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DESIGN AND BIOLOGICAL PROFILING OF A NOVEL (2,4-BIS(ARYLAMINO) THIAZOL-5-YL) (THIOPHEN-2-YL) METHANONE DERIVATIVE: IMPACT OF SUBSTITUENT VARIATIONS

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Keywords:

Ketothiophene, Thiazole ring, Synthesis, NLO, NBO, Anti-bacterial activity

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ABSTRACT: A series of novel (2,4-bis(arylamino) thiazol-5-yl) (thiophen-2-yl) methanone derivatives were synthesized and analyzed using various analytical and spectral techniques, including elemental analysis, IR spectroscopy, ^{1}H NMR, ^{13}C NMR, and mass spectrometry to ensure comprehensive structural validation and accurate determination of their chemical composition and framework. Structural optimization and theoretical vibrational spectral interpretations were performed using density functional theory (DFT) calculations. The study examined critical molecular properties, such as charge transfer phenomena, chemical stability, HOMO-LUMO energy gaps, Natural Bond Orbital (NBO) analysis, Molecular Electrostatic Potential (MEP) mapping, and Non-linear Optical (NLO) properties. Biological testing indicated that all synthesized compounds exhibited significant antibacterial activity. Among these, (4-((4-chlorophenyl) amino)-2-(4-ethoxyphenyl) amino) thiazol-5-yl) (thiophen-2-yl) methanone emerged as the most potent antibacterial agent. Molecular docking studies were conducted with the 3IP4 and 1KEB receptor proteins, shedding light on the potential binding interactions and underlying mechanisms. This comprehensive study showcases the synthesis, theoretical evaluation, and biological potential of these thiazole-based derivatives, highlighting their promise as candidates for developing effective antibacterial agents.

INTRODUCTION: Heterocyclic compounds are widely distributed in nature and are essential for life, playing a critical role in cellular metabolism across living organisms.

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Because of their significant therapeutic and pharmaceutical potential, keto-thiophene derivatives and their related fused heterocyclic structures have garnered substantial interest from researchers over the years [1].

Thiophene attached to carbonyl group are widely utilized in pharmaceuticals with various biological activities including anti-inflammatory [2], anti-mycobacterial agents [3], allosteric enhancer [4], antimitotic agents [5], anticoagulant [6], antimicrobial [7], anticancer [8], antidiabetic [9] and as antibiotics [10].

They also serve as antibiotics and are known as potent antiplatelet agents, particularly valuable in treating coronary artery disease [11]. Recently, several thiophene compounds have demonstrated strong selectivity and activity toward CB1 (cannabinoid) receptors [12].

Additionally, some keto-thiophene derivatives have proven useful in advanced functional materials, including electrically conductive materials [13], semiconductors [14], organic light-emitting diodes, organic field-effect transistors [15], organic solar cells [16], lasers [17], dyes, liquid crystals and molecular wires [18]. The purpose of this article is the synthesis of new keto-thiophene derivatives **Fig. 1** fused with substituted thiazoleand characterized by spectral techniques. Theoretical calculations were done using DFT/B3LYP method. The synthesized compounds were investigated for potential antibacterial activity against selected two gram positive and two gram negative bacterial strains. Molecular docking analysis was also performed against 3IP4 and 1KEB receptors.

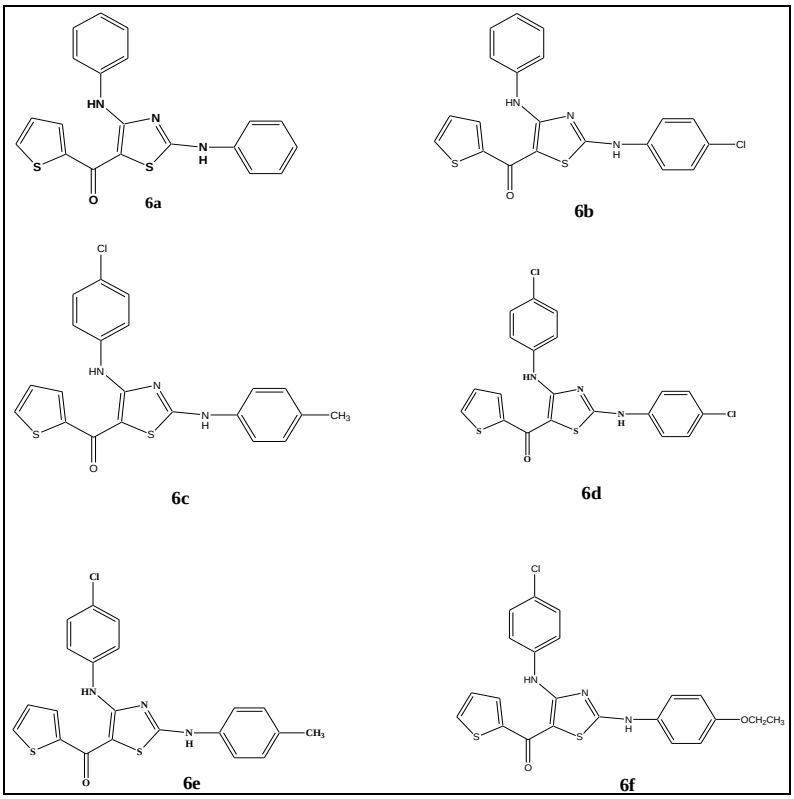


FIG. 1: GENERAL STRUCTURE PRESENTATION OF THE THIOPHENE CONTAINING CARBONYL DERIVATIVES

MATERIALS AND METHODS: All solvents and reagents were obtained from Sigma-Aldrich (India). All melting points are in degree centigrade (uncorrected) and were determined on digital electric melting point apparatus. ^{1}H NMR spectra were recorded by using Bruker Avance 400 spectrometer and chemical shifts are described in parts per million (ppm) relative to TMS. Mass spectra were recorded with Agilent 6520 (QTOF) positive mode ESI-MS instrument. Infrared spectra were measured by using a Nicolet 400 FTIR spectrometer within the range. Elemental analyses (C, H, and N) were carried out at CDRI Lucknow (India), the results were found to agree favorably with the calculated values. TLC analysis was carried out on silica gel (60-120 mesh) precoated glass plates. The aryl isothiocyanates (1), N,N′–diarylguanidine (2), 1 - aryl - 3 - (N, N′-diphenylamidino) - 3-arylthioureas (3), and 2-(2-bromoacetyl) thiophene (5) were prepared by the reported methods (Supplementary file).

Synthesis of substituted (2,4-bis (arylamino) thiazol-5-yl) thiophen-2-yl) methanone (6a-6f):

General Procedure; A mixture of compound 2-(2-bromoacetyl) thiophene 5 (0.254 g, 1mmol) and substituted 1-aryl-3-(N,N'-diarylamidino) thiourea 3 (1 mmol) were heated on a water bath at 80-85 ºC

for 5 minutes. To this 0.15 ml triethylamine (1mmol) was added and heating was continued for another 10 minutes. Then the reaction solution was allowed to cool to room temperature and poured into ice-cold water[19]. The product precipitate obtained was filtered, wash with water, dried and recrystallized from methanol-water (2:1) to give 6a-6f respectively.

(2,4-bis(phenylamino) thiazol-5-yl) (thiophen-2-yl) methanone (6a): The compound was obtained from the reaction of **5** with 3-(N,N'-diphenylamidino)-1-phenylthiourea as yellow crystals; Yeild: 69 %; mp: 132-135 ^{o}C ; IR (KBr) cm^{-1}: 3446 cm^{-1}, 3252 cm^{-1}, (υ_{N-H}), 3068cm^{-1} (aromatic υ_{C-H}). 1621cm^{-1} ($\upsilon_{C=O}$); ^{1}H NMR: (DMSO-d_6) δ ppm: 7.91 (d, 1H,J=5.2 Hz, H-1 of thiophene), 7.19 (t, 1H, J=1.2 Hz, H-2 of thiophene), 7.90 (d, 1H, J=6.4 Hz, H-3 of thiophene), 8.70 (s, 1H, H-4), 7.89 (d, 2H, J=1.6 Hz, 2ArH), 7.32 (t, 2H, J=10.4Hz, 2ArH), 7.08 (t, 1H,1.2 Hz, 1ArH), 11.30, (s, 1H, H-10), 7.68 (d, 2H, J=10 Hz, 2ArH), 7.37 (t, 2H, J=6.8 Hz, 2ArH), 7.07, (t,1H, J=1.2 Hz, 1ArH). ^{13}C (DMSO-d_6) δ ppm: 93.62, 161.56, 138.93, 145.53, 134.82, 141.19, 133.25, 129.47, 139.21, 139.09, 119.74, 119.39, 119.17, 118.10, 129.30, 129.14, 129.06, 129.01. ESI-MS MH^{+} (378.07 m/z)**.** Anal.Calc. (Found) for$C_{20}H_{15}N_3OS_2$ (377.48); C, 63.64 (63.59); H, 4.01 (3.99), N, 11.13 (11.08); S, 16.99 (16.87).

