Synthesis and characterization of new 1,3-benzodioxole derivatives based on Suzuki-Miyaura coupling reaction

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Abstract
In this work, new heterocyclic compound derivatives of 1,3-benzodioxole 6a-s have been prepared in good yields (33-89%). This work included using (6-bromobenzo[d][1,3]dioxol-5-yl)methanol (1) as a starting material in the synthetic route. Appel conditions (CBr_4/PPh_3, DCM) were applied on 1, which provided compound 2 in an excellent yield (91%). Nucleophilic substitution of 2 with NaN_3 in MeOH gave 5-(azidomethyl)-6-bromobenzo[d][1,3] dioxole (3) in a very good yield (88%).

Subsequent Huisgen 1,3-dipolar cycloaddition reaction (click-reaction) between 3 and phenylacetylene in the presence of CuI as a catalyst afforded only single 1,4-regioisomer of 1-((6-bromobenzo[d][1,3]dioxol-5-yl)methyl)-4-phenyl-1H-1,2,3-triazole (4) in 82% yield. Followed by Suzuki-Miyaura coupling reaction of 4 with different substituents of boronic acid 5a-s in the presence of $PdCl_2(PPh_3)_2$ as a catalyst, PPh_3 as a ligand and K_2CO_3 as base furnished the desired products 6a-s.

Keywords: 1,3, benzodioxole, Suzuki-Miyaura Coupling Reactions, Heterocyclic compounds.

Introduction

In recent years, 1,3-benzodioxole (BZD) moiety has been found to possess a broad range of biological activities such as anti-inflammatory[1], anticancer[2,3], antihypertensive[4], antioxidant[5,6] and immunomodulatory[7]. Furthermore, presence of this bicyclic molecule was found in many natural products that play an important role in drug discovery. For example, laetispicine showed a significant antidepressant activity[8], stiripentol (diacomit) was used as an anticonvulsant[9]. Amidebenzodioxole derivative (ABT-627) showed a potent antinociceptive activity[10]. Thiazolebenzodioxole derivative also showed remarkable antiproliferative activity against cancer of breast (cell line MCF-7) in human[2] (Figure 1).

In addition, triazole ring constitutes an important structure in the organic compounds and is found to be associated with a wide range of biological activities such as anti-allergic[11], anti-fungal[12], anti-herbicide[13], anti-influenza[14] and anti-HIV activity[15]. The interest in this research is combining two important moieties (the 1,3-benzodioxole and 1,2,3-triazole) together to form 4. Thereafter, product 4 will be developed *via* substitution with different type of groups using Suzuki-Miyaura coupling, to furnish a new selection of chemical compounds 6.

Material and Methods

General Experimental procedures: All reagents were purchased from commercial sources and used without additional purification unless stated otherwise. THF was freshly distilled over sodium and benzophenone under nitrogen gas. Anhydrous CH_3OH, CH_3CN, DCM, benzene, dioxane and toluene were purchased. All reactions were conducted in flame-dried glassware under an inert atmosphere of nitrogen or argon. Brine is a saturated aqueous solution of sodium chloride. Petroleum ether refers to light petroleum ether (b.p. 40-60 °C), and water refers to deionised water. Solvents evaporation was performed using a rotary evaporator under reduced pressure. TLC was performed on Merck silica gel 60 F_{254} and visualised by UV lamp and aqueous alkaline potassium permanganate.

Flash column chromatography was performed over silica gel Fluka 60 or Merck aluminium oxide 90. ^1H and ^{13}C NMR spectral data were recorded using a Bruker AV400 or Bruker AV(III)400HD spectrometer. Chemical shifts are quoted in ppm downfield from tetramethylsilane (TMS) as internal standard or deuterated chloroform either in ^1H NMR or ^{13}C NMR as reference (δ_H 7.26 ppm or δ_C 77.16 ppm respectively). Multiplicities in the ^1H NMR spectra are described as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad; coupling constant values *J* are given in Hertz. Infrared spectral data were recorded using Perkin-Elmer 1600 FTIR spectrometer. Mass spectrometry data were recorded using a Bruker MicroTOF spectrometer in ESI mode. Compound names are assigned according to standard IUPAC nomenclature.

Preparation of 5-bromo-6-(bromomethyl)benzo[d] [1,3] dioxole (2): This compound was prepared according to the modified procedure of Appel reaction[16].To a solution of 6-bromobenzo[d][1,3]dioxol-5-yl)methanol (1) (10 g, 43.3 mmol, 1.0 equiv.) in anhydrous DCM (75 mL), CBr_4 (15.5 g, 46.6 mmol, 2.0 equiv.) and PPh_3 (12.2 g, 46.6 mmol, 2.0 equiv.) in anhydrous DCM (25 mL) was then added slowly and heated to reflux for 7 hours. This was followed by the addition of silica gel (10 g) and the resulting suspension was concentrated *in vacuo*. Flash column chromatography over silica gel (eluting with 6:1 petroleum ether/ethyl acetate) gave 2 (11.6 g, 38.4 mmol, 91%) as a yellow solid; IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ = 3071, 3039 (C-H_{aro}), 2949, 2860 (C-H_{ali}), 1231, 1063 (C-O-C); ^1H NMR (400 MHz, $CDCl_3$) d_H

= 7.37 (1H, s), 7.15 (1H, s), 6.07 (2H, s), 4.52 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) d_C = 149.1, 148.1, 128.3, 121.4, 113.3, 108.1, 102.0, 37.2; HRMS (ESI) m/z, calculated for $[C_8H_7Br_2O_2]$ $[M+H]^+$ 294.8787, found 294.8786.

Synthesis of 5-(azidomethyl)-6-bromobenzo [d][1,3] dioxole (3): This product was prepared according to the literature[17]. To a solution of compound 2 (9.5 g, 32.3 mmol, 1.0 equiv.), NaN_3 (2.6 g, 38.8 mmol, 1.2 equiv.) and anhydrous MeOH (100 mL) were purged with nitrogen gas. The reaction mixture was heated to reflux for 24 hours under argon atmosphere. H_2O (100 mL) was added before extracting the organic layer with ethyl acetate (2 × 20 mL), washed with saturated brine (2 × 20 mL), and dried over anhydrous $MgSO_4$. Flash column chromatography over silica gel (eluting with 5:1 petroleum ether/ethyl acetate) afforded 3 (7.3 g, 28.4 mmol, 88%) as a pale-yellow solid; IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ = 3211 (N_3), 3069, 3042 (C-H_{aro}), 2957, 2862 (C-H_{ali}), 1239, 1052 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$,) d_H = 7.31 (1H, s), 7.19 (1H, s), 6.08 (2H, s), 4.78 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) d_C = 148.5, 147.4, 128.6, 121.3, 113.9, 108.2, 102.1, 51.2; HRMS (ESI) m/z, calculated for $[C_8H_7BrN_3O_2]$ $[M+H]^+$ 255.9716, found 255.9717.

