

Design, Synthesis and *in vitro* Anticancer Evaluation of New 2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one Based 1,2,3-Triazoles

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A series of novel 2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one derived from 1,4-disubstituted 1,2,3-triazole derivatives (**4a-j** and **5a-j**) were synthesized using Cu(I) catalyzed azide alkyne cyclization (CuAAC) reaction of the compounds **2** and **3** with various aromatic azides. The examination of *in vitro* anticancer activity revealed that the compounds **4d** and **5d** were found to possess a broad spectrum of anticancer activity against three cell lines MCF-7, HeLa and IMR-32 with IC₅₀ values ranging from 26.28 ± 1.5 to 32.06 ± 0.3 M mL⁻¹, respectively. The remaining compounds have shown good to moderate activity against the tested cell lines.

Keywords: 2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one, 1,2,3-triazole; Anticancer activity

INTRODUCTION

1,2,3-Triazoles have become potentially useful therapeutic molecules that have attracted the attention of both synthetic and medicinal chemists because of their varied biological activities, which include antimicrobial [1], anticancer [2], anti-HIV [3], anticonvulsant [4], antioxidant activities [5]. Such compounds have also been reported as selective adrenergic receptor agonists [6], inhibitors of kinase [7,8] and other enzymatic inhibitors [9,10]. By combining 1,2,3-triazoles with another pharmacophore *via* [3+2]cycloaddition reaction, a number of compounds with biological activity were synthesized [11-13].

On the other hand, chemistry of heterocyclic compounds containing 1,4-benzothiazine and its analogues has received considerable attention due to its effective pharmacological importance. For example, a large amount of 1,4-benzothiazine has been incorporated in a wide variety of candidates for biologically interesting drugs that possess anticancer agents [14], antimicrobial [15], antifungal [16,17], antagonists [18] and antidiabetic activities [19]. On the basis of broad spectrum of important pharmaceutically active compounds and natural products, 1,4-benzothiazine derivatives have triggered sustainably increasing attention.

By considering the importance and successful synthesis and anticancer activity of reported benzoxazine hybrids [20,21]

and 1,2,3-triazole derivatives [13,22,23], we designed the moieties that embodied both the active pharmacophore units in one molecular platform to evaluate their anticancer activity. Therefore, in this study and in the continuation of our work on the development of new biologically active 1,2,3-triazole systems [24-35], we report herein the synthesis of 1,2,3-triazole linked benzothiazine derivatives and screened for their anticancer activity.

EXPERIMENTAL

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 ¹H NMR spectra. The instrument was set at 100 MHz for acquiring ¹³C NMR spectra. Coupling constant (*J*) values are presented in Hertz. Mass spectra were recorded by using ESI-MS.

Synthesis of 4-(prop-2-yn-1-yl)-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one (2**):** A mixture of 2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one (**1**) (8 g, 0.048 mol), Cs₂CO₃ (31.5 g, 0.0967 mol) and propargyl bromide (8.4 g, 0.072 mol) in acetone (60 mL) was

stirred at room temperatures for 1 h. After the completion of the reaction as evidenced by TLC, the solvent was evaporated under vacuum. The mixture was diluted with water (30 mL) and extracted by ethyl acetate (3 × 30 mL). The combined organic phase was washed with brine (2 × 15 mL), then dried by adding anhydrous MgSO₄ and concentrated to afford compound **2**. White solid; Yield: 76 %; ¹H NMR (400 MHz, CDCl₃): 7.52–7.34 (m, 2H), 7.31–7.20 (m, 1H), 7.10–7.00 (m, 1H), 4.70 (s, 2H, N-CH₂), 3.44 (s, 2H, S-CH₂), 2.29 (s, 1H, -CH); MS (ESI) *m/z*: 204 [M+H]⁺. Anal. calcd. (found) % for C₁₁H₉NOS: C, 65.00 (65.07); H, 4.46 (4.51); N, 6.89 (6.92).

Synthesis of 4-(prop-2-yn-1-yl)-2H-benzo[b][1,4]thiazin-3(4H)-one-1,1-dioxide (3): 4-(Prop-2-yn-1-yl)-2H-benzo[b][1,4]thiazin-3(4H)-one (**1**) (0.0197 mol) was dissolved in DCM (40 mL) and *m*-CPBA (0.059 mol) was added slowly at 0 °C. The reaction mixture was stirred at room temperature for 12 h and the progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was quenched with a saturated aqueous solution of sodium bicarbonate (50 mL), extracted with DCM (2 × 30 mL). The combined organic layers were washed with brine, dried over anhydrous MgSO₄ and concentrated under reduced pressure to afford compound **3**. (Yield 66 %), White solid; m.p.: 124–126 °C; ¹H NMR (400 MHz, CDCl₃, δ in ppm): 8.00 (d, *J* = 8.0 Hz, 1H), 7.77–7.68 (m, 1H), 7.64–7.54 (m, 1H), 7.44–7.32 (m, 1H), 4.77 (s, 2H, N-CH₂), 4.27 (s, 2H, SO₂-CH₂), 2.36 (s, 1H, -CH); MS (ESI) *m/z*: 236 [M+H]. Anal. calcd. (found) % for C₁₁H₉NO₃S: C, 56.16 (56.21); H, 3.86 (3.82); N, 5.95 (5.89).

General procedure for the synthesis of 1,4-disubstituted 1,2,3-triazoles (4a-j and 5a-j): To a solution of alkyne (**2**, **3**) (0.0015 mol) and arylazide (0.002 mol) in THF (10 mL) was added copper(I) iodide (10 mol %) and the reaction mixture was stirred at room temperature for 10–12 h. After completion of the reaction by TLC analysis, the reaction mixture was diluted with water (10 mL) and the product was extracted with ethyl acetate (3 × 20 mL). The combined organic layer was dried over anhydrous MgSO₄ and the solvent was evaporated under vacuum to afford the crude product. The crude compound was purified by column chromatography (hexane/ethyl acetate gradient) to afford the pure desired product.

