Research Article

QSAR Study on Some HETP Derivatives to Predict a New Compound with Best Drug Potency

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ABSTRACT

The use of theoretical approaches to predict or describe the activity of pharmaceutical compounds has accomplished more and more along the later years. Quantitative Structure Activity Relationship QSAR has been derived for a set of 1-[2- hydroxyethoxy-methyl]-6-(phenylthio) thymine] (HEPT) derivatives a potent inhibitor of the human immunodeficiency virus type 1, HIV-1 reverse transcriptase (RT) to explore the relationship between a geometrical properties(such as : bond length, bond angle and electron density on each atom) for a group of HEPT derivative descriptors (as independent variables) and anti-HIV-1 activity expressed as log EC50 (as a dependent variable), multi-linear regression technique (MLR) have been employed. The present study aims to predict a new HETP derivative with best drug potency. Three new HETP derivatives have been predicting with an interested high value of activity compared with the trading derivatives, where the value of Log EC50 was -5.47533, -1.73123 and -5.9288 for N1-HETP, N2-HETP and N3-HETP respectively. The results showed that the anti-HIV activity of HEPT derivatives was strongly dependent on electron withdrawing ability and steric effect of the substitute group.

Keywords: Computational Drug Design,HEPT,QSAR,GUSSAIN, DFT, MLR.

INTRODUCTION

HEPT (1-[(2-hydroxyethoxy)methyl]-6-(phenylthio) thymine) derivatives are non-nucleosidic reverse transcriptase inhibitors (NNRTI) and they are analogues of the natural substrate. HEPT derivatives are expected not to determine side effects, as it does not interact with the binding site of the DNA or RNA dependent DNA-polymerase.

HEPT ligands don't directly affect the substrate binding to the allosteric site of the enzyme as it interacts un-competitively with. NNRTI binding affinity to the ligand-enzyme complex is considered higher than to the free enzyme. The enzyme's active site affinity to the natural substrate decreased through the HEPT ligand – enzyme interaction, which leads to enzymatic conformational variations, which is only the case for the HIV-1 RT, while HEPT ligands are inactive against HIV-2 or other retroviruses. The exclusive specificity of NNRTI for the HIV-1 RT is a result of the presence of a flexible extreme hydrophobic pocket at the level of this enzyme in which HEPT derivatives can fit and be bound unlike the natural substrate analogues.[1-7]

The importance of quantitative structure-activity relationship (QSAR) methods in a computational drug design is earthbound since QSAR can make the premature prediction of activity-related characteristics of drug candidates and can exclude molecules with undesired properties[8]. Many QSAR studies have been reported for HEPT compounds[9-16].

Computational drug design is an effective strategy to accelerate and economize drug discovery and development process. Because of the stunning increase in the availability of biological macromolecule and small molecule information, the applicability of computational drug design has been expanded and broadly applied to nearly every stage in the drug discovery and development workflow[17].

METHODOLOGY

The common Skelton numbering is suggested[18] in order to Facilitate reviewing of results, shown in figure (1)

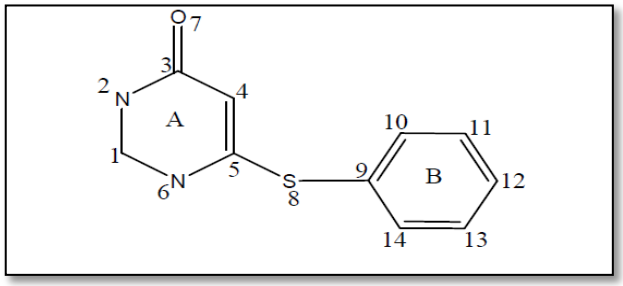

Figure 1: Common Skelton numbering

Molecules were selected from a set reported in Ref[2]. The details of molecules are shown in Table (1).

The research is directed towards a series of HEPT derivatives with a certain activity (the anti-HIV-1 activity, measured as the effective concentration of compound required to achieve 50% protection of MT-4 cells against the cytopathic effect of HIV-1.)

The selective series of HEPT derivatives was used to built up a QSAR models. Hansch model has employed with structural descriptors adapted to multi-linear regression technique (MLR).

