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DFT Study and ADMET Investigation of Bioactive 2-Phenoxyquinolines

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Abstract

Pharmacologically active quinoline compounds show interesting functionalities. However, there is still a dearth of information on the potential wide applications of the quinoline scaffolds especially when the substituents on the rings or functionalities are modified. In this study 2-phenoxyquinoline-3-carbaldehyde derivatives were synthesized and investigated using DFT to determine the molecular parameters, electronic and chemical reactivity descriptors including their possible application as drug candidates. Geometry optimisations were carried out using Becke three-parameter hybrid functional combined with Lee-Yang-Parr correlation functionals and augmented basis set with added sets of diffuse s- and p-functions: BL3YP /6-311++G(d,p). Drug-likeness scores and bioactivity prediction were carried out using the webserver programs ADMET Sar 2. Our results showed slightly lower energy values in water than in ethanol depicting high reactiveness of the 2-phenoxyquinolines in water especially compounds with fluoro- and methoxy substituted having the lowest E_{gap} of 3.79 eV and 3.381 eV respectively. The methoxy substitution confers higher susceptibility to electron transfer and chemical reactive in aqeous medium. The ionization potential energies were lower in water and ethanol when compared to the other gas states calculated values. The MEP surfaces of all the compounds investigated reveals the ether oxygen atoms and carbonyl groups as necessities for effective antioxidant properties. It is noteworthy that five of the compounds investigated have high activity values above 3.0 octanol–water partition coefficient value indicating an excellent inhibitory activity and strong chemical reactivity. Good oral bioavailability was shown by the compounds depicting their excellent activity as kinase inhibitors, nuclear receptor compounds and enzyme inhibitors. It is noteworthy that cytochromes CYP2C19, CYP2C29, CYP2D6 and CYP3A4 are not inhibited and therefore do not pose potential adverse drug reactions or toxicity. Interestingly, only one compound showed one violation. Consequently, such scaffolds are potential drug candidates.

Keywords: 2-phenoxyquinolines; drug-likeness; cytochrome substrate; structural activity relationship.

INTRODUCTION

Quinoline an aromatic organic compound is prevalent in various pharmacologically active synthetic and natural compounds. It is characterized by a double-ring structure containing a benzene ring fused to pyridine at two adjacent carbon atoms (Jain et al., 2016) and have been found highly useful as antimalarial, anticancer, anti-inflammatory agents, etc. (Dib et al., 2021) leading to its attraction of great interest in the scientific community. Researchers have synthesized hybrid quinoline scaffolds using different procedures (Figure 1a).

Conventional chemotherapy kills most tumour cells and it is believed that cells left behind might recur thereby becoming stem cells which are likely to share similar properties of parent cells, such as resistance to drugs and toxicity via ATP-binding cassette (ABC) transporter expressions (Suzuki *et al*., 1997). A series of quinoline derivatives has been reported to show MDR-reversing activities in K562 cancer cells that are resistant to doxorubicin (an anthracycline multi-cancer therapy) which has been identified as a novel, orally active, quinoline-derivative inhibitor of ABCB1 / P-gp (Kouznetsov et al., 2016). Drugs and candidates such as Lenvatinib, Cabozantinib and Dofequidar are anticancer drugs based on the C-4 and C-5 substituted aryloxyquinoline and alkoxyquinoline derivatives respectively have also been found to contain high efficacies as shown in Figure 1b (Suzuki et al., 1997; Katayama et al., 2009).

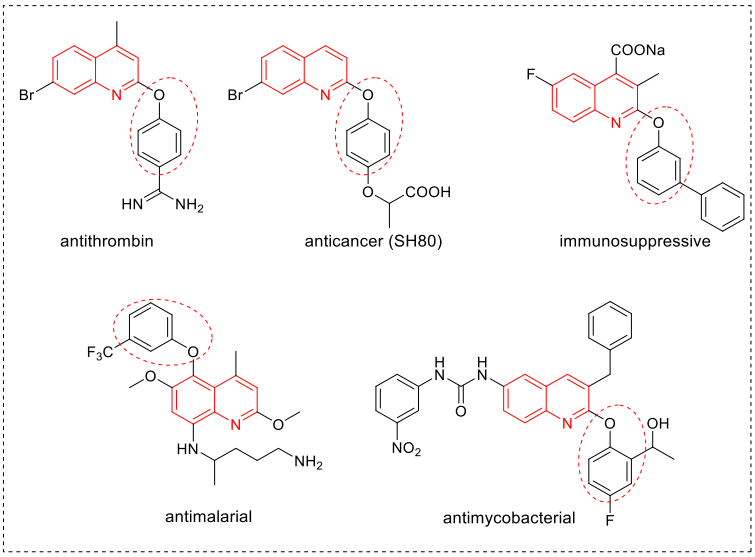


Figure 1a. Some applications of 2-phenoxyquinoline derivatives.

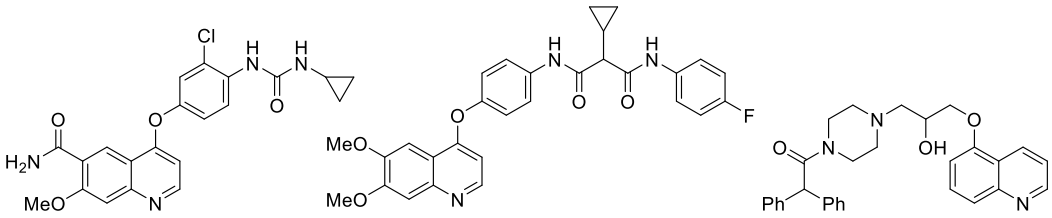


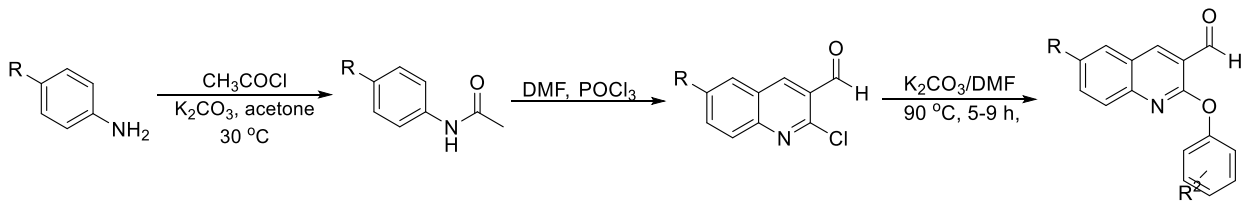
Figure 1b. Anticancer drugs with the alkyl/aryloxyquinoline moiety.

