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Synthesis, DFT calculations, NBO analysis and docking studies of 3-(2-arylamino-4-aminothiazol-5-oyl)pyridine derivatives

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Electronic structure of 3-(2-arylamino-4-aminothiazol-5-oyl)pyridine derivatives are investigated theoretically using B3LYB/6-31G (d,p) method. The energy gap between HOMO-LUMO and several thermodynamic properties in the ground state are calculated by means of B3LYP hybrid density functional theory (DFT) method together with 6-31G basis sets. A series of pyridinyl thiazoles were synthesized and characterized. The molecular docking studies were done using PyRx virtual screening tool in the active site of Hepg-2 (PDB code 4mmh) to study the hydrogen bonding interaction of these analogs. ADME properties and the hydrophobicity are found to be critical for activity. It is observed that all the synthesized compounds can be used orally as good drug candidates and the docking scores are comparable to the standard compounds. The compound C3 is found to have the highest activity against the cancer (PDB code: 4mmh) protein.

Keywords: HOMO, LUMO, DFT, docking, pyridine

In the recent days heterocyclic compounds like pyridine has been used very frequently as a proton acceptor in hydrogen bonded complexes[1-2]. All the pyridine derivatives are used as non-linear materials[3] and photo chemicals[4–9]. Some of the pyridine derivatives form an acceptor fragment of 2-adamantylamino-5-nitropyridine (AANP). Final crystal shows the large optical non-linearity[10]. Pyridine derivatives are involved in many biological activities with applications in pharmaceutical drugs and agricultural products [11–13]. Complexes with metals are biologically important ligands are sometimes more effective than free ligands. Many pyridine derivatives are used to the treatment of certain brain diseases, and prodrugs for treating neuronal damage caused by stroke. Pyridine derivatives are prepared from thiourea derivatives have been shown to have cholesterol lowering properties, anti cancer and anti-inflammatory agents[11]. And its derivatives continue to attract the attention of biologists because of their wide use in the treatment of the biological systems. Many articles have been published on the use of these compounds as antimicrobial[12–14], antifungal[15], anti-inflammatory activity[16-17], anesthetic[18] and antiviral drugs[19-20]. Hence the structural and medicinal properties of thiazole analogs, we obtained a detailed investigation on the electronic properties, molecular structure, biological activity and vibrational spectra of the pyridinylthiazole derivatives. The literature inspired us to study this theoretical and experimental vibrational research [21-22]. A well ordered quantum chemical and spectroscopic study of the feasible conformations and their relative stabilities has been performed in this paper. Bond length, bond angle ,electronic properties, wave number, intensity of the vibrational bands and optimized geometry of feasible conformers were obtained by density functional theory (DFT) utilize B3LYP using 6-31G(d,p) basis set. The infrared spectrum calculated is compared with the results of observed Fourier transform FT-IR spectrum and the comprehensive assignments of the vibrational spectra have been compared with the vibrational frequencies predicted theoretically. DFT methods, mainly hybrid functional methods have be a significant chemical quantum tool for the assessment of the electronic structure of molecules. B3LYP functional and standard valence basis set 6-31G (d,p) has been shown to provide a perfect agreement between accuracy and computational assignment of vibrational spectra for huge and medium-sized molecules [23].

Experimental Section

General procedure

Resultant compounds was prepared through the reaction of aryl-2-(N,N-dimethylamidino)thiourea in DMF and 3-bromoacetylpyridine. The resulted

mixture was stirred well and triethylamine was added. Then the reaction mixture was heated to about 80-85ºC. Then it was allowed to cool in ice-cold water. An orange coloured precipitate was obtained and filtered. Washed with distilled water and finally dried. The obtained crude product was crystallized from ethanol: water (2:1) mixture produce slightly orange coloured crystalline solid. The proton NMR data are tabulated.

3-(2-Phenylamino-4-aminothiazol-5-oyl)pyridine (C1)

7.01(t, 1H, 1ArH), 7.21-7.34(m, 3H, H-5, 2ArH), 7.50(t, 1H, H-6), 8.17(d,1H, H-4),6.46(d, 2H, 2ArH), 8.17(d, 1H), 8.79(br, 1H, NH), 10.97 (s, 1H, NH).

