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SYNTHESES, ANTIBACTERIAL AND ANTIFUNGAL ACTIVITIES OF 2-ARYL-4-QUINOLINE- CARBOXAMIDE DERIVATIVES

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Abstract

Reaction of aryl methyl ketone with isatin in the presence of a base afforded 2-arylquinoline-4-carboxylic acid (**3**). Reaction of diazomethane with compound **3** yielded the ester **4**. Compound **5** was prepared from the reaction of N, N'-dialkylethyl (or propyl) amine with **4**. Addition of hydrazine hydrate to compound **4a** gave 2- (2-pyridyl) quinoline-4-carboxylic acid hydrazide (**6**). Reaction of 1-methyl-5-nitroimidazole-2-carboxaldehyde (**7**) with **6** in ethanol afforded compound 8 in good yield. The antibacterial and antifungal activities of compounds **5**,**6** and **8** were determined.

Introduction

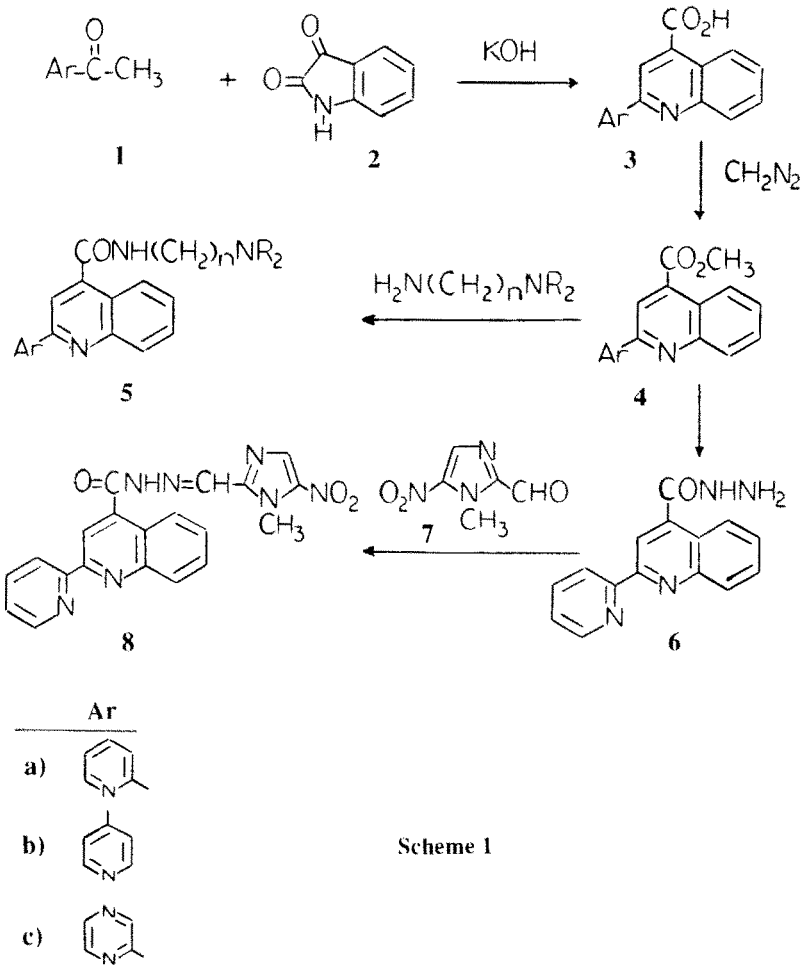
Pyridine carboxyhydrazide (Isoniazid) and pyrazinamide have antituberculous activity [1,2]. In addition, phenylquinoline-8-carboxamide and 4-quinolinecarboxamide derivatives have antitumor and tranquilizer activity [3,4]. Recently, the syntheses of 2(1-methyl-5-nitro-2-imidazolyl) quinolines as possible effective drugs against tropical diseases have been reported [5]. In the present work, the syntheses, antibacterial and antifungal activities of 2-(pyridyl)-4-quinoline- carboxamides and 2-(pyrazinyl)-4-quinolinecarboxamide derivatives are reported.

Results and Discussion

The most common approach employed to synthesize substituted quinolines is the condensation of lithium aryl with 2-chloroquinoline, condensation of an aldehyde with aniline and subsequent condensation cyclization of the intermediate with propiolic acid or maleic acid and paraldehyde [6] and the condensation-cyclization of an aniline with α,β-unsaturated-aldehyde (Skraup synthesis) [7]. In our case, these reactions either failed or afforded low yield. However, we could synthesize the desired compounds according to Pfitzinger reaction of a ketone with isatin (8) (See Scheme 1).

