

Synthesis, computational and biological activities of 2-[2-(4-arylamino)-4-methylphenylaminothiazol-5-oyl]naphthalenes

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2-[2-(4-Arylamino)-4-methylphenylaminothiazol-5-oyl]naphthalenes have been synthesized by the reaction of 2-bromoacetyl naphthalene and 1-aryl-3-(N,N¹-diarylamidino)thiourea in the presence of triethyl amine. The structures of the newly synthesized analogues have been confirmed by spectroscopic techniques. The *in vitro* antioxidant activity has been studied using DPPH assay and anticancer activity has been studied using MTT assay against cancer cells. *In silico* studies have been performed to predict the binding modes of the compounds with the cyclin-dependent kinase protein 6WUU. It is evident from the current results that all the synthesized compounds exhibit remarkable antioxidant and anticancer potential.

Keywords: Naphthalene, B3LYP/6-31G, DFT, SARS-CoVPLpro, Mulliken, DPPH, MTT

Natural products have been the most productive source of leads for the development of drugs. They possess an enormous range of unique structures and a valuable source of drug regimens that form the cornerstone of modern pharmaceutical care¹. Naphthalene constitutes a flexible and multifaceted platform in medicinal chemistry. This scaffold emerges as a promising moiety in drug design due to its diverse biological activities generated from structural modifications². Various antagonistic activities were reported for naphthalene-based compounds such as antimicrobial, anticancer, antiviral, anticonvulsant, antitubercular, and anti-inflammatory³.

Among the various types of heterocyclic compounds, thiazole derivatives have received considerable attention towards synthetic medicinal chemists as they are endowed with wide range of therapeutic properties and applications⁴. Compounds containing thiazole nucleus are unique molecules reported to possess an array of biological activities such as antibacterial, antifungal, antitumor, anti-inflammatory, anticonvulsant, anthelmintic activity, *etc.*⁵

Thiazoloyl naphthalene derivatives are fascinating chemical products used in the field of medicine as they have been found to possess a wide spectrum of biodynamic properties^{6,7}. Thiazoloyl naphthalene analogs have been attracted a great deal of interest due

to their biological and commercial importance⁸. The study of naphthoyl thiazoles is therefore, of practical and theoretical importance. A series of naphthalene derivatives were synthesized and found to possess a wide spectrum of biological activity. Accordingly, the synthesis and bioactivity screening of 2-[2-(4-arylamino)-4-methylphenylaminothiazol-5-oyl]naphthalenes have been reported in the present work.

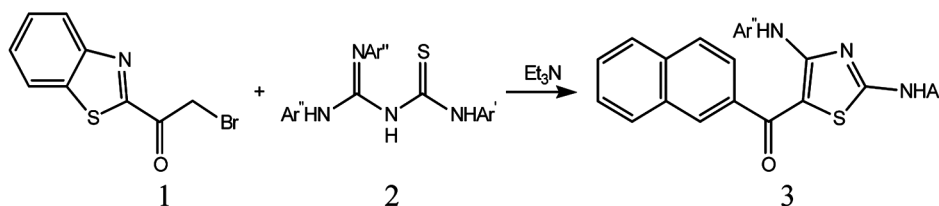
Experimental Section

The reagents and solvents used were of AR grade and purchased from Sigma-Aldrich and were used without further purification. NMR spectra (400MHz for both ¹H NMR and ¹³C NMR) and ESI-mass spectra were carried out at Central Drug Research Institute, Lucknow, India. FT-IR were recorded from the Instrumentation Centre, Ayya Nadar Janaki Ammal College, Sivakasi. The progress of the reactions were checked by thin layer chromatography (TLC) on pre-coated silica gel plates (Merck Co.).

The novel naphthoyl thiazole derivatives were synthesised according to Scheme 1.

Preparation of 1-aryl-3-(N,N¹-di(4-methylphenyl)amidino)thioureas

1-Aryl-3-(N,N¹-di(4-methylphenyl)amidino)thioureas was obtained from N,N¹-di(4-methylphenyl)guanidine



Scheme 1

and aryl isothiocyanates. The required N,N' -di(4-methylphenyl)guanidine could be obtained by the reaction between 4-methylphenyl cyanamide and 4-methylaniline hydrochloride. These N,N' -di(4-methylphenyl)guanidine on treatment with aryl isothiocyanates afforded 1-aryl-3-[(N,N' -di(4-methylphenylamidino))]thioureas in 70% yield.

Synthesis of 2-[2-(2-arylamino-4-(4-methylphenylamino)thiazol-5-oyl)naphthalenes

The reaction of 2-bromoacetylnaphthalene with 1-aryl-3-(N,N' -di(4-methylphenyl)amidino)thiourea in the presence of triethylamine afforded a yellow solid. Crystallisation from ethanol-water (2:1) gave a yellow crystalline compound.

