Research Article

Synthesis, antiproliferative and antibacterial activity of novel Phenothiazine-[1, 2, 3] triazole hybrids

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Abstract

Objective: Twenty five 1,2,3-triazole derivatives of phenothiazines (**5a-5k**, **6a-6g**, and **7a-7g**) were synthesized in order to evaluate their anti-proliferative and antibacterial activities. **Material and methods:** The newly synthesized compounds were characterized by spectroscopic (FTIR, ^{1}H NMR, ^{13}C NMR and Mass) analysis after synthesis. All compounds were screened for their *in vitro* anticancer activity against MCF-7 (breast), HeLa (cervical) and A-549 (alveolar) cell lines. The minimum inhibitory concentrations (*MIC*) of the synthesized compounds (**5a-5k**, **6a-6g** and **7a-7g**) were tested against the gram-positive organisms *B. subtilis*, *S. aureus* and *S. epidermidis* and the gram-negative organisms *E. coli*, *P. aeruginosa*, and *K. pneumoniae*. **Results:** The *in vitro* cytotoxic examination results revealed that compounds **7a** and **7b** exhibited good anti-proliferative activity against three cancer cell lines, MCF-7, HeLa and A-549 with IC_{50} values ranging from 09.11 ± 0.3 μM to 20.11 ± 1.0 μM respectively. Antibacterial activity revealed that the compounds **5d, 6d,** and **7d** against *B. subtilis* and *S. aureus*, compound **5i** against *P. aeruginosa* and compound **5j** against *E. coli* and *P. aeruginosa* have shown equipotent activity on comparing with the standard drugs penicillin and streptomycin. **Conclusion:** We succeeded in guiding the change of substituents in the triazole ring together with the phenothiazine-5,5-dioxide group, which played a crucial role in the development of a promising anticancer activity and also shown equipotent antibacterial activity against gram-positive and gram-negative organisms. By making a simple modification of the structure, a new potent analog having the desired anticancer and antibacterial activity can be produced with good efficiency.

***Keywords*:** Phenothiazine, 1, 2, 3-triazole, anticancer activity, antibacterial activity

Introduction

The past decades have established many attempts to identify the structural features of compounds essential for anticancer activity. It is found that the number of deaths due to breast, liver, and lung cancer is increasing dramatically. The immortality and morbidity of cancer patients is the second highest among all diseases in the world, after cardiovascular diseases (Shewach et al., 2009). The World Cancer Congress has released a report stating that 7.6 million cancer deaths (around 13% of all deaths) in 2008 are expected to continue by 2030 it is estimated to be 13.1 million. Finding new drugs that can be targeted cancer cells are the current target of cancer therapy, and many pharmaceutical industries are investing billions of dollars to develop effective agents for the diagnosis and treatment of cancer. Scientists have followed many strategies to identify new molecules for more efficient treatment of cancer (Lloyd et al., 2006). On the other hand, bacterial infections have increased at an alarming rate, causing deadly diseases. The treatment of infectious diseases remains an important issue due to the increasing number of multidrug-resistant microbial pathogens (Pfeltz et al., 2004; Tenoverand McDonald, 2005). In view of this, the advancement of newer chemotherapeutic agents that act selectively and without side effects on the target has become a major issue for medicinal chemists.

Organic compounds containing 1,2,3-triazoles have been synthesized as useful chemotherapeutic agents for many diseases (Wang et al., 2008). The compounds containing a

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1,2,3-triazole core display broad spectrum of biological activities which includes antimicrobial (Holla et al., 2005; Anis et al., 2019), anticonvulsant (Kelley et al., 1995), antioxidant (Mady et al., 2014), antiviral (Alvarez et al., 1994; Velazquez et al., 1998), and anti-inflammatory activities (Rao et al., 2014). There are some 1,2,3-triazoles linked pharmacophores with potent anti-proliferative activity (Chen et al., 2009; Kamal et al., 2011; Cindy et al., 2013; Kurumurthy et al., 2014; Freitas et al., 2014). 1, 2, 3-triazole core containing drugs such as tazobactam, cefatrizine and carboxyamidotriazole (CAI) (Figure. 1) are available. On the other hand, the chemistry of phenothiazine derivatives has known to possess biological importance (Pluta et al., 2011). As shown in figure 1, some phenothiazine derivatives have been reported as biologically active drug candidates for many years, and the phenothiazine drug chlorpromazine (CPZ) is reported to have been successfully used to treat a TB patient (Hollister et al., 1960). Such compounds have also been reported as histamine H1 antagonists (Katsumi et al., 2009), human farnesyltransferase inhibitors (Dalila et al., 2012), and cholinesterase inhibitors (Sultan et al., 2013). The association of the phenothiazine with the 1,2,3-triazole ring resulted recently in the synthesis of new agents with anti-tubercular potential (Dinesh et al., 2014).

Owing to the remarkable pharmacological properties of phenothiazine and 1,2,3-triazole derivatives, we aimed to design a moiety that embodied both the active pharmacophores in a single molecular framework and to evaluate their biological activities especially anti-proliferative activity (Figure 1). Therefore, in the present study and in continuation of our work on1,2,3-triazole containing heterocycles (Narsimha et al., 2014, 2016, 2016a, 2018; Reddy et al., 2016, 2017; Kumar et al., 2017; Swamy et al., 2016, 2017, 2017a), we report the synthesis of novel1,2,3-triazole-phenothiazine along with alipophilic spacer and evaluation of their antiproliferative and antibacterial activity.

Materials and methods

All the solvents and the starting materials were purchased from commercial sources and used without further purification. Column chromatography was performed on silica gel 60–120 mesh. Melting points were determined using a Cintex apparatus. Elemental analysis was measured by means of Perkin Elmer 2400 CHN elemental analyzer. IR spectra were obtained on a PerkinElmer BX serried FTIR 5000 spectrometer using KBr pellet. 400 MHz NMR spectrometer was used to acquire ^{1}H-NMR spectra. The instrument was set at 100 MHz for acquiring ^{13}C NMR spectra. Coupling constant (J) values are presented in Hertz and spin multiples are given as s (singlet), d (doublet), t (triplet), and m (multiplet). Mass spectra were recorded by using ESI–MS.

General procedure for the preparation of 10-(prop-2-yn-1-yl)-10H-phenothiazine (2)

A mixture of 10H-phenothiazine (1) (25 mmol) and tBuOK (75 mmol) in DMF (50 mL) was treated with propargyl bromide (32.6 mol) at room temperature for 8h and the progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured carefully into ice-cold water (50 mL), the solid was filtered off, washed with water, and dried. Pale yellow solid (88% yield). Yellow solid, mp 101–103°C.^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.41-7.35 (m, 4H), 7.30-7.26 (m, 2H), 7.09-7.03 (m, 2H), 4.71 (s, 2H, N-CH2), 2.28 (s, 1H, -CH) ESI-MS m/z: 238 [M+H].

