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Review Article

In silico Adme-Tox Profiling of 4-(3*H*)-Quinazolinone Analogues

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Abstract

Quinazolinone is an excellent reservoir of various bioactive substances. The versatility in pharmacological activities and stability of the quinazoline nucleus has inspired medicinal chemists to introduce many bioactive moieties to this nucleus to synthesize new potential medicinal agents. Within this study, we use some new computational tools for predicting absorption, distribution; metabolism, elimination and toxicity, the pharmacokinetic profile of some novel some 2, 3 di-substituted quinazolin-4-one analogs. The investigated analogue does not possess drug-like properties. The side effects during the investigation are mutagenicity, hepatotoxicity.

Keywords: Pharmacokinetic; Toxicity; Mutagenicity; Carcinogenicity; Hepatotoxicity; Cytotoxicity

Introduction

Heterocycles are among the most frequently encountered scaffolds in drug and pharmaceutically relevant substances. Quinazoline-4(3*H*)-ones and its derivatives are versatile nitrogen heterocyclic compounds which have long been known as a promising class of biologically active compounds. Quinazolinone is an excellent reservoir of various bioactive substances. The versatility in pharmacological activities and stability of the quinazoline nucleus has inspired medicinal chemists to introduce many bioactive moieties to this nucleus to synthesize new potential medicinal agents. Quinazoline and quinazolinone derivatives have continuing to attract a widespread interest for an extended time because of their various pharmacological activities like antibacterial [4,5], antitubercular [6], antifungal [7], hypoglycemic [8] and anti tumour [9]. During a literature survey for our ongoing medicinal chemistry research program, we found that quinazolines and condensed quinazolines exhibit potent central nervous systems (CNS) activities like analgesic, anti-inflammatory [12] and anticonvulsant [13]. Quinazolin-4(3*H*)-ones with 2, 3-disubstitution is reported to possess significant analgesic, anti-inflammatory and anticonvulsant activities [10]. The basic aim of this study is to predict the ADME – Tox profiles, pharmacokinetic properties, and toxic adverse effects of some novel 2, 3 di-substituted quinazolin-4-one analogues [1-3].

Materials and Methods

In Silico ADME screening

The pharmacokinetics and drug likeliness prediction of compounds were performed online on Swiss ADME tool. Swiss ADME tool was used for online pharmacokinetic properties evaluation of compounds [14]. The 2 Dimensional structures were drawn in ChemDraw Ultra. SMILES of each compound were created online in SMILES translator [18]. The online prediction was done to check the compound were inhibitors of cytochrome P450.In addition to the pharmacokinetic properties such as Gastrointestinal absorption, Blood-Brain Barrier penetration, Skin Permeation, synthetic associability and drug-likeness prediction like Lipinski, Ghose and Veber rules and bioavailability score [19].

Toxicity prediction

The PreTOX II tool is used to predict the toxicity/adverse effect of the compound. PreTOX II tool predicts such as acute toxicity, hepatotoxicity, cytotoxicity, carcinogenicity, mutagenicity, immunotoxicity, and adverse outcomes pathways (Tox21) and toxicity targets. The biological activity spectra and adverse effect prediction of the compound were done using PASS online tool. Prediction of Activity Spectra of substances (PASS) is a tool for online prediction of biological activity/or toxic and side effects of compounds. Pred-Herg is an online tool to predict QSAR models of

hERG K +channel blockage. The accuracy of the prediction result is up to 89%. Pred-Skin tool is based on statistically significant and externally predictive QSAR models of skin sensitization it is the only tool available for the prediction of skin sensitization based on human data. This method provides an easy interpretation of the predicted activity and also allowing the user to easily propose structural modifications.

