Indian Journal of Biochemistry & Biophysics
Vol. 57, October 2020, pp. 606-612

Synthesis, quantification, dft Calculation and molecular docking of (4-amino-2-(4-methoxyphenyl)aminothiazol-5yl)(thiophene-2-yl)methanone

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Received 08 April 2020; *revised 20 May 2020*

In this study, the novel compound (4-amino-2-(4-methoxyphenyl)aminothiazol-5yl)(thiophene-2-yl)methanone was synthesized and structure of the compound was elucidated by FTIR, ^{1}H NMR, ^{13}C NMR, and High resolution mass spectrometric techniques. The compound was optimized with B3LYP-6-311+G (d, p) density functional theory method. Stability and intermolecular charge transfer have been analyzed by natural bond orbital analysis. Total energy levels of HOMO-LUMO orbitals, Mulliken atomic charges, and vibrational calculation were analyzed. Molecular docking was carried out to understand the antiviral activity, the pharmacokinetic behaviour and hydrogen bonding interaction of the analogue with the help Hex 8.0 software.

Keywords: Density functional theory, Molecular modelling, Mulliken atomic charges, Natural bond orbital analysis

Heterocyclic compounds considered as one of the energetic classes of organic compounds, which are used in many biological arena due to its activity in multiply illness. Because, all the vitamins, DNA, RNA, haemoglobin present in the living organism contains the heterocyclic ring as the major skeleton. Nowadays synthetic heterocyclic resources attract the attention of human beings and it is used as drugs, pesticides, dyes, and plastics. Among this, thiophene nucleus plays a major role as a pharmacophore moieties. The physiological behaviour of thiophene is similar to that of benzene with an increase in pharmacodynamics and pharmacokinetic activities. Ketothiophene derivatives are the combination of thiophene and carbonyl group, which increases the biological activities like anti-inflammatory agents[1], anti-mycobacterial agents[2], anti-bacterial activities[3], anti-fungal activities[4], antiviral activities[5].

On the way of promising biological activities in the literature review, we decided to start our research in the synthesis of new ketothiophene derivative with expected biological activities and their characterization by IR, ^{1}HNMR, ^{13}CNMR and High resolution mass spectrometric techniques. The geometry of the compound was optimized using density functional theory by Becke's three-parameter exchange functional in combination with the Lee-Yang-Parr correlation (B3LYP) Gaussian 09 with standard 6-311+G basis software set. Molecular modelling was carried out using software Hex 8.0 dock and visualized using Discovery studio 3.5.

Experimental

Material and Methods

The chemicals used were of AR grade and experimented without purification. The spectra had been documented on Bruker Avance 400 FTNMR spectrometer (four hundred MHz for ^{1}H and ^{13}CNMR spectra), mass spectrometer on Agilent 6520(QTOF) positive mode ESI-MS and Nicolet 400 FTIR spectrometer. The melting point was examined using the Digital melting point apparatus and uncorrected.

The Density Functional Theory (DFT) was performed with Gaussian-03 B3LYP/6-311+G (d, p) basis set. Docking studies were carried out using the Hex 8.0 dock software with a grid dimension of 0.6. Discovery studio 3.5 visualizer was used to examine the docking results.

General Procedure for the Synthesis of (4-amino-2-(arylamino)thiazol-5yl)(thiophene-2-yl)methanone

1 aryl-3-(N-nitroamidino)thiourea[6] (1 mmol) in DMF (2 mL) was added to the mixture of 2-(2-bromoacetyl)ketothiophene[7] in DMF(2 mL). The reaction mixture changed into heated water bath

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at 80-85°C for 5 min. To this triethylamine (0.15 mL, 1 mmol) was brought and heating become persevered for every other 10 min. This aggregate was cooled and poured into ice-cold water with stirring. The yellow precipitate obtained changed into filtered, washed with water, and dried[8]. The crude sample was crystallized from methanol-water (2:1) (Scheme 1).

