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Screening and Toxicity Risk Assessment of Selected Compounds to Target Cancer using QSAR and Pharmacophore Modelling

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Abstract : To target TGFβ type I receptor, around 63 compounds have been identified from the binding database and3D-QSAR study was carried out using PHASE of Schrodinger software. Through thorough validation, a best pharmacophore model screened 4000 compounds from National Cancer Institute(NCI) and Zinc database. Further docking studies around 4000 molecules were docked by targeting the protein TGFβ type I (PDB**ID**: **1VJY**). Based on docking or Glide score 25best compounds were identified. In addition to these, QikProp module 7 lead compounds were screened and their toxicity parameters evaluated using OSIRIS property explorer and Molinspiration and ToxTree software.
The molecular parameters like clogS, clogP and Molecular weight were calculated using Molinspiration software as well as the drug-likeness and drug score using the OSIRIS property explorer. Their toxicity parameters like mutagenic, tumorigenic, irritant and reproductive effective were calculated using data warrior. The teratogenicity of the compounds was calculated using *insilico* first software and its toxicity to *S.typhimurium* TA100 mutagen, eye irritation as well as corrosion, skin sensitation alerts, negative for genotoxic carcinogenicity and non genotoxic carcinogenicity. From the results the compound 7 (Zinc-69489055) was found to be 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 and Molinspiration.

Introduction

In drug design and discovery process, the ligand based approaches were performed using the pharmacophore mapping and Three Dimensional Quantitative Structure Activity Relationship (3D-QSAR). The search of molecules from the various databases using the pharmacophore helps to identify the important structural features for their functional activity and to identify a stable drug like molecules with fewer side effects(Prashantet al[1]).The essential hypothesis of the QSAR model is that when a toxic property was chosen which describes about the relation to a chemical, which can be explained using certain parameters

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(Emilio[2]). Since the year 1950's humans were exposed to many chemicals, which were not tested for tumerogenicity. Currently about 35,000 commercial chemicals being prepared on usual basis and about 1,000 new ones are added every year. In case if only 1% of the known chemicals are mutagens or carcinogens, this will lead to a severe problem(Puratchikody et al[3]).

Currently various computational softwares or programs being used to predict the toxicity of the chemical compounds and this trend has been adopted while developing new chemical descriptors, algorithms, and statistical perspectives, followed by programs having specific applications in relation to drug discovery (Emilio[2]).More recently, different chemical descriptors and fragments have been utilized, including those that are constitutional, quantum mechanical, topological, geometrical, charge related, semi-empirical, thermodynamicetc (Hermens et al[4]). Since many number of softwares have been developed which will predict toxicity based on the chemical structure. The software programs available for calculating the amount of toxicity are namely, Osiris property explorer (Ayatiet al[5]), *insilico* first (Larvolet al[6]), TOPKAT (Michael at al[7], Barun et al[8]), Toxtree(Barun et al[8]), Toxpredict(Subramanian et al[9]) etc. In addition to these the programme for property calculation being used which includes, Molinspiration(Kovacevicet al[10]), Osiris property explorer, simulation property calculator and so on.

The present study is concerned with the prediction of certain toxicity parameters and evaluation of some important physicochemical parameters using the data warrior from Osiris property explorer, Toxtree, *insilico* first and Molinspiration softwares. Seven drug-like molecules obtained from the QSAR studies were submitted for the prediction of toxicity parameters like mutagenic, tumorigenic, irritant and reproductive effective as well as *insilico* screening for its drug score and drug-likeness evaluation to analyze their overall potential to be qualified as drugs.

Materials and Methods

Seven compounds obtained from the QSAR study were docked against TGFβ-I (PDB**ID**: 1VJY). The compounds were further used to predict the following parameters, which includes molecular properties and toxicity. The molecular properties were predicted using online web server "Molinspiration programme Ver. 2011.06"(www.molinspiration.com[11])to evaluate the oral bioavailability and drug likeness of the compounds. The Osiris properties explorer,(http://www.organic-chemistry.org/prog/peo/[12])an online server was used for the prediction of parameters like drug score. In addition, the data warrior a new software tool of organic portal (OSIRIS) was used to predict the values of molecular mutagenic, tumorigenic, irritant and reproductive effective properties of the compounds.