Comp Code	SMILES
B16	CCCC1=NC2=CC(=CC=C2C(=O)N1C)N(O)=O
B17	CCCC1=NC2=CC(=CC=C2C(=O)N1CC)N(O)=O
B18	CCCC1=NC2=CC(=CC=C2C(=O)N1C1=CC=CC=C1)N(O)=O
B19	CCCC1=NC2=CC(=CC=C2C(=O)N1C1=CC=C(C=C1)N(O)=O)N(O)=O
B20	CCCC1=NC2=CC(=CC=C2C(=O)N1C1=CC(=CC=C1)N(O)=O)N(O)=O
B23	CCCC1=NC2=CC(=CC=C2C(=O)N1C1=CC(Cl)=CC=C1)N(O)=O
B24	CCCC1=NC2=CC(=CC=C2C(=O)N1C1=C(Cl)C=CC=C1)N(O)=O
B26	CCCC1=NC2=CC(=CC=C2C(=O)N1C1=CC(F)=CC=C1)N(O)=O
B27	CCCC1=NC2=CC(=CC=C2C(=O)N1C1=C(F)C=CC=C1)N(O)=O
B28	CCCC1=NC2=CC(=CC=C2C(=O)N1C1=CC=C(Br)C=C1)N(O)=O
B29	CCCC1=NC2=CC(=CC=C2C(=O)N1C1=CC(Br)=CC=C1)N(O)=O
B30	CCCC1=NC2=CC(=CC=C2C(=O)N1C1=C(Br)C=CC=C1)N(O)=O
B31	CCCC1=NC2=CC(Br)=CC=C2C(=O)N1C
B32	CCCC1=NC2=CC(Br)=CC=C2C(=O)N1CC
B33	CCCC1=NC2=CC(Br)=CC=C2C(=O)N1C1=CC=CC=C1

Table 1: Molecules of quinazolinones considered in this study.

Result and Discussion

The outcomes of swissADME and Toxicity Predictions are summarized in Tables (1,2). The result presented in table 2 indicates that all the investigated compounds present a high gastrointestinal absorption, good skin permeation and they inhibit cytochrome CYP1A and CYP2D6 involved in the metabolism of xenobiotics. These predictions are in agreement with few available studies concerning human oral administration conducting to fast absorption and fast metabolism. The PreTOX II computational tool revealed that all investigated quinazolin-4-one analogues produce some hepatotoxicity and mutagenicity [16]. The outcomes of Pred-hERG result indicate that all investigated compounds are a nonblocker for the hERG k+ blocker. The skin sensitivity prediction through Pred-Skin online tool indicates that all molecules are non sensitizer to human skin. The radar picture (Figure 1) shows the predicted toxicity in percentage.

Comp No	GI	BBB	P-gp	CYP1A2	CYP2D6	Log K_p (Cm/s)	Bioavaliability Score
B16	High	Yes	No	Yes	Yes	-5.8	0.55
B17	High	No	Yes	Yes	No	-7.05	0.55
B18	High	No	Yes	Yes	No	-6.88	0.55
B19	High	No	Yes	Yes	No	-6.33	0.55
B20	Low	No	Yes	Yes	No	-7.06	0.55
B23	High	No	Yes	Yes	No	-6.1	0.55
B24	High	No	Yes	Yes	No	-6.1	0.55
B26	High	No	Yes	Yes	No	-6.36	0.55
B27	High	No	Yes	Yes	No	-6.36	0.55
B28	High	No	Yes	Yes	No	-6.36	0.55
B29	High	No	Yes	Yes	No	-6.32	0.55
B30	High	No	Yes	Yes	No	-6.32	0.55
B31	High	No	Yes	Yes	No	-6.32	0.55
B32	High	Yes	No	Yes	Yes	-6.32	0.55
B33	High	Yes	No	Yes	Yes	-6.14	0.55

Table 2: Pharmacokinetis of compound: GI-Gastrointestinal absorption, BBB-Blood Brain Barrier penetration, P-gp- Substrate of the P-gp protein [19], CYP: Cytochrome P450, Log Kp-Skin Permeation Coefficient.