Synthesis of (4-Amino-2-(4-methoxyphenyl)Aminothiazol-5yl)(Thiophene-2-yl)Methanone(MATM)

The orange yellow precipitate obtained was recrystallized using 2:1 ethanol-water solution. Yeild 78%, melting point: 146-148°C. Molecular weight: 331.41, Chemical formula: $C_{15}H_{13}N_3O_2S_2$. Elemental analysis of carbon, hydrogen, nitrogen, oxygen and sulphur found as: 54.36, 3.95, 12.68, 9.66, 19.35; Determined: 54.39, 3.89, 12.65, 9.65, and 19.29. FTIR (KBr) spectrum consists of bands at 3591.46 cm^{-1}, 3701.40 cm^{-1} (ν_{N-H}), 1595.13cm^{-1} ($\nu_{C=O}$), 3101.54 cm^{-1} (aromatic ν_{C-H}). ^{1}H NMR: (400 MHz, DMSO-d_6) δ7.83 (d, 1H, J=1.6 Hz, H-1 of thiophene), δ7.20 (t, 1H, J=5.2 Hz, H-2 of thiophene), δ8.04 (d, 1H, J=1.2 Hz, H-3 of thiophene) δ 8.314 (s, 2H, H-4), δ7.397 (d, 2H, J=2.8 Hz, 2ArH), δ7.210 (d, 2H, J=1.6 Hz, 2ArH), δ3.81 (s, 3H, 1.2 Hz), δ 10.22, (s, 1H, H-5). ^{13}C (75MHz, DMSO-d_6) 173.46, 166.29, 146.21, 138.46, 131.28, 128.95, 128.14, 128.39, 126.91, 120.43, 143.08, 90.09 .ESI-MS MH^+ (332.04).

Results and Discussion

Characterization of the Synthesized (4-Amino-2-(4-methoxyphenyl)Aminothiazol-5yl)(Thiophene-2-yl)Methanone (MATM)

The elemental analysis of the synthesized titled compound and its melting point is mentioned in (Table 1). The functional groups in the compounds were analyzed with the support of the FTIR spectroscopic method. It was found that the absorption band at 3591.46 cm^{-1}, 3701.40 cm^{-1} is due to the vibration of two N-H groups. The carbonyl group stretching vibration is specified at 1595.13 cm^{-1} and aromatic C-H stretching vibration is indicated at 3101.54 cm^{-1}. The C-H aliphatic stretching vibration is observed at 2924.09 cm^{-1}. The ^{1}H NMR shows the presence of aromatic hydrogen in the range of 7-8, hydrogen in the NH group lies in 11.01. The ^{13}C NMR spectrum shows thirteen peaks, two of which arise from two-carbon each, thus accounting for all the fifteen carbons.

Geometrical Optimization with DFT Method

The compound (4-amino-2-(4-methoxyphenyl) aminothiazol-5yl)(thiophene-2-yl)methanone(MATM) was optimized using B3LYP/6-311+G (d, p) basis set function using Gaussian 09 package. The optimized structure (Fig. 1), theoretically obtained structural parameters such as bond distance, angles, and dihedral angles are tabulated (Table 2).

All the atoms in the molecule including thiophene ring, thiazole ring and phenyl ring are on the same plane. Due to the attachment of the carbonyl group in the thiophene and thiazole ring, there is a slight variation in the bond length and bond angle. The C-C-S bond angle in thiophene decreases to 110.74°, the C-S bond length falls from 1.74 A° to 1.725 A°. The thiazole ring is more influenced by the addition of the C=O group. The bond distance of C-S in the thiazole ring rises from 1.728 A°

Table 1 — Elemental analysis and melting point of the compound MATM

Compound	Melting point °C	Elemental Analysis	
		Found	Determined
MATM	146-148	C=54.36H=3.95 N=12.68 O=9.66S=19.35	C=54.39 H=3.89 N=12.65 O=9.65 S=19.29