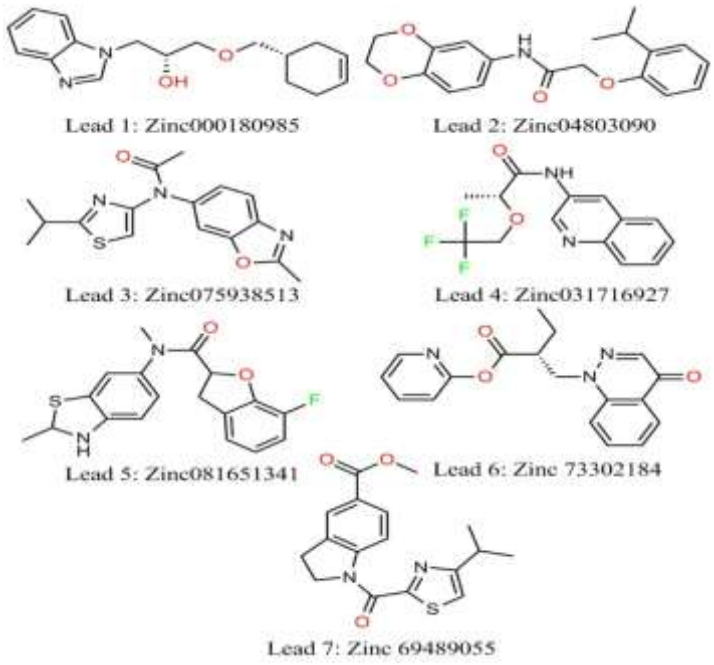

Figure: 1 The 7 compounds drawn using Chemdraw obtained from the Zinc database with their identity number Zinc-000180985, Zinc-04803090, Zinc-075938513, Zinc-031716927, Zinc-081651341, Zinc-73302184 and Zinc-69489055.

The 7 compounds used for the molecular properties and toxicity prediction were screened from the zinc database and their identity number are000180985, 04803090, 075938513, 031716927, 081651341, 73302184 and 69489055(**Figure 1)**. The molecular structures of the compounds were drawn using the ChemDraw(Li. Pet al[13], Balachandran et al[14])software and the Small Incision Lenticule Extraction(SMILES) (David et al[15])format of the structure was pasted on the data warrior software. The teratogenicity was calculated using the *insilico* first software. The toxicity for *S.typhimurium* TA100 mutagen, eye irritation as well ascorrosion and skin sensitation alerts were calculated based on the Toxtree software. It was also used to predict whether the compounds were negative for genotoxic carcinogenicity and for non genotoxic carcinogenicity.

Results and Discussion

The molecular properties of the selected compounds were calculated using Molinspiration and Data warrior (OSIRIS) of organic portal and the values are given in **Table 1.**The values of clogS (aqueous solubility), clogP (partition coefficient between n-octanol and water)(Nicholaset al[16]),molecular weight, drug likeness and the drug score were compared. The logP value of a compound denotes the logarithm of its partition coefficient between n-octanol and water log (c octanol /c water) is a well recognized as the measure of the compound's hydrophilicity (Naliniet al[17]). Low hydrophilicities associated with high logP values which cause poor absorption or permeation. The reasonable probability of being well absorbed if the compounds logP value must not be greater than 5.0(Klauset al[18]).The result of the study showed that the calculated values using Molinspiration software for all the 7 compounds were found less than 5.

Table 1: Predicted molecular properties using Molinspiration and Data warrior software.

S. No	Compound	clogS	clogP<5	Molecular Wt<500	Drug Likeness	Drug Score
1	Zinc-000180985	-2.385	2.0568	286.374	-2.6637	0.47
2	Zinc-04803090	-3.961	3.5478	327.379	-6.4039	0.37
3	Zinc-075938513	-3.491	3.1215	315.396	3.1942	0.68
4	Zinc-031716927	-3.703	2.4304	298.263	-4.7691	0.33
5	Zinc-081651341	-4.749	3.1185	344.409	3.845	0.21
6	Zinc-73302184	-2.757	2.2282	323.351	0.8541	0.63
7	Zinc-69489055	-3.519	3.178	330.407	3.3899	0.73

To make the best or most effective compounds for its high activity on a biological target almost often goes along with increased molecular weights(Behera et al[19]).On the other hand,the compounds with higher weights are less likely to be absorbed and therefore to ever reach the destination of action. But some of the macrolide antibiotics like erythromycin and quinoxaline containing antibiotic "echinomycin" have molecular weight exceeding 500 Daltons(Portugal[20]).More than 80 % of all marketed drugs have a molecular weight below 450 Daltons(Lakshmipathy et al[21]).The molecular weights of the 7 compounds were found to be less than 500. Drug likeness may be defined as a complex balance of various molecular properties and structural features that determine whether particular molecule is similar to the known drugs. In drug-likeness property a positive value for the chemicals states that the molecule contains predominantly fragments which are frequently present in commercial drugs (Ursu et al[22]). The compounds 3, 5, 6 and 7 had shown positive value for the drug likeness property.

