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In-silico determination of *p*Ka and log*p* values of some isoniazid synthetic analogues using Marvin software

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Abstract: Among the physicochemical properties, *p*Ka and Log*P* values help us in studying drug parameters like ADME and could be predicted to some extent. With this view, here we wish to predict these two properties of our previously synthesized biologically active derivatives of isoniazid using on-line available program Marvin, a Java-based chemical software application frequently used for chemical modeling. According to Marvin, *p*Ka values predicted 99.99% unionized states of INH and some derivatives at physiological *p*H 7.4. Marvin calculated Log*P* values estimated good oral absorption for all the synthesized compounds. Therefore it can be said that the findings of the study emerged in an ideal region that permits the formulation of these derivatives. Since this was just a theoretical study, it demands more experimentation to determine accurate situation.

Keywords: Virtual screening, Pyridine-4-carbohydrazide, dissociation constant, partition coefficient.

INTRODUCTION

In-silico (also known as Virtual Screening) is a terminology frequently used to specify something executed on computer. It served as a key component in 'lead molecule generation' in finding the structures having equilibrium between dynamic and good ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity). Several of the drug candidates let down when they approach clinical trial. This disappointment may then be related to their problems of kinetics and toxicity. *In-silico* study helped us in foretelling the "drug-likeness" of candidate molecules in the early phases of drug discovery where it has assumed that drug like structures would have good ADMET (Clark and Pickett, 2000; Matter *et al.*, 2001; Podlogar *et al.*, 2001; Walters and Murcko, 2002; Roche and Guba, 2005). Knowledge of drug-receptor binding and predicted ADMET is therefore useful in ranking the compounds as drugs.

Among the physicochemical parameters, Acid Dissociation Constant (*p*Ka) and Partition Coefficient (Log*P)* assisted us in studying different drug properties like absorption, excretion and could be predicted to some extent (Guo and Shen, 2004). *p*Ka explains the protonation (or deprotonation) of a compound undergoing a chemical process and governs the degree of ionization with respect to biological *p*H. Log*P* measures hydrophobicity and hydrophilicity of a chemical molecule. Several of the biological parameters such as drug receptor binding, absorption, metabolism and toxicity are found associated with hydrophobic characteristics. Thus, the knowledge of both these factors guide us in anticipating the distribution of compound in a biological system (Lipinski, 2000; Park *et al.*, 2000). With this scope, here we determined these two properties of our previously synthesized seventeen derivatives of isoniazid by *in-silico* tools (fig. 1) (Naeem *et al.*, 2014; Naeem *et al.*, 2016).

MATERIALS AND METHODS

Structures of INH and the synthesized compounds 1-17 were drawn using software Chem Draw Ultra 8.0 and their *p*ka and Log*P* values were computed with the help of on-line available program Marvin Sketch 5.5.0.0. This is a Java-based chemical software application used for structure-drawing and estimating number of physico-chemical properties (Settimo *et al.*, 2014). The *p*Ka plug-in predicted *p*Ka values of all protons receiving or donating atoms in a molecule and considered as an efficient and robust way to locate the most acidic and basic sites in a molecule under user-defined conditions while the predicted partition coefficients Log*P* were composed of the molecules atomic increments.

RESULTS

The predicted *p*Ka and Log*P* values of the synthesized compounds were given in table 1. According to table 1, INH displayed three *p*Ka values, 3.35 for the pyridine Nitrogen, 2.36 for hydrazide Nitrogen and 13.61 for Nitrogen of the hydrazide group. Compounds 1-2, 3-4, 5-6, 7-17 showed *p*Ka values 3.16, 3.15, 3.19 and 3.22 for pyridine nitrogen respectively. Similarly 1-4 and 7-17 exhibited *p*Ka of -7.59 and -9.61 for oxygen of the hydrazide group respectively.