2 (2-((4-chlorophenyl) amino)-4-(phenylamino) thiazol-5-yl) (thiophen-2-yl) methanone (6b): The compound was obtained from the reaction of **5** with 3-(N, N'-4-chlorophenylamidino) – 1 - phenylthiourea as dark yellow crystals; Yield:87 %; mp:135-139 ^{o}C; IR (KBr) cm^{-1}: 3737.79 cm^{-1}, 3419.56 cm^{-1}(υ_{N-H}), 3087.82 cm^{-1} (aromatic υ_{C-H}), 1669.28 cm^{-1}($\upsilon_{C=O}$); ^{1}H NMR: (DMSO-d_6) δ ppm: 8.20 (d, 1H, J=1.6 Hz, H-1 of thiophene), 7.22 (t, 1H, J=2.4 Hz, H-2 of thiophene), 8.06 (d, 1H, J=3.6 Hz, H-3 of thiophene), 8.70 (s, 1H, NH), 7.56 (d, 2H, J= 10 Hz, 2ArH), 7.33 (t, 2H, J=2.4 Hz, 2ArH),) 7.09 (t, 1H,4.4 Hz, 1ArH), 10.00 (s, 1H, NH), 7.54 (d, 2H, J=2 Hz, 2ArH), 7.29 (d, 2H, J=4.8Hz, 2ArH). ^{13}C (DMSO-d_6) δ ppm: 161.20, 136.58, 145.58, 135.34, 139.92, 133.15, 129.05, 126.20, 138.94, 139.22, 129.71, 123.08, 119.15, 129.30, 119.71, 119.06, 129.17, 186.09; ESI-MS MH^{+} (412.42); Anal. Calc. (Found) for $C_{20}H_{14}ClN_3OS_2$ (411.92): C, 58.32 (58.09); H 3.43 (3.48); N, 10.20 (10.19), S, 15.57 (15.49).

(4-(phenylamino)-2-(p-tolylamino) thiazol-5-yl) (thiophen-2-yl) methanone (6c): The compound was obtained from the reaction of 5 with 1-phenyl-3-(N, N'-dimethylphenylamidino) thiourea as dark yellow crystals; Yield:85 %; mp:162-165 ^{o}C; IR (KBr) cm^{-1} : 3595 cm^{-1}, 3588 cm^{-1}(υ_{N-H}), 3087.82 cm^{-1} (aromatic υ_{C-H}), 1693 cm^{-1}($\upsilon_{C=O}$),. ^{1}H NMR: (DMSO-d_6) δ ppm: 8.04 (d, 1H, J=1.6 Hz, H-1 of thiophene), 7.22 (t, 1H, J=3.4 Hz, H-2 of thiophene), 7.83(d, 1H, J=2.9 Hz, H-3 of thiophene), 8.82 (s, 1H, NH), δ7.75 (d, 2H, J= 8 Hz, 2ArH), 7.33(t, 2H, J=2.4 Hz, 2ArH),) 7.02 (t, 1H,4.4 Hz, 1ArH), 10.22 (s, 1H, NH), 7.33 (d, 2H, J=2 Hz, 2ArH), 7.24 (d, 2H, J=2.8Hz, 2ArH).^{13}C (DMSO-d_6) δ ppm: 21.3, 131.2, 129.8, 120.3, 137.5, 159.1, 142.0, 137.3, 180.7, 144.3, 133.7, 129.0, 135.8, 140.9, 117.8, 129.5, 122.4; ESI-MS MH^{+} (392.63). Anal. Calc. (Found) for $C_{21}H_{17}N_3OS_2$ (391.51): C, 64.43 (64.40); H, 4.38 (4.40); N, 10.73 (10.69); S, 16.38 (16.35).

(2, 4-bis (chlorophenylamino) thiazol – 5 - yl) thiophen-2-yl) methanone (6d): The compound was obtained from the reaction of 5 with 1-(4-chlorophenyl) – 3 - (N, N'-di(4-chlorophenyl) amidinothioureaas yellow crystals; Yield: 75 %; mp: 145-147 ^{o}C; IR (KBr) cm^{-1}: 3445cm^{-1}, 3382, cm^{-1}(υ_{N-H}), 3095 cm^{-1} (aromatic υ_{C-H}) 1661 cm^{-1}($\upsilon_{C=O}$),. ^{1}H NMR: (DMSO-d_6) δ ppm: 8.05 (d, 1H,J=3.9 Hz, H-1), 7.23 (t, 1H, J=1.5 Hz, H-2), 8.03 (d, 1H, J=0.9 Hz, H-3), 8.16 (s, 1H, H-4), 7.60 (d, 4H, J=6.9 Hz, 4ArH), 7.39 (d, 2H, J=2.4Hz, 2ArH), 7.29 (d, 2H,1.8 Hz, 2ArH), 10.20, (s, 1H, H-10).^{13}C (DMSO-d_6) δ ppm: 122.1, 129.6, 129.0, 133.7, 135.8, 137.3, 139.0, 138.6, 142.0, 144.3, 180.7. ESI-MS MH^{+}(447); Anal. Calc. (Found) for $C_{20}H_{13}Cl_2N_3OS_2$ **(**446.36): C. 53.82 (53.09); H, 2.94 (3.01); N, 9.41 (9.38); S, 14.36 (14.39).

(4-((4-chlorophenyl) amino)-2-(p-tolylamino) thiazol-5-yl) (thiophen-2-yl)methanone (6e): The compound was obtained from the reaction of **5** with 1-(4-methylphenyl) – 3 - (N, N'-di(4-chlorophenyl) amidinothioureaas yellow crystals; Yield: 85 %; mp: 141-143 ^{o}C; IR (KBr) cm^{-1}: 3382cm^{-1}(υ_{N-H}), 3095 cm^{-1} (aromatic υ_{C-H}), 1662 cm^{-1}($\upsilon_{C=O}$); ^{1}H NMR: (DMSO-d_6) δ ppm: 8.05 (d, 1H,J=0.9 Hz, H-1), 7.06(t, 1H, J=3.3 Hz, H-2), 8.03 (d, 1H, J=1.2

Hz, H-3), 8.15 (s, 1H, H-4), 7.11 (d, 2H, J=3.3 Hz, 2ArH), 7.10 (d, 2H, J=2.1 Hz, 2ArH), 7.09 (d, 2H, 4.8 Hz, 2ArH), 9.90, (s, 1H, NH), 7.08 (d, 2H, 2.1 Hz, 2ArH), 2.31 (s, 3H). ^{13}C (400MHz, DMSO-d_6) δ ppm: 20.42, 113.70, 119.43, 124.24, 128.45, 128.74, 129.54, 130.00, 133.35, 134.87, 141.38, 147.13, 154.48, 162.84, 190.23. ESI-MS MH^+(426). Anal. Calc. (Found) for$C_{21}H_{16}ClN_3OS_2$ **(**425.95): C, 59.22 (59.30); H, 3.79 (3.77); N, 9.87 (9.780); S, 15.05 (15.09).

(4-((4-chlorophenyl) amino)-2-(4-ethoxyphenyl) amino) thiazol-5-yl) (thiophen-2-yl) methanone (6f): The compound was obtained from the reaction of 5 with 1-(4-ethoxyphenyl)-3-(N,N'-di(4-chlorophenyl) amidinothiourea as yellow crystal; Yield: 84 %; mp: 172-174 ^oC; IR (KBr) cm^{-1}: 3741cm^{-1}, 3444cm^{-1}(υ_{N-H}), 2924cm^{-1} (aromatic υ_{C-H}), 1678cm^{-1}($\upsilon_{C=O}$), ^{1}H NMR: (DMSO-d_6) δ ppm: 8.04 (d, 1H,J=2.5 Hz, H-1), 7.22(t, 1H, J=2.8 Hz, H-2), 7.83 (d, 1H, J=3.7 Hz, H-3), 8.82 (s, 1H, H-4), 7.66 (d, 2H, J= 4.2 Hz, 2ArH), 7.39 (d, 2H, J=3.6 Hz, 2ArH), 7.55 (d, 2H, 3.9 Hz, 2ArH), 10.22, (s, 1H, NH), 6.95 (d, 2H, 1.9 Hz, 2ArH), 4.05 (m, 2H, J=1.5 Hz), 1.34 (t, 3H, J= 3.2 Hz). ^{13}C (DMSO-d_6) δ ppm: 14.8, 64.6, 115.2, 121.3, 122.1, 127.7, 129.0, 129.6, 132.1, 133.7, 135.8, 137.3, 180.7. ESI-MS MH^+(456). Anal. Calc. (Found) for$C_{22}H_{18}ClN_3O_2S_2$ (455.98): C, 57.95 (57.96); 3.98 (3.99); 9.22 (9.24);14.06 (14.09).

Computational Study: The electronic structures of molecules (6a-f) were fully optimized by solving self-consistent field equation and the theoretical calculations of harmonic vibrational wave numbers was also performed using Gaussian 09 program, at B3LYP/6-311G (d,p) basis set. The calculated structural parameters were compared with the experimental data. To determine various second-order interactions between the filled and vacant orbitals, the Natural Bond Orbital (NBO) calculations performed using NBO 03W software package. NLO, FMO, MEP.

***In-vitro* Bacterial Studies:** The synthesized series of (2,4-bis(arylamino)thiazol-5-yl) thiophen-yl) methanone was subjected to antibacterial activity and were screened to determine *in-vitro* ability to inhibit the growth of selected pathogens by well diffusion method using Mueller Hinton agar. The antibacterial inhibition was tested against two Gram-positive bacterial strains such as *Staphylococcus aureus* (MTCC 916), *Bacillus subtilis (*MTCC 1134), and two Gram-negative bacterial strains such as *Pseudomonas aeruginosa* (MTCC 741), *Escherichia coli* (MTCC 1671). The zone of inhibition was calculated in mm using a standard agar well diffusion method.

Pure culture from the plate were inoculated into Nutrient Agar plate and sub cultured at 37ºC for 24 h. Inoculum was prepared by aseptically adding the fresh culture into 2 ml of sterile 0.145 mol/L saline tube and the cell density was adjusted to 0.5 McFarland turbidity standard to yield a bacterial suspension of 1.5×108 cfu/ml. Standardized inoculum used for antimicrobial test. The medium was prepared by dissolving 38 g of Muller Hinton Agar Medium (Hi Media) in 1000 ml of distilled water. The dissolved medium was autoclaved at 15 Lbs pressure at 121^0C for 15 min (pH 7.3). The autoclaved medium was cooled, mixed well and poured petriplates (25 ml/plate) the plates were swabbed with Pathogenic Bacteria culture viz. analysis *Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa* and *Bacillus subtilis.* Finally, The Sample loaded Disc was then placed on the surface of Muller-Hinton medium and the plates were kept for incubation at 37°C for 24 hours.

