Regioselective Synthesis of Pentacyclic Polyheterocycles: Sequential [3,3] Sigmatropic Rearrangement of 4-(4'-Aryloxybut-2'-ynyloxy)-1-phenyl-1,8-naphthyridin-2(1*H*)-ones

Krishna C. Majumdar* and Rafique-ul-Islam

Department of Chemistry, University of Kalyani, Kalyani 741235, W.B. India.
E-mail: kcm_ku@yahoo.co.in

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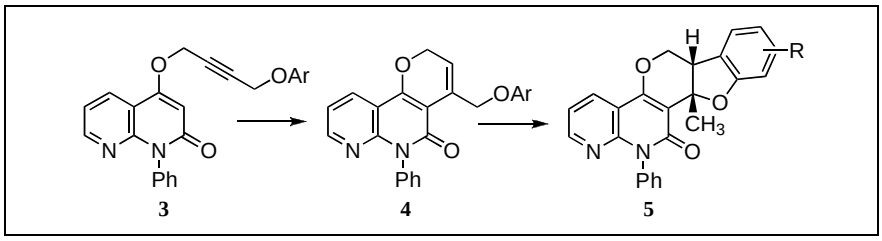

A number of 4-aryloxymethyl-6-phenyl-2*H*-pyrano[3,2-*c*][1,8]naphthyridin-5(6*H*)-ones (**4a-f**) are regioselectively synthesized in 72-78% yield by the Claisen rearrangement of 4-(4'-aryloxybut-2'-ynyloxy)-1-phenyl-1,8-naphthyridin-2(1*H*)-ones (**3a-f**) in refluxing chlorobenzene for 4-6 h. These products are then subjected to a second Claisen rearrangement catalyzed by anhydrous $AlCl_3$ at room temperature for 2 h to give hitherto unreported pentacyclic heterocycles (**5a-f**) in 78-85% yield.

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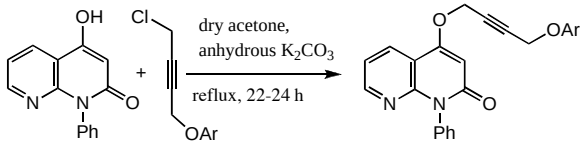
INTRODUCTION

1,8-Naphthyridin-2(1*H*)-ones and their derivatives are known to possess anti-inflammatory, anti-allergic, potent antisecretary, antitumor, broncodilator properties [1-3]. 4-Hydroxy-1-phenyl-1,8-naphthyridin-2(1*H*)-one and its derivatives have been used as antiallergic agent [4]. 2-Oxo-1,8-naphthyridin-3-carboxylic acid derivatives possess potent gastric antisecretary properties and anti-inflammatory activities [5,6]. A series of novel imidazo-[4,5-*c*][1,8]naphthyridin-4(5*H*)-ones exhibited potent bronchodilator activity [7]. Earlier, we reported the sequential [3,3] sigmatropic rearrangement of suitably substituted but-2-ynes to give interesting results [8]. Few pyrano[3,2-*c*][1,8]naphthyridin-5-one derivatives possess antiallergic, antiinflammatory and cytoprotective activity [9]. In view of the medicinal importance of 1,8-naphthyridinone and its derivatives, this prompted us to undertake a study to synthesize a number of polyheterocycles derived from 4-hydroxy-1-phenyl-1,8-naphthyridin-2(1*H*)-one by the application of Claisen rearrangement of 4-(4'-aryloxybut-2'-ynyl-1-yloxy)-1-phenyl-1,8-naphthyridin-2(1*H*)-ones. These substrates are chosen as they may provide additional scope for further [3,3] sigmatropic rearrangement to give polyheterocycles. They are also unique for comparing the relative ease of [3,3] sigmatropic rearrangement of aryloxy-propynyl moieties with those of naphthyridinyloxy-propynyl moieties suitably tailored in the same molecule. Here, we report the result of this investigation.

