

Unravelling the potential of 2-(Bromo/polybromophenylamino) substituted-4-arylthiazoles: Synthesis, characterization, anticancer, antimicrobial, molecular docking, and ADMET studies

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ABSTRACT

A total of twenty-four 2-(bromo/dibromo/tribromophenylamino)-4-arylthiazole derivatives (**3a-x**) were prepared to explore their biological potential, particularly to evaluate the effect of bromine substituent(s) on the phenylamino group attached at position-2 of the thiazole nucleus. The reaction of α -bromoacetophenones with different N-bromoarylthioureas at room temperature in alcohol afforded the target products in good yields. Their structures were established based on analysis of spectroscopic data and results of single-crystal X-ray diffraction technique. The anticancer evaluation revealed that compound **3p** exhibited excellent selectivity (SI = 8.86) with an IC₅₀ value of $129.37 \pm 8.0 \mu\text{M}$ toward lung cancer cells (A549), surpassing the standard drug, Carboplatin (IC₅₀ = $128.83 \pm 2.0 \mu\text{M}$, SI = 1.21). It was observed that compounds possessing a 2,4-dibromophenylamino moiety linked at position-2 of the thiazole ring demonstrated the highest selectivity for A549 cells and the lowest cytotoxicity against Vero cells. Antimicrobial screening revealed that compounds **3g** and **3h** were highly effective against the bacterial strain, *Staphylococcus aureus*, and the fungal strain *Candida albicans*, with MIC values of 0.038 $\mu\text{g/mL}$ (Ampicillin = 1 $\mu\text{g/mL}$) and 0.021 $\mu\text{g/mL}$ (Fluconazole = 0.31 $\mu\text{g/mL}$), respectively. Furthermore, molecular docking studies were conducted on the newly synthesized candidates, which support their potential as effective biological agents. ADMET analysis for key pharmacokinetic and toxicological properties of these compounds was also conducted to assess their drug-likeness nature.

1. Introduction

Cancer remains one of the most challenging and deadliest diseases worldwide. In men, lung, prostate, colorectal, and bronchus cancers together account for approximately 48 % of newly diagnosed cases, whereas colorectal, breast, and lung cancers represent about 51 % of cases in women [1]. Among these, lung cancer is the leading cause of cancer-related mortality, accounting for nearly 350 deaths daily [2]. Notably, twenty percent of all human cancers are caused by infectious pathogens, which include bacteria and viruses [2]. At the same time, antimicrobial resistance (AMR) has emerged as a critical global health concern due to the misuse or overuse of antimicrobial drugs [3]. Moreover, toxicity, poor selectivity, and development of resistance are

some of the major issues associated with available marketed drugs, thereby highlighting the urgent need for new therapeutic agents with potential anti-lung cancer and antimicrobial activities.

Thiazole derivatives have been extensively studied owing to their wide applications. They are five-membered azoles containing a stable S-C-N linkage that serve as privileged scaffolds in the field of medicinal and synthetic organic chemistry. They exhibit diversified biological properties, including anti-inflammatory, analgesic, antibacterial, anti-cancer, antifungal, antiretroviral, antitumor, and antioxidant activities [4–10]. They are also associated with dyestuffs, fertilizers and photographic sensitizers [11]. Many FDA-approved drugs possess a thiazole ring as one of their essential structural features [12–14]. Some of the critically and widely used drugs containing a thiazole moiety are

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Cefiderocol, Alpelisib, Sulfathiazole, Ravuconazole, Ritonavir, Meloxicam, and Penicillin [15–22]. Structural variations through substitution on the thiazole ring, particularly at positions-2 and -4, offer diversified biological properties [23]. Substitution at second position of the thiazole nucleus by an amino group makes the thiazole derivatives more attractive to medicinal chemists. The 2-aminothiazole pharmacophoric unit is present in various drugs, including Famotidine [24], Abafungin [25], Carumonam [26], Meloxicam [27], Cefditoren [28], Sudoxicam [29], and Fenitizole [30].

Among halogens, which are present in the majority of FDA-approved drugs, bromine is one of the top five heteroatoms found in medications used to treat respiratory, nervous, and sensory diseases, owing to its ability to pass through biological barriers (blood-brain). The incorporation of bromine into a potential drug's framework exhibits several advantages, including improved drug metabolism, enhanced binding affinity, prolonged duration of action, increased lipophilicity, and improved therapeutic activity [31]. A noteworthy example of such compounds is the brominated natural compounds extracted from marine organisms (*Spongosorites*, *Pterocella Vesiculosa*, *Iotrochota purpurea* and *Aplidium meridianum*), which are effective against various diseases and beneficial in antibiotic therapy against resistant bacteria [32]. Moreover, R. Gupta *et al.* reported that 2-(4-Bromophenylamino) linked thiazole is known to exhibit insecticidal activity against the highly polyphagous insect *Helicoverpa armigera*, which is responsible for damaging various crops, including cotton, legumes, corn, and tomato

[33]. 2-(4-Bromophenylamino)-4-(3-pyridinyl)thiazole acts as an anti-Alzheimer's agent with the potential to be a Gp130 agonist by increasing pSTAT3 mimetic NH and shows a tendency to protect neurons from excitotoxicity and amyloid-beta [34]. Further, compounds possessing *p*-bromophenyl linked thiazolyl-pyrazoline unit displayed significant anticancer activity against B16F10 cells (mouse melanoma cell lines), HER-2 (EGFR family) and MCF-7 (human breast cancer cell lines) in comparison with the reference drug, Erlotinib. A structure-activity relationship (SAR) analysis in one report revealed that the presence of bromine atom at position-4 of the phenyl ring attached to the thiazole ring exhibited excellent HER-2 inhibitory activity, which was further supported by the results obtained from molecular docking analysis [35]. Interestingly, it was noted that compounds containing a 4-bromophenyl amino group linked at position-2 of the thiazole moiety or presence of bromine at position-4 of the phenyl group attached at position-4 of thiazole ring enhance the biological efficacy (Fig. 1) [36].

Although there are reports that disclose the advantages of thiazoles possessing a monobromosubstituted phenyl group, mainly at the *para*-position, there is a lack of sufficient scientific reports that have explored the biological potential of such compounds in the presence of bromine substitution at the *ortho* and *para* sites individually and synergistically. Therefore, the substitution of bromine at the *ortho* and *para* positions of the phenyl group attached to position-2 of the thiazole nucleus may result in alterations of biological potency and selectivity.

Furthermore, to overcome drug resistance issues it is always

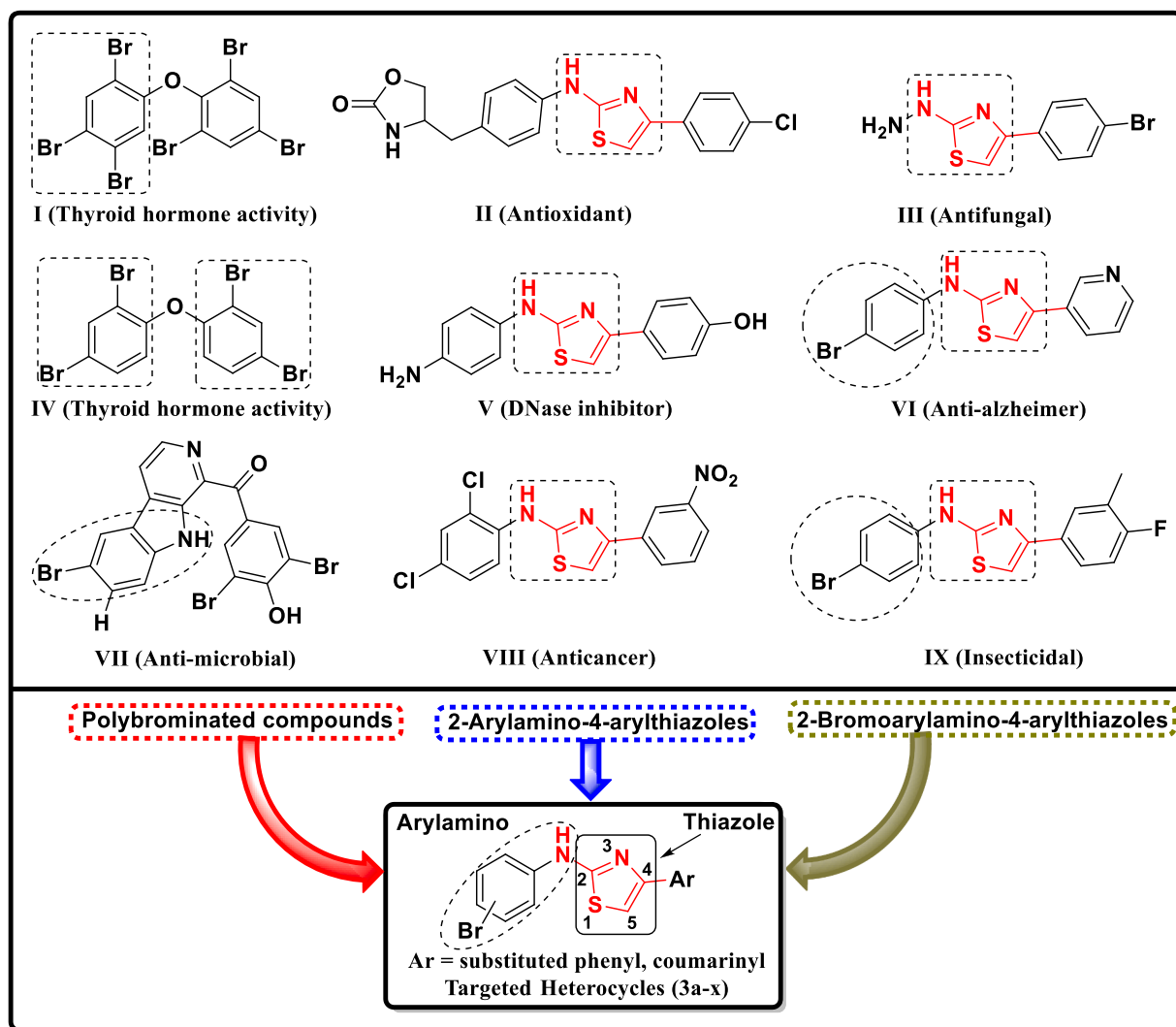


Fig. 1. Some biologically active chloro/bromo-substituted 2-arylamino-4-arylthiazoles, polybrominated indole/diphenyl ether and targeted thiazoles.

worthwhile to generate a library of new bioactive candidates. Keeping the aforementioned facts in mind and in continuation of our ongoing work related to the synthesis of biologically potent heterocycles [37–39], it was worth planning to construct a series of 2,4-disubstituted thiazole derivatives, particularly, focusing on the incorporation of 4-bromophenyl, 2,4-dibromophenyl, and 2,4,6-tribromophenylamino motifs at position-2 of thiazole nucleus to explore the effect of bromo substitution on their biological potential. This study provides a comparative evaluation of the anticancer and antimicrobial properties resulting from changes in the number and position of bromine substituents on the phenylamino group attached to position-2 of thiazole derivatives.

2. Results and discussion

A series of 2-(Bromo/polybromophenylamino)-4-aryl thiazole derivatives (**3a-x**) was synthesized by adopting the Hantzsch-thiazole process (Scheme 1). The reaction of phenacyl bromides (**1**) with three different *N*-bromophenyl thiourea derivatives (**2a-c**) at stirring in ethanol yielded the final products (**3**). The starting materials **1a-h** and **2a-c** were synthesized according to the reported methods [40–42].

The structures of the prepared compounds were elucidated through rigorous analysis of various spectroscopic techniques, including FT-IR, $^1\text{H}/^{13}\text{C}$ NMR spectroscopy, mass spectrometry, and single-crystal X-ray diffraction (for compounds **3r** and **3u**).