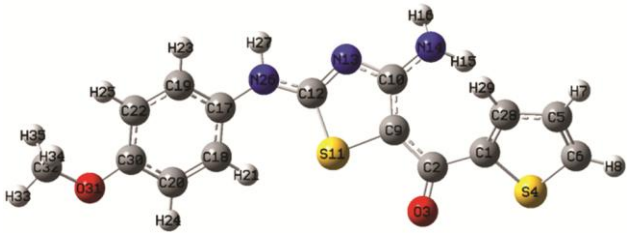
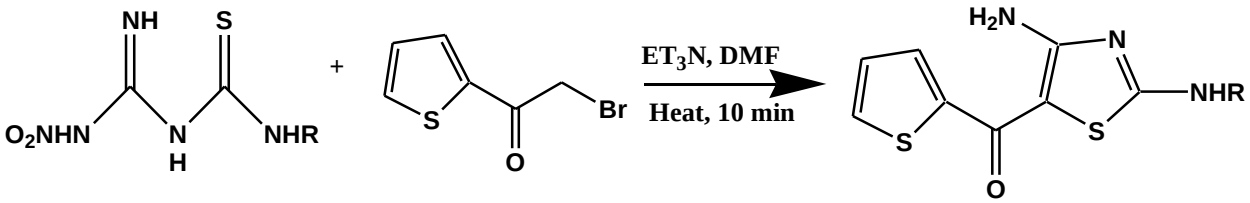


Fig. 1 — Optimized structure of the compound (4-amino-2-(4-methoxyphenyl)aminothiazol-5yl)(thiophene-2-yl)methanone



Scheme 1 — Synthetic Route of the titled compound

Table 2 — Optimized parameters of (4-amino-2-(4- methoxyphenyl)aminothiazol-5yl)(thiophene-2-yl)methanone (*Contd.*)

Parameter	Bond length	Parameter	Bond angle	Parameter	Dihedral angle
R (1, 2)	1.4873	A (2, 1, 4)	117.6568	D (4, 1, 2, 3)	–154.1242
R (1, 4)	1.7457	A (2, 1, 28)	131.0827	D (28, 1, 2, 3)	–144.3958
R (1, 28)	1.3761	A (4, 1, 28)	110.7604	D (2, 1, 4, 6)	–174.5425
R (2, 3)	1.233	A (1, 2, 3)	118.9491	D (2, 1, 28, 5)	173.0137
R (2, 9)	1.4461	A (1, 2, 9)	120.4505	D (4, 1, 28, 29)	–176.8933
R (4, 6)	1.7254	A (3, 2, 9)	120.6446	D (1, 2, 9, 11)	–168.8534
R (5, 6)	1.3684	A (1, 4, 6)	91.4048	D (3, 2, 9, 10)	-159.4538
R (5, 7)	1.082	A (6, 5, 7)	123.6189	D (1, 4, 6, 8)	–178.6228
R (5, 28)	1.4211	A (6, 5, 28)	112.3787	D (7, 5, 6, 4)	178.4031
R (6, 8)	1.0795	A (7, 5, 28)	124.0001	D (28, 5, 6, 8)	179.2297
R (9, 10)	1.3959	A (4, 6, 5)	112.2166	D (6, 5, 28, 29)	178.0896
R (9, 11)	1.7766	A (4, 6, 8)	119.7998	D (7, 5, 28, 1)	–179.7977
R (10, 13)	1.3633	A (5, 6, 8)	127.983	D (2, 9, 10, 13)	172.3601
R (10, 14)	1.3697	A (2, 9, 10)	135.8285	D (11, 9, 10, 14)	–178.3994
R (11, 12)	1.7468	A (2, 9, 11)	115.0791	D (2, 9, 11, 12)	–174.6835
R (12, 13)	1.3168	A (10, 9, 11)	108.4978	D (14, 10, 13, 12)	179.7471
R (12, 26)	1.3609	A (9, 10, 13)	116.184	D (9, 10, 14, 16)	162.1341
R (14, 15)	1.008	A (9, 10, 14)	127.9647	D (13, 10, 14, 15)	–160.3051
R (14, 16)	1.0085	A (13, 10, 14)	115.85	D (9, 11, 12, 26)	–176.4279
R (17, 18)	1.3979	A (9, 11, 12)	88.3984	D (26, 12, 13, 10)	177.3317
R (17, 19)	1.4022	A (11, 12, 13)	115.6257	D (11, 12, 26, 27)	173.1904
R (17, 26)	1.406	A (11, 12, 26)	125.6397	D (13, 12, 26, 17)	179.2335
R (18, 20)	1.3928	A (13, 12, 26)	118.7156	D (19, 17, 18, 21)	177.0035
R (18, 21)	1.0809	A (10, 13, 12)	111.2389	D (26, 17, 18, 20)	-179.4439
R (19, 22)	1.3868	A (10, 14, 15)	118.0657	D (18, 17, 19, 23)	–179.6782
R (19, 23)	1.0854	A (10, 14, 16)	114.1033	D (26, 17, 19, 22)	178.9616
R (20, 24)	1.085	A (15, 14, 16)	116.2784	D (18, 17, 26, 27)	162.4671
R (20, 30)	1.3956	A (18, 17, 19)	118.6489	D (19, 17, 26, 12)	159.6801
R (22, 25)	1.0852	A (18, 17, 26)	123.8471	D (17, 18, 20, 24)	–179.9912
R (22, 30)	1.3999	A (19, 17, 26)	117.4813	D (21, 18, 20, 30)	–177.5178
R (26, 27)	1.0112	A (17, 18, 20)	119.9029	D (17, 19, 22, 25)	–179.8869
R (28, 29)	1.0814	A (17, 18, 21)	121.0043	D (23, 19, 22, 30)	–179.2079
R (30, 31)	1.43	A (20, 18, 21)	119.0694	D (18, 20, 30, 31)	–175.714
R (31, 32)	1.43	A (17, 19, 22)	120.6155	D (24, 20, 30, 22)	–178.9046
R (32, 33)	1.07	A (17, 19, 23)	119.5168	D (19, 22, 30, 31)	175.1116
R (32, 34)	1.07	A (22, 19, 23)	119.867	D (25, 22, 30, 20)	179.4084
R (32, 35)	1.07	A (18, 20, 24)	118.4706	D (20, 30, 31, 32)	–118.6781
		A (18, 20, 30)	122.0443	D (30, 31, 32, 33)	164.6887
		A (24, 20, 30)	119.4811		
		A (19, 22, 25)	118.9786		
		A (25, 22, 30)	119.6205		
		A (12, 26, 17)	132.0792		
		A (12, 26, 27)	111.5553		
		A (17, 26, 27)	116.2363		
		A (1, 28, 5)	113.2084		
		A (1, 28, 29)	122.9943		
		A (5, 28, 29)	123.7777		

