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Ferric Chloride-catalyzed Synthesis of 2-Oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate Derivatives and Their Biological Evaluation[1]

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Abstract—A new methodology has been developed for the synthesis of novel 2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylates from 2-aminonicotinaldehyde, Meldrum's acid, and the corresponding alcohols in the presence of anhydrous iron(III) chloride as a cheap and readily available catalyst. The structure of the synthesized compounds was established by IR, ^{1}H NMR, and mass spectral data and elemental analyses. All the synthesized compounds were evaluated for their *in vitro* antibacterial and antifungal activity, and the activity of some derivatives was comparable with the activity of Ciprofloxacin and Nystatin used as reference drugs.

Keywords: 2-aminonicotinaldehyde, Meldrum's acid, anhydrous iron(III) chloride, antimicrobial activity.

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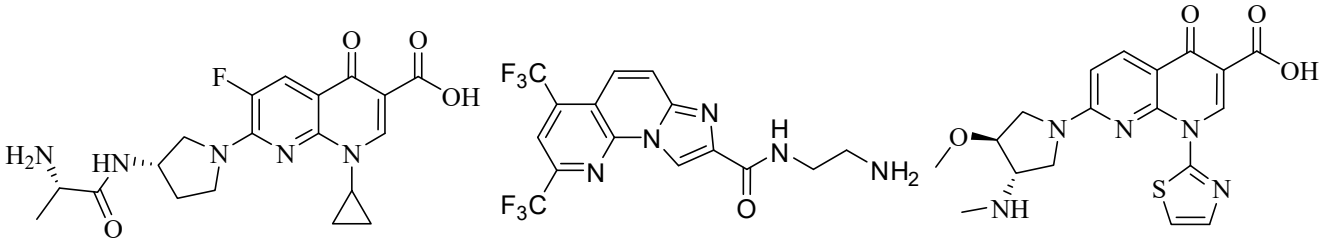
1,8-Naphthyridine derivatives constitute an important class of heterocyclic compounds possessing diverse biological properties, in particular antibacterial [1], antimycobacterial [2], antitumor [3], anti-inflammatory [4], analgesic [5], antiplatelet [6], gastric antisecretory [7], local anesthetic [8], anticonvulsant [9], and antihypertensive activity [10, 11]. Some of biologically potent 1,8-naphthyridines are shown in Scheme 1.

Multicomponent coupling reactions (MCRs) provide an efficient synthetic tool for the construction of chemically and biologically active compounds. Their distinctive advantages include generation of highly diverse and complex products from readily available substrates in a single synthetic step without isolation of intermediates, maximum selectivity in minimal time, high atom economy, and high purity of products with excellent yields [12–14]. In view of pharmacological importance of 1,8-naphthyridines, we have developed a novel methodology for the synthesis of these compounds from 2-aminonicotinaldehyde (**1**), Meldrum's acid (**2**), and alcohol **3a**–**3k** in the presence of anhydrous ferric chloride and obtained the corresponding 2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylates **4a**–**4k** with good yields. To the best of our knowledge, there is no method reported for the construction of these compounds using anhydrous ferric chloride as a catalyst.

Scheme 2 illustrates the formation of 2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylates **4a**–**4k** catalyzed by anhydrous ferric chloride. Initially, 2-aminonicotinaldehyde (**1**), Meldrum's acid (**2**), and ethanol were

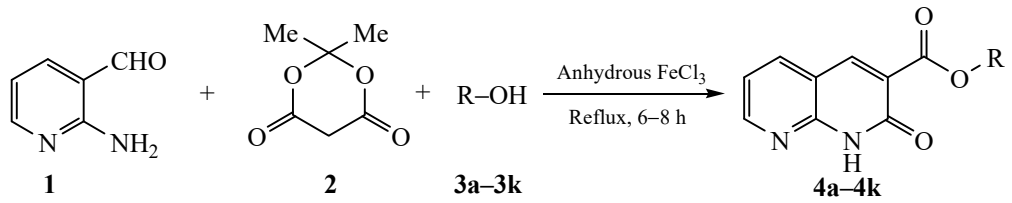
Scheme 1.



Antibacterial agent | Potent anti-HCV agent | Anticancer agent

[1] The text was submitted by the authors in English.

Scheme 2.