3-(2-Chloroamino-4-aminothiazol-5-oyl)pyridine (C2)

7.51(t, 1H, H-5), 8.78(d, 2H, 2ArH), 7.49(t, 1H, H-6), 7.44(s, 1H, H-3), 8.13(d,1H, H-4), 6.44(d, 2H, 2ArH), 6.40(d, 1H, H-7), 8.78(br, 1H, NH), 11.03(s, 1H, NH).

3-(2-Methylamino-4-aminothiazol-5-oyl)pyridine (C3)

2.35(s, 3H, CH_3), 6.81(d, 2H, 2ArH), 7.45(t,1H, H-5),7.39-7.43(m, 2H, H-3, H-6), 6.34(d,2H, 2ArH), 7.60(d, 1H, H-4), 7.79(d, 1H, H-7),8.74(br, 1H, NH), 10.91(s, 1H, NH).

3-(2-Methoxyamino-4-aminothiazol-5-oyl)pyridine (C4)

3.73(s, 3H, OCH_3), 6.52(d, 2H, 2ArH), 7.48(t, 1H, H-5), 7.17-7.79.(m, 2H, H-3, H-6), 7.54(d, 2H, 2ArH), 8.14(d, 1H, H-4), 7.74(d,1H, H-7),8.79(br, 1H, NH), 11.01(s, 1H, NH).

3-(2-Ethoxyamino-4-aminothiazol-5-oyl)pyridine (C5)

1.33(t, 3H, CH_3), 3.98(s, 2H, CH_2), 6.53(d,2H, 2ArH), 7.51 (t,1H, H-5), 7.59-7.62(m, 2H, H-3, H-6), 7.48 (d, 2H, 2ArH), 7.83(d,1H, H-4), 7.79(d,1H, H-7), 8.78(br, 1H, NH), 11.08 (s, 1H, NH).

Computational details

Gaussian 09 package is used to calculate the geometry optimization and harmonic frequencies of pyridinylthiazole molecules was performed with the B3LYP, that is, Becke three hybrid exchange, were utilized in the DFT calculation with 6-31G basis sets.

Docking study

Docking studies were extinct using AutoDock Vina in PyRx virtual shielding tool, only for the compounds which obey Lipinski rule of five. On the basis of lowest binding affinity value AutodockVina dispensed in ranked nine best docking modes. For the study of computer-aided drug design, the most powerful visualization engine is PyRx.

Protein structure preparation

The X-ray crystallographic structure of cancer (PDB code: 4mmh) protein was found from Brookhaven protein data bank. The observed protein was found to have ligand, Water molecules and ligands were removed from the complex. Atomic charges were computed by OPLS AA force field and the protein structure was optimized then saved as PDB file used for docking studies.

Preparation of ligands

With the help of ACD\ChemSketch 1.1 software all the compounds were converted into 2D structure to 3D. Followed by all the structures were optimized with Avagadro package. Derived compounds were examined for their hydrophobicity because of protein molecules are hydrophobic property and most of the binding sites is hydrophobic. The slowly absorbed drugs are hydrophilic drugs. Determined binding sites and reported docking score of the ligand into 4mmh has successfully analyzed by PyRx.

Results and Discussion

Molecular geometry

In the geometrical calculations the most stable optimized geometry obtained from B3LYP/6-31G (d,p) method and the scheme of numbering the atoms of the all compounds(C1,C2,C3,C4 and C5) are shown in Figure 1. Molecular property, dipole moment and its spectroscopic transitions are calculated using molecular symmetry.

