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MICROWAVE ASSISTED SYNTHESIS OF 2-AMINO-4-(ARYL)-4*H*-PYRANO [3,2-*h*] QUINOLINE-3-CARBONITRILES IN POLYETHYLENE GLYCOL AND THEIR ANTIBACTERIAL ACTIVITY

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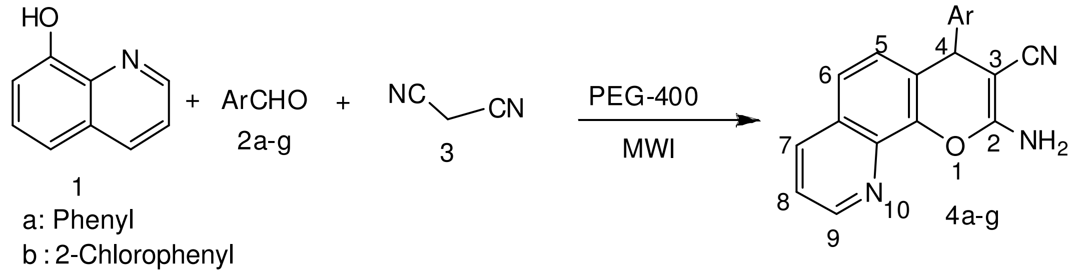
A series of 2-amino-4-(aryl)-4*H*-pyrano [3,2-*h*] quinoline-3-carbonitriles have been synthesized by microwave assisted multicomponent one-pot cyclocondensation reaction of aromatic aldehydes, malononitrile and 8-hydroxy quinoline in PEG-400. All these compounds were characterized by means of IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. All the compounds were screened for their antibacterial activity.

Multicomponent reactions (MCRs) are highly efficient for construction of complex molecules and attracted considerable interest owing to their synthetic efficiency. This process consists of two or more steps which are carried out without isolation of any intermediate. The advantage of multicomponent reactions are a) high atom-economy b) structural diversity c) operational simplicity d) avoid waste product formed in multi-step reaction. Quinolines have been reported to possess a wide variety of biological activities such as antituberculosis[1], antiinflammatory[2], antimalarial[3], antimicrobial[4] and antileishmanial[5] activities. The microwave-assisted synthesis under green solvent is promising alternative to conventional methods as these reactions are clean, efficient, safe, economical and eco-friendly[6]. Recently PEG's have attracted increasing interest as green solvent due to their excellent properties. Unlike organic solvents, low molecular weight liquid PEG's are non-volatile and biodegradable.

2-Amino-4*H*-pyran derivatives are of considerable interest as they possess wide range of biological properties such as antitumor[7], antimicrobial[8] and central nervous system activity[9]. In view of potential bioactivity of quinoline and pyran moieties and also in continuation of our interest[10] in synthesis of biologically important condensed heterocycles herein we wish to report a simple and convenient microwave assisted multicomponent one-pot synthesis of 2-amino-4-(aryl)-4*H*-pyrano [3,2-*h*] quinoline-3-carbonitriles (**4**a-g).

A perusal of literature reveals that 2-amino-4*H*-pyrans are generally synthesized by refluxing aldehyde, phenol and malononitrile in the presence of hazardous bases such as piperidine, K_2CO_3 etc. in acetonitrile or ethanol for several hr[11-13]. Polyethylene glycol (PEG) is a readily available, safer and eco-friendly green solvent. PEG is an effective and recyclable reaction medium with unique properties and potentials for organic reactions. Microwave-induced



Ar = a: Phenyl
b : 2-Chlorophenyl
c: 4-Chlorophenyl
d: 4-Methoxy phenyl
e : 3-Nitrophenyl
f: 4-Fluorophenyl
g: 4-Methylphenyl

SCHEME-1

Table-1
Physical data of 2-amino-4-(aryl)-1-4*H*-pyrano [3,2-*h*] quinolines-3-carbonitriles

Compd	Conventional heating		MWI Irradiation	
	Time (hr)	Yield (%)	Time (min)	Yield (%)
4a	6	76	6	92
4b	5	75	7	90
4c	6	71	6	94
4d	5	78	6	93
4e	6	72	5	90
4f	5	81	6	94
4g	5	74	6	93

organic reaction enhancement chemistry has gained popularity as a non conventional technique for rapid organic synthesis; it is eco-friendly and economical and is believed to be a step toward green chemistry.

