Synthesis, characterisation, DFT and biological evaluation of 4-(1-ethylbenzimidazol-2-yl)-2-(arylamino)thiazoles

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Abstract

The compounds 4-(1-ethylbenzimidazol-2-yl)-2-(arylamino)thiazoles were expected to have many biological activities and were synthesized from 1,2-diaminobenzene and lactic acid. The synthesized compounds are characterised by FT-IR, ^{1}H NMR and mass spectroscopy. Thiazole moiety present in the compounds was found to possess anticancer, anti-HIV activities. Theoretical information on the optimized geometry, vibrational frequencies and atomic charges in the ground state were determined by means of density functional theory (DFT) using standard B3LYP/6-31G basis set with Gaussian '09 software. Mulliken population analysis was performed on the atomic charges and the HOMO-LUMO energies were calculated.

From the HOMO-LUMO energy gap, we know that the charge transfer occurs within the molecule. Docking studies are also done by using PyRx and are visualized by PyMoL software. By 2, 2-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging method, anti-oxidant activity of the synthesized compounds was evaluated. In vitro cytotoxic activity of the compounds against A549 cell lines was evaluated by MTT assay.

Keywords: DFT, Docking, DPPH, Gaussian09, HOMO-LUMO, MTT assay, Mulliken Charge.

Introduction

In medical chemistry, heterocyclic molecules play a significant function. Most manufactured drugs and naturally occurring compounds with biological importance have at least one heterocyclic ring. Benzimidazole is a significant heterocyclic system because it exhibits numerous biological activities formed by the fusion of benzene and imidazole moiety[11]. Biological activities include antifungal, antiviral[4,21], antitubercular[12], anti-histaminic, anti-convulsant, anti-inflammatory[17], antiparasitic[20] and anticancer[13] properties. N-substituted benzimidazole derivatives show potent antiviral action against a number of viruses, including human cytomegalovirus(HCMV), influenza, picorna hepatitis C and HIV. Thiazoles are significant heterocyclic compounds found in a variety of therapeutics[9], much like benzimidazoles. Any drug containing a thiazole or thiazolyl moiety will exhibit a variety of biological properties including those that are anti-HIV[19], anti-cancer[14], anti-diabetic[10], anti-microbia[24], anti-hypertensive[23] and anti-inflammatory[22].

In this research work, a series of novel benzimidazolylthiazoles were synthesized. Molecular properties were studied by means of DFT using standard B3LYP/6-31G basis set and by molecular docking studies the interactions between the titled compounds and SARS-CoV-2 (PDB code: 7EN8) are studied. By using molecular docking, binding energies for all ligands were determined. The outcomes were more useful for creating drugs that would effectively treat coronavirus. Anti-oxidant studies are done by DPPH assay. Anticancer studies were also done against A549 Cell line.

Material and Methods

Preparation of 4-(1-ethylbenzimidazol-2-yl)-2-(arylamino)thiazole: The bromo compound prepared (1.245g,0.01mol) from bromination of N-ethyl-2-acetylbenzimidazole was suspended in hot ethanol. Thiourea (0.01 mol) was added and heated, a clear solution is obtained which soon deposited some crystals. The crystals are filtered off and then boiled in water containing sodium acetate which was then filtered and dried. The yellowish orange colour product was crystallized from ethanol.

Computational section: Quantum chemical studies for all the compounds are done by using Gaussian '09 program software using B3LYP/6-31G basis set. DFT study is one of the most prominent calculation approaches due to its accuracy and less time duration.

Molecular docking studies: The process of describing how synthesised pharmaceuticals interact with proteins is known as molecular docking. Final targets were docked separately using PyRx's AutoDock Vina software. Protein Data Bank was used to download the appropriate protein (http://www.rcsb.org/pdb/home.home.do). All ligands and water molecules were removed from the protein and the enhanced protein structure was saved as a PDB file. SARS-CoV-2 is the protein (PDB code: 7EN8). Utilising Gaussview and OpenBabel, the 2D structures of the synthesised compounds were transformed to fch files and saved as PDB files.

Anti-oxidant studies: The newly synthesised benzimidazolylthiazoles were tested for their anti-oxidant activity using the DPPH assay. Using ethanol, a solution of

DPPH at a concentration of 10^{-5}M was created. Novel benzimidazolylthiazoles were prepared at different concentrations of ethanolic solution (0.1, 0.25, 0.5, 0.75 and 1 mM). After adding 0.5 mL of an ethanolic solution of benzimidazolylthiazole derivatives to 2.8 mL of DPPH solution, it was allowed to stand in the dark for around 30 minutes. At 517 nm, the absorbance of the individual test samples was obtained using ethanol as the standard.

$$\% \text{ inhibition} = \frac{\text{Control absorbance} - \text{Sample absorbance}}{\text{Control absorbance}} \times 100 \quad (1)$$

With the help of the aforementioned equation, it was possible to compare the standard butylated hydroxyanisole (BHA) to other test solutions and to determine that the concentration of the DPPH radicals had decreased. The percentage inhibition was plotted versus the test sample concentration. We can calculate the DPPH scavenging activity (IC_{50}) from the plots.

Anticancer studies

MTT assay: The MTT assay is a colorimetric assay that measures the proliferation of cells and cytotoxicity based on the formation of formazan crystals from the reduction of the yellow, water-soluble tetrazolium dye MTT. When MTT is reduced to insoluble formazan crystals by mitochondrial lactate dehydrogenase generated by living cells, it turns purple and can be detected spectrophotometrically at 570 nm. This purple colour is proportional to the amount of viable cells.

Cell culture conditions: It is possible to buy the A549 (Human alveolar lung adenocarcinoma cell line) from NCCS in Pune, India. The cells were maintained in DMEM high glucose media supplemented with 10% FBS and the 1% antibiotic-antimycotic solution at 37^0C temperature in the CO_2 incubator with 5% CO_2, 18-20% O_2 atmosphere. Subcultures were performed every two days. The present investigation used passage number 47.