In the FT-IR spectrum of phenacyl bromides (**1**), two firm characteristic peaks appeared; a peak at 1687 cm^{-1} appeared due to C=O stretching vibrations and another peak at 532 cm^{-1} due to C-Br stretching absorptions, confirming the formation of intermediate **1**. Furthermore, the appearance of N—H stretching bands at 3258 and 3315 cm^{-1} , corresponding to the symmetric and asymmetric stretching absorption bands of the amino (NH_2) group, respectively, and at 3138 cm^{-1} , due to N—H symmetric stretching, confirms the formation of *N*-bromophenyl thiourea derivatives (**2**). Additionally, the disappearance of C = O stretching vibrations at 1687 cm^{-1} of phenacyl bromide (**1**) and the absence of N—H stretching bands at 3315 and 3258 cm^{-1} due to the NH_2 group of thiourea (**2**) confirm the formation of thiazoles (**3**). Moreover, an intense peak observed at 3366 cm^{-1} , due to the N—H stretching vibration, supports the presence of an NH group in the final product, thiazole derivative.

In the NMR spectrum of **1**, it was observed that a signal due to a set of CH_2 protons appeared downfield, and a singlet signal appeared at δ 4.45 ppm due to the electron-withdrawing effect of directly attached carbonyl and bromine groups. Aromatic protons resonate in the range of δ 7.2–8.5 ppm. In ^1H NMR spectra of thioureas **2**, the NH proton at δ 10 ppm, whereas a broad signal due to NH_2 protons appeared at δ 4 ppm

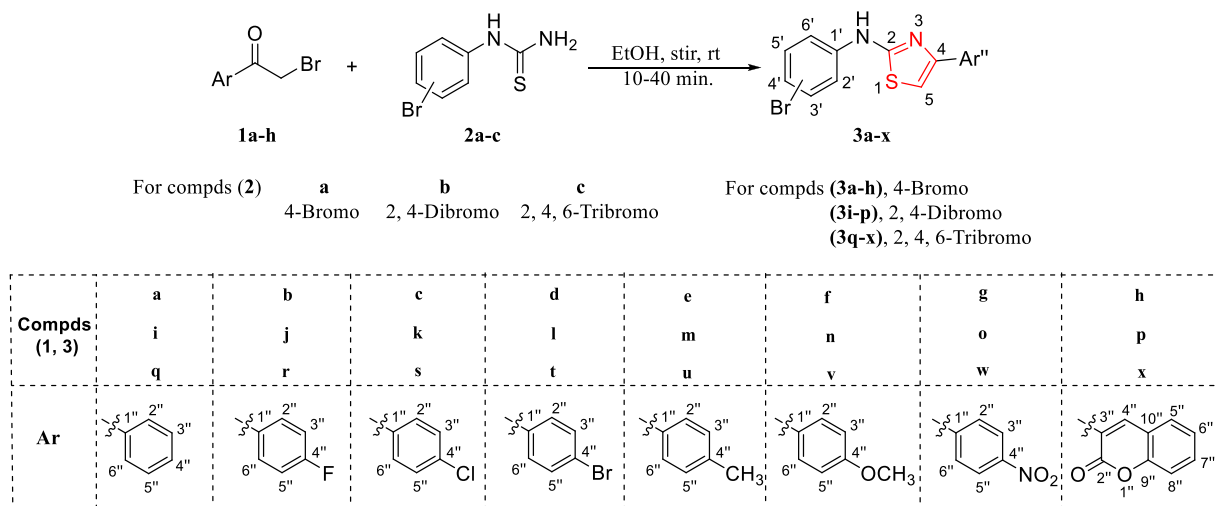
confirmed the formation of intermediate **2**. From the NMR spectrum of the representative compound **3r**, the disappearance of a broad signal at δ 4 ppm and a signal at δ 4.45 ppm due to the CH_2 protons of phenacyl bromide confirmed the formation of the desired compounds. Further, an appearance of a characteristic signal at δ 7.2 ppm due to the 5-H of the thiazole ring confirms the formation of the thiazole ring, which is in close agreement with the reported values [1]. Also, the appearance of a broad signal due to the NH proton (D_2O exchangeable) at δ 9.67–9.88 ppm confirms the presence of the NH functionality in the final product. Aromatic protons of phenyl rings resonate in the range of δ 7.22–8.10 ppm. The formation of the thiazole nucleus was further confirmed by the appearance of the three characteristic carbon signals at δ 160.5, 149.4, and 115.2 ppm, corresponding to the C-2, C-4, and C-5 carbon atoms, respectively, in the ^{13}C NMR spectrum of **3**. In the ^{19}F NMR spectrum, a signal appeared at δ -114 ppm due to fluorine attached at position-4 of the phenyl ring linked to the thiazole moiety. The physical data of the synthesized products are listed in Table 1.

Furthermore, the structures of all candidates **3a-x** were supported by the results obtained from single-crystal X-ray diffraction analysis of two representative compounds, **3r** and **3u**. Crystals of compounds **3r** and **3u** were obtained using a simple method involving slow evaporation in ethanol. The crystallographic analysis revealed that both compounds **3r** and **3u** crystallize in the triclinic crystal system with the *P*-1 space group. Notably, the C-S bond lengths (1.735 Å and 1.713 Å) and the angles within the newly formed thiazole ring closely resembled existing values (Figs. 2a and 2b). The lattice structure of compound **3r** shows that molecules are packed in an anti-parallel manner in the *a*-*c* plane, as depicted in Fig. 2c. There are mainly two intermolecular hydrogen bonds observed between the N2 of one molecule and the H on N1a of another. Detailed crystallographic refinement parameters and significant bond angles/lengths for compounds **3r** and **3u** can be found in Tables S1 & S2 (see SI), describing their structural details comprehensively.

3. Biological activity studies

3.1. Anticancer activity

The anticancer activity of all the synthesized compounds was evaluated against two different cell lines: human lung adenocarcinoma (A549) cells and African green monkey kidney (Vero) cells. The cytotoxicity results were compared with those of the FDA-approved anticancer drug, Carboplatin. During the investigation, A549 cell line was treated with different compounds **3a-x** at varying concentrations starting from $1000\text{ }\mu\text{M}$ for 48 h by using dimethyl sulfoxide (DMSO, 0.25 %)



Scheme 1. Synthesis of 2-(Bromo/dibromo/tribromophenylamino)-4-arylthiazoles (**3a-x**).

Table 1

Reaction times (T_1), and percentage yields and observed melting points of the synthesized compounds (**3a–x**).

Compds.	Ar	T_1 (min)	Yield (%)	Color	Observed m.p. (°C)	Lit. m.p. (°C) [Ref.]
3a	C_6H_5	20	74	White	143–145	144–146 [43]
3b	p -F- C_6H_4	20	68	Brown	129–130	131 [44]
3c	p -Cl- C_6H_4	10	70	White	157–158	156–158 [43]
3d	p -Br- C_6H_4	15	65	White	158–160	159–161 [43]
3e	p -CH ₃ - C_6H_4	10	79	White	145–147	N.R. [45]
3f	p -OCH ₃ - C_6H_4	20	70	White	136–137	137–139 [43]
3g	p -NO ₂ - C_6H_4	15	68	Red	132–134	–
3h	Coumarin-3-yl	20	80	Yellow	>300	Above 300 [46]
3i	C_6H_5	30	78	White	160–161	–
3j	p -F- C_6H_4	35	51	White	163–164	–
3k	p -Cl- C_6H_4	25	59	White	214–216	–
3l	p -Br- C_6H_4	40	56	White	209–220	–
3m	p -CH ₃ - C_6H_4	30	60	White	155–157	–
3n	p -OCH ₃ - C_6H_4	20	72	White	139–141	–
3o	p -NO ₂ - C_6H_4	25	58	Yellow	255–256	–
3p	Coumarin-3-yl	35	64	Green	256–257	–
3q	C_6H_5	15	78	White	184–186	–
3r	p -F- C_6H_4	10	60	White	204–205	–
3s	p -Cl- C_6H_4	20	74	White	214–216	–
3t	p -Br- C_6H_4	15	65	White	223–225	–
3u	p -CH ₃ - C_6H_4	15	69	White	179–181	–
3v	p -OCH ₃ - C_6H_4	10	75	White	195–196	–
3w	p -NO ₂ - C_6H_4	20	60	Yellow	139–140	–
3x	Coumarin-3-yl	10	65	Green	215–217	–

N.R. = Not reported.

as a negative control in Dulbecco's Modified Eagle Medium (DMEM). Not all compounds have the potential to exhibit anti-proliferative activity, but those with lower cytotoxicity concentrations and higher selectivity towards cancer cells are most effective. Such compounds may be considered safer for therapeutic use and ideal for further preclinical trials.

The dose-dependent inhibition of viable A549 cells on treatment

with synthesized compounds revealed that compounds exhibit excellent anticancer efficacy with minimal cytotoxicity (Fig. 3, Table 2). Furthermore, based on the 50 % inhibitory concentration of all the synthesized compounds, **3f** depicted the highest anti-proliferative activity on A549 cells, with a half maximal inhibitory (IC_{50}) value of $51.37 \pm 2.9 \mu M$, followed by **3h** ($53.64 \pm 6.5 \mu M$) and **3n** ($55.92 \pm 0.5 \mu M$). However, these compounds exhibited limited selectivity toward cancer cells, with SI values of 1.49, 1.37, and 1.10, respectively. The compounds, **3b**, **3c**, **3d**, **3e**, **3f**, **3g**, **3h**, **3j**, **3k**, **3l**, **3n** and **3v** showed the potent anti-proliferative potential against A549 lung cancer cells with IC_{50} values < 100 μM . Furthermore, compounds **3a**, **3g**, **3i**, **3m** and **3p** showed cytotoxicity activity with IC_{50} values of < 200 μM . Compounds **3f**, **3n**, and **3v** displayed higher selectivity and anti-proliferative potential compared to the reference drug, Carboplatin.

Interestingly, 2-(2,4-dibromophenylamino) substituted thiazoles exhibited excellent selectivity towards cancer cells. Among them, compounds **3k** and **3n** showed the highest anti-proliferative potential with IC_{50} values of 64.90 ± 5.7 and $53.64 \pm 6.5 \mu M$, respectively, whereas **3p**, with an IC_{50} value of $129.37 \pm 8.0 \mu M$ in A549 cells, was found to be equipotent to Carboplatin ($128.83 \pm 2.0 \mu M$). It was also noted that **3p** depicted the least cytotoxicity against Vero cells, with an IC_{50} value of $1150.67 \pm 4.4 \mu M$, among all the screened compounds. Similarly, compounds **3k** (SI = 8.31), **3j** (SI = 7.71), and **3l** (SI = 7.60) exhibited excellent selectivity, with IC_{50} values lower than 100 μM towards A549 cells, indicating them as favourable candidates for further studies. Moreover, compound **3m**, with a selectivity index of 3 exhibits moderate selectivity, followed by **3g** (SI = 2.24), **3b** (SI = 2.10), and **3r** (SI = 2.54). In contrast, tribromophenylamino-substituted thiazoles **3t**, **3u**, and **3x** showed higher IC_{50} values and lower SI values (<1), indicating that they are not ideal for therapeutic use. In conclusion, tribromo-substituted compounds exhibited higher cytotoxicity, followed by mono-bromo-substituted compounds. Whereas, 2,4-dibromo-substituted thiazoles expressed higher selectivity compared to intermediate (**2b**) as well as the standard drug, Carboplatin. All synthesized compounds except **3a**, **3i** and **3p** significantly inhibited the growth of A549 cells when compared with the standard drug, Carboplatin ($P \leq 0.0001$).

