**ABSTRACT**

Quinazolines and 1,2,4-triazoles are important class of nitrogen containing heterocyclic compounds having immense biological importance. From the literature review, pharmacokinetic properties of a drug can be modified or enhanced by building a triazole moiety into a compound like quinazoline. Therefore, the study of new hybrid systems which combines triazole system with quinazoline is still seemed warranted. In the present study, a sequence of novel 1,2,4-triazole derivatives containing quinazolinyl moiety were designed, synthesized and screened for their *in vitro* anticancer activity. Thirteen new hybrids are synthesized from readily accessible 5-bromoanthranilic acid. All the hybrid compounds were well explicated by IR, $^{1}$H, $^{13}$C NMR, and mass spectral data. Out of 13, some of the compounds manifested moderate to good antiproliferative activity against two cancer cell lines (HepG2 and MCF-7). Remarkably, compounds 8A, 16H and 16K displayed potent activity (14-49 μM) on both HepG2 (liver carcinoma) and MCF-7 (breast cancer) cell lines whereas compounds 8B, 8F, 16L, and 15 displayed substantial activity against HepG2 cancer cell line (34-65 μM). Synthetic approach described here is very simple and can be used for the syntheses of related compounds library which is useful for the exploration of further biological activities and is currently underway in our laboratory.

**INTRODUCTION**

Quinazoline motif has substantiated to be a powerful and adaptable constituent for progress of diverse pharmacological entities (Hameed *et al.*, 2018). Amongst various heterocyclics, quinazoline and its cognates have engrossed significant interest because of their synthetic flexibility along with valuable pharmacological activities (Wang and Gao, 2013). Quinazoline and triazoloquinazoline derivatives have gained impact due to their extensive range of biological activities including antimalarial (Bouchut *et al.*, 2019), antimicrobial (Masood *et al.*, 2018; Vani *et al.*, 2016), anti-inflammatory (Mosaad *et al.*, 2005), anticonvulsant (Abeliziz *et al.*, 2017), antidiabetic (Saeedi *et al.*, 2019), anticancer activities (Banerji *et al.*, 2018; Gouhar and Kamel, 2018) and as adenosine receptor antagonists (Burbiel *et al.*, 2016). Quinazolines also display biological roles like cellular phosphorylation inhibitors, ligands for benzodiazepine and GABA receptors in the central ner-

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uous system (Bertelli et al., 2000) and as DNA binding motifs (Lewerenz et al., 2003; Malecki et al., 2004). They have also shown to possess effactual α-adrenergic blocking activity. Intriguing this, in and continuance of our program on the synthesis of diverse novel heterocyclic systems showing significant biological activities (Kumar et al., 2011, 2013; Sriramouju et al., 2019; Santhoshi et al., 2018) here in we designed and synthesized 13 structurally different quinazoline derivatives and assessed for in vitro anticancer activity against HepG2 (liver carcinoma) & MCF-7 (breast cancer) cancer cell lines. Some of the compounds displayed substantial anticancer activity in micro molar (μM) concentration out of various synthesized hybrids.

MATERIALS AND METHODS

Chemicals & reagents were procured from Sigma, Merck and are directly used. Melting Points are ascertained in sulfuric acid bath using narrow capillary tubes. TLC was sprinted on silica gel glass plates containing 60 F-254 and visualization was carried with UV light or with iodine. Perkin–Elmer 1000 instrument was used for recording IR Spectra with KBr pellets. 1H (Proton) NMR was recorded in CDCl3/CD3OD/DMSO-d6 solvents using internal standard tetramethylsilane at 400 MHz / 500 MHz operating frequency. 13C (Carbon 13) NMR spectras were recorded on 100 & 125 MHz frequency instruments. Agilent-LCMS instrument was used for recording mass spectra. General procedure and spectral data

Preparation procedure for 6-bromo-2-cyclopropyl quinazolin-4(3H)-one (4)

5-Bromo-2-(cyclopropylcarboxamido) benzamide (3) as pale brown solid which can be directly used. Yield (91%, 3.3 g). LCMS m/z (M+H)+ = 283.0, 91%; 1HNMR (DMSO-d6, 500 MHz) δ ppm: 11.80 (s, 1H), 8.40 (brs, 2H), 7.97 (d, J = 2 Hz, 1H), 7.84 (s, 1H), 7.66 (dd, J = 9 Hz, 2.5 Hz, 1H), 1.66-1.63 (m, 1H), 0.86-0.83 (m, 4H).