RESULTS AND DISCUSSION

In our present study, the starting materials 4-(4'-aryloxybut-2'-ynyloxy)-1-phenyl-1,8-naphthyridin-2-ones (**3a-f**) were synthesized in 50-55% yield by the reaction of 4-hydroxy-1-phenyl-1,8-naphthyridin-2(1*H*)-one (**1**) with different 1-aryloxy-4-chlorobut-2-ynes (**2a-f**) in refluxing dry acetone in the presence of anhydrous potassium carbonate. Compound (**1**) was prepared as described by Sherlock *et al.* [4]. Compounds **3(a-f)** were characterized from their elemental analyses and spectroscopic data (Scheme 1).

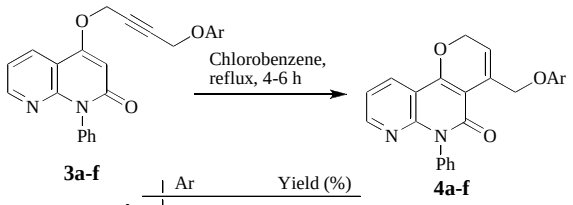
Scheme 1



		Ar	Yield (%)
3	a	4-ClC_6H_4	54
	b	4-$OMeC_6H_4$	55
	c	2-MeC_6H_4	51
	d	4-MeC_6H_4	55
	e	C_6H_5	50
	f	2-ClC_6H_4	50

The substrate **3a** was refluxed in chlorobenzene (132°C) for 4 h to give a solid compound **4a** mp-224-226°C in 78% yield. Compound **4a** was characterized from its elemental analysis and spectroscopic data. Its ^{1}H NMR spectrum (400 MHz) showed two proton doublets at δ 5.05 (J = 2Hz, -OCH_2), 5.20 (J = 2 Hz, -OCH_2) respectively, one proton multiplet at δ 5.93-5.95 (m, 1H, =CH) and a multiplet for twelve aromatic proton at δ 6.89-8.47. The other substrates **3(b-f)** were also treated similarly to give products **4(b-f)** (Scheme 2).

Scheme 2

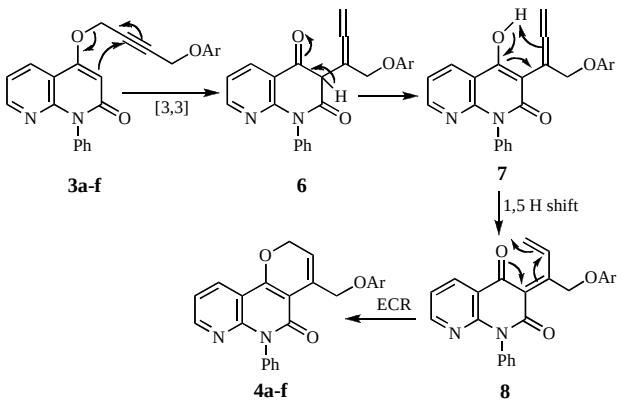


3a-f **4a-f**

		Ar	Yield (%)
4	**a**	4-ClC_6H_4	78
	b	4-$OMeC_6H_4$	78
	c	2-MeC_6H_4	72
	d	4-MeC_6H_4	74
	e	C_6H_5	75
	f	2-ClC_6H_4	75

Although substrates **3(a-f)** possess two potential sites for [3,3] sigmatropic rearrangement aryl-propargyl ether moiety and a vinyl-propargyl ether moiety, all the substrate underwent [3,3] sigmatropic rearrangement at the vinyl-propargyl ether moiety to give compounds **4(a-f)**. The formation of **4(a-f)** from **3(a-f)** may be easily explained by the initial [3,3] sigmatropic rearrangement of **3(a-f)** to **6** and rapid enolization to form **7** followed by [1,5] hydrogen shift and electrocyclic ring closure to give the products **4(a-f)** (Scheme 3).

