Synthesis of novel 1,3-thiazole-triazole and 1,3-thiazole-isoxazole hybrids

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A focused library of thirteen compounds, 3-((1-benzyl-1\textsubscript{H}-1,2,3-triazol-4-yl)methyl)-4-arylthiazol-2(3\textsubscript{H})-ones (6a-j) and 4-aryl-3-((3-arylisoxazol-5-yl)methyl)thiazol-2(3H)-one hybrids has been synthesized. Their chemical structures have been confirmed by HR-MS, IR, \textsuperscript{1}H and \textsuperscript{13}C NMR spectra.

Keywords: Thiazole, triazole, isoxazole, hybrids

Thiazole ring is a part of several natural products which are having useful biological activities such as bleomycin\textsuperscript{1}, epothilone B\textsuperscript{2}, lyngbyabellin\textsuperscript{3} and dolastatin\textsuperscript{4}. Thiazole is a valuable scaffold in the field of medicinal chemistry and has accounted for the display of a variety of biological activities. Diverse modifications of the thiazole ring at various positions has led to a variety of novel compounds with wide spectrum of pharmacological activities such as antioxidant, antibacterial, antifungal, antitubercular, diuretic, anti-inflammatory and anticancer activities\textsuperscript{5}. Thiazole plays vital roles in many drug structures. Dasatinib (antineoplastic agent)\textsuperscript{6}, ritonavir (anti-HIV drug)\textsuperscript{7}, ravuconazole (antifungal agent)\textsuperscript{8}, fentiazac (anti-inflammatory agents)\textsuperscript{9}, are some examples of thiazole bearing products (Figure 1). In addition, triazolyl tethered thiazoles were found to be potent cdk5/p25 inhibitors\textsuperscript{10}. Thiazole derivatives coupled with isoxazole moiety showed excellent potent AMPA receptor agonist activity\textsuperscript{11a} with moderate affinity for native kainate receptor and α4β2 nAChR potentiatators\textsuperscript{11b}.

In view of the above biological importance of thiazoles conjugated with 1,2,3-triazoles and isoxazoles, we aim to further conjugate these two important units for the first time with thiazole under one construct through a nitrogen linkage. Accordingly, we have carried out the synthesis and biological activities of novel thiazole linked 1,2,3-triazole/isoxazole hybrid molecules.

Results and Discussion

Chemistry

4-Arylthiazol-2(3H)-ones (2a-c) were synthesised by cyclisation of α-thiocyanatoacetophenones (1a-c) in acid solution using literature methods\textsuperscript{12}. These compounds were coupled with propargyl bromide in dry THF in the presence of NaH to provide 4-aryl-3-(prop-2-ynyl)thiazol-2(3H)-ones (3a-c) (Scheme I).

Various substituted benzylic azides 4a-d were reacted with N-propargylated thiazolones 3a-c under click chemistry reaction conditions to obtain the novel heterocycles, 3-((1-benzyl-1\textsubscript{H}-1,2,3-triazol-4-yl)methyl)-4-arylthiazol-2(3H)-ones (6a-j) and 4-aryl-3-((3-arylisoxazol-5-yl)methyl)thiazol-2(3H)-one hybrids (7a-c) in good yields (Scheme I).

Experimental Section

All reactions were monitored by TLC (silica-coated plates and visualizing under UV light). n-Hexane (b.p.60-80°C) was used. Yields refer to chromatographically and spectroscopically (\textsuperscript{1}H and \textsuperscript{13}C NMR) homogeneous material. Evaporation of solvents was performed at reduced pressure on a Büchi rotary evaporator. \textsuperscript{1}H and \textsuperscript{13}C NMR spectra of samples in CDCl\textsubscript{3} were recorded on Varian FT-400 MHz, Varian FT-500 MHz and Bruker UXNMR FT-300 MHz (Avance) spectrometers. Chemical shift δ
Figure 1 — Some reported thiadiazole-triazole/isoxazole based drugs