DFT Calculation

The vibrational frequencies of the substances are observed to be real because of the actual minimum in the potential energy surface, which is positive and provides the optimum geometries. Electronic characteristics such as ionisation potential, electron affinity, hardness, softness, and electronegativity were discovered. It was possible to derive structural parameters such as bond angles, bond lengths, and dihedral angles^{9,10}.

$$\mu = -\chi = -(\delta E/\delta N) V(r) \quad \dots (1)$$

$$\chi = -\mu = (I+A)/2 \quad \dots (2)$$

$$\chi_{\text{Koopmans}} = (E_{\text{HOMO}} + E_{\text{LUMO}})/2$$

$$\omega = \mu/2\eta \quad \dots (3)$$

Hardness is defined as

$$\eta = \frac{1}{2} (\delta^2 E/\delta N^2) V(r) \quad \eta = \frac{1}{2} (I - A) \quad \eta = \frac{1}{2} (E_{\text{LUMO}} - E_{\text{HOMO}})$$

By using the above equations (1), (2) and (3), the chemical potential, hardness and electrophilicity index have been calculated^{11,12}.

Protein structure preparation

The suitable protein was downloaded from Protein Data Bank (PDB: <http://www.rcsb.org/pdb/home/home.do>) 6WUU is PDB id of the target protein SARS-CoV PLpro.

Preparation of ligands

Five synthesized compounds were selected as ligand based on their biological activities. Then the 2D structure of these compounds are converted into 3D structures with the help of ACD/ChemSketch 1.1. It explores ways in which two molecules, such as drugs and an enzyme SARS-CoV PLpro (COVID-19 cell line) receptor fit together and dock each other well. The molecules binding to a receptor, inhibit its function and thus act as a drug¹¹. Naphthalene thiazoles and receptors were selected *via* docking and their stabilities were estimated by molecular dynamics and their binding affinities by employing free energy imitations.

Antioxidant effect by DPPH Method

DPPH 1 mg in 10^{-5} mol ethanol was prepared in 250 mL standard flask (control 2.8 mL of this solution+0.05 mL ethanol). 2-[2-(2-arylamino-4-(4-methylphenylamino)thiazol-5-oyl)naphthalene solutions of different concentrations (0.1, 0.25, 0.5, 0.75, 1mM) were prepared. BHA (standard) solutions of different concentrations (0.1, 0.25, 0.5, 0.75, 1 mM) were prepared. The absorbance of the control and the test solutions were recorded out at 517nm. By following similar procedure the absorbance will be measured for BHA solutions. From the absorbance values, % of inhibition was calculated¹². Then the % of inhibition was plotted against concentrations for different samples as well as BHA. The % reduction and IC_{50} were calculated. The IC_{50} value indicates that less IC_{50} is a more antioxidant capacity. The standard BHA shows the IC_{50} value of 624 μ M.

$$\% \text{ inhibition} = \frac{\text{Control absorbance} - \text{Sample absorbance}}{\text{Control absorbance}} \times 100$$

The antioxidant properties of all new compounds were studied and the results were correlated to the nature of the heterocyclic moiety attached to the C-5 of the thiazole, and the substituent present in C-2 position.

Anticancer effect by MTT Method

3-[4,5-dimethylthiazol-2-yl]2,5-diphenyltetrazolium bromide (MTT) is a yellow water soluble tetrazolium salt. A mitochondrial enzyme in living cells, succinate-dehydrogenase, cleaves the tetrazolium ring, converting the MTT to an insoluble purple formazan. Therefore, the amount of formazan produced is directly proportional to the number of viable cells. After 48h of incubation, 15 μ L of MTT (5 mg/mL) in phosphate buffered saline (PBS) was added to each well and incubated at 37°C for 4h. The medium with MTT was then flicked off and the formed formazan crystals were solubilized in 100 μ L of DMSO and then measured the absorbance at 570 nm using micro plate reader. Nonlinear regression graph was plotted between % Cell inhibition and Log concentration and IC₅₀ was determined¹³.

Anti-bacterial studies

An anti-bacterial agent is a compound that kills or slows down the growth of bacteria. The successful outcome of antimicrobial therapy with antibacterial compounds depends on several factors. The inoculum suspension of each bacterial strain was swabbed on the entire surface of Zobel marine agar plates, sterile 6-mm filter paper disks, 100 μ g of the compound was loaded in discs and placed on the Zobel marine agar plate which were previously impregnated with the compounds dissolved in the solvent chloroform, were aseptically placed on ZMA surfaces. Sterile paper disks impregnated with 10% DMSO were used as the negative controls, whereas a disk containing penicillin was placed in the plate as a positive control. The plates were left at ambient temperature for 15 min to allow excess pre diffusion of extracts prior to incubation at 37°C for 24h. Diameters of inhibition zones were measured.

