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Discovery of Inhibitors of TGF-β Type I Receptor Using QSAR, Pharmacophore Modelling and Toxicity Assessment Techniques/Study to Target Cancer

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ABSTRACT

Targeting of the membrane proteins is the current approach to discover new small molecule inhibitors. The protein TGF β type I receptor has been used as a target to identify the potential compounds. Around 64 hit compounds from binding database were identified for3D-QSAR study. The Schrodinger "PHASE" was used to perform the pharmacophore generation and through validation a best pharmacophore has been identified. The features of the pharmacophore were utilized to screen the molecules from National Cancer Institute (NCI) and Zinc database. Using screening techniques, about 5033 molecules were identified and the entire molecules were docked using "GLIDE" to the protein TGF β type I (PDBID: 1VJY). After the successful docking 25 hit molecules were further filtered and screened for ADME properties studies using QikProp tool. About 9 lead molecules preferred and their toxicity parameters evaluated using the softwares namely, OSIRIS property explorer, in silico-first, Molinspiration and Toxtree.

The molecular properties such as clogS, clogP and Molecular weight were predicted by means of Molinspiration software as well as the drug-likeness and drug score using the OSIRIS property explorer. The other toxicity parameters such as mutagenic, tumorigenic, irritant and reproductive effective were predicted using data warrior software. In silico first software tool was used to predict the teratogenicity of the entire compounds. The nine compounds were tested for its toxicity to Salmonella typhimurium TA100 mutagen, eye irritation as well as corrosion. In addition to these, skin sensitation alerts, negative for genotoxic carcinogenicity and non genotoxic carcinogenicity were also calculated. Based on the results the compound 5 also known as Zinc-84409571 was found as a better molecule and safe to use as a drug. Hence, the compound could be further redesigned, synthesized to target cancer.

Keywords: 3D-QSAR, Pharmacophore modelling, NCI and Zinc database, TGF-β type I receptor, QikProp, ToxTree, OSIRIS, Data warrior, Molinspiration

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INTRODUCTION

The abnormal proliferation in any type of cells in the body leads to Cancer. There are more than 100 types of cancer, which may change substantially in their behavior and response to treatment [1]. Although current advances in therapy of cancer, enormous anticancer drugs have reported with severe adverse effects. The development of compounds as chemotherapeutic agents should require a less/limited toxicity profile [2].

An important principle included in quantitative structure-activity relationship (QSAR) is toxicity. The derived compounds from the pharmacophore model can be described in relation to its chemical moiety as well as its parameters such as ADME and toxicity. The recent evolution in computational methods is used to predict the chemical toxicity [3]. Nowadays about thousands of chemical descriptors can be calculated for a chemical structure and many fragments can be obtained using other programs [4]. Among the toxicological effects, the carcinogenicity and mutagenicity are the major concern for human health. As a result they are the main objective of the intense research activity as well as of recognized regulatory testing methods [5].

Due to the pharmacokinetic profile as well as toxicity, about 50% of the lead molecules failed at the development stage of a drug. Hence, the identification/prediction of pharmacokinetic profile (ADME) together with toxicity (ADMET) is the important properties in the definition of bioavailability and toxic effects of a molecule since this will avoid the time and cost involved in drug

discovery process [6]. The software programs currently available for calculating the amount of toxicity associated with the drug molecules are namely, Osiris property explorer [7], *in silico* first [8], TOPKAT [9,10], Toxtree [10], Toxpredict [11] etc. In addition to these, the programmes for property calculation being used are namely, Molinspiration [12], Osiris property explorer, simulation property calculator and so on.

In the current research, the 3D-QSAR study has been carried out with 63 compounds and a best pharmacophore model ADHRR was generated, which was used to screen the compounds from the ZINC, Mayer-Bridge and NCI database. About 9 lead compounds were chosen from the ZINC database and the lead compounds were filtered using the docking study as well as ADME property testing. The nine compounds were employed for the prediction of various toxicity parameters and the evaluation of some important physicochemical parameters using the software "data warrior" of Osiris property explorer, Toxtree, *In silico* first and Molinspiration softwares. The nine molecules were imported to the computerized programs and online tools for the prediction of toxicity parameters like mutagenic, tumorigenic, irritant and reproductive effective as well as *in silico* screening for its drug score and drug-likeness testing to examine their overall potential to be qualified as drugs.