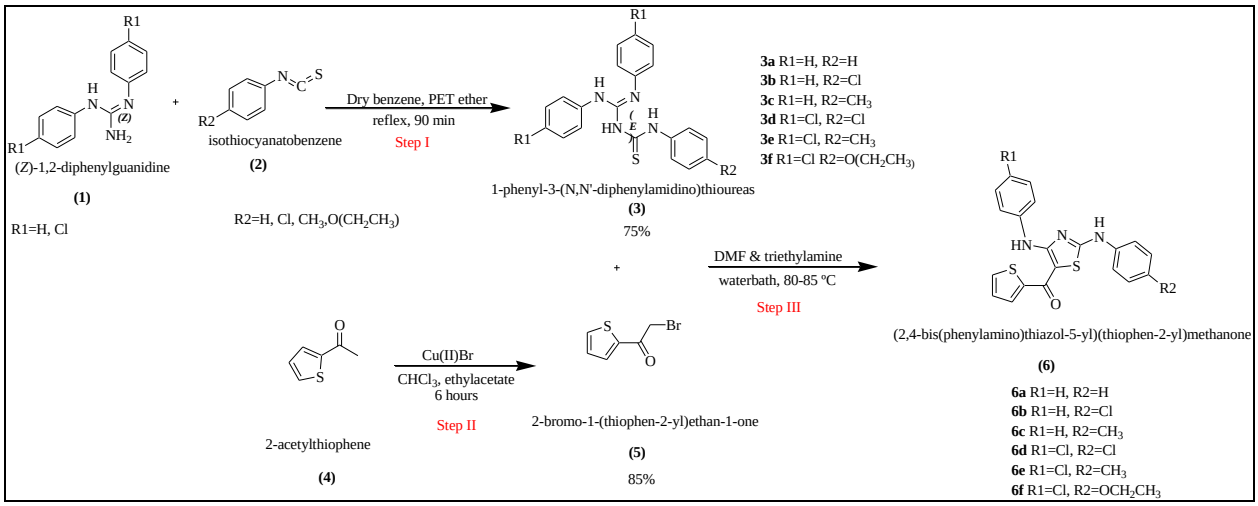
At the end of incubation, inhibition zones were examined around the disc and measured with transparent ruler in millimetres. The size of the zone of inhibition (including disc) was measured in millimeters. The activities are expressed as resistant, if the zone of inhibition was less than 7 mm, intermediate (8-10 mm) and sensitive if more than 11 mm.

Molecular Docking: Molecular modelling was done to find the best orientation of ligand, which would form a complex with the receptor in 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. The structures of the receptor 3IP4 and 1KEBwere obtained from the protein data bank (www.rcsb.com). To find out the anti-bacterial activity and binding energy of the titled compounds, the molecules should bring to

minimized energy level using 6-311g (d,p) software system and docked with the receptors, the resulting binding energies were recorded and the docked poses were visualized on discovery studio 3.5 client molecular docking system. Based on the drug action, it has been performed docking simulation of the newly synthesized titled compounds with the active sites of the high-resolution structure of the bacterial heterotrimeric amidotransferase (PDB code: 3IP4) and crystal structure of double mutant *E. coli* thioredoxin(PDB code: 1KEB), which is downloaded from the protein data bank in PDB format.

RESULT AND DISCUSSION:

Chemistry: The condensation of (Z) 1,2diaryllguanidine (1) and arylisothiocyanate (2) we get derivatives (3). The 2-acetyl thiophene (4) converted to 2-bromo-1-(thiophen-2-yl) ethan-1-one (5) via heterogenous condition with 86% yield. The required (Z)1,2diarylguanidine (1) could be obtained by the reaction between aryl cyanamides and arylamine hydrochlorides [20]. These compounds 1-aryl-3-(N,N'-diarylamidino) thiourea(3a-f) and (5) were utilized in the synthesis of target scaffolds (6a-f). A mix of equimolar 2-(2-bromoacetyl) thiophene (5) [21] and substituted 1-aryl-3-(N,N'-diarylamidino) thiourea (3a-f) were heated on a water bath at 80-85 °C for 5 minutes. Base triethylamine is added in order to remove hydrogen bromide and heating was continued for another 10 minutes. Then the reaction solution was allowed to cool to room temperature and poured into ice-cold water afford the corresponding products (6a-f) respectively Scheme 1. The observed m/z for 6a: 378 (M^+, 21.6%) **Fig. 4**; 6B: 412 (M^+, 21.6%) Fig. S8; 6C: 392.63 (M^+, 21.6%); 6d: 447 (M^+, 21.6%); **6e**: 426(M^+, 21.6%) **Fig. S12**; and **6F**: 456 (M^+, 21.6%); respectively. The obtained vibrational spectra were show good agreement with the calculated one **Fig. 5**.



SCHEME 1: SYNTHESIS OF (2,4-BIS(PHENYLAMINO)THIAZOL-5-YL) (THIOPHEN-2-YL) METHANONE 6A-F

Reaction of 3a with 2-(2-bromoacetyl) thiophene produced 6a. IR spectrum of the compound 6a displayed absorption bands at 3446, 3252and 1621 cm^{-1} assigned to NH and thio-keto groups respectively **Fig. 1.** Furthermore, the ^1H NMR of 6a shows the presence of thiophene ring protons at δ 7.90, 7.91, and 7.19 ppm. The –NH proton adjacent to the thiophene ring (δ 8.70 ppm) downfield shifted than the other –NH (δ 11.31 ppm). The peaks at δ 180.37 ppm on ^{13}C spectra confirms the inclusion of keto-thiophene moiety and the peaks at δ 141.19 ppm, δ 145.53 ppm, δ 138.93 ppm and δ 139.21 ppm are due to the carbon in thiophene ring in its (6a) structure **Fig.** S2 & S3. Reaction of compound 5 with 3b afforded 6b, its υ_{N-H} vibrations seen at 3537 and 3419 cm^{-1} in IR spectra. The carbonyl band shifted to higher wavenumber (1699 cm^{-1}) than the spectra of non-substituted compound 6b (1621 cm^{-1}). The band at 3087 cm^{-1} is assigned to the aromatic C-H stretching vibrations **Fig. 5.** The ^1H NMR of 6b shows multi plets between δ 7.01- δ 8.06 ppm represents the Ar-H. The –NH protons resonates at δ 8.70 (adjacent to thiophene ring) and 10.30 ppm (attached to Ph-Cl). The ^{13}C NMR confirmed the successful addition of keto-thiophene part and the corresponding carbonyl carbon band observed at δ 161.72 ppm **Fig. 6** & **7.**

Reaction of compound 5 with 3c leads to the formation of compound 6c. The IR bands seen at 3595 and 3588 cm^{-1} could be assigned for υ_{N-H} vibrations. Whereas the Ar-H and $\upsilon_{C=O}$ vibrations displayed at 3087 and 1693 cm^{-1}. The Ar-H protons resonates within δ 7.02-7.75 ppm additional peak at δ 2.32 ppm confirmed the presence of one CH_3 group in its structure. Furthermore, on ^{13}C spectra the corresponding methyl-C peak located at δ 21.3 ppm and C=O carbon at δ 180.70 ppm.

The compound (2,4-bis (chlorophenylamino) thiazol-5-yl) thiophen-2-yl) methanone 6d is obtained by the reaction of compound 5 with 3d, the IR peaks at 3382 and 3445 cm^{-1} indicates the presence of υ_{N-H}. Other major vibrations such as Ar-H and keto group connected with thiophene seen at 3095 and 1669 cm^{-1} respectively **Fig. 10.** The two ¯NH protons were seen at δ 8.15 and 10.20 ppm in its ^1H NMR spectrum **Fig. 9.** The peaks at δ 180.17 ppm confirms the presence of carbonyl group and the peaks at δ 141.32 ppm, δ 145.30 ppm, δ 138.23 ppm and δ 139.11 ppm are due to the carbon in thiophene ring in its (6d) structure. Compound 5 reacts with 3e get the compound 6e. The IR spectrum 6e indicated the presence of υ_{N-H} vibration bands at 3382 and 3584 cm^{-1} and keto-thiophene (1662cm^{-1}). The ^1H NMR spectrum of the compound shows a singlet at δ 2.31ppm due to the methyl group connected phenyl ring. While the singlet at δ 8.15 ppm corresponds to -NH attached to chlorophenyl ring and proton at δ 9.90 ppm attributed for -NH attached to methylphenyl ring. ^{13}C NMR of 6e further confirms the presence of methyl group (δ 20.42 ppm) and addition of C=O (δ 180.62 ppm) **Fig. 11**.

Reacting of the compound 5 with 3f got 6f. The IR vibrations of υ_{N-H} (3541 and 3444 cm^{-1}) carbonyl (1690 cm^{-1}) and ethoxy group (3020 cm^{-1}) were also consistent with the theoretical values. The ^1H NMR the quartet at δ 4.05 ppm and triplet at δ 1.34 ppm are responsible for the attached ethoxy group in phenyl ring. Additionally the observed singlet at δ 10.22 and δ 8.23 ppm are due to the presence of two -NH moieties. From ^{13}C NMR the corresponding ($O-CH_2-CH_3$) carbon peaks displayed at δ 14.38, δ 64.52 ppm and carbonyl group at δ 180.08 ppm. The analytical data of all synthesized compounds are tabulated **Table 1**.