METHODOLOGY

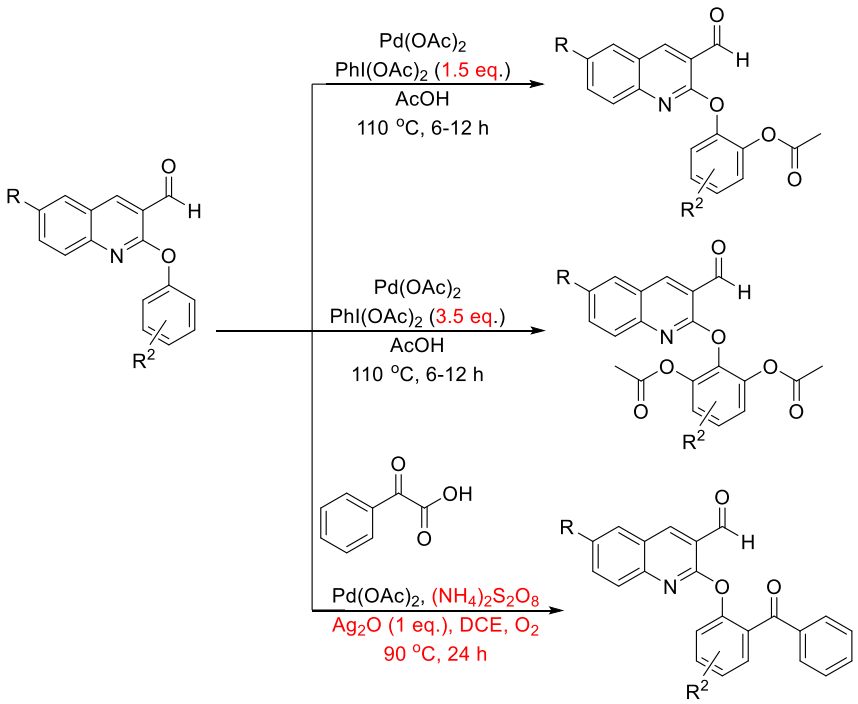
Different novel methods have resulted to synthesis of this bioactive moiety for more than five decades and these methodologies have all been modified with eco-friendly transition metal mediated, traditional methods, microwave or ultrasonic irradiation, oxidation of the corresponding alcohols or greener protocols (Sharma et al., 2018; Ramírez et al., 2022). Amongst the contemporary methodologies are the conventional methods such as condensation of amines and carbonyl compounds with numerous substrate scope (Kouznetsov et al., 2005; Iwai & Sawamura, 2015).

Synthesis of precursors and target compounds

Vilsmeier-Haack reaction of acetanilides, one of the practically important routes to synthesis of 2-chloroquinoline-3-carbaldehydes, involves the processes of chlorination, formylation and cyclization of acetanilides by the action of the Vilsmeier´s reagent ($DMF/POCl_3$) to afford 2-chloroquinoline-3-carbaldehydes as shown in scheme 1 (Meth-Cohn et al., 1981). The adducts obtained from Vismeier reaction could undergo substitution reaction at positions 2 and 3 where the active chloro and the aldehyde groups could lead to numerous functionalization under appropriate reagents (Abdel-Wahab & Khidre, 2013).



Scheme 1. Synthesis of 2-chloroquinoline-3-carbaldehyde and its phenoxylated adducts as precursors (cf: Bakthadoss & Aina et al, 2024).



Scheme 2. Synthesis of acetoxylated and benzoylated 2-phenoxychloroquinoline-3-carbaldehydes via nitrogen-directed palladium-catalysed sp^2 C-H activation strategy (cf: Bakthadoss & Aina et al, 2024).

Interest in the use of these bioactive organic molecules possessing high degree of delocalization has increased in the recent time due to presence of weak van der Waal's and hydrogen bonds resulting to better enzyme-compound interactions (Kumar et al., 2017). To this end, our study therefore presents density function theory (DFT) with detailed chemical reactivities of eight (8) 2-phenoxyquinoline derivatives shown in Figure 2 synthesized using the methods presented in Scheme 2 to investigate their possible application as drug candidates with emphasis on their toxicity. Quantum mechanical calculations were also performed to examine their molecular structures, parameters, molecular electronic and chemical reactivity descriptors.

Computational Methodology

The coordinates of the structures of synthesised compounds were generated from Avogadro 14.0 while molecular optimization calculations were done using the Orca 4.2.1 Quantum Chemical Software. (Neese, 2017). The geometry optimisation was carried out using the Becke three-parameter hybrid functional combined with Lee-Yang-Parr correlation functionals and augmented basis set with added sets of diffuse s- and p-functions: BL3YP /6-311++G(d,p) (Ennaba, 2017; Kodikara et al., 2018; Al Hasanat, 2017). The choice of selected functional and the basis set were based on its reliability in published reports (Haroon et al., 2019). A single-point gas- phase, water-phase and ethanol-phase optimizations were carried out using time-dependent density functional theory (TD-DFT) [13] keyword and solving for 50 excited states. All calculations in solvent was performed using the CPCM keyword together with the SMD solvent model (Fleming et al., 2011; Ho & Ertem, 2016). Drug-likeness scores and bioactivity prediction were carried out using the webserver programs such as ADMET Sar 2 (available at http://lmmd.ecust.edu.cn/admetsar2) and molinspiration --cheminformatics (available at https://www.molinspiration.com/cgi-bin/properties) (Voiculescu et al., 2022).

RESULT AND DISCUSSION

Chemical reactivity descriptors

DFT tools used in this study give a concise structure-chemical reactivity report of 2-phenoxyquinoline-3-carbaldehyde derivatives (Figure 2) to provide an understanding of the chemical reactivity properties whose descriptors are presented in Table 1. Frontier molecular orbitals (FMOs) energies were used to calculate these chemical reactivity descriptors obtained from conceptual DFT. The energy gap, E_{gap} is defined as the energy difference between E_L (the lowest unoccupied molecular orbital, LUMO) and E_H (energy of the highest occupied molecular orbital, HOMO) which determines the chemical reactivity and kinetic stability of the organic molecule. The lower the energy gap, the more reactive a molecule is, indicating the compound is more susceptible to reacting with proteins or enzymes (Miar et al., 2021). The results of the energy gaps (Table 1 and Figure 3) showed slightly lower energy values in water than in ethanol. Since, the preferred medium of drug delivery is water, this depicts the highest reactiveness of the 2-

phenoxyquinolines in water, with 7 and 3 having the lowest E_{gap} of 3.381 eV and 3.79 eV respectively. The concentration of the molecules is proportionately the inverse of the energy gap. That is, the lower the energy gap the higher the concentration of the molecule in water solution and therefore it shows a greater activity of the 2-phenoxyquinolines in aqueous medium. The difference in the energy gap may be mostly attributed to the differences in their functional groups (Table S1). This difference can be attributed to the acetoxyl and benzoyl substituents at para position of the phenoxy group. In compounds 3, 7 and 8, the main chromone skeleton (quinoline) has both electron withdrawing and electron donating substituents attached to it. These substituents may increase or decrease the electron density in the quinoline ring thereby activating or deactivating the ring. The lower energy gap for 3 and 8 may be attributed to F which shows a negative inductive effect due to its high electronegativity and withdraws the electron density from the quinoline ring, so it deactivating the group. The more electrophilic benzyl group in the chromone backbone allows electronic interactions that are pivotal to the quinoline reactivity. Also, the methoxyl groups on the chromone structure of compound 7 which has the lowest energy gap (3.381 eV) activate the benzene ring towards electrophilic substitution and this is also favourable for the radical scavenging activity of the quinoline ring. The feasibility of a molecular system to exchange electron density or an electron escaping from such system to the surrounding environment at the ground state can be expressed as the energy changes of the molecular system with respect to the number of electrons at a fixed external potential, μ (Domingo et al., 2016).