Preparation of 1-((6-bromobenzo[d][1,3] dioxol-5-yl) methyl)-4-phenyl-1H-1,2,3-triazole (4): This compound has been prepared according to the modified procedure of literature[18]. A dry round-bottom flask equipped with a magnetic stirring-bar was purged with N_2 gas and charged with a solution of **3** (7.2 g, 28.1 mmol, 1.0 equiv.) and phenylacetylene (3.7 mL, 33.7 mmol, 1.2 equiv.) in anhydrous MeCN (100 mL). The reaction mixture was then stirred at room temperature for 20 minutes before slowly adding of a solution of CuI (428 mg, 2.25 mmol, 8.0 mol%) in MeCN (30 mL). The temperature of the reaction mixture was then increased to reflux for 24 hours. The organic phase was extracted with Et_2O (2 × 30 mL), washed with H_2O (30 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Flash column chromatography over silica gel (eluting with 7:1 petroleum ether/ethyl acetate) gave the desired product 4 (8.3 g, 23 mmol, 82%) as a pale-yellow solid; IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ = 3070, 3041 (C-H_{aro}), 2955, 2867 (C-H_{ali}), 1622 (C=C) 1236, 1027 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) d_H = 7.76 (2H, d, *J* = 4.5 Hz), 7.40 (1H, s), 7.30-7.18 (3H, m), 7.17 (1H, s), 6.25 (2H, s), 6.05 (1H, s), 4.79 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) d_C = 148.6, 147.7, 136.4, 130.3, 128.8, 127.6, 127.0, 124.9, 121.3, 116.5, 113.4, 108.1, 102.1, 51.4; HRMS (ESI) m/z, calculated for $[C_{16}H_{12}BrN_3NaO_2]$ $[M+Na]^+$ 380.0005, found 380.0007.

General procedure for Suzuki-Miyaura coupling to synthesise 6a-s: A round bottom two-necked flask equipped with rubber septum and a condenser containing a solution of 4 (200 mg, 588 mmol, 1.0 equiv.) in anhydrous dioxane (10 mL), K_2CO_3 (89 mg, 647 mmol, 1.1 equiv.) was added. The reaction mixture was then stirred for 15 minutes before aryl boronic acids 5a-s (1.47 mmol, 2.5 equiv.). $PdCl_2(PPh_3)_2$ (21 mg, 30 mmol, 5.0 mol%) and PPh_3 (16 mg, 59 mmol, 10.0 mol%) were added through a rubber septum at room temperature. The mixture was then heated to reflux under argon atmosphere. When the reaction had reached completion, as mentioned by TLC (petroleum ether/ethyl acetate), the reaction was allowed to cool at room temperature. The cooled mixture was then poured into brine, and the organic layer was extracted with ethyl acetate, then dried over anhydrous $MgSO_4$ before concentrating *in vacuo*. The residue was purified by flash column chromatography over silica gel (eluting with petroleum ether/ethyl acetate) to give the desired products 6a-s.

4-(6-((4-phenyl-1H-1,2,3-triazol-1-yl) methyl)benzo[d] [1,3]dioxol-5-yl)isoxazole (6a): General procedure of Suzuki-Miyaura coupling was followed to give 6a as a pale yellow oil (122 mg, 353 mmol, 60%); IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ = 3071, 3022 (C-H_{aro}), 2967, 2854 (C-H_{ali}), 1681 (C=N), 1655 (C=C), 1237, 1040 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) d_H = 8.74 (1H, s), 8.20 (1H, s), 7.74-7.68 (2H, m), 7.48 (1H, s), 7.13-7.02 (3H, m), 6.83 (1H, s), 6.76 (1H, s), 6.06 (2H, s), 4.80 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) d_C = 159.4, 149.9, 149.2, 147.1, 131.9, 129.8, 128.9, 127.9, 127.2, 124.8, 121.2, 116.8, 113.5, 108.1, 101.2, 99.4, 51.3; HRMS (ESI) m/z, calculated for $[C_{19}H_{15}N_4O_3]$ $[M+H]^+$ 347.1139, found 347.1138.

2-ethoxy-5-(6-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl) benzo[d][1,3]dioxol-5-yl) pyrimidine (6b): General procedure of Suzuki-Miyaura coupling was followed to afford 6b as a yellow oil (135 mg, 335 mmol, 57%); IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ = 3070, 3024 (C-H_{aro}), 2966, 2851 (C-H_{ali}), 1681 (C=N), 1649 (C=C), 1239, 1033 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) d_H = 9.23 (2H, s), 7.57-7.52 (2H, m), 7.48 (1H, s), 7.33-7.26 (3H, m), 7.09 (1H, s), 7.02 (1H, s), 6.10 (2H, s), 4.77 (2H, s), 4.28-4.24 (2H, m), 1.34-1.27 (3H, t, *J* = 7.2 and 3.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) d_C = 169.1, 148.1, 148.0, 146.5, 145.9, 132.2, 131.0, 130.4, 129.8, 128.9, 124.9, 121.4, 116.5, 113.6, 108.1, 101.8, 62.1, 51.8, 14.4; HRMS (ESI) m/z, calculated for $[C_{22}H_{19}N_5NaO_3]$ $[M+Na]^+$ 424.1380, found 424.1378.

3-ethoxy-2-(6-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl) benzo[d][1,3] dioxol-5-yl)pyridine (6c): General procedure of Suzuki-Miyaura coupling was followed to give 6c as a yellow-orange oil (165 mg, 412 mmol, 70%); IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ = 3079, 3021 (C-H_{aro}), 2955, 2834 (C-H_{ali}), 1678 (C=N), 1637 (C=C), 1233, 1025 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$,) d_H = 8.56 (1H, s), 7.70-7.63 (1H, m), 7.61-7.55 (2H, m), 7.37-7.33 (2H, m), 7.22-7.17 (2H, m), 6.92 (1H, s), 6.77-6.60 (2H, m), 6.05 (2H, s), 4.90 (2H, s), 4.24-4.20 (2H, m), 1.23-1.19 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) d_C = 166.8, 148.7, 148.6, 146.9, 146.0, 141.7, 132.0, 131.9, 128.9, 126.1, 124.6, 121.9, 121.1, 117.8, 113.2, 109.2, 108.1, 101.4, 64.8, 51.6, 16.3; HRMS (ESI) m/z, calculated for $[C_{23}H_{21}N_4O_3]$ $[M+H]^+$ 401.1608, found 401.1607.