Structural properties

Bond length and bond angle of the optimized structural compounds are determined at B3LYP method using 6-31G (d,p) basis sets are presented in Table I and Table II. All the structural parameters derived from B3LYP/6-31G (d,p) method were only considered for comparative discussion of the compounds due to the more responsible of this method. Observed mean C-C bond distance calculated 1.40 and C-H 1.08 bond lengths are found to be not significantly deviated with the substitutions at

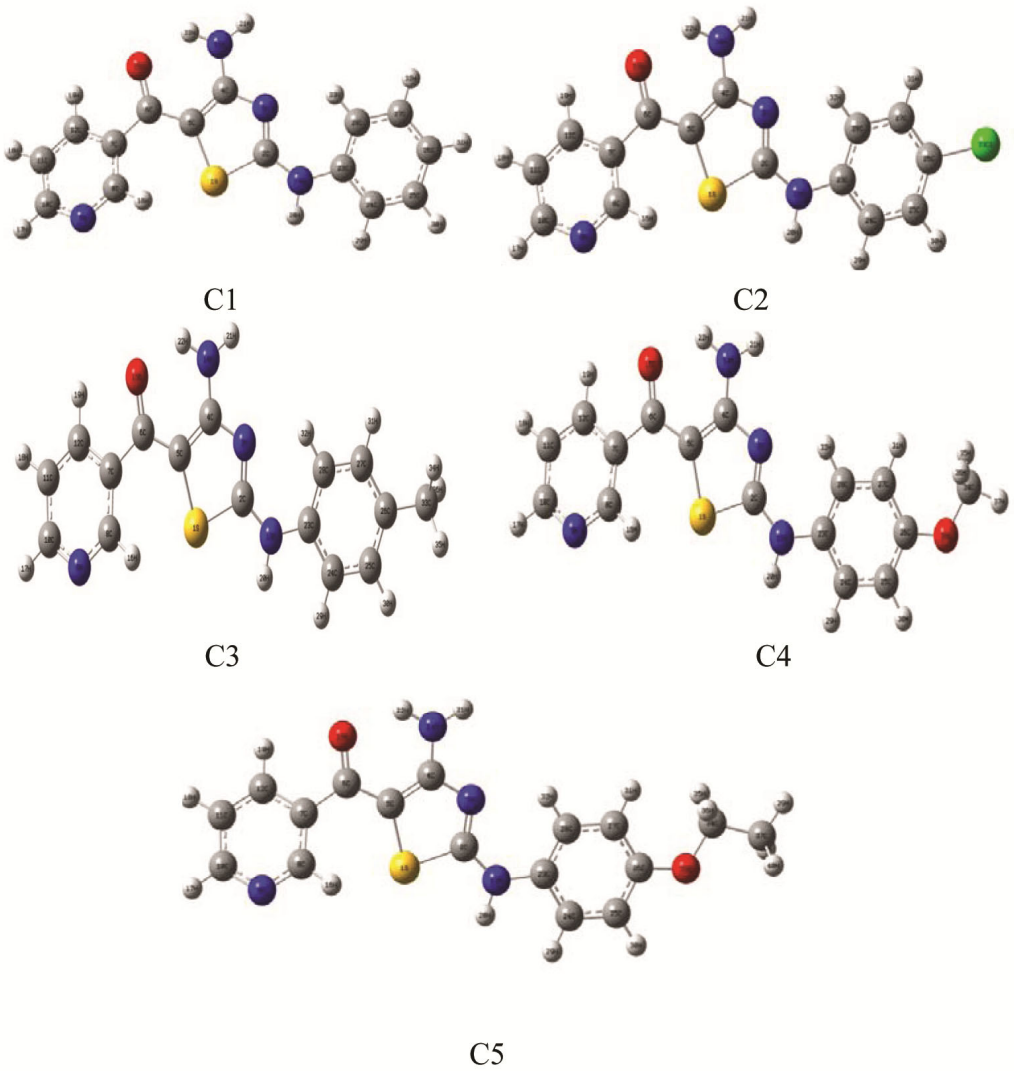

Figure 1 — Optimized structure of synthesized compounds (C1, C2, C3, C4, C5)