4-((1-(4-Methoxyphenyl)-1H-1,2,3-triazol-4-yl)methyl)-2H-benzo[b][1,4]thiazin-3(4H)-one (4a): White solid, yield: 71 %; m.p.: 141–143 °C; IR (KBr, cm⁻¹): 3140 (CH-triazole), 1658 (C=O), 1593 (C=C), 1496, 1043, 667 (C-S); ¹H NMR (400 MHz, CDCl₃, δ in ppm): 8.01 (s, 1H, triazole-H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 2H), 7.43–7.31 (m, 3H), 7.06–6.99 (m, 2H), 5.28 (s, 2H, N-CH₂), 3.88 (s, 3H, O-CH₃), 3.47 (s, 2H, S-CH₂); ¹³C NMR (100 MHz, CDCl₃, δ in ppm): 162.23, 159.03, 145.96, 143.83, 129.24, 127.9, 125.27, 121.67, 121.62, 119.27, 117.43, 114.76, 55.58, 40.73, 30.53; MS (ESI) *m/z*: 353 [M+H]; Anal. calcd. (found) % for C₁₈H₁₆N₄O₂S: C, 61.35 (61.37); H, 4.58 (4.53); N, 15.90 (15.86).

4-((1-(2,3-Dimethylphenyl)-1H-1,2,3-triazol-4-yl)methyl)-2H-benzo[b][1,4]thiazin-3(4H)-one (4b): White solid, yield: 69 %; m.p.: 129–131 °C; IR (KBr, cm⁻¹): 3144 (CH-triazole), 1668 (C=O), 1594 (C=C), 1493, 1047, 662 (C-S); ¹H NMR (400 MHz, CDCl₃, δ in ppm): 7.85 (d, *J* = 8.0 Hz, 1H), 7.79 (s, 1H, triazole-H), 7.40–7.22 (m, 2H), 7.20 (t, *J* = 8.0

Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 7.07–7.03 (m, 2H), 5.30 (s, 2H, N-CH₂), 3.42 (s, 2H, S-CH₂), 2.35 (s, 3H, Ar-CH₃), 1.98 (s, 3H, Ar-CH₃); ¹³C NMR (100 MHz, CDCl₃, δ in ppm): 163.04, 143.22, 137.67, 134.34, 129.63, 126.77, 126.01, 124.91, 123.87, 123.17, 122.19, 118.47, 117, 112.70, 40.41, 30.41, 21.78, 13.84; MS (ESI) *m/z*: 351 [M+H]; Anal. calcd. (found) % for C₁₉H₁₈N₄OS: C, 65.12 (65.17); H, 5.18 (5.13); N, 15.99 (16.04).

4-((1-(3,5-Dichlorophenyl)-1H-1,2,3-triazol-4-yl)methyl)-2H-benzo[b][1,4]thiazin-3(4H)-one (4c): Yellow solid, yield: 72 %; m.p.: 154–156 °C; IR (KBr, cm⁻¹): 3144 (CH-triazole), 1655 (C=O), 1596 (C=C), 1476, 1038, 658 (C-S); ¹H NMR (400 MHz, CDCl₃, δ in ppm): 8.10 (s, 1H, triazole-H), 7.78 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.69 (s, 2H), 7.43 (t, *J* = 4.0 Hz, 1H), 7.37 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.32–7.27 (m, 1H), 7.07–7.03 (m, 1H), 5.26 (s, 2H, N-CH₂), 3.43 (s, 2H, S-CH₂); ¹³C NMR (100 MHz, CDCl₃, δ in ppm): 164.80, 144.12, 138.70, 137.07, 135.25, 127.73, 127.24, 126.74, 123.06, 122.28, 121.05, 117.84, 117.58, 40.53, 30.61; MS (ESI) *m/z*: 392 [M+H]; Anal. calcd. (found) % for C₁₇H₁₂N₄OSCl₂: C, 52.18 (52.22); H, 3.09 (3.15); N, 14.32 (14.36).

4-((1-(3,5-Dimethylphenyl)-1H-1,2,3-triazol-4-yl)methyl)-2H-benzo[b][1,4]thiazin-3(4H)-one (4d): White solid, yield: 81 %; m.p.: 129–131 °C; IR (KBr, cm⁻¹): 3138 (CH-triazole), 1666 (C=O), 1595 (C=C), 1494, 1048, 666 (C-S); ¹H NMR (400 MHz, CDCl₃, δ in ppm): 8.07 (s, 1H, triazole-H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.52 (s, 1H), 7.40–7.30 (m, 2H), 7.08–7.02 (m, 2H), 7.00 (s, 1H), 5.26 (s, 2H, N-CH₂), 3.43 (s, 2H, S-CH₂), 2.39 (s, 6H, Ar-CH₃); ¹³C NMR (100 MHz, CDCl₃, δ in ppm): 163.61, 145.55, 143.18, 139.31, 136.35, 129.94, 127.95, 125.26, 121.52, 119.29, 117.50, 114.82, 40.63, 30.70, 20.78; MS (ESI) *m/z*: 351 [M+H]; Anal. calcd. (found) % for C₁₉H₁₈N₄OS: C, 65.12 (65.19); H, 5.18 (5.16); N, 15.99 (16.03).

4-((1-*o*-Tolyl-1H-1,2,3-triazol-4-yl)methyl)-2H-benzo[b][1,4]thiazin-3(4H)-one (4e): White solid, yield: 59 %; m.p.: 122–124 °C; IR (KBr, cm⁻¹): 3157 (CH-triazole), 1662 (C=O), 1594 (C=C), 1488, 1031, 662 (C-S); ¹H NMR (400 MHz, CDCl₃, δ in ppm): 8.15 (s, 1H, triazole-H), 8.05–8.00 (m, 1H), 7.88–7.82 (m, 1H), 7.77–7.73 (m, 1H), 7.41–7.25 (m, 5H), 5.33 (s, 2H, N-CH₂), 3.40 (s, 2H, S-CH₂), 2.11 (s, 3H, Ar-CH₃); ¹³C NMR (100 MHz, CDCl₃, δ in ppm): 163.31, 145.78, 143.38, 139.61, 136.32, 129.94, 127.94, 125.25, 121.56, 119.27, 117.75, 114.51, 40.77, 30.30, 18.37; MS (ESI) *m/z*: 337 [M+H]; Anal. calcd. (found) % for C₁₈H₁₆N₄OS: C, 64.26 (64.21); H, 4.79 (4.83); N, 16.65 (16.61).