8-(6-((4-phenyl-1H-1,2,3-triazol-1-yl) methyl)benzo[d] [1,3]dioxol-5-yl)quinolone (6d): General procedure of Suzuki-Miyaura coupling was followed to afford 6d as a yellow-orange solid (148 mg, 365 mmol, 62%); IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ = 3075, 3011 (C-H_{aro}), 2961, 2853 (C-H_{ali}), 1681 (C=N), 1631 (C=C), 1239, 1027 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$,) d_H = 8.94 (1H, s), 8.30 (1H, d, *J* = 7.0 Hz), 8.23 (1H, d, *J* = 7.5 Hz), 7.82 (1H, d, *J* = 6.5 Hz), 7.21-7.17 (2H, m), 7.46 (1H, s), 7.36-7.25 (3H, m), 7.11-6.99 (2H, m), 6.78 (1H, s), 6.65 (1H, d, *J* = 6.6 Hz), 6.09 (2H, s), 4.73 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) d_C = 152.9, 152.2, 151.5, 149.4, 148.8, 147.6, 138.5, 133.9, 133.1, 132.7, 132.2, 130.2, 129.9, 128.2, 128.0, 124.5, 121.2, 116.4, 113.3, 109.9, 108.1, 102.8, 51.5; HRMS (ESI) m/z, calculated for $[C_{25}H_{18}N_4NaO_2]$ $[M+Na]^+$ 429.1322, found 429.1320.

1-((6-(1H-inden-3-yl)benzo[d][1,3]dioxol-5-yl)methyl)-4-phenyl-1H-1,2,3-triazole (6e): General procedure of Suzuki-Miyaura coupling was followed to give 6e as a pale yellow solid (187 mg, 476 mmol, 81%); IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ = 3081, 3023 (C-H_{aro}), 2955, 2843 (C-H_{ali}), 1634 (C=C), 1237, 1029 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) d_H = 7.76-7.66 (3H, m), 7.51-7.46 (2H, m), 7.44-7.36 (2H, m), 7.28 (1H, s), 7.22-7.16 (2H, m), 7.05-6.95 (1H, m), 6.93-7.85 (1H, m), 6.72-6.66 (1H, m), 6.06 (2H, s), 4.78 (2H, s), 3.12 (2H, d, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) d_C = 149.8, 148.8, 148.1, 147.1, 144.6, 133.5, 132.8, 130.2, 129.8, 129.0, 128.9, 128.4, 127.1, 124.8, 123.8, 121.4, 118.9, 116.1, 113.3, 108.1, 101.1, 52.8, 40.0; HRMS (ESI) m/z, calculated for $[C_{25}H_{20}N_3O_2]$ $[M+H]^+$ 394.1550, found 394.1551.

1-methyl-2-(6-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl) benzo[d][1,3]dioxol-5-yl)-1H-indole (6f): General procedure of Suzuki-Miyaura coupling was followed to afford 6f as a yellow oil (163 mg, 400 mmol, 68%); IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ = 3077, 3029 (C-H_{aro}), 2967, 2851 (C-H_{ali}), 1641 (C=C), 1241, 1027 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$,) d_H = 8.57 (2H, d, *J* = 6.9 Hz), 8.12-8.09 (2H, m), 7.79-7.76 (3H, m), 7.74-7.71 (3H, m), 7.67-7.61 (3H, m), 6.07 (2H, s), 5.63 (3H, s), 4.76 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) d_C = 149.8, 149.0, 147.6, 138.5, 132.4, 131.8, 131.2, 129.9, 129.0, 128.8, 128.0, 127.9, 124.7, 123.7, 121.2, 118.5, 116.1, 113.2, 108.2, 102.9, 99.9, 52.6, 22.7; HRMS (ESI) m/z, calculated for $[C_{25}H_{21}N_4O_2]$ $[M+H]^+$ 409.1659, found 409.1660.

2-cyclopropyl-5-(6-((4-phenyl-1H-1,2,3-triazol-1-yl) methyl)benzo[d][1,3]ioxol-5-yl)pyrimidine (6g): General procedure of Suzuki-Miyaura coupling was followed to give 6g as a deep yellow oil (77 mg, 194 mmol, 33%); IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ = 3081, 3033 (C-H_{aro}), 2969, 2849 (C-H_{ali}), 1679 (C=N), 1640 (C=C), 1245, 1032 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) d_H = 9.29 (2H, s), 7.58-7.51 (1H, m), 7.41-7.26 (5H, m), 7.10 (1H, s), 6.88 (1H, s), 6.10 (2H, s), 4.77 (2H, s), 1.46-1.38 (1H, m), 1.25-1.17 (2H, m), 1.09-1.02 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) d_C = 172.1, 152.3, 149.8, 149.1, 148.7, 131.9, 129.9, 128.9, 128.1, 127.1, 123.9, 121.3, 116.9, 113.2, 108.1, 101.8, 51.7, 21.2, 8.7; HRMS (ESI) m/z, calculated for $[C_{23}H_{19}N_5NaO_2]$ $[M+Na]^+$ 420.1431, found 420.1430.

5-(6-((4-phenyl-1H-1,2,3-triazol-1-yl) methyl)benzo[d] [1,3]dioxol-5-yl)-2-(pyrrolidin-1-yl)pyridine (6h): General procedure of Suzuki-Miyaura coupling was followed to afford 6h as a yellow oil (118 mg, 276 mmol, 47%); IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ = 3074, 3026 (C-H_{aro}), 2959, 2851 (C-H_{ali}), 1646 (C=C), 1244, 1023 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) d_H = 8.31 (1H, s), 7.72-7.62 (2H, m), 7.60-7.48 (3H, m), 7.43-7.33 (2H, m), 7.08 (1H, s), 5.89 (1H, s), 6.73-6.69 (1H, m), 6.09 (2H, s), 4.78 (2H, s), 3.74-3.59 (4H, m), 1.97-1.82 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) d_C = 157.3, 149.8, 149.0, 148.3, 141.7, 133.6, 131.9, 130.5, 129.8, 128.5, 127.5, 126.8, 124.7, 121.1, 116.3, 113.3, 108.2, 102.1, 54.7, 51.3, 24.9; HRMS (ESI) m/z, calculated for $[C_{25}H_{23}N_5NaO_2]$ $[M+Na]^+$ 448.1744, found 448.1743.