Table I — Bond length data of derived compounds

Atom	Bond Length				
	C1	C2	C3	C4	C5
S1-C2	1.83931	1.83632	1.83998	1.82029	1.84019
C2-N3	1.31283	1.31203	1.31339	1.28684	1.31440
N3-C4	1.38574	1.38713	1.38526	1.38007	1.34696
C4-C5	1.40955	1.40874	1.40986	1.38102	1.41000
C5-C6	1.42542	1.42663	1.42502	1.41893	1.42462
C6-O15	1.28339	1.28254	1.28368	1.24185	1.28398
C6-C7	1.49439	1.49380	1.49510	1.49302	1.49464
C7-C8	1.40480	1.40484	1.40480	1.38444	1.40486
C8-H16	1.08356	1.08356	1.08355	1.06816	1.08351
C8-N9	1.35138	1.35119	1.35144	1.33102	1.35144
N9-C10	1.35076	1.35079	1.35075	1.32852	1.35069

(*contd.*)

Table I — Bond length data of derived compounds (*contd.*)

Atom	Bond Length				
	C1	C2	C3	C4	C5
C10-H17	1.08500	1.08494	1.08502	1.07034	1.08500
C10-H11	1.39974	1.39979	1.39972	1.38343	1.39970
C11-H18	1.08440	1.08435	1.08442	1.07003	1.08441
C11-C12	1.39408	1.39405	1.39409	1.37853	1.39410
C12-H19	1.08364	1.08364	1.08364	1.06958	1.08361
C4-N14	1.34673	1.34653	1.34682	1.32604	1.34696
N14-H22	1.01741	1.01733	1.01746	1.00135	1.01756
N14-H21	1.00651	1.00652	1.00649	1.99565	1.00640
C2-N13	1.35782	1.36029	1.35675	1.33419	1.35529
N13-H20	1.01055	1.01041	1.01052	0.99942	1.01039
N13-C23	1.42030	1.41704	1.42104	1.41888	1.42241
C23-C24	1.40776	1.40787	1.40668	1.39334	1.40947
C24-C25	1.39456	1.39455	1.39334	1.37214	1.38866
C24-H29	1.08735	1.08661	1.08747	1.07295	1.08704
C25-H30	1.08510	1.08278	1.08617	1.06929	1.08329
C25-C26	1.40043	1.39349	1.40590	1.38857	1.40416
C26-C27	1.98756	1.39170	1.40373	1.37835	1.39985
C27-C28	1.3988	1.39862	1.39792	1.38746	1.40057
C27-H31	1.08535	1.08302	1.08634	1.06944	1.08278
C28-H32	1.07998	1.07995	1.08009	1.06488	1.08015
C26-H33	1.08467	-	-	-	-
C26-Cl33	-	1.82575	-	-	-
C26-C33	-	-	1.51235	-	-
C33-H34	-	-	1.09502	-	-
C33-H36	-	-	1.09879	-	-
C33-H35	-	-	1.09562	-	-
C26-O33	-	-	-	1.37110	1.38980
O33-C34	-	-	-	1.43628	1.46171
C34-H37	-	-	-	1.07748	-

Table II — Bond Angle data

Atom	Bond Angle				
	C1	C2	C3	C4	C5
S1 –C2-N3	115.12	115.24	115.10	114.75	115.09
C2-N3-C4	112.4	112.3	112.42	113.42	112.4
N3-C4-C5	117.4	117.2	117.4	117.4	117.4
C4-C5-C6	123.78	123.79	123.78	123.78	123.76
C5-C6-C7	123.37	123.37	123.37	121.91	123.39
C7-C8-H16	121.40	121.47	121.40	121.40	121.41
C7-C8-N9	123.33	123.32	123.32	121.37	123.34
C8-N9-C10	118.08	118.08	118.08	119.03	118.08
C10-C11-H18	120.29	120.29	120.29	120.48	120.29
C10-C11-C12	118.71	118.71	118.71	118.38	118.71
C11-C12-H19	121.88	121.86	121.88	121.60	121.89
C12-C7-C6	117.7	117.80	117.76	116.86	117.76

(*contd.*)

Table II — Bond Angle data (*contd.*)