Scheme I — Synthesis of thiadiazole-triazole/isoxazole hybrids

6a, R = R¹ = H, R² = 2-F, 80%
6b, R = R¹ = H, R² = 4-NO₂, 80%
6c, R = R¹ = F, R² = H, 80%
6d, R = R¹ = F, R² = 2-F, 85%
6e, R = R¹ = F, R² = 2-Br, 80%
6f, R = R¹ = F, R² = 4-NO₂, 90%
6g, R = H, R¹ = Br, R² = H, 85%
6h, R = H, R¹ = Br, R² = 2-Br, 90%
6i, R = H, R¹ = Br, R² = 4-NO₂, 90%
6j, R = R¹ = H, R² = 2-F, 80%
6l, R = R¹ = H, R² = 4-NO₂, 90%
6m, R = R¹ = H, R² = 2-Br, 80%
6n, R = R¹ = H, R² = 4-NO₂, 90%
6o, R = R¹ = H, R² = 2-Br, 80%
6p, R = R¹ = H, R² = 4-NO₂, 90%
6q, R = R¹ = H, R² = 2-Br, 80%
6r, R = R¹ = H, R² = 4-NO₂, 90%
6s, R = R¹ = H, R² = 2-Br, 80%
Preparation of 4-arylthiazol-2(3H)-ones\textsuperscript{12, 2a-c}

The corresponding \(\alpha\)-thiocyanatoacetophenone (1) (0.1 mol) was dissolved in glacial acetic acid (10 mL), 50% sulfuric acid (2 mL) was added and then the mixture was heated to boiling for 10 min. The products 2 crystallised out or had to be precipitated by addition of water. They were collected on suction and purified by recrystallisation from methanol.

General procedure for the synthesis of 4-aryl-3-(prop-2-ynyl)thiazol-2(3H)-ones, 3a-c

To a suspension of NaH (3.46 mmol, 2 eq) in anhydrous THF (5 mL) was added a solution of 4-arylthiazol-2(3H)-one (2) (1.73 mmol, 1 eq) in anhydrous DMF (5 mL) in drop-wise manner at 0°C. After 30 min, propargyl bromide (2.76 mmol, 1.6 eq) was added at 0°C and the mixture allowed to stir for 30 min at RT. After completion, followed by TLC, the mixture was quenched with ice-H\textsubscript{2}O (2 mL), CuSO\textsubscript{4} and washed with brine, dried over anhydrous MgSO\textsubscript{4}. The organic layer was dried over anhydrous Na\textsubscript{2}SO\textsubscript{4}, concentrated in vacuo and purified by column chromatography (hexane:ethyl acetate, 9:1) to afford the pure \(O\)-propargylated compound 3.

4-Phenyl-3-(prop-2-yn-1-yl)thiazol-2(3H)-one, 3a: White solid. Yield 98%. m.p.90°C. IR (KBr): 2939, 2753, 1657, 1516, 1340, 854 cm\textsuperscript{-1}; \(^1\)H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta\) 7.51–7.44 (m, 5H), 6.05 (s, 1H) 4.39 (d, J = 2.6 Hz, 2H), 2.28 (t, J = 2.4 Hz, 1H); \(^{13}\)C NMR (125 MHz, CDCl\textsubscript{3}): \(\delta\) 172.7, 160.5 (d, J = 24.8 Hz), 137.8 (2c), 137.6, 129.4, 128.9, 128.8, 128.6, 98.8, 77.8, 72.4, 33.5; HRMS (ESI) for C\textsubscript{12}H\textsubscript{10}N\textsubscript{2}O\textsubscript{3} [M + H]\textsuperscript{+}: m/z Found 216.0486. Caled 216.0480.