2-(methylsulfonyl)-5-(6-((4-phenyl-1H-1,2,3-triazol-1-yl) methyl)benzo[d][1,3]dioxol-5-yl) pyrimidine (6i): General procedure of Suzuki-Miyaura coupling was followed to give 6i as a pale-yellow oil (154 mg, 353 mmol, 60%); IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ = 3081, 3023 (C-H_{aro}), 2987, 2844 (C-H_{ali}), 1677 (C=N), 1641 (C=C), 1240, 1019 (C-O-C), 1381, 1067 (S=O); ^{1}H NMR (400 MHz, $CDCl_3$) d_H = 9.76 (2H, s), 7.33-7.28 (1H, m), 7.26-7.15 (5H, m), 6.96-6.88 (1H, m), 6.79-6.76 (1H, m), 6.08 (2H, s), 4.75 (2H, s), 2.80 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) d_C = 166.1, 150.4, 149.9, 148.4, 147.1, 138.6, 131.8, 129.2, 128.7, 127.7, 124.0, 121.4, 116.4, 113.3, 108.1, 101.8, 51.4, 42.7; HRMS (ESI) m/z, calculated for $[C_{21}H_{17}N_5NaO_4S]$ $[M+Na]^+$ 458.0893, found 458.0892.

1-((6-(3,4-dihydro-2H-benzo[b][1,4] dioxepin-7-yl)benzo [d][1,3]dioxol-5-yl) methyl)-4-phenyl-1H-1,2,3-triazole (6j): General procedure of Suzuki-Miyaura coupling was followed to afford 6j as a deep yellow oil (186 mg, 435 mmol, 74%); IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ = 3075, 3035 (C-H_{aro}), 2982, 2821 (C-H_{ali}), 1643 (C=C), 1245, 1026 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$,) d_H = 7.87-7.80 (2H, m), 7.71-7.67 (1H, m), 7.59-7.51 (1H, m), 7.47-7.39 (1H, m), 7.37-7.32 (2H, m), 7.29-7.24 (1H, m), 7.23-7.13 (1H, m), 6.84-6.79 (2H, m), 6.08 (2H, s), 4.80 (2H, s), 4.28-4.04 (4H, m), 2.31-2.26 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) d_C = 151.7, 149.8, 149.1, 148.0, 146.1, 132.5, 131.9, 130.8, 130.1, 129.3, 128.2, 127.9, 127.1, 124.8, 121.4, 114.9, 113.4, 108.2, 101.8, 61.9, 61.8, 51.9, 32.8; HRMS (ESI) m/z, calculated for $[C_{25}H_{22}N_3O_4]$ $[M+H]^+$ 428.1605, found 428.1604.

4-phenyl-1-((6-phenylbenzo[d][1,3]dioxol-5-yl)methyl)-1H-1,2,3-triazole (6k): General procedure of Suzuki-Miyaura coupling was followed to give 6k as a yellow oil (186 mg, 523 mmol, 89%); IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ = 3082, 3033 (C-H_{aro}), 2977, 2823 (C-H_{ali}), 1646 (C=C), 1241, 1029 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) d_H = 8.34 (2H, d, *J* = 6.6 Hz), 8.18-8.12 (2H, m), 8.10-8.06 (2H, m), 7.82-7.55 (4H, m), 7.47-7.38 (1H, m), 7.01-6.94 (1H, m), 6.81-6.77

(1H, m), 6.07 (2H, s), 4.79 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) d_C = 150.8, 149.8, 148.9, 135.9, 133.5, 132.3, 129.9, 129.3, 128.8, 127.9, 127.1, 124.3, 121.4, 116.6, 113.3, 108.2, 101.1, 51.1; HRMS (ESI) m/z, calculated for $[C_{22}H_{18}N_3O_2]$ $[M+H]^+$ 356.1394, found 356.1390.

5-(6-((4-phenyl-1H-1,2,3-triazol-1-yl) methyl)benzo[d] [1,3]dioxol-5-yl)-2-(piperidin-1-yl)pyrimidine (6l): General procedure of Suzuki-Miyaura coupling was followed to afford 6l as a yellow solid (137 mg, 312 mmol, 53%); IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ = 3077, 3028 (C-H_{aro}), 2974, 2821 (C-H_{ali}), 1683 (C=N), 1641 (C=C), 1244, 1031 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) d_H = 9.13 (2H, s), 7.64 (2H, d, *J* = 6.7 Hz), 7.37-7.27 (3H, m), 7.18 (1H, s), 6.85-6.80 (2H, m), 6.07 (2H, s), 4.78 (2H, s), 3.85-3.76 (4H, m), 1.33-1.26 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) d_C = 159.6, 157.9, 149.7, 146.4, 131.9, 130.7, 129.5, 128.6, 128.0, 127.9, 124.7, 121.4, 116.5, 101.3, 113.3, 108.2, 57.1, 55.0, 27.9, 24.9; HRMS (ESI) m/z, calculated for $[C_{25}H_{24}N_6NaO_2]$ $[M+Na]^+$ 463.1853, found 463.1852.

4-(3-(6-((4-phenyl-1H-1,2,3-triazol-1-yl) methyl)benzo [d][1,3]dioxol-5-yl)pyridin-2-yl)morpholine (6m): General procedure of Suzuki-Miyaura coupling was followed to give 6m as a yellow solid (158 mg, 359 mmol, 61%); IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ = 3087, 3045 (C-H_{aro}), 2976, 2833 (C-H_{ali}), 1680 (C=N), 1642 (C=C), 1245, 1030 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) d_H = 8.18-8.11 (2H, m), 7.85-7.79 (2H, m), 7.78-7.71 (3H, m), 7.70-7.65 (4H, m), 6.06 (2H, s), 4.77 (2H, s), 4.66-4.62 (4H, m), 4.50-4.44 (4H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) d_C = 160.9, 150.7, 149.6, 148.1, 136.9, 132.3, 134.7, 133.5, 131.9, 129.8, 128.9, 127.9, 124.6, 121.4, 116.6, 113.3, 108.2 101.7, 68.1, 67.9, 52.8, 48.3, 48.1; HRMS (ESI) m/z, calculated for $[C_{25}H_{23}N_5NaO_3]$ $[M+Na]^+$ 464.1693, found 464.1692.