Synthesis of 10-(prop-2-yn-1-yl)-10H-phenothiazine 5-oxide (3)

To a solution of 10-(prop-2-yn-1-yl)-10H-phenothiazine (2) (0.0197 mol) in DCM (40 mL) was added m-CPBA (0.03 mol) at 0^{o}C and the reaction mixture was stirred at room temperature for 12h. After completion of the reaction by TLC analysis, the reaction mixture was quenched with a saturated aqueous solution of sodium bicarbonate (40 mL), extracted with DCM (2 x 30 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to afford crude compound 3. Pale yellow solid (Yield 63%), Pale yellow solid, mp 116–118°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.75-7.51 (m, 6H), 7.32-7.23 (m, 2H), 4.73 (s, 2H, N-CH_2), 2.34 (s, 1H, -CH) ESI-MS m/z: 254 [M+H].

Synthesis of 10-(prop-2-yn-1-yl)-10H-phenothiazine 5, 5-dioxide (4)

To a solution of 10-(prop-2-yn-1-yl)-10H-phenothiazine (**2**) (0.0197 mol) in DCM (40 mL), was added m-CPBA (0.06 mol) at 0^{o}C and the reaction mixture was stirred at room temperature for 12h. After completion of the reaction, the reaction mixture was quenched with a saturated aqueous solution of sodium bicarbonate (40 mL), extracted with DCM (2 x 30 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to afford crude compound 4. White solid (Yield 72%), mp 125–127°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.01-7.95 (m, 2H), 7.77-7.70 (m, 2H), 7.60-7.57 (m, 2H), 7.40-7.36 (m, 2H), 4.77 (s, 2H, N-CH_2), 2.36 (s, 1H, -CH); ESI-MS m/z: 270 [M+H].

General procedure for the preparation of (**5a-k**, **6a-g** and **7a-g**)

To a solution of alkyne (1.5 mmol) and aryl azide (2.0 mmol) in THF (15 mL) was added copper iodide (10 mol %) and the reaction mixture was stirred at room temperature for

8-10h. After completion of the reaction, the reaction mixture was diluted with water (15 mL) and the product was extracted with ethyl acetate (2 x 15 mL). The combined organic layer was dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated under vacuum and the crude product obtained was purified by column chromatography (hexane/ethyl acetate gradient) to afford the pure desired product.

10-((1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methyl)-10H-phenothiazine(5a)

White solid (89%), mp 151–153°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.687 (s, 1H, triazole), 7.550 (d, *J*= 8.8 Hz, 2H), 7.140- 7.052 (m, 4H), 6.973- 6.821(m, 6H), 5.281 (s, 2H, N-CH_2), 3.870 (s, 3H, O-CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.83, 144.18, 127.45, 127.21, 123.77, 122.88, 122.06, 115.21, 114.71, 55.62, 45.06. IR (υ, cm^{-1}): 3162, 2922, 1588, 1462, 1215, 1033, 751. ESI-MS m/z: 387 [M+H]. Anal. Cal for $C_{22}H_{18}N_4OS$: C, 68.37; H, 4.69; N, 14.50; found: C, 68.43; H, 4.63; N, 14.44.

10-((1-(3,5-dimethylphenyl)-1H-1,2,3-triazol-4-yl)methyl)-10H-phenothiazine(5b)

Pale yellow solid (78%), mp 122–124°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.766 (s, 1H, triazole), 7.289 (s, 2H), 7.240-7.120 (m, 2H), 7.110- 7.010 (m, 3H), 7.000- 6.900(m, 2H), 6.890- 6.700 (m, 2H), 5.301 (s, 2H, N-CH_2), 2.373 (s, 6H, Ar-CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.13, 139.72, 130.38, 127.49, 127.20, 123.64, 122.68, 118.22, 115.14, 45.11, 21.26. IR (υ, cm^{-1}): 3165, 2913, 1589, 1422, 122, 1036, 668. ESI-MS m/z: 385 [M+H]. Anal. Cal for $C_{23}H_{20}N_4S$: C, 71.85; H, 5.24; N, 14.57; found: C, 71.93; H, 5.18; N, 14.52.

10-((1-(2,3-dimethylphenyl)-1H-1,2,3-triazol-4-yl)methyl)-10H-phenothiazine (5c)

Pale yellow solid (70%), mp 110–112°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.474 (s, 1H, triazole), 7.290- 7.272 (m, 1H), 7.205-7.080 (m, 6H), 6.945- 6.908 (m, 2H), 6.865 (d, *J*= 8Hz, 2H), 5.342 (s, 2H, N-CH_2), 2.325 (s, 3H, Ar-CH_3), 1.854 (s, 3H, Ar-CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.30, 138.71, 136.49, 132.64, 131.37, 127.32, 127.22, 126.05, 124.68, 124.19, 123.87, 122.87, 45.01, 20.29, 13.99. IR (υ, cm^{-1}): 3133, 2962, 1574, 1460, 1217, 1039, 702. ESI-MS m/z: 385 [M+H]. Anal. Cal for $C_{23}H_{20}N_4S$: C, 71.85; H, 5.24; N, 14.57; found: C, 71.96; H, 5.21; N, 14.49.

10-((1-(3,5-dichlorophenyl)-1H-1,2,3-triazol-4-yl)methyl)-10H-phenothiazine (5d)

Yellow solid (82%), mp 166–168 C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.730(s, 1H, triazole), 7.607 (s, 2H), 7.410- 7.360 (m, 1H), 7.190- 7.100 (m, 2H), 7.090- 7.010 (m, 2H), 6.987- 6.899 (m, 2H), 6.840- 6.760 (m, 2H), 5.285 (s, 2H, N-CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.04, 138.11, 136.27, 128.69, 127.50, 127.36, 123.97, 123.06, 120.34, 118.81, 115.09, 44.81. IR (υ, cm^{-1}): 3142, 2937, 1578, 1463, 1219, 1039, 694. ESI-MS m/z: 426 [M+H]. Anal. Cal for $C_{21}H_{14}Cl_2N_4S$: C, 59.30; H, 3.32; N, 13.17; found: C, 59.26; H, 3.27; N, 13.20.