Preparation procedure for 6-bromo-2-cyclopropyl quinazolin-4(3H)-one (4)

5-Bromo-2-(cyclopropylcarboxamido) benzamide (3) (3.30 g, 11.6 mmol) was taken in 2M NaOH solution (50 mL) & refluxed the mixture for ~2 h. Then the mixture was brought to rt & acidified by using 1N HCl. The ensuing white solid was filtered, cleansed with water & dried out over vacuum to get 6-bromo-2-cyclopropylquinazolin-4(3H)-one (4) as white solid. Yield (92%, 2.85 g). LCMS m/z (M+H)+ = 264.9, 99%; 1HNMR (DMSO-d6, 400 MHz) δ ppm: 12.61 (brs, 1H), 8.11 (d, J = 2.4 Hz, 1H), 7.84 (dd, J = 8.8 Hz, 2.4 Hz, 1H), 7.41 (d, J = 8.8 Hz, 1H), 1.98-1.94 (m, 1H), 1.10-1.02 (m, 4H).

Preparation procedure for 6-bromo-4-chloro2-cyclopropylquinazoline (5)

Cyclopropylquinazolinone 4 (2.8 g, 10.5 mmol) was dissolved in POCl3 (16 mL) at rt and was refluxed for 2 h. Afterwards, the mixture was concentrated to get the residue. To the residue, cold water (25 mL) was added and extracted with EtOAc (3 X 25 mL). The extracts were washed with saturated sodium sulphate (anhdyrous), filtered & evaporated to obtain 6-bromo-4-chloro-2-cyclopropylquinazoline (5) as light yellow solid. Yield (87%, 2.65 g). LCMS m/z (M+H)+ = 229.9, 91%; 1HNMR (CDCl3, 500 MHz) δ ppm: 8.32 (dd, J = 2.0 Hz, 0.5 Hz, 1H), 7.93 (dd, J = 9 Hz, 2.0 Hz, 1H), 7.77 (d, J = 9 Hz, 1H), 2.36-2.31 (m, 1H), 1.29-1.26 (m, 2H), 1.17-1.14 (m, 2H).

Preparation procedure for 5-bromo-2-(cyclopropylcarboxamido) benzamide (3)

6-Bromo-2-cyclopropyl-4H-benzo[1,3]oxazin-4-one 2 (3.40 g, 12.7 mmol) in ammonia solution (50 mL) was stirred at rt for 16 h. The ensuing solid was filtered, cleansed with water & dried out under vacuum to obtain 5-bromo-2-(cyclopropylcarboxamido) benzamide (3) as pale brown solid which can be directly used. Yield (91%, 3.3 g). LCMS m/z (M+H)+ = 283.0, 91%; 1HNMR (DMSO-d6, 500 MHz) δ ppm: 11.80 (s, 1H), 8.40 (brs, 2H), 7.97 (d, J = 2 Hz, 1H), 7.84 (s, 1H), 7.66 (dd, J = 9 Hz, 2.5 Hz, 1H), 1.66-1.63 (m, 1H), 0.86-0.83 (m, 4H).

