An efficient one- pot catalyzed synthesis of 2,5-disubstituted-1,3,4-oxadiazoles and evaluation of their antimicrobial activities

Mohamed S. Behalo

Chemistry Department, Faculty of Science, Benha University, Benha, P. O. Box 13518. Egypt

mohamed.behalo@fsc.bu.edu.eg

2. Experimental Section

2.1 Materials

The chemical reagents were purchased from Sigma-Aldrich. Solvents were commercially available from El-nasr chemicals Co. in analytical grade and were used without further purification. TLC was conducted on precoated silica gel polyester sheets (Kieselgel 60 F254, 0.20 mm, Merck).

Melting points are uncorrected and FT-IR spectra were recorded on a JASCO FT-IR 660 Plus spectrometer. NMR spectra were recorded on a Bruker Avance 400 (400 MHz) using DMSO and $CDCl_3$ as the solvents. Mass spectra were obtained using a Shimadzu GCMS-QP 1000 EX mass spectrometer.

2.2 Synthesis

2.2.1 Synthesis of ethyl-2-((4-phenoxathiin-2-yl)phthalazin-1-yl)oxy)acetate 2

A mixture of phthalazinone **1** (0.01 mol), ethylchloroacetate (0.01 mol) in dry acetone (30 mL) containing anhydrous potassium carbonate (0.04 mol) was heated under reflux for 24 h. After cooling, the reaction mixture was poured into cold water and the formed solid was filtered off, dried and crystallized from ethanol.

White crystals, yield: 71 %; m.p. 167-169 ^{o}C. IR spectrum (KBr, ν, cm^{-1}): 2938, 2855 (CH_2), 1743 (CO), 1632 (C=N); ^{1}H NMR (DMSO-d_6, δ ppm): 1.19-1.24 (t, 3H, CH_3), 4.14-4.21 (q, 2H ,CH_2), 4.98 (s, 2H, OCH_2), 7.12-7.97 (m, 11H, Ar-H); ^{13}C NMR, 14.3, 61.2, 65.4, 114.5, 117,4, 118.3, 118.6, 119.2, 119.6, 120.3, 122.5, 123.7, 125.5, 127.3, 128.7, 131.3, 132.2, 133.6, 135.5, 136.6, 144.5, 153.5, 170.4; MS: *m/z*: 430 (M+); Anal. calcd. for $C_{24}H_{18}N_2O_4S$ (430.48): C, 66.96; H, 4.21; N, 6.51%. Found: C, 66.88; H, 4.15; N, 6.46 %.

2.2.2 Synthesis of 2-((4-Phenoxathiin-2-yl)phthalazin-1-yl)oxy)acetohydrazide 3

Heat a mixture of ester **2** (0.01 mol) and hydrazine hydrate (0.01 mol) under reflux in ethanol (20 mL) for 6 h. The precipitated solid after cooling was collected by filtration and recrystallized from ethanol to give pure crystals of hydrazide **3**

Pale yellow powder, yield: 82 %; m.p. 212-214 ^{o}C. IR spectrum (KBr, ν, cm^{-1}): 3432-3156 (NH_2, NH), 2925, 2840 (CH_2), 1669 (CO), 1591 (C=N); ^{1}H NMR (DMSO-d_6, δ ppm): , 12.82 (s, 1H, NH exchangeable), 5.81 (s, 2H ,NH_2, exchangeable), 4.72 (s, 2H, OCH_2), 7.12-7.92 (m, 11H, Ar-H); ^{13}C NMR, 61.5, 114.4, 115.7, 116.6, 117,9, 118.3, 119.3, 122.2, 123.8, 127.6, 129.2, 131.4, 132.6, 133.5, 134.3, 135.8, 144.6, 155.5, 158.4, 169.6; MS: *m/z*: 416 (M+); Anal. calcd. for $C_{22}H_{16}N_4O_3S$ (416.46): C, 63.45; H, 3.87; N, 13.45 %. Found: C, 63.37; H, 3.78; N, 13.38 %.

2.2.3 General procedure for synthesis of hydrazones 4a-d

To a mixture of hydrazide **3** (0.01 mol) and aromatic aldehydes (0.01 mol) namely benzaldehyde, 4-chlorobenzaldehyde, 4-N,N-dimethylbenzaldehyde and thiophene-2-carbaldehyde in ethanol (10 mL), cerium (IV) ammonium nitrate (0.0025 mol) was added and the whole mixture was stirred and heated under reflux for 1h. Water (5 mL) was added and the product solid was filtered, washed and recrystallized from proper solvent.