1-((6-(anthracen-9-yl)benzo[d][1,3]dioxol-5-yl)methyl)-4-phenyl-1H-1,2,3-triazole (6n): General procedure of Suzuki-Miyaura coupling was followed to afford 6n as a yellow oil (158 mg, 347 mmol, 59%); IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ = 3087, 3045 (C-H_{aro}), 2984, 2829 (C-H_{ali}), 1642 (C=C), 1248, 1025 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) d_H = 8.72 (1H, d, *J* = 6.4 Hz), 8.36-8.26 (2H, m), 8.09-7.98 (2H, m), 7.78-7.73 (2H, m), 7.67-7.61 (1H, m), 7.32-7.28 (3H, m), 7.26-7.18 (4H, m), 7.05-6.98 (2H, m), 6.08 (2H, s), 4.77 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) d_C = 150.0, 149.3, 147.7, 137.4, 136.7, 135.5, 134.6, 133.9, 133.3, 132.5, 131.8, 130.3, 129.8, 128.6, 127.6, 127.1, 124.3, 121.3, 116.8, 113.3, 108.2, 51.9; HRMS (ESI) m/z, calculated for $[C_{30}H_{21}N_3NaO_2]$ $[M+Na]^+$ 478.1526, found 478.1525.

1-((6-(dibenzo[b,d]furan-4-yl)benzo[d][1,3] dioxol-5-yl) methyl)-4-phenyl-1H-1,2,3-triazole (6r): General procedure of Suzuki-Miyaura coupling was followed to give 6r as a yellow-orange oil (149 mg, 335 mmol, 57%); IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ = 3081, 3034 (C-H_{aro}), 2975, 2855 (C-H_{ali}), 1645 (C=C), 1247, 1031 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) d_H = 8.05-7.95 (1H, m), 7.84-7.74 (1H, m), 7.63-7.51 (2H, m), 7.51-7.11 (9H, m), 7.09 (1H, d, *J* = 6.3 Hz), 6.79 (1H, d, *J* = 5.5 Hz), 6.09 (2H, s), 4.77 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) d_C = 157.9, 156.1, 150.8, 149.7, 148.6, 141.3, 140.1, 139.0, 138.1, 137.5, 136.4, 135.5, 133.4, 132.7, 131.5, 130.8, 129.0, 128.7, 127.6, 124.6, 121.4, 116.9, 113.3, 108.2, 102.1, 51.7; HRMS (ESI) m/z, calculated for $[C_{28}H_{20}N_3O_3]$ $[M+H]^+$ 446.1499, found 446.1498.

1-((6-(5a,9a-dihydrothianthren-1-yl)benzo [d][1,3] dioxol-5-yl)methyl)-4-phenyl-1H-1,2,3-triazole (6s): General procedure of Suzuki-Miyaura coupling was followed to afford 6s as a yellow solid (154 mg, 312 mmol, 53%); IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ = 3080, 3055 (C-H_{aro}), 1642 (C=C), 1245, 1034 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) d_H = 7.88-7.78 (1H, m), 7.66-7.51 (2H, m), 7.39-7.31 (3H, m), 7.30-7.18 (6H, m), 7.08-7.01 (3H, m), 6.06 (2H, s), 4.76 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) d_C = 153.4, 150.9, 149.8, 148.7, 147.5, 144.1, 142.2, 141.3, 140.6, 134.1, 133.8, 132.5, 130.9, 130.2, 129.7, 129.0, 128.5, 128.1, 127.7, 124.8, 121.4, 116.3, 113.3, 108.2, 101.1, 51.8; HRMS (ESI) m/z, calculated for $[C_{28}H_{19}N_3NaO_2S_2]$ $[M+Na]^+$ 516.0811, found 516.0810.

Results and Discussion

Our synthetic route includes using 1,3-benzodioxoles bearing a triazole ring 4 as a substrate to access the desired product 6 *via* Suzuki-Miyaura coupling. The product 4 was prepared over three steps starting from 1, as described in Scheme 1.

Compound 1 was employed as a starting material for the synthesis of 6a-s, which was treated with CBr_4 and PPh_3 in DCM (Appel conditions) to afford 5-bromo-6-(bromomethyl)benzo[d][1,3]dioxole (2) in 91% yield[16]. Thereafter, compound 2 was used to prepare 3 *via* reaction with NaN_3 in dry MeOH[17]. Following this, a 1,3-dipolar cycloaddition reaction of 3 with phenylacetylene in the presence of CuI as a catalyst was used to furnish 4.

It was observed that there is just one product formed (1,4-regioisomer) in the crude material as identified by ^{1}H NMR spectroscopy. This is because a copper catalyst was used, which prevented formation of the undesired 1,5-triazole regioisomer as reported in the literature[18-21]. To investigate the optimal conditions for the Suzuki-Miyaura coupling procedure, different types of solvents, bases and palladium catalysts were used. For these attempts, the phenylboronic acid 5k was the chosen as a model substrate, as shown in Table 1. Subsequently, the target compounds 6a-s were synthesised *via* the optimised reaction conditions of the Suzuki-Miyaura coupling, which involved the reaction of 4 and aryl boronic acid derivatives 5a-s as outlined in table 2.

It was observed that $PdCl_2(PPh_3)_2$ (Table 1, Entry 4) was the best palladium catalyst tested (55% yield) compared with the other catalysts (Table 1, Entries 1-3); only trace amounts of 6k was obtained when $Pd(PPh_3)_4$ was employed (Table 1, Entry 1). No desired product 6k was detected when

$Pd(OAc)_2$ was used and only the starting materials 4 and 5k were recovered by TLC or ^1H NMR spectroscopy (Table 1, Entry 2). Using $Pd(dba)_2$ gave 6k in a low yield (<5%) (Table 1, Entry 3). In terms of the solvent, the reaction was found to work in anhydrous THF, MeCN or dioxane. The desired product 6k was isolated in a low yield (30%) when MeCN was employed (Table 1, Entry 5). The use of dioxane gave the best yield (59%) (Table 1, Entry 9).