TABLE 1: ANALYTICAL DATA OF THE SYNTHESIZED COMPOUNDS

Comps.	M.P(°C)	Elemental analysis (C, H, N, S) Calculated/determined values	Molecular Formula	M.W	Yield [%]
6a	132-135	C(63.64/63.59), H(4.01/3.99), N(11.13/11.08), S(16.99/16.87).	$C_{20}H_{15}N_3OS_2$	377.48	69
6b	135-139	C(58.32/58.09), H(3.43/3.48), N(10.20/10.19), S(15.57/15.49).	$C_{20}H_{14}ClN_3OS_2$	411.92	87
6c	162-165	C(64.43/64.40), H(4.38/4.40), N(10.73/10.69), S(16.38/16.35)	$C_{21}H_{17}N_3OS_2$	391.51	85
6d	145-147	C(53.82/53.09), H(2.94/3.01), N(9.41/9.38), S(14.36/14.39).	$C_{20}H_{13}Cl_2N_3OS_2$	446.36	75
6e	141-143	59.22, 3.79, 9.8715.05. 59.30, 3.77, 9.78, 15.09	$C_{21}H_{16}ClN_3OS_2$	425.95	85
6f	172-174	C(57.95/57.96), H(3.98/3.99), N(9.22/9.24), S(14.06/14.09)	$C_{22}H_{18}ClN_3O_2S_2$	455.98	84

Computational Method:

Geometry Optimization with DFT Method: The optimized geometries of heterocyclic compounds 6a-f **Fig. 2** were obtained by performing DFT computations at the at B3LYP/6-311G (d,p) level theory and the associated bond parameters were represented on **Table 2.** The total self-consistent field (SCF) energies for 6a-f were found to be -1806.67, -2266.92, -1846.35, -2726.55, -2305.4, and -2420.46a.u; with corresponding dipole moment values 3.634, 2.663, 3.599, 2.18, 3.06, 3.71 Debye and C1 point group respectively. The compounds substituted (2,4-bis(arylamino)thiazol-5-yl) thiophen-2-yl) methanone 6a-f consist of two substituted phenyl ring, one thiazole ring connected with thiophene ring through carbonyl group. The geometry shows distorted structure due to the thiophene ring, where the two phenyl ring attached to the thiazole and keto group are coplanar. In compound 6b, 6d, 6e, 6f, the C-C bond length of the phenyl ring attached to the chlorine atom are shortened when compared to the other C-C bond

length, the endoangle, C-C-C has been increased in the range of 120.35°-120.51°, leading to the distortion from the regular hexagon structure, due to the substitution of the electronegative chlorine atom. In compound 6c, 6e and 6f, the methyl and ethoxy substituents are planar with the phenyl ring, which is shown by the dihedral angle C_{31}-C_{32}-C_{33}-C_{41} 6c (-178.03°), 6e(-177.97°), 6f(-178.58°).The electron donating methyl and methoxy substituent in 6c, 6e and 6f on the benzene ring distorts the symmentry of the phenyl ring yielding a decrease in angle C-C-C 6c(117.45°), 6e(117.46°) and 6f(118.93°) at the point of substituents.

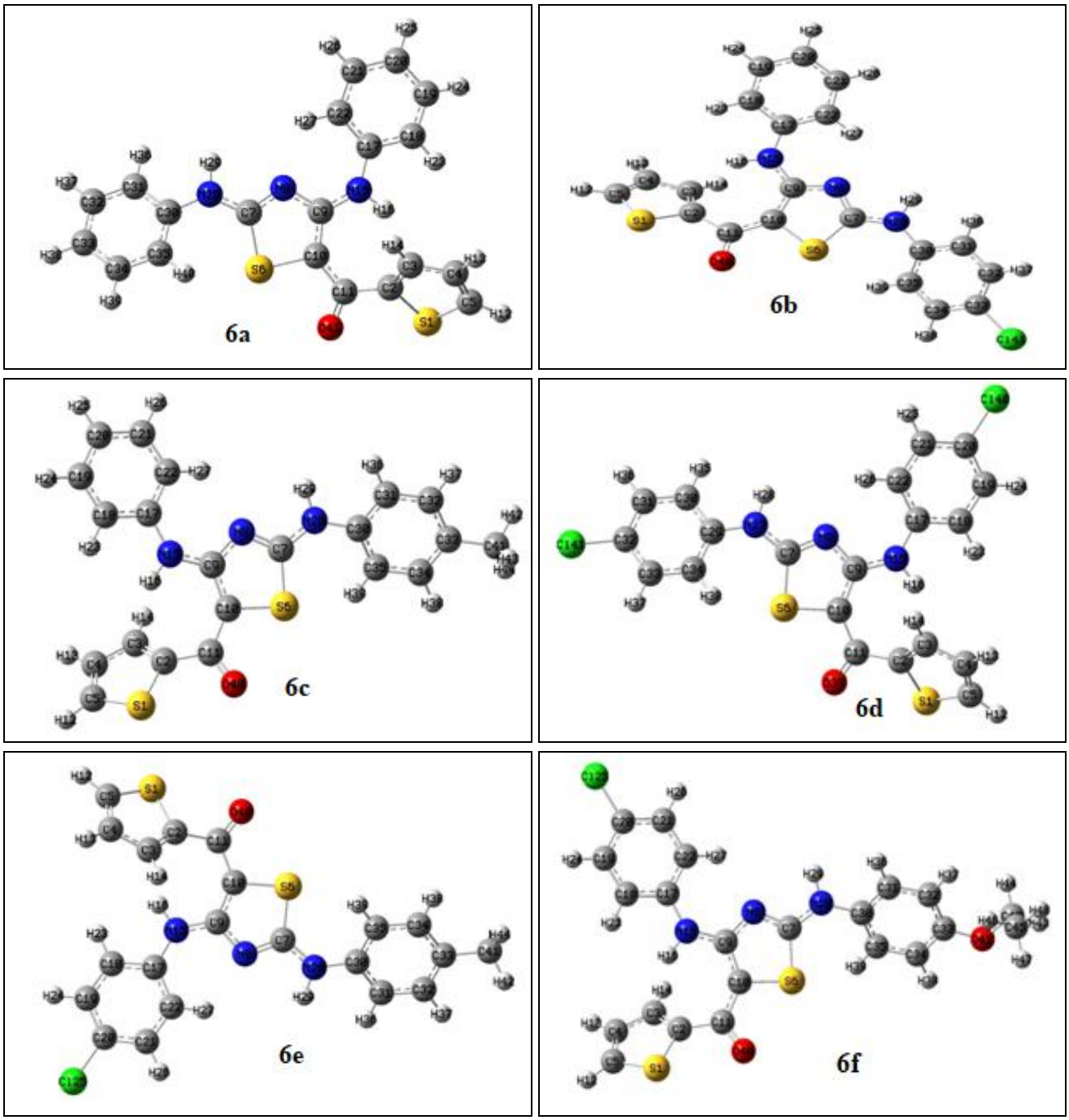


FIG. 2: OPTIMIZED GEOMETRY OF THE SYNTHESIZED COMPOUNDS

TABLE 2: SOME GEOMETRIC PARAMETERS BELONGS TO TITLED MOLECULES AT B3LYP/6-311G (D,P) BASIS SET

Assignments	6a	6b	6c	6d	6e	6f
			Bond length (Å)			
S1-C2	1.8140	1.8137	1.7445	1.7441	1.8137	1.7468

S1-C5	1.7925	1.7925	1.7254	1.7253	1.7925	1.7276
S6-C7	1.8131	1.8131	1.7446	1.7443	1.8131	1.7477
S6-C10	1.8396	1.8389	1.7721	1.7718	1.8380	1.7725
C7-N8	1.3245	1.3257	1.3175	1.3184	1.3250	1.3217
N8-C9	1.3805	1.3795	1.3614	1.3505	1.3795	1.3638
C9-N15	1.3727	1.3753	1.3689	1.3706	1.3753	1.3720
C11-O41	1.2671	1.2662	1.2328	1.2321	1.2662	1.2353
H28-N29	1.0136	1.0136	1.0112	1.0111	1.0136	1.0122
Bond Angle (deg.)						
C2-S1-C5	91.59	89.56	91.44	91.45	89.56	89.51
C11-C2-S1	117.83	118.09	118.15	118.27	118.09	118.03
N28-C30-C7	131.46	131.47	131.99	131.80	131.48	131.58
C7-N28-C29	112.02	112.44	111.70	111.86	112.45	112.31
C2-C11-O40	118.82	120.08	120.39	119.03	118.82	118.69
C10-C11-O40	120.49	120.48	120.66	120.69	120.48	120.51
C7-C6-C10	88.45	86.96	88.41	88.45	86.96	86.92
C7-N8-C9	110.92	112.77	111.36	111.31	112.77	112.84
C9-N15-C10	123.93	124.12	124.12	124.00	124.26	124.34

Quantum chemical parameters such as Dipole moment, molecular polarizability, as well as substitution changes were influence the Mulliken atomic charge. Based on these data, all hydrogen carries positive charge and nitrogen atoms N-8, N-15 and N-28 has a more negative charge **Fig. 13.** Among this, the C-9 of the compounds has a more positive charge and the carbonyl oxygen atom possesses negative charge and they are responsible for the H-bonding interaction in the compounds[22].

