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PREDICTION OF TOXICOLOGICAL EFFECT OF SCHIFF BASE LIGAND USING ONLINE COMPUTER SOFTWARE PROGRAMS

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ABSTRACT

The aim of the present work was to evaluate In silico the toxicity, metabolic sites, and metabolites of the ligand 2-[(1*E*)-*N*-{2-[(2-{(*Z*)-[1-(2-hydroxyphenyl) ethylidene] amino}ethyl) amino]ethyl} ethanimidoyl] phenol. In silico, toxicity of the ligand was predicted by online computer software programs such as ACD/I-Lab, **Pred** hERG, Lazar and BioZyne. Our results showed non-carcinogenicity and non- mutagenicity effects were predicted. We conclude that the ligand has low toxicity, which was the possibility to be a safe drug-candidate in the future.

Keywords: bioactivity, toxicity, online

MATERIALAND METHODS

For the prediction of Human Ether-a-go-go-Related Gene Inhibition (hERG) and the cardiotoxicity, the free online Pred hERG was used. Acute toxicity, carcinogenicity, and mutagenicity, were confirmed by Lazar toxicity predictions. BioZyne was used for the P-glycoprotein substrates pecificity modeling.

RESULTS AND DISCUSSIONS

The P-glycoprotein, which is expressed in various body tissues such as liver, kidney, intestine, testes, and brain and belongs to the ATP-binding cassette transporter family (Colabufo et *al.,* 2009), (Staud et *al.,* 2010), the ligand exhibits P-glycoprotein substrate with a probability of 0.8236. Furthermore, the ligand was considered as non- P-glycoprotein Inhibitor. These results are in good agreement with predictions shown in (**Figure 1)**, which indicate that the ligand is likely to be a substrate of the P-gp drug efflux pump, with 50 atoms (including hydrogen) and a specific volume of 6.75 Aº/atom. This confirms that our ligand cannot be used in chemotherapy, because P-gp-mediated efflux affects each step which a drug comes across during its presence in the body (Bansal et al., 2009).