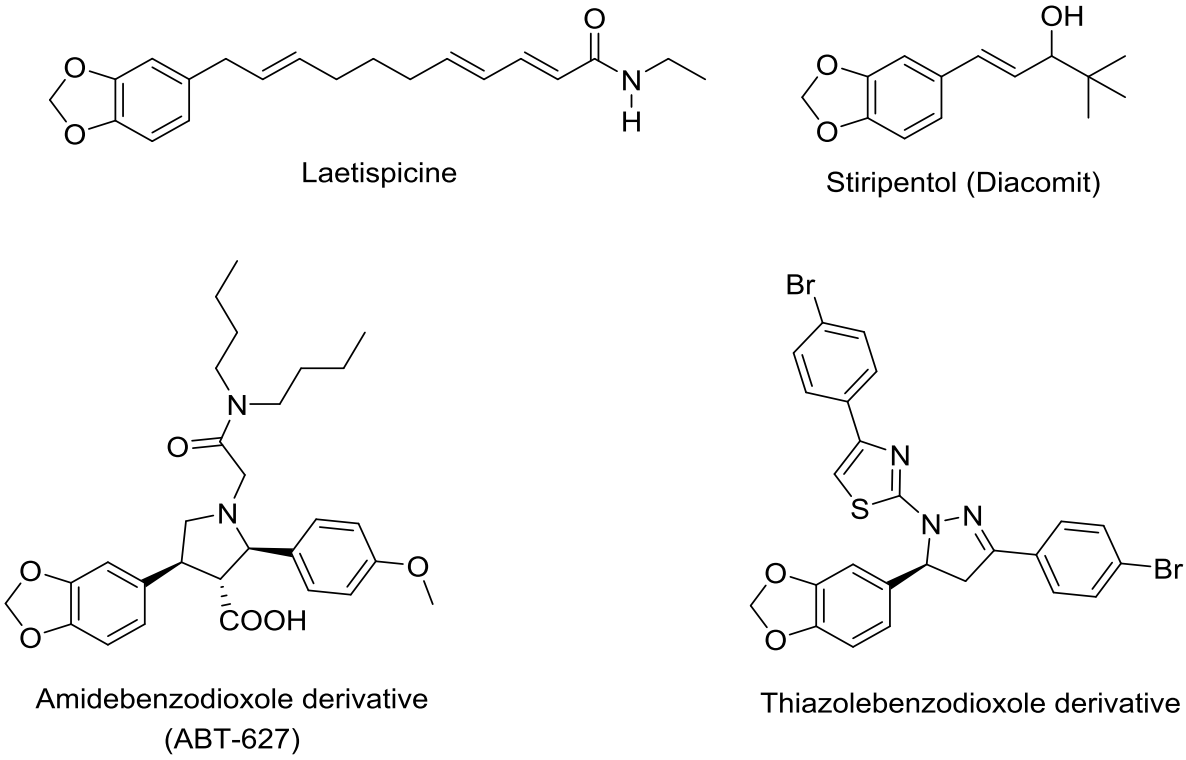
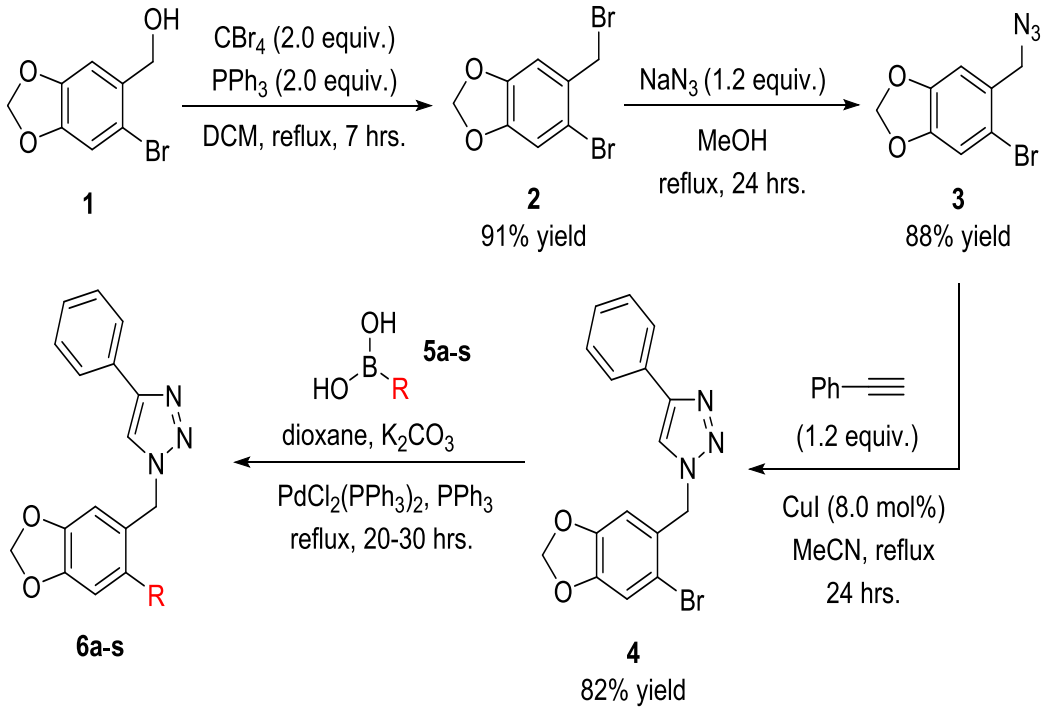
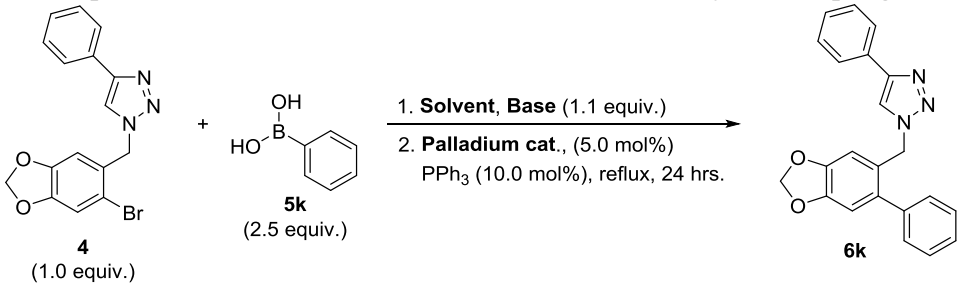


Figure 1: Some examples of biologically active compounds containing a 1,3-benzodioxole motif



Scheme 1: Outline of the synthesis of 1,3-benzodioxole derivatives 6a-s over four steps

Table 1
Optimization of reaction conditions for the Suzuki-Miyaura coupling



Entry	Solvent	Base	Pd catalyst	Yield (%)
1	THF	Et_3N	$Pd(PPh_3)_4$	trace
2	THF	Et_3N	$Pd(OAc)_2$	0
3	THF	Et_3N	$Pd(dba)_2$	<5
4	THF	Et_3N	$PdCl_2(PPh_3)_2$	55
5	MeCN	Et_3N	$PdCl_2(PPh_3)_2$	30
6	toluene	Et_3N	$PdCl_2(PPh_3)_2$	0
7	benzene	Et_3N	$PdCl_2(PPh_3)_2$	0
8	DCM	Et_3N	$PdCl_2(PPh_3)_2$	0
9	dioxane	Et_3N	$PdCl_2(PPh_3)_2$	59
10	dioxane	$^{n}BuLi$	$PdCl_2(PPh_3)_2$	<5
11	dioxane	$^{s}BuLi$	$PdCl_2(PPh_3)_2$	trace
12	dioxane	NaH	$PdCl_2(PPh_3)_2$	12
13	dioxane	LDA	$PdCl_2(PPh_3)_2$	<10
14	dioxane	LiHMDS	$PdCl_2(PPh_3)_2$	<10
15	dioxane	K_2CO_3	$PdCl_2(PPh_3)_2$	89
16	dioxane	$^{t}BuOK$	$PdCl_2(PPh_3)_2$	41

