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NOTE

Synthesis of some new cyanopyrans and cyanopyridines and their biological activities

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Chalcones 1-aryl-3-*m*-chlorophenyl-2-propene-1-ones, 1a-j, underwent Michael addition on refluxing with malononitrile in the presence of pyridine and ammonium acetate in ethanol to give compounds 2-amino-3-cyano-4-(3′-chlorophenyl)-6-(4-phenyl)-pyran, 2a-j and 2-amino-3-cyano-4-(3′-chlorophenyl)-6-(4-phenyl)-pyridine, 3a-j, respectively. The newly synthesized compounds have been screened for their anticancer, antitubercular and antimicrobial activities.

Biological activities of several heterocyclic analogues of chalcones have been reported in the literature[1]. There is a considerable interest in the chemotherapeutic activity of pyridine and pyran nuclei bearing carbonitrile group[2]. Chalcones are used to synthesize 2-amino-3-cyanopyran/pyridine derivatives[157]. In the present study, we have followed this strategy for the synthesis of these compounds with the hope that they may possess different biological activities.

The chalcones **(1a-j)** were prepared from the reaction of benzaldehyde with different substituted aryl methyl ketones, in the presence of aqueous sodium hydroxide in the molar ratio (1 : 1). Condensation of chalcones **(1a-j)** with malononitrile in pyridine afforded corresponding pyrans **(2a-j)**. While chalcones **(1a-j)** were condensed with malononitrile and ammonium acetate in ethanol to give the corresponding pyridines **(3a-j)**.

IR spectrum of **(2a-j)** and **(3a-j)** was in well agreement to the assigned structure, showing the absence of sharp band of carbonyl group and appearance of the sharp bands in the region of 3250–3400 cm^{-1} due to $-NH_2$ group and in the region of 2200–2300 cm^{-1} due to -C≡N group.

Disappearance of ^1H NMR signals for -CH=CH- and appearance of signal for $-NH_2$ between δ 8 to 9.5 for structure **(2a-j)** and **(3a-j)** indicates cyclisation of **(1a-j)** to **(2a-j)** or **(3a-j)**.

The structures of the synthesized compounds were assigned on the basis of elemental analyses, IR, ^1H NMR and mass spectral data. The compounds were screened for their *in vitro* anticancer, antitubercular and antimicrobial activities.

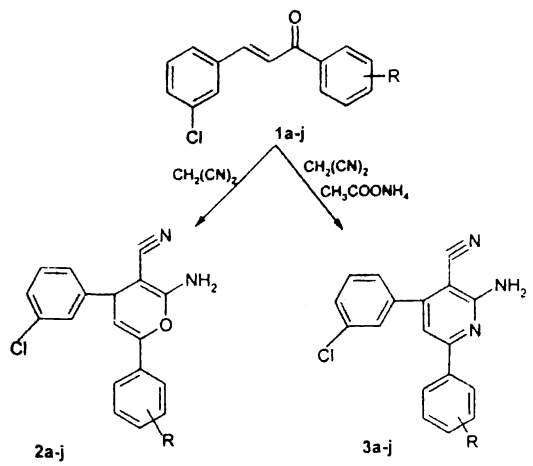
The anticancer screening of some selected compounds was carried out at National Cancer Institute, Department of Health and Human Service, Bethesda, U.S.A. The study is related with *in vitro* anticancer screen aimed at identifying agents having cell type specificity using batteries of cell lines derived from human solid tumors. At its primary anticancer assay, a 3-cell panel consisting of NCI-H 460 (Lung), MCF-7 (Breast) and SF-268 (CNS) has been used. A 48 h continuous drug exposure protocol is used, and a sulforhodamine B (SRB) protein assay is used to estimate cell viability or growth[4].

Comparing the known structure activity relationship, compounds **3e** and **3g** have been selected for the primary anticancer screening.

The antitubercular evaluation of the compounds was carried out at Tuberculosis Antimicrobial Acquisition Coordinating Facility (TAACF), U.S.A. Primary screening of the compounds for antitubercular activity has been conducted at minimum inhibition concentration 6.25μg/ml against *Mycobacterium tuberculosis* $H_{37}Rv$ in BACTEC 12B medium using the ALAMAR radiometric system. The antimycobacterial activity data were compared with standard drug Rifampin at 0.25 μg/ml concentration, which showed 98% inhibition. Compounds having 4-bromo, 4-methyl, 2-hydroxy, 4-methyl and 4-bromo showed higher activity than the others.