4-((1-Phenyl-1H-1,2,3-triazol-4-yl)methyl)-2H-benzo[b][1,4]thiazin-3(4H)-one (4f): White solid, yield: 66 %; m.p.: 114–116 °C; IR (KBr, cm⁻¹): 3138 (CH-triazole), 1668 (C=O), 1598 (C=C), 1493, 1052, 660 (C-S); ¹H NMR (400 MHz, CDCl₃, δ in ppm): 8.10 (s, 1H, triazole-H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.74–7.68 (m, 2H), 7.58–7.48 (m, 2H), 7.46–7.40 (m, 1H), 7.38–7.22 (m, 2H), 7.08–7.01 (m, 1H), 5.27 (s, 2H, N-CH₂), 3.43 (s, 2H, S-CH₂); ¹³C NMR (100 MHz, CDCl₃, δ in ppm): 163.73, 142.32, 133.58, 133.07, 130.27, 128.32, 127.82, 126.35, 125.24, 123.86, 121.81, 119.35, 117.57, 114.85, 40.26, 30.54; MS (ESI) *m/z*: 323 [M+H]; Anal. calcd. (found) % for C₁₇H₁₄N₄OS: C, 63.33 (63.29); H, 4.38 (4.33); N, 17.38 (17.42).

4-((1-(4-Bromophenyl)-1H-1,2,3-triazol-4-yl)methyl)-2H-benzo[b][1,4]thiazin-3(4H)-one (4g): Yellow solid, yield:

63 %; m.p.: 149-151 °C; IR (KBr, cm⁻¹): 3131 (CH-triazole), 1660 (C=O), 1589 (C=C), 1487, 1049, 664 (C-S); ¹H NMR (400 MHz, CDCl₃, δ in ppm): 8.09 (s, 1H, triazole-H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.66-7.60 (m, 4H), 7.37-7.27 (m, 2H), 7.05 (t, *J* = 8.0 Hz, 1H), 5.26 (s, 2H, N-CH₂), 3.42 (s, 2H, S-CH₂); ¹³C NMR (100 MHz, CDCl₃, δ in ppm): 163.88, 139.84, 135.90, 132.91, 128.23, 127.76, 124.04, 123.29, 122.51, 122.04, 121.98, 121.88, 118.72, 40.63, 30.66; MS (ESI) *m/z*: 403 [M+2H]; Anal. calcd. (found) % for C₁₇H₁₃N₄OSBr: C, 50.88 (50.91); H, 3.27 (3.23); N, 13.96 (14.01).

4-((1-(3-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one (4h): Pale yellow solid, yield: 64 %; m.p.: 148-150 °C; IR (KBr, cm⁻¹): 3151 (CH-triazole), 1658 (C=O), 1593 (C=C), 1496, 1043, 667 (C-S); ¹H NMR (400 MHz, CDCl₃, δ in ppm): 8.10 (s, 1H, triazole-H), 7.83-7.78 (m, 2H), 7.65-7.62 (m, 1H), 7.47-7.27 (m, 4H), 7.05 (t, *J* = 8.0 Hz, 1H), 5.27 (s, 2H, N-CH₂), 3.43 (s, 2H, S-CH₂); ¹³C NMR (100 MHz, CDCl₃, δ in ppm): 163.37, 145.79, 143.33, 137.99, 135.17, 128.00, 127.78, 125.38, 125.28, 122.09, 119.34, 118.55, 117.35, 114.85, 41.07, 30.24; MS (ESI) *m/z*: 357 [M+H]; Anal. calcd. (found) % for C₁₇H₁₃N₄OSeCl: C, 57.22 (57.27); H, 3.67 (3.73); N, 15.70 (15.76).

4-((1-(3-(Trifluoromethyl)phenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one (4i): Yellow solid, yield: 53 %; m.p.: 130-132 °C; IR (KBr, cm⁻¹): 3142 (CH-triazole), 1659 (C=O), 1594 (C=C), 1490, 1048, 659 (C-S); ¹H NMR (400 MHz, CDCl₃, δ in ppm): 7.89 (s, 1H, triazole-H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.73 (s, 1H), 7.38-7.30 (m, 3H), 7.28-7.14 (m, 1H), 7.11-7.02 (m, 2H), 5.30 (s, 2H, N-CH₂), 3.42 (s, 2H, S-CH₂); ESI-MS *m/z*: 391 [M+H]; Anal. calcd. (found) % for C₁₈H₁₃N₄OSF₃: C, 55.38 (55.33); H, 3.36 (3.40); N, 14.35 (14.39).

4-((1-(2-Fluorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one (4j): Pale red solid, yield: 67 %; m.p.: 147-149 °C; IR (KBr, cm⁻¹): 3149 (CH-triazole), 1662 (C=O), 1584 (C=C), 1490, 1037, 662 (C-S); ¹H NMR (400 MHz, CDCl₃, δ in ppm): 8.10 (s, 1H, triazole-H), 7.93-7.87 (m, 2H), 7.82-7.74 (m, 2H), 7.65-7.61 (m, 1H), 7.49-7.28 (m, 2H), 7.06-7.02 (m, 1H), 5.28 (s, 2H, N-CH₂), 3.43 (s, 2H, S-CH₂); MS (ESI) *m/z*: 341 [M+H]; Anal. calcd. (found) % for C₁₇H₁₃N₄OSF: C, 59.99; H, 3.85; N, 16.46; found: C, 60.04; H, 3.92; N, 16.51.

4-((1-(4-Methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one-1,1-dioxide (5a): White solid, yield: 79 %; m.p.: 206-208 °C; IR (KBr, cm⁻¹): 3133 (CH-triazole), 1680 (C=O), 1588 (C=C), 1480, & 1132 (SO₂); ¹H NMR (400 MHz, CDCl₃, δ in ppm): 8.14 (m, 1H), 8.03 (s, 1H, triazole-H), 7.99-7.94 (m, 1H), 7.73 (t, *J* = 8 Hz, 1H), 7.61-7.57 (m, 2H), 7.39-7.33 (m, 1H), 7.04-6.98 (m, 2H), 5.36 (s, 2H, N-CH₂), 4.35 (s, 2H, SO₂-CH₂), 3.86 (s, 3H, O-CH₃); ¹³C NMR (100 MHz, CDCl₃, δ in ppm): 160.73, 159.35, 145.70, 143.05, 135.92, 133.03, 129.86, 127.96, 125.24, 121.62, 119.27, 117.45, 114.75, 57.51, 55.77, 41.25; MS (ESI) *m/z*: 385 [M+H]. Anal. calcd. (found) % for C₁₈H₁₆N₄O₄S: C, 56.24 (56.18); H, 4.20 (4.25); N, 14.57 (14.63).