Atom	Bond Angle				
	C1	C2	C3	C4	C5
C2-N13-H20	115.7	115.7	115.8	116.62	115.88
N3-C4-N14	118.74	118.75	118.75	117.65	118.78
C4-N14-H21	119.67	119.75	119.65	119.22	119.66
C4-N14-H22	116.60	116.61	116.58	118.02	116.54
N13-C23-C24	116.64	116.87	116.85	117.19	116.86
C23-C24-H29	119.847	120.08	119.91	119.93	119.96
C24-C25-C26	120.23	118.90	121.16	120.42	120.03
C24-C25-H30	119.46	120.48	119.20	121.19	-
C25-C26-C27	119.29	121.41	117.62	118.88	119.60
C25-C26-H33	120.28	-	121.05	-	-
C26-C27-H31	119.91	120.27	119.23	120.82	120.97
C26-C27-C28	121.21	119.80	122.14	120.899	120.45
C27-C28-C32	121.29	120.79	121.11	120.55	120.60
C27-C28-C23	119.17	119.61	119.29	120.17	119.93
C25-C26-Cl33	-	119.15	-	-	-
C26-C33-C35	-	-	111.49	-	-
C25-C26-O33	-	-	-	116.19	115.90
C26-O33-C34	-	-	-	120.63	119.23
O33-C34-H36	-	-	-	111.31	109.40
O33-C34-C37	-	-	-	-	106.74
C34-C37-H40	-	-	-	-	110.4

Table III — Energies of pyridinylthiazole derivatives

Parametres	B3LYP/6-31G				
(a.u)	C1	C2	C3	C4	C5
HOMO	-0.2518	-0.26188	-0.24648	-0.32381	-0.25498
LUMO	-0.04295	-0.04963	-0.04140	0.09667	-0.04096
HOMO-LUMO	0.20886	0.21225	0.20508	0.42048	0.21402
I	0.2518	0.26188	0.24648	0.32381	0.25498
A	0.04295	0.04963	0.04140	0.09667	0.04096
X	0.1339	0.15575	0.14394	0.21024	0.14797
ϩ	0.10443	0.10612	0.10254	0.11357	0.10701

I-Ionisation potential; A-Electron affinity; χ-Electronegativity; ηϩ-Hardness

different positions. Bond angles are also in excellent agreement in all levels of calculations. The computed values of C-C (ring) are well agreed with that of the experimental values.

Electronic properties

Electronic properties of HOMO, LUMO were calculated. The HOMO–LUMO energy gap, electron affinity, electronegativty, hardness of pyridinylthiazoles have been calculated at the B3LYP/6-31G level are given in the following table (Table III, Figure 2).

Docking energy evaluation of synthesized compounds

According to the docking studies to predict the best conformational position within the active region of all the synthesized ligands, were docked against receptor molecule. Docked complexes were analysed on the basis of minimum energy values (kcal/mol) and bonding interaction pattern such as hydrogen and hydrophobic bonds, respectively. However, all these compounds have no big docking energy value difference more than standard error value (Table IV, Table V, Figure 3). The standard error for Autodock is reported as 2.5 kcal/mol (http://autodock.scripps.edu/).