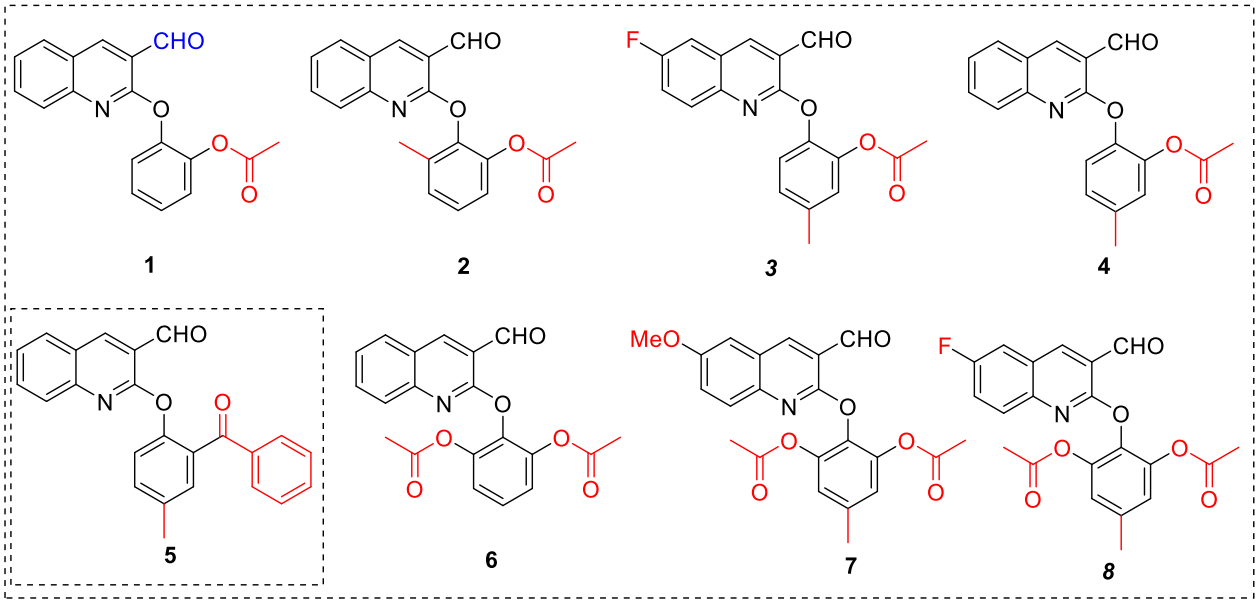


Figure 2. Structures of synthesized phenoxyquinoline compounds investigated.

The calculated electronic chemical potential of the molecules shows no significant difference for the 2-phenoxyuinolines. In water, the chemical potential values range from -4.688 eV (8) to -4.301 eV **(7)** while in ethanol, it ranges from -4.681eV (8) to -4.294 eV (**7**) with both media having the ascending and descending order of **7**, 3, 5, 8, 1, 2, 6 and 4 hardness and softness, η and s respectively define the extent of resistance and susceptibility to polarization or transfer of electron cloud of atoms, ions or molecules in response to a chemical process (Islam & Ghosh, 2011). These periodic properties calculated as global softness, s are the inverse of global hardness, η. Compound 7 shows the most minor resistance or highest susceptibility to charge or electron transfer with η and s values (1.691 eV and 0.592 eV) in water respectively. Conversely, compound **4** has η value of **2.106** eV and s value of **0.475** eV in aqueous medium. Therefore, of all the 2-phenoxyuinolines compounds, 7 is the most susceptible to electron transfer and the most chemically reactive in aqeous medium while compound **4** poses the highest resistance to the transfer of electron density in the medium and hence, the least reactive. Electronegativity, χ, represents electron attraction power of an atom in a molecule towards itself or a measure of molecular electron distribution.[23] The highly probable electron acceptability of these molecules was indicated by high electronegativity values. Compounds 8 and 6 had the highest χ value (4.688 eV and 4.681 eV) in aqueous medium while 7 had the lowest (4.301 eV). A possible explanation for high electronegativity for compound 8 and 6 is the presence of fluoro group (a deactivating group) with high inductive effect. Compound 7, on the other hand has an activating group that is mostly resonance donors (+M), that is,

methoxyl group. Although it also inductively withdraws (–I) electrons, which is a deactivating effect, the resonance (or mesomeric) effect is stronger, hence an even electron distribution which accounts for the reduced electronegativity.

The information about the physico-chemical properties and chemical reactivity phenomena of a molecule can also be revealed by a measure of the stabilization energy of the molecule when it accepts an arbitrary number of electrons approaching from the surroundings. This concept is termed electrophilicity index (ω) (Tandon et al., 2020). This approach can be explained in two ways; the global electro-accepting power ω+ and electro-donating power ω−. The electrondonating power is a measure of the nucleophilicity of the system and it involves the destabilizing change in energy required by a system to attain zero chemical potential with accompanied a decrease in the number of electrons of the system. On the other hand, the electronaccepting power ω+ of a molecular system, can be defined base on the stabilizing energy change of such system when it is saturated with maximum number of electrons (Gazquez et al., 2014).

The net electrophilicty Δω±, describes of intermolecular reactivity (Frau & Glossman-Mitnik, 2017). The results from the calculations show that the 2-phenoxyuinolines have an average approximate electron donating power, ω− of 9 eV. This approximate destabilizing energy is higher than the average approximate electron accepting power, ω+ of about 6 eV except for compound **4** which shows a very lower electrophilic index or stabilizing energy change accompanying electron gain with ω+ value of approximately 1 eV. This suggests that the 2-phenoxyuinolines are strongly nucleophilic and electrophilic but more nucleophilic in reactivity than being electrophilic.

The ionization potential, I and electron affinity values also show the relative tendencies of an atoms or molecule to gain or lose electrons in reaction and useful in the calculation of heats of various reactions and physical changes (Smalo et al., 2010). Reactivity is inversely proportional to Ionization potential so lower ionization potential would depicts a higher the chemical reactivity.

Table 1. Chemical reactivity descriptors for the synthesised 2-Phenoxyquinolines.