4-((1-(2,3-Dimethylphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one-1,1-dioxide (5b): White solid, yield: 73 %; m.p.: 179-181 °C; IR (KBr, cm⁻¹): 3140 (CH-triazole), 1672 (C=O), 1591 (C=C), 1475 & 1133 (SO₂); ¹H NMR (400 MHz, CDCl₃, δ in ppm): 8.16 (d, *J* = 8.0

Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.83 (s, 1H, triazole-H), 7.75 (t, *J* = 8 Hz, 1H), 7.37 (t, *J* = 8 Hz, 1H), 7.31 (d, *J* = 4.0 Hz, 1H), 7.20 (t, *J* = 8 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 1H), 5.39 (s, 2H, N-CH₂), 4.25 (s, 2H, SO₂-CH₂), 2.35 (s, 3H, Ar-CH₃), 1.96 (s, 3H, Ar-CH₃); ¹³C NMR (100 MHz, CDCl₃, δ in ppm): 160.98, 138.88, 135.39, 132.51, 131.52, 128.25, 126.15, 124.88, 124.37, 123.81, 120.01, 117.80, 57.00, 41.43, 20.36, 14.26; MS (ESI) *m/z*: 383 [M+H]; Anal. calcd. (found) % for C₁₉H₁₈N₄O₃S: C, 59.67 (59.71); H, 4.74 (4.69); N, 14.65 (14.70).

4-((1-(3,5-Dichlorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one-1,1-dioxide (5c): Pale yellow solid, yield: 84 %; m.p.: 222-224 °C; IR (KBr, cm⁻¹): 3158 (CH-triazole), 1677 (C=O), 1592 (C=C), 1472, & 1128 (SO₂); ¹H NMR (400 MHz, CDCl₃, δ in ppm): 8.12 (s, 1H, triazole-H), 8.07 (d, *J* = 8 Hz, 1H), 7.98 (d, *J* = 8 Hz, 1H), 7.74 (t, *J* = 8 Hz, 1H), 7.67 (s, 2H), 7.43 (s, 1H), 7.39 (m, 1H), 5.36 (s, 2H, N-CH₂), 4.26 (s, 2H, SO₂-CH₂); ¹³C NMR (100 MHz, CDCl₃, δ in ppm): 160.50, 144.17, 138.70, 137.05, 135.25, 127.77, 127.22, 126.74, 123.06, 122.28, 121.05, 117.79, 117.57, 57.31, 41.01; MS (ESI) *m/z*: 424 [M+H]. Anal. calcd. (found) % for C₁₇H₁₂N₄O₃SCl₂: C, 48.24 (48.27); H, 2.86 (2.90); N, 13.24 (13.29).

4-((1-(3,5-Dimethylphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one-1,1-dioxide (5d): White solid, yield: 65 %; m.p.: 184-186 °C; IR (KBr, cm⁻¹): 3129 (CH-triazole), 1670 (C=O), 1585 (C=C), 1488 & 1137 (SO₂); ¹H NMR (400 MHz, CDCl₃, δ in ppm): 8.13 (t, *J* = 8.0 Hz, 1H), 8.09 (s, 1H, triazole-H), 7.96 (dd, *J* = 4.0, 4.0 Hz, 1H), 7.74 (t, *J* = 8.0 Hz, 1H), 7.36-7.25 (m, 3H), 7.06 (s, 1H), 5.35 (s, 2H, N-CH₂), 4.26 (s, 2H, SO₂-CH₂), 2.38 (s, 6H, Ar-CH₃); ¹³C NMR (100 MHz, CDCl₃, δ in ppm): 160.34, 144.15, 141.69, 138.77, 136.70, 132.05, 129.78, 126.72, 123.00, 122.26, 121.05, 119.73, 117.39, 117.66, 56.97, 41.58, 21.13; MS (ESI) *m/z*: 383 [M+H]; Anal. calcd. (found) % for C₁₉H₁₈N₄O₃S: C, 59.67 (59.63); H, 4.74 (4.71); N, 14.65 (14.69).

4-((1-(*o*-Tolyl)-1*H*-1,2,3-triazol-4-yl)methyl)-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one-1,1-dioxide (5e): White solid; yield: 69 %, m.p.: 169-171 °C; IR (KBr, cm⁻¹): 3157 (CH-triazole), 1680 (C=O), 1594 (C=C), 1475 & 1137 (SO₂); ¹H NMR (400 MHz, CDCl₃, δ in ppm): 8.18-8.13 (m, 1H), 8.00-7.92 (m, 1H), 7.88 (s, 1H, triazole-H), 7.75 (t, *J* = 8.0 Hz, 1H), 7.43-7.27 (m, 5H), 5.39 (s, 2H, N-CH₂), 4.25 (s, 2H, SO₂-CH₂), 2.17 (s, 3H, Ar-CH₃); ¹³C NMR (100 MHz, CDCl₃, δ in ppm): 160.38, 143.93, 141.38, 138.30, 136.22, 135.33, 133.45, 131.55, 129.99, 128.37, 126.87, 125.81, 124.84, 124.33, 119.98, 57.03, 41.33, 18.41; ESI-MS *m/z*: 369 [M+H]; Anal. calcd. (found) % for C₁₈H₁₆N₄O₃S: C, 58.68 (58.75); H, 4.38 (4.33); N, 15.21 (15.29).

4-((1-(Phenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one-1,1-dioxide (5f): White solid; yield: 67 %, m.p.: 144-146 °C; IR (KBr, cm⁻¹): 3131 (CH-triazole), 1674 (C=O), 1587 (C=C), 1485 & 1138 (SO₂); ¹H NMR (400 MHz, CDCl₃, δ in ppm): 8.15 (s, 1H), 8.12 (s, 1H, triazole-H), 8.00-7.92 (m, 1H), 7.78-7.67 (m, 3H), 7.57-7.49 (m, 2H), 7.47-7.40 (m, 1H), 7.38-7.30 (m, 1H), 5.37 (s, 2H, N-CH₂), 4.26 (s, 2H, SO₂-CH₂); ¹³C NMR (100 MHz, CDCl₃, δ in ppm): 160.34, 143.08, 139.45, 137.57, 136.49, 130.12, 126.72, 124.88, 123.02, 122.14, 120.29, 117.80, 114.26, 57.06, 41.12; MS (ESI) *m/z*: 355 [M+H]; Anal. calcd. (found) % for C₁₇H₁₄N₄O₃S: C, 57.62 (57.67); H, 3.98 (3.93); N, 15.81 (15.74).