1 **2** **3a–3k** **4a–4k**

3, **4**, R = Et (**a**), Me (**b**), *i*-Pr (**c**), *t*-Bu (**d**), Pr (**e**), Bu (**f**), C_5H_{11} (**g**), *i*-Bu (**h**), $CH{\equiv}CCH_2$ (**i**), furan-2-ylmethyl (**j**), $PhCH_2$ (**k**).

chosen as starting materials for the model reaction where the alcohol acted as both reactant and solvent. The reaction in the absence of a catalyst failed to provide the desired product. When iron(III) chloride was used as catalyst, the yield of **4a** was 60–80%. Under these conditions (0.05 mmol of $FeCl_3$, 0.01 mmol of 2-aminonicotinaldehyde, 0.01 mmol of Meldrum's acid, and 3 mL of alcohol **3a**–**3k**; reflux), we have successfully synthesized a series of 2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylates **4a**–**4k** (Table 1).

All newly synthesized compounds were screened for their *in vitro* antibacterial activity against *Streptococcus pyogenes* (Gram positive) and *Escherichia coli* (Gram positive) using Ciprofloxacin as reference drug. The activity was evaluated by the agar well diffusion technique according to [15]. The results are collected in Table 2. Compounds **4b**, **4i**, and **4j** showed a good activity comparable with the activity of Ciprofloxacin. Compounds **4a**–**4k** were also screened for antifungal activity against *Saccharomyces cerevisiae* and *Aspergillus terreus* by the agar well diffusion technique according to [16] using Nystain as reference drug. All these compounds showed inhibitory activity against the tested pathogenic fungal strains; among them, compounds **4i**, **4b**, and **4j** showed the highest antifungal activity (Table 2).

In summary, we have synthesized a series of novel 2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylates in good yields by the conventional method using anhydrous ferric chloride as catalyst. Some of the synthesized compounds showed high antibacterial and antifungal activity *in vitro*, which was comparable to the activity of Ciprofloxacin and Nystatin used as reference drugs.

EXPERIMENTAL

All the starting materials were purchased from commercial sources and used as received; the solvents were purified and dried by standard procedures. Technical grade solvents for chromatographic separations were distilled prior to use. Column chromatography was performed using 100–200 mesh silica gel according to standard techniques. The melting points were determined in open capillary tubes with a Büchi melting point apparatus and are uncorrected. The ^1H NMR spectra were recorded on a Bruker 400 MHz spectrometer using DMSO-d_6 as solvent. The mass spectra (electrospray ionization) were obtained with an Agilent 6120 single quadrapole time-of-flight mass spectrometer. The IR spectra were recorded in KBr with a Bruker Tensor 27 spectrometer. The elemental analyses were obtained using a Carlo Erba EA 1108 analyzer.

General procedure for the synthesis of 2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylates 4a–4k. Anhydrous $FeCl_3$ (0.05 mmol) was added to a stirred solution of 2-aminonicotinaldehyde (**1**, 0.01 mmol) and Meldrum's acid (**2**, 0.01 mmol) in alcohol **3a**–**3k** (3 mL). The mixture was heated on an oil bath at

Table 1. Synthesis of 2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylates **4a**–**4k** in the presence of anhydrous $FeCl_3$

Compound no.	Reaction time, h	Yield,[a] %	mp, °C
4a	7.0	76	107
4b	8.0	65	99
4c	6.0	80	121
4d	6.5	73	138
4e	7.0	67	118
4f	7.0	71	133
4g	7.5	56	141
4h	7.5	72	134
4i	8.0	65	128
4j	6.0	59	139
4k	7.5	64	148

[a] After isolation and purification.

Table 2. Antibacterial and antifungal activities (inhibition zone diameter, mm) of compounds **4a**–**4k** at 100 μg/disk at three different concentrations (10, 20, and 30 μg/mL)[a]