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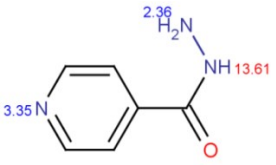
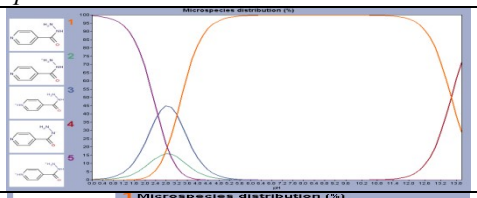
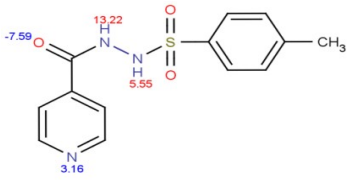
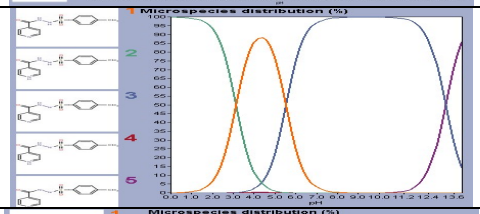
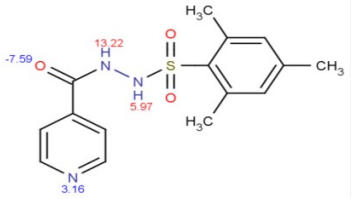
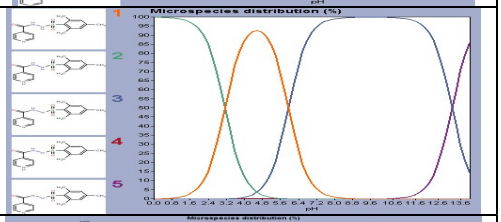
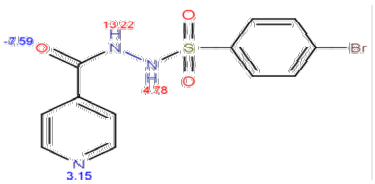
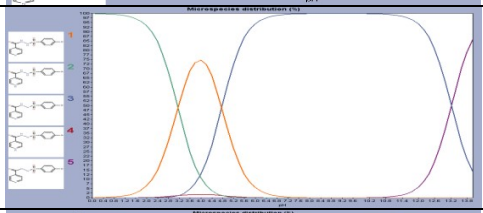
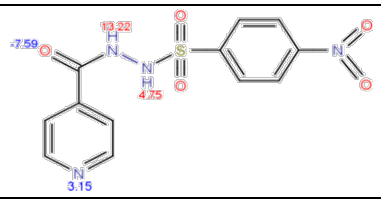
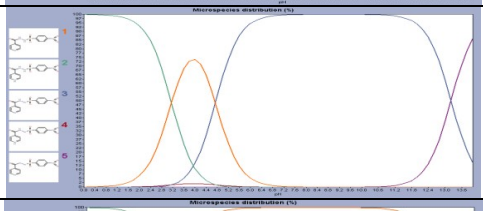
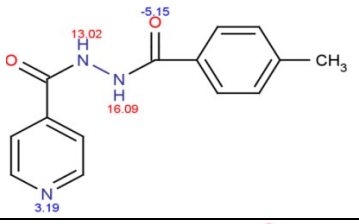
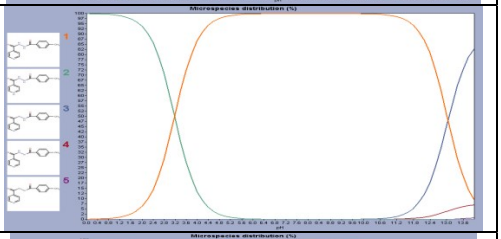
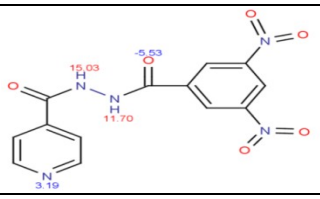
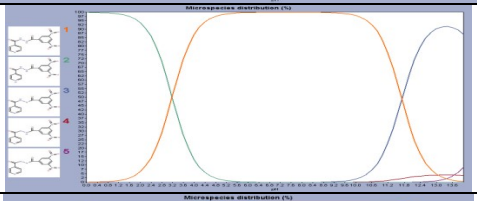
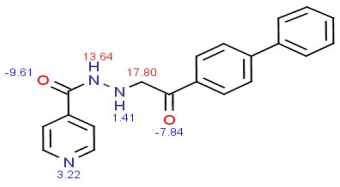
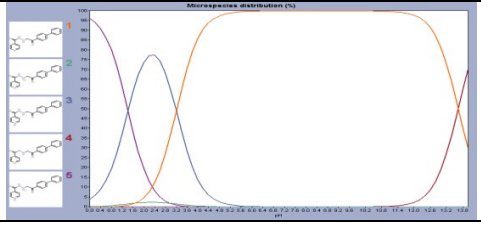
Table 1: Marvin calculated *p*Ka and Log*P* values of INH and derivatives 1-17