Preparation procedure for 5-bromo-2-(cyclopropylcarboxamido) benzamide (3)
Figure 1: Dose response curves with IC\textsubscript{50} values for selected compounds on HepG2 cell line

Table 1: IC\textsubscript{50} values of synthesized quinazoline compounds (8A-G) in \( \mu M \)

| Cell line | 8A \( \mu M \) | 8B \( \mu M \) | 8C \( \mu M \) | 8D \( \mu M \) | 8E \( \mu M \) | 8F \( \mu M \) | 8G \( \mu M \) | Puromycin \( \mu M \) |
|-----------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|------------------|
| HepG2     | 22            | 44            | ~0            | ~0            | ~0            | 34            | 0             | 0.60             |
| MCF7      | 14            | ~0            | ~0            | ~0            | ~0            | ~0            | 0             | 0.94             |

Table 2: IC\textsubscript{50} values of synthesized quinazoline compounds (15 & 16H-L) in \( \mu M \)

| Cell line | 16H \( \mu M \) | 16I \( \mu M \) | 16J \( \mu M \) | 16K \( \mu M \) | 16L \( \mu M \) | 15 \( \mu M \) | Puromycin \( \mu M \) |
|-----------|---------------|---------------|---------------|---------------|---------------|---------------|------------------|
| HepG2     | 21            | ~0            | ~0            | 28            | 65            | 35            | 0.60             |
| MCF7      | 49            | ~0            | ~0            | 18            | ~0            | ~0            | 0.94             |
To the 6-Bromo-2-cyclopropyl-4-hydrazinylquinazoline 6 (0.61 g, 2.14 mmol), acetic anhydride (3 mL) & acetic acid (3 mL) was added at rt and refluxed for ~90 min. Afterwards, the mixture was concentrated under reduced pressure to get residue. To the residue, cold water (20 mL) was added and extracted with EtOAc (2 X 20 mL). Organic layers separated and washed with sat.NaHCO₃ (15 mL), dried over sodium sulphate (anhydrous), filtered & concentrated to get crude compound. The compound was then purified by Grace (40 g Silica gel cartridge, eluent 2-4% MeOH in DCM) to obtain 7 as dark yellow solid. Yield (44%, 0.29 g). LCMS m/z (M+H)⁺ = 303.04, 97%; ¹HNMR (CD₃OD, 400 MHz) ppm: 8.55 (d, J = 2.0 Hz, 1H), 7.87 (dd, J = 8.8 Hz, 2.0 Hz, 1H), 7.71 (d, J = 8.8 Hz, 1H), 3.12 (s, 3H), 2.72-2.71 (m, 1H), 1.44-1.41 (m, 2H), 1.27-1.24 (m, 2H).

General procedure for compound 8C-8G

Boronic acid (0.49 mmol) and K₂CO₃ (92 mg, 0.66 mmol) was added to quinazoline 7 (100 mg, 0.33 mmol) in 1,4-dioxane (5 mL) at rt and was purged with argon for 5 min., & heated at 100 °C for ~2 h in sealed tube. Afterwards, filtered the mixture through celite pad & washed the pad with EtOAc (10 mL). Then the filtrate was concentrated to get crude and was purified by Grace (40 g Silica gel cartridge, eluent 2 to 6% MeOH in DCM) to obtain compounds 8C-8G.

5-Cyclopropyl-3-methyl-9-phenyl-[1,2,4]triazolo[4,3-c]quinazoline (8C)

Off-white solid, yield (65%, 67 mg). Melting Range (°C): 203-207, LCMS m/z (M+H)⁺ = 301.1, 97%; IR (KBr): 3109, 2992, 1612, 1526, 1445, 1392 cm⁻¹; ¹HNMR (CDCl₃; 400 MHz) ppm: 8.75 (d, J = 1.6 Hz, 1H), 7.91 (dd, J = 8.4 Hz, 1.6 Hz, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.50-7.38 (m, 3H), 3.13 (s, 3H), 2.55-2.51 (m, 1H), 1.51-1.47 (m, 2H), 1.25-1.21 (m, 2H); ¹³CNMR (CDCl₃; 100 MHz) ppm: 149.5, 147.9, 145.2, 141.0, 139.9, 139.4, 130.2, 128.9, 128.0, 127.9, 127.2, 120.9, 116.5, 15.1, 14.1, 9.3.