(*Contd.*)

Table 2 — Optimized parameters of (4-amino-2-(4- methoxyphenyl)aminothiazol-5yl)(thiophene-2-yl)methanone

Parameter	Bond length	Parameter	Bond angle	Parameter	Dihedral angle
		A (20, 30, 22)	117.3744		
		A (20, 30, 31)	121.3761		
		A (22, 30, 31)	121.13		
		A (30, 31, 32)	109.5		
		A (31, 32, 33)	109.4712		
		A (31, 32, 34)	109.4712		
		A (31, 32, 35)	109.4712		
		A (33, 32, 34)	109.4713		
		A (33, 32, 35)	109.4712		
		A (34, 32, 35)	109.4712		

Table 3 — Second-order perturbation theory analysis of the titled compound

Donor (i)	Acceptor (j)	Energy($E^{2)}$ Kcal/mol	Occupancy
LP (2) O_3	π^*C_1-C_2	18.42	1.97528
LP (2) O_3	π^*C_2-C_9	16.25	1.88525
LP (2) S_4	π^*C_1-C_{28}	21.89	1.98358
LP (2) S_4	π^*C_5-C_6	23.87	1.58499
LP (1) S_{11}	σ^*C_{18}-H_{21}	0.57	1.98114
LP (2) S_{11}	π^*C_9-C_{10}	13.17	1.68750
LP (2) S_{11}	π^*C_{12}-N_{13}	33.84	1.68750
LP (1) N_{13}	σ^*S_{11}-C_{12}	14.17	1.89118
LP (1) N_{14}	π^*C_9-C_{10}	40.90	1.79475
LP (1) N_{26}	π^*C_{12}-N_{13}	54.78	1.66686
LP (1) N_{26}	π^*C_{17}-C_{18}	32.23	1.66686

to 1.778 A° and 1.714 A° to 1.748 A°. The C-C and C-N bond length increase to 1.396 A° and 1.316 A° (Fig. 1). There is a major deviation of the bond dimension from 1.40 A° to 1.38 A° and bond angle to 119° and 118° due to the attachment of the methoxy group in the phenyl ring.