Table 1: structure and activity (Log EC50) of HETP derivatives

No	abbreviation	Compound name	Log EC50
1	HETP1	1-((2-hydroxyethoxy)methyl)-5-methyl-2-thioxo-6-((2,3,5-trimethylphenyl)thio)-2,3-dihydropyrimidin-4(1H)-one	-0.66
2	HETP2	5-ethyl-1-((2-hydroxyethoxy)methyl)-6-(phenylthio)-2-thioxo-2,3-dihydropyrimidin-4(1H)-one	-0.96
3	HETP3	1-((2-hydroxyethoxy)methyl)-5-isopropyl-6-(phenylthio)-2-thioxo-2,3-dihydropyrimidin-4(1H)-one	-1.23
4	HETP4	6-((3,5-dichlorophenyl)thio)-5-ethyl-1-((2-hydroxyethoxy)methyl)-2-thioxo-2,3-dihydropyrimidin-4(1H)-one	-1.37
5	HETP5	6-((3,5-dichlorophenyl)thio)-1-((2-hydroxyethoxy)methyl)-5-isopropylpyrimidine-2,4(1H,3H)-dione	-1.85
6	HETP6	6-((3,5-dimethylphenyl)thio)-1-((2-hydroxyethoxy)methyl)-5-isopropylpyrimidine-2,4(1H,3H)-dione	-2.11
7	HETP7	6-((3,5-dimethylphenyl)thio)-1-((2-hydroxyethoxy)methyl)-5-isopropyl-2-thioxo-2,3-dihydropyrimidin-4(1H)-one	-2.30

Table 2: Geometrical Properties of HETP derivatives

Compound / Property		HETP1	HETP2	HETP3	HETP4	HETP5	HETP6	HETP7
B. L/A°	C(4)-C(5)	1.3634	1.3616	1.3612	1.3607	1.3605	1.3578	1.3567
	C(5)-S(8)	1.8286	1.8161	1.8061	1.8059	1.8013	1.8004	1.7986
	S(8)-C(9)	1.7825	1.7791	1.7783	1.7764	1.7719	1.7713	1.7685
	C(9)-C(10)	1.4021	1.3977	1.3961	1.3959	1.3947	1.3927	1.3915
B. A/A^0	C(4)-C(5)-S(8)	120.118	120.86	121.4921	121.6071	121.936	122.579	123.001
	C(5)-S(8)-C(9)	103.618	104.1571	105.2294	105.5362	105.696	106.486	107.540
	S(8)-C(9)-C(10)	117.083	119.4023	120.1784	121.4023	122.461	122.98	124.461
e$^-$density	C(4)	6.0333	6.0368	6.043209	6.085482	6.0895	6.10119	6.1120
	C(5)	5.9254	5.9480	5.965408	5.975789	5.9873	5.99734	6.0106
	S(8)	15.401	15.413	15.41844	15.42014	15.431	15.4461	15.464
	C(9)	6.3726	6.3890	6.405406	6.41366	6.4188	6.43238	6.446
	C(10)	5.9891	6.1036	6.122108	6.149004	6.1628	6.18747	6.2042
Molecular volume/ bohr^{3}mol^{-1}		2814.38	2838.79	3010.259	3059.12	3099.77	3116.7	3345.23
Molecular length/A^0		10.238	10.8	10.96	12.029	10.442	10.81	10.96
Molecular width/A^0		8.12	7.99	8.62	8.048	8.613	9.48	9.76
L/W %		1.26	1.35	1.27	1.24	1.21	1.14	1.12

Gaussian 03 Software was adopted to calculate all interested properties of selected compounds.

DFT with a hybrid functional B3LYP/6-311G (d,p) level found to be suitable to study pharmacological compounds[19].

RESULTS AND DISSCUSSION

Gaussian software ,Density function theory and hybrid functionalP3LYP/6-311G was using to minimized the total energy of each derivative and optimizes the equilibrium electronic structure of molecules which related to its physical and geometrical properties, then many geometrical properties were calculated such as (bond length B.L, bond angle B.A, electron density on each atom, molecular volume, molecular length , molecular width and length/width ratio), then selected the properties which found proportional to activity (LogEC50) with the higher R^2 value.

The study indicate that for all HEPT derivatives HOMO orbital is in the core of the compound figure(2) .So

Focusing was on the atoms of molecule core, the results reported in table (2).