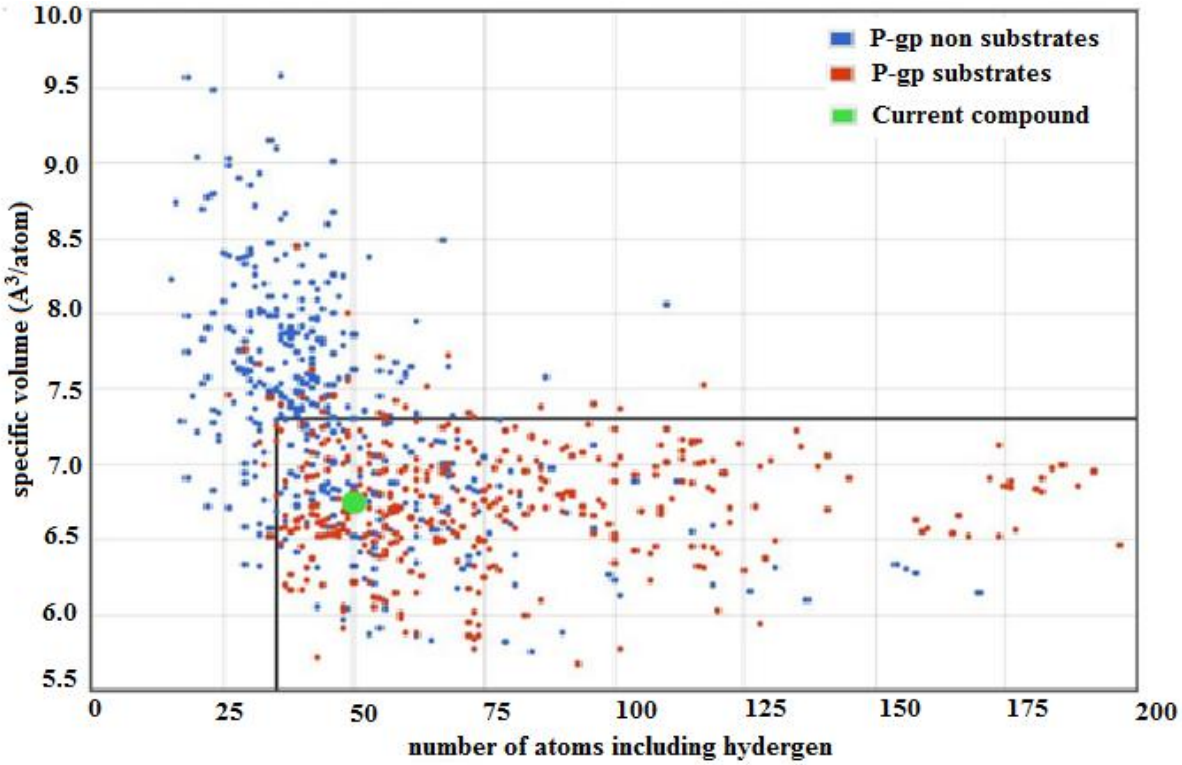

FIGURE 1. P-glycoprotein drug efflux pump prediction of the ligand

On the other hand, calculations revealed that the Schiff base can actas an inhibitor for the renal organic cation transporter. For the subcellular localization which is predicted in the mitochondria with a probability of 0.8310, this prediction is in agood agreement with previous studies (Zhao et *al.*, 2004), (Bertz et al., 1997) which showed that small molecules are being targeted to mitochondria by conjugating these compounds to cell-penetrating, lipophilic peptides, oligoguanidinium, or triphenylphosphonium moieties. After drug absorption and distribution steps, the CYP450s become the major enzymes involved in drug metabolism. Results obtained showed that the synthesized ligand substrate inhibits the CYP450 2D6, this effect as similar to the effect of Fluoxitine (as Antidepressant agent). Under the toxicity category, our ligand is a non-carcinogenic, non-AMES toxic (non mutagens) (Ames et *al.*, 1973), and does not induce sensation of skin. For human ether-a-go-go-related gene inhibition (hERGI), results from (**Figure 2)**, show that the ligand exhibits non inhibition effect against hERG I.

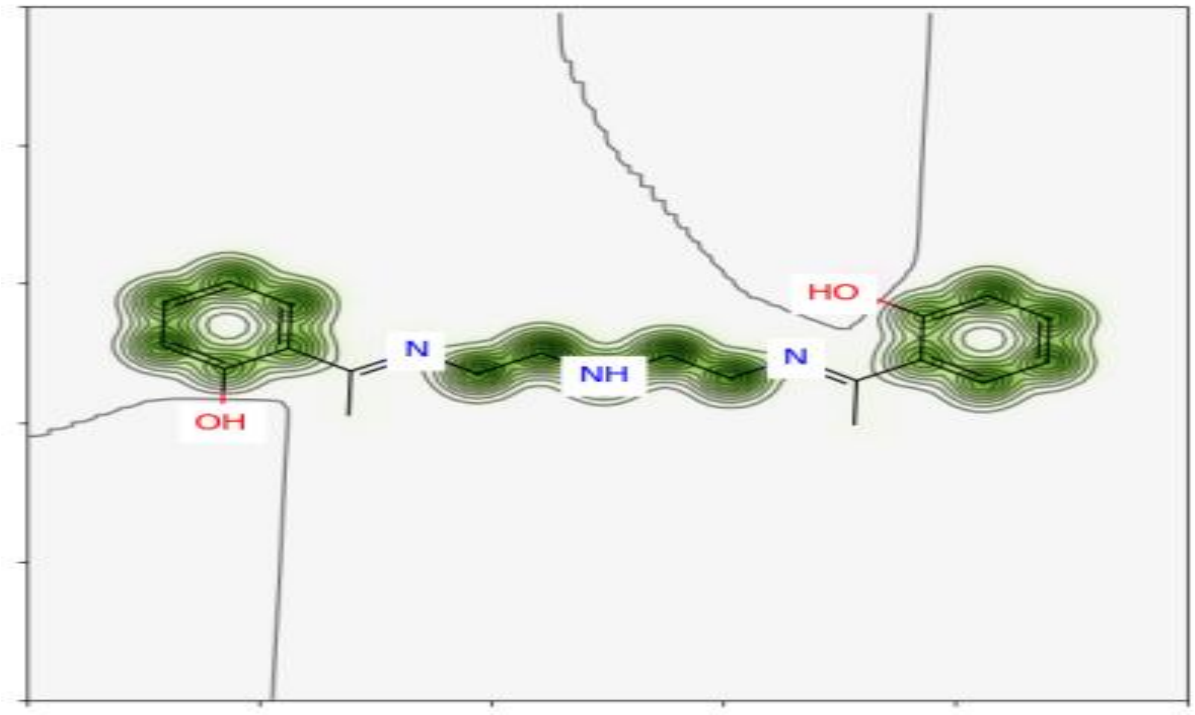

FIGURE2: PredhERG Results of the ligand

Furthermore, prediction of toxicity indicates that the Schiff base, as a strong inhibitor of hERG II ,is highly toxic to fish (pLC50= 1.2667mg/L), high toxic to tetrahymena (pIGC50= 0.6843µg/L), low toxic to honey bee, and can induce hepatoxicity. Moreover, the Acute Oral Toxicity: Category III includes compounds with LD50 values greater than 500 mg/kg but less than 5,000 mg/kg. Carcinogenicity (three-class): Carcinogenic compounds with TD50 (tumorigenic dose rate 50) B10 mg/kg body wt/day were assigned as ‘‘Danger,’’ those with TD50[10 mg/kg body wt/day were assigned as ‘‘Warning,’’ and non-carcinogenic chemicals were assigned as ‘‘Non-required.’’ Probability indicates scale between 0 and 1 (Siddappa et *al.*, 2016).