Compound	Log*P*	*p*Ka	
INH	-0.69		
1	1.14		
2	2.17		
3	1.40		
4	0.57		
5	1.38		
6	0.75		
7	-0.73		

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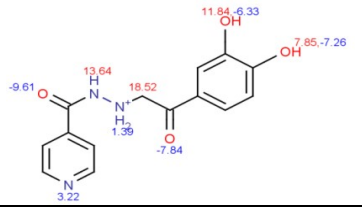
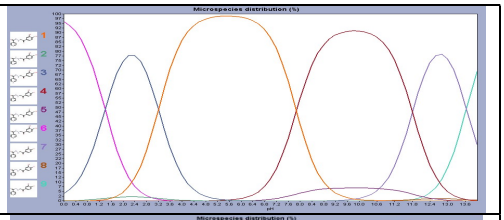
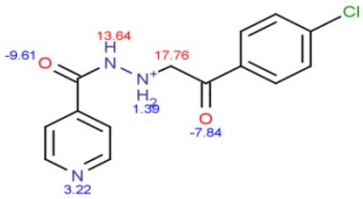
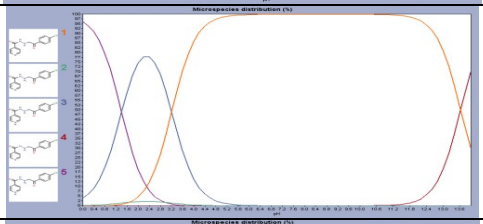
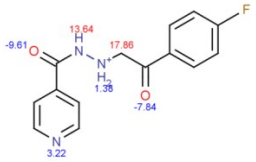
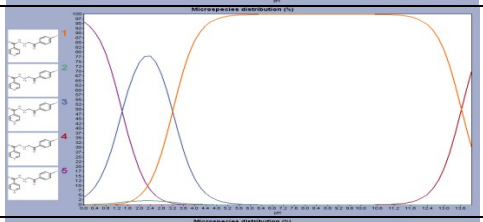
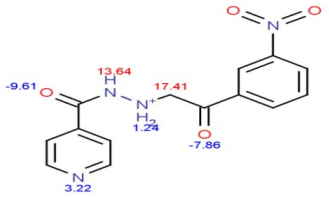
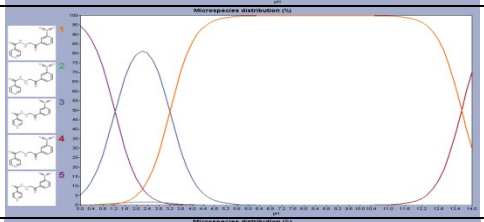
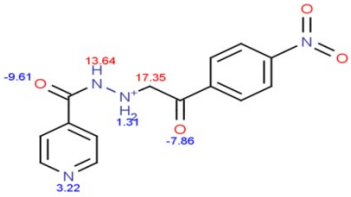
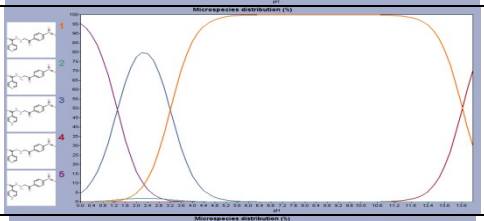
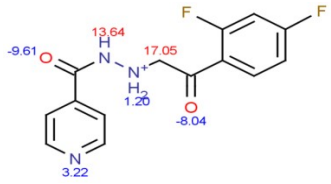
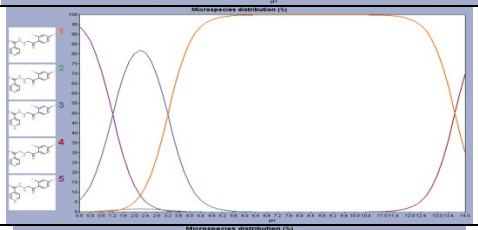
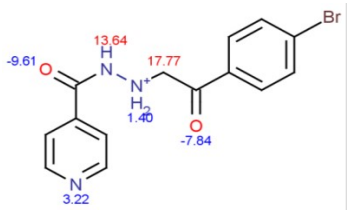
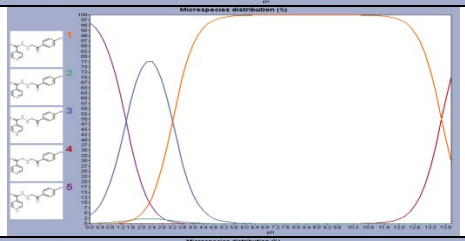
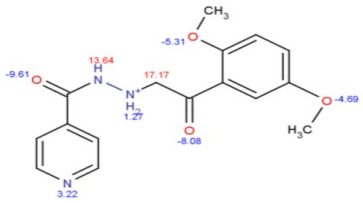
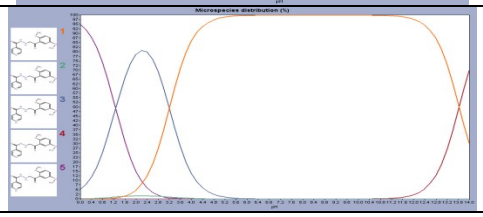
8	-2.98		
9	-1.78		
10	-2.24		
11	-2.44		
12	-2.44		
13	-2.09		
14	-1.61		
15	-2.69		