In literature, it has been reported that the substitution of haloaryl groups at the 2-aminothiazole motif exhibits moderate cytotoxicity against breast and lung cancer cell lines, with an IC_{50} value of 100–150 μM . In contrast, **3p** shows an IC_{50} value of 129.37 μM , accompanied by a remarkably high selectivity index value of 8.86 [47]. Sharma et al. also reported that thiazole hybrids with electron-donating substituents (methyl and methoxy) showed IC_{50} values greater than 90 μM against A549 cells. In contrast, **3n** substituted with a 4-methoxyphenyl group showed enhanced cytotoxicity with an IC_{50} value of 53.64 μM [48]. Therefore, a comparative analysis highlights that the substitution of a 2,

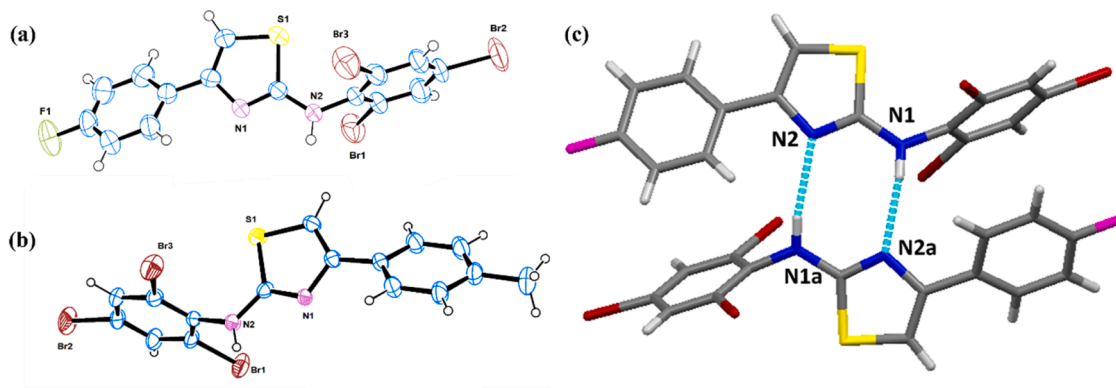


Fig. 2. ORTEP diagrams of compounds **3r** (a) and **3u** (b) with thermal ellipsoids set to 50 % probability level, lattice picture of compound **3r** along a-c plane and representation of intermolecular H-bonding interactions within the molecules (c).

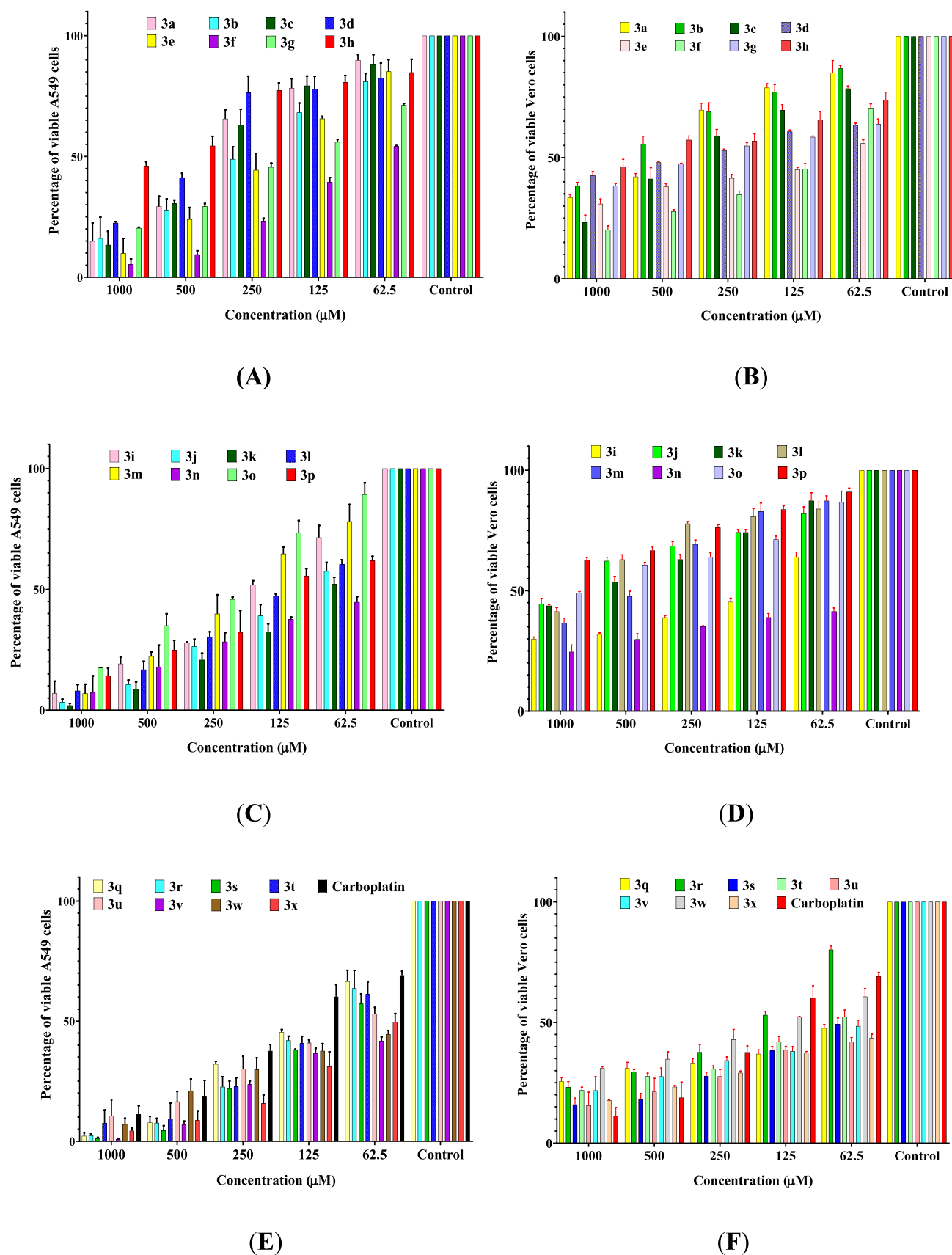


Fig. 3. Percentage of viable A549 cells; (A) 3a-h and Carboplatin; (C) 3i-p and Carboplatin; (E) 3q-x and Carboplatin; and Vero cells; (B) 3a-h and Carboplatin; (D) 3i-p and Carboplatin; (F) 3q-x and Carboplatin on treatment with varying concentrations of test compounds.

Table 2Effect of compounds **3a-x** on A549 lung adenocarcinoma and Vero cells IC₅₀ (μM).

Compounds	IC ₅₀ in μM (Mean ± SEM) A549 Cells	IC ₅₀ in μM (Mean ± SEM) Vero Cells	Selectivity Index (SI)
3a	108.34 ± 7.5	93.16 ± 2.0	0.86
3b	89.09 ± 4.2	187 ± 2.7	2.1
3c	76.49 ± 2.7	69.84 ± 1.5	0.91
3d	89.90 ± 4.2	91.79 ± 1.7	1.02
3e	91.08 ± 0.8	58.88 ± 1.7	0.65
3f	51.37 ± 2.9	76.36 ± 2.0	1.49
3g	68.96 ± 5.4	154.2 ± 2.4	2.24
3h	55.92 ± 0.5	61.29 ± 1.2	1.1
3i	134.07 ± 6.4	150.97 ± 1.0	1.12
3j	83.87 ± 3.7	646.93 ± 2.8	7.71
3k	64.90 ± 5.7	539 ± 2.5	8.31
3l	97.01 ± 4.3	737.53 ± 2.5	7.60
3m	174.1 ± 3.2	526.8 ± 2.6	3.03
3n	53.64 ± 6.5	73.73 ± 1.5	1.37
3o	275.4 ± 9.3	628.5 ± 2.3	2.28
3p	129.37 ± 8.0	1150.67 ± 4.4	8.86
3q	327.63 ± 7.8	453.2 ± 3.1	1.38
3r	224.6 ± 7.0	569.6 ± 4.2	2.54
3s	316.62 ± 5.8	317.8 ± 2.1	1.00
3t	424.5 ± 4.7	297.33 ± 0.8	0.70
3u	207.03 ± 8.8	128.87 ± 0.6	0.62
3v	74.86 ± 3.4	139.8 ± 1.8	1.87
3w	193.6 ± 4.0	263.27 ± 3.8	1.36
3x	693 ± 1.6	452.2 ± 2.3	0.65
2a	130.57 ± 1.8	201.17 ± 3.0	1.54
2b	200.97 ± 5.3	219.6 ± 1.0	1.09
2c	143.00 ± 6.0	133.53 ± 1.6	0.93
Carboplatin	128.83 ± 2.0	155.9 ± 2.2	1.21

4-dibromophenylamino group at position-2 of the thiazole ring, in combination with electron-donating groups at position-4, enhances selectivity and biological potency compared to similar thiazole-based compounds, thus validating our structural design rationale.

Overall, compounds **3j**, **3k**, **3l**, and **3p** are the most potent and exhibited excellent cytotoxicity with high selectivity. Therefore, they may be considered suitable and safer for further target exploration. Screening results suggested that the substitution of bromine at the *ortho* and *para*-positions of the phenyl group attached at position-2 of thiazole ring results in enhanced selectivity and cytotoxicity. However, it is noteworthy to report that the introduction of additional bromine beyond the di-substituted framework led to enhanced cytotoxicity.

Some key findings related to structure-activity relationships from anticancer activity results are emphasized below:

- The 4-bromophenylamino group, when substituted at position-2 of the thiazole ring, resulted in enhanced cytotoxicity but reduced selectivity.
- The presence of a 2,4-dibromophenylamino group at position-2 of the thiazole ring led to higher selectivity towards A549 cells.
- Substitution of the 2,4,6-tribromophenylamino group at position-2 of the thiazole ring leads to diminished anticancer activity.
- In the case of chromenyl substitution at position-4 of the thiazole ring, the least cytotoxicity was observed against Vero cells compared to other substituents.
- Compounds **3i-p** exhibited higher selectivity towards A549 cells after the formation of the thiazole ring, as compared to the thiourea **2b**

3.2. Antimicrobial activity

The antimicrobial potential of all the synthesized compounds was estimated against Gram-positive *Staphylococcus aureus* (*S. aureus*), Gram-negative *Escherichia coli* (*E. coli*) bacterial strains, and fungal pathogen, *Candida albicans* (*C. albicans*) through agar well diffusion

method [49], using Ampicillin and Fluconazole as positive controls for bacteria and fungus, respectively. Based on preliminary screening results using the zone of inhibition (ZOI), potent compounds were selected for the determination of minimum inhibitory concentration (MIC) values (mg/ml). MIC values were calculated using a broth microdilution assay, and the details are presented in Table 3. Among all the screened compounds, two, fourteen and seven compounds were found to be active against *E. coli*, *S. aureus* and *C. albicans*, respectively.

It was noted that compounds **3g** and **3h** exhibited excellent anti-bacterial potential against *S. aureus*, with MIC values of 0.03812 and 0.03893 mg/ml, respectively, which was approximately 97 % more effective than the reference drug, Ampicillin. In addition, compound **3w** exhibited a relatively good inhibitory profile, with an MIC value of 0.11 mg/mL, which was approximately 90 % of that of the standard drug. However, all other compounds, **3a**, **3b**, **3c**, **3i**, **3l**, **3m**, **3n**, **3p**, **3q**, **3u**, and **3v** depicted low inhibitory potential against *S. aureus*. Among the fourteen most potent compounds against *S. aureus*, all of them except **3i**, **3l**, and **3v** significantly inhibited the growth of *S. aureus* cells when compared with the standard drug, Ampicillin. Moreover, none of the candidates were found to be working against the bacterial strain *E. coli*, except for **3g** and **3h**, which showed relatively less inhibitory activity; **3h** showed significant inhibition of *E. coli* cells compared to the reference drug, Ampicillin. All potent compounds except **3i**, **3l**, and **3v** significantly inhibited the growth of *S. aureus* cells when compared with the standard drug, Ampicillin ($P \leq 0.002$).

