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Research Article

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Virtual Screening Identifies New Scaffolds for Testosterone 17β-Dehydrogenase (NADP+) Inhibitor

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ABSTRACT

The development of new and safer drugs is based on the use of existing physical and information resources. Furthermore, the tremendous development of the new generation of simulation techniques and advanced computer hardware provides high computing power and various molecular modeling or computational chemistry approaches over the last decade to simulate, predict, and analyze the properties and behaviors of molecules on an atomic level to perform virtual drug screening for novel drug compounds. By these computational screening, synthesized compounds are showing Testosterone 17β-dehydrogenase (NADP+) Inhibitor activity on 5EN4 and 5ICM enzymes. In that C1 and C5 are having minimum energies with 5EN4 and 5ICM where as C2 and C6 are with 4HMN and 5EN4.

Keywords: Dehydrogenase (NADP+) inhibitor; HEX; PASS; Computational screening; Docking

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INTRODUCTION

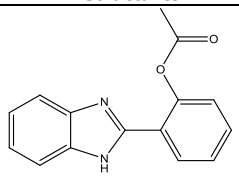
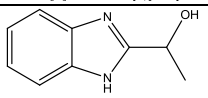
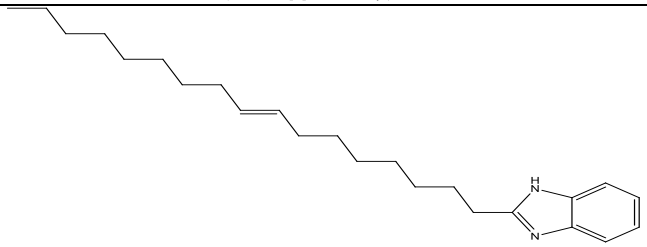
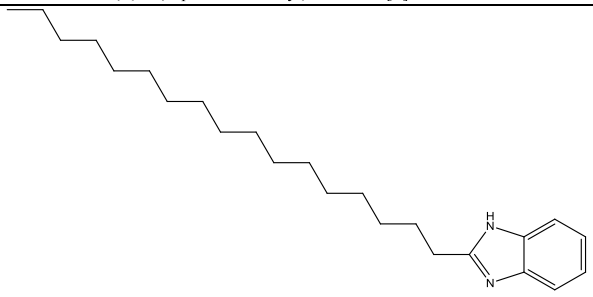
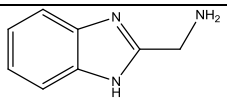
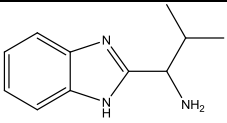
The diverse molecular modeling packages have converged to offer a core of similar capabilities for molecules. They differ in their user interfaces and level of sophistication. Several newly emerged programs have specialized functions for fields such as virtual drug screening, virtual combinatorial chemistry, denovo drug design, chemical synthesis pathway predication and toxicology (ADME) prediction as reviewed. Software packages are marketed to simplify our work by providing extensive default choices, which simplifies a calculation [1-5]. Packages like Molinspiration cheminformatics software, PASS (Prediction of Activity Spectra for Substances), and HEX 8.0 are used in current study to detect molecular properties, biological activities and docking scores respectively. Prediction of this spectrum by PASS is based on SAR analysis of the training set containing more than 35,000 compounds which have more than 500 kinds of biological activity [6]. Chemical descriptors used in PASS analysis, called multilevel neighborhoods of atoms (MNA), are recently considered in detail [7]. They are automatically generated by on the basis of MOL-file [8] of a molecule. The list of MNA descriptors currently consists of more than 35700 different items. The new ones are added to this list being founded in a novel compound refreshing the training set. MNA descriptors are effectively applied in SAR, QSAR and similarity analysis [6]. They can be also used as keys or fingerprints to cluster the libraries of chemical compounds, to select the representative sub-sets from chemical databases, etc. PASS algorithm was selected by theoretical and empirical comparison of many different mathematical methods to provide high accuracy of prediction and robustness of calculated estimates. It was shown that the mean accuracy of prediction with PASS is about 86% in LOO cross-validation. Using MDDR database to create heterogeneous training and evaluation sets it was recently demonstrated that the predictions are robust despite excluding up to 60% of information. PASS testing in a blind mode by 9 scientists from 8 countries versus the heterogeneous set of 118 compounds having 138 activities demonstrated the mean accuracy of prediction 82.6% [9]. Lead compounds possess desired pharmacological properties and plays an important role in drug design and development. To develop an orally active compound, certain properties of the lead compound should be taken into consideration such as Lipinski's rule of five that help pharmaceutical scientists to select the best candidates for development

and to reject those with a low probability of success [10,11]. Computer based (*in silico*) molecular modeling (bioinformatics and cheminformatics) are quite useful for this purpose, because they are extremely fast and cost efficient and can be applied even when a compound is not physically available [12,13]. *Hex* 8.0.0 protein docking using spherical polar Fourier Correlations [4]. *Hex* is an interactive molecular graphics program for calculating and displaying feasible docking modes of pairs of protein and DNA molecules. *Hex* can also calculate protein-ligand docking, assuming the ligand is rigid, and it can superpose pairs of molecules using only knowledge of their 3D shapes. It is the first protein docking program to be able to use modern graphics processor units (GPUs) to accelerate the calculations.