4-(4-Bromophenyl)-3-(prop-2-yn-1-yl)thiazol-2(3H)-one, 3c: White solid. Yield 88%. m.p. 90°C. IR (KBr): 2924, 2864, 1657, 1516, 1413, 837 cm\textsuperscript{-1}; \(^1\)H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta\) 7.61 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.5 Hz, 2H), 6.07 (s, 1H), 4.37 (d, J = 2.4 Hz, 2H), 2.29 (t, J = 2.4 Hz, 1H); \(^{13}\)C NMR (125 MHz, CDCl\textsubscript{3}): \(\delta\) 171.8, 135.9, 132.2(2c), 130.3(2c), 129.7, 124.0, 99.5, 77.7, 72.8, 33.6; HRMS (ESI) for C\textsubscript{12}H\textsubscript{10}BrN\textsubscript{2}O [M + H]\textsuperscript{+}: m/z Found 293.9586. Caled 293.9576.

General procedure for the synthesis of 3-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-4-arylthiazol-2(3H)-ones, 6a-i

To a mixture of (azidomethyl)-benzene (4) (0.2 mmol), propargyl compound (3) (0.18 mmol) in t-BuOH:H\textsubscript{2}O (1:1, 8 mL), CuSO\textsubscript{4} and 3.03 mmol) and sodium ascorbate (0.17 mmol) were added at RT. The mixture was stirred for 2 h at the same temperature. The mixture was poured into ice-water (5 mL) with stirring. The solution was extracted with EtOAc (3 × 20 mL), and washed with brine, dried over anhyd. MgSO\textsubscript{4} and concentrated \textit{in vacuo}. The crude product was purified by column chromatography (hexane:ethyl acetate, 5:5) to afford the thiazolo-triazole hybrid compound (6).

3-((1-(2-Fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-4-phenylthiazol-2(3H)-one, 6a: Pale yellow solid. Yield 80%. m.p. 125°C. IR (KBr): 2924, 2868, 1657, 1516, 1413, 854 cm\textsuperscript{-1}; \(^1\)H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta\) 7.60 (s, 1H). 7.47–7.40 (m, 5H), 7.38–7.33 (m, 1H), 7.26–7.21 (m, 1H), 7.16–7.09 (m, 2H), 6.0 (s, 1H), 5.53 (s, 2H), 4.90 (s, 2H); \(^{13}\)C NMR (125 MHz, CDCl\textsubscript{3}): \(\delta\) 172.7, 160.5 (d, J = 248 Hz), 137.8(2c), 130.9(2c), 130.8, 130.5 (d, J\textsubscript{2} = 22 Hz (2c), 129.4, 129.3, 128.8, 128.4 (d, J\textsubscript{3} = 3.7 Hz), 123.8, 121.7 (d, J\textsubscript{3} = 14.7 Hz), 115.8 (d, J\textsubscript{2} = 21.3 Hz), 98.6, 60.3, 39.6; HRMS (ESI) for C\textsubscript{19}H\textsubscript{13}FN\textsubscript{2}O\textsubscript{3} [M + H]\textsuperscript{+}: m/z Found 367.1028. Caled 367.1020.

3-((4-Nitrobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-4-phenylthiazol-2(3H)-one, 6b: Pale yellow solid. Yield 80%. m.p. 125°C. IR (KBr): 2939, 2753, 1657, 1510, 1340 854 cm\textsuperscript{-1}; \(^1\)H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta\) 8.23 (d, J = 8.8 Hz, 2H), 7.68 (s, 1H), 7.50–7.45 (m, 5H), 7.40 (d, J = 8.6 Hz, 2H) 6.03 (s, 1H), 5.60
(s, 2H) 4.96 (s, 2H); 13C NMR (125 MHz, CDCl3): δ 172.8, 148, 143.7, 141.4, 137.7, 130.7, 129.5(2c), 129.2(2c), 128.8(2c), 128.6(2c), 124.2(2c), 98.7, 53.1, 39.5 HRMS (ESI) for C19H16F2N3O5S [M + H]+: m/z Found 394.0974. Calcd 394.0968.