4-((1-(4-Bromophenyl)-1H-1,2,3-triazol-4-yl)methyl)-2H-benzo[b][1,4]thiazin-3(4H)-one-1,1-dioxide (5g): Yellow solid, yield: 73 %; m.p.: 174-176 °C; IR (KBr, cm^{-1}): 3138 (CH-triazole), 1678 (C=O), 1589, 1481, & 1130 (SO_2); ^1H NMR (400 MHz, CDCl_3 , δ in ppm): 8.11 (brs, 1H), 8.09 (s, 1H, triazole-H), 8.00-7.92 (m, 1H), 7.78-7.70 (m, 1H), 7.76-7.56 (m, 4H), 7.40-7.30 (m, 1H), 5.37 (s, 2H, N-CH_2), 4.25 (s, 2H, $\text{SO}_2\text{-CH}_2$); ^{13}C NMR (100 MHz, CDCl_3 , δ in ppm): 160.70, 145.75, 143.75, 137.00, 131.47, 127.88, 125.93, 125.27, 123.11, 122.23, 119.31, 117.37, 114.63, 57.07, 41.22; MS (ESI) m/z : 434 [$\text{M}+2\text{H}$]; Anal. calcd. (found) % for $\text{C}_{17}\text{H}_{13}\text{N}_4\text{O}_3\text{SBr}$: C, 47.12 (47.03); H, 3.02 (3.11); N, 12.93 (12.98).

4-((1-(3-Chlorophenyl)-1H-1,2,3-triazol-4-yl)methyl)-2H-benzo[b][1,4]thiazin-3(4H)-one-1,1-dioxide (5h): Pale yellow solid, yield: 67 %; m.p.: 181-183 °C; IR (KBr, cm^{-1}): 3138 (CH-triazole), 1678 (C=O), 1589 (C=C), 1481 & 1130 (SO_2); ^1H NMR (400 MHz, CDCl_3 , δ in ppm): 8.12-8.17 (m, 1H), 8.10 (s, 1H, triazole-H), 7.98 (s, 1H), 7.92-7.84 (m, 1H), 7.78-7.72 (m, 1H), 7.44-7.28 (m, 4H), 5.33 (s, 2H, N-CH_2), 4.25 (s, 2H, $\text{SO}_2\text{-CH}_2$); ^{13}C NMR (100 MHz, CDCl_3 , δ in ppm): 160.69, 145.82, 143.55, 137.35, 134.15, 131.60, 128.47, 127.89, 125.27, 121.90, 119.69, 119.30, 118.58, 117.35, 114.77, 57.12, 41.33; MS (ESI) m/z : 389 [$\text{M}+\text{H}$]; Anal. calcd. (found) % for $\text{C}_{17}\text{H}_{13}\text{N}_4\text{O}_3\text{SCl}$: C, 52.51 (52.43); H, 3.37 (3.45); N, 14.41 (14.46).

4-((1-(3-(Trifluoromethyl)phenyl)-1H-1,2,3-triazol-4-yl)methyl)-2H-benzo[b][1,4]thiazin-3(4H)-one-1,1-dioxide (5i): Pale yellow solid, yield: 60 %; m.p.: 161-163 °C; IR (KBr, cm^{-1}): 3144 (CH-triazole), 1679 (C=O), 1594 (C=C), 1485 & 1142 (SO_2); ^1H NMR (400 MHz, CDCl_3 , δ in ppm): 8.21 (s, 1H, triazole-H), 8.11-7.90 (m, 3H), 7.83 (brs, 2H), 7.77-7.68 (m, 2H), 7.42-7.30 (m, 1H), 5.35 (s, 2H, N-CH_2), 4.31 (s, 2H, $\text{SO}_2\text{-CH}_2$); MS (ESI) m/z : 423 [$\text{M}+\text{H}$]; Anal. calcd. (found) % for $\text{C}_{18}\text{H}_{13}\text{N}_4\text{O}_3\text{SF}_3$: C, 51.18 (51.11); H, 3.10 (3.07); N, 13.26 (13.33).

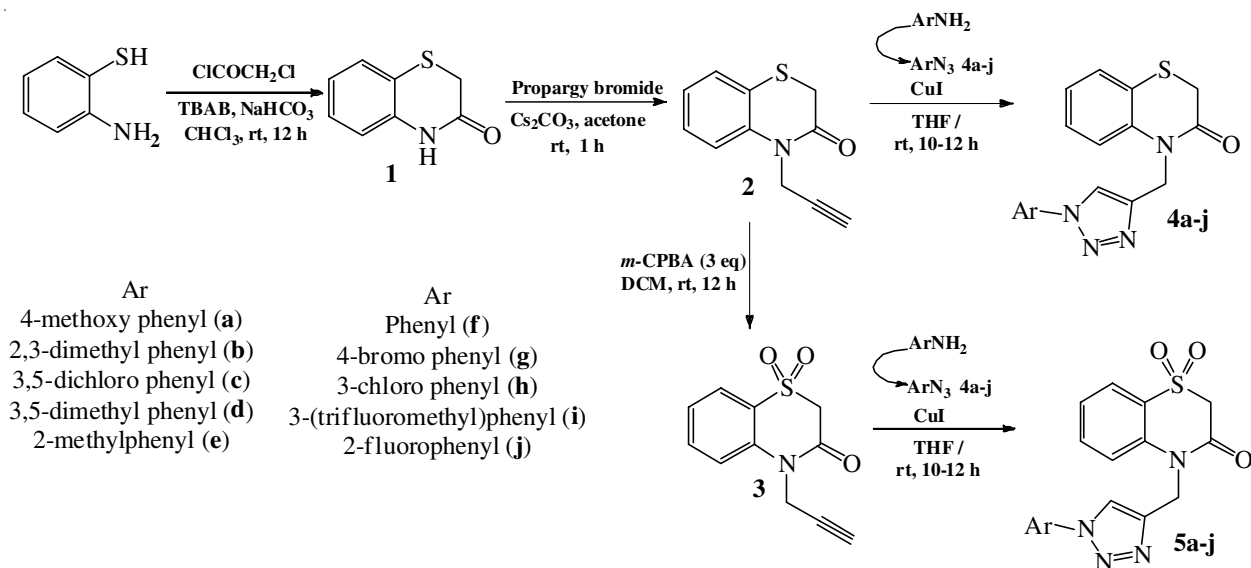
4-((1-(2-Fluorophenyl)-1H-1,2,3-triazol-4-yl)methyl)-2H-benzo[b][1,4]thiazin-3(4H)-one-1,1-dioxide (5j): Pale red solid, yield: 68 %; m.p.: 158-160 °C; IR (KBr, cm^{-1}): 3141 (CH-triazole), 1688 (C=O), 1593 (C=C), 1477 & 1140 (SO_2); ^1H NMR (400 MHz, CDCl_3 , δ in ppm): 8.17-8.11 (m, 1H),