10-((1-(4-butylphenyl)-1H-1,2,3-triazol-4-yl)methyl)-10H-phenothiazine (5e)

White solid (72%), mp 114–116°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.684 (s, 1H, triazole), 7.580-7.480 (m, 2H), 7.300- 7.200 (m, 2H), 7.150- 7.000 (m, 4H), 6.930- 6.860 (m, 2H), 6.820- 6.750 (m, 2H), 5.258 (s, 2H, N-CH_2), 2.700- 2.560 (m, 2H, Ar-*CH_2*-CH_2-CH_2-CH_3), 1.640- 1.480 (m, 2H, Ar-CH_2-*CH_2*-CH_2-CH_3), 1.400- 1.270 (m, 2H, Ar-CH_2-CH_2-*CH_2*-CH_3), 0.989- 0.810 (m, 3H, Ar-CH_2-CH_2-CH_2-*CH_3*). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.06, 127.43, 127.20, 123.76, 122.88, 122.06, 115.23, 114.78, 45.06, 34.72, 32.06, 21.83, 13.29. IR (υ, cm^{-1}): 3161, 3057, 1589, 1462, 1215, 1031, 754. ESI-MS m/z: 413 [M+H]. Anal. Cal for $C_{25}H_{24}N_4S$: C, 72.78; H, 5.86; N, 13.58; found: C, 72.86; H, 5.92; N, 13.51.

10-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methyl)-10H-phenothiazine (5f). Pale yellow solid(81%), mp 138–140 C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.687 (s, 1H, triazole), 7.458 (d, *J*= 8.4 Hz, 2H), 7.272 (s, 1H), 7.149-7.058 (m, 4H), 6.983- 6.831 (m, 5H), 5.305 (s, 2H, N-CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.83, 135.17, 128.00, 127.78, 125.38, 125.28, 122.09, 119.34, 118.55, 117.34, 114.85, 45.24. IR (υ, cm^{-1}): 3142, 3012, 1590, 1461, 1217, 1038, 694. ESI-MS m/z: 391 [M+H]. Anal. Cal for $C_{21}H_{15}ClN_4S$: C, 64.53; H, 3.87; N, 14.33; found: C, 64.58; H, 3.81; N, 14.27.

10-((1-(4-bromophenyl)-1H-1,2,3-triazol-4-yl)methyl)-10H-phenothiazine(5g)

Yellow solid (68%), mp 127–129°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.720 (s, 1H, triazole), 7.601- 7.525 (m, 3H), 7.251 (s, 1H), 7.139- 7.043 (m, 4H), 6.926- 6.791 (m, 4H), 5.275 (s, 2H, N-CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 145.00, 132.84, 127.49, 127.30, 122.99, 121.80, 115.16, 45.02. IR (υ, cm^{-1}): 3131, 3022, 1579, 1451, 1212, 1028, 747. ESI-MS m/z: 437 [M+2H]. Anal. Cal for $C_{21}H_{15}BrN_4S$: C, 57.94; H, 3.47; N, 12.87; found: C, 57.88; H, 3.42; N, 12.93.

10-((1-(3-nitrophenyl)-1H-1,2,3-triazol-4-yl)methyl)-10H-phenothiazine(5h)

Yellow solid (70%), mp 171–173°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.540-8.530 (m, 1H), 8.277- 8.249 (m, 1H), 7.872 (s, 1H, triazole), 7.716- 7.675 (m, 1H), 7.169- 7.146 (m, 2H), 7.107- 7.084 (m, 2H), 6.951- 6.910 (m, 2H), 6.833-6.811 (m, 2H), 5.316 (s, 2H, N-CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.92, 146.46, 144.07, 137.60, 130.87, 127.50,

127.40, 125.77, 124.08, 123.19, 123.09, 120.38, 115.28, 115.13, 44.77. IR (υ, cm^{-1}): 3142, 3014, 1589, 1457, 1219, 1037, 689. ESI-MS m/z: 402 [M+H]. Anal. Cal for $C_{21}H_{15}N_5O_2S$: C, 62.83; H, 3.77; N, 17.45; found: C, 62.77; H, 3.69; N, 17.53.

10-((1-(4-chloro-3,5-dimethoxyphenyl)-1H-1,2,3-triazol-4-yl)methyl)-10H-phenothiazine (5i). White solid (66%), mp 184–186°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.953 (s, 1H, triazole), 7.485(s, 2H), 7.281- 6.866 (m, 8H), 5.322 (s, 2H, N-CH_2), 3.931 (s, 3H, O-CH_3), 3.689 (s, 3H, O-CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.52, 144.47, 144.36, 127.33, 127.19, 124.19, 124.11, 123.27, 122.85, 115.45, 115.01, 108.98, 56.90, 56.68, 45.02. IR (υ, cm^{-1}): 3151, 2987, 1582, 1457, 1225, 1044, 694. ESI-MS m/z: 451 [M+H]. Anal. Cal for $C_{23}H_{19}ClN_4O_2S$: C, 61.26; H, 4.25; N, 12.42; found: C, 61.33; H, 4.21; N, 12.37.

10-((1-(3-(trifluoromethyl)phenyl)-1H-1,2,3-triazol-4-yl)methyl)-10H-phenothiazine (5j) Pale yellow solid (69%), mp 155–157°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.716 (s, 1H, triazole), 7.488 (s, 1H), 7.292- 7.103 (m, 7H), 6.947- 6.853 (m, 4H), 5.348 (s, 2H, N-CH_2). IR (υ, cm^{-1}): 3152, 3012, 1578, 1460, 1241, 1029, 747. ESI-MS m/z: 425 [M+H]. Anal. Cal for $C_{22}H_{15}F_3N_4S$: C, 62.25; H, 3.56; N, 13.20; found: C, 62.17; H, 3.51; N, 13.25.

10-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)-10H-phenothiazine(5k)

White solid (73%), mp 118–120°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.780 (s, 1H, triazole), 7.720- 7.620 (m, 2H), 7.600- 7.380 (m, 3H), 7.200- 7.120 (m, 2H), 7.110- 7.040 (m, 2H), 7.000- 6.900 (m, 2H), 6.890- 6.800 (m, 2H), 5.316 (s, 2H, N-CH_2). IR (υ, cm^{-1}): 3131, 3024, 1589, 1461, 1214, 1033, 751. ESI-MS m/z: 357 [M+H]. Anal. Cal for $C_{21}H_{16}N_4S$: C, 70.76; H, 4.52; N, 15.72; found: C, 70.83; H, 4.44; N, 15.67.

10-((1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methyl)-10H-phenothiazine 5-oxide (6a) White solid (74%), mp 178–180°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.200-7.980 (m, 2H), 7.750 (s, 1H, triazole), 7. 619- 7.580 (m, 2H), 7.530 (d, *J*= 9 Hz, 2H), 7.472 (d, *J*= 8.4 Hz, 2H), 7.314- 7.282 (m, 2H), 6.945 (d, *J*= 9 Hz, 2H), 5.726 (s, 2H, N-CH_2), 3.834 (s, 3H, O-CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.02, 143.25, 136.26, 126.55, 124.52, 122.79, 121.78, 121.58, 119.92, 114.55, 108.10, 55.28, 45.15. IR (υ, cm^{-1}): 3130, 3071, 1589, 1456, 1047. ESI-MS m/z: 403 [M+H]. Anal. Cal for $C_{22}H_{18}N_4O_2S$: C, 65.65; H, 4.51; N, 13.92; found: C, 65.72; H, 4.54; N, 13.85.