Scheme 3

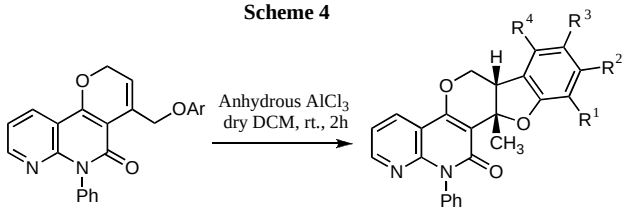


3a-f **6** **7** **8** **4a-f**

A close examination of the structure of products **4(a-f)** revealed that these still contain an allyl-aryl ether moiety well suited for a second Claisen rearrangement. Therefore, substrate **4a** was treated with anhydrous $AlCl_3$ in dry dichloromethane solution, as $AlCl_3$ is a versatile catalyst for the catalytic Claisen rearrangement [10]. After two hours of stirring at room temperature a new compound was obtained. This was characterized as 8-chloro-11a-methyl-13-phenyl-6a,11a,12,13-tetrahydro-6*H*-benzo[4',5']furo[2',3':4,5]pyrano[3,2-*c*][1,8]naphtha-yridin-12-one (**5a**) from its elemental analysis and spectroscopic data.

Its ^{1}H NMR (400 MHz) spectrum displayed a three proton singlet at δ 2.01 (-CH_3), δ 3.54-3.57 (dd, 1H, J = 4 Hz, 8 Hz, ring juncture H), δ 4.23-4.28 (dd, 1H, J = 8 Hz, 11 Hz, -OCH_2), δ 4.49-4.53 (dd, 1H, J = 4 Hz, 11 Hz, -OCH_2) and δ 6.83-8.44 (m, 11H, ArH). Substrates **4b-f** were similarly treated to give products **5b-f**. The stereochemistry of the ring junction of products **5** can only be surmised from the molecular model (Dreiding model), which shows a strain free *cis*-arrangement (Scheme 4).

Scheme 4

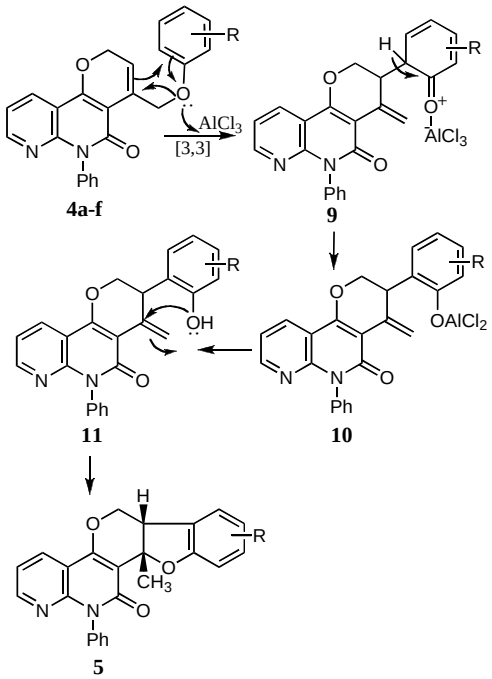


4a-f **5a-f**

		R^1	R^2	R^3	R^4	Yield (%)
5	**a**	H	H	Cl	H	82
	b	H	H	OCH_3	H	84
	c	CH_3	H	H	H	80
	d	H	H	CH_3	H	78
	e	H	H	H	H	82
	f	Cl	H	H	H	85

The formation of products **5a-f** from **4a-f** can be mechanistically rationalized by a series of steps involving an initial charge-accelerated [3,3] sigmatropic rearrangement. Substrates **4** form an ether-oxygen-$AlCl_3$ complex that may undergo [3,3] sigmatropic rearrangement through a charge delocalized transition state to give intermediate **9** followed by rapid tautomerization and proton exchange to give intermediate phenol **11** which on 5-*exo*-cyclization afford the products **5** (Scheme 5).