EXPERIMENTAL SECTION

All the 6 compounds represented in Table 1 were synthesised in chemistry laboratory in CES College of Pharmacy, Kurnool. Structures of all the derivatives were drawn by using ACD labs Chemsketch v 12.0 and their SMILES notations were generated.

Table 1: Compounds and its IUPAC name

Compound	Structures
C1	 2-(1*H*-benzo[*d*]imidazol-2-yl)phenyl acetate
C2	 1-(1*H*-benzo[*d*]imidazol-2-yl)ethanol
C3	 (*E*)-2-(heptadec-8-en-1-yl)-1*H*-benzo[*d*]imidazole
C4	 2-heptadecyl-1*H*-benzo[*d*]imidazole
C5	 (1*H*-benzo[*d*]imidazol-2-yl)methanamine
C6	 1-(1*H*-benzo[*d*]imidazol-2-yl)-2-methylpropan-1-amine

Smiles notations of the selected compounds were fed in the online molinspiration software version 2011.06 (www.molinspiration.com) for calculation of molecular properties (Log P, Total polar surface area, number of hydrogen bond donors and acceptors, molecular weight, number of atoms, number of rotatable bonds etc.) listed

in Table 2 Computer system PASS (*Prediction of Activity Spectra for Substances*) predicts simultaneously several hundreds of biological activities of each derivative are predicted with PASS, and listed in Table 3 Docking studies with HEX 8.0 version are reported in Table 4. Testosterone 17beta-dehydrogenase (NADP+) inhibitors are targeted receptors for docking like 4HMN, 5EN4, 5ICM, 1ZBQ (Figure 1).

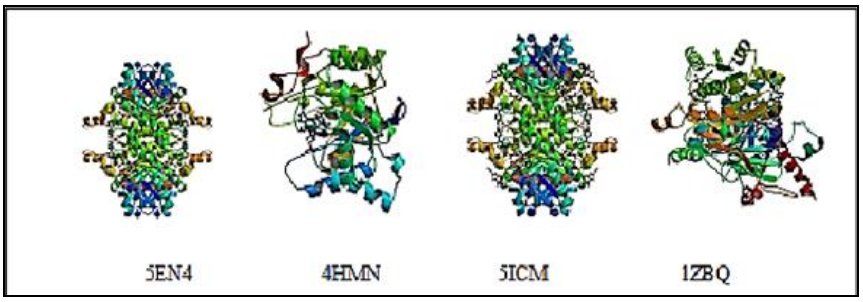


Figure 1: Docking structures

RESULTS AND DISCUSSION

The calculated values of various parameters of the isolated compounds for drug likeness are presented in Table 2. Among 6 compounds except C3 and C4 (deviated from log P values), all follows drug likeness properties. Lipinski's rule is widely used to determine molecular properties that are important for drug's pharmacokinetic *in vivo*. According to Lipinski's rule of five, a candidate molecule is more likely to be orally active if: a) the molecular weight is under 500, b) the calculated octanol/water partition coefficient (log P) is less than 5, c) there are not more than 5 hydrogen bond donors (OH and NH groups), d) there are not more than 10 hydrogen bond acceptors (notably N and O). However, there are some exceptions to this rule and a compound is likely to be orally active as long as it did not break more than one of his rules because some of orally active drugs such as atorvastatin, cyclosporin do not obey the rule of five. Partition coefficient or Log P is an important parameter used in rational drug design to measure molecular hydrophobicity. Hydrophilic/lipophilic nature of drug molecule affects drug absorption, bioavailability, drug-receptor interactions, metabolism of molecules, as well as their toxicity. Log P values of BAs derivatives were found to be in the range of 5-688-7.899 and is a clear violation of Lipinski's rule of five. Total polar surface area (TPSA) is closely related to the hydrogen bonding potential of a molecule and is a very good predictor of drug transport properties such as intestinal absorption, bioavailability, blood brain barrier penetration etc.