10-((1-(3,5-dimethylphenyl)-1H-1,2,3-triazol-4-yl)methyl)-10H-phenothiazine 5-oxide (6b)

Yellow solid (73%), mp 159–161°C, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.250-7.970 (m, 2H), 7.749 (s, 1H, triazole), 7. 623-7.580 (m, 2H), 7.500- 7.430 (m, 2H), 7.320- 7.230 (m, 4H), 7.025 (s, 1H), 5.721 (s, 2H, N-CH_2), 2.345 (s, 6H, Ar-CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 139.70, 138.69, 136.63, 133.14, 131.36, 130.49, 125.33, 122.47, 120.51, 118.15, 116.32, 45.15, 21.22. IR (υ, cm^{-1}): 3140, 3072, 1590, 1426, 1039. ESI-MS m/z: 401 [M+H]. Anal. Cal for $C_{23}H_{20}N_4OS$: C, 68.98; H, 5.03; N, 13.99; found: C, 69.04; H, 5.11; N, 13.93.

10-((1-(2,3-dimethylphenyl)-1H-1,2,3-triazol-4-yl)methyl)-10H-phenothiazine 5-oxide (6c).

Pale yellow solid (68%), mp 155–157°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.230-7.960 (m, 2H), 7.753 (s, 1H, triazole), 7. 645- 7.578 (m, 2H), 7.510- 7.420 (m, 3H), 7.330- 7.232 (m, 4H), 5.723 (s, 2H, N-CH_2), 2.445 (s, 3H, Ar-CH_3), 2.245 (s, 3H, Ar-CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.73, 132.99, 131.44, 131.19, 126.03, 123.78, 122.40, 45.20, 20.24, 14.06. IR (υ, cm^{-1}): 3151, 3068, 1588, 1442, 1043. ESI-MS m/z: 401 [M+H]. Anal. Cal for $C_{23}H_{20}N_4OS$: C, 68.98; H, 5.03; N, 13.99; found: C, 68.96; H, 5.07; N, 13.94.

10-((1-(3,5-dichlorophenyl)-1H-1,2,3-triazol-4-yl)methyl)-10H-phenothiazine 5-oxide (6d)

Yellow solid (72%), mp 169–171°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.100-7.960 (m, 2H), 7.924 (s, 1H, triazole), 7. 630- 7.580 (m, 4H), 7.470- 7.410 (m, 2H), 7.371 (s, 1H), 7.367- 7.240 (m, 2H), 5.752 (s, 2H, N-CH_2). IR (υ, cm^{-1}): 3120, 3078, 1589, 1456, 1047, 748. ESI-MS m/z: 442 [M+H]. Anal. Cal for $C_{21}H_{14}C_{12}$N4OS: C, 57.15; H, 3.20; N, 12.69; found: C, 57.08; H, 3.15; N, 12.72.

10-((1-(4-butylphenyl)-1H-1,2,3-triazol-4-yl)methyl)-10H-phenothiazine 5-oxide (6e)

White solid (69%), mp 147–149°C, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.100-7.980 (m, 2H), 7.800 (s, 1H, triazole), 7. 630- 7.580 (m, 2H), 7.550- 7.460 (m, 2H), 7.330-7.220 (m, 6H), 7.367- 7.240 (m, 2H), 5.744 (s, 2H, N-CH_2), 2.638 (t, *J*= 8 Hz, 2H, Ar-*CH_2*-CH_2-CH_2-CH_3),1.400-1.200 (m, 4H, Ar-CH_2-*CH_2*-*CH_2*-CH_3), 0.926 (t, *J*= 7.6 Hz, 3H, Ar-CH_2-CH_2-CH_2-*CH_3*). IR (υ, cm^{-1}): 3120, 3078, 1589, 1456, 1047. ESI-MS m/z: 429 [M+H]. Anal. Cal for $C_{25}H_{24}N_4OS$: C, 70.07; H, 5.64; N, 13.07; found: C, 70.15; H, 5.71; N, 13.13.

10-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methyl)-10H-phenothiazine 5-oxide (6f)

Yellow solid (70%), mp 180–182°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.100-7.928 (m, 2H), 7.893 (s, 1H, triazole), 7.800- 7.200 (m, 10H), 5.728 (s, 2H, N-CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 145.15, 138.75, 135.21, 134.57, 133.15, 131.22, 129.85, 125.73, 122.60, 121.39, 120.58, 116.44, 44.81. IR (υ, cm^{-1}): 3141, 3022, 1589, 1436, 1039. ESI-MS m/z: 407 [M+H]. Anal. Cal for $C_{21}H_{15}ClN_4OS$: C, 61.99; H, 3.72; N, 13.77; found: C, 62.06; H, 3.66; N, 13.72.

10-((1-(4-bromophenyl)-1H-1,2,3-triazol-4-yl)methyl)-

10H-phenothiazine 5-oxide (6g)

Pale yellow solid (71%), mp 161–163°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.100-7.950 (m, 2H), 7.940 (s, 1H, triazole), 7.630-7.440 (m, 7H), 7.320-7.270 (m, 3H), 5.780 (s, 2H, N-CH_2). IR (υ, cm^{-1}): 3150, 3028, 1578, 1431, 1044. ESI-MS m/z: 452 [M+2H]. Anal. Cal for $C_{21}H_{15}BrN_4OS$: C, 55.88; H, 3.35; N, 12.41; found: C, 55.83; H, 3.31; N, 12.47.

10-((1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methyl)-10H-phenothiazine 5,5-dioxide (7a)

White solid (81%), mp 191–193°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.210-8.120 (m, 1H), 8.100-8.090 (m, 1H), 7.800 (s, 1H, triazole), 7.700 (s, 1H), 7.620-7.500 (m, 2H), 7.440-7.340 (m, 2H), 7.330-7.230 (m, 2H), 7.220-7.150 (m, 1H), 7.050-6.950 (m, 2H), 5.611 (s, 2H, N-CH_2), 3.845 (s, 3H, O-CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.83, 144.28, 127.35, 126.81, 123.87, 123.18, 122.16, 115.81, 114.31, 55.62, 55.57, 45.12. IR (υ, cm^{-1}): 3151, 3012, 1589, 1474, 1268, 1147, 753. ESI-MS m/z: 419 [M+H]. Anal. Cal for $C_{22}H_{18}N_4O_3S$: C, 63.14; H, 4.34; N, 13.39; found: C, 63.08; H, 4.39; N, 13.43.