Results and Discussion

2-[(2-Phenylamino-4-(4-methylphenylamino)thiazol)-5-oyl]naphthalene, 3a: Yellow solid. Yield 67%. Mol. Wt. 435.14. IR (KBr): 3083 (C-H), 1686 (C=N), 1609 cm⁻¹ (C=O); ¹H NMR (DMSO-*d*₆): δ 1.567(s, 3H, CH₃), 7.194-7.397(m, 4H, ArH), 7.404-7.455(m, 4H, ArH), 7.505(s, 1H, -NHAr), 7.598(t, *J*=2.6Hz, 1H, ArH), 11.011(s, 1H, -NH). 8.846(s, 1H, H-1 of naphthalene), 7.521(d, *J*=6.8Hz, 2H, H-2, H-3 of naphthalene), 7.365 – 7.516(m, 4H, H-4, H-5, H-6 and H-7 of naphthalene). Anal. Calcd for

C₂₇H₂₁N₃OS: C, 75.01; H, 5.02; N, 9.58; O, 4.06; S, 6.99. Found: C, 74.46; H, 4.86; N, 9.65; O, 3.67; S, 7.36%.

2-[(2-Chlorophenylamino-4-(4-methylphenylamino)thiazol)-5-oyl]naphthalene, 3b: Yellow crystalline solid. Yield 72%. Mol. Wt. 469.99; IR (KBr): 3099 (C-H), 1713 (C=N), 1680 cm⁻¹ (C=O); ¹H NMR (DMSO-*d*₆): δ 2.354(s, 3H, CH₃), 8.463(s, 1H, H-4 of naphthalene), 7.788(d, *J*=13.6Hz, 1H, H-5 of naphthalene), 7.913-8.012(m, 2H, H-6 and H-8 of naphthalene), 6.995(d, *J*=4.4Hz, 2H, ArH), 7.096(d, *J*=1.2Hz, 2H, ArH), 7.102-7.151(m, 4H, ArH), 9.775(s, 1H, -NH), 10.09(s, 1H, -NH). Anal. Calcd for C₂₇H₂₀N₃OS: C, 71.02; H, 4.84; Cl, 8.12; N, 9.03; O, 4.00; S, 6.93. Found: C, 69.00; H, 4.29; Cl, 7.54; N, 8.94; O, 3.40; S, 6.82%.

2-[(2-Methylphenylamino-4-(4-methylphenylamino)thiazol)-5-oyl]naphthalene, 3c: Yellow solid. Yield 72%. Mol. Wt. 449.09; IR (KBr): 3092 (C-H), 1686 (C=N), 1650 cm⁻¹ (C=O); ¹H NMR (DMSO-*d*₆): δ 2.488(s, 6H, 2CH₃), 7.030(t, *J*=1.9Hz, 1H, ArH), 7.096(t, *J*=7.8Hz, 2H, ArH), 7.145(d, *J*=3.4Hz, 2H, ArH), 7.318(d, 2H, ArH), 7.345(d, *J*=7.2Hz, 2H, ArH), 8.289(s, 1H, H-4 of naphthalene), 7.921(d, *J*=12.4Hz, 1H, H-5 of naphthalene), 7.357 – 7.487(m, 4H, H-6, H-7 and H-8 of naphthalene), 8.312(s, 1H, -NH), 8.739, 11.895(s, 1H, -NH). Anal. Calcd for C₂₇H₂₃N₃OS: C, 73.24; H, 5.09; N, 10.20; O, 4.03; S, 6.87. Found: C, 74.81; H, 5.16; N, 9.35; O, 3.56; S, 7.13%.

2-[(2-Methoxyphenylamino-4-(4-methylphenylamino)thiazol)-5-oyl]naphthalene, 3d: Yellow solid. Yield 67%. Mol. Wt. 465.57; IR (KBr): 3083 (C-H), 1686 (C=N), 1609 cm⁻¹ (C=O); ¹H NMR (DMSO-*d*₆): δ 1.244(s, 3H, CH₃), 3.043(s, 3H, -OCH₃), 7.172(d, *J*=3.2Hz, 2H, ArH), 7.189(d, *J*=1.9Hz, 2H, ArH), 7.215(t, *J*=2.6Hz, 2H, ArH), 7.334(t, *J*=10.8Hz, 1H, ArH), 7.379(d, 2H, *J*=12.4Hz, ArH), 8.153(s, 1H, H-4 of naphthalene), 7.978(d, *J*=8.4Hz, 2H, H-2, H-3 of naphthalene), 7.702 – 7.804(m, 4H, H-4, H-5, H-6 and H-7 of naphthalene), 8.324(s, 1H, -NH), 10.583(s, 1H, -NH). Anal. Calcd for C₂₇H₂₃N₃OS: C, 71.46; H, 5.03; N, 10.12; O, 6.69; S, 6.78. Found: C, 72.23; H, 4.98; N, 9.03; O, 6.87; S, 6.89%.