Cytotoxicity assay: Without the use of a test agent, 200µ L cells were planted in a 96-well plate at a density of 20,000 cells per plate and for roughly 24 hours to proliferate. The test agents (synthesised compounds) were introduced to the plate and incubated for 24 hours at 37°C in 5% CO_2 atmosphere. The test agents were added in various concentrations (100 µg, 50 µg, 25 µg, 12.5 µg, 6.25 µg in 100 µL of 5% DMEM). In order to prevent exposure to light, each plate was wrapped with aluminium foil. MTT reagent (0.5 mg/mL) was applied to each plate after the incubation period. Once more, the plates underwent a 3-hour incubation period. After that, 100 µL of DMSO solubilization solution was added. To facilitate dissolution, the plates are shaken in a gyratory machine. An instrument called an ELISA reader or a spectrophotometer at 570nm wavelength was used to read absorbance. Using below formula %, cell viability is calculated:

% cell viability = [Mean abs of treated cells/Mean abs of Untreated cells] x 100

In order to calculate the IC50 value, the linear regression equation Y = Mx + C was used. Here, Y = 50. From the reliability graph, values for M and C were calculated.

Result and Discussion

4-(1-ethylbenzimidazol-2-yl)-2-(phenylamino)thiazole: 1a : IR (cm^{-1}) (KBr): 830 (Ar C-H bending), 1370 (C-N str), 1565 (Ar C=C str), 1660 (C=N Str), 3040 (Ar C-H str), 3230 (NH) ; ^{1}H NMR (DMSO): δ 1.76 (s, 3H, CH_3 of ethyl), 3.98 (s, 2H, CH_2 of ethyl), 6.4 (s, 1H, CH), 7.20-7.50 (m, 5H, ArH), 7.50-7.66 (m, 4H, ArH), 13.07 (s, 1H, NH) ; MS (ESI) : *m/z* 320 [M+].

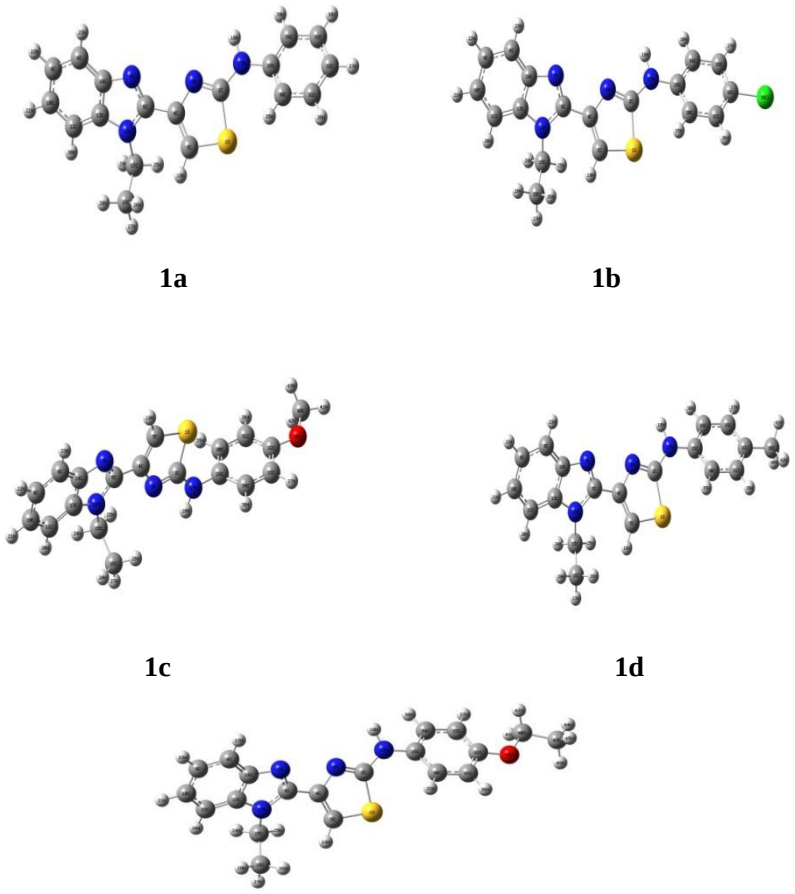
4-(1-ethylbenzimidazol-2-yl)-2-(chlorophenylamino) thiazole: 1b: IR (cm^{-1}) (KBr): 825 (Ar C-H bending), 1360 (C-N str), 1568 (Ar C=C str), 1660 (C=N Str), 3046 (Ar C-H str), 3228 (NH) ; ^{1}H NMR (DMSO): δ 1.52 (s, 3H, CH_3 of ethyl), 4.08 (s, 2H, CH_2 of ethyl), 6.39 (s, 1H, CH), 7.25-7.50 (m, 5H, ArH), 7.50-7.72 (m, 4H, ArH), 10.37 (s, 1H, NH) ; MS (ESI) : *m/z* 354 [M+].

4-(1-ethylbenzimidazol-2-yl)-2-(methoxyphenylamino) thiazole: 1c: IR (cm^{-1}) (KBr): 834 (Ar C-H bending), 1378 (C-N str), 1555 (Ar C=C str), 1674 (C=N Str), 3050 (Ar C-H str), 3236 (NH) ; ^{1}H NMR (DMSO): δ 1.60 (s, 3H, CH_3 of ethyl), 3.88 (s, 2H, CH_2 of ethyl), 6.22 (s, 1H, CH), 7.0-7.40 (m, 5H, ArH), 7.45-7.76 (m, 4H, ArH), 10.04 (s, 1H, NH) ; MS (ESI) : *m/z* 350 [M+].