Activity = ∫ (properties) +constant ….1

The above equation can be written in another expression:

Activity= LogEC$_{50}$ (Y) = $a_o \pm \sum \grave{a}_i X_i$…….2

By applied Hansch model[20]

y= a0 + a1D1 + a2 D2 + ……..+ a D ……3

y : practical activity

a : regression coefficient

D : descriptors (S * property)

the general equation will be :

$$Y = a_0 \pm a_1 * slop * X_1 \pm a_2 * slop * X_2 \pm a_3 * slop * X_3 \pm a_4 * slop * X_4 \pm a_5 * slop * X_5 \pm a_6 * slop * X_6$$ …….4

Where :

X1= Bond Length of **S(8)-C(9)**

X2= Bond Angle of **C(4)-C(5)-S(8)**

X3= Bond Angle of **S(8)-C(9)-C(10)**

X4= Electron Density on **C(5)**

X5= Electron Density on **S(8)**

X6= Electron Density on C(9)

$$-0.66 = a_0 + a_1 * 0.01426 - a_2 * 189.667 - a_3 * 464.471 - a_4 * 0.2785 - a_5 * 0.50824 - a_6 * 0.25491$$ …….5

$$-0.96 = a_0 + a_1 * 0.014233 - a_2 * 190.838 - a_3 * 473.669 - a_4 * 0.27956 - a_5 * 0.50864 - a_6 * 0.25556$$ …….6

$$-1.23 = a_0 + a_1 * 0.014226 - a_2 * 191.836 - a_3 * 476.748 - a_4 * 0.28037 - a_5 * 0.50881 - a_6 * 0.25622$$ ……7

$$-1.37 = a_0 + a_1 * 0.014211 - a_2 * 192.018 - a_3 * 481.603 - a_4 * 0.28086 - a_5 * 0.50886 - a_6 * 0.25655$$……8

$$-1.85 = a_0 + a_1 * 0.014175 - a_2 * 192.538 - a_3 * 485.806 - a_4 * 0.28141 - a_5 * 0.50924 - a_6 * 0.25675$$ ……9

$$-2.11 = a_0 + a_1 * 0.01417 - a_2 * 193.553 - a_3 * 487.862 - a_4 * 0.28188 - a_5 * 0.50972 - a_6 * 0.2573$$ ……10

$$-2.30 = a_0 + a_1 * 0.014148 - a_2 * 194.219 - a_3 * 493.74 - a_4 * 0.2825 - a_5 * 0.51031 - a_6 * 0.25785$$ ……11

By solving set of mathematical equations (eq.5-eq.11) using wolfram alpha program to find the final activity equation :

a_0 =- 855.554

a_1 =29830.2

a_2 =0.584474

a_3 = -0.0250508

a_4 =-1190.21

a_5 =-898.698

a_6 =1017.97

So the final equation of activity is :

$$Y = -855.55 + 29830.2 * slop * X_1 + 0.584474 * slop * X_2 - 0.0250508 * slop * X_3 - 1190.21 * slop * X_4 - 898.698 * slop * X_5 + 1017.97 * slop * X_6 \ldots\ldots 12$$

the activity of each compound has calculated depending on the above results, then Comparisons were made between theoretical and experimental value of activity table (5). The Comparisons show an excellent linear relation with R^2 and slope of unity figure (3).