Natural Bond Orbital Analysis

NBO analysis provides detailed descriptions of the various second-order interaction between filled orbitals of one system and the vacant orbitals of another subsystem, the natural bond orbital (NBO) calculations were performed using Gaussian 09 package at the DFT/B3LYP/6-311G* level. NBO analysis has been performed to explain the intramolecular interaction and delocalization of electron density within the molecule, higher E^2 value shows the intensive interaction among electron-donors and electron-acceptors[9] and also the more extent of conjugation of the entire system, the probable intensive interactions are given in (Table 3). Biological activity of the targeted compound increases due to the hyperconjugative interaction of the methoxy group with the phenyl ring.

A very strong interaction has been observed between lone electron pair of S_4 and neighbour antibonding orbital of C_1-C_{28}, C_5-C_6 and the other lone pair of S_{11} and neighbour antibonding orbital of C_9-C_{10}, C_{12}-N_{13}, C_{18}-H_{21} with the occupancy of 1.98358 and 1.98114. The intramolecular hyperconjugative interaction in MATM is formed by the orbital overlap between σ (C-C), σ *, π (C-C), π* (C-C) bond orbitals which results in the intramolecular charge transfer (ICT) causing stabilization of the system. The hyper conjugative interaction of lone pair, LP (1) S_{11}>σ*C_{18}-H_{21} possibility of intramolecular interaction whose energy contribution is 0.57 kcal/mol with Vander wall radii of 3.23 A°.

Atomic Charges

Atomic charge quantifies electronic shape divergences beneath atomic displacement. The uniformity in charge distribution is indicated by the smaller dipole moment (5.68 Debye). From the charge distribution bar, we can find that the entire nitrogen atom poses negative charge and the nitrogen atom N_{14} retains more negative charge of (–0.47228) a.u due to high electronegativity. Maximum charge magnitude is observed in C_{10} (0.42114) a.u. All the hydrogen holds a positive charge, since the charge transfer is from carbon to hydrogen. Oxygen (O_3) conveys the charge of (–0.34475) a.u and the two sulphur conveys positive charge of S_4 (0.31993) a.u and S_{11} (0.30064) a.u (Fig. 2).

Frontier molecular orbitals and it's chemical reactivity

HOMO-LUMO energy gap explains the chemical reactivity of the molecule. If the energy gap is less, it is more reactive and if it is high, the compound is thermally stable. The thermal stability of the compound related to the hardness of the molecule[10]. It is found that the charge distribution of the HOMO level of the compound MATM is mostly localized on the thiophene ring and charge distribution of the LUMO level is delocalized throughout the thiazole

ring (Fig. 3). The energy gap is found to be less of –0.13832 a.u.

Vibrational assignment

MATM consists of 35 atoms with 99 normal modes of vibration. The bands at 3622.53 cm^{-1} are due to the N-H stretching vibration of the secondary amine and the bands at 3597.24, 3722.81 are due to primary amine, which is in close agreement with the theoretical value of 3564.21 cm^{-1}, 3739.72 cm^{-1}. The band at 1669.70 cm^{-1} is due to the C=O stretching vibration, which is seen in the theoretically calculated bands at 1680.85 cm^{-1} The bands at 3251.14 cm^{-1}, 3240.61 cm^{-1}, 3211.97 cm^{-1} are due to the aromatic C-H stretching and it is very close to the theoretical value of 3289.37 cm^{-1} and the bands at 3045.40 cm^{-1}, 3186.60 cm^{-1}, 3110.31 cm^{-1} are due to aliphatic C-H stretching, which is close to 3090.71 cm^{-1} (Fig. 4).