2-[2-(2-Ethoxyphenylamino-4-(4-methylphenylamino)thiazol)-5-oyl]naphthalene, 3e:

Orange solid. Yield 69%. Mol. Wt. 479.59; IR (KBr): 3215 (C-H), 2307 (C=N), 1760 (C=C), 1220 (C=N), 1682 cm^{-1} (C=O); $^1\text{H NMR}$ (DMSO- d_6): δ 1.244 (s, 3H, CH_3), 1.411 (t, $J=3.45$ Hz, 3H, CH_3), 4.098 (q, $J=1.8$ Hz, 2H, $-\text{OCH}_2$), 6.589 (d, $J=8.7$ Hz, 2H, 2ArH), 6.855-7.392 (m, 10H, 6ArH, H-4, H-7, H-5, H-6, 8.352 (s, 1H, H-4 of naphthalene), 7.978 (d, $J=8.4$ Hz, 2H, H-2, H-3 of naphthalene), 7.702 – 7.804 (m, 4H, H-4, H-5, H-6 and H-7 of naphthalene), 9.137 (s, 1H, NH), 11.876 (s, 1H, NH). Anal. Calcd for $\text{C}_{27}\text{H}_{25}\text{N}_3\text{OS}$: C, 73.20; H, 4.98; N, 9.62; O, 6.88; S, 6.39. Found: C, 72.63; H, 5.25; N, 8.76; O, 6.67; S, 0.69%.

Optimized geometry

Optimizations of the synthesized compounds have been carried out using the DFT/B3LYP methods with

the 6-31G(d,p) basis sets. The optimized structure in theoretical is shown in Figure 1. The calculated geometric parameters are obtained in Table 1. The C-C bond lengths of naphthalene ring were obtained at about ~ 1.39 Å for 6-31G (d,p) basis set. The above data shows that there is conjugation of electrons in naphthalene ring like in benzene ring that means it has no distinction of single bond or double among these bonds. As the size of atom increases, bond length also increases. Example for the derived compound 2-[2-(4-arylamino)-4-methylphenylaminothiazol-5-oyl] naphthalene containing, C-N, C-C and C-S bonds, the size of sulfur atom is bigger than all other atoms carbon and nitrogen hence the bond length is greater for sulfur in this compound. The order of bond length is $\text{C-S} > \text{C-N} > \text{C-C}$. On the basis of these results, it may be finalized that the B3LYP/6-31G (d,p) method well reproduce the geometry for the naphthalene derivatives.