Thus it is clear that the combined approach of microwave superheating and PEG as a reaction medium could be considered a promising and green synthetic strategy for the construction of important fused heterocycles. In view of the emerging importance of microwave irradiation and PEG as a novel reaction media, we wish to report a mild and highly efficient method for the synthesis of title compounds (**4**a-g) in PEG-400 without any catalyst under microwave irradiation. A series of 2-amino-4-(aryl)-4*H*-pyrano [3,2-*h*] quinoline-3-carbonitrile (**4**a-g) derivatives have been synthesized by one-pot condensation of 8-hydroxy quinoline (**1**), aromatic aldehydes (**2**a-g) and malononitrile (**3**) in polyethylene glycol as a solvent under conventional heating and microwave irradiation.

Antibacterial activity

All the compounds were screened for their antibacterial activity against bacterial strains such as *Bacillus subtilis* (ATCC-6633), *Staphylococcus aureus* (ATCC-29737), *Escherichia coli* (ATCC-10536) and *Pseudomonas aeruginosa* (ATCC-27853) using Streptomycin, Tetracycline, Chloramphenicol and Carbenicillin as standard drugs. The activity was determined using cup-plate agar diffusion method[16] by measuring the inhibition zone in mm. Nutrient agar was used as a culture medium. The agar medium was inoculated with bacterial cultures tested. After 24 hr of incubation at 37^0, the diameter of inhibition zone (in millimetres) was measured. Among the compounds screened, **4**a, **4**b and **4**f showed moderate activity against all bacteria.

Experimental

Melting points were determined in open capillaries and are uncorrected. The purity of the compounds was checked by the silica gel 60 F_{254} (Merck). Microwave reactions were carried out in Milestone multi SYNTH microwave system. IR spectra were recorded on Shimadzu FT-IR 8400s spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance 300 MHz spectrometer and Mass spectra were recorded on Shimadzu mass spectrometer. Elemental analysis was determined by using Thermofinnigan CHNS analyzer.

Synthesis of 2-amino-4-(aryl)-4*H*-pyrano [3,2-*h*] quinoline-3-carbonitriles (4a-g)

Conventional heating method

A mixture of 8-hydroxy quinoline (**1**) (0.01 mol), aromatic aldehydes (**2**a-g) (0.01 mol), malononitrile (**3**) (0.01 mol) in PEG-400 (10 ml) was heated to 80^0 for 5-6 hr. Progress of the reaction was monitored by thin layer chromatography (TLC). After completion of the reaction, the reaction mass was cooled to room temp and then it was diluted with cold water. The precipitate formed was filtered, washed with water and ethyl acetate. The solid was recrystallized from ethanol to afford the pure compounds. The aqueous filtrate was evaporated on rotary evaporator to remove water and the separated PEG-400 was reused.

Microwave irradiation method

A mixture of 8-hydroxy quinoline (**1**) (0.005 mol), aromatic aldehydes (**2**a-g) (0.005 mol) and malononitrile (**3**) (0.005 mol) in PEG-400 (5 ml) was taken in a quartz tube and inserted into Teflon vial with screw capped and then subjected to microwave irradiation at 160W for 5-7 min. After completion of the reaction, the reaction mass was cooled to room temp and then it was diluted with cold water. The precipitate formed was filtered, washed with water and ethyl acetate. The solid was recrystallized from ethanol to afford the pure compounds.

Spectral data (4a-g)

4a: M.p. 260^0; IR (KBr): 3467, 3325 (NH_2), 3189, 3020, 2191 (CN), 1653, 1627, 1597, 1565, 1500, 1468, 1317, 1297, 1245, 1187, 1105, 1047 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.96 (s, 1H, pyran H_4), 7.15 (s, 2H, NH_2), 7.22 (d, 1H, ArH), 7.25-7.35 (m, 5H, ArH), 7.60 (dd, 1H, ArH), 7.64 (d, 1H, ArH), 8.34 (dd, 1H, ArH), 8.95 (d, 1H, ArH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 42.0 (pyran C_4), 57.5 (pyran C_3), 120.4 (CN), 122.4, 123.9, 127.2, 128.1, 128.2, 129.1, 136.2, 138.2, 143.7, 145.8, 150.6 (pyran C_6), 160.9 (pyran C_2). MS : [M+H]$^+$ m/z 299 (100%). [Found : C, 76.29, H, 4.04, N, 14.32 $C_{19}H_{13}N_3O$ requires C, 76.25, H, 4.01, N, 14.04%].