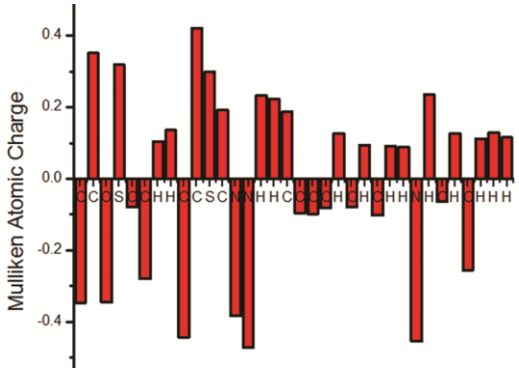


Fig. 2 — Charge distribution bar of the compound (4-amino-2-(4-methoxyphenyl)aminothiazol-5yl)(thiophene-2-yl)methanone

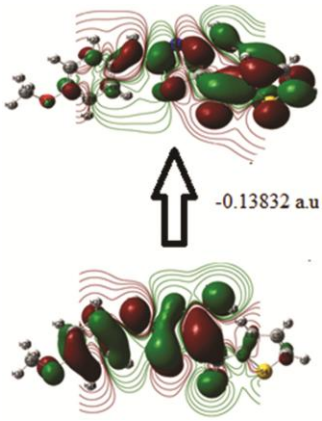


Fig. 3 — HOMO-LUMO energy diagram of the compound MATM

Molecular modelling and structure-based drug designing method

Molecular modelling was done to find the best orientation of ligand, which would form a complex with overall minimum energy. HEX is an interactive molecular graphics program for calculating and displaying achievable docking modes by hundred docking runs converged on a top-ranked cluster among the protein and the DNA molecules. To find out the antiviral activity and binding energy of the titled compound, the molecule should bring to minimized energy level using 6-311+g (d, p) software system. Hydrogen atoms were added, water molecules and ligands were physically deleted[11] and also the compound should obey the Lipinski rule of five to evaluate the toxicity and to analyze their harmful effect on the human body[12], which is shown in (Table 4).

Picorna virus, the most common respiratory virus responsible for the acute infection with respiratory illness. The crystal structure of empty hepatitis A virus (PDB code: 4QPG) obtained from the protein data bank. Docking results were analyzed on binding energy and hydrogen bonding (Fig. 5). The titled compound has the

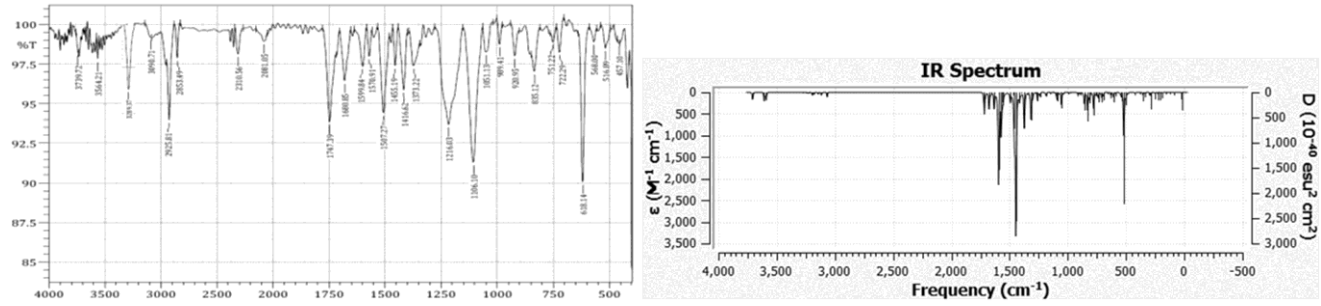


Fig. 4 — Experimental and Theoretical FTIR of the compound (4-amino-2-(4-methoxyphenyl)aminothiazol-5yl)(thiophene-2-yl)methanone

Table 4 — Lipinski rule of 4-amino-2-(4- methoxyphenyl)aminothiazol-5yl)(thiophene-2-yl)methanone

Compound	Molecular weight <500 Dalton	HB donar<5	HB acceptor <10	Log *P* <5	Molecular refractivity 40-130
MATM	331.00	3	5	3.7699	90.554