The antimicrobial activity was assayed by using the cup-plate agar diffusion method[5] by measuring the zone of inhibition in mm. All the compounds were screened *in vitro* for their antimicrobial activities against varieties of bacterial strains such as *E. coli, P. vulgaris, B. megaterium, S. aureus* and fungi *A. niger* at 40 μg/ml concentration. Standard drugs like amoxycillin, ampicillin, cipofloxacin, erythromycin and griseofulvin were used for the comparison purpose. It could

be observed that compounds **1e** (20), **1f** (19), **2h** (17), **3b** (21) and **3f** (18) were active against *E. coli.* Compounds **1c** (22), **2e** (19), **2i** (19), **3b** (22) and **3d** (20) were active against *P. vulgaris*. Compounds **1g** (19), **2f** (20), **3a** (19), **3d** (20) and **3g** (19) were active against *B. mega.* Compounds **1c** (19), **2b** (20), **2f** (20), **3a** (21) and **3h** (26) were active against *S. aureus.* The compounds **1g** (18), **2g** (20) and **3j** (17) displayed maximum activity against *A. niger.*



1-3a : R = H-
1-3b : R = 4-Br-
1-3c : R = 4-Cl-
1-3d : R = 2,4-$(Cl)_2$-
1-3e : R = 2-OH-
1-3f : R = 4-OH-
1-3g : R = 2-OH-5-CH_3-
1-3h : R = 4-OCH_3-
1-3i : R = 4-CH_3-
1-3j : R = 4-NO_2-

Scheme 1

Experimental

TLC was used to access the reactions and purity of the compounds synthesized. All m.ps. are uncorrected. IR spectra were recorded on Shimadzu FTIR-8400 instrument in KBr disc. ^1H NMR spectra were recorded on Bruker AC-300 MHz FT NMR using TMS as an internal standard, chemical shift in δ ppm. Mass spectra were recorded on Jeol D-300 spectrometer. All the compounds gave satisfactory elemental analyses.

1-(4-Methoxy phenyl)-3-(3′-chlorophenyl)-2-propen-1-one (**1h**) :

An ethanolic solution of 3-chlorobenzaldehyde (1.41g, 0.01 mol) and 4-methoxy acetophenone (1.50 g, 0.01 mol) in presence of catalytic amount of 30% KOH was stirred for 24 h at RT. The resulting solution was then poured over crushed ice, isolated and crystallized from ethanol to give **1h**, (88%), m.p. 95° (Found : C, 70.56; H, 4.70. Requires for $C_{16}H_{13}O_2Cl$: C, 70.59; H, 4.78%); ν_{max} 3044 (CH=CH, vinyl), 2996 (CH_3, sym.), 1676 (C=O), 1259 cm^{-1} (C–O–C); δ 3.89 (3H, s, OCH_3), 7.26 (1H, d, CH=CH), 7.73 (1H, d, CH=CH), 6.97 to 8.04 (8H, m, Ar-*H*) ppm; *m/z* 272.5.

Similarly other compounds : **1a**, m.p. 70°; **b**, 70°; **c**, 100°; **d**, 108°; **e**, 120°; **f**, 71°; **g**, 135°; **h**, 95°; **i**, 80°; **j**, 124° (yields 62–88%) were prepared.

Preparation of 2-amino-3-cyano-4-(3′-chlorophenyl)-6-(4-methoxy phenyl)-pyran (**2h**) :

A mixture of **1h** (2.72 g, 0.01 mol) and malononitrile (0.66 g, 0.01 mol) dissolved in pyridine (20 ml) was heated under reflux for 10 h in oil bath. The reaction mixture was cooled and poured over crushed ice. The product was isolated and crystallized from ethanol to give **2h**, (76%), m.p. 270° (Found : C, 67.45; H, 4.42; N, 8.26. Requires for $C_{19}H_{15}N_2OCl$: C, 67.45; H, 4.43; N, 8.28%); ν_{max} 3284 (N–H), 2219 (C≡N), 1613 (C=C), 1254 cm^{-1} (C–O–C); δ 3.90 (3H, s, OCH_3), 4.67 (1H, d, CH-pyran ring), 7.01 to 7.96 (9H, m, Ar-H + py-H), 8.58 (2H, s, NH_2) ppm; *m/z* 338.

Similarly other compounds : **2a**, m.p. 300°; **b**, 210°; **c**, 273°; **d**, 192°; **e**, 280°; **f**, 216°; **g**, 190°; **h**, 270°; **i**, 190°; **j**, 198° (yields 58–78%) were prepared.

Preparation of 2-amino-3-cyano-4-(3′-chlorophenyl)-6-(4-methoxy phenyl)-pyridine (**3h**) :

A mixture of **1h** (2.72 g, 0.01 mol), malononitrile (0.66 g, 0.01 mol), ammonium acetate (6.61 g, 0.08 mol) dissolved in ethanol (20 ml), was heated under reflux for 12 h. The product was isolated and recrystallized from ethanol, **3h** (87%), m.p. 150° (Found : C, 68.24; H, 4.15; N, 12.50. Requires for $C_{19}H_{14}N_3OCl$: C, 68.26; H, 4.19; N, 12.53%); ν_{max} 3219 (N–H), 2208 (C≡N), 1602 cm^{-1} (C=C pyran); δ 3.88 (3H, s, OCH_3), 7.79 (1H, s, CH-pyr.), 6.98 to 8.02 (8H, m, Ar-H), 8.64 (2H, s, NH_2) ppm; *m/z* 335.

Similarly other compounds : **3a**, m.p. 180°; **b**, 202°; **c**, 265°; **d**, 185°; **e**, 268°; **f**, 197°; **g**, 215°; **h**, 150°; **i**. 160°; **j**, 280° (yileds 55–69%) were prepared.

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