8.05 (s, 1H, triazole-H), 7.96-7.88 (m, 2H), 7.78-7.72 (m, 1H), 7.35 (t, $J = 8.0$ Hz, 1H), 7.32-7.27 (m, 1H), 7.25-7.20 (m, 1H), 7.18-7.10 (m, 1H), 5.38 (s, 2H, N-CH_2), 4.26 (s, 2H, $\text{SO}_2\text{-CH}_2$); MS (ESI) m/z : 373 [$\text{M}+\text{H}$]; Anal. calcd. (found) % for $\text{C}_{17}\text{H}_{13}\text{N}_4\text{O}_3\text{SF}$: C, 54.83 (54.77); H, 3.52 (3.47); N, 15.05 (15.13).

RESULTS AND DISCUSSION

The synthesis of the title compounds was carried out by the synthetic sequence as shown in **Scheme-I**. The first step of the synthesis involves the subsequent acylation of 2-aminothiophenol using chloroacetyl chloride in chloroform to form 2H-benzo[b][1,4]thiazin-3(4H)-one **1**. Compound **1** was treated with propargyl bromide in the presence of base in acetone to afford compound **2** in good yield [36]. The oxidation of sulfur in compound **2** with 3-chlorobenzoperoxoic acid (*m*-CPBA) in dichloromethane at room temperature afforded compound **3** in good yield [37]. The intermediate alkynes **2** and **3** treated with different aryl azides in tetrahydrofuran containing a copper(I) iodide affords the title compounds (**4a-j** and **5a-j**) in good yields [38,39].

Anticancer activity: Newly synthesized compounds were screened for their *in vitro* anticancer activity against three cancer cell lines such as MCF-7, HeLa and IMR-32. The viability of cells in the presence of the test compounds was measured by the MTT-assay [40,41]. The IC_{50} values for 1,4-benzothiazine-[1,2,3]triazole derivatives (**4a-j** and **5a-j**) are presented in Table-1. Among all the tested compounds, the compound derived from 3,5-dimethyl phenyl triazole on 2H-benzo[b][1,4]thiazin-3(4H)-one 1,1-dioxide *i.e.*, compound **5d** has shown potent activity against three cell lines MCF-7, HeLa and IMR-32 with IC_{50} values 27.81 ± 1.1 , 26.28 ± 1.5 and 31.50 ± 1.3 M mL^{-1} , respectively. Similarly, compound **4d** has shown good activity against MCF-7, HeLa and IMR-32 with IC_{50} values ranging from 31.50 ± 0.6 , 32.06 ± 0.3 and 27.10 ± 0.8 M mL^{-1} , respectively. Compounds **4a** and **5a** have shown moderate activity with IC_{50} values ranging from 44.65 ± 1.0 to 54.86 ± 0.5 and 38.76 ± 0.9 to 42.11 ± 1.2 M mL^{-1} . Similarly, compounds **4b** and **5b** with 2,3-dimethyl phenyl substitution on triazole ring



Scheme-I: Synthesis of 1,4-benzothiazine-[1,2,3]triazole hybrids (**4a-j** and **5a-j**)

TABLE-1
in vitro^{ab} CYTOTOXIC ACTIVITY OF TITLED COMPOUNDS (4*a-j* AND 5*a-j*)

Product	MCF-7	HeLa	IMR-32	Product	MCF-7	HeLa	IMR-32
4 <i>a</i>	44.65 ± 1.0	53.90 ± 0.9	54.86 ± 0.5	5 <i>a</i>	38.76 ± 0.9	40.17 ± 0.1	42.11 ± 1.2
4 <i>b</i>	73.49 ± 0.3	88.17 ± 0.5	61.02 ± 0.7	5 <i>b</i>	78.43 ± 0.8	97.18 ± 1.0	106.92 ± 1.4
4 <i>c</i>	88.19 ± 1.3	79.67 ± 0.7	68.52 ± 0.9	5 <i>c</i>	62.59 ± 0.3	59.41 ± 1.0	58.22 ± 0.5
4 <i>d</i>	31.50 ± 0.6	32.06 ± 0.3	27.10 ± 0.8	5 <i>d</i>	27.81 ± 1.1	26.28 ± 1.5	31.50 ± 1.3
4 <i>e</i>	79.41 ± 0.7	66.93 ± 0.5	87.80 ± 0.6	5 <i>e</i>	59.56 ± 0.7	56.23 ± 0.8	57.49 ± 0.6
4 <i>f</i>	110.69 ± 0.7	126.64 ± 1.1	97.52 ± 0.8	5 <i>f</i>	76.36 ± 1.9	83.11 ± 0.7	69.31 ± 0.7
4 <i>g</i>	130.69 ± 1.0	116.29 ± 1.5	137.82 ± 1.3	5 <i>g</i>	112.36 ± 1.1	99.14 ± 0.8	93.67 ± 0.7
4 <i>h</i>	64.15 ± 0.7	61.99 ± 0.6	74.16 ± 1.5	5 <i>h</i>	100.73 ± 0.8	122.83 ± 1.2	97.18 ± 1.0
4 <i>i</i>	97.18 ± 1.0	70.09 ± 1.2	70.88 ± 0.9	5 <i>i</i>	50.17 ± 1.1	61.02 ± 0.9	55.19 ± 0.8
4 <i>j</i>	58.32 ± 0.9	51.11 ± 1.1	62.81 ± 0.8	5 <i>j</i>	53.16 ± 0.4	50.89 ± 0.7	59.88 ± 1.0
–	–	–	–	Cisplatin	4.61 ± 0.2	3.86 ± 0.1	3.71 ± 0.2

^aValues are expressed as mean ± SEM; ^bData represent the mean ± SEM values of these independent determinations.

shows reasonable activity and rest of the compounds exhibited less significant as compared with standard cisplatin.