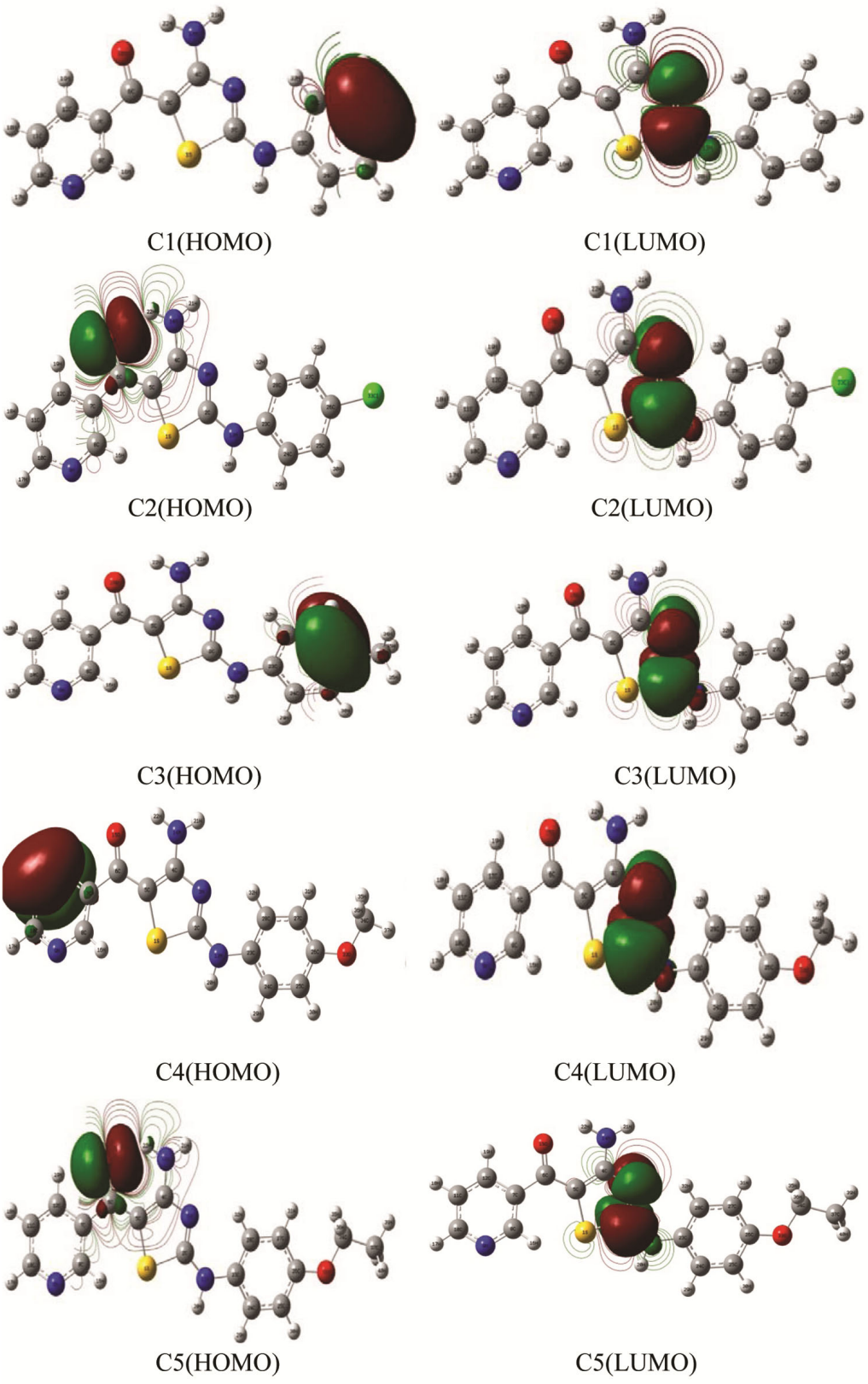

Figure 2 — HOMO and LUMO structures of C1, C2, C3, C4 and C5

Table IV — Hydrogen Bonding Interaction and Docking Score values of synthesized compounds

Compd	R	Docking Score Kcal/mol 4mmh	H-Bonding Interaction
C1	Phenyl	-7.2	GLU-245,ALA-246,GLN-247,PHE-251
C2	Chloro	-7.3	ALA-246,SER-255
C3	Methyl	-7.5	SER-255
C 4	Methoxy	-7.3	SER-255,GLN-247,ALA-246,PRO-189
C5	Ethoxy	-7.2	GLU-245,SER-255

Table V — Abbreviation of 3-(2-arylamino-4-aminothiazol-5-oyl)pyridine

Abbreviation	Compd
C1	3-(2-Phenylamino-4-aminothiazol-5-oyl)pyridine
C2	3-(2-Chloroamino-4-aminothiazol-5-oyl)pyridine
C3	3-(2-Methylamino-4-aminothiazol-5-oyl)pyridine
C4	3-(2-Methoxylamino-4-aminothiazol-5-oyl)pyridine
C5	3-(2-Ethoxyamino-4-aminothiazol-5-oyl)pyridine