Natural Bond Orbital Analysis: The natural bond orbital (NBO) analysis identifies the individual bonds and the energies related with lone-pair electrons. It explains the intra-molecular interaction and delocalization of electron density within the molecule, higher E^2 value shows the intensive interaction among electron-donors and electron-acceptors[23]. While the extent of conjugation of the entire system leads to intensive interactions between the donor-acceptor orbitals. Biological activity of the studied compounds increases with the greater hyper conjugative interaction within the molecule [24]. The hyperconjugative interaction of lone pair, LP(1)N_8 with the $\sigma^*(C_{22}\text{-}H_{27})$ antibonding shows the possibility of C-H···N intramolecular interaction whose energy contribution is 3.48 Kcal/mol. The charge transferred from the hyperconjugative interaction of LP(2)S_6 with the $\sigma^*(C_{35}\text{-}H_{40})$ having the energy of 0.83 Kcal/mol leads to the stability of the molecules. Energies for the LP(2)S_6 with the antibonding orbitals $\sigma^*(C_7\text{-}N_8)$ and $\sigma^*(C_9\text{-}C_{10})$ are 26.87 and 11.11Kcal/mol respectively signifying that the electron localised in the area of the $N_8\text{-}C_7$ bond. This is well shown in the geometry as a reduction in the bond length of $N_8\text{-}C_7$ bond. The conjugation between the sulphur lone pair electrons with the carbonyl oxygen atom (LP(1)O→ $\sigma^*(S_6\text{-}C_7)$→1.57 Kcal/mol) shows isolated physical and chemical properties responsible for the bioactivity of the molecules. The enormous amount of energy (56.05 Kcal/mol, 55.07 Kcal/mol, 54.45Kcal/mol, 53.58 Kcal/mol, 52.68 Kcal/mol and 53.18 Kcal/mol) concerning the order of the compounds of charge transfer arises from the hyperconjugative interaction of LP(1)N15 with the $\sigma^*(C_9\text{-}C_{10})$, which subsidises the stability of the molecules **Table 3.** In compounds 6b, 6d, 6e and 6f, the increased electron density at the chlorine atom leads to the lengthening of C-Cl and a lowering of the C-Cl stretching wavenumber. The electron density is transferred from the lone pair of chlorine atom to the antibonding orbital of phenyl ring(C32-C33) and (C33-C34), explaining both elongation and red shift.

TABLE 3: SECOND-ORDER PERTURBATION THEORY ANALYSIS OF THE TITLED COMPOUNDS

Donor (i)	Acceptor (j)	6a	6b	6c	6d	6e	6f
		Energy (E^2) Kcal/mol					
LPS1	σ^*(C2-C3)	17.85	21.68	21.73	22.32	17.66	21.82
LPS1	σ^*(C4-C5)	19.15	23.35	23.44	23.81	19.06	23.44
LPS6	σ^*(C7-N8)	26.87	33.47	32.90	34.74	26.19	32.91
LPS6	σ^*(C9-C10)	11.11	13.30	13.26	13.91	10.72	13.35

LPN8	σ^*(S6-C7)	16.94	14.86	14.86	14.12	15.69	14.83
LPN15	σ^*(C9-C10)	56.05	55.07	54.45	53.58	52.68	53.18
LPN15	σ^*(C17-C22)	35.35	35.75	36.09	36.26	36.08	37.12
LPN28/N27	σ^*(C7-N8)	60.86	54.93	55.36	54.40	58.34	56.52
LPN28	σ^*(C30-C35)	30.57	32.20	30.13	32.86	29.00	22.06
LPO41/O40/O39	σ^*(C2-C11)	17.44	19.65	20.26	18.65	17.60	20.08
LPO41/40/O39	σ^*(C10-C11)	14.42	16.95	17.26	16.30	14.66	17.15
LPCl41	σ^*(C10-C11)	-	11.93	-	-	-	-
LPCl40	σ^*(C20-C21)	-	-	-	11.73	-	-

HOMO-LUMO and Molecular Electrostatic Potential: Qualitative evaluation of the extent of the HOMO-LUMO energy gap plays a significant role in the chemical reactivity and as well as the observed biological properties. The relative energies of HOMO-LUMO of the compounds were tabulated **Table 4.** From this, we recognize that the HOMO-LUMO energy gap of 6f is smaller than the other compounds **Fig. 3**. A large Egap implies good thermodynamic stability whereas a small gap represents an easy electronic transition i.e reactivity of the compounds. A molecule with a small energy gap is generally associated with high synthetic reactivity, low kinetic stability and leads to enhance its molecular softness [25]. In compounds 6b, 6c, 6d and 6f, the HOMO energy distributed on the thiazole ring, whereas, LUMO energy localized on the thiophene, benzene and keto group. In compounds 6a and 6e, the HOMO and LUMO energies are localized on the whole structure.

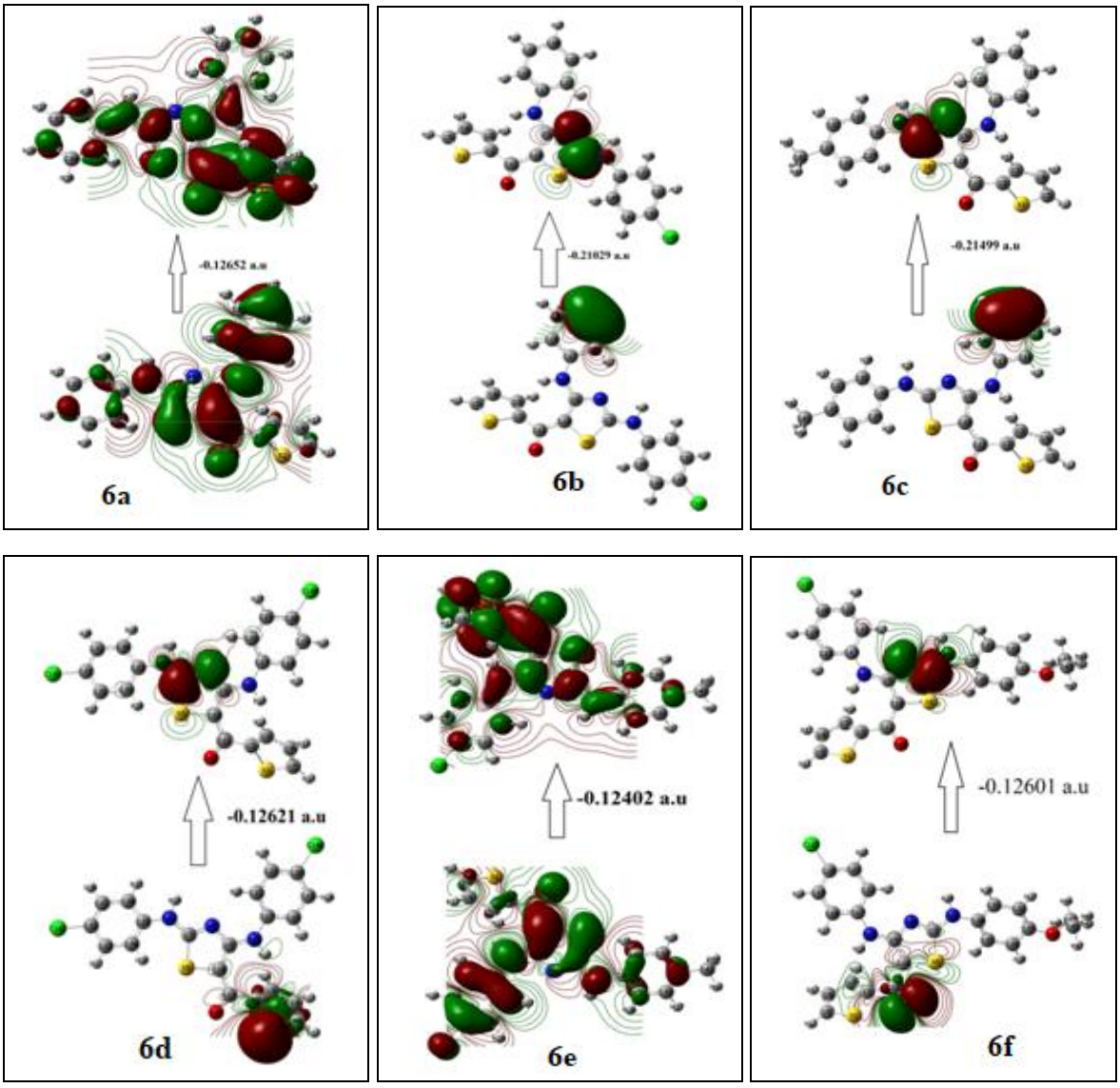


FIG. 3: HOMO-LUMO OF THE SYNTHESIZED COMPOUNDS 6A-F

TABLE 4: HOMO-LUMO ENERGY VALUES

Parameters	6a	6b	6c	6d	6e	6f
HOMO	-0.1905	-0.1950	-0.1891	-0.2082	-0.1971	-0.1998
LUMO	-0.0065	-0.0692	-0.0632	-0.0820	-0.0730	-0.0732
HOMO-LUMO	0.1255	0.1258	0.1259	0.1262	0.1241	0.1265

Molecular electrostatic potential (MEP) is measured as the first-order interaction between molecular charge distribution and a positive unit charge at any point around the molecule in the space [26]. The charge transfer characteristics and total density surface distribution can be estimated using MEP plots. The 3D plots of the compound 6a is shown in the **Fig. 4** and the rest of the compounds 6b, 6c, 6d, 6e and 6f are given in **Fig. 14**, in which the potential decreasing in the order blue>green>yellow>red. From the MEP plots, it is observed that the carbonyl group attach to the thiophene possess negative charge and it is the preferential site for the electrophilic attack and the most important hydrogen acceptor sites for the H-bonding in the compounds. The NH group attaches to both the phenyl and the thiazole ring possess positive charge and act as a nucleophile region.