MATERIALS AND METHODS

The programs or software tools were designed to evaluate the general biological potential of an organic drug-like molecule. The nine compounds identified from the 3D-QSAR study were further used to calculate the parameters such as, molecular properties and toxicity. The organic molecules and their molecular properties were calculated by using the online web server "Molinspiration programme Ver. 2011.06" [13] and the website Organic portal-OSIRIS property explorer [14] to evaluate the oral bioavailability, drug likeness as well as drug score of the compounds. Data warrior alternative software to "Osiris property explorer" was also employed in this study to predict the values of molecular mutagenic, tumorigenic, irritant and reproductive effective properties of the compounds.

The identity number for the nine hit molecules are Zinc-81934069, Zinc-80319005, Zinc-81942670, Zinc-84975470, Zinc-84409571, Zinc-80770573, Zinc-80070769, Zinc-72273865 and Zinc-81934199. The molecules are from the ZINC database, which are used for the molecular properties and toxicity prediction (Figure 1). The 2D structures of the compounds were drawn using the ChemDraw tool [15,16]. The Small Incision Lenticule Extraction (SMILES) [17] format of the structure was used to import the structure into the Osiris property explorer to predict the toxicity parameters. To import the molecules into the data warrior software, the 2D structure was saved in .sdf format.

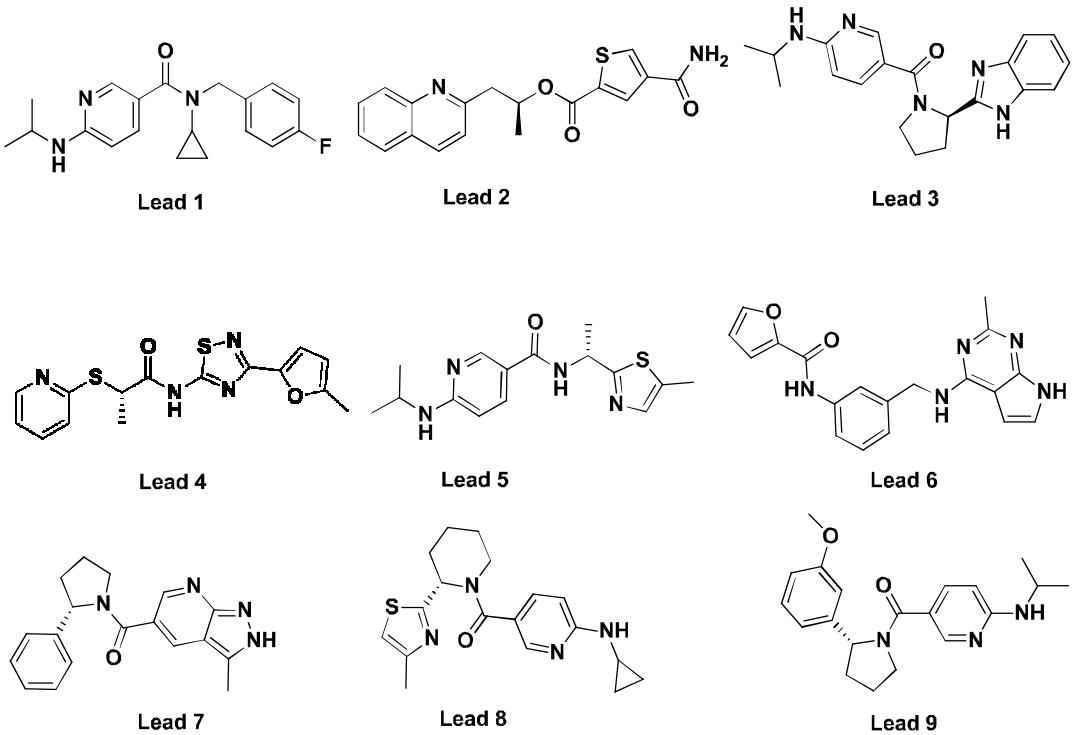

Figure 1: The 9 compounds drawn using Chemdraw obtained from the Zinc database with their identity numbers: Zinc-81934069 (Lead 1), Zinc-80319005 (Lead 2), Zinc-81942670 (Lead 3), Zinc-84975470 (Lead 4), Zinc-84409571 (Lead 5), Zinc-80770573 (Lead 6), Zinc-80070769 (Lead 7), Zinc-72273865 (Lead 8) and Zinc- 81934199 (Lead 9).