4-(5-Cyclopropyl-3-methyl-[1,2,4]triazolo[4,3-c]quinazolin-9-yl)benzonitrile (8D)

Off-white solid, yield (67%, 67 mg). Melting Range (°C): 223-227, LCMS m/z (M+H)⁺ = 326.1, 98%; IR (KBr): 3091, 2919, 2850, 2218, 1606, 1526, 1445,
Scheme 2: Synthesis of phenyl substituted triazolo[4,3-c]quinazoline hybrids

5-Cyclopropyl-9-(4-methoxyphenyl)-3-methyl-[1,2,4]triazolo[4,3-c]quinazoline (8E)

Off-white solid, yield (62%, 68 mg). Melting Range (°C): 216-220, LCMS m/z (M+H)+ = 331.2, 97%; IR (KBr): 3016, 1478, 1265, 1165 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ ppm: 8.74 (d, J = 2 Hz, 1H), 8.10 (dd, J = 8.5 Hz, 2 Hz, 1H), 7.98 (d, J = 8.5 Hz, 2H), 7.93 (d, J = 8.5 Hz, 1H), 7.88 (d, J = 8.5 Hz, 2H), 3.14 (s, 3H), 2.78-2.74 (m, 1H), 1.48-1.45 (m, 2H), 1.30-1.26 (m, 2H); ¹³C NMR (CDCl₃, 100 MHz) ppm: 149.5, 148.5, 145.4, 143.8, 142.7, 141.0, 138.7, 132.7, 130.2, 128.6, 127.8, 121.5, 118.6, 116.8, 111.6, 29.6, 15.5, 14.1, 9.6.

5-Cyclopropyl-3-methyl-9-(3-(triﬂuoromethoxy)phenyl)-[1,2,4] triazolo[4,3-c]quinazoline (8F)

Off-white solid, Yield (65%, 82 mg). Melting Range (°C): 168-172, LCMS m/z (M+H)+ = 385.1, 97%; IR (KBr): 3067, 2923, 1610, 1525, 1399, 1277, 1032 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ ppm: 8.69 (d, J = 2 Hz, 1H), 8.10 (d, J = 6.8 Hz, 1H), 7.87-7.86 (m, 1H), 7.83 (d, J = 6.8 Hz, 1H), 7.62 (d, J = 4.0 Hz, 1H), 7.58-7.56 (m, 1H), 3.13 (s, 3H), 2.75-2.71 (m, 1H), 1.46-1.42 (m, 2H), 1.28-1.25 (m, 2H); ¹³C NMR (CDCl₃, 100 MHz) δ ppm: 149.5, 147.7, 145.3, 141.8, 140.7, 139.7, 135.6, 129.7, 128.3, 126.7, 126.7, 126.1, 121.6, 120.0, 116.6, 15.5, 14.1, 9.31.

Preparation procedure for 3-Methyl-9-phenyl-5-(prop-1-en-2-yl)-[1,2,4] triazolo[4,3-c]quinazoline (8A)

Phenylboronic acid (61 mg, 0.49 mmol) and K₂CO₃ (92 mg, 0.66 mmol) was added to quinazoline 7
Scheme 3: List of 1,2,4-triazolo[4,3-c]quinazoline hybrids synthesized