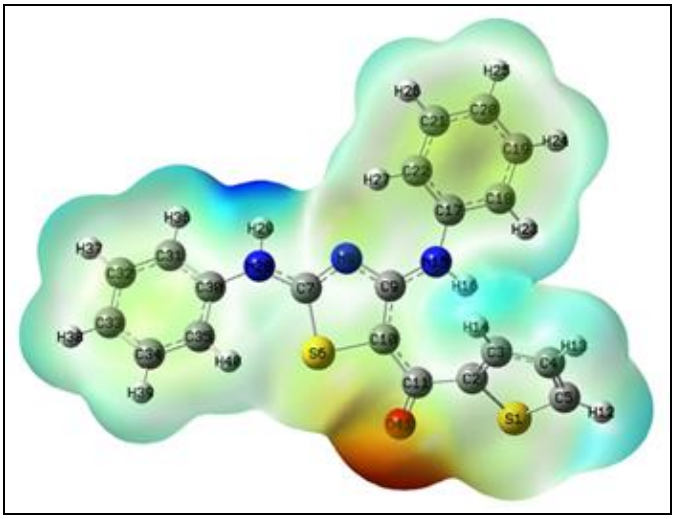


FIG. 4: MEP PLOTS OF THE COMPOUND 6A

Non-linear optical Property Analysis: Non-linear optical (NLO) materials are those which can influence light waves and form the key elements for technological application including optical processing, lasers, optical filters and optical recording. Organic materials are frequently formed by weak van-der Waals and hydrogen bonds; hence possess a high degree of delocalization.

The presence of electron donor or acceptor substituents attached to the molecular structure could stimulate the asymmetric electronic distribution and enhance the NLO properties [27]. Some Quantum chemical descriptions (QCDs) can be used in the determination of theoretical NLO properties **Table 5.**

NLO activity increases with an increase in energy of HOMO, softness, polarisability, electronic delocalisation and additional electronic charges of the compounds and decreases in the energy of LUMO, HOMO-LUMO energy gap, global electronegativity. NLO capabilities of the compounds are compared with the calculated quantum chemical parameters of urea as a standard reference **Table 6**.

The first hyperpolarizability of the compounds 6a-f were greater than that of urea, hence the titled molecules can have considerable NLO activity. β_{total} for the compound 6d is 67.3 times higher compared to urea, this is because the compound possess better charge transfer character due to the electron rich substituents.

TABLE 5: QUANTUM CHEMICAL DESCRIPTION OF THE TITLED COMPOUNDS

Parameters	6a	6b	6c	6d	6e	6f
E_{HOMO}	-5.4367	-6.5401	-6.4416	-5.666	-5.3619	-5.1839
E_{LUMO}	-1.9940	-0.8179	-0.5915	-2.2318	-1.9872	-1.7551
E_{HOMO}- E_{LUMO}	-3.4427	-5.7222	-5.8500	-3.4343	-3.3747	-3.4288
Ionization Energy (I)	5.4367	6.5401	6.4416	5.6661	5.3619	5.1839
Electron Affinity(A)	1.9940	0.8179	0.5915	2.2318	1.9872	1.7551
Absolute electro negativity(χabs)	3.7153	3.6790	3.5166	3.9489	3.6745	3.4695
Absolute hardness(η)	1.72136	2.8611	2.9204	1.7171	1.6873	1.7144
Absolute softness(σ)	0.58093	0.34951	0.3418	0.5823	0.5926	0.5832
Optical softness(σ_0)	-0.2904	-0.1747	-0.17093	-0.2911	-0.2963	-0.2916
Global softness(S)	7.90388	4.7553	4.6513	7.9233	8.0632	7.9358
Chemical potential(μ)	-3.7153	-3.6790	-3.5166	-3.9489	-3.6745	-3.4695

Electrophilicity index(ω)	4.0096	2.3654	2.113	4.5408	4.0010	3.5107
Nucleophilicity index(N)	0.24939	0.4227	0.4730	0.2202	0.2499	0.2848
Additional electronic charge(ΔN_{max})	2.1583	1.2858	1.2022	2.2997	2.1777	2.0237
E_{HOMO}-1	-6.2685	-6.6500	-6.4416	-6.4324	-6.0985	-5.8193
E_{LUMO}+1	-1.0027	0.0410	-0.5915	-1.2753	-0.9510	-0.6976
E_{LUMO}+1- E_{HOMO}-1	-5.2658	-6.6920	-5.8500	-5.1570	-5.1475	-5.1216

TABLE 5: NLO CONSTRAINTS RESEMBLING STATIC DIPOLE MOMENT (M_0), MEAN POLARIZABILITY $|\alpha_0|$, ANISOTROPY OF POLARIZABILITY (ΔA_0), FIRST HYPERPOLARIZABILITY B_0 OF THE COMPOUNDS

Parameters	6a	6b	6c	6d	6e	6f
Dipole Moments						
μ_x	-0.5535	1.9772	-0.9904	1.2002	-2.0224	2.8812
μ_y	3.4186	3.9324	3.2863	1.4627	1.8486	2.3209
μ_z	1.1019	1.1300	1.0837	1.0861	1.3571	-0.2917
μ_0 [Debye]	3.6341	4.5442	3.5994	2.1816	3.0576	3.7111
Polarizability						
α_{xx}	-124.0030	-157.1987	-123.9908	-187.26	-145.364	-148.2871
α_{yy}	-170.1699	-176.2743	-173.7763	-201.37	-95.05	-208.20
α_{zz}	-169.5325	-177.7853	-172.3478	-193.21	-43.79	-194.29
$\|\alpha o\|$	154.56	170.41	156.70	193.95	94.7391	183.59
$\|\alpha o\|$ [10^{-24}esu]	2.290	2.525	2.3223	2.874	1.404	2.720
$\Delta\alpha_0$	45.8515	19.8742	49.0868	12.26	87.95	54.31
$\Delta\alpha_0$[10^{-24}esu]	6.7952	2.9453	7.2746	1.818	13.035	8.049
Hyperpolarizability						
β_{xxx}	-23.2191	247.5037	-36.0873	-181.94	-154.12	-272.08
β_{xxy}	-26.2496	-6.4450	-37.9921	-120.06	-95.05	-64.18
β_{xyy}	-17.7288	-21.6095	-11.8220	-54.73	43.79	56.22
β_{yyy}	78.8637	75.2688	73.5749	31.64	30.10	22.42
β_{xxz}	-9.0299	-3.1739	-5.2839	-2.40	3.96	58.09
β_{xyz}	12.4221	12.4481	10.7817	15.64	11.75	17.55
β_{yyz}	8.9674	6.4676	7.1578	4.66	7.52	-6.07
β_{xzz}	13.0584	-6.7678	3.2337	3.186	8.78	9.68
β_{yzz}	-12.3660	-13.5168	-13.3308	-6.64	-5.88	-5.83
β_{zzz}	0.0547	0.1751	-0.5237	0.4468	0.848	-0.576
β_0	86.74	328.79	70.68	151.92	125.53	294.40
β_0[10^{-30}esu]	7.493	2.840	0.611	13.12	1.084	2.54

According to the previous reports the NLO properties of the studied compounds were listed below.

A. Dipole moment 6b > 6f>6a > 6c >6e>6d urea(1.3197 D)

B. Polarizability 6e>6f>6c > 6a > 6b>6d>urea (30.937 a.u.)

C. Hyperpolarizability 6d>6a> 6b>6f> 6e>6c> urea (0.1947×10^{-30}esu)

D. E_{HOMO} 6f>6e>6a >6d> 6c > 6b > urea (-9.051 eV)

E. E_{LUMO} 6c > 6b >6f>6e> 6a > 6d>urea (0.168 eV)

F. E_{gap}6e>6f>6d>6a > 6b > 6c > urea (9.219 eV)

G. Absolute hardness 6c > 6c> 6a >6d>6f>6e>urea (4.610 eV)

H. Absolute electronegativity 6d> 6a > 6b >6e> 6c >6f>urea (4.441 eV)

From this, the 6c, 6d, 6e exhibit better NLO activity and other compounds also exhibit significant NLO activity when compare with the standard reference material (urea).

Vibrational Assignment: The spectroscopic signature of the titled compounds was performed by FT-IR spectra. The theoretical vibrational frequency of the compound 6a, 6b, 6d, 6f was calculated using the B3LYP/6-311G method. The experimental and theoretically calculated FTIR (KBr) spectrum of the compounds shows a good agreement with the calculated values **Fig. 5.**

The carbonyl stretching band is expected in the range of 1750-1680 cm^{-1} [28]. In the above mentioned compounds, the C=O stretching vibrations are recorded at 1621, 1669, 1661 and 1678 cm^{-1} respectively.

The shifting of the C=O towards the lower wavelength due to the interaction of carbonyl oxygen with the lone pair electron of the sulphur atom, which is shown by (LP(1)O→ $\sigma^*(S_6\text{-}C_7)$→1.57 Kcal/mol). The C-H stretching vibration is expected to appear within the range 3100-3000 cm^{-1} [29]. The C-H stretching vibration of the titled compounds was observed at 3068, 3087 and 3095 cm^{-1} in the FTIR spectrum.

The stretching vibration of the amino group appeared around 3500-3000 cm^{-1} in IR spectra [30]. The NH_2 asymmetric and symmetric stretching vibrations of the targeted compounds were observed experimentally at 3446, 3479, 3445 and 3444 cm^{-1} respectively.