10-((1-(3,5-dimethylphenyl)-1H-1,2,3-triazol-4-yl)methyl)-10H-phenothiazine 5,5-dioxide (7b)

Pale yellow solid (71%), mp 172–174°C.^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.200-8.150 (m, 1H), 8.110-8.070 (m, 1H), 7.720 (s, 1H, triazole), 7.640-7.560 (m, 1H), 7.550-7.470 (m, 1H), 7.400-7.200 (m, 6H), 7.049 (s, 1H), 5.623 (s, 2H, N-CH_2), 2.359 (s, 6H, Ar-CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 145.55, 136.35, 129.94, 127.95, 125.26, 121.52, 119.29, 117.50, 114.82, 45.63, 20.78. IR (υ, cm^{-1}): 3131, 2947, 1589, 1469, 1271, 1164,755. ESI-MS m/z: 417 [M+H]. Anal. Cal for $C_{23}H_{20}N_4O_2S$: C, 66.33; H, 4.84; N, 13.45; found: C, 66.42; H, 4.77; N, 13.40.

10-((1-(2,3-dimethylphenyl)-1H-1,2,3-triazol-4-yl)methyl)-10H-phenothiazine 5,5-dioxide (7c)

White solid (78%), mp 152–154°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.200-8.100 (m, 2H), 7.800 (s, 1H, triazole), 7.700-7.350 (m, 5H), 7.300-6.950 (m, 4H), 5.641 (s, 2H, N-CH_2), 2.649 (s, 3H, Ar-CH_3), 2.313 (s, 3H, Ar-CH_3). IR (υ, cm^{-1}): 3180, 2923, 1603, 1581, 1474, 1266, 1158,753. ESI-MS m/z: 417 [M+H]. Anal. Cal for $C_{23}H_{20}N_4O_2S$: C, 66.33; H, 4.84; N, 13.45; found: C, 66.39; H, 4.75; N, 13.39.

10-((1-(3,5-dichlorophenyl)-1H-1,2,3-triazol-4-yl)methyl)-10H-phenothiazine 5,5-dioxide (7d)

Yellow solid (73%), mp 212–214°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.200-8.120 (m, 2H), 7.800 (s, 1H, triazole), 7.650-7.550 (m, 4H), 7.420-7.300 (m, 6H), 5.644 (s, 2H, N-CH_2). IR (υ, cm^{-1}): 3090, 2927, 1608, 1585, 1475, 1269, 1153,752. ESI-MS m/z: 457 [M+H]. Anal. Cal for $C_{21}H_{14}Cl_2N_4O_2S$: C, 55.15; H, 3.09; N, 12.25; found: C, 55.19; H, 3.15; N, 12.20.

10-((1-(4-butylphenyl)-1H-1,2,3-triazol-4-yl)methyl)-10H-phenothiazine 5,5-dioxide (7e)

White solid (69%), mp 162–164°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.200-8.130 (m, 2H), 7.720 (s, 1H, triazole), 7.630-7.510 (m, 4H), 7.410-7.250 (m, 6H), 5.641 (s, 2H, N-CH_2), 2.654 (t, *J*= 7.6 Hz, 2H, Ar-*CH_2*-CH_2-CH_2-CH_3),1.700-1.400 (m, 4H, Ar-CH_2-*CH_2*-*CH_2*-CH_3), 0.933 (t, *J*= 7.3 Hz, 3H, Ar-CH_2-CH_2-CH_2-*CH_3*). IR (υ, cm^{-1}): 3161, 2987, 1589, 1472, 1257, 1163,736. ESI-MS m/z: 445 [M+H]. Anal. Cal for $C_{25}H_{24}N_4O_2S$: C, 67.54; H, 5.44; N, 12.60; found: C, 67.63; H, 5.49; N, 12.55.

10-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methyl)-10H-phenothiazine5,5-dioxide (7f)

Pale yellow solid (77%), mp 188–190°C.^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.172-8.149 (m, 2H), 8.075-8.058 (m, 1H), 7.780 (s, 1H, triazole), 7.620-6.970 (m, 9H), 5.629 (s, 2H, N-CH_2). IR (υ, cm^{-1}): 3151, 3021, 2920, 1600, 1472, 1254, 1161,759. ESI-MS m/z: 423 [M+H]. Anal. Cal for $C_{21}H_{15}ClN_4O_2S$: C, 59.64; H, 3.58; N, 13.25; found: C, 59.59; H, 3.62; N, 13.19.

10-((1-(4-bromophenyl)-1H-1,2,3-triazol-4-yl)methyl)-10H-phenothiazine5,5-dioxide (7g)

White solid (73%), mp 198–200°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.198-8.100 (m, 2H), 7.810 (s, 1H, triazole), 7.601-7.032 (m, 10H), 5.647 (s, 2H, N-CH_2). IR (υ, cm^{-1}): 3130, 3093, 2957, 1588, 1476, 1263, 1151, 752. ESI-MS m/z: 468 [M+2H]. Anal. Cal for $C_{21}H_{15}BrN_4O_2S$: C, 53.97; H, 3.24; N, 11.99; found: C, 54.06; H, 3.19; N, 11.93.

Results and discussion

Chemistry

The synthesis of title compounds was accomplished by thesynthetic sequence shown in **Scheme 1**. Commercially available10H-phenothiazine (**1**) was treated with propargyl bromide in the presence of ^{t}BuOK in DMF at room temperature to afford10-(prop-2-ynyl)-10H-phenothiazine (**2**). Oxidation of sulphur in compound-**2** with 3-chlorobenzoperoxoic acid (*m*-CPBA) in dichloromethane at room temperature afforded 10-(prop-2-yn-1-yl)-10H-phenothiazine 5-oxide (**3**)and10-(prop-2-yn-1-yl)-10H-phenothiazine 5, 5-dioxide(**4**)(Javad et al., 2008).The intermediate alkynes **2**,**3**and**4**were treated with different aryl azidesin the presence of a catalytic amount of copper iodide in tetrahydrofuran (THF)at room temperature (Himo et al., 2005) afforded the title compounds (**5a-k**, **6a-g,** and **7a-g**) in good to excellent yields. It is important to explain that the aromatic azides containing electron donating groups at *meta*- and *para*- positions reacted easily with alkynes (**2**, **3** & **4**) and gave excellent yields of the synthesized triazoles. On the other hand, aromatic azides containing electron withdrawing groups exhibited longer reactions times, not reacted smoothly

Table 1. Cytotoxic activity of potential phenothiazine derived 1,2,3-triazole [*in vitro*][a]