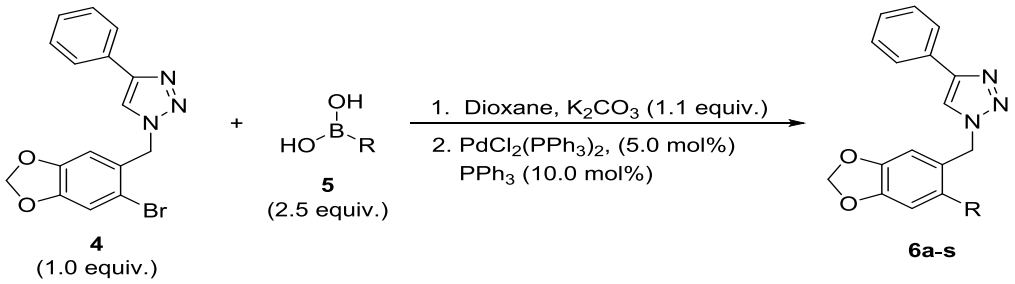
In addition, the solvents toluene, benzene and DCM were used during the optimisation. But, unfortunately, the desired product 6k could not be detected after 24 hours by HRMS and ^{1}H NMR spectroscopy (Table 1, 6-8). On the other hand, the type of base was found to be crucially important in this reaction. The stronger bases were observed to be inefficient for this system (Table, 1, Entries 10-14); the yields were less than 5% and trace amounts when *n*- and *sec*-butyl lithium were employed respectively (Table, 1, Entries 10 and 11). In addition, NaH, LDA and LiHMDS afforded low yields (*circa* 10-12%) (Table, 1, Entries 12-14). Conversely, the weaker bases afforded the desired product 6k in better yield. The use of K_2CO_3 enabled the full conversion of 4 within 6 hours (monitored by TLC and LCMS). However, the desired product 6k was isolated in a good yield (89%) (Table 1, Entry 15). The yield of 6k dropped to 41% if ^{t}BuOK was employed in place of K_2CO_3 (Table 1, Entry 16).

Following the above encouraging optimisation (Table 1, Entry 15), the scope of substrates was further explored. The coupling of substituted boronic acids 5a-s with 4 was achieved successfully to give 6a-s in yields ranging from medium to very good (33-89%). It was found that the boronic acid compounds bearing three fused ring systems such as 5n, 5r and 5s (Table 2, Entries 14-16) gave the desired products 6n, 6r and 6s in lower yields (59%, 57% and 53% respectively) than two fused ring systems 5d, 5e, 5f and 5j (62%, 81%, 68% and 74% respectively). (Table 2, Entries 4,5,6 and 10). This may be attributed to the nature of the size of the fused ring system.

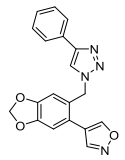
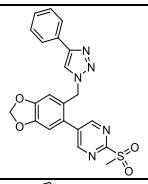
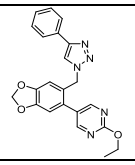
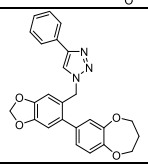
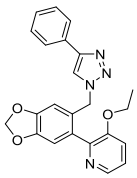
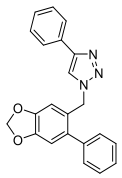
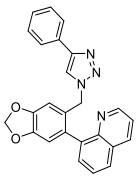
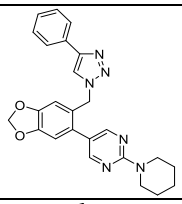
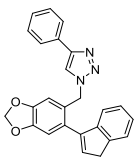
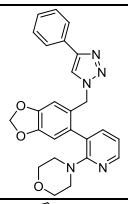
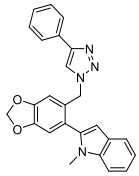
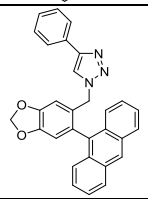
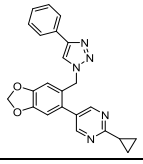
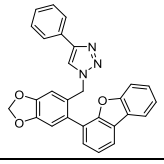
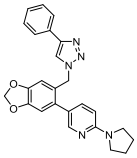
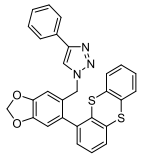
Notably, it was observed that using boronic acids non-bearing heteroatom in the ring gives yields better than those bearing heteroatom in their structures. For example, the substrates 5e and 5k (Table 2, Entries 5 and 11) afforded the desired products 6e and 6k in very good yields (81% and 89% respectively). While, the substrates 5a, 5b, 5g, 5h, 5i and 5l (Table 2, Entries 1,2,7,8,9 and 12) provide the corresponding products 6a, 6b, 6g, 6h, 6i and 6l in lower yields (60%, 57%, 33%, 47%, 60% and 53% respectively). This is explained by the presence of electron-withdrawing atom which deactivates the aromatic ring in an arylboronic acid toward the coupling with 4.

In conclusion, the synthesis of new 1,3-benzodioxole containing 1,2,3-triazole ring has been investigated. Suzuki-Miyaura coupling reaction of aryl bromide substituted with 1H-1,2,3-triazole (from 1,3-dipolar cycloaddition reaction) and boronic acid derivatives has been successfully optimised. The optimised reaction conditions were then applied on a wide range of aryl boronic acids to synthesise compounds containing a variety substituted of cyclic-, aromatic- and heterocyclic rings.