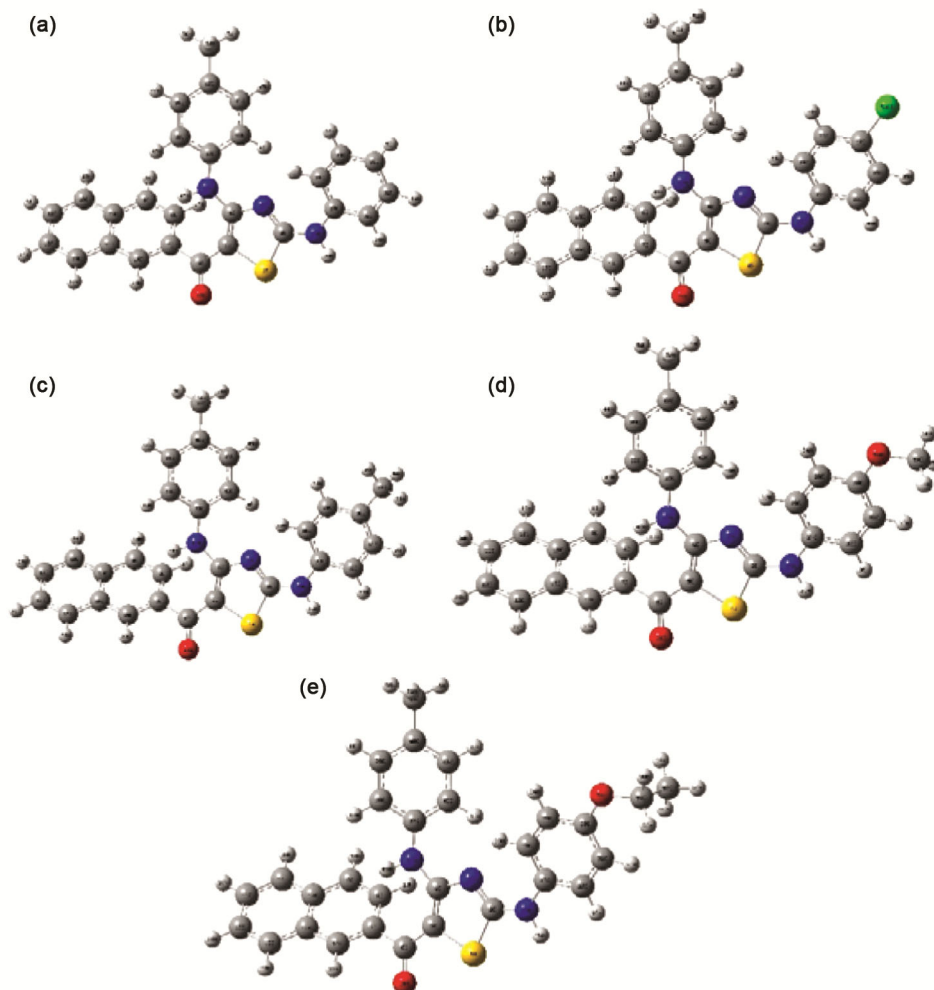


Fig. 1 — Optimized Structure of 2-[2-(4-arylamino)-4-methylphenylaminothiazol-5-oyl]naphthalene

Table 1 — Geometrical parameters of 2-[2-(4-arylamino)-4-methylphenylaminothiazol-5-oyl]naphthalene

Position	Parameter	3a	3b	3c	3d	3e
Thiazole	C - N	1.3536	1.3566	1.3538	1.3563	1.3562
Thiazole	C = N	1.3107	1.3098	1.3109	1.3196	1.3197
Thiazole	C - S	1.8563	1.8527	1.8564	1.8461	1.8463
Thiazole	C - H	1.0786	1.0782	1.0783	1.0805	1.0809
Naphthalene	C - C	1.4048	1.4055	1.4048	1.4073	1.4077
Naphthalene	C - N	1.3493	1.3488	1.3491	1.3511	1.3511
Naphthalene	C - H	1.0845	1.0843	1.0842	1.0849	1.0849
Phenyl	C - C	1.4048	1.4056	1.4048	1.4032	1.4032
Phenyl	C - H	1.0854	1.0849	1.0856	1.0873	1.0871
Phenyl	C - Cl	—	1.8349	—	—	—
Chain	C - C	—	—	—	—	1.5191
Chain	C - N	1.4189	1.4153	1.4189	1.4223	1.4222
Chain	N - H	1.0168	1.0167	1.0168	1.0102	1.0102
Chain	C - O	—	—	—	1.3908	1.3896

Atomic charge distribution

The calculation of effective atomic charges involves figuring out each atom's electron population according to its definition in the basic functions. Based on the B3LYP/631G (d,p) model, the solvent effect for the atomic charge distributions of generated compounds. The majority of the atoms in carbon and nitrogen are negatively charged, while those in sulphur and hydrogen are positively charged. Positively charged atoms are an electron-donating group, whereas negatively charged species are electron acceptors. The most notable examples are the high positive charge of S1 (S1 0.534) and the large negative charge of N3 (-0.847). In the Mulliken population analysis, charges are calculated by equally dividing orbital overlap between the two atoms. The distribution of positive and negative charges determines whether the bond length between the atoms increases or decreases. Because of charges, dipole moments, molecule polarizability, electronic structure, acidity-basicity behaviour, and many other aspects of molecular systems, literature demonstrates that Mulliken charge calculations played a significant role in the application of chemical calculations to molecular systems (Figure 2).

HOMO-LUMO

The highest occupied molecular orbital (HOMO) and lowest unoccupied orbital (LUMO) are the two most important molecular orbitals. In chemical reactions HOMO and the LUMO are very important parameters. Primarily acting orbital HOMO is simply known as electron and the LUMO is commonly known as the electron acceptor. The molecular chemical stability can be characterized by the energy gap between HOMO and LUMO orbitals.

Determining the molecular electrical transport properties the energy gap between the HOMO and the LUMO molecular orbitals is a critical parameter because it is a measure of electron conductivity¹⁴. HOMO–LUMO energies and energy gap (ΔE) were calculated and the values are listed in Table 2. HOMO–LUMO energies divulge that the HOMO orbitals are derived from 3p orbitals of sulphur and 2p orbitals of nitrogen atoms present in the thiozole moiety. The LUMO orbitals are localized on the phenyl ring and 2p orbitals of nitrogen, oxygen and carbon present in the phenyl substitution.

Docking Study

The docking results concluded that hydrogen bonding interactions contributed significantly for its ligand binding and minimum binding affinity values (Table 3). In this article, all the pyridinyl derivative ligands shows highest binding efficiency with suitable protein hence it has high potential for anticancer drug (Figure 3). From the evidence further understanding the structures, their authenticity and biomolecular activity is obtained.