Conclusion

In conclusion, the synthesis of new 2*H*-benzo[*b*][1,4]-thiazine-3(4*H*)-one-[1,2,3-triazoles] are reported. The newly synthesized hybrids (4*a-j* and 5*a-j*) were evaluated for *in vitro* anticancer activity. It has been shown that compound 5*d* has a remarkable anticancer activity and compound 4*d* has shown a moderate anticancer activity. By performing a simple structural modification, a powerful new anticancer drug can be generated with good activity.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

REFERENCES

1. B.S. Holla, M. Mahalinga, M.S. Karthikeyan, B. Poojary, P.M. Akberali and N.S. Kumari, *Eur. J. Med. Chem.*, **40**, 1173 (2005); <https://doi.org/10.1016/j.ejmech.2005.02.013>.
2. C.J. Carroux, G.M. Rankin, J. Moeker, L.F. Bornaghi, K. Katneni, J. Morizzi, S.A. Charman, D. Vullo, C.T. Supuran and S.-A. Poulsen, *J. Med. Chem.*, **56**, 9623 (2013); <https://doi.org/10.1021/jm401163e>.
3. R. Alvarez, S. Velazquez, A. San-Felix, S. Aquaro, E.D. Clercq, C.-F. Perno, A. Karlsson, J. Balzarini and M.J. Camarasa, *J. Med. Chem.*, **37**, 4185 (1994); <https://doi.org/10.1021/jm00050a015>.
4. J.L. Kelley, C.S. Koble, R.G. Davis, E.W. McLean, F.E. Soroko and B.R. Cooper, *J. Med. Chem.*, **38**, 4131 (1995); <https://doi.org/10.1021/jm00020a030>.
5. M.F. Mady, G.E.A. Awad and K.B. Jørgensen, *Eur. J. Med. Chem.*, **84**, 433 (2014); <https://doi.org/10.1016/j.ejmech.2014.07.042>.
6. L.L. Brockunier, E.R. Parmee, H.O. Ok, M.R. Candelore, M.A. Cascieri, L.F. Colwell Jr., L. Deng, W.P. Feeney, M.J. Forrest, G.J. Hom, D.E. MacIntyre, L. Tota, M.J. Wyvrat, M.H. Fisher and A.E. Weber, *Bioorg. Med. Chem. Lett.*, **10**, 2111 (2000); [https://doi.org/10.1016/S0960-894X\(00\)00422-4](https://doi.org/10.1016/S0960-894X(00)00422-4).
7. P.H. Olesen, A.R. Sørensen, B. Urso, P. Kurtzhals, A.N. Bowler, U. Ehrbar and B.F. Hansen, *J. Med. Chem.*, **46**, 3333 (2003); <https://doi.org/10.1021/jm021095d>.
8. M. Klein, P. Dinér, D. Dorin-Semlat, C. Doerig and M. Grötl, *Org. Biomol. Chem.*, **7**, 3421 (2009); <https://doi.org/10.1039/b906482f>.
9. V.P. Mocharla, B. Colasson, L.V. Lee, S. Röper, K.B. Sharpless, C.-H. Wong and H.C. Kolb, *Angew. Chem. Int. Ed.*, **44**, 116 (2005); <https://doi.org/10.1002/anie.200461580>.
10. A. Krasinski, Z. Radic, R. Manetsch, V. Raushel, P. Taylor, B.K. Sharpless and H.C. Kolb, *J. Am. Chem. Soc.*, **127**, 6686 (2005); <https://doi.org/10.1021/ja043031t>.
11. D.M. Reddy, J. Srinivas, G. Chashoo, A.K. Saxena and H.M. Sampath Kumar, *Eur. J. Med. Chem.*, **46**, 1983 (2011); <https://doi.org/10.1016/j.ejmech.2011.02.016>.
12. P. Singh, R. Raj, V. Kumar, M.P. Mahajan, P.M.S. Bedi, T. Kaur and A.K. Saxena, *Eur. J. Med. Chem.*, **47**, 594 (2012); <https://doi.org/10.1016/j.ejmech.2011.10.033>.
13. J.A. Stefely, R. Palchaudhuri, P.A. Miller, R.J. Peterson, G.C. Moraski, P.J. Hergenrother and M.J. Miller, *J. Med. Chem.*, **53**, 3389 (2010); <https://doi.org/10.1021/jm1000979>.
14. R.R. Gupta, P.K. Dev, M.L. Sharma, C.M. Rajorla, A. Gupta and M. Nyat, *Anticancer Drugs*, **4**, 589 (1993); <https://doi.org/10.1097/00001813-199310000-00010>.
15. V.L. de M. Guarda, M. Perrissin, F. Thomasson, E.A. Ximenes, S.L. Galdino, I.R. Pitta and C. Luu-Duc, *IL Farmaco.*, **56**, 689 (2001); [https://doi.org/10.1016/S0014-827X\(01\)01113-2](https://doi.org/10.1016/S0014-827X(01)01113-2).
16. L. Pitzurra, R. Fringuelli, S. Perito, F. Schiaffella, R. Barluzzi, F. Bistoni and A. Vecchiarelli, *Antimicrob. Agents Chemother.*, **43**, 2170 (1999); <https://doi.org/10.1128/AAC.43.9.2170>.
17. R. Fringuelli, F. Schiaffella, F. Bistoni, L. Pitzurra and A. Vecchiarelli, *Bioorg. Med. Chem.*, **6**, 103 (1998); [https://doi.org/10.1016/S0968-0896\(97\)10016-5](https://doi.org/10.1016/S0968-0896(97)10016-5).
18. M. Fujita, S. Ito, A. Ota, N. Kato, K. Yamamoto, Y. Kawashima, H. Yamauchi and J. Iwao, *J. Med. Chem.*, **33**, 1898 (1990); <https://doi.org/10.1021/jm00169a011>.
19. T. Matsui, Y. Nakamura, H. Ishikawa, A. Matsuura and F. Kobayashi, *Jpn. J. Pharmacol.*, **64**, 115 (1994); <https://doi.org/10.1254/jjp.64.115>.
20. H.I. E.-Subbagh, A.H. Abadi, L.E. Al-Khawad and K.A. Al-Rashood, *Arch. Pharm. Pharm. Med. Chem.*, **332**, 19 (1999); [https://doi.org/10.1002/\(SICI\)1521-4184\(19991\)332:1<19::AID-ARDP19>3.0.CO;2-M](https://doi.org/10.1002/(SICI)1521-4184(19991)332:1<19::AID-ARDP19>3.0.CO;2-M).
21. E.M.H. Abbas and T.A. Farghaly, *Monatsh. Chem.*, **141**, 661 (2010); <https://doi.org/10.1007/s00706-010-0312-6>.
22. X.L. Li, Y.J. Lin, Q.Q. Wang, Y.K. Yuan, H. Zhang and X.H. Qian, *Eur. J. Med. Chem.*, **46**, 1274 (2011); <https://doi.org/10.1016/j.ejmech.2011.01.050>.
23. M.J. Soltis, H.J. Yeh, K.A. Cole, N. Whittaker, R.P. Wersto and E.C. Kohn, *Drug Metab. Dispos.*, **24**, 799 (1996).
24. S. Narsimha, K.S. Battula, S.K. Nukala, R. Gondru, Y.N. Reddy and V.R. Nagavelli, *RSC Adv.*, **6**, 74332 (2016); <https://doi.org/10.1039/C6RA12285J>.