Cpd	Medium	EL (eV)	EH (eV)	Egap (eV)	H	S	μ	χ	Ω	ω^{-}	ω^{+}	Δω±	μD	I
1	**Gas**	**-2.597**	**-6.713**	**4.116**	**2.058**	**0.486**	**-4.655**	**4.655**	**1.316**	**9.345**	**6.389**	**15.734**	**2.597**	**6.713**
	Water	**-2.591**	**-6.625**	**4.034**	**2.017**	**0.496**	**-4.608**	**4.608**	**1.316**	**9.257**	**6.424**	**15.680**	**2.591**	**6.625**
	Ethanol	**-2.565**	**-6.614**	**4.049**	**2.025**	**0.494**	**-4.590**	**4.590**	**1.301**	**9.215**	**6.321**	**15.536**	**2.565**	**6.614**
2	**Gas**	**-2.584**	**-6.769**	**4.185**	**2.093**	**0.478**	**-4.677**	**4.677**	**1.306**	**9.382**	**6.298**	**15.680**	**2.584**	**6.769**
	Water	**-2.599**	**-6.659**	**4.060**	**2.030**	**0.493**	**-4.629**	**4.629**	**1.319**	**9.298**	**6.434**	**15.732**	**2.599**	**6.659**
	Ethanol	**-2.573**	**-6.651**	**4.078**	**2.039**	**0.490**	**-4.612**	**4.612**	**1.304**	**9.259**	**6.330**	**15.589**	**2.573**	**6.651**
3	**Gas**	**-2.750**	**-6.678**	**3.928**	**1.964**	**0.509**	**-4.714**	**4.714**	**1.414**	**9.507**	**7.092**	**16.598**	**2.750**	**6.678**
	Water	**-2.670**	**-6.577**	**3.907**	**1.954**	**0.512**	**-4.624**	**4.624**	**1.368**	**9.313**	**6.808**	**16.120**	**2.670**	**6.577**
	Ethanol	**-2.649**	**-6.554**	**3.905**	**1.953**	**0.512**	**-4.602**	**4.602**	**1.356**	**9.265**	**6.731**	**15.996**	**2.649**	**6.554**
4	**Gas**	**-2.536**	**-6.076**	**3.54**	**1.77**	**0.565**	**-4.306**	**4.306**	**1.309**	**8.695**	**6.612**	**15.306**	**2.536**	**6.076**
	Water	**-2.416**	**-6.628**	**4.212**	**2.106**	**0.475**	**-4.522**	**4.522**	**1.214**	**9.055**	**5.714**	**14.770**	**2.416**	**6.628**
	Ethanol	**-2.388**	**-6.599**	**4.211**	**2.1055**	**0.475**	**-4.494**	**4.494**	**1.199**	**8.996**	**5.623**	**14.619**	**2.388**	**6.599**
5	**Gas**	**-2.373**	**-6.499**	**4.126**	**2.063**	**0.485**	**-4.436**	**4.436**	**1.192**	**8.884**	**5.618**	**14.502**	**2.373**	**6.499**
	Water	**-2.564**	**-6.514**	**3.950**	**1.975**	**0.506**	**-4.539**	**4.539**	**1.304**	**9.122**	**6.386**	**15.508**	**2.564**	**6.514**
	Ethanol	**-2.528**	**-6.496**	**3.968**	**1.984**	**0.504**	**-4.512**	**4.512**	**1.283**	**9.061**	**6.245**	**15.306**	**2.528**	**6.496**
6	**Gas**	**-2.633**	**-6.801**	**4.168**	**2.084**	**0.480**	**-4.717**	**4.717**	**1.335**	**9.470**	**6.481**	**15.951**	**2.633**	**6.801**
	Water	**-2.642**	**-6.72**	**4.078**	**2.039**	**0.490**	**-4.681**	**4.681**	**1.343291**	**9.406582**	**6.575077**	**15.98166**	**2.642**	**6.72**
	Ethanol	**-2.615**	**-6.712**	**4.097**	**2.049**	**0.488**	**-4.664**	**4.664**	**1.327**	**9.366**	**6.465**	**15.831**	**2.615**	**6.712**
7	**Gas**	**-2.694**	**-6.140**	**3.446**	**1.723**	**0.580**	**-4.417**	**4.417**	**1.415**	**8.971**	**7.337**	**16.308**	**2.694**	**6.140**
	Water	**-2.610**	**-5.991**	**3.381**	**1.691**	**0.592**	**-4.301**	**4.301**	**1.368**	**8.726**	**7.062**	**15.788**	**2.610**	**5.991**
	Ethanol	**-2.599**	**-5.988**	**3.389**	**1.695**	**0.590**	**-4.294**	**4.294**	**1.360**	**8.708**	**7.009**	**15.717**	**2.599**	**5.988**
8	**Gas**	**-2.771**	**-6.810**	**4.039**	**2.020**	**0.495**	**-4.791**	**4.791**	**1.420**	**9.651**	**7.078**	**16.729**	**2.771**	**6.810**
	Water	**-2.696**	**-6.680**	**3.984**	**1.992**	**0.502**	**-4.688**	**4.688**	**1.379**	**9.438**	**6.843**	**16.281**	**2.696**	**6.680**
	Ethanol	**-2.676**	**-6.686**	**4.010**	**2.005**	**0.499**	**-4.681**	**4.681**	**1.366**	**9.418**	**6.749**	**16.167**	**2.676**	**6.686**

a Units for the chemical reactivity descriptors are in electron volts (eV) EL: LUMO energy, EH: HOMO energy, Egap: HOMO-LUMO energy gap, η: Chemical hardness, S: Chemical softness, μ: Chemical potential, χ: Electronegativity, ω: Electrophilicity index, ω-: Electron donating power, ω+: Electron accepting power, Δω±: Net electrophilicity, μD: Dipole moment, I: Ionization potential, g: gas phase, w: water and eth: ethanol.

In water and ethanol, the ionization potential energies were lower when compared to the other gas states calculated values. This emphasizes the fact that the chemical reactivity of the 2-phenoxyquinolines is well improved in water and ethanol media. Since, the desired medium (water) gives favourable intermolecular interactions via hydrogen bonding, therefore, it reflects in lower ionization potential. Compound 7 has the lowest I value (5.991 eV) in water compared to other 2-phenoxyquinolines.

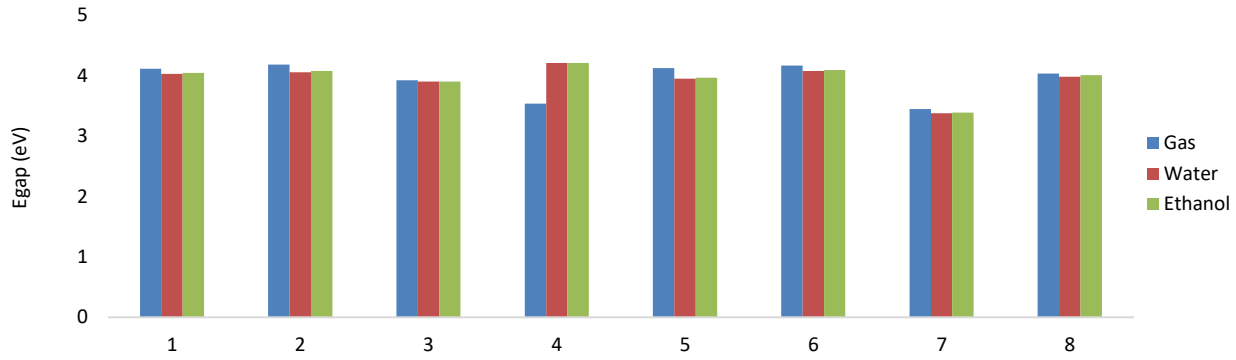


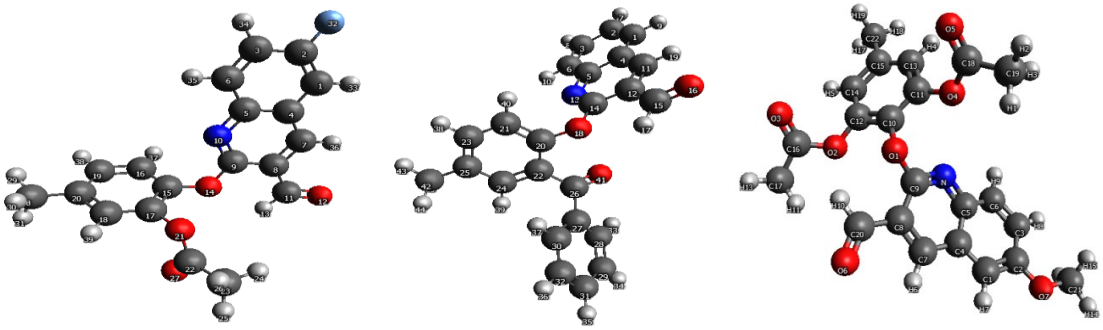
Figure 3. Comparison of the energy gaps in gas-phase, water and ethanol.