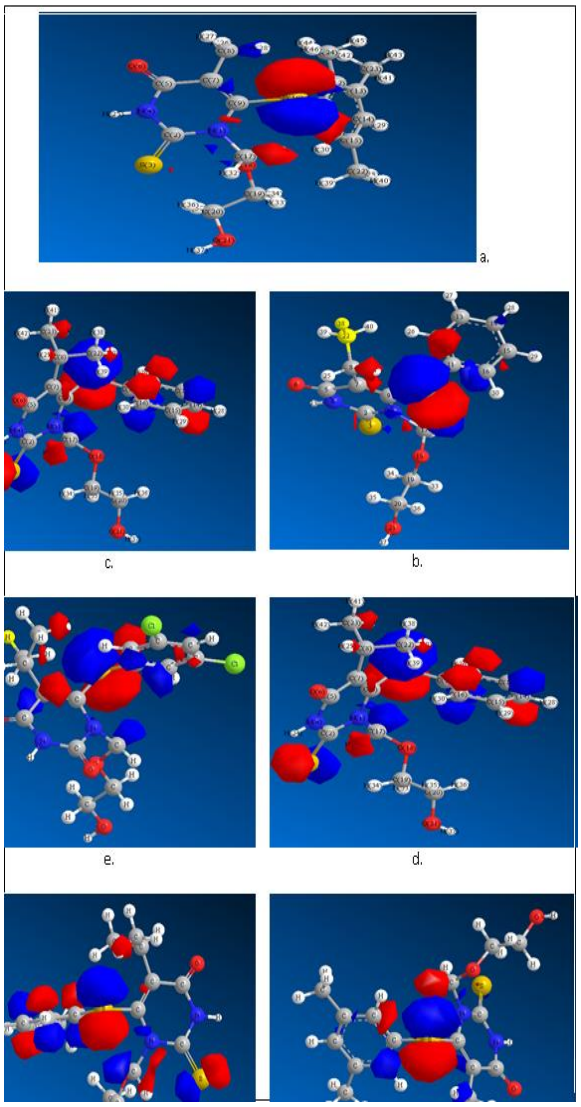

Figure 2: HOMO molecular orbital for a. HETP1 b. HETP2 c. HETP3 d.HETP4 e.HETP5 f.HETP6 g.HETP7

Table 3: Linear Regression and correlation coefficient for Geometrical Properties of HETP derivatives

X=Geometrical properties		Drugs	HETP1	HETP2	HETP3	HETP4	HETP5	HETP6	HETP7
		Y= Log EC50	-0.66	-0.96	-1.23	-1.37	-1.85	-2.11	-2.3
		R^2		Linear Regression					
B.L/A°	C(4)-C(5)	0.899		y = 0.003x + 1.365					
	C(5)-S(8)	0.818		y = 0.015x + 1.832					
	S(8)-C(9)	0.984		y = 0.008x + 1.787					
	C(9)-C(10)	0.910		y = 0.005x + 1.404					
B.A/A°	C(4)-C(5)-S(8)	0.961		y = -1.579x + 119.2					
	C(5)-S(8)-C(9)	0.929		y = -2.105x + 102.3					
	S(8)-C(9)-C(10)	0.954		y = -3.967x + 115.2					
e- density	C(4)	0.890		y = -0.051x + 5.995					
	C(5)	0.962		y = -0.047x + 5.902					
	S(8)	0.933		y = -0.033x + 15.37					
	C(9)	0.954		y = -0.040x + 6.351					
	C(10)	0.828		y = -0.107x + 5.970					
Molecular volume/bohr^{3}mol^{-1}		0.873		y = -277.1x + 2625					
Molecular length/ A°		0.155		y = -0.240x + 10.24					
Molecular width/ A°		0.772		y = -1.021x + 7.132					
L/W %		0.757		y = 0.113x + 1.398					

For each property; select a sharing percent to the activity depending on the slope (S) of properties linearity behavior to activity table-4 .

Table 4: sharing of selected Geometrical Properties to the activity of HETP derivatives

Property	B.L	B.A		e$^-$ Density		
Drug	S(8)-C(9)*S	C(4)-C(5)-S(8)* S	S(8)-C(9)-C(10)* S	C(5)* S	S(8)*S	C(9)*S
HETP1	0.01426	-189.667	-464.471	-0.2785	-0.50824	-0.25491
HETP2	0.014233	-190.838	-473.669	-0.27956	-0.50864	-0.25556
HETP3	0.014226	-191.836	-476.748	-0.28037	-0.50881	-0.25622
HETP4	0.014211	-192.018	-481.603	-0.28086	-0.50886	-0.25655
HETP5	0.014175	-192.538	-485.806	-0.28141	-0.50924	-0.25675
HETP6	0.01417	-193.553	-487.862	-0.28188	-0.50972	-0.2573
HETP7	0.014148	-194.219	-493.74	-0.2825	-0.51031	-0.25785

Table 2: Geometrical Properties of HETP derivatives

Compound		HETP1	HETP2	HETP3	HETP4	HETP5	HETP6	HETP7
Property								
B. L/A°	C(4)-C(5)	1.3634	1.3616	1.3612	1.3607	1.3605	1.3578	1.3567
	C(5)-S(8)	1.8286	1.8161	1.8061	1.8059	1.8013	1.8004	1.7986
	S(8)-C(9)	1.7825	1.7791	1.7783	1.7764	1.7719	1.7713	1.7685
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B. A/A0	C(4)-C(5)-S(8)	120.118	120.86	121.4921	121.6071	121.936	122.5795	123.001
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e-density	C(4)	6.0333	6.0368	6.043209	6.085482	6.0895	6.101195	6.1120