4-(1-ethylbenzimidazol-2-yl)-2-(methylphenylamino) thiazole: 1d: IR (cm^{-1}) (KBr): 830 (Ar C-H bending), 1360 (C-N str), 1555 (Ar C=C str), 1650 (C=N Str), 3045 (Ar C-H str), 3228 (NH) ; ^{1}H NMR (DMSO): δ 1.66 (s, 3H, CH_3 of ethyl), 3.98 (s, 2H, CH_2 of ethyl), 6.30 (s, 1H, CH), 7.20-7.50 (m, 5H, ArH), 7.60-7.87 (m, 4H, ArH), 9.45 (s, 1H, NH) ; MS (ESI) : *m/z* 334 [M+].

4-(1-ethylbenzimidazol-2-yl)-2-(ethoxyphenylamino) thiazole: 1e: IR (cm^{-1}) (KBr): 828 (Ar C-H bending), 1358 (C-N str), 1555 (Ar C=C str), 1676 (C=N Str), 3048 (Ar C-H str), 3239 (NH); ^{1}H NMR (DMSO): δ 1.29 (s, 3H, CH_3 of ethyl), 3.78 (s, 2H, CH_2 of ethyl), 5.92 (s, 1H, CH), 7.30-7.50 (m, 5H, ArH), 7.50-7.76 (m, 4H, ArH), 10.72 (s, 1H, NH); MS (ESI) : *m/z* 364 [M+].

Molecular geometry: The optimized molecular geometry of all compounds is shown in fig. 1. From the optimized molecular geometry, we know about the geometrical parameters such as bond length, bond angle and dihedral angle of a structure. Bond length datas are shown in table 1. These data show that there is a slight change in bond lenth depend on the substituent present in the compound. From the bond angle analysis C-N-C of benzimidazole ring, lowest bond angle is 105.73^0, C-C-C bond angle of phenyl ring is 120.40^0 and the bond angle of S-C-N of thiazole ring is 113.76^0.



1a **1b**

1c **1d**

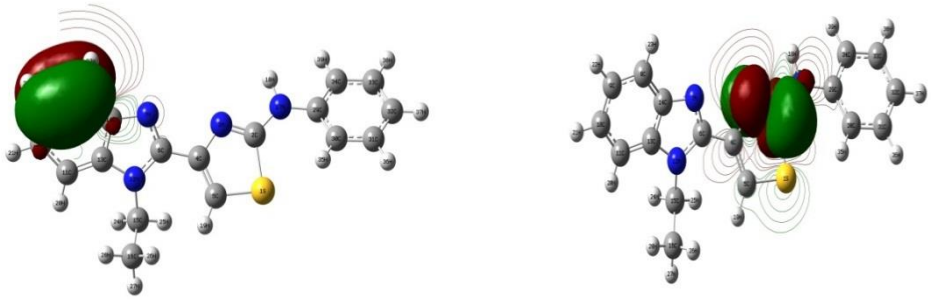
e

Fig. 1: Optimized structures of 4-(1-ethylbenzimidazol-2-yl)-2-(arylamino)thiazole.

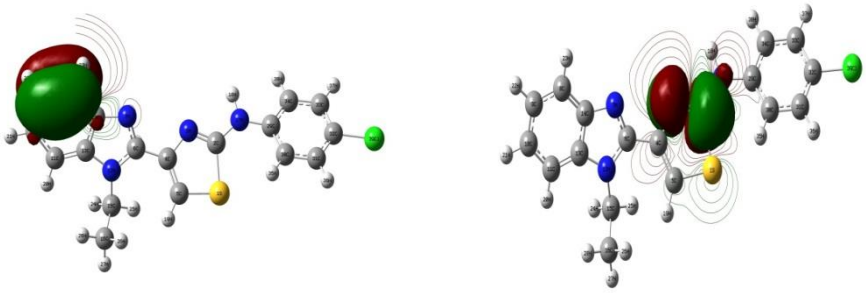
1a - 4-(1-ethylbenzimidazol-2-yl)-2-(phenylamino)thiazole.
1b - 4-(1-ethylbenzimidazol-2-yl)-2-(chlorophenylamino)thiazole.
1c - 4-(1-ethylbenzimidazol-2-yl)-2-(methoxyphenylamino)thiazole.
1d - 4-(1-ethylbenzimidazol-2-yl)-2-(methylphenylamino)thiazole.
1e - 4-(1-ethylbenzimidazol-2-yl)-2-(ethoxyphenylamino)thiazole.

Table 1
Bond length data of 4-(1-ethylbenzimidazol-2-yl)-2-(arylamino)thiazole

Atoms	Bond length (Å)				
	1a	**1b**	**1c**	**1d**	**1e**
S-C (thiazole)	1.8503	1.8489	1.8491	1.8471	1.8502
N-C (thiazole)	1.3977	1.3982	1.3895	1.3960	1.3880
C-H (thiazole)	1.0765	1.0796	1.0768	1.0788	1.0779
C-C (benzimidazole)	1.4014	1.4125	1.4069	1.4085	1.4122
C-H (benzimidazole)	1.0854	1.0829	1.0840	1.0841	1.0912
C-N (benzimidazole)	1.3955	1.4012	1.3962	1.3982	1.3986
C-C (ethyl)	1.5356	1.5286	1.5385	1.5315	1.5298
C-H (ethyl)	1.0959	1.0923	1.0896	1.0913	1.0911
N-H (phenyl, thiazole)	1.0129	1.0348	1.0236	1.0286	1.0241
N-C (phenyl, thiazole)	1.4112	1.4076	1.4265	1.4122	1.4155
C-C (phenyl)	1.3981	1.3939	1.3917	1.3982	1.3901
C-H (phenyl)	1.0846	1.0815	1.0724	1.0825	1.0795
C-Cl (phenyl)	-	1.8260	-	-	-
C-O (sub)	-	-	1.3683	-	1.3902
C-H (sub)	-	-	-	1.0987	1.0939