Antioxidant studies

The *in vitro* antioxidant activity of 2-[2-(4-arylamino)-4-methylphenylaminothiazol-5-oyl]naphthalene was evaluated using DPPH radical scavenging assay. DPPH is responsible for the absorbance at 517nm hence, decolouration can be quantitatively measured from the changes in absorbance at 517nm. The antioxidant activity of the synthesized compounds was compared with standard antioxidant (BHA). The results shows that the compounds 2-(butylamino)-4-(naphth-2-yl)thiazole(1d) exhibited significant antioxidant capacity (Table 4).

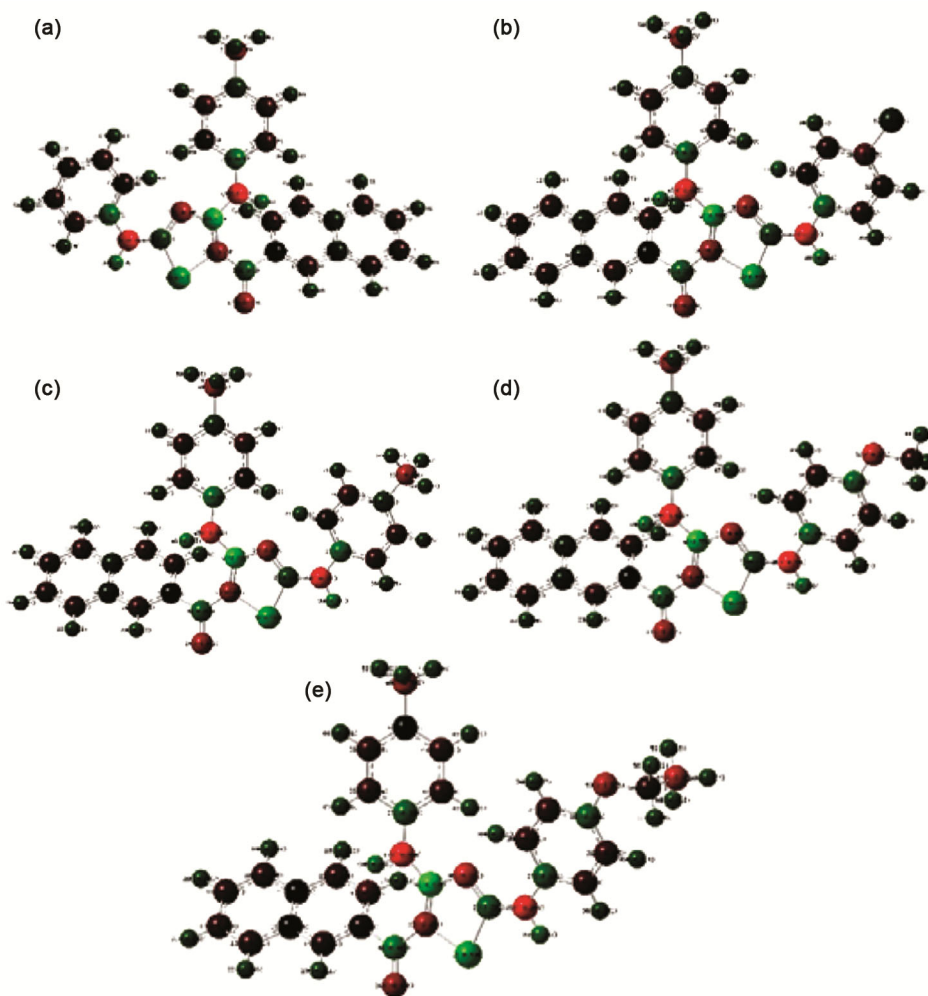


Fig. 2 — Mulliken's Atomic Charges of 2-[2-(4-arylamino)-4-methylphenylaminothiazol-5-oyl]naphthalene

Table 2 — Calculated electronic parameters of 2-[2-(4-arylamino)-4-methylphenylaminothiazol-5-oyl]naphthalene

Parameters	3a	3b	3c	3d	3e
Total Energy (a.u)	-1209.39	1666.80	-1254.90	-1330.08	-1369.42
Dipole Moment (debye)	2.5268	2.6211	3.1648	5.1547	5.2108
EHOMO	-0.25312	-0.26065	-0.24630	-0.25263	-0.25173
ELUMO	-0.04372	-0.05062	-0.03967	-0.04195	-0.04145
ΔE	0.2094	0.21003	0.20663	0.21068	0.21027
Electronegativity (χ)	0.1484	0.1556	0.14298	0.1472	0.1465
Ionisation Potential (I)	0.25312	0.26065	0.24630	0.25263	0.25173
Hardness (η)	0.1047	0.1050	0.1033	0.1053	0.1051
Softness (S)	4.7755	4.7619	4.8402	4.7483	4.7573