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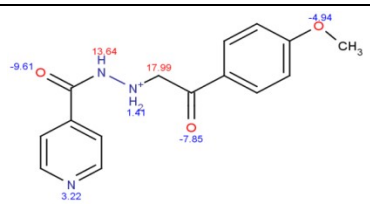
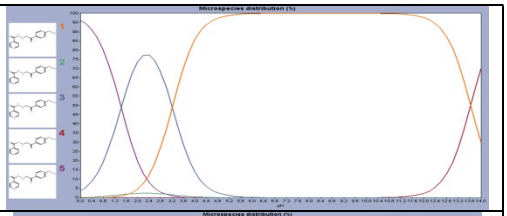
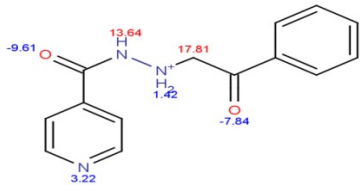
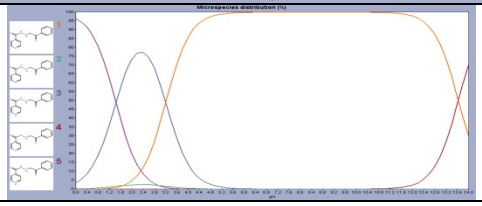
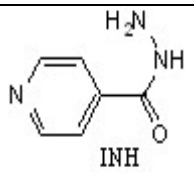
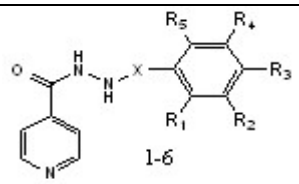
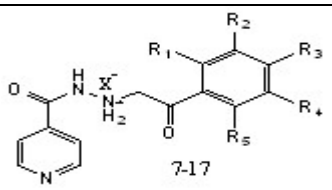
16	-2.54		
17	-2.38		