1a



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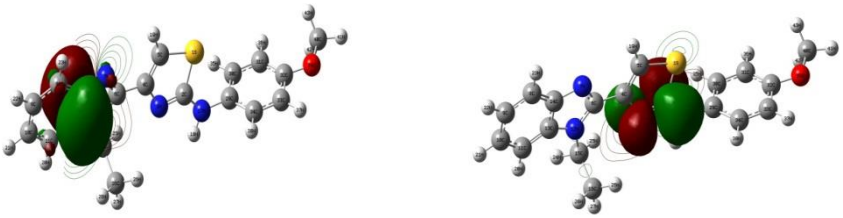
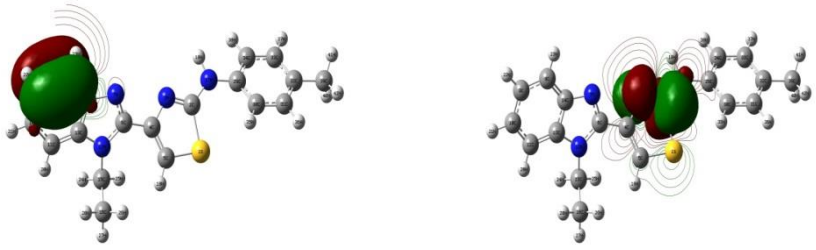


1c



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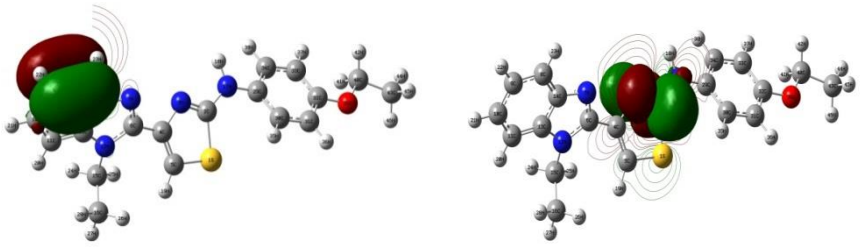


1e

Fig. 2: HOMO-LUMO structures of 4-(1-ethylbenzimidazol-2-yl)-2-(arylamino)thiazole.

Frontier molecular orbitals: The molecular's interactions with other species are determined by its frontier orbital. The outermost orbital that contains electrons, called HOMO (Highest Occupied Molecular Orbital) has the tendency to give these electrons acting as an electron donor. Likewise, LUMO (Lowest Unoccupied Molecular Orbital) can be considered as the innermost orbital with open spaces for electrons. Because of this, LUMO energy is directly tied to the electron affinity and HOMO energy is directly related to the ionisation potential. The energy gap, which refers to the energy difference between the HOMO and LUMO orbitals, is a crucial structural stability.

A molecule with a small energy gap is more polarized and is known as soft molecule. To ascert the biological activity of the compounds, some additional parameters such as electronegativity (c), chemical potential (m), hardness (h) and softness (S) are calculated from the following equations and are given in table 2.

$$c = -1/2\ (E_{HOMO} + E_{LUMO}) \quad (1)$$
$$m = -c = 1/2\ (E_{HOMO} + E_{LUMO}) \quad (2)$$
$$h = 1/2\ (E_{HOMO} - E_{LUMO}) \quad (3)$$
$$S = 1/2\ h \quad (4)$$

Table 2
Electronic Parameters of 4-(1-ethylbenzimidazol-2-yl)-2-(arylamino)thiazole.

Parameters (a.u)	**B3LYP/6-31G**				
	1a	**1b**	**1c**	**1d**	**1e**
Total Energy(a.u)	-1312.47	-1772.05	-1419.68	-1351.78	-1466.26
Dipole Moment (debye)	3.5926	3.8274	5.8207	3.8972	4.3672
E_{HOMO}	-0.23705	-0.24005	-0.29813	-0.23616	-0.23521
E_{LUMO}	-0.02007	-0.02673	-0.12638	-0.01786	-0.01523
ΔE	0.21698	0.21332	0.17175	0.21830	0.21998
Ionization Potential(I)	0.23705	0.24005	0.2981	0.23616	0.2352
Electron Affinity(A)	0.0201	0.0267	0.1264	0.0179	0.0152
Electronegativity(*X*)	0.12856	0.13339	0.21226	0.12701	0.12522
Hardness(*h*)	0.1085	0.1067	0.08588	0.1092	0.10999
Softness(S)	4.6083	4.6860	5.8221	4.5788	4.5459