Reaction of 2-acetylpyridine (**1a**) with isatin (**2**) in the presence of potassium hydroxide afforded 2- (2-pyridyl) quinoline-4-carboxylic acid (3a). Reaction of diazomethane with the latter gave methyl 2-(2-pyridyl) quinoline-4-carboxylate (**4a**). Compound **5a** was prepared from the reaction of N, N' -dialkylethyl (or propyl) amine with **4a**. Addition of hydrazine hydrate to compound **4a** yielded 2-(2-pyridyl) quinoline -4-carboxylic acid hydrazide (**6**). Reaction of 1-methyl-5-nitroimidazole-2-carboxaldehyde (**7**) [9] with **6** in ethanol gave compound **8**. Other compounds **3** to **6** were prepared similarly. The antibacterial and antifungal activities of compounds **5** ,**6** and **8** were determined. None of the compounds showed significant antibacterial and antifungal activities.

Keywords: Quinoline derivatives; 2-Aryl-4-quinoline derivatives; Syntheses of quinoline derivatives; Antibac. and Antifung. of quinoline derivatives



Scheme 1

Experimental Section

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. The IR spectra were obtained using a Perkin-Elmer Model 267 spectrograph (potassium bromide disks). The NMR spectra were recorded on a Bruker FT-80 spectrometer and chemical shifts (δ) are in ppm relative to internal tetramethylsilane. Mass spectra were run on a Varian Model MAT MS-311 spectrometer at 70 ev.

2- (2-pyridyl) quinoline-4-carboxylic acid (3a)

A mixture of 2-acetylpyridine (6.05 g, 0.05 mol), isatin (7.35 g, 0.05 mol), potassium hydroxide (12.88 g, 0.23 mol) and 50% ethanol (65 ml) was refluxed for 2 hrs. Ethanol (50%, 65 ml) was added and the mixture was acidified with acetic acid. The precipitate was filtered and crystallized from dimethylformamide to give 11.2 g (92%) of **3a**; mp 304-306°C. IR: ν 3100 (aromatic), 3080 (aromatic), 1700 cm^{-1} (C=0). MS: m/z (%) 250, (M^+, 100), 222 (11), 207(99), 206(88), 58(14) and 30(45).

Anal. Calcd. for $C_{15}H_{10}N_2O_2$: C, 72.00; H, 4.00; N, 11.20.

Found: C, 72. 15; H, 3.86; N, 11.06.

2-(4-pyridyl) quinoline-4-carboxylic acid (3b)

Starting from 4-acetylpyridine, compound **3b** was prepared similar to **3a** in 70% yield; mp 317-319°C; IR: ν 2500 (OH of acid), 3080 (aromatic), 1720 cm^{-1} (C = 0).

Anal. Calcd. for $C_{15}H_{10}N_2O_2$: C, 72.00; H, 4.00; N, 11.20.

Found: C, 71.91; H, 4.16; N, 11.31.

2-(2-pyrazinyl) quinoline-4-carboxylic acid (3c)

Starting from 2-acetylpyrazine [10] compound **3c** was prepared similar to **3a** in 50% yield; mp 313-315°C. IR: ν 3060 (aromatic), 1710 cm^{-1} (C=0). MS: m/z (%) 251 (M^+, 100), 223(14), 207(97), 200(95), 174(57), 154(18), 129(20),

102(19) and 30(36).

Anal. Calcd. for $C_{14}H_9N_3O_2$: C, 66.93; H, 3.59; N, 16.73.

Found: C, 66.81; H, 3.72; N, 16.85.

Methyl 2-(2-pyridyl) quinoline-4-carboxylate (4a)

A suspension of compound **3a** (5 g, 0.02 mol) with excess diazomethane in ether (250 ml) was stirred overnight. Diazomethane in ether (250 ml) was added and stirring was continued until all the acid was converted to ester. The ether was evaporated under reduced pressure and the residue was crystallized from methanol to give 4.2 g (80%) of **4a**, mp 111-112°C. IR: ν 3020 (aromatic), 1725 cm^{-1} (C = 0): ^{1}H-NMR ($CDCl_3$): 9.10 (d, 1H, H_6 of pyridine), 8.77 (m, 4H, aromatic), 7.80 (m, 4H, aromatic) and 4.10 ppm (s, 3H, CH_3O). MS: m/z (%) 264 (M^+, 98), 249 (10), 233 (32), 207 (91), 206 (100), 205 (96), 179 (16), 152(13) and 30(17).

Anal. Calcd. for $C_{16}H_{12}N_2O_2$: C, 72.73; H, 4.55; N, 10.61.

Found: C, 72.61; H, 4.67; N, 10.42.

Methyl 2-(4-pyridyl) quinoline-4-carboxylate (4b)

This compound was prepared similar to **4a** in 75% yield; mp 145-146°C. IR: ν 3080 (aromatic), 1715 cm^{-1} (C = 0). ^{1}H-NMR ($CDCl_3$): 8.76 (d, 2H, $H_{2,6}$ of pyridine), 8.28 (m, 3H, aromatic) 7.77 (m, 4H, aromatic) and 4.17 ppm (s, 3H, CH_3O).

Anal. Calcd. for $C_{16}H_{12}N_2O_2$: C, 72.73; H, 4.55; N, 10.61.

Found: C, 72.58; H, 4.39; N, 10.80.