(100 mg, 0.33 mmol) in 1,4-dioxane (5 mL) at rt and was purged with argon for 5 min., and added SPhos (2.5 mg, 0.005 mmol) followed by Pd(OAc)$_2$ (2.25 mg, 0.003 mmol) at rt. It was further purged with argon for 5 min., & heated at 100 °C for 16h in sealed tube. Afterwards, filtered the mixture through celite pad & washed the pad with EtOAc (10 mL). Then the filtrate was concentrated to get crude and was purified by Grace (40 g Silica gel cartridge, eluent 2 - 6% MeOH in DCM) to obtain 3-methyl-9-phenyl-5-(prop-1-en-2-yl)-[1,2,4]triazolo[4,3-c]quinazoline (8A) as pale yellow solid. Yield (37%, 36 mg). Melting Range (°C): 201-203; LCMS m/z (M+H)$^+$ = 301.2, 95%; $^1$HNMR (CDCl$_3$, 500 MHz) δ ppm: 8.80 (d, $J$ = 1.5 Hz, 1H), 7.99-7.93 (m, 2H), 7.77-7.75 (m, 2H), 7.51-7.48 (m, 2H), 7.43-7.40 (m, 1H), 7.31-7.28 (m, 1H), 6.97 (dd, $J$ = 15 Hz, 2 Hz, 1H), 3.05 (s, 3H), 2.12 (dd, $J$ = 7 Hz, 2 Hz, 3H).

Preparation procedure for 4-(3-Methyl-5-(prop-1-en-2-yl)-[1,2,4]triazolo[4,3-c]quinazolin-9-yl)benzonitrile (8B)

Cyanophenylboronic acid (73 mg, 0.49 mmol) and K$_2$CO$_3$ (92 mg, 0.66 mmol) was added to quinazoline 7 (100 mg, 0.33 mmol) in 1,4-dioxane (5 mL) at rt and was purged with argon for 5 min., and added SPhos (2.5 mg, 0.005 mmol) followed by Pd(OAc)$_2$ (2.25 mg, 0.003 mmol) at rt. It was further purged with argon for 5 min., & heated at 100 °C for 16h in sealed tube. After completion of reaction, same work up and purification procedure was adopted as mentioned above to obtain 4-(3-methyl-5-(prop-1-en-2-yl)-[1,2,4]triazolo[4,3-c]quinazolin-9-yl)benzonitrile (8B) as yellow solid. Yield (40%, 42 mg). Melting Range (°C): 195-198; LCMS m/z (M+H)$^+$ = 325.8, 96%; $^1$HNMR (CD$_3$OD, 500 MHz) δ ppm: 8.77 (d, $J$ = 2 Hz, 1H), 8.13 (dd, $J$ = 8.5 Hz, 2 Hz, 1H), 8.03-7.99 (m, 3H), 7.90-7.88 (m, 2H), 7.33-7.29 (m, 1H), 7.14 (dd, $J$ = 15 Hz, 2 Hz, 1H), 3.04 (s, 3H), 2.12 (dd, $J$ = 7 Hz, 2 Hz, 3H).

Note- Experimental procedure for the compound-10 to compound-15 is same as described for the synthesis of compound-2 to 7 in Scheme 1, whereas
benzoyl chloride is used in step 1 instead of cyclopropane carbonyl chloride.

6-Bromo-2-phenyl-4H-benzo[d][1,3]oxazin-4-one (10)

Off white solid, yield (68%, 4.8 g). LCMS m/z (M+H)^+ = 302.0, 94%; \(^1\)HNMR (DMSO-d_6, 500 MHz) δ ppm: 8.25-8.10 (m, 3H), 8.11 (dd, \(J = 8.5\) Hz, \(2.5\) Hz, 1H), 7.68-7.59 (m, 4H).

2-Benzamido-5-bromobenzamide (11)

Off white solid, yield (90%, 4.5 g). LCMS m/z (M+H)^+ = 319.0, 95%; \(^1\)HNMR (DMSO-d_6, 500 MHz) δ ppm: 12.72 (s, 1H), 8.23 (d, \(J = 8.5\) Hz, 2.5 Hz, 1H), 7.68 (d, \(J = 8.8\) Hz, 1H), 7.61-7.54 (m, 3H).

6-Bromo-4-chloro-2-phenylquinazoline (13)

Pale yellow solid. Yield (86%, 3.6 g). LCMS m/z (M+H)^+ = 318.9, 94%; \(^1\)H NMR (CDCl_3, 400 MHz) δ ppm: 8.59-8.56 (m, 2H), 8.42 (d, \(J = 1.6\) Hz, 1H), 8.02-7.95 (m, 2H), 7.55-7.52 (m, 3H).