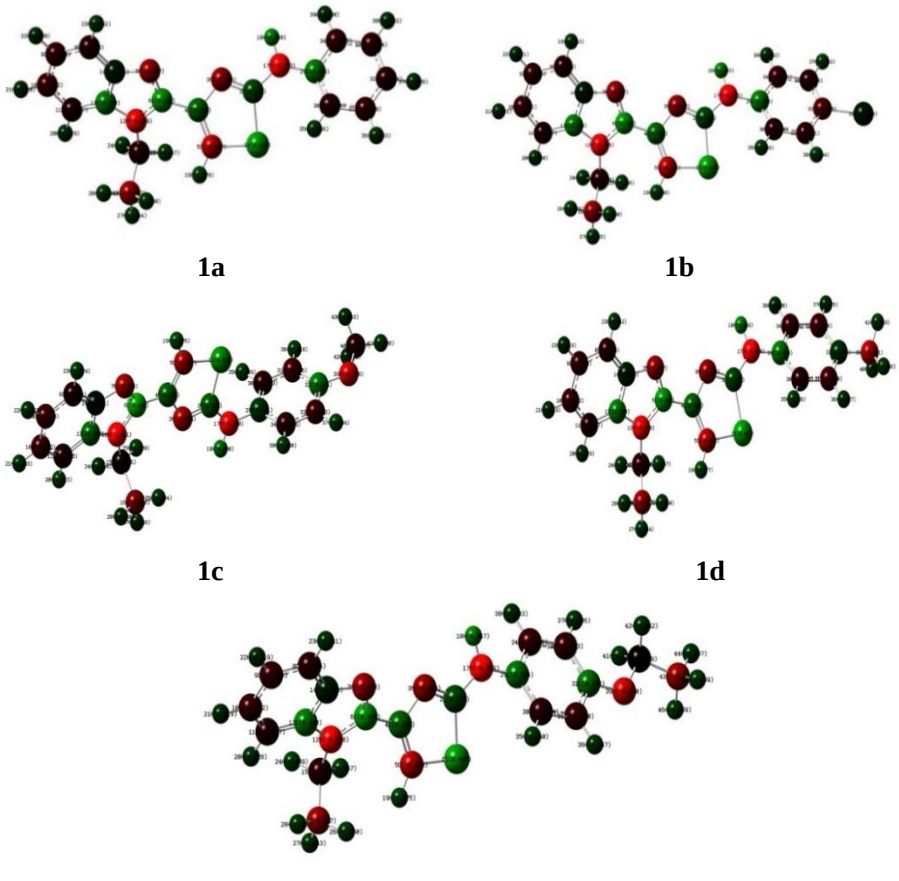


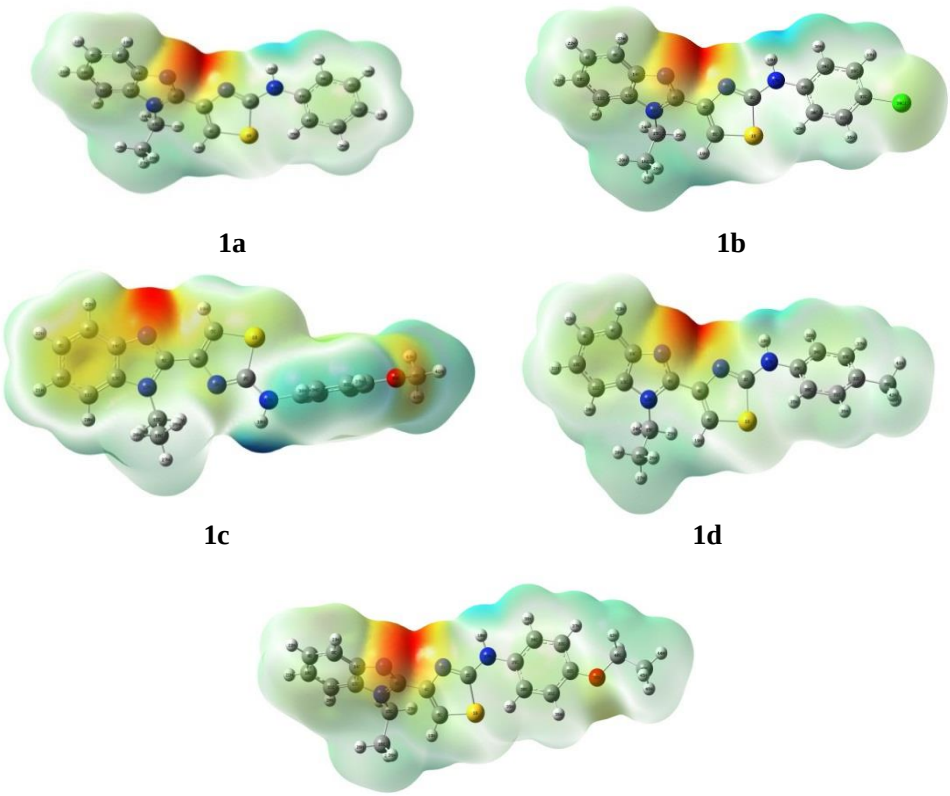
Fig. 3: Mulliken atomic charge structures of 4-(1-ethylbenzimidazol-2-yl)-2-(arylamino)thiazole.

Mulliken atomic charges: The bonding structure and molecular conformation were resolved by electronic charge of the atom. The net atomic charge was obtained from Mulliken charge analysis. In the titled compounds, the magnitude of C atom was found to be positive and negative and the O atom exhibits negative and H atom exhibits positive. The magnitude of N atom is found to be negative. Mulliken charge distribution of the titled compounds is shown in fig. 3 and the charges on atom is given in table 3.

Molecular electrostatic potential (MEP): MEP mapping in DFT techniques is used in biochemistry to know about the molecular interaction, chemical molecules behaviour and their reactivity with other chemical species. For interpreting and predicting relative reactivity sites for electrophilic and nucleophilic attack and hydrogen bonding interactions, it is highly helpful. In MEP, there are different regions represented by red, yellow, blue and green.

Table 3
Mulliken atomic charges of 4-(1-ethylbenzimidazol-2-yl)-2-(arylamino)thiazole.