4b : M.p. 278^0; IR (KBr): 3478, 3326 (NH_2), 3185, 3048, 2196 (CN), 1657, 1600, 1565, 1499, 1469, 1315, 1297, 1251, 1187, 1106, 1053. ^{1}H NMR (300 MHz, DMSO-d_6): 5.47 (s, 1H, pyran C_4), 7.21 (s, 2H, NH_2), 7.11 (d, 1H, ArH), 7.45-7.47 (m, 1H, ArH), 7.30-7.31 (m, 3H, ArH), 7.62 (dd, 1H, ArH), 7.65 (d, 1H, ArH), 8.35 (dd, 1H, ArH), 8.96 (dd, 1H, ArH). ^{13}C NMR (75 MHz, DMSO-d_6): 39.2 (pyran C_4), 56.21 (pyran C_3), 120.05 (CN), 121.19, 122.58, 124.19, 126.46, 126.49, 128.32, 128.44, 129.31, 130.27, 131.64, 132.69, 136.29, 138.13, 144.04, 150.71 (pyran C_6), 161.12 (pyran C_2). MS : [M+H]$^+$ m/z 334 (25%). [Found : C, 68.49, H, 3.68, N, 12.66 $C_{19}H_{12}ClN_3O$ requires C, 68.46, H, 3.60, N, 12.61%].

4c: M.p. 250^0 (Lit[14] m.p. 249-250^0) ; IR (KBr): 3425, 3244 (NH_2), 3139, 3060, 2191 (CN), 1657, 1629, 1597, 1489, 1469, 1372, 1316, 1290, 1247, 1195, 1111, 1056. ^{1}H NMR (300 MHz, DMSO-d_6): 5.02 (s, 1H, pyran H_4), 7.20 (s, 2H, NH_2), 7.22 (d, 1H, ArH), 7.39 (d, 2H, ArH), 7.30 (d, 2H, ArH), 7.61 (dd, 1H, ArH), 7.66 (d, 1H, ArH), 8.35 (dd, 1H, ArH), 8.95 (dd, 1H, ArH). ^{13}C NMR (75 MHz, DMSO-d_6): 42.12 (pyran C_4), 57.10 (pyran C_3), 120.34 (CN), 121.91, 122.59, 124.15, 127.10, 127.13, 128.35, 129.14, 129.98, 132.29, 136.35, 138.13, 143.73, 144.78, 150.72 (pyran C_6), 160.90 (pyran C_2). MS : [M+H]$^+$, m/z 334 (100%). [Found : C, 68.41, H, 3.66, N, 12.68 $C_{19}H_{12}ClN_3O$ requires C, 68.46, H, 3.60, N, 12.61%].

4d: M.p. 220; IR (KBr):3298 (NH_2), 3123, 2958, 2934, 2202 (CN), 1658, 1611, 1568, 1512, 1470, 1374, 1316, 1251, 1175, 1110, 1059. ^{1}H NMR (300 MHz, DMSO-d_6): 3.72 (s, 3H, OCH_3), 4.90 (s, 1H, pyran H_4), 7.09 (s, 2H, NH_2), 7.17 (d, 1H, ArH), 7.20 (d, 2H, ArH), 6.88 (d, 2H, ArH), 7.63 (dd, 1H, ArH), 7.61 (dd, 1H, ArH), 8.33 (dd, 1H, ArH), 8.94 (dd, 1H, ArH). ^{13}C NMR (75 MHz, DMSO-d_6): 41.2 (pyran C_4), 55.65 (pyran C_3), 57.84, 114.79 (CN), 120.49, 122.41, 122.50, 122.79, 123.91, 127.34, 128.21, 129.20, 136.27, 138.16, 138.24, 143.65, 150.58, 158.97 (pyran C_6), 160.74 (pyran C_2). MS [M]$^+$ m/z 329 (30%). [Found : C, 72.94, H, 4.55, N, 12.76 $C_{20}H_{15}N_3O_2$ requires C, 72.99, H, 4.59, N, 12.71%].