Compound no.	Bacterial strains						Fungal strains					
	Streptococcus pyogenes			*Escherichia coli*			*Saccharomyces cerevisiae*			*Aspergillus terreus*		
	10	20	30	10	20	30	10	20	30	10	20	30
4a	6	13	24	5	11	19	7	12	19	5	11	21
4b	**8**	**17**	**27**	**7**	**18**	**26**	**8**	**17**	**26**	**8**	**16**	**26**
4c	6	11	21	5	10	19	7	12	21	6	13	22
4d	6	14	23	7	13	21	6	11	22	7	15	21
4e	5	10	19	4	9	17	5	13	20	7	13	19
4f	4	11	21	5	10	18	6	12	19	6	10	16
4g	5	10	19	4	11	21	6	11	20	5	12	19
4h	7	14	23	6	13	22	5	14	22	4	11	15
4i	**9**	**18**	**28**	**8**	**19**	**27**	**8**	**18**	**27**	**9**	**17**	**27**
4j	**8**	**16**	**26**	**7**	**17**	**25**	**7**	**17**	**25**	**8**	**16**	**25**
4k	7	13	19	5	11	17	6	15	19	5	9	17
Ciprofloxacin	10	18	30	10	19	29	–	–	–	–	–	–
Nystatin	–	–	–	–	–	–	9	19	30	10	19	29

[a] The bold values indicate the compounds of the highest antimicrobial activity.

60–80°C for 6-8 h. The mixture was then cooled down to room temperature, and excess alcohol was removed under reduced pressure. The residue was purified by column chromatography on silica gel with ethyl acetate and petroleum ether (1 : 6, v/v) as eluent. The yields and melting points of compounds **4a**–**4k** are given in Table 1.

Ethyl 2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate (4a). Light brown solid. IR spectrum, ν, cm^{-1}: 3396, 1741, 1647, 1616, 1224. ^1H NMR spectrum, δ, ppm: 1.20 m (3H), 4.11 m (2H), 7.51 m (1H), 8.53 d (1H, J = 8.5 Hz), 8.79 s (1H), 9.0 d (1H, J = 6.9 Hz), 13.57 s (1H). Mass spectrum: m/z 219.1 $[M + H]^+$. Found, %: C 60.55; H 4.62; N 12.84. $C_{11}H_{10}N_2O_3$. Calculated, %: C 60.59; H 4.73; N 12.89.

Methyl 2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate (4b). Yellow solid. IR spectrum, ν, cm^{-1}: 3332, 1720, 1651, 1618, 1217. ^1H NMR spectrum, δ, ppm: 4.07 s (3H), 7.56 m (1H), 8.42 d (1H, J = 6.5 Hz), 8.61 s (1H), 8.99 d (1H, J = 6.9 Hz), 13.49 s (1H). Mass spectrum: m/z 205.07 $[M + H]^+$. Found, %: C 58.82; H 3.95; N 13.72. $C_{10}H_8N_2O_3$. Calculated, %: C 58.93; H 3.97; N 13.95.

Ppropan-2-yl 2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate (4c). Light brown solid. IR spectrum, ν, cm^{-1}: 3400, 1720, 1649, 1602, 1224. ^1H NMR spectrum, δ, ppm: 1.17 d (6H, J = 7.3 Hz), 4.17 m (1H), 7.49 m (1H), 8.53 d (1H, J = 6.5 Hz), 8.86 s (1H), 9.10 d (1H, J = 7.3 Hz), 13.62 s (1H). Mass spectrum: m/z 233.0 $[M + H]^+$. Found, %: C 62.06; H 5.21; N 12.06. $C_{12}H_{12}N_2O_3$. Calculated, %: C 62.43; H 5.29; N 12.14.

***t*-Butyl 2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate (4d).** Yellow solid. IR spectrum, ν, cm^{-1}: 3320, 1751, 1681, 1651, 1210. ^1H NMR spectrum, δ, ppm: 1.08 s (9H), 7.50 m (1H), 8.51 d (1H, J = 6.9 Hz), 8.79 s (1H), 8.99 d (1H, J = 7.5 Hz), 13.56 s (1H). Mass spectrum, m/z 247.00 $[M + H]^+$. Found, %: C 63.54; H 5.56; N 11.23. $C_{13}H_{14}N_2O_3$. Calculated, %: C 63.86; H 5.73; N 11.46.

Propyl 2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate (4e). Yellow solid. IR spectrum, ν, cm^{-1}: 3400, 1739, 1649, 1616, 1224. ^1H NMR spectrum, δ, ppm: 1.24 m (3H), 1.82 m (2H), 3.34 m (2H), 7.49 m (1H), 8.50 d (1H, J = 6.6 Hz), 8.79 s (1H), 8.99 d (1H, J = 6.9 Hz), 13.55 s (1H). Mass spectrum: m/z 233.10 $[M + H]^+$. Found, %: C 62.36; H 5.27; N 11.06. $C_{12}H_{12}N_2O_3$. Calculated, %: C 62.12; H 5.39; N 11.87.