3-((1-Benzyl-1H-1,2,3-triazol-4-yl)methyl)-4-(2,4-difluorophenyl)thiazol-2(3H)-one, 6c: Pale brown solid. Yield 80%. m.p. 155°C. IR (KBr): 2989, 1652, 1127, 1053, 715 cm−1; 1H NMR (400 MHz, CDCl3): δ 7.60 (d, J = 8.8 Hz, 2H), 7.44-7.23 (m, 6H), 6.34 (s, 1H), 6.11 (s, 1H), 4.96 (s, 2H), 2.43 (s, 3H); 13C NMR (125 MHz, CDCl3): δ 171.9, 163.7 (dd, J1 = 253.47 Hz, J2 = 11.8 Hz), 160.3 (dd, J1 = 251.6 Hz, J2 = 11.8 Hz), 142.8, 134.3, 133.1 (dd, J1 = 9.9 Hz, J2 = 2.7 Hz), 128.9(2c), 126.6(2c), 127.9, 129.9, 114.8 (dd, J1 = 15.4 Hz, J2 = 3.6 Hz), 111.9 (dd, J1 = 20.9 Hz, J2 = 2.7 Hz), 104.5 (dd, J1 = 25.4 Hz, J2 = 11.8 Hz), 101.3, 54, 39.1; HRMS (ESI) for C19H16F2N3O5S [M+H]+: m/z Found 385.0934. Calcd 385.0930.

4-(2,4-Difluorophenyl)-3-((1-(2-fluorobenzo-1H-1,2,3-triazol-4-yl)methyl)thiazol-2(3H)-one, 6d: Pale yellow solid. Yield 85%. m.p. 106°C. IR (KBr): 2927, 1662, 1510, 1259, 834 cm−1; 1H NMR (400 MHz, CDCl3): δ 7.53 (s, 1H), 7.39–7.31 (m, 2H), 7.24-7.20 (m, 1H), 7.16–7.08 (m, 2H), 6.93–6.85 (m, 2H), 6.09 (s, 1H), 5.50 (s, 2H), 4.83 (s, 2H); 13C NMR (125 MHz, CDCl3): δ 171.8, 163.6 (dd, J1 = 253.4 Hz, J2 = 11.8 Hz), 160.3 (dd, J1 = 251.6 Hz, J2 = 11.8 Hz), 142.7, 134.3, 133.1 (dd, J1 = 9.1 Hz, J2 = 2.7 Hz), 130.7 (d, J1 = 9.1Hz, J2 = 2.7Hz), 130.7 (d, J1 = 8.2 Hz, J2 = 2.7 Hz), 129.8, 124.6 (d, J1 = 2.7 Hz), 123, 121.6 (d, J1 = 14.5 Hz), 115.7 (d, J1 = 20.9 Hz, J2 = 11.4 Hz, J2 = 15.4 Hz, J2 = 3.6 Hz), 111.8 (d, J1 = 20.9 Hz), 104.4 (dd, J1 = 25.4 Hz, J2 = 25.4 Hz, 101.3, 60, 39.0; HRMS (ESI) for C19H16F2N3O5S [M+H]+: m/z Found 403.0838. Calcd 403.0830.