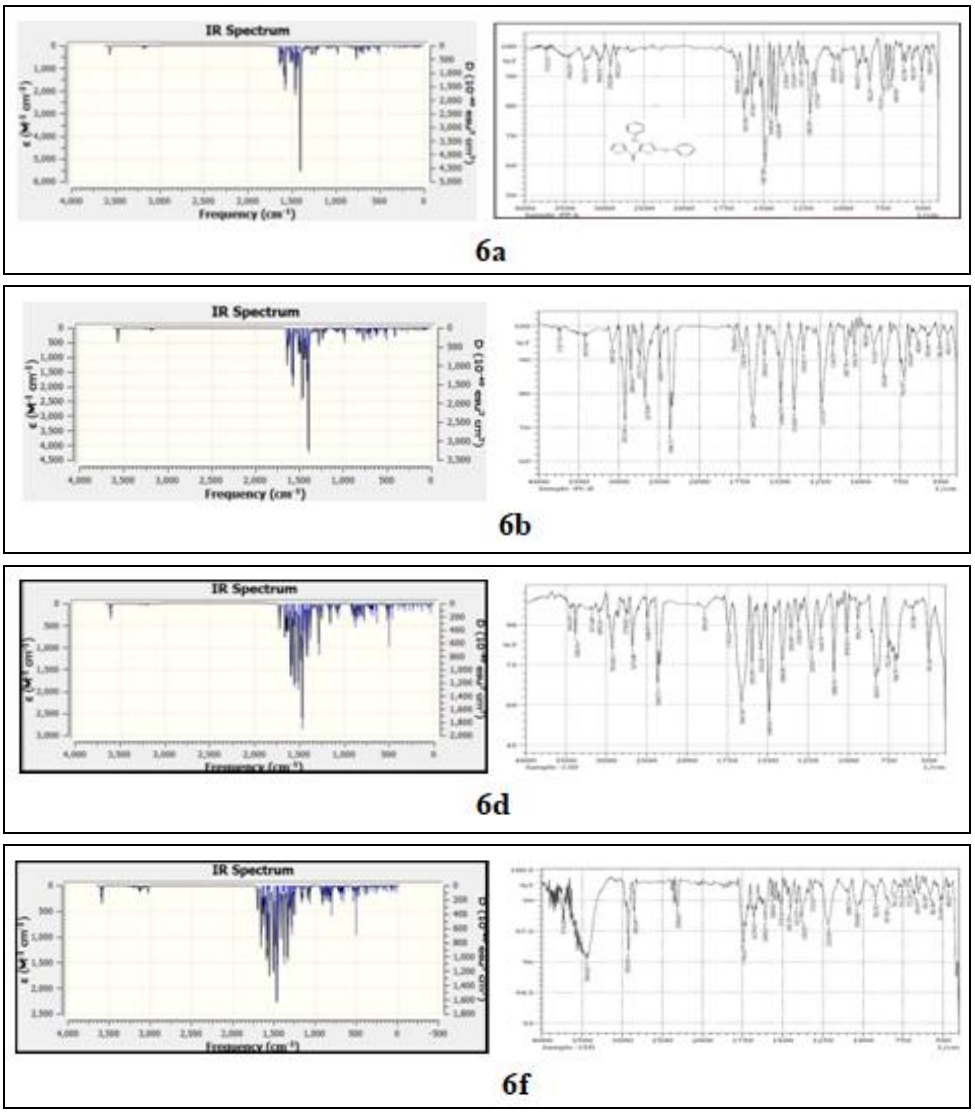


FIG. 5: VIBRATIONAL ANALYSIS OF THE COMPOUNDS 6A, 6B, 6D, 6F

In-vitro **Antibacterial Activity:** All the synthesized compounds (6a-f) were screened for their antimicrobial activities against two gram-positive (*Staphylococcus aureus and Bacillus subtilis*) and two gram-negative (*E. coli* and *Pseudomonas aeruginosa*) bacteria using an agar well diffusion method and *Streptomycin* was used as a reference compound in this assay. The results, that is, the Zone of inhibition (mm), obtained were presented in **Table 7**. Most of the compounds displayed moderate to reasonable activities against all bacterial strains. Certainly, the compound 6f was identified as the most capable among these compounds as it exhibited good activity against

both Gram-positive and Gram-negative bacterial species. Without a doubt, the compound 6f showed significant inhibitory activity against *E. coli* with 15 mm and *Staphylococcus aureus* with 16 mm were comparable to the reference compound *Streptomycin*. Among other compounds 6b, 6c, and 6d also showed activities against Gram-positive and Gram-negative bacteria. Moreover, compound 6a and 6e also showed good activity against gram-negative strain. However, the structure activity relationship (SAR) summary of anti-bacterial activities of compound 6 is presented in **Fig. 6**. It is evident that the activity was varied with the change of position and nature of "R" group attached to the benzene ring connected to the thiazole moiety via a phenyl linker. Good activity was observed when the R group presented methyl, ethoxy and hydrogen whereas activity was reduced when R group existing as chloro atom **Fig. 7**.

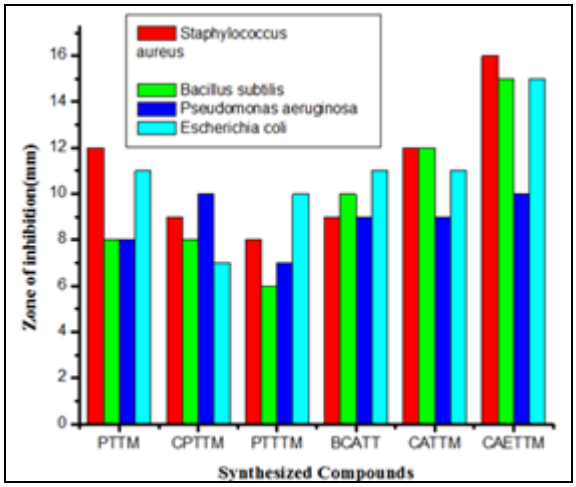


FIG. 6: ANTIBACTERIAL ACTIVITIES OF THE SYNTHESIZED COMPOUNDS AGAINST GRAM-POSITIVE & GRAM-NEGATIVE BACTERIAL STRAINS

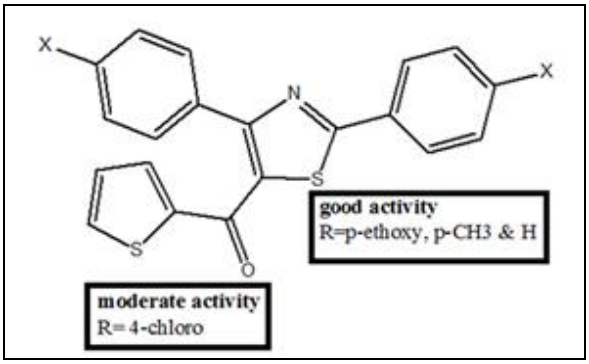


FIG. 7: SAR SUMMARY OF ANTIBACTERIAL ACTIVITIES OF THE COMPOUND 6 AGAINST 3IP4 AND 1KEB RECEPTOR

TABLE 7: ANTIBACTERIAL SCREENING OF THE SYNTHESIZED COMPOUNDS

Compounds	Microbial strains			
	Staphylococcus aureus **(G+) MTCC 916**	***Bacillus subtilis*** **(G+) MTCC 1134**	***Pseudomonas aeruginosa*** **(G-) MTCC 741**	***Escherichia coli*** **(G-) MTCC 1671**
	Zone of inhibition (Millimetre in diameter)			
6a	12	8	8	11
6b	9	8	10	7
6c	8	6	7	10
6d	9	10	9	11
6e	12	12	9	11
6f	16	15	10	15
Control (streptomycin)	15	16	15	16

G+ (Gram Positive Organism), G-(Gram Negative Organism)

Molecular Docking: The molecular docking results reveal that the investigated heterocyclic compounds were forming stable complexes with studied receptors (3PI4 and 1KEB) through non covalent interactions like hydrogen bonding, hydrophobic and van der Waals interactions **Fig. 8** and **9**.

The docking calculations show that the binding affinity values of the studied compounds 6a-f towards 3IP4 receptor are -303.29, -307.97, -295.65, -323.62, -336.75 and -331.23 kcal mol^{-1} respectively **Table 8**.

Whereas these compounds against IKEB receptor shows the corresponding binding affinities are -265.95, -285.41, -276.34, -291.97, -298.55 and -309.31 kcal mol^{-1} respectively **Table 9**.

The more negative the relative binding, the stronger the binding between protein and target molecules [31]. Therefore, the 6e compound is the most strongly binding to 3IP4 receptor and the compound 6f binds strongly the 1KEB receptor. These docking results were show good agreement with the experimental findings.