4e: M.p. 198^0 (Lit[15] m.p. 198-200^0); IR (KBr): 3497, 3369 (NH_2), 3185, 3048, 2194 (CN), 1660, 1609, 1532, 1503, 1473, 1412, 1347, 1297, 1191, 1108, 1027. ^{1}H NMR (300 MHz, DMSO-d_6): 5.27 (s, 1H, pyran H_4), 7.32 (s, 2H, NH_2), 7.27 (d, 1H, ArH), 7.75-7.77 (m, 2H, ArH), 8.11-8.16 (m, 2H, ArH), 7.63 (dd, 1H, ArH), 7.69 (d, 1H, ArH), 8.36 (dd, 1H, ArH), 8.97 (dd, 1H, ArH). ^{13}C NMR (75 MHz, DMSO-d_6): 41.2 (pyran C_4), 56.55 (pyran C_3), 120.17 (CN), 121.26, 122.51, 122.53, 122.71, 124.38, 127.01, 128.52, 130.83m 134.83, 136.36, 138.19, 143.96, 148.06, 148.82, 150.82 (pyran C_6), 161.17 (pyran C_2). MS : [M+H]$^+$ m/z 345 (70%). [Found : C, 66.30, H, 3.52, N, 16.34 $C_{19}H_{12}N_4O_3$ requires C, 66.37, H, 3.48, N, 16.27%].

4f: M.p. 201^0; IR (KBr): 3438, 3254 (NH_2), 3142. 2198 (CN), 1649, 1618, 1596, 1494, 1471, 1362, 1321, 1282, 1249, 1184, 1118, 1054. ^{1}H NMR (300 MHz, DMSO-d_6): 5.12 (s, 1H, pyran H_4), 7.14 (s, 2H, NH_2), 7.28 (d, 1H, ArH), 7.42 (d, 2H, ArH), 7.36 (d, 2H, ArH), 7.68 (dd, 1H, ArH), 7.62 (d, 1H, ArH), 8.41 (dd, 1H, ArH), 8.92 (dd, 1H, ArH). ^{13}C NMR (75 MHz, DMSO-d_6): 41.24 (pyran C_4), 54.32 (pyran C_3), 117.82 (CN), 122.42, 123.14, 124.81, 129.26, 129.46, 130.41, 131.22, 134.21, 136.49, 139.26,144.82, 146.21, 151.62 (pyran C_6), 161.20 (pyran C_2). MS: [M+H]$^+$ m/z 317 (100%). [Found : C, 71.98, H, 3.74, N, 13.30 $C_{19}H_{12}N_3OF$ requires C, 71.92, H, 3.78, N, 13.24%].

4g: M.p. 207^0; IR (KBr): 3268 (NH_2), 3142, 3012, 2964, 2216 (CN), 1642, 1621, 1572, 1536, 1482, 1386, 1324, 1272, 1186, 1124, 1072. ^{1}H NMR (300 MHz, DMSO-d_6): 2.62 (s, 3H, CH_3), 4.82 (s, 1H, pyran H_4), 7.14 (s, 2H, NH_2), 6.98 (d, 1H, ArH), 7.08 (d, 2H, ArH), 6.82 (d, 2H, ArH), 7.54 (dd, 1H, ArH), 7.68 (dd, 1H, ArH), 8.24 (dd, 1H, ArH), 8.79 (dd, 1H, ArH). ^{13}C NMR (75 MHz, DMSO-d_6): 25.62, 43.6 (pyran C_4), 54.12 (pyran C_3), 117.24 (CN), 123.62, 122.68, 122.76, 124.81, 128.21, 128.46, 129.20, 137.42, 139.61, 148.72, 152.14, 159.26 (pyran C_6), 162.14 (pyran C_2). MS : $[M]^+$ m/z 314 (60%). [Found : C, 76.92, H, 4.63, N, 12.98 $C_{20}H_{15}N_3O_2$ requires C, 76.67, H, 4.71, N, 13.41%].

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3235/2013