It was also observed that compound **3g** (MIC = 0.02 mg/ml) depicted twelve-fold inhibitory potential against the growth of *C. albicans*, as compared to the reference drug, Fluconazole (MIC = 0.31 mg/ml), followed by **3h** (MIC = 0.05 mg/ml) and **3b** (MIC = 0.09 mg/ml). Moreover, compounds **3e** and **3p** exhibited relatively good inhibitory profiles, with MIC values of 0.2 and 0.18 mg/ml, respectively. Unfortunately, compounds **3k** and **3q** exhibited the least antifungal potential. Except **3k** and **3w**, other active compounds significantly inhibited the *C. albicans* cells as compared to the standard drug, Fluconazole. All potent compounds except **3k** and **3w** significantly inhibited the growth

Table 3MIC values of the synthesized compounds (**3a-x**) against *E. coli*, *S. aureus* and *C. albicans*.

Compds.	Minimum Inhibitory Concentration (mg/ml)		
	Gram negative <i>E. coli</i>	Gram positive <i>S. aureus</i>	Fungal Strain <i>C. albicans</i>
3a	–	2.307	–
3b	–	2.444	0.09047
3c	–	4.791	–
3d	–	–	–
3e	–	–	0.2277
3f	–	–	–
3g	8.401	0.03812	0.02150
3h	5.845	0.03893	0.05815
3i	–	4.255	–
3j	–	–	–
3k	–	–	1.576
3l	–	8.864	–
3m	–	2.301	–
3n	–	2.557	–
3o	–	–	–
3p	–	2.651	0.1862
3q	–	1.898	1.228
3r	–	–	–
3s	–	–	–
3t	–	–	–
3u	–	4.079	–
3v	–	4.896	–
3w	–	0.1153	–
3x	–	–	–
Ampicillin	4	1	N.A
Fluconazole	N.A	N.A	0.31

N.A: Not applicable.

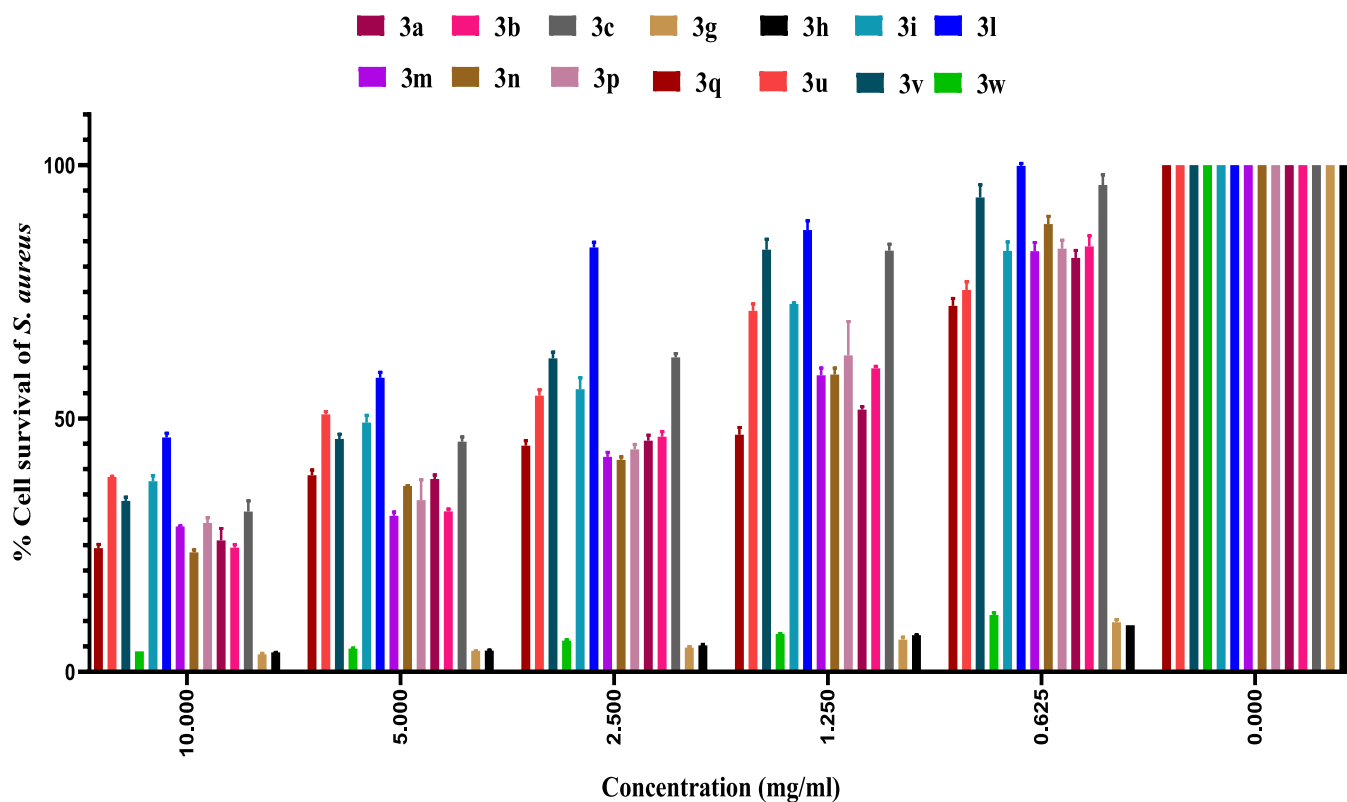
of *C. albicans* cells when compared with the standard drug, Fluconazole ($P \leq 0.004$).

The comparative efficacy of all the compounds (**3a-x**) is presented in Fig. 4.

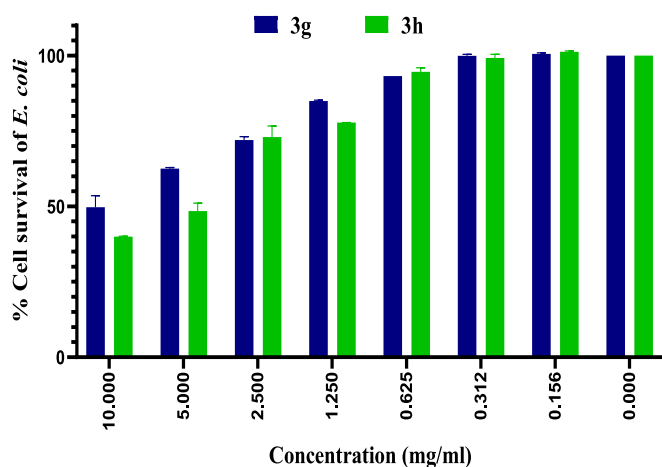
In conclusion, compounds **3g**, **3h**, **3w**, and **3b**, **3g**, **3h**, **3e**, **3p** showed remarkable potential against bacterial (*S. aureus*) and fungal (*C. albicans*) pathogens, respectively. Furthermore, modifications to their structural framework may lead to the development of potential antifungal and antibacterial agents in the future.

The antimicrobial screening results supported the following findings based on the structure-activity relationship (SAR):

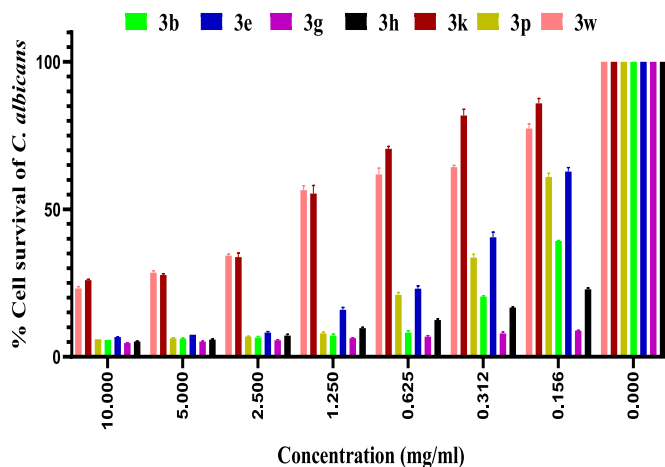
- Compounds bearing electron-withdrawing (NO_2) and chromenyl groups were found to be active against both bacterial and fungal strains.
- It was observed that 4-nitrophenyl substitution at position-4 of thiazole ring depicted remarkable antifungal activity against *C. albicans* followed by chromenyl substitution.
- Most of the compounds exhibited promising antibacterial potential against the gram-positive bacterial strain *S. aureus*.
- Thiazole bearing 4-bromophenylamino group at position-2 exhibited excellent antibacterial and antifungal potential as compared to 2,4-



(A)



(B)



(C)

Fig. 4. Percentage of (A) *S. aureus*; (B) *E. coli*; (C) *C. albicans* viable cells on treatment with varying concentration of synthesized compounds (**3a-x**).

dibromophenylamino and 2,4,6-tribromophenylamino substituted compounds.

3.3. Molecular docking studies

Molecular docking simulation is an important and highly informative tool in the field of structure-based drug discovery. It enables the evaluation of how compounds interact with the binding sites of the target proteins. Docking studies play a crucial role and most importantly are widely employed as a popular simulated screening method owing to their ability to judge and give insights into the structure of protein-ligand complexes [50,51]. In this context, we have executed the molecular docking simulation. For this process, we have chosen the human epidermal growth factor receptor (EGFR) kinase domain protein. EGFR is a glycoprotein and part of the ErbB family of tyrosine kinase receptors. It is frequently found to be overexpressed or mutated in several cancer types, particularly in non-small cell lung cancer (NSCLC) [52]. These alterations often result in the continuous activation of EGFR signaling, which promotes unchecked cell proliferation, survival, and metastasis. Because of this, EGFR has emerged as an important and critical target for cancer therapy. When specific ligands bind to EGFR, it triggers a cascade of intracellular signalling pathways that regulate key cellular processes, including growth, gene expression, and apoptosis. Therefore, inhibiting EGFR signalling represents an effective strategy to suppress tumor growth and facilitate cancer regression [53]. For docking purposes, the crystallographic structure of the protein (PDB ID: 3W2S) was procured from the Protein Data Bank (<https://www.rcsb.org/structure/3W2S>). The resolution value, being below 2 Å (i.e., 1.90 Å), is considered a decent threshold in the scientific community for reliable molecular docking studies. Molecular docking experiments were performed using AutoDock Vina to evaluate the binding affinity of the compounds [54]. Before docking, all water molecules were eliminated from the target structure, and the active site was defined within a grid box measuring 62 × 60 × 60 Å, centered at coordinates $X = 4.0014$, $Y = 9.0020$, and $Z = 15.0207$. The resulting docked conformations and molecular interactions with protein were visualized and analyzed using Discovery Studio Visualizer 4.0 [55]. This facilitated the identification of optimal binding orientations and interaction patterns.

Herein, novel and potent 2-(bromophenylamino)-4-arylthiazole derivatives were evaluated to explore their binding energies and favorable interaction modes with the EGFR kinase domain. Molecular docking was performed, and ligand-receptor interactions were analyzed for further investigations. Also, various docked poses were explored to assess hydrophobic interactions, hydrogen bonding, and the free energy of binding (FEB) affinity. The molecular docking results demonstrated that the phenyl thiourea derivative **2b**, an intermediate, has a lower free energy of binding (FEB) affinity, whereas the **3h** molecule has a higher FEB affinity with the protein among all (Table 4). In this study, the docked poses represent the most energetically favorable conformations, indicating that all synthesized compounds (**3h**, **3p** and **3x**) interact significantly with the protein through key interactions, such as hydrogen bonding, Pi-sigma, and Pi-alkyl interactions (see Figs. S1 and S2 in the ESI).