3-((1-Benzyl-1H-1,2,3-triazol-4-yl)methyl)-4-(2,4-difluorophenyl)thiazol-2(3H)-one, 6f: Pale yellow solid. Yield 90%. m.p. 145°C. IR (KBr): 3012, 2916, 1662, 1500, 1142, 785 cm−1; 1H NMR (400 MHz, CDCl3): δ 7.60 (d, J = 8.8 Hz, 2H), 7.63 (s, 1H), 7.43–7.36 (m, 3H), 7.0–6.89 (m, 2H), 6.11 (s, 1H), 5.59 (s, 2H), 4.84 (s, 2H); 13C NMR (125 MHz, CDCl3): δ 172, 163.9 (dd, J1 = 251.3 Hz, J2 = 11.8 Hz), 160.4 (dd, J1 = 251.6 Hz, J2 = 11.7 Hz), 148, 143.3, 141, 133.2 (dd, J1 = 9.5 Hz, J2 = 2.2 Hz), 129.9, 128.9, 128.6(2c), 124.3(2c), 114.8 (dd, J1 = 14.7 Hz, J2 = 3.7 Hz), 114.7 (dd, J1 = 21.3 Hz, J2 = 3.7 Hz), 104.7 (dd, J1 = 24.9 Hz, J2 = 25.7 Hz), 101.5, 53.1, 39.2; HRMS (ESI) for C19H16F2N3O5S [M+H]+: m/z Found 463.0039. Calcd 463.0028.

3-((1-Benzyl-1H-1,2,3-triazol-4-yl)methyl)-4-(2,4-difluorophenyl)thiazol-2(3H)-one, 6g: White solid. Yield 85%. mp 119°C. IR (KBr): 2922, 1640, 1456, 1050, 825, 725 cm−1; 1H NMR (400 MHz, CDCl3): δ 7.40–7.38 (m, 1H), 7.60–7.50 (m, 3H), 7.42–7.35 (m, 5H), 7.29–7.24 (m, 2H), 6.01 (s, 1H), 5.48 (s, 2H), 4.85 (s, 2H); 13C NMR (125 MHz, CDCl3): δ 172.5, 143.0, 136.7, 134.3, 132.1(2c), 130.9(2c), 129.7, 129.1(2c), 128.8, 128.1(2c), 123.9, 123.8, 99.1, 54.2, 39.6; HRMS (ESI) for C19H16F2N3O5S [M+H]+: m/z Found 427.0239. Calcd 427.0234.

3-((1-(2-Bromobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-4-(2,4-difluorophenyl)thiazol-2(3H)-one, 6h: White solid. Yield 90%, mp 130°C. IR (KBr): 3091, 1655, 1452, 1048, 817, 725 cm−1; 1H NMR (400 MHz, CDCl3): δ 7.66 (s, 1H), 7.61 (dd, J = 7.9 Hz, 1.1 Hz, 1H), 7.57 (d, J = 8.5 Hz, 2H), 7.40 (d, J = 8.5 Hz, 2H), 7.31 (td, 8.6 Hz, 1.2 Hz, 1H), 7.23 (td, 9.4 Hz, 1.7 Hz, 1H), 7.15 (dd, J1 = 7.6 Hz, 1.5 Hz, 1H), 6.03 (s, 1H), 5.62 (s, 2H), 4.87 (s, 2H); 13C NMR (125 MHz, CDCl3): δ 172.47, 142.84, 136.6, 133.8, 133.1, 132.0, 130.8(2c), 130.4, 130.3, 129.7(2c), 128.1, 124.1, 124, 123.4, 99.1, 53.8, 39.4; HRMS (ESI) for C19H16BrF2N3O5S [M+H]+: m/z Found 504.9333. Calcd 504.9330.

4-(2,4-Difluorophenyl)-3-((1-(4-nitrobenzyl)-1H-1,2,3-triazol-4-yl)methyl)thiazol-2(3H)-one, 6i: White solid. Yield 90%, mp 130°C. IR (KBr): 1252, 1648,
1518, 1347, 1047 735; 1H NMR (400 MHz, CDCl3): δ 8.24 (d, J = 8.7 Hz, 2H), 7.73 (s, 1H), 7.61 (d, J = 8.4 Hz, 2H), 7.45–7.39 (m, 4H), 6.04 (s, 1H), 5.67 (s, 3H), 4.87 (s, 2H); 13C NMR (125 MHz, CDCl3): δ 172.6, 148.1, 143.5, 141.3, 136.6, 132.2(2c), 130.9(2c), 129.6, 128.7(2c), 124.4, 124.3(2c), 124.1, 99.2, 53.1, 39.5. HRMS (EI) for C20H162.1, 161.0, 137.0, 130.5, 129.7, 129.0(2c), 128.9(2c), 128.2, 128.1(2c), 121.0, 114.2(2c), 101.3, 99.2, 55.3, 39.5; HRMS (ESI) for C30H19BrN3O3S[M +H]+: m/z Found 472.0078. Calcd 472.0069.