2.2.3.1 N-Benzylidene-2-((4-(phenoxathiin-2-yl)phthalazin-1-yl)oxy)acetohydrazide 4a

Yellow powder, yield: 85 %; m.p. 186-188 ^{o}C. IR spectrum (KBr, ν, cm^{-1}): 3432 (NH), 2939, 2880 (CH_2), 1670 (CO), 1606 (C=N); ^{1}H NMR (DMSO-d_6, δ ppm, 4.63 (s, 2H, OCH_2), 7.93-7.13 (m, 16H, Ar-H), 8.35 (s, 1H, CH=N), 12.82 (s, 1H, NH, exchangeable); ^{13}C NMR, 64.3, 113.5, 114.3, 114.7, 115.2, 115.6, 116.8, 117.8, 118.6, 119.5, 120.2, 122.6, 123.5, 127.6, 129.5, 131.8, 133.6, 134.4, 134.6, 135.8, 144.4, 147.8, 154.6, 155.5, 170.2 MS: *m/z*: 504 (M+); Anal. calcd. for $C_{29}H_{20}N_4O_3S$ (504.56): C, 69.03; H, 4.00; N, 11.10 %. Found: C, 69.00; H, 3.95; N, 11.02 %.

2.2.3.2 N-(4-Chlorobenzylidene)-2-((4-(phenoxathiin-2-yl)phthalazin-1-yl)oxy) acetohydrazide 4b

Yellow powder, yield 86 %; m.p. 193-195 ^{o}C. IR spectrum (KBr, ν, cm^{-1}): 3432 (NH), 2938, 2855 (CH_2), 1670 (CO), 1599 (C=N); ^{1}H NMR (DMSO-d_6, δ ppm): 4.35 (s, 2H, OCH_2), 7.69-6.47 (m, 15H, Ar-H), 8.42 (s, 1H, CH=N), 8.58 (s, 1H, NH, exchangeable); ^{13}C NMR, 65.2, 113.8, 114.6, 115.2, 115.6, 116.4, 117.2, 117.8, 118.5, 119.6, 121.5, 122.3, 123.8, 126.5, 128.4, 132.5, 133.2, 133.8, 134.2, 135.3, 145.5, 146.5, 152.2, 154.3, 171.5; MS: *m/z*: 439 (M^{+}), 540 (M^{+1}); Anal. calcd. for $C_{29}H_{19}ClN_4O_3S$ (539.01): C, 64.62; H, 3.55; N, 10.39 %. Found: C, 64.55; H, 3.49; N, 10.25 %.

2.2.3.3 N-(4-(Dimethylamino)benzylidene)-2-((4-(phenoxathiin-2-yl)phthalazin-1-yl)oxy)acetohydrazide 4c

Yellow powder, yield: 83%; m.p. 225-227 ^{o}C. IR spectrum (KBr, ν, cm^{-1}): 3441 (NH), 2945, 2860 (CH_2), 1671 (CO), 1615 (C=N); ^{1}H NMR (DMSO-d_6, δ ppm): 3.65 (s, 6H, 2 CH_3), 4.86 (s, 2H, OCH_2), 7.12 – 7.92 (m, 15H, Ar-H), 8.36 (s, 1H, CH=N), 12.81 (s, 1H, NH, exchangeable); ^{13}C NMR 41.8, 58.4, 112.5, 116.2, 117.5, 118.3, 119.1, 119.8, 120.4, 120.9, 122.2, 122.7, 128.3, 128.6, 129.3, 130.1, 132.2, 145.3, 147.5, 156.3, 173.4; MS: *m/z*: 547 (M+); Anal. calcd. for $C_{31}H_{25}N_5O_3S$ (547.63): C, 67.99; H, 4.60; N, 12.79 %. Found: C, 67.89; H, 4.54; N, 12.71 %.

2.2.3.4 2-((4-(Phenoxathiin-2-yl)phthalazin-1-yl)oxy)-*N*-(thiophen-2-ylmethylene) acetohydrazide 4d

Yellow powder, yield: 86 %; m.p. 199-201 ^{o}C. IR spectrum (KBr, ν, cm^{-1}): 3440 (NH), 2950, 2866 (CH_2), 1672 (CO), 1609 (C=N); ^{1}H NMR (DMSO-d_6, δ ppm): 5.10 (s, 2H, OCH_2), 7.28-6.76 (m, 14H, Ar-H), 8.44 (s, 1H, CH=N), 10.01 (s, 1H, NH, exchangeable); ^{13}C NMR, 61.5, 112.7, 114.4, 115.3, 115.5, 116.4, 117.2, 118.3, 118.7, 120.5, 121.5, 122.3, 126.5, 129.7, 131.7, 133.5, 134.3, 135.6, 144.7, 146.5, 153.8, 155.2, 171.5 ; MS: *m/z*: 510 (M+), 511 (M^{+1}); Anal. calcd. for $C_{27}H_{18}N_4O_3S_2$ (510.59): C, 63.51; H, 3.55; N, 10.97 %. Found: C, 63.46; H, 3.47; N, 10.91 %.