Compound Code	Predicted LD 50	Predicted Accuracy	Hepatotoxicity	Carcinogenicity	Immunotoxicity	Mutagenecity	Aryl Hydrocarbon Receptor Toxicity
B16	859 mg/kg	70.97%	Active	Inactive	Active	Inactive	Inactive
B17	859mg/kg	69.26%	Active	Inactive	Inactive	Inactive	Active
B18	751mg/kg	69.26%	Active	Inactive	Inactive	Inactive	Active
B19	1500mg/kg	72.97%	Inactive	Inactive	Inactive	Active	Inactive
B20	580mg/kg	70.97%	Inactive	Inactive	Active	Inactive	Active
B23	580mg/kg	70.97%	Active	Inactive	Inactive	Inactive	Active
B24	751mg/kg	69.26%	Active	Inactive	Inactive	Inactive	Active
B26	680mg/kg	70.97%	Inactive	Inactive	Inactive	Inactive	Inactive
B27	1400mg/kg	70.97%	Active	Inactive	Inactive	Active	Active
B28	751mg/kg	70.97%	Active	Inactive	Inactive	Inactive	Inactive
B29	680mg/kg	70.97%	Inactive	Inactive	Inactive	Inactive	Active
B30	680mg/kg	69.26%	Inactive	Inactive	Inactive	Inactive	Inactive
B31	680mg/kg	70.97%	Inactive	Inactive	Inactive	Inactive	Active
B32	1400mg/kg	69.26%	Active	Inactive	Inactive	Inactive	Inactive
B33	751mg/kg	69.26%	Active	Inactive	Inactive	Inactive	Inactive

Table 3: Toxicity prediction of molecules.

Compound Code	Pred-hERG	Pred-skin
B16	Non blocker	Non Sensitizer
B17	Non blocker	Non Sensitizer
B18	Non blocker	Non Sensitizer
B19	Non blocker	Non Sensitizer
B20	Non blocker	Non Sensitizer
B23	Non blocker	Non Sensitizer
B24	Non blocker	Non Sensitizer
B26	Non blocker	Non Sensitizer
B27	Non blocker	Non Sensitizer
B28	Non blocker	Non Sensitizer
B29	Non blocker	Non Sensitizer
B30	Non blocker	Non Sensitizer
B31	Non blocker	Non Sensitizer
B32	Non blocker	Non Sensitizer
B33	Non blocker	Non Sensetizer

Table 4: Cardio toxicity and skin skin sensitivity prediction.

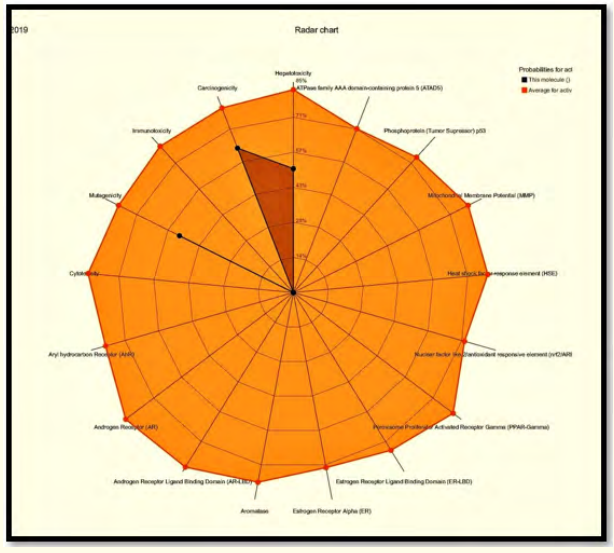

Figure 1: Radar Picture of predicted toxicity of compounds.

Conclusion

Within this study we predicted the biological activities and side effects of some novel 2, 3 di-substituted quinazolin-4-one analogues. Our study confirmed that the investigated compounds reveals good oral bioavailability and skin permeability and also they have high gastrointestinal absorption. Some Invistigated 2, 3 di-substituted quinazolin-4-one analogues reveal hepatotoxicity and mutagenicity and hERGk+ nonblocker. Some quinazolinones inhibit cytochrome CYP1A and CYP2D6 which affects the metabolism of numerous xenobiotics. As humans are exposed to many xenobiotics (food additives, pesticides etc.).All these results are important for people awareness. The results are obtained by computational tool can complete the in silico toxicity test to improve predictive toxicity and safety assessment of some novel 2, 3 di-substituted quinazolin-4-one analogues.

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Conflict of Interest

The authors have declared that this text content has no conflicts of interest.

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Volume 3 Issue 7 July 2019