General procedure for the synthesis of 4-phenyl-3-(3-phenylisoxazol-5-yl)methyl)thiazol-2(3H)-ones, 7a-c

Propargylated compound (3) (0.18 mmol) and triethylamine (0.18 mmol) were taken in DCM (5 mL) and the resulting mixture was cooled to 0°C. Addition of aqueous sodium hypochlorite (11%, 4 mL) over 30 min at 0°C was followed by aryl aldehyde oxime (5) (0.36 mmol) and the reaction mixture maintained at RT. After completion of reaction monitored by TLC, the reaction mixture was concentrated under vacuum and extracted with ethyl acetate. The organic layers was separated and dried over anhydrous Na2SO4. The resulting crude product was washed with n-pentane to obtain thiazolo-isoxazole hybrid product (7).

3-((4-Methoxyphenyl)isoxazol-3-yl)methyl)-4-phenylthiazol-2(3H)-one, 7a: Pale brown solid. Yield 80%, mp 155°C. IR (KBr): 2927, 1606, 1509, 1253, 829 cm−1; 1H NMR (400 MHz, CDCl3): δ 7.69 (d, J = 8.8 Hz, 2H), 7.52–7.41 (m, 3H), 7.37–7.33 (m, 2H), 6.94 (d, J = 8.7 Hz, 2H), 6.40 (s, 1H), 6.08 (s, 1H), 4.94 (s, 2H), 3.83 (s, 3H); 13C NMR (125 MHz, CDCl3): δ 166.7, 162.1, 161.0, 137.0, 130.5, 129.7, 129.0(2c), 128.9(2c), 128.2, 128.1(2c), 121.0, 114.2(2c), 101.3, 99.2, 55.3, 39.5; HRMS (ESI) for C20H162.1, 161.0, 137.0, 130.5, 129.7, 129.0(2c), 128.9(2c), 128.2, 128.1(2c), 121.0, 114.2(2c), 101.3, 99.2, 55.3, 39.5; HRMS (ESI) for C30H19BrN3O3S[M +H]+: m/z Found 472.0078. Calcd 472.0069.

4-(4-Bromophenyl)-3-(5-(p-tolyl)isoxazol-3-yl) methyl)thiazol-2(3H)-one, 7c: White solid. Yield 90%, mp 130°C. IR (KBr): 2952, 1640, 1458, 1045, 725 cm−1; 1H NMR (400 MHz, CDCl3): δ 7.60 (d, J = 8.4 Hz, 2H), 7.44–7.23 (m, 6H), 6.34 (s, 1H), 6.11 (s, 1H), 4.96 (s, 2H), 2.43 (s, 3H); 13C NMR (125 MHz, CDCl3): δ 165.7, 163.2, 136.8, 135.8, 132(3c), 131.0 130.6(2c) 129.6, 129.4, 128.1, 125.9(2c), 124.3, 124.3(2c), 124.1, 99.2, 53.1, 39.5. HRMS (ESI) for C30H19BrN3O3S[M +H]+: m/z Found 427.0116. Calcd 427.0114.

Conclusion

In the present study, a novel series of heterocycles encompassing thiazolo-1,2,3-triazole/isoxazole moieties conjugated through a nitrogen linkage have been synthesized.

Supplementary Information

Supplementary information is available in the website http://nopr.niscair.res.in/handle/123456789/60.

References


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