2.2.4 General procedures for the synthesis of 2,5-disubstituted-1,3,4-oxadiazoles 5a-d

Method A: A mixture of hydrazones **4a-d** (0.01 mol) and cerium (IV) ammonium nitrate (0.01 mol) was grinded together in mortar at room temperature for 30 min. Methylene chloride (10 mL) was added followed by water (10 mL) and the organic phase was separated and dried over magnesium sulfate. The product solid after evaporation of solvent was collected and recrystallized from proper solvent to give oxadiazoles **5a-d**.

Method B: A mixture of hydrazide (0.01 mol), the same aromatic aldehydes (0.01 mol) and cerium (IV) ammonium nitrate (0.01 mol) in methylene chloride (20 mL) was stirred and heated under reflux for 8 h. the progress of the reaction was monitored by TLC. Water (10 mL) was added and the organic phase was separated and dried over magnesium sulfate. The product solid after evaporation of solvent was collected and recrystallized from proper solvent to give oxadiazoles **5a-d**.

Alternative synthesis of oxadiazoles 5a-d: A mixture of hydrazide **3**, aromatic carboxylic acids (0.01 mol) namely benzoic acid and 4-chlorobenzoic acid (0.01 mol) and cerium (IV) ammonium nitrate (0.01 mol) in polyethylene glycol (5 mL) was stirred and refluxed for 2 h. After completion of the reaction as examined by TLC, the mixture was cooled, extracted with diethyl ether and the ether layer was washed with brine solution (10 mL x 3), then dried with anhydrous magnesium sulfate. The solvent was removed in vacuo and the crude product was recrystallized from proper solvent.

2.2.4.1 2-((4-(Phenoxathiin-2-yl)phthalazin-1-yl)oxy)methyl-5-phenyl-1,3,4-oxadiazole 5a

Yellow powder, Yield: 72 %; m.p. 158-160 ^{o}C. IR (KBr, ν, cm^{-1}): 2945, 2899 (CH_2), 1657 (C=N); ^{1}H NMR (DMSO-d_6, δ ppm): 5.40 (s, 2H, OCH_2), 7.94- 7.12 (m, 16H, Ar-H); ^{13}C NMR, 62.3, 113.5, 113.8, 115.4, 115.6, 116.2, 117.4, 117.8, 118.2, 118.6, 119.4, 122.5, 123.5, 127.2, 127.6, 128.6, 131.5, 133.2, 134.8, 135.3, 136.2, 144.2, 152.5, 155.6, 158.2, 160.2 ; MS: *m/z*: 502 (M+); Anal. calcd. for $C_{29}H_{18}N_4O_3S$ (502.55): C, 69.31; H, 3.61; N, 11.15 %. Found: C, 69.24; H, 3.52; N, 11.04 %.

2.2.4.2 2-(4-Chlorophenyl)-5-((4-(phenoxathiin-2-yl)phthalazin-1-yl)oxy)methyl-1,3,4-oxadiazole 5b

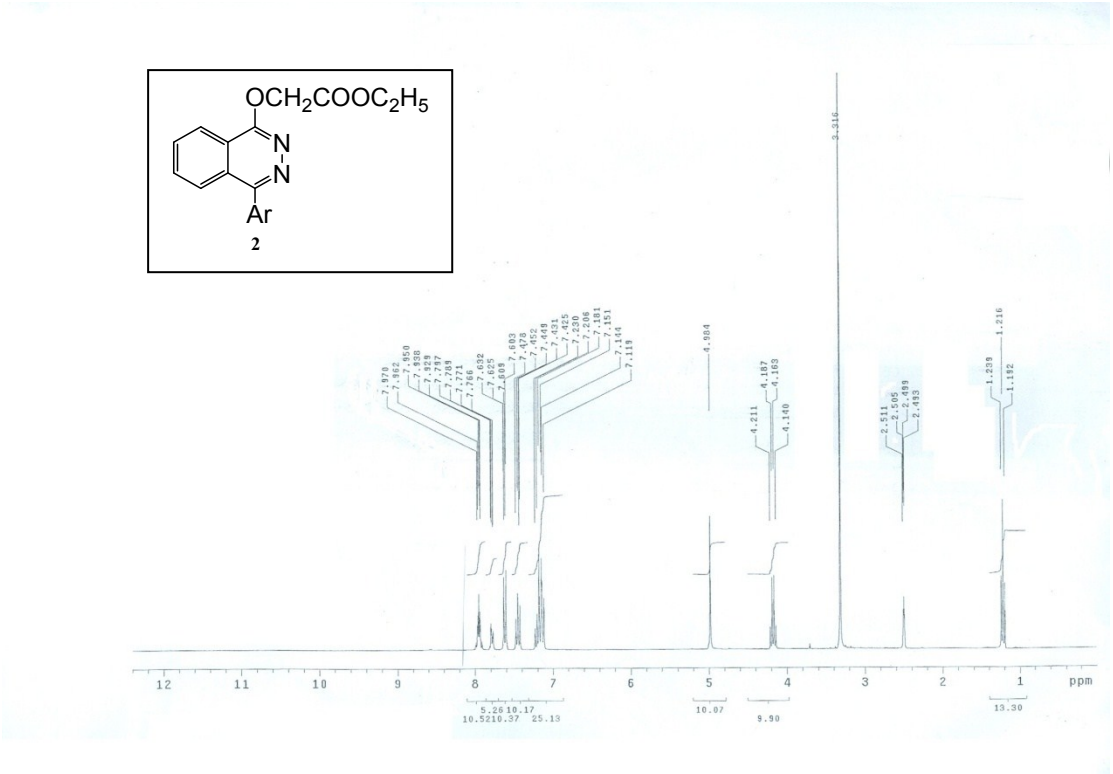
Yellow powder, yield: 68 %; m.p. 170-172 ^{o}C. IR (KBr, ν, cm^{-1}): 2935, 2850 (CH_2), 1610 (C=N); ^{1}H NMR (DMSO-d_6, δ ppm): 5.20 (s, 2H, OCH_2), 8.02-7.13 (m, 14H, Ar-H); MS: *m/z*: 537 (M+), 538 (M^{+1}), 539 (M^{+2}); Anal. calcd. for $C_{29}H_{17}ClN_4O_3S$ (536.99): C, 64.87; H, 3.19; N, 10.43 %. Found: C, 64.79; H, 3.13; N, 10.34 %.