Scheme 5



4a-f **9** **11** **10** **5**

In conclusion, we have executed the sequential Claisen rearrangement, an *oxy*-Claisen rearrangement of propynyl-vinyl ether followed by another *oxy*-Claisen rearrangement of allyl-aryl ether. This methodology represents a straightforward approach for the construction of the furopyran ring system. The synthesis of pentacyclic heterocycles has been achieved in three steps starting from 4-hydroxy-1-phenyl-1,8-naphthyridin-2(1*H*)-one.

EXPERIMENTAL

Melting points were determined in an open capillary and are uncorrected. IR spectra were recorded on a Perkin-Elmer L 120-000A spectrometer (ν_{max} in cm^{-1}) on KBr disks. UV absorption spectra were recorded in EtOH on a Shimadzu UV-2401PC spectrophotometer (λ_{max} in nm). ^{1}H NMR (400 MHz, 500 MHz) and ^{13}C NMR (125.7 MHz) spectra were recorded on a Vaian-400 MHz FT NMR and Bruker DPX-500 spectrometers in $CDCl_3$ (chemical shifts in δ) with TMS as internal standard. Elemental analyses and mass spectra were recorded on a Leco 932 CHNS analyzer and on a QTOF Micromass (Waters) instrument respectively. ^{1}H NMR and ^{13}C NMR spectra were recorded at the Indian Institute of Chemical Biology, Kolkata and Bose Institute, Kolkata. Silica gel [(60-120 mesh), Spectrochem, India] was used for chromatographic separation. Silica gel G [E-Merck (India)] was used for TLC. Petroleum ether refers to the fraction boiling between 60° and 80°C.

The 1-aryloxy-4-chlorobut-2-ynes **2(a-f)** were prepared according to the earlier published procedure [11].

General procedure for the preparation of compounds 3a-f. A mixture of 1-aryloxy-4-chlorobut-2-ynes (**2a-f**) (10 mmol), 4-hydroxy-1-phenyl-1,8-naphthyridin-2(1*H*)-one (**1**) (2.38 g, 10 mmol), anhydrous K_2CO_3 (3 g) was refluxed in dry acetone for 22-24 h. The reaction mixture was cooled, filtered and washed with acetone. The solvent was removed from the combined filtrate and the residual mass extracted with chloroform (3 X 25 ml). The extract washed with brine (2 X 25 ml) and dried (Na_2SO_4). The residual crude mass was then purified by column chromatography over silica gel. Elution of the column with petroleum ether: ethyl acetate (2:1) furnished compounds **3(a-f)**.

4-[4-(4-Chlorophenoxy)-2-butynyl]oxy-1-phenyl-1,2-dihydro-[1,8]naphthyridin-2-one 3a. Yield: 2.24 g (54 %), white solid, mp 136-138°; ir (KBr): ν_{max} 2935, 2226 (C≡C), 1658 (C=O), 1585, 1448 cm^{-1}; uv (EtOH): λ_{max} 240 (log ε 4.01), 270 (log ε 3.68), 278 (log ε 3.65), 320 (log ε 3.94), 333 (log ε 3.89) nm; ^{1}H nmr (400 MHz, $CDCl_3$): δ_H 4.74 (t, 2H, J = 2 Hz, $-OCH_2$), 4.91 (t, 2H, J = 2 Hz, $-OCH_2$), 6.22 (s, 1H, =CH), 6.88-6.90 (dd, 2 H, J = 2 Hz, 7 Hz, ArH), 7.13-7.17 (dd, 1H, J = 4.8 Hz, 8 Hz, ArH), 7.23-7.28 (m, 4H, ArH), 7.49-7.59 (m, 3H, ArH), 8.23-8.25 (dd, 1H, J = 1.6 Hz, 8 Hz, ArH), 8.45-8.47 (dd, 1H, J = 1.6 Hz, 4.8 Hz, ArH); ms: m/z 417 (M^++H), 439 (M^++Na); *Anal.* Calcd for $C_{24}H_{17}N_2O_3Cl$: C, 69.15; H, 4.11; N, 6.72%; Found C, 69.24; H, 4.17; N, 6.68%.