The docking analysis denotes that the **3h** molecule shows two significant hydrogen bonding interactions with SER A:720 residue in a

distance of 2.566 Å and with LEU A:718 residue in a distance of 2.875 Å; also, it shows carbon hydrogen bonding with GLY A:719 residue at a distance of 3.587 Å (Fig. 5). Molecule **3p** interacts with the protein with three substantial H-bonding interactions in a range of 2.758 Å to 3.084 Å. Similarly, noteworthy interactions with the protein (see Figs. S1 and S2 for more details) were observed in case of docking analysis of **3x**. Based on FEB affinity, the overall order of studied molecules for binding energies with target protein is **3h** > **3p** > **3x** > **2b**. The results of the docking analysis supported the concept that presence of thiazole ring as in case of targeted compounds (**3**), is important to show excellent biological activity, anticancer, in this particular case.

3.4. ADMET properties

The pharmacokinetic relevance, utility index, and predictive accuracy of the model used were assessed through ADMET profiling using the pkCSM online tool (<https://biosig.lab.uq.edu.au/pkcsm/>), which is widely utilized in the design of small-molecule drug candidates [57]. Predicting *in vivo* behavior, particularly gastrointestinal absorption following oral administration, is crucial in early drug development, as poor absorption may negatively impact distribution and metabolism, and may lead to neurotoxicity or nephrotoxicity. The ADMET analysis included predictions of solubility, permeability, volume of distribution, unbound drug fraction, blood-brain barrier permeability, CNS exposure, systemic clearance, and multiple toxicity parameters (for details see Table S2 in ESI). The Caco-2 cell line, acquired from human intestinal epithelium, served as an *in vitro* model for estimating intestinal absorption. The ADMET profiles of **2b**, **3h**, **3p** and **3x** were considered and the best candidates were identified based on a balanced profile of favorable LogP, good absorption and distribution, minimal toxicity, and acceptable metabolism/excretion in each case (Fig. 6).

Toxicological predictions included LD₅₀ for acute toxicity and hepatotoxicity, the latter being a key concern due to its impact on liver function. Among all, molecule **3h** and **3p** found rationally good molecules because of the lowest LogP, best water solubility, highest intestinal absorption and permeability, and better clearance. Also, from the radar plot, it is portrayed that **3h** and **3p** consistently cover a broader area, meaning it's generally superior across most ADMET properties compared to **3x**. Thus, based on the ADMET analysis, the **3h** and **3p** molecules are found as the best compromise among all (for more details see Table S2 in ESI).

3.5. Structure-activity relationship

All the synthesized compounds were evaluated for assessing their antimicrobial and anticancer potential. It is observed that 4-bromophenylamino and 2,4-dibromophenylamino substitution at position-2 of thiazole ring results in a significant increase in the antimicrobial and anticancer activities, respectively. Moreover, an electron-donating group present on the phenyl ring, substituted at position-4 of the thiazole nucleus, exhibited prominent anticancer potential, whereas an electron-withdrawing group enhanced antimicrobial potential. A structure-activity relationship indicated that a chromenyl group substituted at position-4 of thiazole ring exhibited remarkable selectivity towards A549 cells. A trend observed in anticancer activity for haloaryl substitution at position-4 of the thiazole ring is Cl > F > Br, whereas F > Cl > Br was observed in the case of the 2,4,6-tribromophenylamino group. In comparison to intermediate compounds, **2a** and **2c**, decreased selectivity (A549) and increased cytotoxicity (Vero cells) were observed with the formation of a thiazole ring. However, 2,4-dibromophenylthiourea (**2b**) was found to be highly cytotoxic to Vero cells, with a selectivity index (SI) of approximately 1, comparable to that of the reference drug, Carboplatin. However, the cyclized thiazole derivatives (**3i-p**) exhibited higher selectivity toward A549 cells and reduced cytotoxicity against Vero cells (Fig. 7). Therefore, the thiazole ring plays a crucial role in enhancing the pharmacological efficacy of the

Table 4
Binding energies of favourable docked poses with the EGFR kinase domain.

Compounds	Binding Energy (kcal/mol)
Carboplatin	-5.5 [56]
2b	-5.3
3h	-8.8
3p	-8.7
3x	-8.1

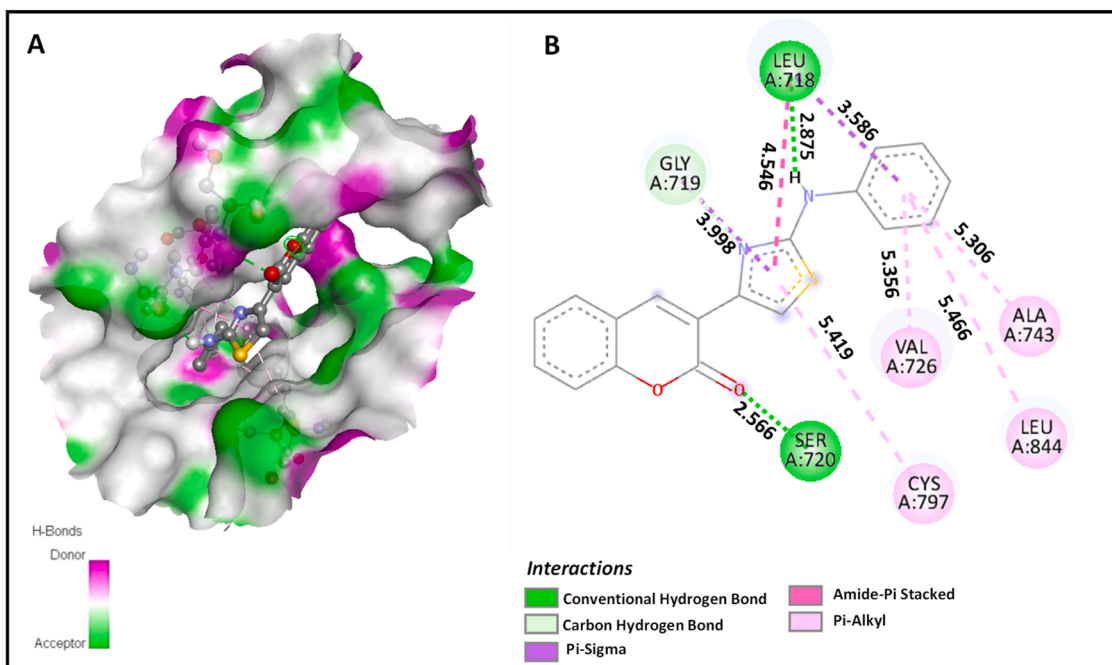


Fig. 5. Molecular docking model of **3h** molecule with EGFR kinase domain (PDB Id: 3W2S). (Given Interaction distances are in Å).

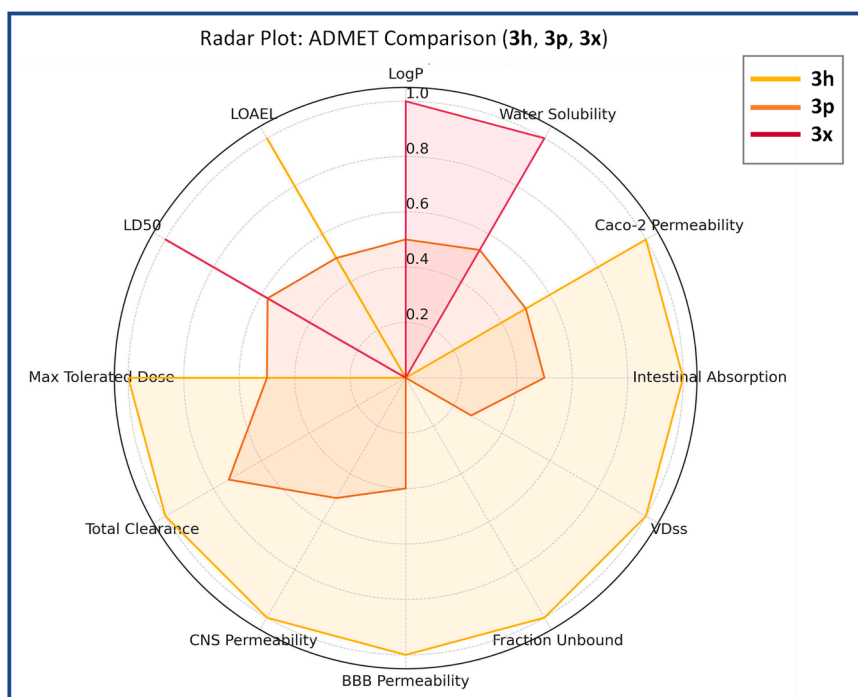


Fig. 6. Radar plot of the ADMET parameters comparison among **3h**, **3p** and **3x**.

synthesized compounds in presence of 2-(2,4-dibromophenylamino) group.

Overall, the impact of substitution patterns on biological activities is also summarized in Fig. 8.

4. Experimental section

4.1. Chemistry

Chemicals and reagents were commercially acquired from supplier

and utilized without further purification. The Biogen Scientific melting point apparatus was used to measure the melting points using the open capillary method, and the results are uncorrected. The FT-IR spectra were recorded on an ATR-FTIR spectrometer (Model ALPHA, Bruker), which facilitates the analysis of solid samples without further preparation. A Bruker 500 MHz spectrophotometer was used to record ^1H NMR and ^{13}C NMR spectra, referencing TMS as an internal standard, and chemical shifts were expressed in parts per million (ppm). Thermo-fischer Orbitrap Q-Exactive Plus Mass Spectrometer was used to record the mass spectra. A Single crystal was adeptly mounted onto Hampton

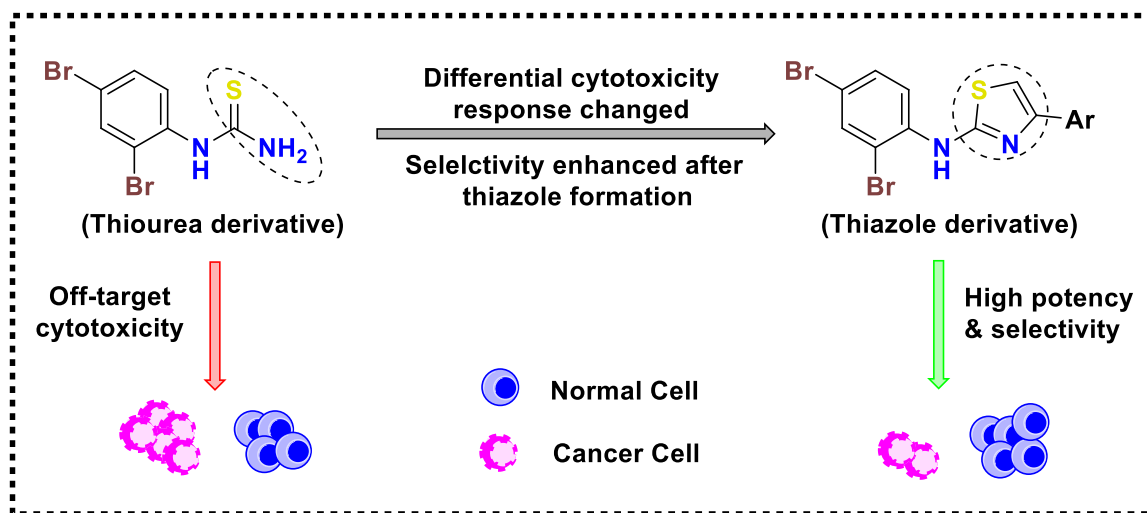


Fig. 7. Comparative anti-proliferative potential of potent 2-(2,4-Dibromophenylamino)-4arylthiazoles 3(i-p) with corresponding intermediate, 2b.