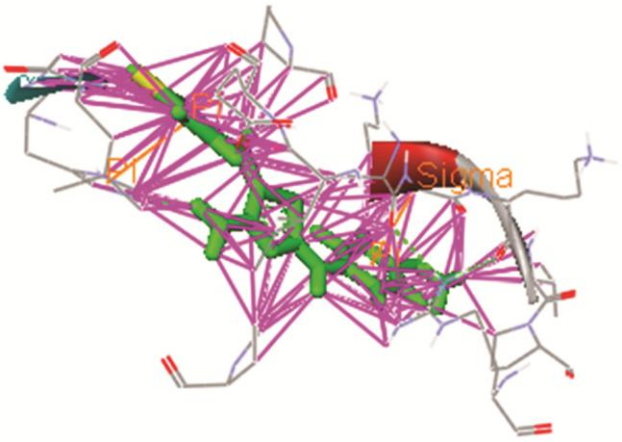


Fig. 5 — 3D diagram of ligand and the protein (4QPG)

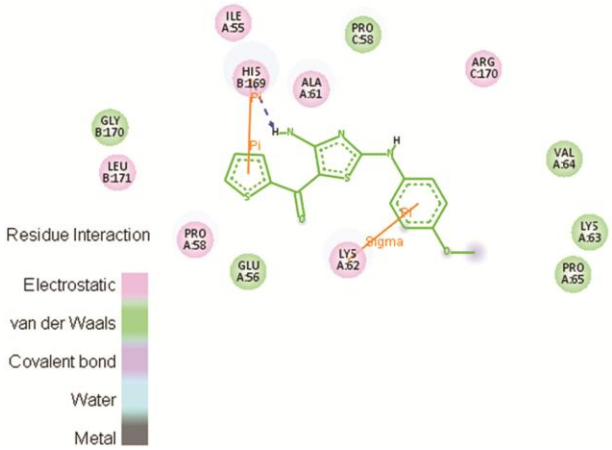


Fig. 6 — 2D representation of the ligand and the protein (4QPG)

Table 5 — Docking score and interaction of the compound MATM with the protein 4QPG

Compound	Active sites of interactions			
	π- σ interactions	π- π interactions	Vander Waals	Electrostatic
MATM	LYS A62	HIS B169	GLU A56, GLY B170, PRO C58	HIS B169, LYS A62, ALA A61, PRO A58

relative binding energy of –8.54 kcal/mol. The thiophene and benzene ring of the titled compound form a π bond with His B169 and LYS A62. They form Vander wall interaction with GLU A56, GLY B170, PRO C58 and electrostatic interaction with HIS B16, LYS A62 at the bond distance of 4.05 A° and 3.67 A° (Fig. 6). The correct interaction conformation between ligand and protein receptor is explained by the pi bond, hydrogen bond, and van der wall interaction (Table 5). The more negative the relative binding, the stronger the binding between DNA and target molecules[13]. The anti-viral activity of the compound was proved by the optimization method. In NBO analysis, there is a charge transfer takes place from N_{14} lone pair electron to C9-C10 with the energy of 40.90 kcal/mole, which influences the bioactivity of the molecule[14, 15], and also leads to the interaction of viral protein His B169 with the amino group of thiazole ring and thiophene ring. Based on the results, it is clear that the compound binds favourably with the protein receptor.

Conclusion

We have established the modest synthetic techniques of ketothiophene analogs of dendrodoine viz(4-amino-2-(4-methoxyphenyl)aminothiazol-5yl)(thiophene-2-yl) methanoneand characterized by IR, ^{1}H NMR, ^{13}CNMR and High-Resolution Mass spectra. Theoretical information on the optimized geometry, NBO analysis, vibrational frequencies, and atomic charges in the ground state were obtained using Density Functional Theory (DFT) using standard B3LYP/6-311+G basis sets with Gaussian'09 software. The results indicate that the B3LYP method could provide satisfactory results for predicting vibrational frequencies and structural parameters. Mulliken population analysis was performed on the atomic charges and the HOMO-LUMO energies were calculated and found that the compound MATM is more reactive which is clearly shown in the docking study. The binding score of the compound MATM towards the protein receptor is –8.58 kcal/mol and it interacts more efficiently with the protein receptor.

Acknowledgement

The authors thank CDRI Lucknow for spectral and analytical data. The authors gratefully acknowledge Dr. T. F. Abbs Fen Reji, Associate Professor, Department of Chemistry, NMCC, Marthandam, for DFT studies.

Conflict of interest

All authors declare no conflict of interest.

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