The teratogenic property of the compounds was calculated using the *in silico* first software. In addition to these, the Toxtree software was also used to predict the toxicity for *S. typhimurium* TA100 mutagen, eye irritation as well as corrosion and skin sensitation alerts. Additionally, it was also used to predict whether the compounds were negative for genotoxic carcinogenicity as well as non genotoxic carcinogenicity.

RESULTS AND DISCUSSION

Selected nine compounds were executed for their molecular properties using Molinspiration, a online sever, data warrior software of organic portal. The drug score was predicted using the OSIRIS property explorer is also another online server, and their values are given in Table 1. The molecular properties predicted are namely, clogS (aqueous solubility), clogP (partition coefficient between n-octanol and water), molecular weight were calculated using the Molinspiration tool, The drug likeness and drug score were predicted using the data warrior software and OSIRIS property explorer respectively. The calculated values of clogS [18], clogP [19], molecular weight, drug likeness and the drug score were compared for the nine compounds.

The logP rate of a compound seams to the logarithm of its partition coefficient between n-octanol and water logs (c-octanol/c-water), is best recognized measure of a compound's hydrophilicity. The low hydrophilicities are therefore high logP values lead to root of poor absorption or permeation [20]. The rational possibility of a compound is being well absorbed if its value must not be greater than 5.0 [21]. clogS denotes the aqueous solubility, which is a measure of this ability for a particular substance in a particular solvent, equal to the quantity of substance dissolving in a fixed quantity of solvent to form a saturated solution under specified temperature and pressure [22]. The values of aqueous solubility should fall between -6.5 to 0.5 for its better solubility [23]. From the calculated values using Molinspiration server, the clogP for all the 9 lead compounds were less than 5 and the clogS values were between -6.5 to 0.5. To target the biological molecules, the compounds for its potent activity should frequently goes with an increase in molecular weight [24]. According to Lipinski rule the molecular weight should be less than 500 Daltons [25]. The predicted molecular weights of the nine compounds were less than 500.

The concept of drug-likeness is recognized using the analyses of the physiochemical properties/and structural features of the available small organic drugs/and drug candidates, that can be widely used to filter out the compounds with undesirable properties [26]. All the nine compounds showed positive values for the property of drug likeness. The drug score combines with the drug-likeness, clogP, clogS, and molecular weight as well as toxicity risks in one versatile value. The value can be utilized to judge the compound's overall potential to qualify for a drug [27]. If the score of drug is high then the compound seems to be good drug candidate. For an example, the drug score such as 1.0, 0.8 and 0.6 are associated with no risk, medium risk and high risk, respectively. The predicted drug score values calculated using the OSIRIS property explorer for all the nine compounds were 0.74, 0.53, 0.82, 0.77, 0.88, 0.66, 0.53, 0.81, 0.78 (Table 1). Especially the compound 3, 5 and 8 showed better drug score and possesses the medium risk and can be used as a drug molecule.

Table 1: Predicted molecular properties of nine compounds calculated using Molinspiration and Data warrior software

S. No.	Compound	clogS (-6.5 to 0.5)	clogP<5	Molecular weight <500	Drug Likeness	Drug Score
1	Zinc-81934069	-4.13	3.18	327	4.22	0.74
2	Zinc-80319005	-4.40	3.10	340	1.55	0.53
3	Zinc-81942670	-3.00	2.92	349	5.43	0.82
4	Zinc-84975470	-3.36	3.34	346	3.01	0.77
5	Zinc-84409571	-2.97	1.82	304	4.75	0.88
6	Zinc-80770573	-4.71	2.40	347	1.88	0.66
7	Zinc-80070769	-2.88	1.77	308	7.40	0.53
8	Zinc-72273865	-3.26	2.77	342	3.11	0.81
9	Zinc-81934199	-3.53	3.37	339	4.82	0.78

The data warrior software from the OSIRIS was used to calculate the toxicity risk for the nine compounds. The values were predicted based on none or low or high for its mutagenic, tumorigenic, irritant, reproductive effective properties. The parameter of toxicity includes, mutagenicity, tumorigenic, irritant, reproductive effective properties and the calculated values are shown in Table 2. The level of toxicity was illustrated as low and high and the drug conform behavior was shown as "none". The compounds 1, 3-6, 8 and 9 showed "none" for mutagenic, tumorigenic, irritant, reproductive effective properties. In addition to these, the compounds 2 and 7 were confirmed "as low" risk for mutagenic and irritant as well as "none" for tumorigenic and reproductive effective properties. All nine (1-9) compounds showed "none" for its teratogenicity properties as calculated using *in silico* first program (Table 2).