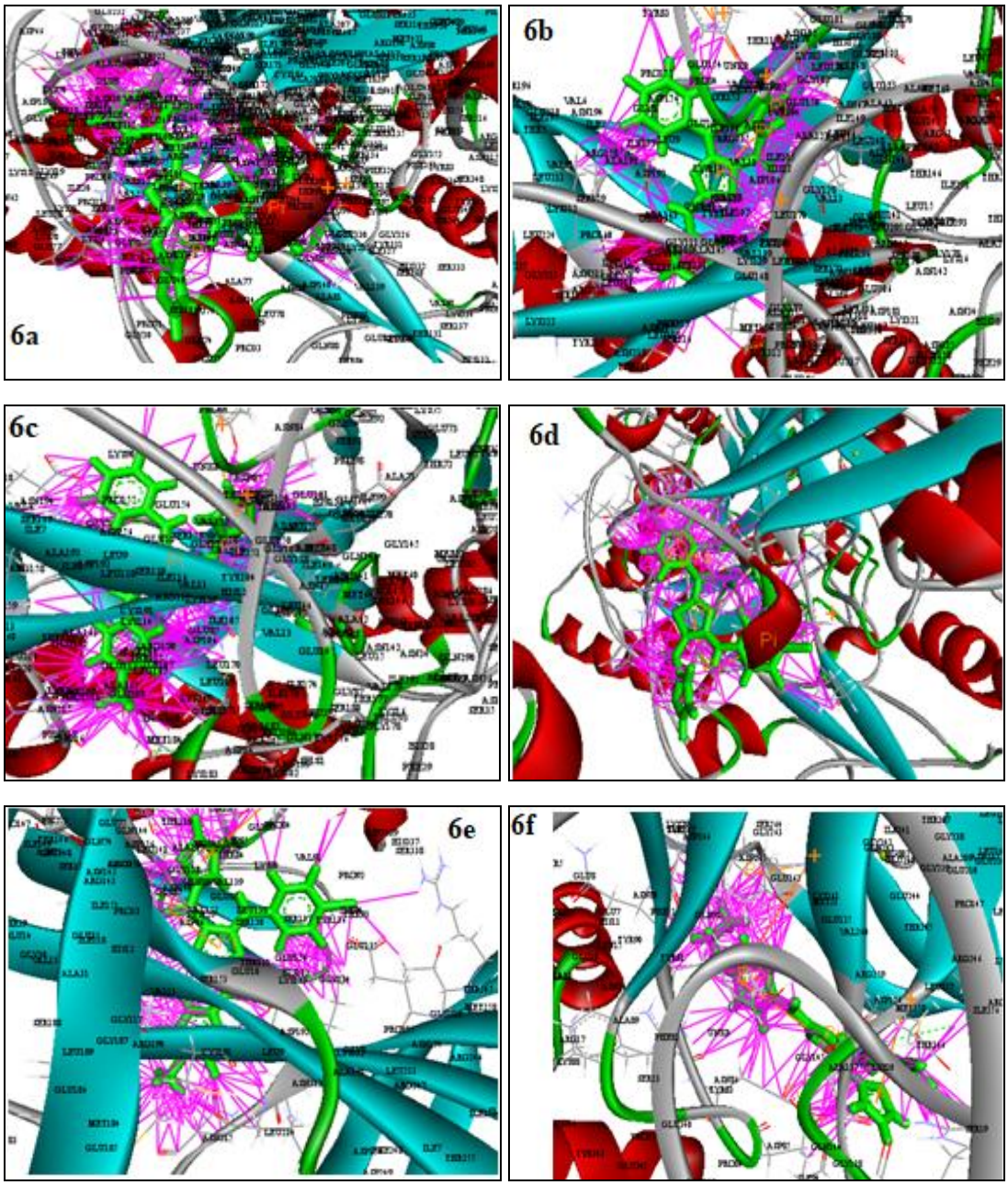


FIG. 8: DOCKING POSSESS OF THE TITLED COMPOUNDS AND THE RECEPTOR 3IP4

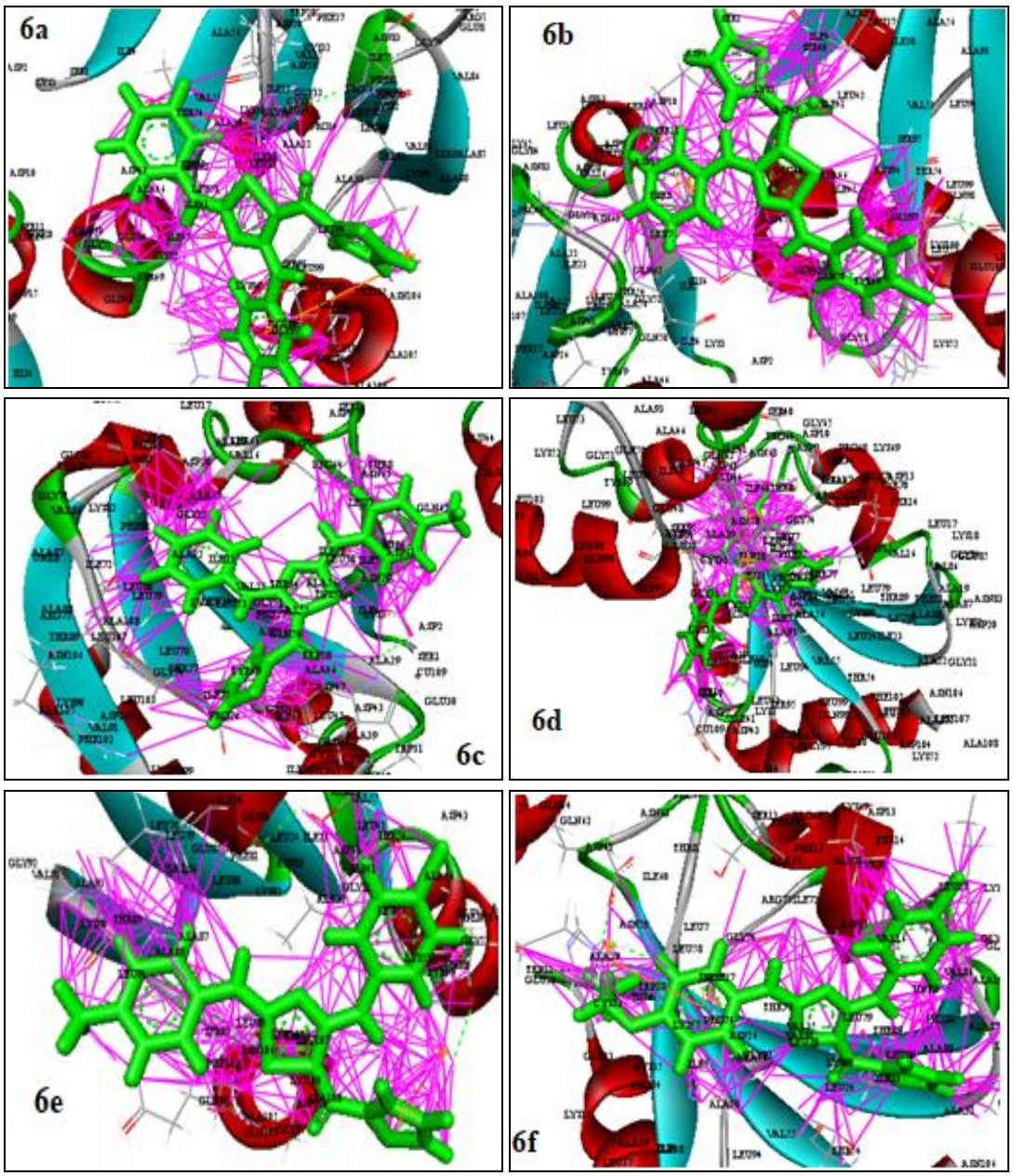


FIG. 9: DOCKING POSSESS OF THE TITLED COMPOUNDS AND THE RECEPTOR 1KEB

TABLE 8: DOCKING SCORE AND INTERACTION OF THE COMPOUNDS WITH THE PROTEIN 3IP4

Comp.	Binding Energy (KJ/mol)	Active sites of interactions					
		π- σ interactions	π-cation interactions	π-π interactions	Electrostatic	Vanderwaals	Metal
6a	-303.29	-	ARG B:143	PHE B:29	HIS B:28	ARG B:143	-
6b	-307.97	-	LYS B:79, MG C:802	HIS B:12	ARG B:190, HIS B:12	LYS B:79	MG C:802
6c	-295.65	-	LYS B:79, MG C:802	HIS B:12	ARG B:190, HIS B:12, GLN B:91	LYS B:79	MG C:802
6d	-323.62	ALA B:27	ARG B:143	PHE B:29	ALA B:27, HIS B:28, PHE B:29, THR B:17, ARG B:143	-	-
6e	-336.75	-	LYS B:79	HIS B: 12	GLN B:91, HIS B:12, ARG B:190	LYS B:79	MG C:802
6f	-331.23	-	LYS B:212	TYR B:83, TYR B:81	ARG B: 143, LYS B:212, TYR B:83, TYR B:81	-	-

TABLE 9: DOCKING SCORE AND INTERACTION OF THE COMPOUNDS WITH THE PROTEIN 1KEB

Comp.	Binding Energy (KJ/mol)	Active sites of interactions				
		π- σ interactions	**π-cation interactions**	**π-π interactions**	**Electrostatic**	**Vanderwaals**
6a	-265.95	-	LYS B:82	-	LYS B:52, ALA B:22	LYS B:82
6b	-285.41	-	LYS B:3	-	LYS B:3	-
6c	-276.34	-	-	-	ASP A:61, TRP A:31	ILE A:75, ARG A:73, GLY A:74
6d	-291.97	-	LYS B:96	-	GLU B:44, ASP A:15	LYS B:96
6e	-298.55	-	LYS B:96	-	LYS B:96	ALA B:93, LEU B:37
6f	-309.31	-	LYS B:96	-	LYS B:96, ASP A:15	-

CONCLUSION: In summary, we have synthesized substituted (2,4-bis (phenylamino) thiazol-5-yl) (thiophen-2-yl) methanone compounds and characterized by various analytical and spectral techniques. The electronic structures of the heterocyclic compounds were optimized by solving self –consistent field equation obtained by DFT/B3LYP method with standard 6-311G basis set. NBO analysis performed to define the intra-molecular interaction and delocalization of electron density within the molecule. The reduction of HOMO-LUMO energy gap value has large influence on the intramolecular charge transfer and bioactivity of the molecule 6f. All the compounds exhibit good NLO activity among this 6c, 6d, and 6e are considered as good NLO candidates. The experimental vibrational spectrum of the compounds shows a good agreement with the theoretical vibrational frequencies. The titled compounds were investigated for their *in-vitro* antibacterial activity against *Staphylococcus aureus, Bacillus subtilis, Pseudomonas aeruginosa*, and *Escherichia coli*. From this the introduction of ethoxy group in the phenyl ring ((4-((4-chlorophenyl) amino)-2-(4-ethoxyphenyl) amino) thiazol-5-yl) (thiophen-2-yl) methanone) 6f enhances the antibacterial activity than the other substituted heterocycles. The bimolecular docking results were show good agreement with the experimental antimicrobial activities.

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