When $Pa > 0.7$, the chances of finding experimental activity are rather high but the compounds found may be close structural analogs of known drugs. If we select in the range $0.5 < Pa < 0.7$, the chances for detecting experimental activity will be lower but the compounds will be less similar to known pharmaceutical agents. For $Pi < Pa < 0.5$, the chances of detecting experimental activity will be even lower but if the prediction is confirmed, the compound found may prove a parent compound for a new chemical class for the biological activity examined. According to PASS prediction all the 6 compounds exhibiting Antihelmintic and Testosterone 17beta-dehydrogenase (NADP+) inhibitor activity. Among this Testosterone 17beta-dehydrogenase (NADP+) inhibitor activity was selected for docking studies. This enzyme involves in conversion of androstenedione to testosterone.

Table 2: Drug likeness score for compounds (C1-C6)

Properties	C1	C2	C3	C4	C5	C6
logP	3.07	1.1	8.8	9	0.72	0.15
TPSA	54.99	48.91	28.68	28.68	54.71	54.71
n atoms	19	12	26	26	11	14
MW	252.27	162.19	354.56	356.6	147.18	189.26
nON	4	3	2	2	3	3
nOHNH	1	2	1	1	3	3
N violations	0	0	1	1	0	0
nrotb	3	1	15	16	1	2
Volume	224.8	150.27	388.07	394.25	136.96	186.93

logP: Octanol-water coefficient; TPSA: Polar surface area; MW: Molecular weight; nON: No. of hydrogen bond acceptors (O and N atoms); nOHNH: No. of hydrogen bond donars (OH and NH groups); nviolations: No. of rule of 5 violation (Lipinski's rule); nrtob: No. of rotatable bonds; Volume: Molecular volume

Table 3: Activity predicition through PASS

Ligand	Pa	Pi	Activity
C1	0.74	0.004	Antihelmintic (Nematodes)
	0.58	0.025	Antiviral (Picornavirus)
	0.54	0.113	Testosterone 17beta-dehydrogenase (NADP+) inhibitor
	0.81	0.016	Mucomembranous protector
C2	0.81	0.003	Antiviral (Picornavirus)
	0.76	0.037	Testosterone 17beta-dehydrogenase (NADP+) inhibitor
	0.81	0.004	Pterin deaminase inhibitor
	0.42	0.036	Antihelmintic (Nematodes)
C3	0.69	0.007	Antiviral (Picornavirus)
	0.71	0.053	Testosterone 17beta-dehydrogenase (NADP+) inhibitor
	0.51	0.015	Antihelmintic (Nematodes)
	0.63	0.014	Leukopoiesis stimulant
C4	0.69	0.007	Antiviral (Picornavirus)
	0.76	0.007	Vasoprotector
	0.7	0.056	Testosterone 17beta-dehydrogenase (NADP+) inhibitor
	0.56	0.009	Antihelmintic (Nematodes)
C5	0.68	0.008	Antiviral (Picornavirus)
	0.4	0.041	Antihelmintic (Nematodes)
	0.59	0.007	Imidazoline receptor agonist
	0.61	0.088	Testosterone 17beta-dehydrogenase (NADP+) inhibitor
C6	0.69	0.007	Antiviral (Picornavirus)
	0.51	0.015	Antihelmintic (Nematodes)
	0.71	0.053	Testosterone 17beta-dehydrogenase (NADP+) inhibitor
	0.52	0.03	Antineoplastic (non-Hodgkin's lymphoma)

Table 4: Docking studies

Ligand	4HMN		5EN4		5ICM		1ZBQ	
	E min	E max	E min	E max	E min	E max	E min	E max
C1	-266.48	244.71	-361.7	328.69	-317.7	348.8	-124.62	143.09
C2	-302.26	300.95	-279.35	338.69	-275.14	268.56	-57.73	89.51
C3	-156.28	210.98	-136.03	187.32	-246.19	115.64	-91.69	145
C4	-156.28	210.98	-136.03	187.32	-246.19	115.64	-91.69	145
C5	-176	123.14	-242.23	335.12	-253.67	323.73	-64.5	96.05
C6	-330.94	283.51	-314.96	292.17	-228.83	185.18	-82.39	113.06

Out of all the energy values C1, C2 and C6 were shown minimum energy values with 4HMN, 5EN4, 5ICM where as C5 with 5EN4 and 5ICM.

CONCLUSION

It can be conclude that synthesized 6 compounds are biologically important molecules and possess desirable molecular properties for drug likeness except log P values of C3 and C4. Therefore, some structural modifications should be made in the skeleton of compounds to improve their hydrophilicity and bioavailability. In this paper we predicted biological activity of synthesized compounds by using PASS spectrum and done docking studies with HEX 8.0. All the compounds are showing 17beta-dehydrogenase (NADP+) inhibitor activity in that, 5EN4 and 5ICM receptors and synthesised compounds showing docking with minimum energy score.

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