Table 2
Scope of the coupling of boronic acid substituted with 4



4 (1.0 equiv.) + **5** (2.5 equiv.) → **6a-s**

Entry	Product	No.	Time (h)	Yield (%)	Entry	Product	No.
1		6a	23	60	9		6i
2		6b	23	57	10		6j
3		6c	24	70	11		6k
4		6d	24	62	12		6l
5		6e	24	81	13		6m
6		6f	26	68	14		6n
7		6g	27	33	15		6r
8		6h	25	47	16		6s

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References
1. Barreiro E.J. and Lima M.E.F., The synthesis and anti-inflammatory properties of a new sulindac analogue synthesised from natural safrole, *J. Pharm. Sci.*, **81(12)**, 1219-1222 **(1992)**

2. Wang H.H., Qiu K.M., Cui H.E., Yang Y.S., Yin L., Xing M., Qiu X.Y., Bai L.F. and Zhu H.L., Synthesis, molecular docking and evaluation of thiazolyl-pyrazoline derivatives containing benzodioxole as potential anticancer agents, *Bioorg. Med. Chem*., **21(2)**, 448-455 **(2013)**

3. Chen Y.F., Lin Y.C., Huang P.K., Chan H.C., Kuo S.C., Lee K.H. and Huang L.J., Design and synthesis of 6,7-methylenedioxy-4-substituted phenylquinolin-2(1H)-one derivatives as novel anticancer agents that induce apoptosis with cell cycle arrest at G2/M phase, *Bioorg. Med. Chem*., **21(17)**, 5064-5075 **(2013)**

4. Taqvi M., Husain S.I., Jabbar A. and Hassan G., Blood Pressure lowering and vasomodulator effect of piperine, *J. Cardio. Pharm.*, **52(5)**, 452-458 **(2008)**

5. Yu H.Y., Chen Z.Y., Sun B., Liu J., Meng F.Y., Liu Y., Tian T., Jin A. and Ruan H.L., Lignans from the fruit of Schisandra glaucescens with antioxidant and neuroprotective properties, *J. Nat. Prod*., **77(6)**, 1311-1320 **(2014)**

6. Jinno S., Otsuka N., Okita T. and Inouyeb K., Total synthesis of a natural antioxidant and structure-activity relationships of related compounds, *Chem. Pharm. Bull*., **47(9)**, 1276-1283 **(1999)**

7. Sunila E.S. and Kuttan G., Immunology and antitumor activity of piper longum linn and piperine, *J. Ethanopharm.*, **90(2)**, 339-346 **(2004)**

8. Yao S., Xie H., Zhang L., Meng T., Zhang Y., Wang X., Chen L., Pan S. and Shen J., Total synthesis and antidepressant activities of laetispicine and its derivatives, *Molecules*, **17(2)**, 1425-1436 **(2012)**

9. Aboul-Enein M.N., El-Azzouny A.A., Attia M.I., Maklad Y.A., Amin K.M., Abdel-Rehim M. and El-Behairy M.F., Design and synthesis of novel stiripentol analogues as potential anticonvulsants, *Eur. J. Med. Chem.*, **47(1)**, 360-369 **(2012)**

10. Jarvis M.F., Wessale J.L., Zhu C.Z., Lynch J.J., Dayton B.D., Calzadilla S.V., Padley R.J., Opgenorth T.J. and Kowaluk E.A., ABT-627, an endothelin ET(A) receptor-selective antagonist, attenuates tactile allodynia in a diabetic rat model of neuropathic pain, *Eur. J. Pharmacol*., **388(1)**, 29-35 **(2000)**

11. Buckle D.R., Outred D.J., Rockell C.J.M., Smith H. and Spicer B.A., Studies on v-triazoles. 7. Antiallergic 9-oxo-1H,9H-benzopyrano[2,3-d]-v-triazoles, *J. Med. Chem*., **26(2)**, 251-254 (**1983)**

12. Cao X., Li F., Hu M., Lu W., Yu G.A. and Liu S.H., Chiral γ-aryl-1H-1,2,4-triazole derivatives as highly potential antifungal agents: Design, synthesis, structure and in vitro fungicidal activities, *J. Agric. Food Chem*., **56(23)**, 11367-11375 **(2008)**

13. Simmons K.A., Dixson J.A., Halling B.P., Plummer E.L., Plummer M.J., Tymonko J.M., Schmidt R.J., Wyle M.J., Webster C.A., Baver W.A., Witkowski D.A., Peters G.R. and Gravelle W.D., Synthesis and activity optimization of herbicidal substituted 4-aryl-1,2,4-triazole-5(1H)-thiones, *J. Agric. Food Chem*., **40(2)**, 297-305 **(1992)**

14. Cheng H., Wan J., Lin M.I., Liu Y., Lu X., Liu J., Xu Y., Chen J., Tu Z., Cheng Y.S.E. and Ding K., Design, synthesis and *in vitro* biological evaluation of 1H-1,2,3-triazole-4-carboxamide derivatives as new anti-influenza a agents targeting virus nucleoprotein, *J. Med. Chem*., **55(5)**, 2144-2153 **(2012)**

15. Alvarez R., Velazquez S., San F.A., Aquaro S., Clercq E.D., Perno C.F., Karlesson A., Balzarini J. and Camarasa M.J., 1,2,3-Triazole-[2,5-Bis-O-(*tert*-butyldimethylsilyl)-.beta.-D-ribofurano syl]-3'-spiro-5"-(4"-amino-1",2"-oxathiole 2",2"-dioxide) (TSAO) analogs: Synthesis and anti-HIV-1 activity, *J. Med. Chem*., **37(24)**, 4185-4194 **(1994)**

16. NoemÍ V., Pedro B., Dolores V., Mattia S., Stefano M. and Carmen T., Synthesis, biological evaluation and molecular modeling studies of phthalazin-1(2*H*)-one derivatives as novel cholinesterase inhibitors, *RSC Adv*., **6**, 46170-46185 **(2016)**

17. Zhi X., Xu F.S., Min Q. and Zao S.L., 1*H*-1,2,3-triazole-tethered 8-OMe ciprofloxacin and isatin hybrids: Design, synthesis and *in vitro* anti-mycobacterial activities, *J. Heterocyclic Chem*., **54(60)**, 3735-3741 **(2017)**

18. Riadh S., Shiva K.M., Baptiste P. and Christian G., A-21·CuI as a catalyst for Huisgen's reaction: about iodination as a side-reaction, *Tetrahedron Lett*., **56(29)**, 4339-4344 **(2015)**

19. Liyuan L. and Didier A., The copper(I)-catalyzed alkyne-azide cycloaddition (CuAAC) "click" reaction and its applications, An overview, *Coord. Chem. Rev*., **255(23)**, 2933-2945 **(2011)**

20. Harriet S. Thomas L.M. and Roger S., Metal chelating systems synthesized using the copper(I) catalysed azide-alkyne cycloaddition, *Dalton Trans.*, **39**, 675-696 **(2010)**

21. Christian G., Esra O., Marie A., Sophie B., Edmond S. and Jean H., Reusable polymer-supported catalyst for the [3+2] Huisgen cycloaddition in automation protocols, *Org. Lett*., **8(8)**, 1689-1692 **(2006)**.