Table 3 — Binding affinity and residues of 2-[2-(4-arylamino)-4-methylphenylaminothiazol-5-oyl]naphthalene

Compd	Docking Score (Kcal/mol)	Residue involved in Hydrogen bonding
3a	-7.9	GLN-121, ILE-123, LEU-125
3b	-9.4	PHE-258, THR-259, LYS-306
3c	-8.6	SER-294, HIS-255, PRO-248
3d	-8.6	GLN-121, LEU-125, LYS-126
3e	-8.3	LYS-274, THR-247, LYS-217

Table 4 — Antioxidant Activity of 2-[2-(4-arylamino)-4-methylphenylaminothiazol-5-oyl]naphthalene

Compd	IC ₅₀ Value (μ M)
3a	76
3b	134
3c	271
3d	262
3e	192
Standard (BHA)	624

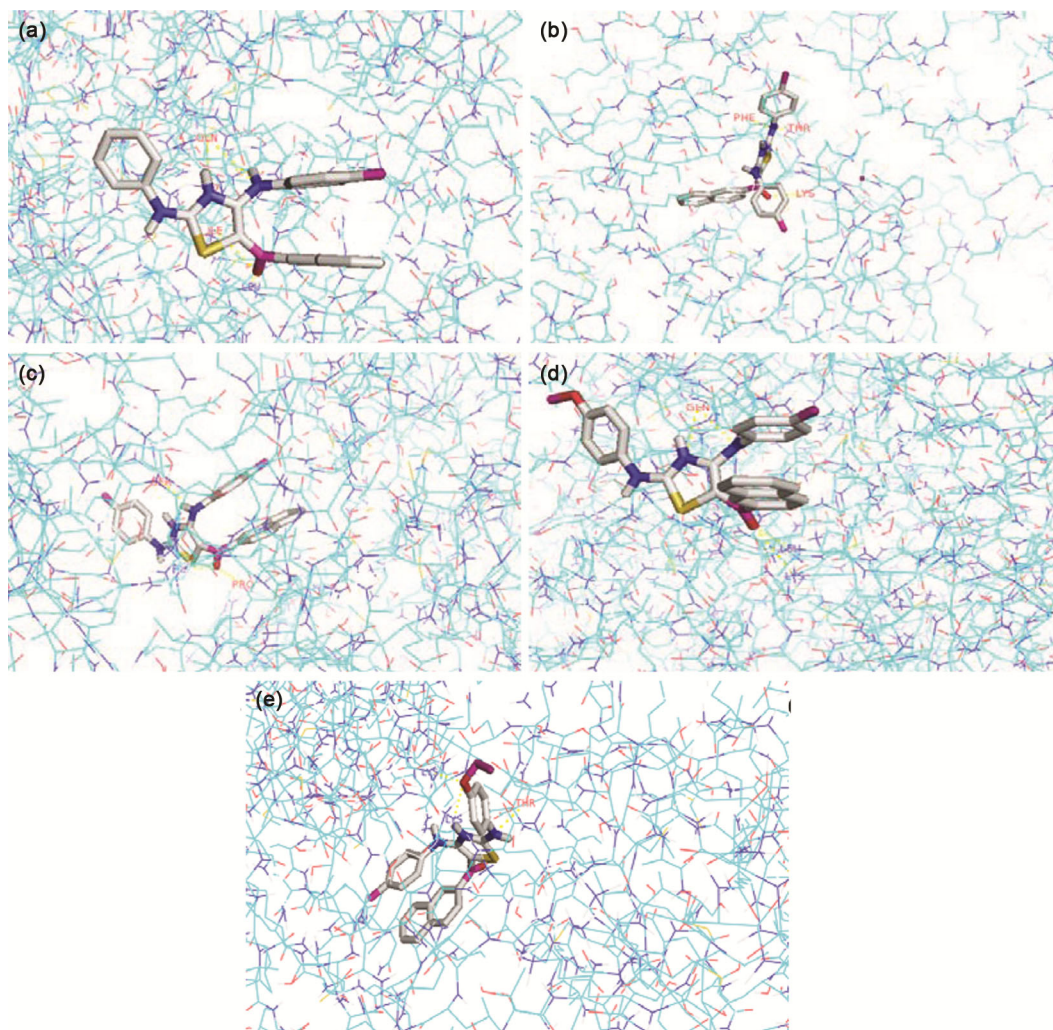


Fig. 3 — Docking images of -[2-(4-aryl-amino)-4-methylphenylaminothiazol-5-oyl]naphthalene