	C(5)	5.9254	5.9480	5.965408	5.975789	5.9873	5.997341	6.0106
	S(8)	15.401	15.413	15.41844	15.42014	15.431	15.44614	15.464
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	C(10)	5.9891	6.1036	6.122108	6.149004	6.1628	6.187474	6.2042
Molecular volume/ bohr3mol-1		2814.38	2838.79	3010.259	3059.12	3099.77	3116.7	3345.23
Molecular length/A0		10.238	10.8	10.96	12.029	10.442	10.81	10.96
Molecular width/A0		8.12	7.99	8.62	8.048	8.613	9.48	9.76
L/W %		1.26	1.35	1.27	1.24	1.21	1.14	1.12

Table 3: Linear Regression and correlation coefficient for Geometrical Properties of HETP derivatives

X=Geometrical properties		**Drugs**	**HETP1**	**HETP2**	**HETP3**	**HETP4**	**HETP5**	**HETP6**	**HETP7**
		Y= Log EC50	**-0.66**	**-0.96**	**-1.23**	**-1.37**	**-1.85**	**-2.11**	**-2.3**
		R^2		**Linear Regression**					
B.L/A°	**C(4)-C(5)**	0.899		y = 0.003x + 1.365					
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For each property; select a sharing percent to the activity depending on the slope (S) of properties linearity behavior to activity table-4 .

Table 4: sharing of selected Geometrical Properties to the activity of HETP derivatives

Property	**B.L**	**B.A**		**e⁻ Density**		
Drug	**S(8)-C(9)*S**	**C(4)-C(5)-S(8)* S**	**S(8)-C(9)-C(10)* S**	**C(5)* S**	**S(8)*S**	**C(9)*S**
HETP1	0.01426	-189.667	-464.471	-0.2785	-0.50824	-0.25491
HETP2	0.014233	-190.838	-473.669	-0.27956	-0.50864	-0.25556
HETP3	0.014226	-191.836	-476.748	-0.28037	-0.50881	-0.25622
HETP4	0.014211	-192.018	-481.603	-0.28086	-0.50886	-0.25655
HETP5	0.014175	-192.538	-485.806	-0.28141	-0.50924	-0.25675
HETP6	0.01417	-193.553	-487.862	-0.28188	-0.50972	-0.2573
HETP7	0.014148	-194.219	-493.74	-0.2825	-0.51031	-0.25785

By applying the values of the calculated properties in QSAR equation :

Table 5: Comparisons between theoretical and experimental value of Log EC_{50}

Compound	Experimental Log EC_{50}	Theoretical Log EC_{50}
HETP1	-0.66	-0.65838
HETP2	-0.96	-0.95838
HETP3	-1.23	-1.22838
HETP4	-1.37	-1.36837
HETP5	-1.85	-1.84837
HETP6	-2.11	-2.10837
HETP7	-2.30	-2.29837

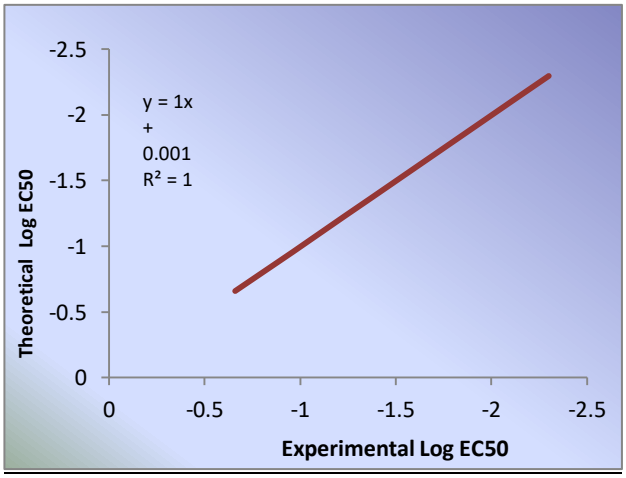


Figure 3: Practical activities (Log EC50) as measured and theoretical activities as calculated

The electronic effects of different substituent have clearly effect on a drug's ionization or Polarity, which in turn may have an effect on how easily a drug can pass through cell membranes or how strongly it can bind to a receptor, which has a direct effect on the value of activity of the drug.