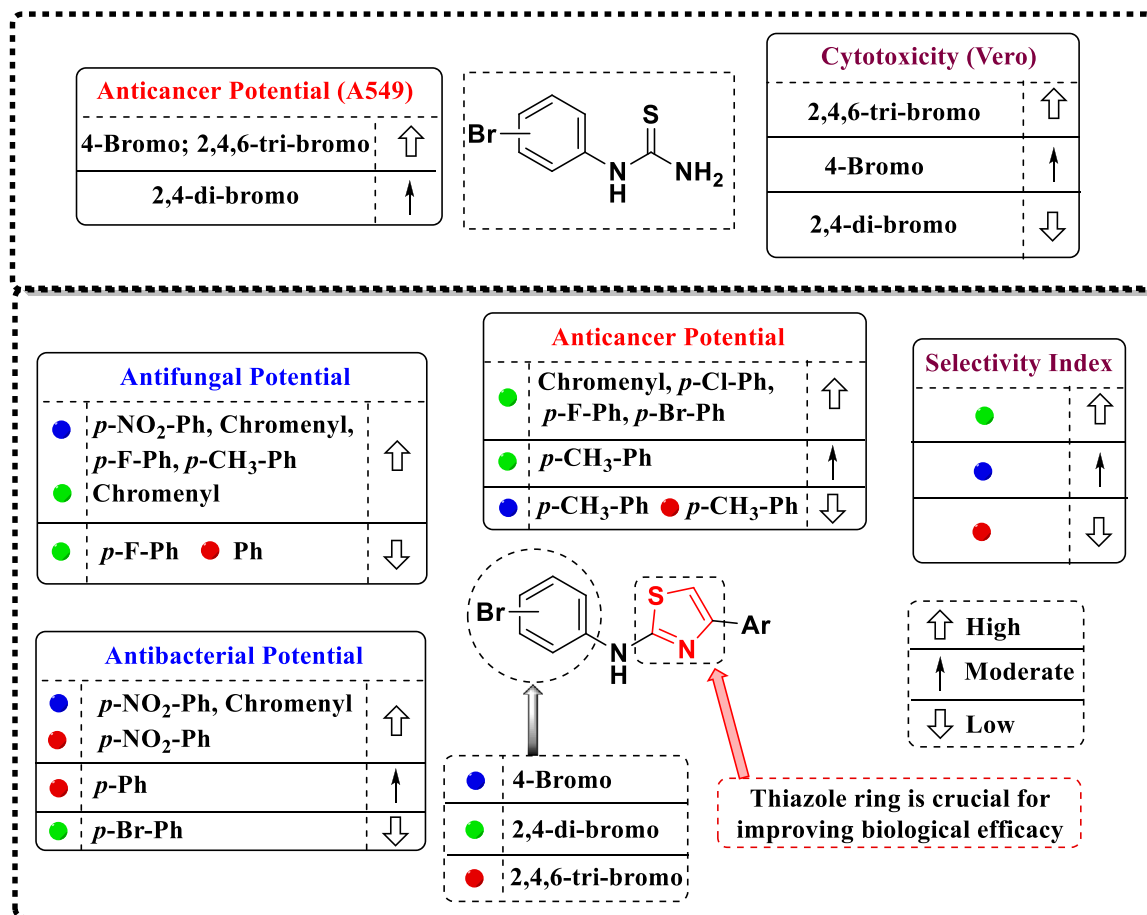


Fig. 8. Bioactivity and structure-activity relationship.

cryoloops for examination via X-ray diffraction at 293 K temperature, with a Rigaku Super-Nova X-ray diffractometer equipped with a Mo-K radiation source ($\lambda = 0.71073$), and a HyPix3000 CCD detector facilitating data capture. Data processing and extraction were performed using CrysAlisPro software. Following this, CrysAlisPro software was employed for data processing and extraction. The structure was initially determined using the SIR2004 [58] software's Direct Methods in conjunction with Olex2 [59], followed by refinement using the

least-squares minimization technique within the ShelXL3 [60] package. The solved crystallographic data for compounds **3r** and **3u** have been submitted to the Cambridge Crystallographic Data Centre as CCDC numbers 2372,249 and 2446,829, respectively. The data can be made available without any cost upon application with The Director, CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: Int. code +(1223) 336-033; e-mail: deposit@ccdc.cam.ac.uk). TLC plates were used to assess the purity of starting materials and products. The key

intermediates, α -bromoketones **1a-h** and **2**, were synthesized according to the literature procedures [40–42].

4.2. Synthesis of 2-(bromo/dibromo/tribromophenylamino)-4-arylthiazole derivatives (3a-x)

General procedure: Initially, substituted thiourea derivative (**2b**, 0.62 g, 2 mmol) was dissolved completely in ethanol. Added sodium bicarbonate (0.17 g, 2 mmol) and an appropriate phenacyl bromide (**1a**, 0.4 g, 2 mmol) to the reaction mixture and stirred it until complete precipitation at room temperature. Reaction progress was monitored by thin-layer chromatography using ethyl acetate and hexane as an eluent system in a 2:8 ratio. After completion of the reaction, the precipitates obtained were filtered and washed thoroughly with a mixture of cold water and ethanol to yield the targeted compound **3i**.

Similarly, other derivatives were also prepared.

4.2.1. Physical and detailed characterization data of the compounds (3a-x) are given below

4.2.1.1. 2-(4'-Bromophenylamino)-4-phenylthiazole (3a). Yield: 0.49 g, 74 %; ^1H NMR (80 MHz, CDCl_3 , δ_{H}): 7.24–8.19 (m, 10H, 2', 3', 5', 6', 2'', 3'', 4'', 5'', 6''-H, $\text{NH}(\text{D}_2\text{O}$ exchangeable)), 6.82 (s, 1H, 5-H).

4.2.1.2. 2-(4'-Bromophenylamino)-4-(4''-fluorophenyl)thiazole (3b). Yield: 0.47 g, 68 %; ^1H NMR (80 MHz, CDCl_3 , δ_{H}): 7.72–7.89 (m, 2H, 3'', 5''-H), 6.97–7.51 (m, 7H, 2', 3', 5', 6', 2'', 4'', 6''-H, $\text{NH}(\text{D}_2\text{O}$ exchangeable)), 6.77 (s, 1H, 5-H).

4.2.1.3. 2-(4'-Bromophenylamino)-4-(4''-chlorophenyl)thiazole (3c). Yield: 0.51 g, 70 %; ^1H NMR (80 MHz, CDCl_3 , δ_{H}): 7.77 (d, 2H, 3'', 5''-H, $^3J_{\text{H-H}} = 8.5$ Hz), 7.26–7.53 (m, 7H, 2', 3', 5', 6', 2'', 4'', 6''-H, $\text{NH}(\text{D}_2\text{O}$ exchangeable)), 6.84 (s, 1H, 5-H).

4.2.1.4. 2-(4'-Bromophenylamino)-4-(4''-bromophenyl)thiazole (3d). Yield: 0.53 g, 65 %; ^1H NMR (80 MHz, CDCl_3 , δ_{H}): 7.26–7.78 (m, 9H, 2', 3', 5', 6', 2'', 3'', 5'', 6''-H, NH , D_2O exchangeable)), 6.85 (s, 1H, 5-H).

4.2.1.5. 2-(4'-Bromophenylamino)-4-(4''-tolyl)thiazole (3e). Yield: 0.54 g, 79 %; ^1H NMR (80 MHz, CDCl_3 , δ_{H}): 7.26–7.78 (m, 9H, 2', 3', 5', 6', 2'', 3'', 5'', 6''-H, NH , D_2O exchangeable)), 6.79 (s, 1H, 5-H), 2.38 (s, 3H, 4'- CH_3).

4.2.1.6. 2-(4'-Bromophenylamino)-4-(4''-nitrophenyl)thiazole (3g). Yield: 0.51 g, 68 %; ^1H NMR (80 MHz, $\text{DMSO}-d_6$, δ_{H}): 10.08 (s, 1H, NH , D_2O exchangeable), 7.94–8.24 (m, 4H, 2', 3', 5'', 6''-H), 7.21–7.69 (m, 5H, 2', 3', 5', 6', 5-H).

4.2.1.7. 2-(4'-Bromophenylamino)-4-(2''-oxo-2H-chromen-3''-yl)thiazole (3h). Yield: 0.54 g, 80 %; ^1H NMR (80 MHz, $\text{DMSO}-d_6$, δ_{H}): 10.09 (s, 1H, NH , D_2O exchangeable), 8.85 (s, 1H, 4''-H), 7.29–7.77 (m, 9H, 5, 2', 3', 5', 6', 5'', 6'', 7'', 8''-H), 7.21–7.69 (m, 5H, 2', 3', 5', 6', 5-H).

4.2.1.8. 2-(2',4'-Dibromophenylamino)-4-phenylthiazole (3i). Yield: 0.64 g, 78 %; FTIR: (ν_{max} , cm^{-1}): 3388 (N–H str.), 1588 (C = N str.), 1543 (C = C str.); ^1H NMR (500 MHz, CDCl_3 , δ_{H}): 8.22 (d, 1H, 6'-H, $^3J_{\text{H-H}} = 9$ Hz), 7.79 (d, 2H, 2'', 6''-H, $^3J_{\text{H-H}} = 7$ Hz), 7.63 (d, 1H, 3'-H, $^4J_{\text{H-H}} = 2.5$ Hz), 7.40 (dd, 1H, 5'-H, $^3J_{\text{H-H}} = 6.5$ Hz, $^4J_{\text{H-H}} = 2.5$ Hz), 7.33–7.36 (m, 2H, 3'', 5''-H), 7.24–7.27 (m, 1H, 4''-H), 6.85 (s, 1H, 5-H); ^{13}C NMR (125 MHz, CDCl_3 , δ_{C}): 162.2, 151.8, 137.3, 134.6, 134.3, 131.5, 128.1, 126.1, 119.23, 114.1, 112.2, 103.3; HRMS: (m/z) M^+ calcd. for $\text{C}_{15}\text{H}_{10}\text{Br}_2\text{N}_2\text{S}$: 407.89, Found: 408.8999 ($\text{M}^+ + \text{H}$).

4.2.1.9. 2-(2',4'-Dibromophenylamino)-4-(4''-fluorophenyl)thiazole (3j). Yield: 0.43 g, 51 %; FTIR: (ν_{max} , cm^{-1}): 3388 (N–H str.), 1589 (C = N str.), 1539 (C = C str.); ^1H NMR (500 MHz, CDCl_3 , δ_{H}): 8.18 (d, 1H, 6'-H, $^3J_{\text{H-H}} = 8.8$ Hz), 7.73–7.77 (m, 2H, 3'', 5''-H), 7.62 (d, 1H, 3'-H, $^4J_{\text{H-H}} = 1.2$ Hz), 7.39–7.41 (m, 2H, 5'-H, $\text{NH}(\text{D}_2\text{O}$ exchangeable)), 7.00–7.05 (m, 2H, 2'', 6''-H), 6.77 (s, 1H, 5-H); ^{13}C NMR (125 MHz, CDCl_3 , δ_{C}): 163.8, 162.4, 161.4, 150.8, 137.2, 134.7, 131.5, 130.6, 127.8, 119.2, 115.7, 114.2, 112.3, 102.8; HRMS: (m/z) M^+ calcd. for $\text{C}_{15}\text{H}_9\text{Br}_2\text{FN}_2\text{S}$: 428.12 Found: 428.8887 (M^+).

4.2.1.10. 2-(2',4'-Dibromophenylamino)-4-(4''-chlorophenyl)thiazole (3k). Yield: 0.52 g, 59 %; FTIR: (ν_{max} , cm^{-1}): 3374 (N–H str.), 1588 (C = N str.), 1543 (C = C str.); ^1H NMR (500 MHz, $\text{DMSO}-d_6$, δ_{H}): 9.67 (s, 1H, NH , D_2O exchangeable), 8.29 (d, 1H, 6'-H, $^3J_{\text{H-H}} = 8.5$ Hz), 7.86–7.89 (m, 3H, 3'', 3'', 5''-H), 7.60 (dd, 1H, 5'-H, $^3J_{\text{H-H}} = 6.5$ Hz, $^4J_{\text{H-H}} = 2.5$ Hz), 7.45–7.46 (m, 3H, 2'', 6'', 5-H); ^{13}C NMR (125 MHz, $\text{DMSO}-d_6$, δ_{C}): 163.6, 148.3, 138.3, 134.5, 133.1, 131.9, 131.1, 128.5, 127.2, 123.2, 114.3, 114.1, 105.6; HRMS: (m/z) M^+ calcd. for $\text{C}_{15}\text{H}_9\text{Br}_2\text{ClN}_2\text{S}$: 444.57, Found: 444.8591 (M^+).