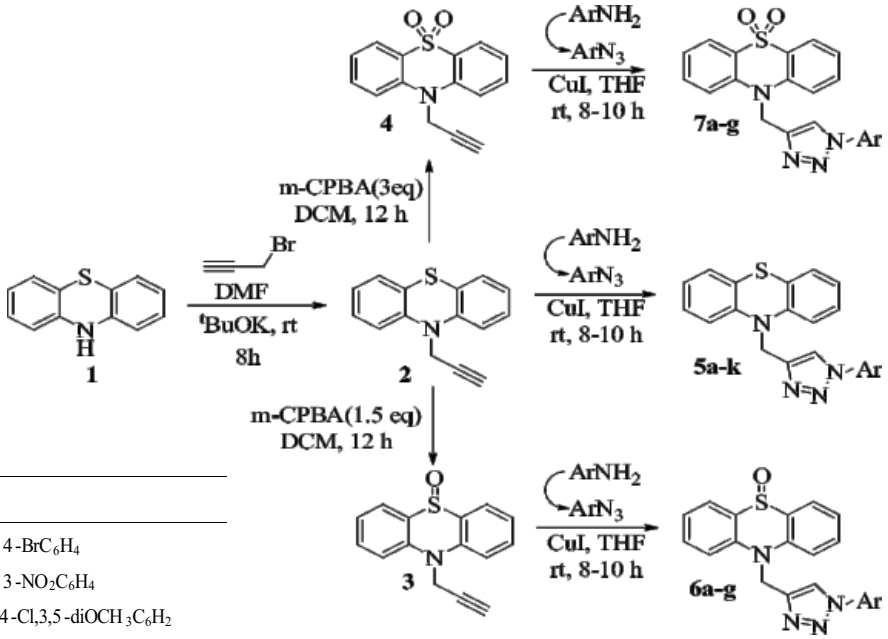
Analogs	[IC_{50} μM/mL]			Analogs	[IC_{50} μM/mL]		
	MCF-7	HeLa	A-549		MCF-7	HeLa	A-549
5a	**28.49 ± 1.1**	**30.90 ± 0.6**	**44.86 ± 0.8**	**6c**	42.12 ± 1.6	36.20 ± 1.1	31.60 ± 1.5
5b	**22.44 ± 0.3**	**18.17 ± 0.5**	**21.02 ± 0.7**	**6d**	63.51 ± 0.8	72.23 ± 1.0	58.13 ± 1.6
5c	38.19 ± 1.3	29.67 ± 1.1	38.52 ± 0.9	**6e**	83.24 ± 1.1	89.43 ± 1.4	79.33 ± 1.9
5d	61.50 ± 0.9	52.06 ± 0.6	67.10 ± 1.8	**6f**	104.31 ± 1.8	117.11 ± 1.5	98.66± 1.7
5e	69.47 ± 1.2	56.93 ± 1.5	77.20 ± 0.9	**6g**	122.71 ± 1.3	131.24 ± 1.7	108.48 ± 1.5
5f	70.69 ± 1.0	76.64 ± 1.3	87.52 ± 1.5	**7a**	**13.47 ± 0.7**	**11.10 ± 0.4**	**20.11 ± 1.0**
5g	110.69 ± 1.8	116.29 ± 1.3	127.82± 1.4	**7b**	**09.11 ± 0.3**	**12.81 ± 0.6**	**11.81 ± 0.8**
5h	63.53 ± 0.7	61.34 ± 0.6	72.12 ± 1.7	**7c**	**24.22 ± 1.0**	**31.97 ± 0.8**	**30.18 ± 0.7**
5i	37.10 ± 0.8	40.09 ± 1.1	42.63 ± 1.7	**7d**	44.16 ± 1.2	39.11 ± 1.7	43.37 ± 1.0
5j	41.82 ± 1.0	24.17 ± 0.8	40.21 ± 1.2	**7e**	55.22 ± 1.8	49.70 ± 1.8	57.14 ± 0.8
5k	68.08 ±1.3	70.54 ± 1.2	62.33 ± 1.0	**7f**	52.73 ± 0.7	49.31 ± 1.1	38.89 ± 1.6
6a	33.13 ± 1.5	37.11 ± 1.2	36.21 ± 1.1	**7g**	38.37 ± 1.0	53.15 ± 1.7	41.48 ± 2.3
6b	25.59 ± 0.3	49.41 ± 1.0	45.22 ± 0.5	**Cisplatin**	**4.61 ± 0.2**	**3.86 ± 0.1**	**5.65 ± 0. 2**

Values are expressed as mean ± SEM. [a]Cytotoxicity as IC_{50} for each cell line, is the concentration of compound which reduced by 50% the optical density of treated cells with respect to untreated cells using the MTT assay

with alkynes. This may be explained by the formation of active aryl azides with electron donating groups.

In vitro cytotoxic activity

In vitro, cytotoxic activity was carried out in human cell cultures MCF-7 (breast), HeLa (cervical) and A-549 (alveolar). Cisplatin was used as a reference drug. Cell viability in the presence of the test samples was measured by the MTT-micro culture tetrazolium assay (Denizot and Lang, 1986). The relationship between surviving fraction and drug concentration was plotted to obtain the survival curves of MCF-7, HeLa, and A-549 (Figure 2, 3 & 4). The response parameter calculated was the IC_{50} value, whichcorresponds



Ar	Ar
a: 4-$OCH_3C_6H_4$	g: 4-BrC_6H_4
b: 3,5-di$CH_3C_6H_3$	h: 3-$NO_2C_6H_4$
c: 2,3-di$CH_3C_6H_3$	i: 4-Cl,3,5-di$OCH_3C_6H_2$
d: 3,5-diClC_6H_3	j: 3-$CF_3C_6H_4$
e: 4-$C_4H_9C_6H_4$	k: C_6H_5
f: 4-ClC_6H_4	

Scheme 1. Synthesis of phenothiazine based 1,2,3-triazole hybrids (**5a-5k, 6a-6g & 7a-7g**)

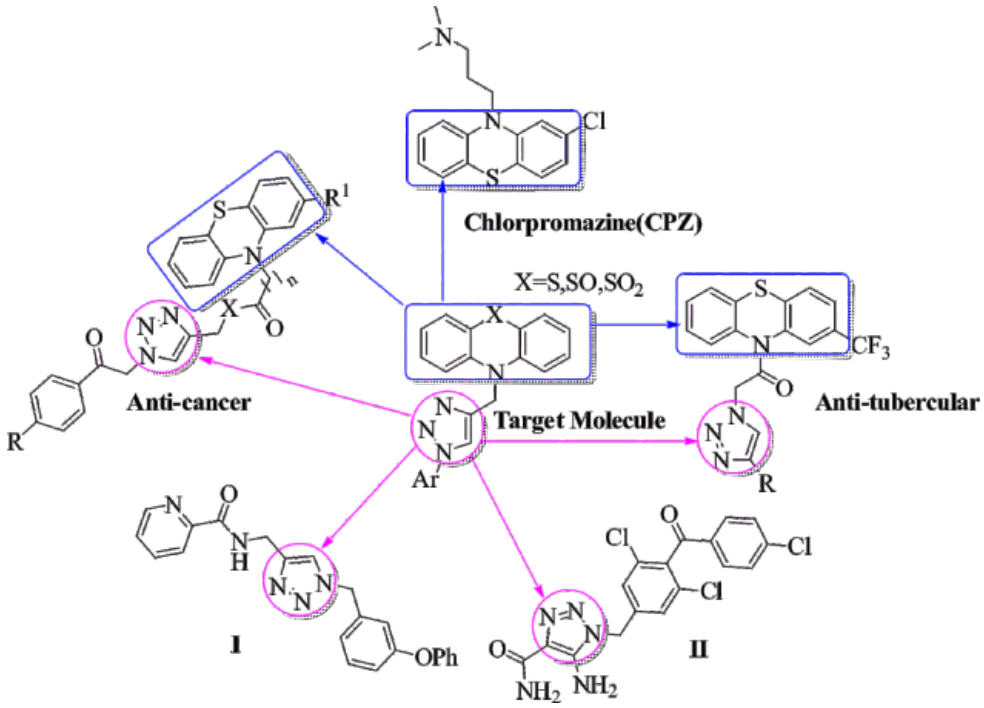


Figure 1. Representative examples of biologically active heterocyclic molecules possessing phenothiazine and 1,2,3-triazole moieties