Atom	1a	1b	1c	1d	1e
S1	0.416	0.420	0.515	0.411	0.405
C2	0.185	0.184	0.308	0.183	0.178
N3	-0.390	-0.387	-0.604	-0.389	-0.389
C4	0.263	0.264	0.329	0.261	0.262
C5	-0.507	-0.505	-0.587	-0.505	-0.505
C6	0.396	0.396	0.634	0.395	0.395
N7	-0.407	-0.407	-0.593	-0.407	-0.408
C8	-0.105	-0.104	-0.118	-0.105	-0.106
C9	-0.140	-0.140	-0.223	-0.140	-0.140
C10	-0.152	-0.151	-0.215	-0.152	-0.152
C11	-0.087	-0.087	-0.115	-0.087	-0.087
N12	-0.719	-0.719	-1.061	-0.718	-0.718
C13	0.320	0.320	0.362	0.320	0.320
C14	0.076	0.077	0.051	0.076	0.076
C15	-0.108	-0.109	-0.046	-0.108	-0.108
C16	-0.407	-0.407	-0.446	-0.407	-0.407
N17	-0.783	-0.785	-0.950	-0.778	-0.769
H18	0.350	0.353	0.400	0.349	0.347
H19	0.178	0.180	0.276	0.177	0.175
H20	0.129	0.130	0.215	0.129	0.128
H23	0.142	0.143	0.224	0.142	0.141
H24	0.161	0.161	0.169	0.159	0.159
H25	0.167	0.166	0.220	0.167	0.167
H26	0.150	0.150	0.184	0.150	0.150
H28	0.158	0.159	0.160	0.158	0.157
C29	0.319	0.326	0.181	0.308	0.294
C30	-0.116	-0.110	-0.143	-0.113	-0.114
C31	-0.148	-0.121	-0.236	-0.180	-0.150
C32	-0.114	-0.228	0.414	0.125	0.298
C33	-0.134	-0.106	-0.223	-0.164	-0.143
C34	-0.155	-0.151	-0.139	-0.149	-0.158
H35	0.156	0.166	0.229	0.156	0.160
H36	0.133	0.164	0.218	0.127	0.147
H38	0.132	0.142	0.230	0.130	0.133
C39	-	-	-	-0.481	-
Cl39	-	0.068	-	-	-
O39	-	-	-0.778	-	-0.570
C40	-	-	-0.127	-	-0.019
H41	-	-	0.198	0.149	-
H42	-	-	0.161	0.146	0.142
H43	-	-	0.163	-	-



1a **1b**

1c **1d**

1e

Fig. 4: MEP images of 4-(1-ethylbenzimidazol-2-yl)-2-(arylamino)thiazole.

Table 4
Values of +ve and -ve potential of 4-(1-ethylbenzimidazol-2-yl)-2-(arylamino)thiazole.

Compound	Positive potential (a.u)	Negative potential (a.u)
1a	8.666	-8.666
1b	8.212	-8.212
1c	6.461	-6.461
1d	8.800	-8.800
1e	8.947	-8.947

Table 5
Docking scores of 4-(1-ethylbenzimidazol-2-yl)-2-(arylamino)thiazole.

Compound	Docking Score (Kcal/mol)	Residue involved in Hydrogen bonding
1a	-7.6	PRO122
1b	-7.9	VAL20 , THR26
1c	-7.8	VAL20 , THR21 , THR26
1d	-7.7	VAL20 , THR26
1e	-7.7	VAL20 , THR26

Molecular Docking Studies: The docking studies of the prepared compounds were performed by using AutoDock Vina in PyRx and Pymol software is used for visualization. From the molecular docking studies, binding affinity and interaction between the ligand and the active site of the target were identified. The compounds which obey Lipinsky Rule of Five were selected for docking studies. The compounds are docked with SARS-CoV-2 (PDB code: 7EN8). The docking scores of the synthesized compounds are given in table 5. From the obtained docking scores, we know that the compounds are more active against 7EN8. Comparing with all the scores, compound 1b is more active against the protein. The docking scores and H-bonding between the compounds and protein are shown in table 5. The interaction between the protein and the compound is shown in fig. 5.

Anti-oxidant activity of the synthesized compounds(1a-e): The *in vitro* anti-oxidant activity of the synthesised benzimidazolylthiazoles (1a-e) was evaluated using the DPPH free radical scavenging assay. Formula (1) was used

to determine the % inhibition of the compounds at varied concentrations. The % inhibition was plotted against the sample concentration in order to determine the quantity of antioxidants required to reduce the initial strength of DPPH to fifty percentage (IC_{50}). We can determine the IC_{50} values from the plots. A lower IC_{50} value indicates higher anti-oxidant activity. Table 6 lists the IC_{50} values of the synthesised compounds. When compared to standard BHA, compound 1c exhibits excellent anti-oxidant activity (IC_{50} = 22). The remaining substances similarly exhibit excellent to very good anti-oxidant action. The sample concentration is necessary to scavenge half (50%) of the DPPH in the solution.