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2; X= SO_2, R_2, R_4= H, R_1, R_3, R_5 = CH_3
3; X= SO_2, R_1, R_2, R_4, R_5 = H, R_3 = Br
4; X= SO_2, R_1, R_2, R_4, R_5 = H, R_3 = NO_2
5; X= CO, R_1, R_2, R_4, R_5 = H, R_3 = CH_3
6; X= CO, R_1, R_3, R_5 = H, R_2, R_4= NO_2
7; X = Br, R_1, R_2, R_4, R_5 = H, R_3 = C_6H_5
8; X = Cl, R_1, R_4, R_5= H, R_2, R_3 = OH
9; X = Br, R_1, R_2, R_4, R_5 = H, R_3 = Cl
10; X = Br, R_1, R_2, R_4, R_5 = H, R_3 = F
11; X = Br, R_1, R_3, R_4, R_5 = H, R_2 = NO_2,
12; X = Br, R_1, R_2, R_4, R_5 = H, R_3 = NO_2
13; X = Cl, R_2, R_4, R_5 = H, R_1, R_3 = F,
14; X = Br, R_1, R_2, R_4, R_5 = H, R_3 = Br
15; X = Br, R_2, R_3, R_5= H, R_1,R_4 = OCH_3,
16; X = Br, R_1, R_2, R_4, R_5 = H, R_3 = OCH_3
17; X = Br, R_1, R_2, R_3, R_4, R_5 = H

Fig. 1: Isoniazid and Synthetic Analogues

*p*Ka values of 13.22, 13.02, 15.03 and 13.64 was calculated for nitrogen of the hydrazide groups in derivatives 1-4, 5, 6 and 7-17 respectively. *p*Ka values of hydrazide nitrogen were found to be 5.55, 5.97, 4.78, 4.75, 16.09, 11.70, 1.41, 1.39, 1.39, 1.38, 1.24, 1.31, 1.20, 1.40, 1.27, 1.41 and 1.42. Compounds 5 and 6 presented *p*Ka of -5.15 and -5.53 for carbonyl Oxygen and -7.84 to -8.08 for acyl oxygen in structures 7- 17. It was noticed that INH had Log*P* value of -0.69. Marvin-based Log*P* values of derivatives 1-17 were found to be 1.14, 2.17, 1.40, 0.57, 1.38, 0.75, -0.73, -2.98, -1.78, -2.24, -2.44, -2.44, -2.09, -1.61, -2.69, -2.54 and -2.38 respectively.

DISCUSSION

It could be said that the parent drug INH exhibited 99.99% unionized state at physiological *p*H of 7.4. At the same *p*H, structures 1-4 would undergo 98.60%, 96.39%, 99.76% and 99.78% ionization respectively. On the other hand, derivatives 5-7 and 9-17 would have 99.99% unionized state while compound 8 would remain 73.71% unionized at *p*H 7.4.

In case of Log*P*, different theories have been reported. Lipinski *et al.* explicated that poor oral drug absorption was observed when Log*P* value was greater than 5 (Lipinski, 2000). In one study, the observed Log*P* values in a range of 2±0.7 was correlated with an optimum CNS penetration (Leo *et al.*, 1971). Form the results and aforementioned relations, it might be foreseen that the synthetic analogues would reveal good oral absorption as their predicted Log*P* values were less than 5.

CONCLUSION

The knowledge of *p*Ka finds application when ionized form of the compound exhibit good water solubility in contrast to neutral ones having more lipophilic property and greater membrane permeability. The observed Log*P* values were ideal to formulate a drug, keeping this in view that this is just theoretical study require further research to analyze precise situation.

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