4.2.1.11. 2-(2',4'-Dibromophenylamino)-4-(4''-bromophenyl)thiazole (3l). Yield: 0.55 g, 56 %; FTIR: (ν_{max} , cm^{-1}): 3366 (N–H str.), 1586 (C = N str.), 1533 (C = C str.); ^1H NMR (500 MHz, $\text{DMSO}-d_6$, δ_{H}): 9.67 (s, 1H, NH , D_2O exchangeable), 8.28 (d, 1H, 6'-H, $^3J_{\text{H-H}} = 9$ Hz), 7.87 (d, 1H, 3'-H, $^4J_{\text{H-H}} = 2$ Hz), 7.81 (d, 2H, 3'', 5''-H, $^3J_{\text{H-H}} = 8.5$ Hz), 7.58–7.61 (m, 3H, 5', 2'', 6''-H), 7.47 (s, 1H, 5-H); ^{13}C NMR (125 MHz, $\text{DMSO}-d_6$, δ_{C}): 163.6, 148.3, 138.3, 134.5, 133.4, 131.4, 131.1, 127.5, 123.2, 120.5, 114.3, 114.1, 105.7; HRMS: (m/z) M^+ calcd. for $\text{C}_{15}\text{H}_9\text{Br}_3\text{N}_2\text{S}$: 489.02 Found: 488.8087 ($\text{M}^+ - \text{H}$).

4.2.1.12. 2-(2',4'-Dibromophenylamino)-4-(4''-tolyl)thiazole (3m). Yield: 0.48 g, 60 %; FTIR: (ν_{max} , cm^{-1}): 3384 (N–H str.), 1582 (C = N str.), 1508 (C = C str.); ^1H NMR (500 MHz, CDCl_3 , δ_{H}): 8.18 (d, 1H, 6'-H, $^3J_{\text{H-H}} = 8.5$ Hz), 7.64 (d, 2H, 2'', 6''-H, $^3J_{\text{H-H}} = 9$ Hz), 7.58 (d, 1H, 3'-H, $^4J_{\text{H-H}} = 2$ Hz), 7.38 (dd, 1H, 5'-H, $^3J_{\text{H-H}} = 8.5$ Hz, $^4J_{\text{H-H}} = 2$ Hz), 7.12 (d, 2H, 3'', 5''-H, $^3J_{\text{H-H}} = 9$ Hz), 6.57 (s, 1H, 5-H), 2.29 (s, 3H, 4'- CH_3); ^{13}C NMR (125 MHz, CDCl_3 , δ_{C}): 162.1, 159.6, 151.6, 137.3, 134.6, 131.5, 127.4, 127.3, 119.1, 114.1, 114, 112.2, 55.4; HRMS: (m/z) M^+ calcd. for $\text{C}_{16}\text{H}_{12}\text{Br}_2\text{N}_2\text{S}$: 424.15, Found: 424.9129 (M^+).

4.2.1.13. 2-(2',4'-Dibromophenylamino)-4-(4''-methoxyphenyl)thiazole (3n). Yield: 0.57 g, 72 %; FTIR: (ν_{max} , cm^{-1}): 3374 (N–H str.), 1589 (C = N str.), 1517 (C = C str.); ^1H NMR (500 MHz, CDCl_3 , δ_{H}): 8.19 (d, 1H, 6'-H, $^3J_{\text{H-H}} = 9$ Hz), 7.71 (d, 2H, 2'', 6''-H, $^3J_{\text{H-H}} = 8$ Hz), 7.61 (d, 1H, 3'-H, $^4J_{\text{H-H}} = 2.5$ Hz), 7.37–7.39 (dd, 1H, 5'-H, $J_{\text{H-H}} = 7, 2.5$ Hz), 6.87 (d, 2H, 3'', 5''-H, $^3J_{\text{H-H}} = 8$ Hz), 6.69 (s, 1H, 5-H), 3.76 (s, 3H, 4''- OCH_3); ^{13}C NMR (125 MHz, CDCl_3 , δ_{C}): 162.1, 151.9, 137.9, 137.3, 134.6, 131.7, 131.5, 126.1, 119.2, 114.1, 112.2, 102.5, 21.3; HRMS: (m/z) M^+ calcd. for $\text{C}_{16}\text{H}_{12}\text{Br}_2\text{N}_2\text{OS}$: 440.15, Found: 440.9080 (M^+).

4.2.1.14. 2-(2',4'-Dibromophenylamino)-4-(4''-nitrophenyl)thiazole (3o). Yield: 0.51 g, 58 %; FTIR: (ν_{max} , cm^{-1}): 3388 (N–H str.), 1588 (C = N str.), 1543 (C = C str.); ^1H NMR (500 MHz, $\text{DMSO}-d_6$, δ_{H}): 9.78 (s, 1H, NH , D_2O exchangeable), 8.25–8.29 (m, 3H, 6', 3'', 5''-H), 8.11 (d, 2H, 2'', 6''-H, $^3J_{\text{H-H}} = 9$ Hz), 7.88 (d, 1H, 3'-H, $^4J_{\text{H-H}} = 2$ Hz), 7.78 (s, 1H, 5-H), 7.61 (dd, 1H, 4'-H, $^3J_{\text{H-H}} = 6.5$, $^4J_{\text{H-H}} = 2.5$ Hz); ^{13}C NMR (125 MHz, $\text{DMSO}-d_6$, δ_{C}): 163.9, 147.46, 146.2, 140.2, 138.1, 134.5, 131.1, 126.4, 123.9, 123.5, 114.6, 114.4, 109.6; HRMS: (m/z) M^+ calcd. for $\text{C}_{15}\text{H}_9\text{Br}_2\text{N}_3\text{O}_2\text{S}$: 455.12, Found: 455.8832 (M^+).

4.2.1.15. 2-(2',4'-Dibromophenylamino)-4-(2''-oxo-2H-chromen-3''-yl)thiazole (3p). Yield: 0.78 g, 64 %; FTIR: (ν_{max} , cm^{-1}): 3337 (N–H str.), 1728 (C = O str.), 1588 (C = N str.), 1530 (C = C str.); ^1H NMR (500

MHz, DMSO- d_6 , δ_H): 9.77 (s, 1H, NH, D₂O exchangeable), 8.60 (s, 1H, 4''-H), 8.39 (d, 1H, 6'-H, $^3J_{H-H} = 8.5$ Hz), 7.90–7.94 (m, 1H, 5''-H), 7.84 (s, 1H, 5-H), 7.62–7.67 (m, 2H, 5', 7''-H), 7.38–7.47 (m, 2H, 6'', 8''-H); ^{13}C NMR (125 MHz, DMSO- d_6 , δ_C): 162.9, 158.6, 152.2, 143, 138.5, 138.2, 134.4, 131.6, 131.3, 128.8, 124.5, 123.4, 120.1, 119.1, 115.7, 114.4, 114.1, 111.5; HRMS: (m/z) M^+ calcd. for $\text{C}_{18}\text{H}_{10}\text{Br}_2\text{N}_2\text{O}_2\text{S}$: 478.15, Found: 478.8879 (M^+).

4.2.1.16. 2-(2',4',6'-Tribromophenylamino)-4-phenylthiazole (3q). Yield: 0.77 g, 80 %; FTIR: ($\nu_{\max}$, cm^{-1}): 3160 (N–H str.), 1574 (C = N str.), 1529 (C = C str.); ^1H NMR (500 MHz, DMSO- d_6 , δ_H): 9.88 (s, 1H, NH, D₂O exchangeable), 8.05 (s, 2H, 3', 5'-H), 7.76 (d, 2H, 2'', 6''-H, $^3J_{H-H} = 7$ Hz), 7.35–7.38 (m, 2H, 3'', 5''-H), 7.26–7.28 (m, 1H, 4''-H), 7.19 (s, 1H, 5-H); ^{13}C NMR (125 MHz, DMSO- d_6 , δ_C): 165.3, 138.3, 134.8, 134.1, 128.5, 128.4, 127.4, 125.5, 124.9, 120.2, 114.1, 102.9; HRMS: (m/z) M^+ calcd. for $\text{C}_{15}\text{H}_9\text{Br}_3\text{N}_2\text{S}$: 489.02, Found: 488.8089 (M^+ -H).

4.2.1.17. 2-(2',4',6'-Tribromophenylamino)-4-(4''-fluorophenyl)thiazole (3r). Yield: 0.60 g, 60 %; FTIR: ($\nu_{\max}$, cm^{-1}): 3156 (N–H str.), 1578 (C = N str.), 1527 (C = C str.); ^1H NMR (500 MHz, DMSO- d_6 , δ_H): 9.86 (s, 1H, NH, D₂O exchangeable), 8.10 (s, 2H, 3', 5'-H), 7.81–7.84 (m, 2H, 3'', 5''-H), 7.22–7.25 (m, 3H, 5, 2', 6'-H); ^{13}C NMR (125 MHz, DMSO- d_6 , δ_C): 165.4, 162.4, 160.5, 149.2, 134.8, 130.8, 127.5, 124.9, 120.4, 120.3, 115.3, 115.2, 102.8; HRMS: (m/z) M^+ calcd. for $\text{C}_{15}\text{H}_8\text{Br}_3\text{N}_2\text{FS}$: 507.01, Found: 506.7993 (M^+ -H).

4.2.1.18. 2-(2',4',6'-Tribromophenylamino)-4-(4''-chlorophenyl)thiazole (3s). Yield: 0.86 g, 83.4 %; FTIR: ($\nu_{\max}$, cm^{-1}): 3164 (N–H str.), 1581 (C = N str.), 1527 (C = C str.); ^1H NMR (500 MHz, DMSO- d_6 , δ_H): 9.86 (s, 1H, NH, D₂O exchangeable), 8.06 (s, 2H, 3', 5'-H), 7.76 (d, 2H, 3'', 5''-H, $^3J_{H-H} = 8.5$ Hz), 7.42 (d, 2H, 2'', 6''-H, $^3J_{H-H} = 8.5$ Hz), 7.28 (s, 1H, 5-H); ^{13}C NMR (125 MHz, DMSO- d_6 , δ_C): 165.5, 134.8, 133.1, 133.1, 131.8, 128.4, 127.2, 124.9, 120.4, 103.9; HRMS: (m/z) M^+ calcd. for $\text{C}_{15}\text{H}_8\text{Br}_3\text{ClN}_2\text{S}$: 523.46, Found: 524.7669 (M^+ + H).

4.2.1.19. 2-(2',4',6'-Tribromophenylamino)-4-(4''-bromophenyl)thiazole (3t). Yield: 0.73 g, 65 %; FTIR: ($\nu_{\max}$, cm^{-1}): 3405 (N–H str.), 1621 (C = N str.), 1503 (C = C str.); ^1H NMR (500 MHz, DMSO- d_6 , δ_H): 9.88 (s, 1H, NH, D₂O exchangeable), 8.12 (s, 2H, 3', 5'-H), 7.74 (d, 2H, 3'', 5''-H, $^3J_{H-H} = 8$ Hz), 7.62 (d, 2H, 2'', 6''-H, $^3J_{H-H} = 8$ Hz), 7.35 (s, 1H, 5-H); ^{13}C NMR (125 MHz, DMSO- d_6 , δ_C): 165.5, 163.6, 134.8, 134.5, 131.4, 131.4, 131.1, 127.5, 127.5, 123.2, 120.4, 101.9, 20.6; HRMS: (m/z) M^+ calcd. for $\text{C}_{15}\text{H}_8\text{Br}_4\text{N}_2\text{S}$: 567.91, Found: 568.7166 (M^+ + H).