Methyl 2-(2-pyrazinyl) quinoline-4-carboxylate (4c)

This compound was prepared similar to **4a** in 70% yield; mp 143-144°C; IR: ν 3050 (aromatic), 1725 cm^{-1} (C=0). ^{1}H-NMR ($CDCl_3$): 9.00 (s, 1H, H_3 of pyrazine), 8.67 (m, 2H, $H_{5,6}$ of pyrazine), 8.0 (m, 5H, aromatic) and 4.10 ppm (s, 3H, CH_3). MS: m/z (%) 265 (M^+, 84), 234 (17), 207(100), 206(71), 188(22), 154(23), 129(25), 102(35) and 78(17).

Anal. Calcd. for $C_{15}H_{11}N_3O_2$: C, 47.92: H, 4.15; N, 15.85.

Found: C, 47.79; H, 4.03; N, 15.79.

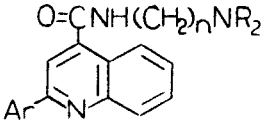
N-[3-(dimethylamino) propyl]-2-(2-pyridyl) quinoline-4-carboxamide (5a)

General Example: A solution of compound **4a** (2.64 g, 0.01 mol) and 3-dimethyl-aminopropylamine (6 ml) in THF (40 ml) was refluxed. The progress of the reaction was followed by TLC. After the reaction was complete, the solvent was evaporated and the residue was added to water. The precipitate was filtered and crystallized from acetone to give 2.17 g (65%) of **5a**, mp 133-134°C; IR: ν 3290 (NH), 3060 (aromatic), 1640 cm^{-1} (C = 0). ^{1}H-NMR: 8.63 (d, 1H, H_6 of pyridine), 8.23 (m, 4H, aromatic), 7.84 (m, 4H, aromatic), 3.61 (m, 2H, CH_2-NHCO), 2.5 (t, 2H, CH_2N), 2.14 (s, 6H, $N(CH_3)_2$) and 1.81 ppm (m, 2H, CH_2). Anal. See Table 1.

2-(2-pyridyl) quinoline-4-carboxylic acid hydrazide (6)

To a stirred solution of compound **4a** (2.64 g, 0.01 mol)

Table 1



Compound No.	n	Ar	R	m.p.°C (a)	yield(C) (%)
$5a_1$	3	2-pyridyl	CH_3	133-134	65
$5a_2$	3	2-pyridyl	C_2H_5	103-104(b)	60
5b	3	4-pyridyl	CH_3	117-118	50
$5c_1$	2	2-pyrazinyl	C_2H_5	149-150	60
$5c_2$	3	2-pyrazinyl	CH_3	165-166	55
$5c_3$	3	2-pyrazinyl	C_2H_5	128-129	50

a) Unless otherwise mentioned the compound was crystallized from acetone.
b) This compound was crystallized from petroleum ether.
c) All compounds gave satisfactory C, H, N analyses.

in methanol (15 ml) hydrazine hydrate (20 ml) was added. After one hour the precipitate was filtered and crystallized from methanol to give 2.38 g (90%) of **6** mp 226-227°C; UV (ethanol): λ_{max} 275 (log ε = 4.76), 254 nm (log ε = 4.03). IR: ν 3278 (NH), 3240 (NH), 3060 (aromatic), 1660 cm^{-1} (C = 0).

Anal. Calcd. for $C_{15}H_{12}N_4O$: C, 56.80; H, 4.55; N, 21.21.

Found: C, 56.93; H, 4.67; N, 21.35.

1-methyl-5-nitroimidazole-2-carboxaldehyde 2-(2-pyridyl) quinoline-4-carboxylic acid hydrazone (8)

To a solution of compound **6** (2.64 g, 0.01 mole) in ethanol (50 ml) a solution of 1-methyl-5-nitroimidazole-2-carboxaldehyde (1.55 g, 0.01 mole) in ethanol (20 ml) was added. The mixture was heated in a water bath until the precipitate appeared. After cooling, the precipitate was filtered to give 2.4 g (60%) of **8**; mp 279-281°C; UV (ethanol): λ_{max} 339 (log ε = 4.71), 279 (log ε = 4.73) and 252 nm (log ε = 4.91). IR: ν 3220 (NH), 3060 (aromatic), 1660 cm^{-1} (C = 0).

Antibacterial and Antifungal Assay:

All compounds were tested against *Bacillus subtilis* (ATCC 6633), *Staphylococcus aureus* (ATCC 6538 p), *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Salmonella paratyphi B*. *Candida albicans*, *Aspergillus niger*, *Penicillium sp*, *Microsporum canis and Microsporum gypseum*.

Antibacterial Assay:

Compounds **5** ,**6** and **8** were dissolved in methanol. They were diluted to 1 mg/1 ml concentration. To a standard paper disk of 6 mm diameter, the latter solution was added until the desired amount of compound was absorbed by the disk (10 to 30 μg). The disks were placed on inoculated assay medium surface. Furazolidone was used for comparison. None of the compounds showed significant antibacterial and antifungal activities.

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