Atomic charge and electrostatic potential

Molecular electrical charge is the driving force of electrostatic interactions characterized by electron density playing an important role in chemical reactions and physicochemical properties (Wang & Truhlar, 2014). Descriptors that are charge based are often employed as chemical reactivity indices or as a measure of weak intermolecular interactions. The partial charge or electron density distribution in a molecule is factor to determination of its reactivity description. The Mulliken atomic charges MAC, may be linked to other chemical parameters such as dipole moment, electric potentials, chemical shifts, electronic structure, molecular polarizability and others (Sumrra et al., 2021). A uniform distribution of charge was found for all molecules. For 3, 5, and 7, which had the lowest energy gap in aqeous medium and were the most reactive, they had the highest negatively charged atom (-2.518 a.u, −2.609 a.u. and **-2.021 a.u.**) which is the carbon atom of the imine group at C9 and C14 positions attached to pyridine nitrogen, respectively (Figure 2). This charge is significant for the bioactivity of the molecules due to the role the F, $–OCH_3$ groups play in scavenging radicals.

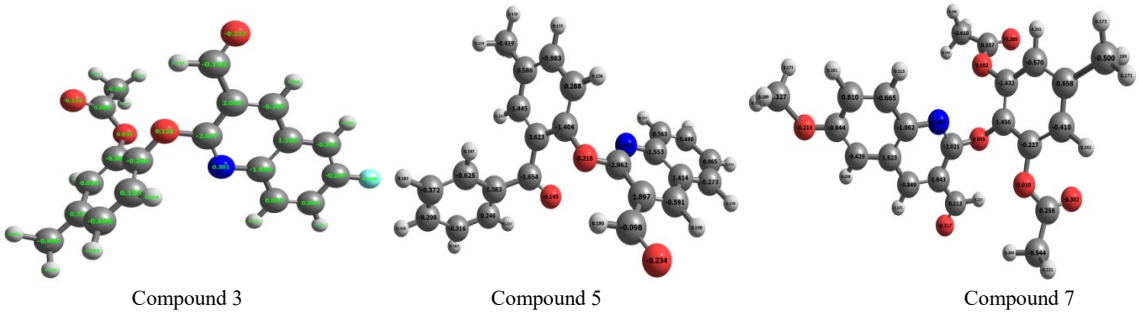
Molecular electrostatic potential surface

Molecular electrostatic potential (MEP) surfaces enhance determination of the reactivity of chemical compounds and it is related to electron density and is a useful chemical descriptor that gives information about sites of nucleophilic attacks, electrophilic attacks and hydrogen bonding interactions (Demircioglu et al., 2019). The blue region indicates the positive potential of the molecule as the area where there is proton repulsion (that is electrophilic attack) while the red region has negative potential and represents proton attraction (nucleophilic attack) (Sheikhi et al., 2016).



Compound 3 Compound 5 Compound 7

Figure 4. Representative optimised structures of synthesized 2-Phenoxyquinolines.



Compound 3 Compound 5 Compound 7

Figure 5. Representative atomic charge distribution in synthesized 2-Phenoxyquinolines.

All the 2-phenoxyquinolines simulated in this study have MEP surfaces with an overall region of positive potential around protons of the C8, C10, and C6 while areas of negative potential are around delocalized pi-electrons, the ether oxygen atoms and that of the carbonyl groups which verifies the necessity of the ether and carbonyl groups for effective antioxidant properties of the quinolines. The carbonyl of the aldehyde and acetate groups of the 2-phenoxyquinolines contributes effectively to the reactive oxygen and hydrogen species' scavenging abilities of the compounds as they offer stability. It is a known phenomenon that the regions of negative potential in the 2-phenoxyquinolines compounds will have an affinity for the positively charged side groups of amino acids (arginine, histidine and lysine) and regions of positive potential of the will bind to the negatively charged side groups of amino acids such as glutamic acid and aspartic acid (Shinde, 2021).

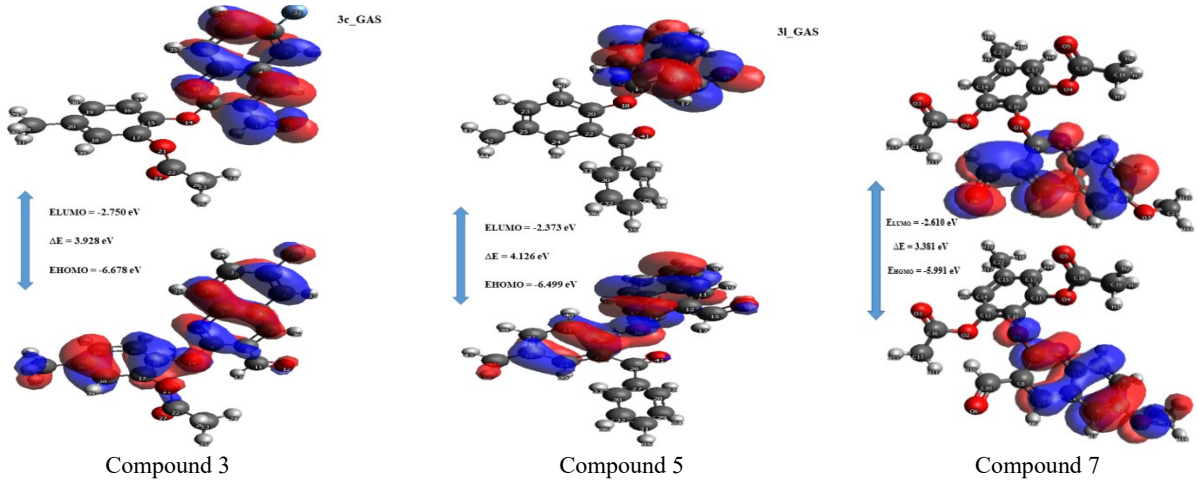
UV–vis spectroscopy

UV–visible spectroscopy has emerged as the most favoured technique to evaluate conjugated organic compounds such as quinoline and its derivatives as the ring in these bioactive molecules have the ability to absorb UV light. Few coloured derivatives also absorb in the visible region thus enabling UV–visible spectroscopy one of the appropriate techniques their bioactivity (Ramešová et al., 2012). Total antioxidant activity is measured by taking absorbance against water to calculate the percentage of inhibition. The presence of the carbonyl groups of the 2-phenoxyquinolines also contributes to an increase in the absorbance. Absorption peak is associated with an electron transition from the ground state to its excited state with corresponding excitation energy and single-point (SP) energy calculation provides the HOMO and LUMO energies as shown in Table 1.

It has been reported that ethanol and water or a mixture of these solvents are suitable since the oxygen of the carbonyl groups easily bond with the hydrogen of the water molecules hence their solubility in the solvents are expected (Blume et al., 1988). We chose water as the solvent for the UV–vis calculation since this is preferred medium for drug delivery. The maximum absorption wavelength (λmax) of the 2-phenoxyquinolines in water and the excitation energies show that maximum wavelength of absorption is inversely proportional to the excitation energy as shown in Table 2, Figure 8.

Table 2. UV–visible Spectroscopy.

Compound	Orbitals	Extinction coeff	Oscil strength	1st Excitation E (eV)	Absorption
1	79 -80	0.548	0.741	3.3711	367.8
2	87 - 88	0.729	0.854	3.159	392.5
3	91 - 92	0.89	0.943	2.865	432.8
4	83 - 84	0.223	0.472	3.368	368.2
5	95 - 96	0.791	0.889	3.186	389.2
6	94-95	0.059	0.243	3.375	367.4
7	106-107	0.94	0.969	2.785	445.2
8	102 - 103	0.317	0.563	3.287	377.2



Compound 3 Compound 5 Compound 7

Figure 6. Representative HOMO-LUMO of synthesized 2-Phenoxyquinoline-3-carbaldehydes.