2.2.4.3 2-(*N,N*-Dimethylaminophenyl)-5-((4-(phenoxathiin-2-yl)phthalazin-1-yl) oxy)methyl-1,3,4-oxadiazole 5c

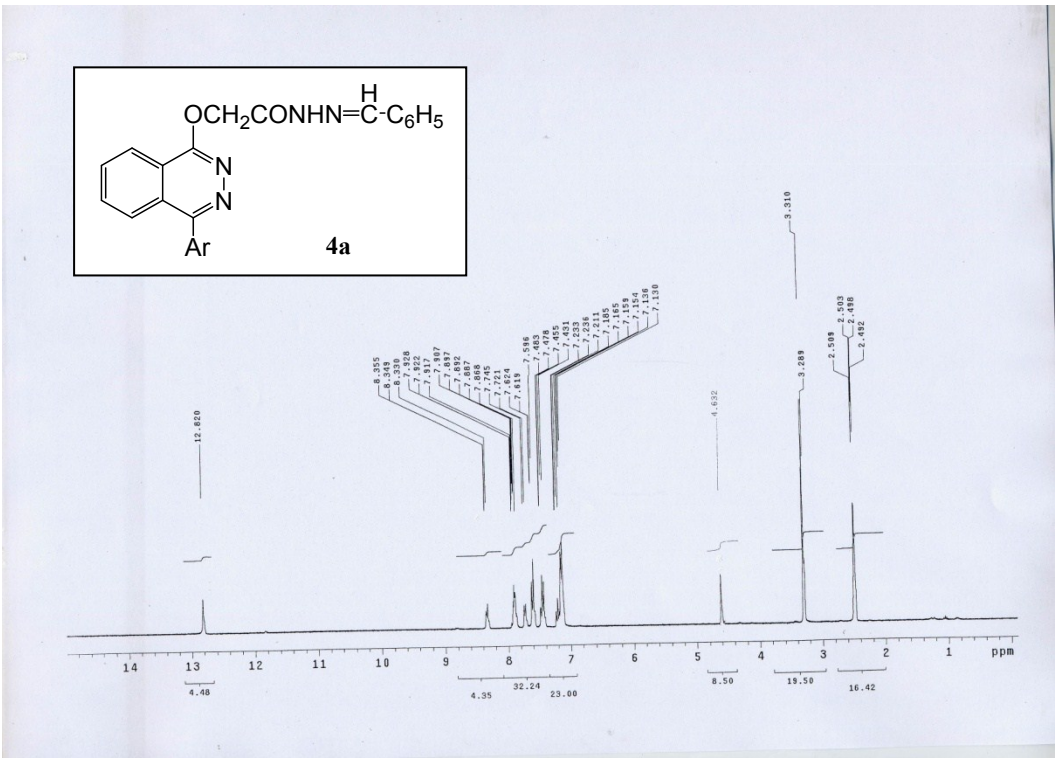
Yellow powder, yield: 65 %; m.p. 144-146 ^{o}C. IR (KBr, ν, cm^{-1}): 2930, 2870 (CH_2), 1615 (C=N); ^{1}H NMR ($CDCl_3$, δ ppm): 3.79 (s, 6H, 2 CH_3), 5.06 (s, 2H, OCH_2), 8.05 – 7.48 (m, 15H, Ar-H); ^{13}C NMR, 43.7, 58.2, 113.2, 113.6, 114.5, 115.8, 116.1, 116.8, 117.4, 118.3, 118.9, 119.5, 123.6, 123.8, 128.5, 129.3, 132.5, 133.0, 134.4, 134.6, 136.5, 145.5, 151.7, 157.8, 160.5, 161.3; MS: *m/z*: 545 (M^{+}); Anal. calcd. for $C_{31}H_{23}N_5O_3S$ (545.62): C, 68.24; H, 4.25; N, 12.84 %. Found: C, 68.12; H, 4.16; N, 12.73 %.