4.2.1.20. 2-(2',4',6'-Tribromophenylamino)-4-(4''-tolyl) thiazole (3u). Yield: 0.68 g, 69 %; FTIR: ($\nu_{\max}$, cm^{-1}): 3131 (N–H str.), 1555 (C = N str.), 1524 (C = C str.); ^1H NMR (500 MHz, CDCl_3 , δ_H): 9.84 (s, 1H, NH, D₂O exchangeable), 8.05 (s, 2H, 3', 5'-H), 7.63 (d, 2H, 3'', 5''-H, $^3J_{H-H} = 8$ Hz), 7.17 (d, 2H, 2'', 6''-H, $^3J_{H-H} = 8$ Hz), 7.09 (s, 1H, 5-H), 2.29 (s, 3H, 4''-CH₃); ^{13}C NMR (125 MHz, CDCl_3 , δ_C): 165.2, 149.5, 138.5, 136.7, 134.8, 131.4, 128.9, 125.4, 124.7, 120.1, 101.9, 20.6; HRMS: (m/z) M^+ calcd. for $\text{C}_{16}\text{H}_{11}\text{Br}_3\text{N}_2\text{S}$: 503.05, Found: 504.8169 (M^+ + H).

4.2.1.21. 2-(2',4',6'-Tribromophenylamino)-4-(4''-methoxyphenyl)thiazole (3v). Yield: 0.77 g, 75 %; FTIR: ($\nu_{\max}$, cm^{-1}): 3127 (N–H str.), 1560 (C = N str.), 1531 (C = C str.); ^1H NMR (500 MHz, DMSO- d_6 , δ_H): 9.87 (s, 1H, NH, D₂O exchangeable), 8.05 (s, 2H, 3', 5'-H), 7.68 (d, 2H, 3'', 5''-H, $^3J_{H-H} = 9$ Hz), 6.93 (d, 2H, 2'', 6''-H, $^3J_{H-H} = 9$ Hz), 6.99 (s, 1H, 5-H), 3.76 (s, 3H, 4''-OCH₃); ^{13}C NMR (125 MHz, DMSO- d_6 , δ_C): 165.2, 158.7, 138.7, 126.8, 124.8, 124.7, 119.9, 113.8, 100.8, 54.9; HRMS: (m/z) M^+ calcd. for $\text{C}_{16}\text{H}_{11}\text{Br}_3\text{N}_2\text{OS}$: 519.04, Found: 520.7723 (M^+ + H).

4.2.1.22. 2-(2',4',6'-Tribromophenylamino)-4-(4''-nitrophenyl)thiazole (3w). Yield: 0.63 g, 60 %; FTIR: ($\nu_{\max}$, cm^{-1}): 3125 (N–H str.), 1560 (C = N str.), 1528 (C = C str.); ^1H NMR (500 MHz, DMSO- d_6 , δ_H): 9.96 (s,

1H, NH, D₂O exchangeable), 8.24 (d, 2H, 3'', 5''-H, $^3J_{H-H} = 9$ Hz), 8.08 (s, 2H, 3', 5'-H), 8 (d, 2H, 2'', 6''-H, $^3J_{H-H} = 9$ Hz), 7.63 (s, 1H, 5-H); ^{13}C NMR (125 MHz, DMSO- d_6 , δ_C): 165.8, 148, 146.1, 140.3, 137.4, 134.8, 133.9, 131.1, 126.3, 125.1, 123.9, 120.7, 108.2; HRMS: (m/z) M^+ calcd. for $\text{C}_{15}\text{H}_8\text{Br}_3\text{N}_3\text{O}_2\text{S}$: 534.02, Found: 534.7915 (M^+ + H).

4.2.1.23. 2-(2',4',6'-Tribromophenylamino)-4-(2''-oxo-2H-chromen-3''-yl) thiazole (3x). Yield: 0.71 g, 65%; FTIR: ($\nu_{\max}$, cm^{-1}): 3356 (N–H str.), 1709 (C=O str.), 1602 (C=N str.), 1551 (C=C str.); ^1H NMR (500 MHz, DMSO- d_6 , δ_H): 9.92 (s, 1H, NH, D₂O exchangeable), 8.41 (s, 1H, 4''-H), 8.11 (s, 2H, 3', 5'-H) 7.84–7.86 (d, 1H, 5''-H, $^3J_{H-H} = 8.0$ Hz), 7.70 (s, 1H, 5-H), 7.60–7.64 (m, 1H, 7''-H), 7.34–7.44 (m, 2H, 6'', 8''-H); ^{13}C NMR (125 MHz, DMSO- d_6 , δ_C): 165.8, 159.2, 152.7, 138.9, 135.5, 132.1, 129.4, 125.9, 125.2, 121.6, 120.8, 119.6, 116.3, 110.7; HRMS: (m/z) M^+ calcd. for $\text{C}_{18}\text{H}_9\text{Br}_3\text{N}_2\text{O}_2\text{S}$: 557.05, Found: 558.7970 (M^+ + H).

4.3. Biological assays

4.3.1. Anticancer activity

Culture of Animal cells: A549 (Human lung adenocarcinoma cell) and Vero (African green kidney monkey cells) cells were cultured in Dulbecco's Modified Eagle Medium (DMEM), Gibco™ media supplemented with 10 % Fetal bovine serum (FBS), Gibco™ and 100 U/mL Pen-Strap antibiotics solution. Cells were maintained in a carbon dioxide (CO₂) incubator with a continuous flow of 5 % CO₂ at 37 °C.

In-vitro cytotoxicity assay: The confluent adherent cells were harvested with 0.25 % trypsin-EDTA solution [61]. Cells with a seeding density of 1×10^4 cells/well were seeded on 96-well plates followed by incubation for 24 h for complete adherence. After incubation, the stock concentration of test compounds prepared in DMSO was added to the wells, with an initial concentration of 1 mM in the initial wells and a final concentration of 0.2 % DMSO in the wells. This was followed by two-fold serial dilutions. The cells were treated with the prepared compounds for 48 h in CO₂ incubator followed by MTT assay.

3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) salt was used to validate the cytotoxicity effect of the test compounds on A549 human lung cancer cells and Vero, normal kidney cell line. On the day of the MTT assay, the media was replaced with fresh media containing 0.5 % MTT solution (5 mg/mL stock in 1X PBS), followed by incubation for 3 h at 37 °C. The insoluble formazan crystals formed were dissolved in DMSO and incubated in a shaker for 30 min at room temperature. The absorbance of the 96-well plates was then read at 492 nm on an ELISA microplate reader, and the percentage of cell viability was calculated.

Selectivity index: The Selectivity index (SI) for compounds with anticancer activity was calculated by dividing the IC₅₀ concentrations of non-cancerous Vero cells by the IC₅₀ concentration of A549 cells.

Statistical Analysis: All experiments were conducted in triplicate ($n = 3$), and data are presented as the standard error of the mean (S.E.M). GraphPad Prism 8.0.1 was used to analyze nonlinear regression and create graphs. One way ANOVA was performed for comparative analysis.

4.3.2. Antibacterial activity

To assess the antimicrobial potential of all synthesized compounds, a cell susceptibility assay was considered against Gram-positive; *S. aureus*, Gram-negative; *E. coli* bacteria, and a fungal pathogen *C. albicans* [49]. A fixed amount (100 µg) of each test compound was used to screen for their antimicrobial potential by performing a spot assay. *E. coli*, *S. aureus*, and *C. albicans* were cultured in LB, MHB, and YEPD broth, respectively. Sterile water is used as a negative control in antibacterial activity. After revival, the cells were plated equally on respective agar plates, and 80 µg of each compound was spotted on the plates. The plates were then incubated overnight (bacterial plates at 37 °C and fungal plate at 30 °C). Based on the zone of inhibition on the plates, the compounds

were narrowed down for determination of IC₅₀ values by performing broth microdilution assay. For broth micro-dilution assay, an equal number of all the cells was seeded in 96-well plates to which the compound was added at the highest concentration of 10 mg/ml and further serially diluted by 2-fold until the concentration of 0.156 mg/ml. The plates were then incubated overnight, followed by the absorbance measurement at 600 nm. Ampicillin and Fluconazole were used as reference drugs for antibacterial and antifungal screening, respectively. One way ANOVA was performed for comparative analysis.

5. Conclusion

2-(Bromo/polybromosubstituted phenylamino)-4-arylthiazoles (**3a-x**) were synthesized via the Hantzsch-thiazole method to investigate their biological potential emphasizing the effect of number and position of bromine substitution on phenylamino group attached at position-2 of the thiazole ring. The compounds were characterized on the basis of advanced spectroscopic and single-crystal X-ray diffraction techniques. All the synthesized compounds were screened for evaluating their anticancer and antimicrobial potential. Among all, 2-(2,4-Dibromophenylamino)-4-arylthiazoles were found to exhibit the least cytotoxicity to Vero cells and excellent selectivity towards A549 cells, making them suitable candidates for further studies. Moreover, **3p** was found to be least cytotoxic to normal Vero cells (IC₅₀ = 1150.67 ± 4.4 µM) and highly selective to A549 cells (SI = 8.86), as compared to the standard drug, Carboplatin. However, 2-(Bromophenyl)-4-arylthiazoles and 2-(2,4,6-Tribromophenyl)-4-arylthiazoles were found to be equally cytotoxic to both A549 as well as Vero cells. In terms of antifungal activity, **3g** exhibited remarkable anti-candida potential, followed by **3h**, **3b**, **3p**, and **3e**, compared to the standard drug, Fluconazole. Among all the synthesized compounds, **3g** and **3h** have prominent antibacterial activity against *S. aureus*, while the rest have moderate or less antibacterial activity. However, none of the prepared compounds were found to be effective against *E. coli*.

The selectivity trend revealed that di-brominated compounds at position-2 and 4 of the phenylamino group exhibited a balance between biological potency and selectivity that might be due to overall enhanced lipophilicity, the electron-withdrawing nature of the molecule, and favourable interactions with biological targets, compared to mono- and tri-brominated analogues. Therefore, they may be considered as suitable candidates for further biological studies and applications. On the other hand, *mono*-brominated derivatives exhibited excellent antimicrobial activity against *S. aureus* and *C. albicans*, hence may be a good choice for antimicrobial studies in the future. Molecular docking analysis elucidated critical ligand-target interactions that likely contribute to the observed high biological activity of **3h** and **3p** compounds. ADMET analysis elucidates the pharmacokinetic and toxicological profiles of these compounds, offering critical insights into their drug-likeness behavior. The results obtained from the studies contribute to the rational design of multifunctional thiazole-based compounds with enhanced biological potential.

Our future research will be focused on strategic structural modifications aimed at improving selectivity and therapeutic efficacy alongside *in vivo* studies to elucidate the mechanism of action and identify specific molecular targets.

CCRediT authorship contribution statement

Aman Kumar: Writing – review & editing, Writing – original draft, Software, Methodology, Investigation, Formal analysis, Data curation. **Mettie Brahma:** Writing – review & editing, Writing – original draft, Investigation. **Shaurya Prakash:** Writing – review & editing, Writing – original draft, Formal analysis. **Antresh Kumar:** Writing – review & editing, Writing – original draft, Funding acquisition, Formal analysis. **Mulaka Maruthi:** Writing – review & editing, Writing – original draft, Methodology, Investigation. **Manjeet Kumar:** Writing – review &

editing, Writing – original draft, Data curation. **Azaj Ansari:** Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Ramesh Kataria:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Project administration, Methodology, Investigation, Conceptualization. **Vinod Kumar:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.molstruc.2025.144301.

Data availability

Data will be made available on request.

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