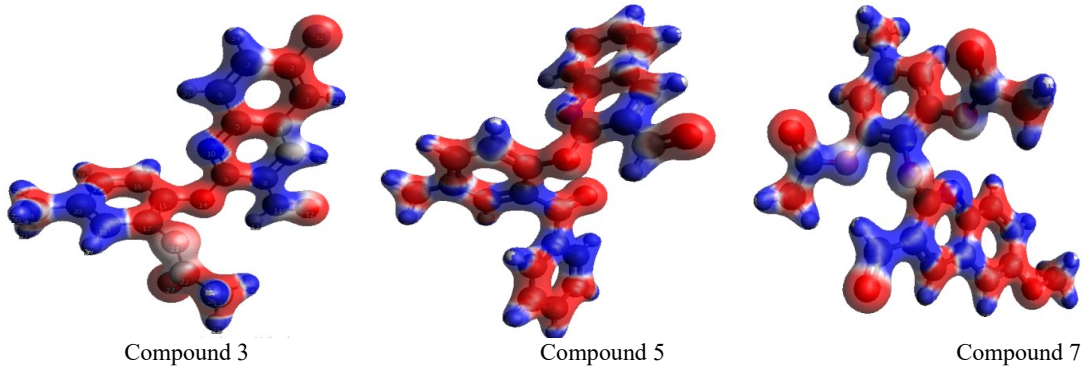


Figure 7. Representative molecular electrostatic potential (MEP) surface of synthesized 2-Phenoxyquinoline-3-carbaldehydes.

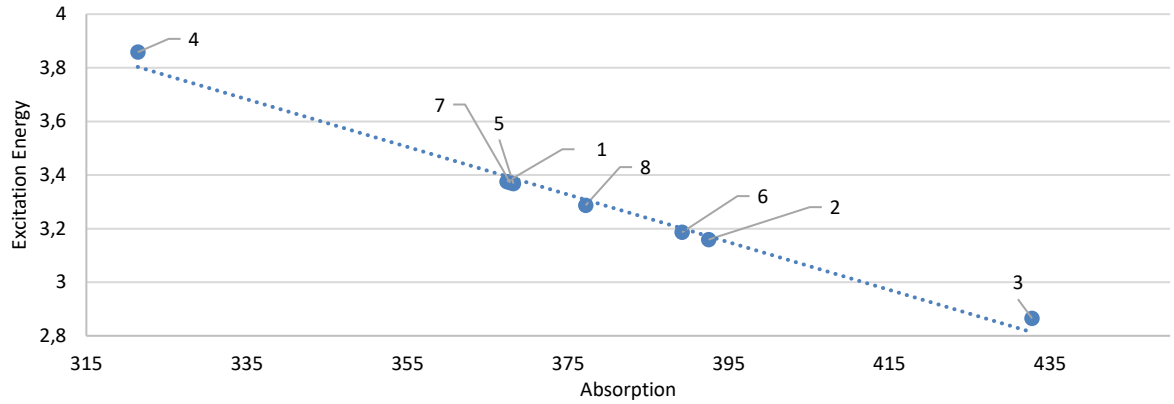


Figure 8. Relationship between excitation energy and maximum absorption wavelength.

Considering the fact that the promotion of an electron from the ground state to the excited state at longer wavelengths require low energy, it is hence apparent the compound 7 with the lowest excitation energy and the highest wavelength, implies most activity while 6 with highest excitation energies has lowest activity. From the time-dependent density functional theory (TD-DFT) calculations, electronic transitions information including which transition orbital was involved, oscillator strength, extinction coefficient, excitation state energies and the electronic states of the transitions support the bioactivity of compound 7.

Molar extinction coefficient, also known as molar absorptivity, is an intrinsic property of the molecule which is dependent on the atomic, chemical, and structural composition. It determines how strongly a species absorbs or reflects radiation or light at a particular wavelength (Ozdemir & SadoGlu, 2018). Compounds 3, 5 and 7 have high molar absorptivity (>0.5 eV), hence, they strongly attenuate light while 4 and 6 have extinction coefficient less than 0.5. Oscillator strength is a dimensionless quantity that expresses the probability of absorption or emission transitions between energy levels of an atom or molecule, that is, a measure of excitation probability (Nizar et al., 2021). The high oscillator strengths which indicate the high probability of excitation gave the strongest transitions (which are presented in Table 1) compared to other transitions.

Molecular and physicochemical properties

Adsorption, distribution, metabolism and excretion (ADME) protocols play crucial roles in the development of new drug molecules as they outline the dose amounts, intervals and overall safety of oral drug administration (McGinnity et al., 2007) making the determination of physicochemical properties feasible (Nithiyanantham et al., 2015) thus providing desirable balance of physicochemical properties for safe drug administration (Belaidi et al., 2016). The logarithm of octanol–water partition coefficient (log POW) is a broadly acknowledged measure of lipophilicity and is determined for numerous compounds (Poole & Poole, 2003). POW is the concentration ratio of the compound distributed between n-octanol and water. (Ribeiro et al., 2011; Jalan et al., 2010). The partition coefficient is an exceedingly important physicochemical parameter in medicinal chemistry, beneficial in pharmacology and toxicology, as long-established by a large numeral of literature data (Balaz, 2009; Sangster, 1997).

Table 3. Physicochemical parameters for 2-phenoxyquinoline-3-carbaldehydes.

Cp	miLog [a]	TPSA [b]	Natoms [c]	MW [d]	nON [e]	nOHNH [f]	Nviolat [g]	Nrotb [h]	Vol [i]
1	3.06	65.5	23	307.31	5	0	0	5	267.79
2	3.46	65.5	24	321.33	5	0	0	5	284.35
3	2.65	65.5	25	339.32	5	0	0	5	289.28
4	3.49	65.5	24	321.33	5	0	0	5	284.35
5	5.59	56.27	28	367.4	4	0	1	5	330.21
6	2.37	91.81	27	365.34	7	0	0	7	312.31
7	3.8	101.04	30	409.39	8	0	0	8	354.42
8	1.94	91.81	29	397.36	7	0	0	7	333.81

a. Octanol–water partition coefficient as reported in Molinspiration. b. Total polar surface area in Å2. c. Total number of atoms. d. Molecular Weight in g mol—1. e. Number of hydrogen bond acceptors. f. Number of hydrogen bond donors. g. Number of violations to Lipinski's rule of 5. h. Number of rotatable bonds. i. Volume in Å3.

Active organic compounds have log P value of 1.6 upward (Buddensiek et al., 2021) implying a reduced inhibitory activity at values below. It is noteworthy to see compounds 1, 2, 4, and 7 have high activity values above 3.0 while compound 5 is well above 5.0 octanol–water partition coefficient value indicating an excellent inhibitory activity coupled with strong chemical reactivity. In the work of Vlahovic *et al.* (2017), hydrophobic substances were reported to have a high octanol–water partition coefficient distributed primarily in the lipid bilayers of cells while hydrophilic substances on the other hand have a low octanol–water partition coefficient and are distributed in blood plasma. They also showed the linear relationship of the octanol–water partition coefficient with log P which explains the high miLogP values obtained for compound 5 with a value of 5.59 as shown in Table 3. This shows the synthesised 2-phenoxyquinolines to be hydrophobic hence would easily distribute in the lipid bilayers. Compound 8 with the least value miLogP value of 1.94 is more hydrophilic than others and will be more readily distributed in blood plasma.