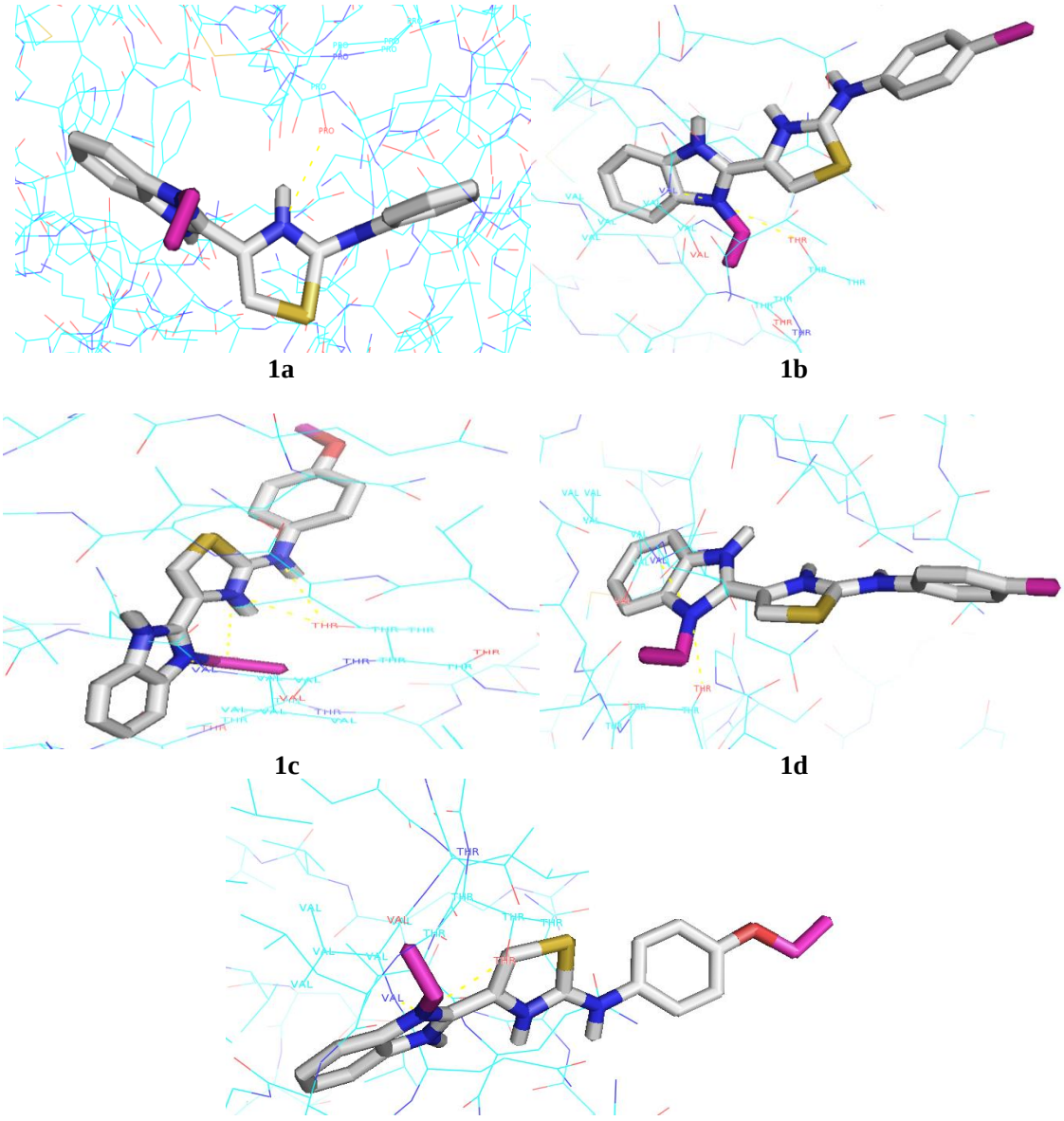


Fig. 5: Docking images of 4-(1-ethylbenzimidazol-2-yl)-2-(arylamino)thiazole.

Table 6
Anti-oxidant Activity of 4-(1-ethylbenzimidazol-2-yl)-2-(arylamino)thiazole.

Compound	IC_{50} Value (µM)
1a	48
1b	34
1c	22
1d	83
1e	106
Standard BHA	624

Anticancer activity of the compound(1c): The compound with high anti-oxidant activity was tested for its antioxidant activity against the A549 cell line. The compound 4-(1-ethylbenzimidazol-2-yl)-2-(methoxyphenyl amino)thiazole, that is compound 1c, has good antioxidant properties. Human alveolar lung cancer cell line (Cell lines A549) was treated with compound 1c at varying doses and the IC_{50} value was discovered to be 12.45 g/mL. Fig.6 depicts the effect of compound 1c on the A549 cell line. Table 7 and graph 1 provided the measured IC_{50} value of sample 1c against the A549 cells as well as the percentage of cell viability values after the treatment. After the incubation period, compound 1c's percentage cell viability values were measured against the cell line A549.

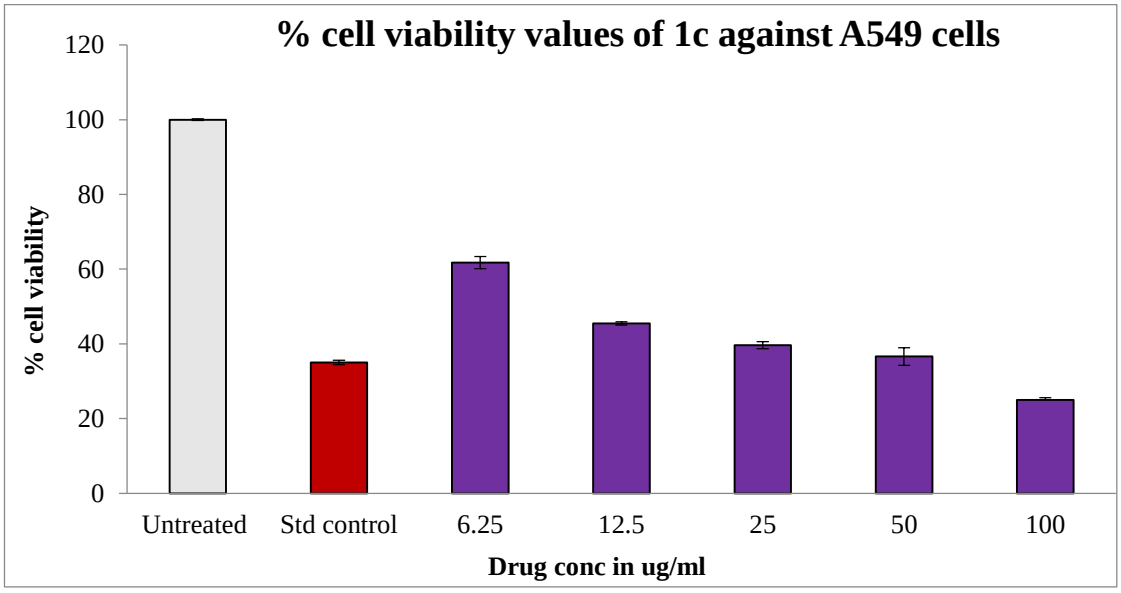
Lipinski's Rule of Five: Lipinski's Rule of Five is used to distinguish between drug like and non drug like molecules. According to this rule, if a compound is biologically active, it should obey the following five rules:

- Molecular mass less than 500 Dalton
- High lipophilicity (Log P) (less than five)
- Less than five hydrogen bond donors
- Less than ten hydrogen bond acceptors
- Molar refractivity between 40-130.

The above compounds 1a to 1e obey all the five rules and the values are given in table 8.