The drug score (ds) is a contributions calculated directly from of parameter of Partition coefficient (cLogP), solublity(clogS), Molecular weight (Mol.Wt), drug-likeness andt oxicity risk within one useful practical value. It could be used for evaluating the potential of the drug candidate(Alonso et al[23]). When the drug score is better, then the compound has a better chance to be a drug candidate. The drug score values such as 1.0, 0.8 and 0.6 are associated with no risk, medium risk and high risk, respectively. The drug score value predicted by the OSIRIS property explorer for the compounds 1-7 were0.47, 0.37, 0.68, 0.33, 0.21, 0.63 and 0.73(**Table 1)**. This shows that the compounds 3, 5 and 7 possesses the values of medium risk and may be used as a drug molecule.

The toxicity risk values were predicted using the software Data warrior (OSIRIS) are shown as none, low and high for its mutagenic, tumorigenic, irritant, reproductive effective properties. The high risks of

undesired effects like mutagenicity tumorigenic, irritant, reproductive effective properties are shown in **Table 2**. The "none" value indicates that the drug-conform behavior of compounds, the low and high values shows about the level of toxicity. The compounds with serial number 2, 4,5 and 7 showed none for its mutagenic, tumorigenic, irritant, reproductive effective properties. In addition to these the compounds 1 and 3 were demonstrated "high" risk in irritant and mutagenic properties as well as "none" in tumorigenic and reproductive effective.

The compound number 6 associated with "low" in irritant and "none" for mutagenic, tumorigenic and reproductive properties. The 7 compounds showed "none" for its teratogenicity properties predicted by the *insilico* first program (**Table 2)**. Estimation of toxicity values were calculated by ToxtreeVer. 2.5.0 software which determines the toxicity level of compounds based on Benigni and Bossa rules(Benigni et al[24]). The predicted toxicity results are shown in **Table 3**. The calculated results showed that the 7 compounds are nontoxic for *S.typhimurium* TA100 mutagen, eye irritation as well as corrosion and skin sensitation alerts. In addition the Toxtree software also showed that the all the 7 compounds were negative for both genotoxic carcinogenicity and non genotoxic carcinogenicity indicates that all the compounds were safe.

Table 2:Toxicityrisk of seven molecules based on Data warrior software of Osiris property explorer and *Insilco* first.

S. No	Compound	Mutagenic	Tumorigenic	Irritant	Reproductive effective	Teratogenicity
1	Zinc-000180985	None	None	High	None	None
2	Zinc-04803090	None	None	None	None	None
3	Zinc-075938513	High	None	None	None	None
4	Zinc-031716927	None	None	None	None	None
5	Zinc-081651341	None	None	None	None	None
6	Zinc-73302184	None	None	Low	Low	None
7	Zinc-69489055	None	None	None	None	None

Table 3: Toxicity properties results of the 7 molecules based on ToxTree software Ver. 2.5.0

S. No	Compound	Negative for genotoxic carcinogenity	Negative for nongenotoxic carcinogenity	Potential *S. Typhiurium* TA 100 mutagen based on QSAR	Potential carcinogen based on QSAR	Eye irritation and corrosion	Skin irritation alerts
1	Zinc-000180985	Yes	Yes	No	No	Non toxic	Non toxic
2	Zinc-04803090	Yes	Yes	No	No	Non toxic	Non toxic
3	Zinc-075938513	Yes	Yes	No	No	Non toxic	Non toxic
4	Zinc-031716927	Yes	Yes	No	No	Non toxic	Non toxic
5	Zinc-081651341	Yes	Yes	No	No	Non toxic	Non toxic
6	Zinc-73302184	Yes	Yes	No	No	Non toxic	Non toxic
7	Zinc-69489055	Yes	Yes	No	No	Non toxic	Non toxic

The molecular properties values obtained from the Data warrior and Molinspiration software, the compounds 3, 6 and 7 were chosen based on the drug score and drug-likeness. When comparing these three compounds, the compound 3 showed high mutagenic and low reproductive effective properties. The compound 7 also showed negative for 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 non toxic for eye irritation and corrosion as well as skin irritation alerts. In considering the above results the compound 7

showed safe in all the properties and molecule can be further designed to synthesize the compound and its biological activity against cancer will be tested.

Conclusion

With reference to, 63 compounds were selected for the 3D-QSAR study. The best pharmacophore was developed and used to screen the compounds from the Zinc and NCI database. The compounds were further docked using GLIDE of Schrodinger software. Followed by using the Glide score and ADME properties the top 7 compounds were identified and tested for their toxicity assessment. The seven compounds were tested for their molecular properties like cloS, clogP, molecular weight, drug-likeness and drug score. In addition to these compounds were tested for their toxicity risk like mutagenic, tumorigenic, irritant, reproductive effective and teratogenicity using the *insilico* first and data warrior software from organic portal web. Additionally interested best compounds were tested and filtered using the Toxtree software for its carcinogenity, mutagen, skin, corrosion and eye irritation properties. Using the software analysis the 7 compounds were compared, finally only one compound "Zinc 69489055" passed in all the analysis and found to be safe to use as a drug molecule and these molecule will be designed, for synthesis and subsequent analysis. Here to conclude that, the discovery of the better lead molecule valor hopefully bring an advancement in the safe and effective treatment of cancer.