Drug likeness and bioactivity score

Medicinal chemists use drug-likeness as the essential guide *via* hit-to-lead optimization for drug discovery (Sagaama & Issaoui, 2020, Maldonado et al., 2021). Pharmacokinetic properties detailed in ADME parameters are also strongly affected by physicochemical properties (Kumar et al., 2017; Zheng et al., 2013). Since drug-like molecules must be soluble in water as well as fat, it is therefore necessary that an orally administered drug passes through the intestinal lining into the bloodstream and is carried to the target immediately after ingestion, penetrating the lipid-based cell membrane to get into the target cell (Kumar et al., 2017). Increased hydrogen bonds leads to increased aqueous solubility making the molecule less hydrophobic since it enables the molecule to permeate into and through the lipid bilayer membrane (Di & Kerns, 2015). As reported by Veber and co-workers, drug candidates will have a high probability of good oral bioavailability if they meet criteria such as: total polar surface area (TPSA) ≤ 140 $Å^2$ and if the number of rotatable bonds (nrotb) ≤ 10 (Veber et al., 2002). Amazingly, all 2-phenoxyquinolinequinoline-3-carbaldehydes investigated in this study fulfil all these criteria. While the monoacetoxylated 1-4 and benzoylated 5 2-phenoxyquinolines have excellent total polar surface area (65-74 A^2), the di-acetoxylated groups have much higher values ranging from 91-101 A^2) as shown in Table 3.

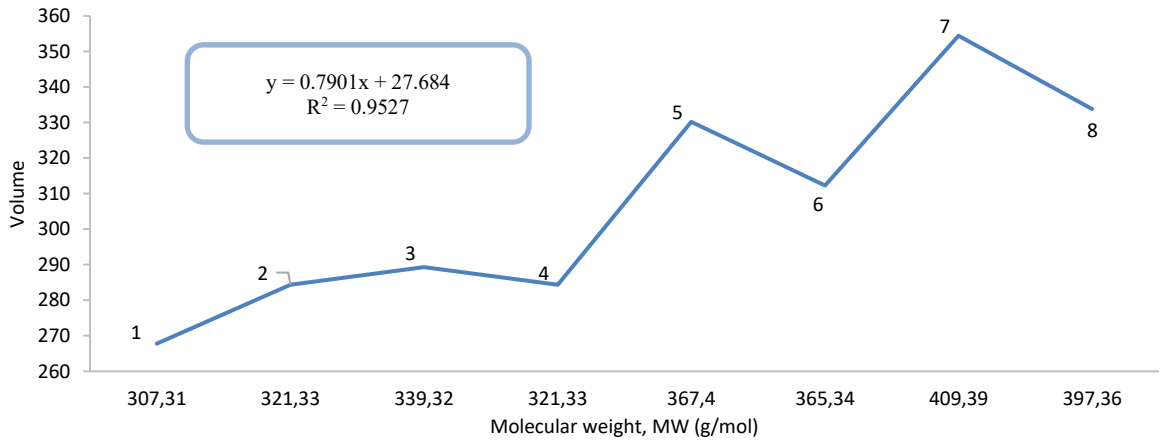


Figure 9. Relationship between volume and molecular weight of synthesised 2-Phenoxyquinolines.

It is noteworthy to express the super permeability of compound 5 (with a TPSA value of 56.27 A^2) in lipid membranes. The Lipinski's rule of 5 states that for a drug molecule to be orally active it should obey important rules such as number of hydrogen bond donors (nOHNH) ≤5, number of hydrogen bond acceptors (nON) ≤ 10, molecular weight (MW) ≤ 500, partition coefficient (miLogP) ≤ 5 and number of violations (nviolations) ≤ 2 (Maurya et al., 2020). Interestingly, all the 2-phenoxyquinoline-3-carbaldehydes comply with the Lipinski rule of 5 (Table 3), testifying to their oral bioavailabilities as potential drug molecules. In compliance, the molecular weight of the compounds is directly proportional to the volume of the compounds (Table 3, Fig. 9) which confirms their correlation with the Pearson correlation co-efficient (r) of 0.97 and R^2 value of 0.94 which states that for an average organic molecule, if the bioactivity score is more than 0 then it is active, a score ranging from -0.50 to 0.0 indicates moderately active and a score of less than -0.50 denotes inactivity (Figure 10) (Alodeani et al., 2015; Akintemi et al., 2022).

To further confirm the correlation by the Pearson correlation coefficient, the bioavailability of the investigated compounds as inhibitors/ substrates were carried out using profile depicting bioactivity score as presented in Figure 10. It is obvious that compound 5 exhibit excellent activity as kinase inhibitors, nuclear receptor compounds and enzyme inhibitors while 3 shows good activity as enzyme inhibitor and nuclear receptor compound. Compounds 3 and 4 exhibit much lower protease inhibitory properties like 2 with moderate kinase inhibitory properties. As shown in Figure 10, all the compounds exhibit good to moderate activity as enzyme inhibitors (EI), G-protein-coupled receptors (GPCR), ion channel modulators (ICM), nuclear receptor compounds (NRL) and kinase inhibitors (KI). It is observed that all the compounds only exhibit moderate activity as protease inhibitors (PI).

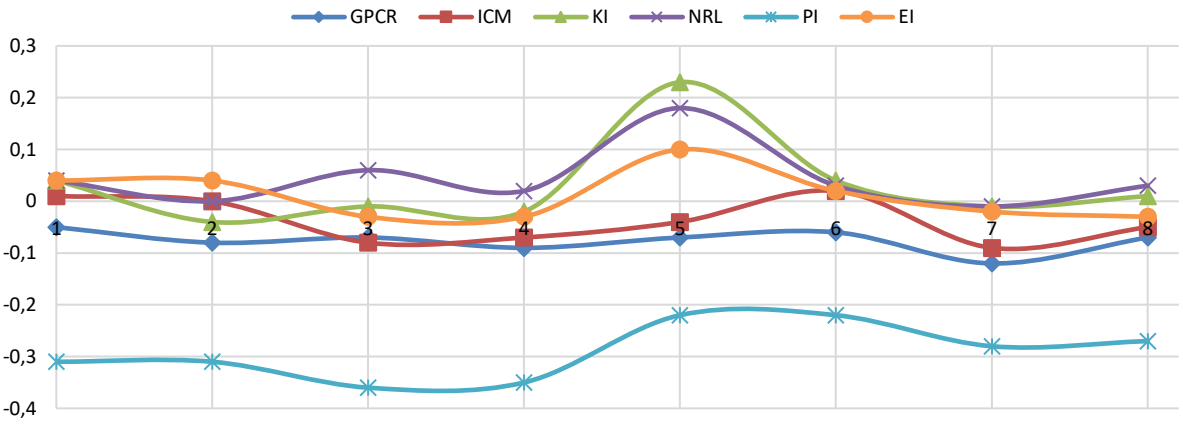


Figure 10. Profile depicting bioactivity score of compounds 1-8.