to the concentration required for 50% inhibition of cell viability. The IC_{50} values for compounds (**5a-5k, 6a-6g** and **7a-7g**) were presented in (**Table 1**). *In vitro* cytotoxic activity, screening results revealed that some of the compounds showed excellent to moderate activity against the tumor cells. Among them, a compound derived from 3, 5-dimethylphenyl triazole on 10H-phenothiazine 5,5-dioxide that is **7b** has shown broad-spectrum activity against three cell lines MCF-7, HeLa and A-549 with IC_{50} values 09.11 ± 0.3, 12.81 ± 0.6and 11.81 ± 0.8μM respectively. A compound derived from 4-methoxy phenyl triazole on 10H-phenothiazine 5, 5-dioxide that is **7a** has shown good activity against MCF-7 and HeLa with IC_{50} values 13.47 ± 0.7 and 11.10 ±0.4μM and moderate activity against A-549 with IC_{50} value 20.11 ± 1.0μM respectively. The compounds derived from 3,5-dimethylphenyl triazole on 10H-phenothiazine that is **5b** has shown good activity against HeLa (IC_{50}:18.17 ± 0.5μM) and moderate activity against MCF-7 (IC_{50}:22.44 ± 0.3μM) and A-549 (IC_{50}:21.02 ± 0.7μM). Similarly, compounds derived from 4-methoxy phenyl triazole on 10H-phenothiazine that is **5a,** 3,5-dimethylphenyl triazole on 10H-phenothiazine 5-oxide that is **6b** and 2,3-dimethylphenyl triazole on 10H-phenothiazine 5,5-dioxide that is **7c** has shown moderate activity against MCF-7 with IC_{50} value 28.49 ± 1.1, 25.59 ± 0.3 and 24.22 ± 1.0μM respectively when compared with the standard drug cisplatin. Remaining compounds have shown moderate

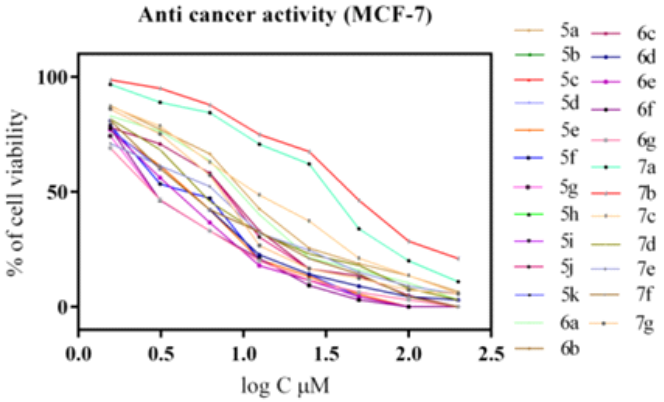


Figure 2. Survival curves of MCF-7for phenothiazine derived 1, 2, 3-triazole hybrids (**5a-7g**)

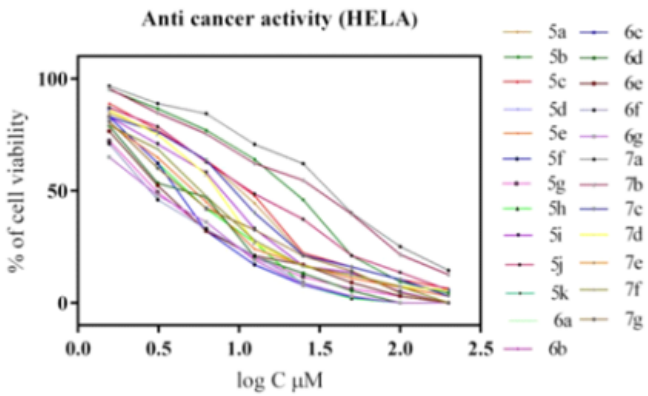


Figure 3. Survival curves of HeLa for phenothiazine derived 1, 2, 3-triazole hybrids (**5a-7g**).

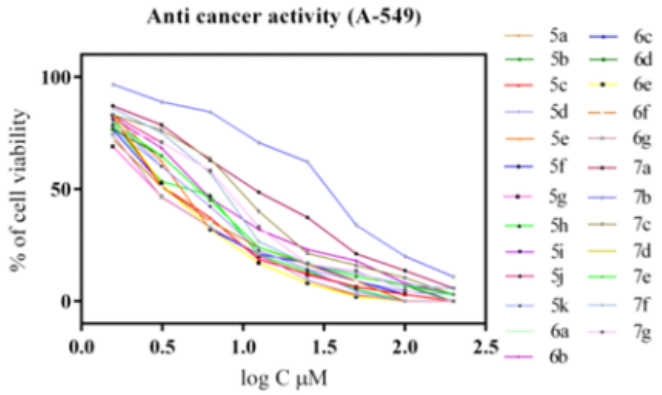


Figure 4. Survival curves of A-549 for phenothiazine derived 1, 2, 3-triazole hybrids (**5a-7g**).

activity with IC_{50} values ranging from 30.18 ± 0.7 - 131.24 ± 1.7 μM against the three cell lines. On overall comparison, electron releasing groups such as methyl and methoxy on the benzene present at triazole ring increased the anticancer activity. Whereas the introduction of electron attracting fluoro, chloro, bromo and nitro groups on the benzene present at triazole ring decreased the activity. It is important to mention that introduction of the 5, 5-dioxide group led to the enhancement of activity of the molecule against all three cell lines. From these results, it can be concluded that presence of a methyl and methoxyphenyl groups on the 10H-phenothiazine 5,5-dioxide significantly enhanced activity.