2.2.4.4 2-((4-(Phenoxathiin-2-yl)phthalazin-1-yl)oxy)methyl-5-(thiophen-2-yl)-1,3,4-oxadiazole 5d

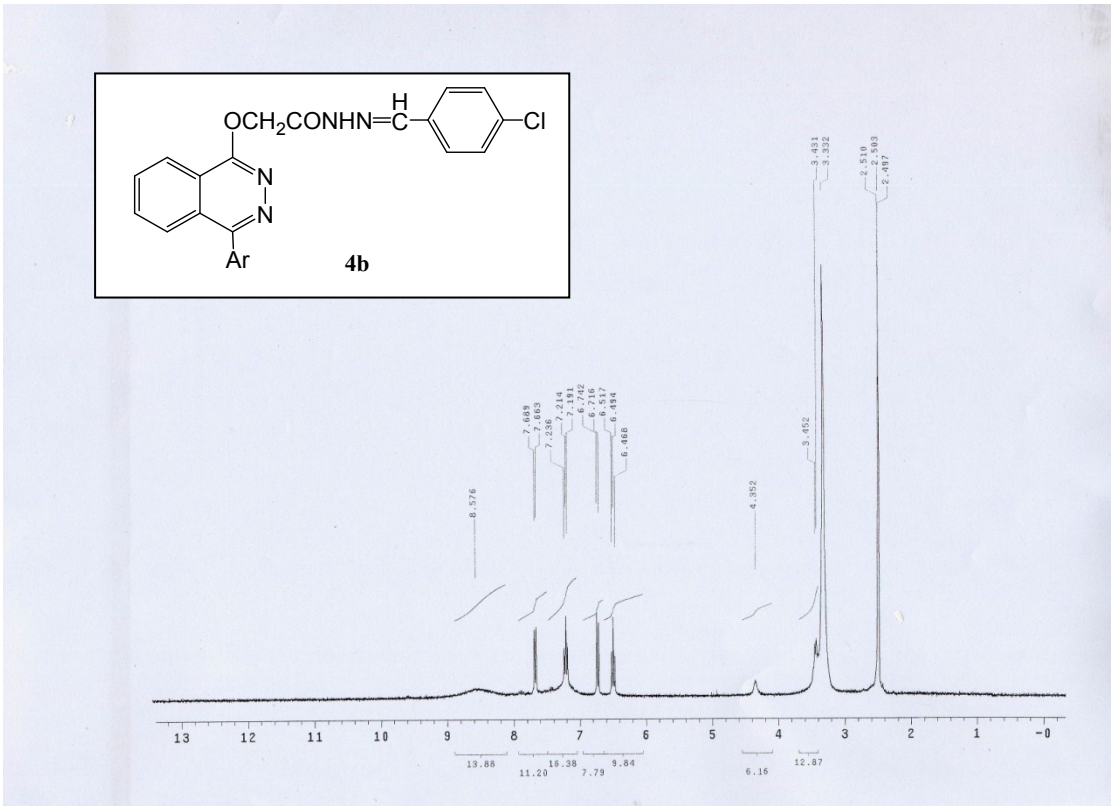
Yellow powder, yield: 67 %; m.p. 153-155 ^{o}C. IR (KBr, ν, cm^{-1}): 2938, 2860 (CH_2), 1610 (C=N); ^{1}H NMR (DMSO-d_6, δ ppm): 4.82 (s, 2H, OCH_2), 6.97 – 8.12 (m, 14H, Ar-H); ^{13}C NMR, 64.2, 114.1, 117.5, 118.6, 120.4, 121.3, 122.3, 123.2, 123.8, 126.4, 128.3, 129.2, 130.1, 130.6, 134.0, 134.4, 135.1, 136.3, 138.8, 141.2, 145.6, 148.2, 152.3, 154.6 156.5; MS: *m/z*: 508 (M^{+}); Anal. calcd. for $C_{27}H_{16}N_4O_3S_2$ (508.57): C, 63.77; H, 3.17; N, 11.02 %. Found: C, 63.69; H, 3.12; N, 10.93 %.



