrachloro-p-benzoquinone. J Struct Chem [Internet]. 2021 Sep 26;62(9):1339–56. Available from: <URL>.

33. Grillo IB, Urquiza-Carvalho GA, Chaves EJF, Rocha GB. Semiempirical methods do Fukui functions: Unlocking a modeling framework for biosystems. J Comput Chem [Internet]. 2020 Apr 5;41(9):862–73. Available from: <URL>.

34. Cardoso FJB, de Figueiredo AF, da Silva Lobato M, de Miranda RM, de Almeida RCO, Pinheiro JC. A study on antimalarial artemisinin derivatives using MEP maps and multivariate QSAR. J Mol Model [Internet]. 2008 Jan 30;14(1):39–48. Available from: <URL>.

35. Obiol-Pardo C, Cordero A, Rubio-Martinez J, Imperial S. Homology modeling of Mycobacterium tuberculosis 2C-methyl-d-erythritol-4-phosphate cytidylyltransferase, the third enzyme in the MEP pathway for isoprenoid biosynthesis. J Mol Model [Internet]. 2010 Jun 15;16(6):1061–73. Available from: <URL>.

36. El-Shamy NT, Alkaoud AM, Hussein RK, Ibrahim MA, Alhamzani AG, Abou-Krisha MM. DFT, ADMET and Molecular Docking Investigations for the Antimicrobial Activity of 6,6′-Diamino-1,1′,3,3′-tetramethyl-5,5′-(4-chlorobenzylidene)bis[pyrimidine-2,4(1H,3H)-dione]. Molecules [Internet]. 2022 Jan 18;27(3):620. Available from: <URL>.

37. Haddadi Z, Meghezzi H, Amar A, Boucekkine A, Bennamane N, Nedjar-Kolli B, et al. DFT and QSAR investigations of substituent effects in pyrazolooxazine derivatives: Activity prediction. J Theor Comput Chem [Internet]. 2019 Feb 10;18(01):1950001. Available from: <URL>.