25. S. Narsimha, T. Ranjith Kumar, N. Satheesh Kumar, S. Yakoob and N. Vasudeva Reddy, *Med. Chem. Res.*, **23**, 5321 (2014); <https://doi.org/10.1007/s00044-014-1076-z>.
26. S. Narsimha, N. Satheesh Kumar, B.K. Swamy, N.V. Reddy, S.K. Althaf Hussain and M.S. Rao, *Bioorg. Med. Chem. Lett.*, **26**, 1639 (2016); <https://doi.org/10.1016/j.bmcl.2016.01.055>.
27. P.N. Reddy, P. Padmaja, B.R. Reddy, G. Rambabu and M.P. Kumar, *Med. Chem. Res.*, **25**, 2093 (2016); <https://doi.org/10.1007/s00044-016-1676-x>.
28. N.V. Reddy, S. Narsimha, L. Sudhakar, K.S. Battula and S.K. Althaf Hussain, *Phosphorus Sulfur Silicon Rel. Elem.*, **191**, 1118 (2016); <https://doi.org/10.1080/10426507.2016.1146273>.
29. R. Thatipamula, S. Narsimha, K. Battula, V. Rajendra Chary, E. Mamidala and N. Vasudeva Reddy, *J. Saudi Chem. Soc.*, **21**, 795 (2017); <https://doi.org/10.1016/j.jscs.2015.12.001>.
30. K. Battula, S. Narsimha, V. Nagavelli, P. Bollepelli and R. Srinivasa, *J. Serb. Chem. Soc.*, **81**, 233 (2016); <https://doi.org/10.2298/JSC150818088B>.
31. N.V. Reddy, S. Narsimha, B.K. Swamy, S. Lavudya and R.K. Thatipamula, *Org. Commun.*, **9**, 32 (2016).
32. B.K. Swamy, S. Narsimha, T.R. Kumar, Y.N. Reddy and N.V. Reddy, *Chemistry Select*, **2**, 4001 (2017); <https://doi.org/10.1002/slct.201700524>.
33. B.K. Swamy, S. Narsimha, T.R. Kumar, Y.N. Reddy and N.V. Reddy, *Chemistry Select*, **2**, 9595 (2017); <https://doi.org/10.1002/slct.201701902>.
34. S. Narsimha, K.S. Battula and V.R. Nagavelli, *Synth. Commun.*, **48**, 1220 (2018); <https://doi.org/10.1080/00397911.2018.1440315>.
35. S. Narsimha, K.S. Battula, Y.N. Reddy and V.R. Nagavelli, *Chem. Heterocycl. Compd.*, **54**, 1161 (2018); <https://doi.org/10.1007/s10593-019-02408-6>.
36. S. Haider, M.S. Alam, H. Hamid, S. Shafi, A. Nargotra, P. Mahajan, S. Nazreen, A.M. Kalle, C. Kharbanda, Y. Ali, A. Alam and A.K. Panda, *Eur. J. Med. Chem.*, **70**, 579 (2013); <https://doi.org/10.1016/j.ejmech.2013.10.032>.
37. J. Mirzaei, F. Siavoshi, S. Emami, F. Safari, M.R. Khoshayand, A. Shafiee and A. Foroumadi, *Eur. J. Med. Chem.*, **43**, 1575 (2008); <https://doi.org/10.1016/j.ejmech.2007.11.019>.
38. C.W. Tornøe, C. Christensen and M. Meldal, *J. Org. Chem.*, **67**, 3057 (2002); <https://doi.org/10.1021/jo011148j>.
39. F. Himo, T. Lovell, R. Hilgraf, V.V. Rostovtsev, L. Noodleman, K.B. Sharpless, V.V. Fokin, DFT Study Predicts Unprecedented Reactivity and Intermediates, *J. Am. Chem. Soc.*, **127**, 210 (2005); <https://doi.org/10.1021/ja0471525>.
40. F. Denizot and R. Lang, *J. Immunol. Methods*, **89**, 271 (1986); [https://doi.org/10.1016/0022-1759\(86\)90368-6](https://doi.org/10.1016/0022-1759(86)90368-6).
41. J.A. Kumar, G. Saidachary, G. Malleshham, B. Sridhar, N. Jain, S.V. Kalivendi, V.J. Rao and B.C. Raju, *Eur. J. Med. Chem.*, **65**, 389 (2013); <https://doi.org/10.1016/j.ejmech.2013.03.042>.