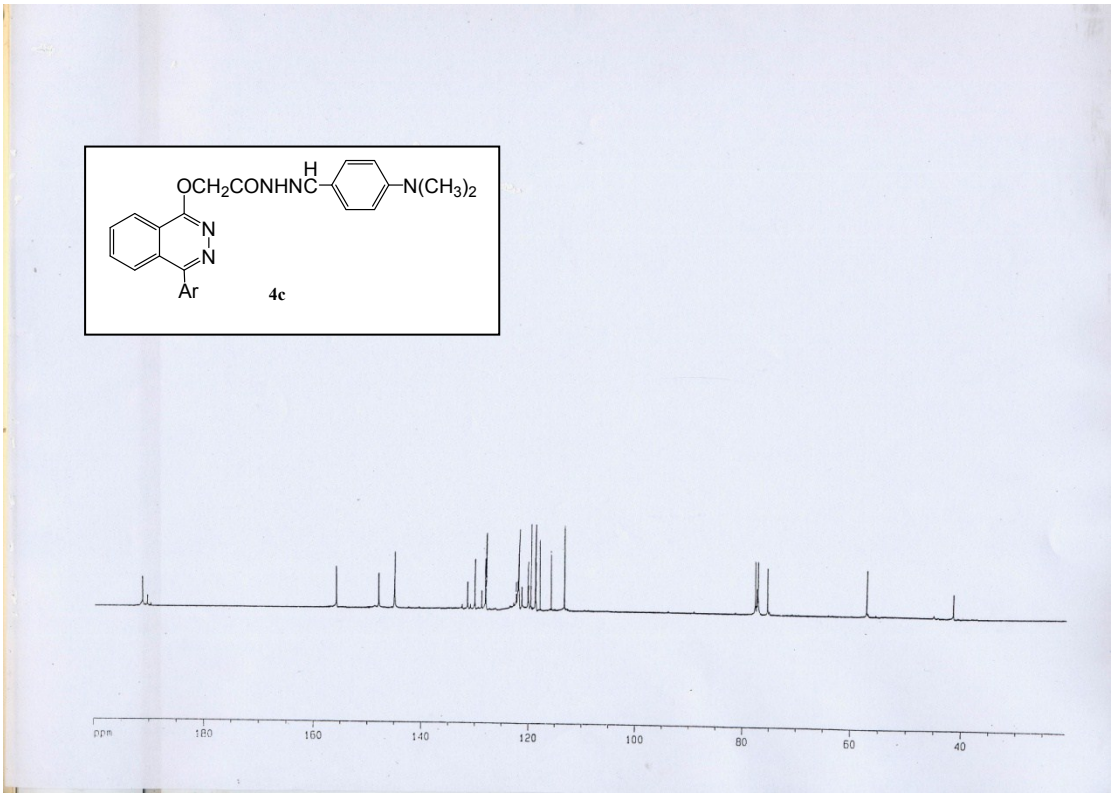
[1]HNMR spectrum of ester 2



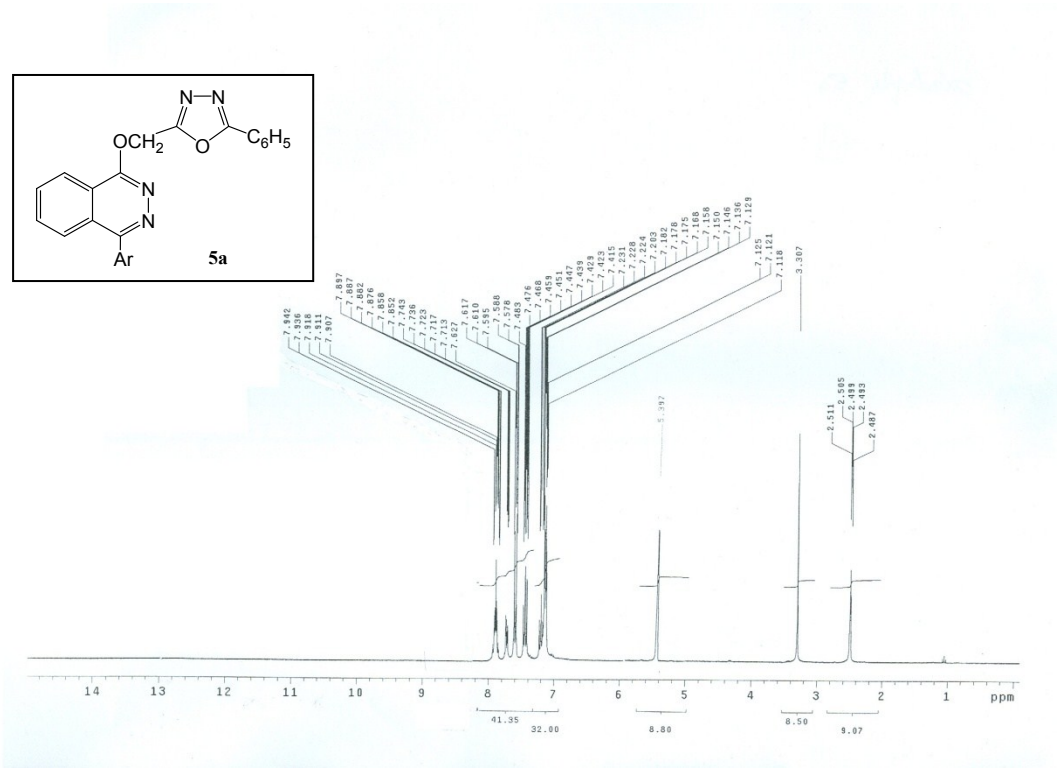
[1]HNMR spectrum of hydrazone 4a