6-Bromo-4-hydrazinyl-2-phenylquinazoline (14)

Yellow solid, yield (85%, 3.05 g). LCMS m/z (M+H)^+ = 316.8, 81%; \(^1\)HNMR (DMSO-d_6, 500 MHz) δ ppm: 9.76 (brs, 1H), 8.57-8.56 (m, 2H), 8.49 (s, 1H), 7.88 (dd, \(J = 9.0\) Hz, 2.0 Hz, 1H), 7.70 (d, \(J = 9.0\) Hz, 1H).
Off-white solid, yield (49%, 78 mg). Melting Range (°C): 240-244, LCMS m/z (M+H)^+ = 355.1, 99%; IR (KBr): 3061, 1620, 1583, 1532, 1475, 1413, 1344 cm⁻¹; ¹HNMR (CDCl₃, 500 MHz) δ ppm: 8.87 (d, J = 2.0 Hz, 1H), 8.03 (d, J = 8.5 Hz, 1H), 8.01 (d, J = 8.5 Hz, 2.0 Hz, 1H), 7.67-7.60 (m, 6H), 7.49-7.46 (m, 2H), 7.15-7.12 (m, 1H), 2.19 (s, 3H); ¹³CNMR (CDCl₃, 100 MHz) δ ppm: 149.2, 146.0, 145.8, 145.6, 141.6, 141.5, 140.7, 132.9, 131.1, 130.6, 130.5, 130.4, 128.8, 123.0, 121.2, 116.9, 115.2, 115.0, 114.4, 114.2, 14.3.

9-(3,5-Dichlorophenyl)-3-methyl-5-phenyl-[1,2,4]triazolo[4,3-c]quinazoline (16L)

Off-white solid, yield (39%, 65 mg). Melting Range (°C): 286-290, LCMS m/z (M+H)^+ = 415.1, 95%; IR (KBr): 3060, 2925, 1626, 1595, 1302, 1151 cm⁻¹; ¹H NMR (DMSO-d₆, 400 MHz) δ ppm: 8.80 (s, 1H), 8.24-8.17 (m, 3H), 8.10-8.05 (m, 3H), 7.80 (d, J = 7.2 Hz, 2H), 7.70-7.60 (m, 3H), 3.27 (s, 3H); ¹³CNMR (DMSO-d₆, 100 MHz) δ ppm: 148.2, 146.5, 145.7, 143.4, 140.3, 140.2, 138.5, 133.0, 130.6, 130.3, 129.1, 128.8, 128.1, 128.0, 127.8, 120.4, 116.8, 43.5, 13.8.

RESULTS AND DISCUSSION

Synthetic sequence of 1,2,4-triazolo [4,3-c]quinazolines (8A-G) be illustrated in Scheme 1. 5-bromoanthranilicacid (1) on reaction with cyclopropanoyl chloride in 2,6-lutidine for 2 h produced benzoazinone (2) in good yield. Compound 2 on treatment with aq. ammonia at ambient temperature afforded corresponding amide (3), which on refluxing with aq. 3N NaOH furnished quinazoline-4-one (4) product. Quinazolone 4 was reacted with POCl₃ to attain chloro quinazoline (5). Chloroquinazoline 5 on further treatment with hydrazine in THF produced 6-bromo-2-cyclopropyl-4-hydrazinylquinazoline (6). Subsequent cyclization of compound 6 was achieved by heating in Ac₂O & AcOH for 2 h to obtain the desired triazoloquinazoline 7. Triazoloquinazoline 7 on reaction with diverse range of aryl boronic acids by Suzuki
coupling reaction (Miyaura et al., 1979; Miyaura and Suzuki, 1995) with the aid of Pd(OAc)₂ catalyst & S-Phos ligand in K₂CO₃ and 1,4-dioxane attained disubstituted triazolotriquinazolines (8A-G). Structures of all new hybrids were envisaged and confirmed on the source of IR, ¹H NMR, ¹³C NMR & mass spectral data. Primarily, when the Suzuki coupling reaction is carried out at reflux conditions for longer time (16 h), interestingly, the side chain cyclopropyl ring moiety due to relatively less stability it undergoes transformation to vinyl moiety and produces the corresponding quinazolines (8A & 8B). In order to rectify this problem, the coupling reaction time is reduced to 2 h and the corresponding products are obtained in good yields (8C-G).