Table 5 — Anti-bacterial Activity of 2-[2-(4-aryl-amino)-4-methylphenylaminothiazol-5-oyl]naphthalene

Compd	Zone of inhibition (mm)					
	<i>E. coli</i>	<i>Klebsilla</i>	<i>Pseudomonas</i>	<i>Bacillus</i>	<i>Staphylococcus</i>	<i>Streptococcus</i>
3a	10	11	–	13	12	9
3b	14	14	14	15	18	12
3c	7	13	11	12	13	9
3d	–	8	8	11	13	14
3e	11	13	10	11	12	11
Amikaci (Standard)	30	18	22	20	18	20

Anti-bacterial activities

The newly synthesised compounds have been screened for antibacterial activity against Gram-negative *Escherichia coli*, *Klebsiella*, *Pseudomonas* and Gram-positive *Bacillus*, *Streptococcus*, *Staphylococcus*. The compound containing phenyl group **3a** is highly active against *Klebsilla*, *Bacillus* and *Staphylococcus*, and fairly active all other bacteria except *Pseudomonas*. The thiazole containing 4-chlorophenyl group **3b** is highly active against

all bacteria strains. The compound containing 4-methylphenyl group **3c** is highly active against *Pseudomonas*, *Bacillus*, *Staphylococcus* and *Klebsiella*, fairly active against *Streptococcus* and moderately active against *E. coli*. The compound containing 4-methoxyphenyl **3d** is highly active against three bacteria, and moderately active all other bacteria except *E. coli*. The compound containing 4-ethoxyphenyl group **3e** is highly active against all bacteria except *Pseudomonas* (Table 5).

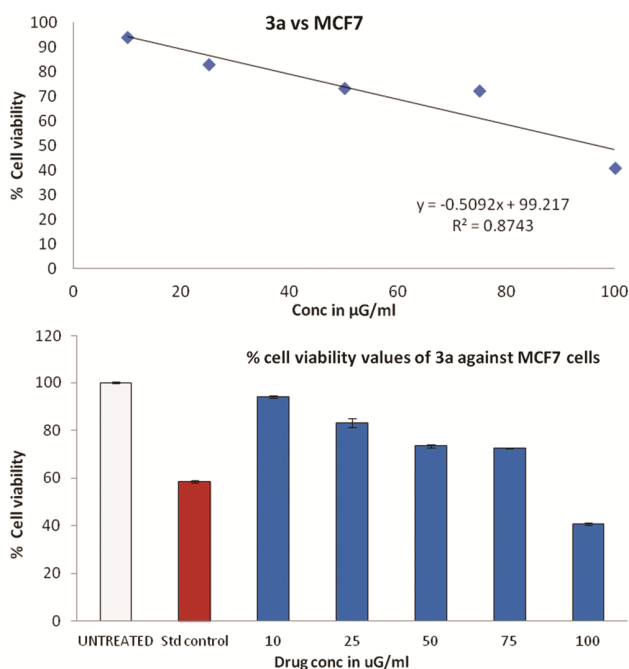


Fig. 4 — Plot of %viability vs conc. of 2-[2-(4-phenylamino)-4-methylphenylaminothiazol-5-oyl]naphthalene

Anticancer Studies

The synthesized compounds with high antioxidant activities is examined for anticancer activity against MCF-7 cell line *in vitro* by MTT assay method and the compound 2-[2-(4-methoxyphenylamino)-4-chlorophenylaminothiazol-5-oyl]naphthalene exhibited excellent anticancer activity against breast cancer with IC_{50} value $96.65\mu M$.

The biological activity has close relationship with electronic property of the compounds. The compound 2-[2-(4-phenylamino)-4-methylphenylaminothiazol-5-oyl]naphthalene exhibited higher activity than the electron donating the other substituents (Figure 4). This confirms that suitable functional groups are necessary in drug design to exhibit better biological activities. The antioxidant and anticancer studies predicts that the compound 2-[2-(4-phenylamino)-4-methylphenylaminothiazol-5-oyl]naphthalene has higher activity against breast cancer.

Conclusion

In summary, 2-[2-(4-aryl amino)-4-methylphenylaminothiazol-5-oyl]naphthalene were designed, synthesized and their structures were characterized by FT-IR, 1H NMR, ^{13}C NMR and ESI-MS. Furthermore, 2-[2-(4-aryl amino)-4-methylphenylaminothiazol-5-oyl]naphthalene were docked towards the active site of cell division SARS-CoVPLpro (PDB code: 6WUU) using PyRx virtual screening tool. The results showed that all the tested compounds have anticancer activity. Among the tested compounds, **3a** showed highest docking score and three hydrogen bond interactions with 6WUU. This revealed that naphthalene derivatives discovered in this study may provide valuable information in the field of drug design and cancer therapy.

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