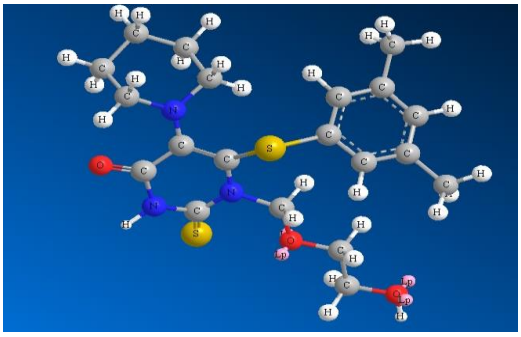
Accordingly in order to predict a new HEPT derivatives with best activity we replace and add different withdrawing group for the compound with relatively high activity (HETP6, HETP7), the geometrical properties have been calculated for the predict compounds table-6. Then the activity calculated according to equation - 12, the result show that the predicted compound have a vert low value of EC50 which reflected on the value of activity, hence the predict compound have an excellent value of activity compared to the set of HETP derivatives under study table (7), structure and activity of predicted HETP compounds have been reviewed in table (8)and figure(4).

Table 6: Geometrical Properties & sharing of selected Geometrical Properties to the activity of predicted HETP derivatives

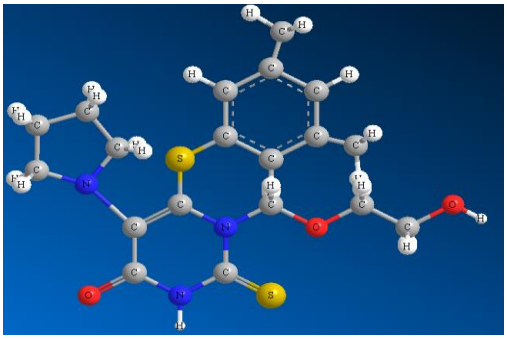
Compound / Property		N1-HETP	N2-HETP	N3-HETP
B.L/A^0	S(8)-C(9)	1.7724	1.7707	1.7741
B.A/A°	C(4)-C(5)-S(8)	121.443	121.473	122.231
	S(8)-C(9)-C(10)	122.781	115.348	118.627
e^- Density	C(5)	5.95148	6.00619	5.92692
	S(8)	15.3751	15.3915	15.4352
	C(9)	6.43223	6.39888	6.43566
sharing of selected Properties to the activity				
B.L	S(8)-C(9) *S	0.0142	0.0142	0.014193
B.A	C(4)-C(5)-S(8) * S	-191.76	-191.807	-193.003
	S(8)-C(9)-C(10) * S	-487.073	-457.586	-470.596
e^- Density	C(5)* S	-0.27972	-0.28229	-0.27857
	S(8)*S	-0.50738	-0.50792	-0.50936
	C(9)*S	-0.25729	-0.25596	-0.25743

Table 8: The structure and the activity of predicted HETP compounds.

No	abbreviation	Compound name	Log EC50
1	N1-HETP	6-((3,5-dimethylphenyl)thio)-1-((2-hydroxyethoxy)methyl)-5-(piperidin-1-yl)-2-thioxo-2,3-	-5.47533
2	N2-HETP	6-((3,5-dimethylphenyl)thio)-1-((2-hydroxyethoxy)methyl)-5-(pyrrolidin-1-yl)-2-thioxo-2,3-	-1.73123
3	N3-HETP	6-((3,5-diisopropylphenyl)thio)-1-((2-hydroxyethoxy)methyl)-5-(pyrrolidin-1-yl)pyrimidine-	-5.9288



a.



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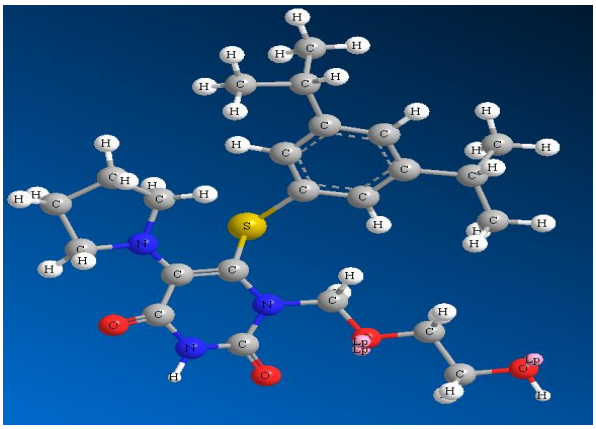

c.

Figure 4: Structure of predicted compound a. N1-HEPT, b.N2-HEPT , c.N3-HEPT

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