Antibacterial activity

The minimum inhibitory concentrations (*MIC*) of the synthesized compounds (**5a-5k**, **6a-6g** and **7a-7g**) were tested against the gram-positive organisms *B. subtilis*, *S. aureus* and *S. epidermidis* and the gram-negative organisms *E. coli*, *P. aeruginosa*, and *K. pneumoniae*using the broth dilution method (Trivedi et al., 2011). Penicillin and streptomycin were also screened under identical conditions for comparison. From results obtained (Table 2), it is clear that some of the compounds have shown good to excellent antibacterial activity against tested microbial strains. Among all the tested compounds, compound **7d**, which contains 3,5-dichlorophenyl triazole moiety on 10H-phenothiazine 5,5-dioxide exhibited potent activity against *B. subtilis* (MIC= 1.56 ± 0.15μg/mL) and *S. aureus* (MIC= 1.56 ± 0.23μg/mL), moderate activity against *S. epidermidis* (MIC= 6.25 ± 0.42μg/mL) and *P. aeruginosa* (MIC= 12 ± 0.39μg/mL). Similarly, the compounds **5d** and **6d**which contain 3, 5-dichlorophenyl triazole on 10H-phenothiazine and 10H-phenothiazine 5-oxide have shown good activity against *B. subtilis* and *S. aureus* with MIC values3.12 ± 0.15 to 6.25 ± 0.36μg/mL. These results are comparable to the standard drugs, penicillin, and streptomycin. Introduction of 4-chloro-3,5-dimethoxyphenyltriazole ring on 10H-phenothiazine that is

Table 2. *In vitro* antibacterial activity data of titled compounds (**5a-5k**, **6a-6g** and **7a-7g**)

Analogs	MIC (μg/mL)					
	B. subtilis	*S. aureus*	*S. epidermidis*	*E. coli*	*P. aeruginosa*	*K. pneumoniae*
5a	25 ± 0.30	-	-	-	50 ± 0.23	-
5b	-	-	**12.5 ± 0.15**	-	-	-
5c	-	-	25 ± 0.31	-	-	50 ± 0.66
5d	**3.12 ± 0.15**	**6.25 ± 0.36**	50 ± 0.34	50 ± 0.52	-	-
5e	50 ± 0.36	-	-	-	25 ± 0.31	-
5f	-	-	25 ± 0.18	50 ± 0.27	25 ± 0.25	-
5g	50 ± 0.65	-	-	-	-	25 ± 0.33
5h	25 ± 0.88	-	50 ± 0.72	-	-	-
5i	**12.5 ± 0.24**	50 ± 0.36	6.25 ± 0.22	50	**3.12 ± 0.26**	-
5j	-	-	-	3.12 ± 0.17	**6.25 ± 0.18**	-
5k	50 ± 0.45	-	-	-	-	25 ± 0.32
6a	-	-	-	12.5 ± 0.32	-	-
6b	-	50 ± 0.43	25 ± 0.19	-	-	-
6c	-	-	25 ± 0.34	-	-	-
6d	**6.25 ± 0.26**	**6.25 ± 0.18**	-	-	50 ± 0.76	-
6e	-	-	-	-	50 ± 0.84	-
6f	50 ± 0.27	-	-	50 ± 0.35	-	-
6g	-	25 ± 0.54	-	-	25 ± 0.20	-
7a	-	-	-	12.5 ± 0.25	-	-
7b	-	-	25 ± 0.19	-	-	-
7c	-	-	**12.5 ± 0.40**	-	-	-
7d	**1.56 ± 0.15**	**1.56 ± 0.23**	**6.25 ± 0.42**	50 ± 0.45	**12.5 ± 0.39**	-
7e	-	25 ± 0.32	-	-	-	50 ± 0.38
7f	50 ± 0.31	-	-	50 ± 0.65	-	-
7g	50 ± 0.37	-	50 ± 0.39	-	-	-
Streptomycin	**6.25 ± 0.25**	**6.25 ± 0.38**	**3.12 ± 0.45**	6.25 ± 0.77	**1.56 ± 0.65**	**3.12 ± 0.21**
Penicillin	**1.56 ± 0.22**	**1.56 ± 0.65**	**3.12 ± 0.23**	12.5 ± 0.35	**12.5 ± 0.22**	**6.25 ± 0.78**

MIC (μg/mL), minimum inhibitory concentration, i.e., the lowest concentration of the test compound to inhibit the growth of bacteria completely "–" Indicates concentration >100μg/mL

5i has shown good activity against *S. epidermidis* (MIC= 6.25 ± 0.22μg/mL) and *P. aeruginosa* (MIC=3.12 ± 0.26μg/mL), moderate activity against *B. subtilis* (MIC= 12.5 ± 0.24μg/mL). Contrarily, however, compound **5j**, containing 3-(trifluoromethyl) phenyltriazole group on 10H-phenothiazine exhibited an enhanced activity profile against *E. coli* and *P. aeruginosa* with MIC values3.12 ± 0.17μg/mL and 6.25 ± 0.18μg/mL, respectively. It is important to mention that introduction of the 2,3-dimethl and 3,5-dimethyl phenyl group on triazole ring (5b, 5c, 6b, 6c, 7b and 7c)have shown moderate activity selectively against *S. epidermidis* with MIC values ranging from12.5 ± 0.15 to 25 ± 0.34μg/mL, respectively. Similarly, compound 6a and 7a which contains 4-methoxyphenyl triazole on 10H-phenothiazine 5-oxideand 10H-phenothiazine5,5-dioxide have shown good activity against *E. coli* with MIC values 12.5 ± 0.32 and 12.5 ± 0.25μg/mL, respectively. Remaining compounds have shown moderate to poor activity when compared with the standard drugs Penicillin and streptomycin. From these results, all potent analogues having chloro substituent on the triazole ring (5d, 5i, 6d and 7d) and this preference is auniform irrespective pattern on phenothiazine ring. Remaining dimethyl, methoxy and trifluoromethyl group on triazole ring have shown moderate to good activity.

Conclusion

In summary, we synthesized a series of new phenothiazine hybrids containing 1,2,3-triazole to test their anticancer and antibacterial activities. Among the compounds tested, compounds **7a** and **7b** showed a promising anti-cancer activity. We succeeded in guiding the change of substituents in the triazole ring together with the phenothiazine-5,5-dioxide group, which played a crucial role in the development of a promising anticancer activity. Compounds **5d**, **6d** and **7d** carrying a 3,5-dichlorophenyl group on the triazole ring have shown an equipotent antibacterial activity against *B. subtilis* and *S. aureus*, while compound **5i**, which is a 4-chloro ring -3,5-dimethoxyphenyltriazole a good activity against *P. aeruginosa* and Compound **5j**, which contains a 3-(trifluoromethyl) phenyltriazole group in 10H-phenothiazine, showed equipotent activity against *E. coli* and *P. aeruginosa*. This study provides valuable information for the design and development of new anticancer and antibacterial agents that are more effective. By making a simple modification of the structure, a new potent analog having the desired anticancer and antibacterial activity can be produced with good efficiency.

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Conflicts of interest

The authors declare no conflict of interest.

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