ADMET/SAR investigation of 2-phenoxyquinoline derivatives

Absorption, distribution, metabolism, excretion (ADMET) was analysed based on data generated from ADME SAR 2 web server. The values obtained are from latest drug-likeness capability tools in drug discovery. Most of the parameters correlate positively and are presented in Table 5 thus confirming their profile depicting bioactivity score in Figure 10. It is noteworthy that cytochromes CYP2C19, CYP2C29, CYP2D6, and CYP3A4 which are significant enzymes responsible for metabolizing commonly used drugs, are not inhibited, hence no effect on plasma levels in vivo which can potentially lead to adverse drug reactions or toxicity while cytochromes CYP2C9 and CYP2D6 act as substrates which metabolise pharmacologically inactive drugs to active form for easy clearance from the body

The Ames test is a biological assay to assess the mutagenic potential of chemical compounds utilizing bacteria to test whether a given chemical can cause mutations in the DNA of the test organism. A negative test indicates that the chemical is non-mutagenic and therefore is not a carcinogen, because cancer is often linked to mutation (Czeczot et al., 1990). Suffice to say that compounds 7 and 8 gave negative Ames test results probably due to the presence of the Fluorine and methoxy oxygen atoms at position 6 of the quinoline ring which withdraws electrons from the ring via inductive effects. Although the methoxy group is electron-donating by resonant effect, that does not apply here. Compounds 1 with fewest substituents shows negative androgen receptor binding, situation where a type of nuclear receptor activated by binding to any of the androgenic hormones, including testosterone and dihydrotestosterone in the cytoplasm and is translocated into the nucleus

thereby increasing interfacial stability when compared with the other steroid receptors (Shaffer et al., 2004). Caco-2 is an immortalized cells line of human colorectal adenocarcinoma cell primarily used as a model for the measurement of the intestinal epithelial barrier functions (Lea, 2015). This returns negative values for compounds 1 and 6. This could be attributed to the fact that, despite being mono- and di-acetoxylated, they are devoid of any other substituted elements.

The only benzoylated compound 5 surprisingly gave negative CYP14 substrate value. This cytochrome is an HMG-CoA reductase, a factor in the treatment of HIV infection by lowering LDL cholesterol and reducing the risk of cardiovascular disease such as myocardial infarction and stroke. CYP substrates are drugs usually metabolized by cytochrome enzymes which require metabolism into an inactive form for clearance from the body (Galetin et al., 2005). It is obvious that the an extra aromatic ring of compound 5 contributed to this effect.

PPAR gamma is a gene that encodes a member of the peroxisome proliferator-activated receptor (PPAR) subfamily of nuclear receptors which form heterodimers with retinoid X receptors (RXRs) to regulate transcription of various genes. Activation of this adipocyte predominant transcription factor regulates glucose and lipid homeostasis playing significant role in the regulation of gene expression of multiple diseases including obesity, diabetes and cancer and highlights the gene isolation transformation role (Janani & Kumari, 2015). Compound 2 has extra methyl groups on position 6 of the 2-phenoxy ring and on the ester group of the 3-methylacetate of the quinoline ring. These special positions of the methyl group could be reason for the negative values of the compounds.

The highest Plasma protein binding value was exhibited by only benzoylated compound 5. The presence of extra resonance stabilization could have contributed to this higher value. Plasma protein binding refers to the degree to which medications attach to proteins within the blood measuring drug's efficiency as it helps determine the degree to which it binds. The less bound a drug is, the more efficiently it can traverse or diffuse through cell membranes. Plasma proteins, by virtue of their high concentration, control the free drug concentration in plasma and in compartments in equilibrium with plasma, effectively attenuating drug potency *in vivo* (Trainor, 2007). Compound 5 has the highest tetrahymena pyriformis value of 1.92. Tetrahymena species found in the original T. pyriformis group provide an invaluable resource for comparative genomic analyses, as evolutionary DNA sequence conservation is a valuable predictor of biological function under natural selection (Sauvant et al., 1999).

Thyroid hormone receptors regulate gene expression by binding to hormone response elements (HREs) in DNA as monomers, heterodimers with other nuclear receptors, or homodimers. Dimerizing with different nuclear receptors leads to the regulation of different genes. They are essential for normal development, differentiation and metabolic balance (Zhang & Lazar, 2000). Compound 5 with the most pi-electrons possessed in its four aromatic rings in addition to the two carbonyl functions bind with thyroid receptors.

Drug oral bioavailability is the fractional extent of the drug dosage that finally reaches the therapeutic site of action. The most relevant measure of lipophilicity with regard to oral absorption by passive diffusion is probably the distribution coefficient (log D) at pH 6.5, which is the pH of the small intestine, where absorption mostly takes place (Yoshida & Topliss, 2000) (Yoshida & Topliss, 2000). Only compound 5 show positive results for human oral bioavailability, hence is predicted to reach the site of action before being eliminated compared to others.

Mitochondrial toxicity is a condition in which the mitochondria of a body's cells become damaged or decline significantly in number; it occurs as a side effect of certain antiretroviral drugs used to treat human immunodeficiency virus (HIV). Rapid increase in reported toxic effects of drugs and pollutants on mitochondria have been documented detailing many genetic differences leading to mitochondrial diseases caused by factors such as as diet, exercise, age, and nonchemical stressors (Meyer et al., 2018). Only compound 7 shows mitochondrial toxicity from this investigation which could be attributed to the presence of the methoxy group at position 6.

Table 4: Toxicity targets of compounds 1 – 8.

Targets	Compounds							
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Hepatotoxicity	Inactive	Inactive	**Active**	Inactive	Inactive	Inactive	Inactive	**Active**
Carcinogenicity	**Active**	Inactive	Inactive	Inactive	**Active**	Inactive	Inactive	Inactive
Cytotoxicity	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive

The respiratory system is a target of toxic effects and a major route of absorption of inhaled gases and atmospheric particles. Lung toxicosis depends on the dose of toxicant delivered to lung tissues and toxicants' acute and chronic effects. Effects can be described in terms of tissue damage and lesions and in terms of deficits in respiratory system function. Cellular responses to toxicants lead to acute effects such as inflammation or chronic effects including fibrosis, emphysema, and cancer (van der Merwe, 2018). It is noteworthy that all

the compounds are inactive cytotoxic as shown in Table 4. While compounds 3 and 8 exhibit slight hepatoxicity, compounds 1, 2, 4, 5, 6 and 7 are completely non-hepatoxic. Compounds 1 and 5 also exhibit minimum carcinogenic toxicity while the rest are non-carcinogens. To this end, compounds 2, 4, 6, and 7 are potential drug candidates as antitumor agents, amidst various other pharmacological applications.

CONCLUSION

Bioactive quinoline compounds have shown consistent applications in drug design. From the DFT study, calculated reactivity descriptors, MEP, MAC and optical properties support the bioactivity of compounds as revealed in their lower energy values in water relative to ethanol and gas. ADMET investigation revealed the extent of compliance of the compounds as potential candidates based on drug-likeness parameters, lead-likeness, cytochrome inhibition, bioavailability and other physicochemical properties. The desired medium (water) gives favourable intermolecular interactions via hydrogen bonding as reflected in their lower ionization potential especially for the 6-methoxy substituted functionality with lowest ionization potential value of 5.991 eV. Generally, uniform distribution of charge was found for all compounds especially the 6-fluoro, benzoylated and 6-methoxy substituted groups which had lower energy gaps in aqeous medium and were the most reactive with respective negative values of -2.518 a.u, −2.609 a.u. and -2.021 a.u. This charge is significant for the bioactivity of the molecules for their role as radical scavengers. From MEP and MAC studies, regions of negative potentials in the 2-phenoxyquinolines with high affinity for the positively charged side groups of amino acids provide enablement for good binding interaction. Additionally, Pearson correlation co-efficient (r) of 0.97 and R^2 value of 0.94 shows the average bioactivity score of all the compounds to be more than 0, therefore are active drug candidates. The results presented here can be used to further evaluate these bioactive compounds in molecular docking studies against infections and diseases.

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