Table 7
% cell viability values and observed IC_{50} value of sample 1c against A549 cells after the treatment period of 24hrs.

Culture condition	% cell viability	IC50 conc (µg/ml)
Untreated	100.00	12.45
Std control	35.04	
5-6.25ug/ml	61.76	
5-12.5ug/ml	45.46	
5-25ug/ml	39.66	
5-50ug/ml	36.64	
5-100ug/ml	24.96	



Graph 1: % cell viability values of 1c against A549 cells after the incubation period of 24hrs.

Table 8
Lipinski rule of 4-(1-ethylbenzimidazol-2-yl)-2-(arylamino)thiazole.

Compound	Mol. Wt <500	HB Donor <5	HB Acceptor <10	Log P <5	Molecular Refractivity 40-130
1a	320	1	3	4.54	94.92
1b	354	1	3	4.42	96.99
1c	350	1	4	4.55	101.47
1d	334	1	3	4.85	99.65
1e	364	1	4	4.94	106.09

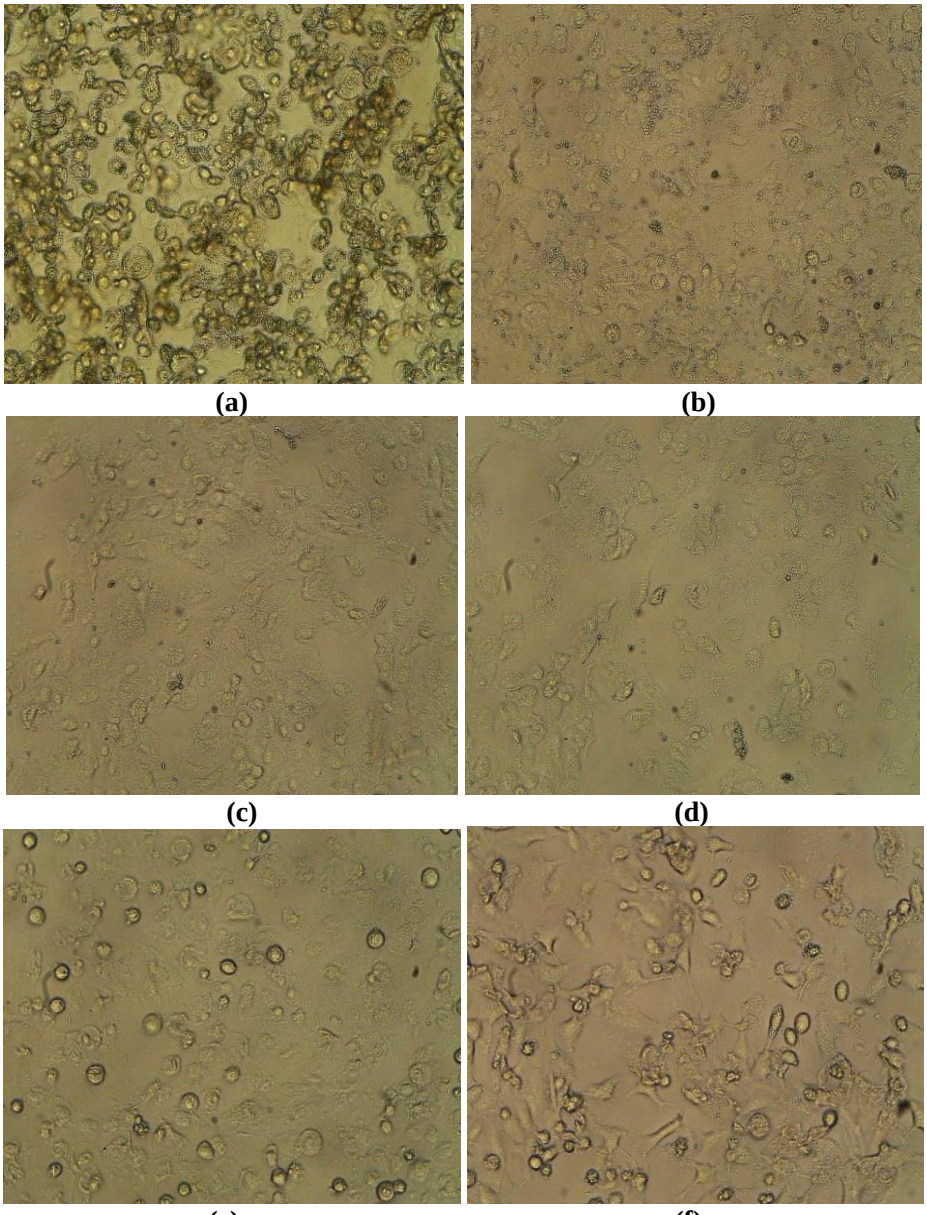


Fig. 6: Effect of compound 1c on viability of A549 cancer cells (a) Control; (b) 100 µg/mL; (c) 50 µg/mL; (d) 25 µg/mL; (e) 12.5 µg/mL; (f) 6.25 µg/mL

Conclusion

The optimized molecular structure, bond length, bond angle, Mulliken atomic charges and differnece in energies of HOMO-LUMO of 4-(1-ethylbenzimidazol-2-yl)-2-(arylamino)thiazole derivatives were optimized by DFT using B3LYP/6-31G basis set. FMO analysis shows that the energy gap between HOMO-LUMO is low, thus charge transfer occurs within the molecule. So the compounds are biologically active. Docking studies were also performed to know about the interaction between ligand and the protein. From the docking score, we know that the compounds show better activity against SARS-CoV-2.

All the synthesized compounds exhibit excellent antioxidant activity and compound 1c shows excellent anticancer activity against human alveolar lung adenocarcinoma cell line (Cell lines A549) with an IC_{50} value of 12.45 µg/mL. Thus all the synthesized compounds may act as the future leads for drug discovery.

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