Butyl 2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate (4f). Yellow solid. IR spectrum, ν, cm^{-1}: 3402, 1735, 1681, 1647, 1080. ^1H NMR spectrum, δ, ppm: 0.87 m (3H), 1.33 m (2H), 1.53 m (2H), 4.07 m (2H), 7.48 m (1H), 8.50 d (1H, J = 6.4 Hz), 8.78 s

(1H), 8.99 d (1H, J = 8.1 Hz), 13.56 s (1H). Mass spectrum: m/z 247.0 $[M + H]^+$. Found, %: C 62.96; H 5.73; N 11.28. $C_{13}H_{14}N_2O_3$. Calculated, %: C 63.10; H 5.77; N 11.44.

Pentyl 2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate (4g). Light yellow solid. IR spectrum, ν, cm^{-1}: 3377, 1739, 1649, 1616, 1224. ^1H NMR spectrum, δ, ppm: 0.93 m (3H), 1.37 m (2H), 1.37 m (2H), 1.53 m (2H), 4.07 m (2H), 7.48 m (1H), 8.50 d (1H, J = 7.3 Hz), 8.72 s (1H), 8.99 d (1H, J = 7.2 Hz), 13.45 s (1H). Mass spectrum: m/z 261 $[M + H]^+$. Found, %: C 64.56; H 6.13; N 10.94. $C_{14}H_{16}N_2O_3$. Calculated, %: C 64.80; H 6.21; N 10.78.

2-Methylpropyl 2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate (4h). Yellow solid. IR spectrum, ν, cm^{-1}: 3404, 1739, 1681, 1651, 1610. ^1H NMR spectrum, δ, ppm: 0.87 d (6H, J = 7.3 Hz), 1.53 m (1H), 4.12 d (2H, J = 9.6 Hz), 7.35 m (1H), 8.56 d (1H, J = 7.9 Hz), 8.82 s (1H), 9.00 d (1H, J = 6.4 Hz), 13.53 s (1H). Mass spectrum: m/z 247.80 $[M + H]^+$. Found, %: C 63.40; H 5.73; N 11.38. $C_{13}H_{14}N_2O_3$. Calculated, %: C 63.66; H 5.85; N 11.73.

Prop-2-yn-1-yl 2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate (4i). Light brown solid. IR spectrum, ν, cm^{-1}: 3232, 1739, 1651, 1616. ^1H NMR spectrum, δ, ppm: 3.13 s (1H), 4.23 s (2H), 6.99 m (1H), 8.34 d (1H, J = 7.5 Hz), 8.58 s (1H), 9.10 d (1H, J = 7.5 Hz), 12.94 s (1H). Mass spectrum: m/z 229.1 $[M + H]^+$. Found, %: C 63.16; H 3.53; N 12.28. $C_{12}H_8N_2O_3$. Calculated, %: C 63.42; H 3.87; N 12.52.

Furan-2-ylmethyl 2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate (4j). Black solid. IR spectrum, ν, cm^{-1}: 3224, 1740, 1680, 1135. ^1H NMR spectrum, δ, ppm: 4.37 s (2H), 6.29 m (1H), 6.37 d (1H, J =3.4 Hz), 7.13 m (1H), 7.82 d (1H, J = 6.9 Hz), 7.86 d (1H, J = 3.6 Hz), 8.48 s (1H), 8.79 d (1H, J = 6.4 Hz), 13.46 s (1H). Mass spectrum: m/z 271.06 $[M + H]^+$. Found, %: C 62.32; H 3.69; N 10.43. $C_{14}H_{10}N_2O_4$. Calculated, %: C 62.74; H 3.69; N 10.33.

Benzyl 2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate (4k). Brown solid. IR spectrum, ν, cm^{-1}: 3342, 1739, 1651, 1616, 1095. ^1H NMR spectrum, δ, ppm: 3.87 s (2H), 7.61–7.27 m (5H), 7.34 m (1H), 8.52 d (1H, J = 7.3 Hz), 8.78 s (1H), 9.17 d (1H, J = 6.1 Hz), 13.43 s (1H). Mass spectrum: m/z 280.04 $[M + H]^+$. Found, %: C 68.56; H 4.32; N 9.99. $C_{16}H_{12}N_2O_3$. Calculated, %: C 68.29; H 4.75; N 10.42.

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