Conflict of Interest

The authors have no conflict of interest.

References

1. P.R. Murumkar, V.P. Zambre and M.R. Yadav, *Aided Mol. Des.*, **24**, 143 (2010); doi:10.1007/s10822-010-9322-z.
2. B. Emilio, *Chem. Cent. J.*, **32**, 1 (2007).
3. A. Puratchikody, D. Mukesh and N. Ramalakshmi, *J. Pharm. Res.*, **5**, 340 (2012).
4. J. Hermens, Edited by: W. Karcher, J.D. Devillers, K. Dordrecht: Quantitative structure-activity relationships for predicting fish toxicity. In Practical applications of Quantitative structure-activity relationships in environmental chemistry and toxicology, Academic Publishers, pp. 263-280 (1990).
5. A. Ayati, M. Falahati, H. Irannejad and S. Emami, *Daru*, **20**, 46 (2012) doi:10.1186/2008-2231-20-46.
6. B.L. Larvol and L.J. Wilkerson, *Nat. Biotechnol.*, **16**, 33 (1998) doi:10.1038/5412.
7. M.J. Prival, *Environ. Mol. Mutagen.*, **37**, 55 (2001) doi:10.1002/1098-2280(2001)37:1<55::AID-EM1006>3.0.CO;2-5.
8. B. Bhhatarai, D.M. Wilson, A.K. Parks, E.W. Carney and P.J. Spencer, *Chem. Res. Toxicol.*, **29**, 810 (2016) doi:10.1021/acs.chemrestox.5b00531.
9. U. Subramanian, A. Sivapunniyam, A. Pudukadu Munusamy and R. Sundaram, *Adv. Bioinforma.*, **2014**, 1 (2014) doi:10.1155/2014/385418.
10. S.Z. Kovacevic and L.R. Jevric, *Iran. J. Pharm. Res.*, **13**, 899 (2014).
11. Cheminformatics on the Web, www.molinspiration.com: MolinspirationChemin-formatics, Novaulica, SK-900 26 SlovenskyGrob, Slovak Republic.
12. Organic Chemistry Portal, http://www.organic-chemistry.org., Reto Müller Hauptstrasse, 70, 4446 Buckten – Switzerland.
13. Z. Li, H. Wan, Y. Shi and P. Ouyang, *J. Chem. Inf. Comput. Sci.*, **44**, 1886 (2004) doi:10.1021/ci049794h.
14. P. Balachandran, V. Parthasarathy and T.V. Ajay Kumar, *Int. Letts. Chem., Phys. Astron.*, **63**, 1 (2016). doi:10.18052/www.scipress.com/ILCPA.63.1.
15. D. Weininger, A. Weininger and J.L. Weininger, *J. Chem. Inf. Comput. Sci.*, **29**, 97 (1989) doi:10.1021/ci00062a008.

16. N.A. Meanwell, *Chem. Res. Toxicol.*, **29**, 564 (2016) doi:10.1021/acs.chemrestox.6b00043.
17. C.N. Nalini, S. Raga Deepthi and N. Ramalakshmi, *Rasayan J. Chem.*, **4**, 829 (2011).
18. K.L.E. Kaiser and I. Valdmanis, *Can. J. Chem.*, **60**, 2104 (1982) doi:10.1139/v82-300.
19. S.M. Behera, R.K. Mohanta, S.K. Mishra, S.K. Sahu, L. Mohanta and M. Banerjee, *Int. J. Drug Develop. Res.*, **6**, 78 (2014).
20. J. Portugal, *BMC Pharmacol.*, **9**, 11 (2009) doi:10.1186/1471-2210-9-11.
21. I. Lakshmipathy and P. Ekambaram, *Drug Invention Today*, **3**, 186 (2011).
22. O. Ursu, A. Rayan, A. Goldblum and T.I. Oprea, *WIREs Computational Mole. Sci.*, **1**, 760 (2011); doi:10.1002/wcms.52.
23. H. Alonso, A.A. Bliznyuk and J.E. Gready, *Med. Res. Rev.*, **26**, 531 (2006) doi:10.1002/med.20067.
24. R. Benigni, C. Bossa, N. Jeliazkova, T. Netzeva and A. Worth, The Benigni=BossaRulebase for Mutagenicity and Carcinogenicity—A Module of Toxtree (European Commission Report EUR 23241), European Commission, Ispra, Italy, 2008.

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