To confirm the non-toxicity prediction of the ligand, we employed Lazar toxicity predictions and ACD/I-Lab software; results are shown in **Table 1**. For the acute toxicity, two methods were used: Fathead minnow and Daphnia magna. In the first method, the dose of the ligand was 22.9 mg/kg which is in the 95% of prediction interval. The same remark for the second method (dose = 0.0232 mg/kg). The risks of carcinogenicity and mutagenicity were also predicted, the carcinogenicity was computed by three methods; Carcinogenicity:“Rodentes (multiples species/sites)”, “Rat” and “Mouse”. Results of these tests demonstrate the inactivity of the ligand, which confirms the non-carcinogenicity. Results for mutagenicity, also demonstrated the inactivity against *Salmonella typhimurium*. In addition, the maximum recommended daily dose is 9.24mg/kg.

TABLE 1. Toxicity predictions using Lazar

Toxicity tests	**Prediction Results**
Acute toxicity (Fathead minnow)	0.0674(mmol) 22.9(mg/kg_bw/day)
Acute toxicity(Daphnia manga)	6.82e-0.5 0.0232(mg/kg_bw/day)
Carcinogenicity (Rodents (multiple species/sites))	Inactive
Carcinogenicity (Rat)	Inactive
Carcinogenicity (Mouse)	Inactive
Maximum Recommended Daily Dose (Human)	0.0272(mmol/kg_bw/day) 9.24(mg/kg_bw/day)
Mutagenicity (*Salmonella typhimurium*)	Inactive

According to previous studies, the effect of the ligand on blood, cardiovascular system, gastrointestinal system, kidney, liver, and lungs can be interpreted as: **moderate effect** (>0.5), **border line effect** (>0.3, <0.5), red and green colors of atoms or fragments of the ligand explain the toxic or non-toxic action of the ligand, respectively (Fu et *al.*, 2017). Our results given in (**Figure 3)** indicate that the ligand has a safe effect on liver and cardiovascular system with probabilities of 0.31and 0.61, respectively, and moderate effects on blood, kidney, gastrointestinal system, and lungs with probabilities of 0.51, 0.74, 0.79, and 0.99, respectively.

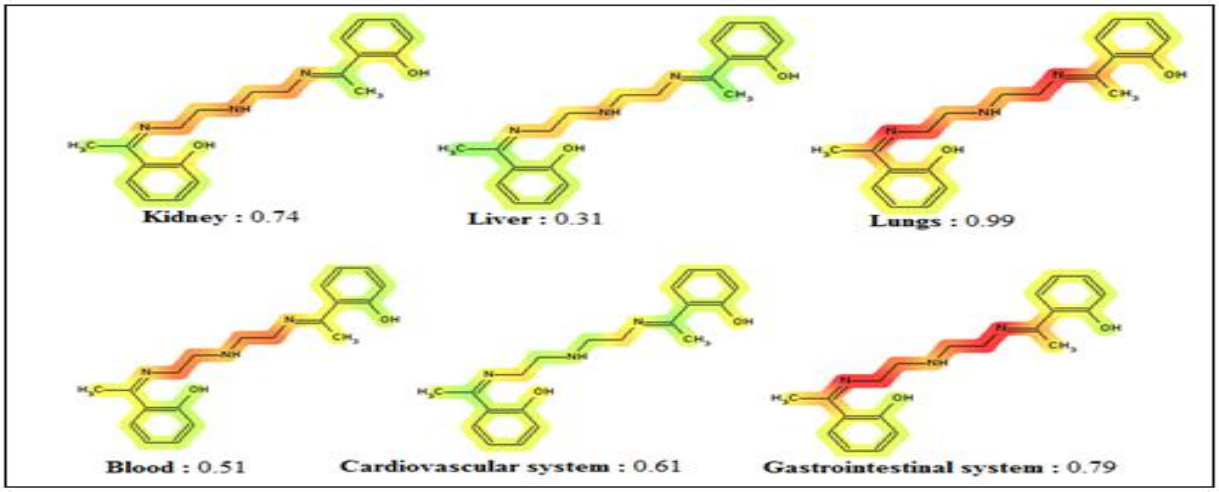

FIGURE 3: Probabilities of health effects of the ligand on blood, cardiovascular system, gastrointestinal system, kidney, liver and lungs

CONCLUSIONS

Results revealed that the ligand has low toxicity. Our theoretical results indicate the possibility of using the ligand as a safe drug in the future. However, more work involving animal models may be needed to establish the efficacy and safety of this compound.

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