The assessment of toxicity was also calculated using the software Toxtree Ver. 2.5.0, which determines the toxicity level of compounds using the Benigni and Bossa rules [28]. The toxicity results predicted from the Toxtree software are shown in Table 3. The calculated toxicity results to the 9 compounds showed that all the compounds were nontoxic for *S. typhimurium* TA100 mutagen, eye irritation as well as corrosion and skin sensitation alerts. In addition to these 9 compounds were negative for its genotoxic carcinogenicity as well as non genotoxic carcinogenicity. This result indicates that all the compounds were found to be safe and encouraging for further study.

From the above results the compounds namely, 3, 5 and 8 possess better score in terms of drug-likeness and drug score. The compound 5 possess the highest drug score value of 0.88, which was calculated using data warrior and OSIRIS property

Table 2: Toxicity risk of nine molecules calculated based on data warrior software of Osiris property explorer and *in silico* first

S. No.	Compound name	Mutagenic	Tumorigenic	Irritant	Reproductive effective	Teratogenicity
1	Z-81934069	None	None	None	None	None
2	Z-80319005	Low	None	None	None	None
3	Z-81942670	None	None	None	None	None
4	Z-84975470	None	None	None	None	None
5	Z-84409571	None	None	None	None	None
6	Z-80770573	None	None	None	None	None
7	Z-80070769	None	None	High	None	None
8	Z-72273865	None	None	None	None	None
9	Z-81934199	None	None	None	None	None

Table 3: Toxicity properties of the nine molecules determined based on Toxtree software Ver. 2.6.0

S. No.	Name of the Compound	Negative for genotoxic carcinogenity	Negative For Non- genotoxic Carcinogenity	Potential *S. typhiurium* TA 100 mutagen based on QSAR	Potential Carcinogen based on QSAR	Eye irritation and corrosion	Skin irritation alerts
1	Z81934069	Yes	Yes	No	No	Non toxic	Non toxic
2	Z80319005	Yes	Yes	No	No	Non toxic	Non toxic
3	Z81942670	Yes	Yes	No	No	Non toxic	Non toxic
4	Z84975470	Yes	Yes	No	No	Non toxic	Non toxic
5	Z84409571	Yes	Yes	No	No	Non toxic	Non toxic
6	Z80770573	Yes	Yes	No	No	Non toxic	Non toxic
7	Z80070769	Yes	Yes	No	No	Non toxic	Non toxic
8	Z72273865	Yes	Yes	No	No	Non toxic	Non toxic
9	Z81934199	Yes	Yes	No	No	Non toxic	Non toxic

explorer. The other toxicity results predicted using the *in silico* first, Toxtree indicated that all the 9 compounds showed negative for teratogenicity, genotoxic carcinogenity as well as nongenotoxic carcinogenity, and has no potential *S. typhiurium* TA 100 mutagen based on QSAR and potential carcinogen based on QSAR along with nontoxic for eye irritation and corrosion as well as skin irritation alerts. In considering all the above results the compound 5 was found as the best molecule and it may be further designed to synthesize to target cancer.

CONCLUSION

A collection of 64 inhibitor compounds were selected for the 3D-QSAR study to target TGF-β type I. The best pharmacophore ADHRR was developed using PHASE of Schrodinger, which was used to screen the compounds from the Zinc and NCI database. The screened compounds were further imported to the XP- GLIDE docking of Schrodinger software. The lead compounds were filtered using the Glide score and ADME properties. The nine lead compounds were scrutinized and evaluated for their toxicity assessment. The 9 hit compounds were calculated to their molecular properties like clogS, clogP, molecular weight, drug-likeness and drug score using the OSIRIS and Molinspiration tools. Additionally the compounds were tested for their toxicity risk properties such as, mutagenic, tumorigenic, irritant, reproductive effective using data warrior software. The teratogenicity was predicted using the *in silico* first.

All the 9 compounds were evaluated using the Toxtree software for its carcinogenity, mutagen, skin, corrosion and eye irritation properties. By using the cheminformatic tools, the 9 compounds were compared and finally three compounds namely 3 (Z81942670), 5 (Z84409571) and 8 (Z72273865) were identified. Based on the drug score, the compound Zinc-84409571" with a drug score of 0.88 was identified as a safe drug molecule to target Cancer cells, which will be taken for redesign, synthesis and biological study for an effective treatment of cancer.

CONFLICT OF INTEREST

The authors have no conflict of interest.

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