By fascinating this, we also used benzyol chloride (9) for the introduction of phenyl ring at the 2nd position and for the synthesis of various phenyl substituted triazolotriquinazoline derivatives. For this, 5-bromoanthranilic acid (1) was treated with benzyol chloride and prepared subsequent benzoazine (10) and the same synthetic sequence was adopted for the synthesis of bromo triazolotriquinazoline (15). Furthermore, Suzuki coupling reaction is successfully employed on compound 15 with various boronic acids with PdCl₂(dppf).DCM complex in 1,4-dioxane for 12 h afforded requisite triazoloquinazolines (16H-16L) in reasonable to good yields depicted in Scheme 2. Thus synthesized quinazolines (Scheme 3) were screened against two cancer cell lines for evaluation of in vitro anticancer activity and considerable results are obtained for some of the compounds (Tables 1 and 2).

The source of the cell lines used in the present study and the culture media are elaborated in reference (Ravichandran and Manoj, 2014). IC₅₀ In vitro growth inhibitory values of the compounds are assessed compared with the reference drug Puromycin. The cytotoxic activity of the compounds were tested using a CellTiter-Glo Luminescence based cellular cytotoxicity assay against HepG2 (ATCC Cat No HB-8065) & MCF7 (ATCC Cat No HTB-22). The titled cell lines were firstly cultured using Dulbecos Modified Eagle Medium (DMEM), and supplemented through 10% heat-inactivated Fetal Bovine Serum; in humidified 5% CO₂ atmosphere. When cells reached to 80-90% confluency, they were separated from the flasks by trypsinization, neutralized, tallied and then seeded 5000 cells/well in a 96 well clear bottom tissue culture plates. After 24 h, the cells were treated with mentioned compounds & incubated for 72 h at 37 °C in 5% CO₂ incubator. Following incubation, 100 μL of CellTiter-Glo ® reagent was added and mixed well for 10 min. The luminescence was calculated using an Envision multimode plate reader. The IC₅₀ (50% inhibitory concentration) were estimated from the conspired absorbance data for the dose response curves (Figures 1 and 2). The cytotoxicity (IC₅₀ values in μM) of the triazolo quinazolines was determined by analyzing the data using Graphpad Prism statistical tool and values are tabulated in Tables 1 and 2. Out of the 13 compounds under study, the compounds 8A, 16H and 16K displayed potent activity (14-49 μM) on both HepG2 (liver carcinoma) and MCF-7 (breast cancer) cell lines. Compounds 8B, 8F, 16L, and 15 displayed substantial activity against HepG2 cancer cell line (34-65 μM). Moreover, compounds 8 C-E, 8G, 16 I-J did not show any activity on the tested cell lines. These results indicate that introduction of vinyl and phenyl moiety is more important rather than cyclopropyl ring for cytotoxicity.

CONCLUSIONS

In the study, a variety of triazolo[4,3-c] quinazolines were synthesized in an efficient manner and the compounds were well characterized by spectroscopic methods. The titled synthesized hybrids were screened for possible anticancer activity with two cancer cell lines and some of the compounds (8A, 16H, 16K) displayed substantial activity. SAR studies and synthesis of other substituted compounds and its library is underway in our laboratory for further biological activity will be reported in due course.

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Conflict of interest

There is no conflict between authors

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