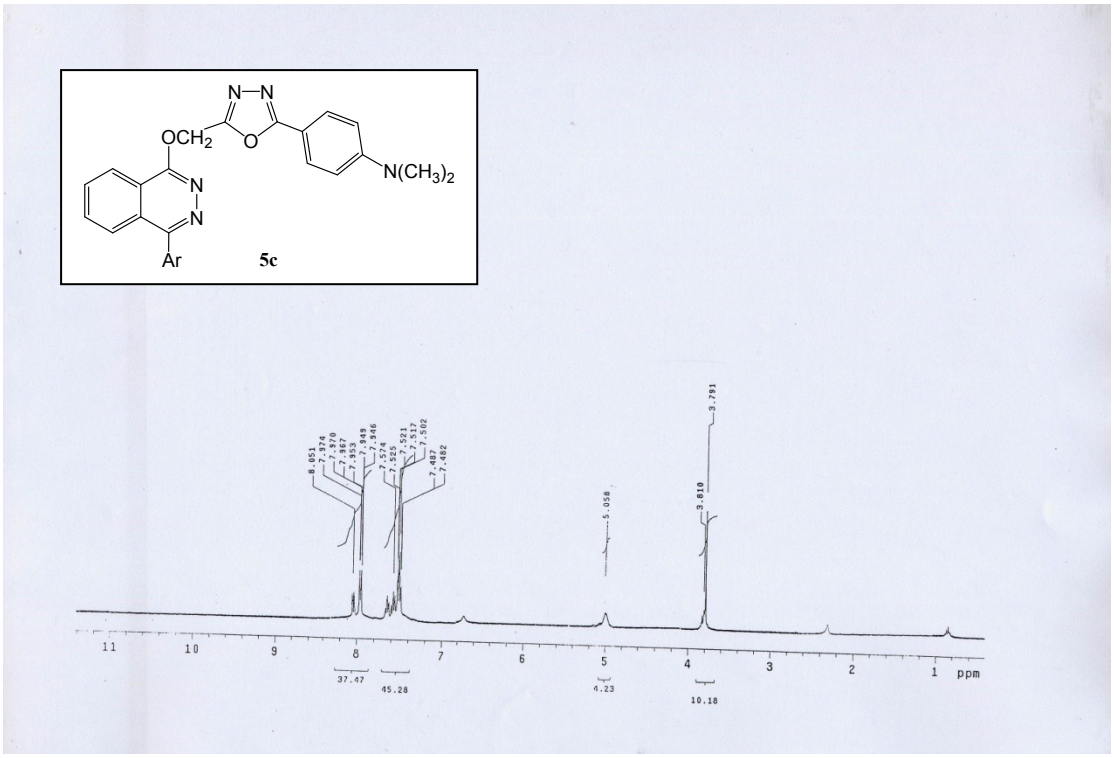
[1]HNMR spectrum of hydrazone 4b



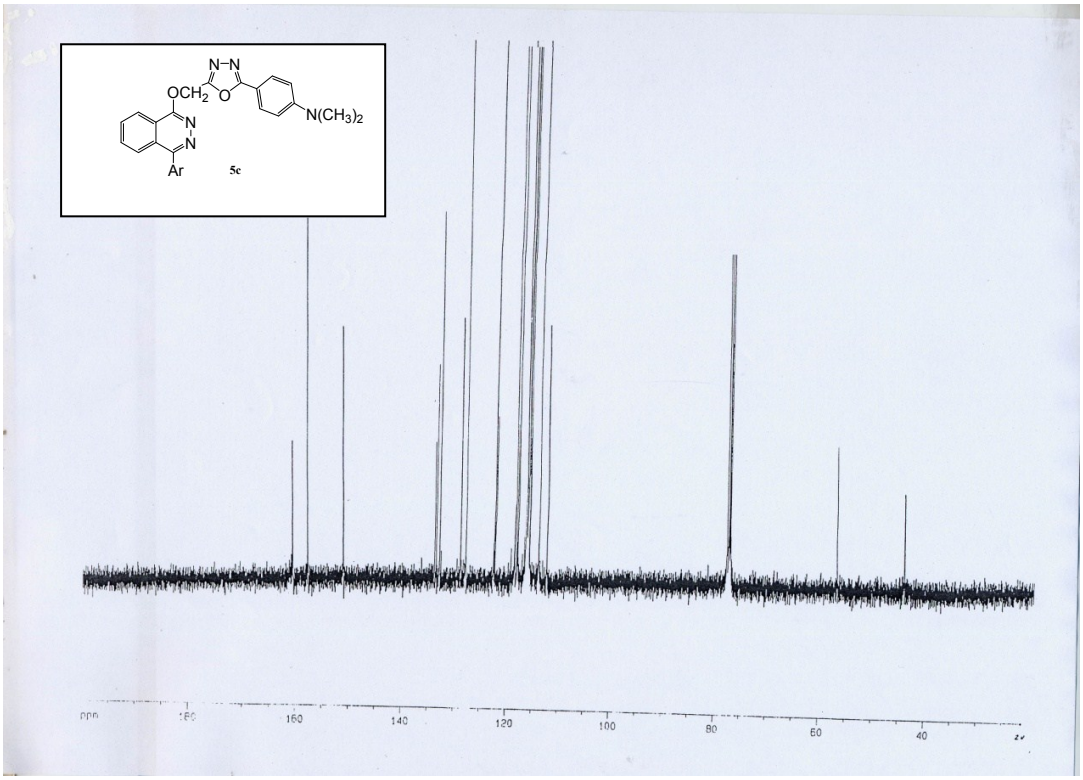
^{13}C NMR spectrum of hydrazone 4c



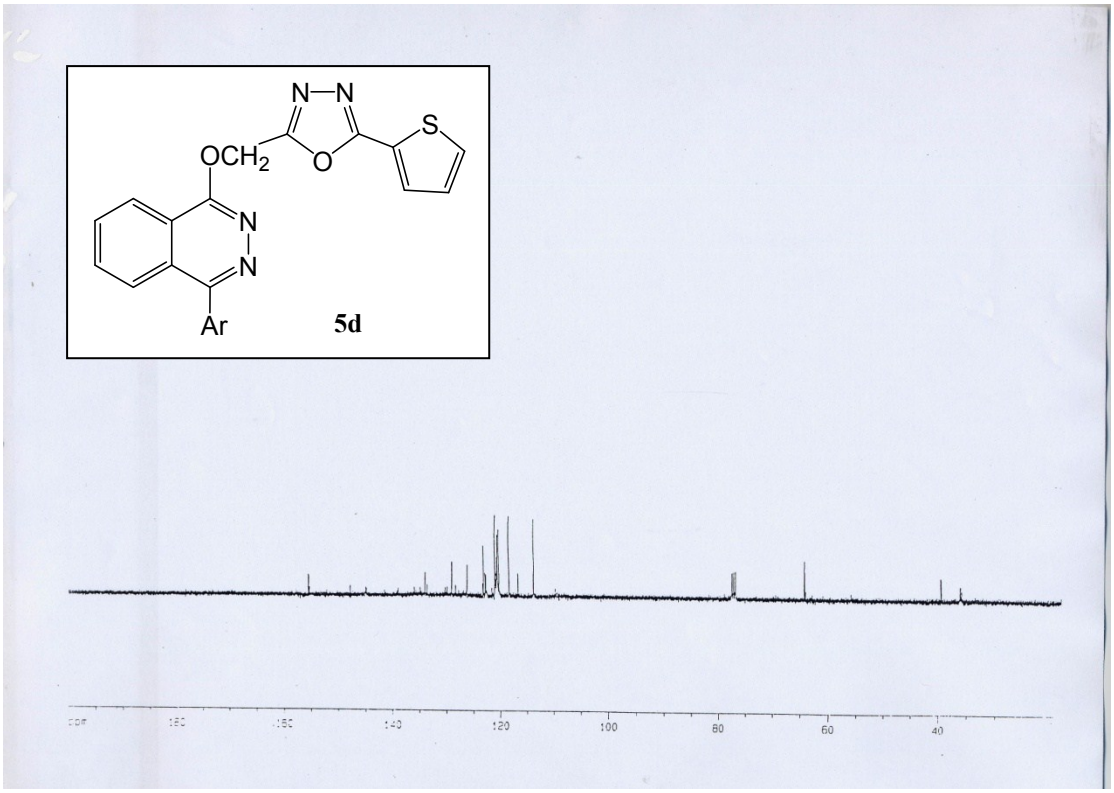
^{1}H NMR spectrum of oxadiazole 5a



^{1}H NMR spectrum of oxadiazole 5c



^{13}C NMR spectrum of oxadiazole 5c



^{13}C NMR spectrum of oxadiazole 5d