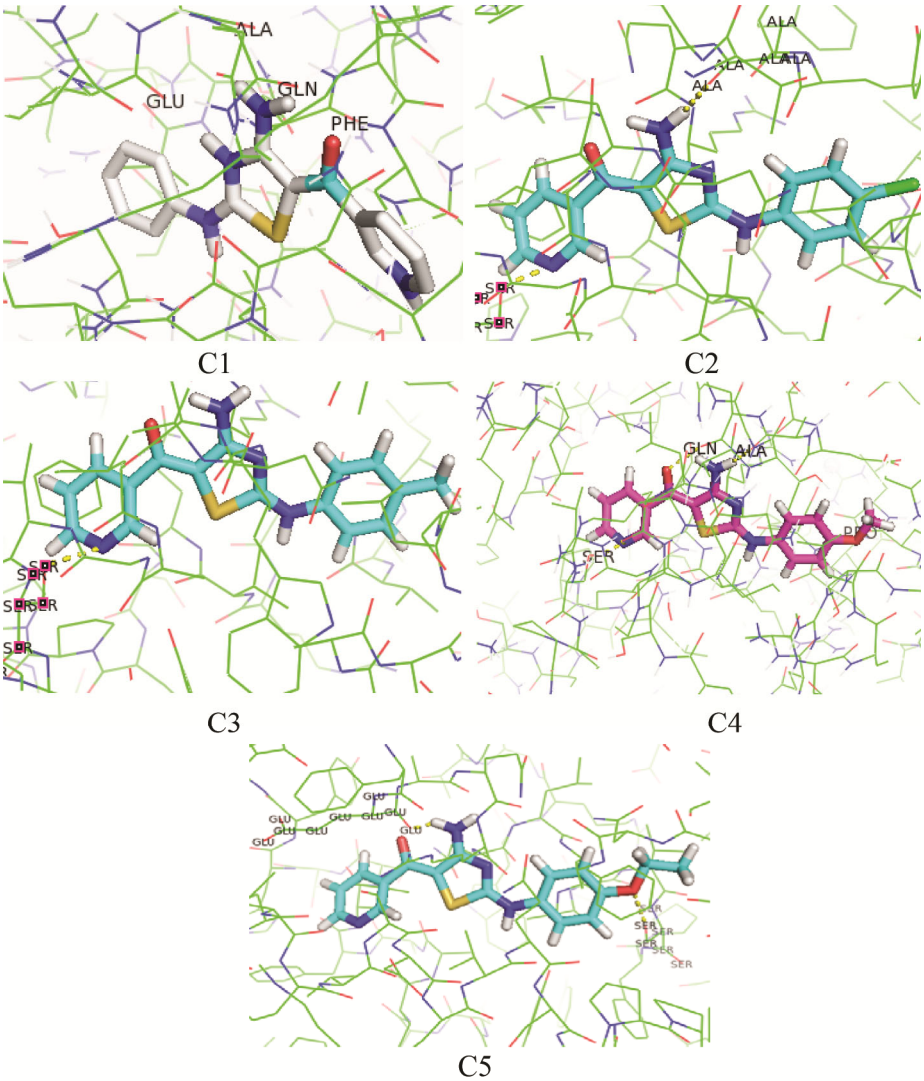

Figure 3 — Docking images of C1, C2, C3, C4 and C5

Conclusions

In summary, electronic structures of all the derived compounds are investigated theoretically at B3LYP/6-311G (d, p). Above studied compounds are found to be non-planar. Mullikan and natural charge distribution of the compounds C**1–C5** were studied which indicated the electronic charge distribution. NBO analysis of the synthesized compounds C**1–C5** indicated the intermolecular charge transfer between the bonding and antibonding orbital's. HOMO-LUMO energy gap confirmed that, the charge transfer takes place within the molecule. And the molecular docking study of the derived compounds concerned the active site of enzyme cytochrome Hepg-2 using PyRx virtual screening tool. The compound **C3** with the highest docking score showed four hydrogen bonding interactions with 4mmh. The data shows that these compounds can be used as good drug. It is concluded from the binding mode analysis that these novel compounds with electron withdrawing and electron donating substituents can be utilized for development of anticancer inhibitors and gives a strong platform for the new structure based drug design.

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