4-[4-(4-Methoxyphenoxy)-2-butynyl]oxy-1-phenyl-1,2-dihydro[1,8]naphthyridin-2-one 3b. Yield: 2.26 g (55 %), solid, mp 122-124°; ir (KBr): ν_{max} 2948, 2226 (C≡C), 1660 (C=O), 1585, 1508 cm^{-1}; uv (EtOH): λ_{max} 240 (log ε 4.00), 270 (log ε 3.73), 279 (log ε 3.68), 321 (log ε 3.96), 331 (log ε 3.87) nm; ^{1}H nmr (500 MHz, $CDCl_3$): δ_H 3.76 (s, 3H, $-OCH_3$), 4.72 (s, 2H, $-OCH_2$), 4.92 (s, 2H, $-OCH_2$), 6.22 (s, 1H, =CH), 6.83-6.87 (m, 2H, ArH), 6.90-6.92 (m, 2H, ArH), 7.14-7.16 (dd, 1H, J = 4.7 Hz, 7.8 Hz, ArH), 7.26-7.29 (m, 2H, ArH), 7.47-7.50 (t, 1H, J = 7.4 Hz, ArH), 7.55-7.58 (t, 2H, J = 7.8 Hz, ArH), 8.25-8.26 (dd, 1H, J = 1.7 Hz, 7.8 Hz, ArH), 8.46-8.47 (dd, 1H, J = 1.7 Hz, 4.6 Hz, ArH); ms: *m/z* 413 (M^++H), 435 (M^++Na); *Anal.* Calcd for $C_{25}H_{20}N_2O_4$: C, 72.80; H, 4.89; N, 6.79%; Found C, 72.68; H, 5.04; N, 6.87%.

4-[4-(2-Methylphenoxy)-2-butynyl]oxy-1-phenyl-1,2-dihydro-[1,8]naphthyridin-2-one 3c. Yield: 2.01 g (51 %), solid, mp 146-148°; ir (KBr): ν_{max} 2922, 2226 (C≡C), 1667 (C=O), 1585, 1448 cm^{-1}; uv (EtOH): λ_{max} 240 (log ε 4.03), 272 (log ε 3.69), 278 (log ε 3.67), 321 (log ε 3.96), 333 (log ε 3.85) nm; ^{1}H nmr (400 MHz, $CDCl_3$): δ_H 2.27 (s, 3H, $-CH_3$) 4.72 (s, 2H, $-OCH_2$), 4.90 (s, 2H, $-OCH_2$), 6.20 (s, 1H, =CH), 6.83-6.87 (m, 2H, ArH), 6.90-6.92 (m, 2H, ArH), 7.14-7.16 (dd, 1H, *J* = 4.7 Hz, 7.8 Hz, ArH), 7.26-7.29 (m, 2H, ArH), 7.47-7.50 (t, 1H, *J* = 7.4 Hz, ArH), 7.55-7.58 (t, 2H, *J* = 7.8 Hz, ArH), 8.25-8.26 (dd, 1H, *J* = 1.7 Hz, 7.8 Hz, ArH), 8.46-8.47 (dd, 1H, J = 1.7 Hz, 4.6 Hz, ArH); ms: (*m/z*) 397 (M^++H), 419 (M^++Na); *Anal.* Calcd for $C_{25}H_{20}N_2O_3$: C, 75.74; H, 5.08; N, 7.07%; Found C, 75.93; H, 5.18; N, 7.19 %.

4-[4-(4-Methylphenoxy)-2-butynyl]oxy-1-phenyl-1,2-dihydro-[1,8]naphthyridin-2-one 3d. Yield: 2.17 g (55 %), solid, mp 146-148°; ir (KBr): ν_{max} 2926, 2226 (C≡C), 1661 (C=O), 1584, 1510 cm^{-1}; uv (EtOH): λ_{max} 240 (log ε 4.02), 270 (log ε 3.68), 278 (log ε 3.65), 321 (log ε 4.00), 333 (log ε 3.90) nm; ^{1}H nmr (400 MHz, $CDCl_3$): δ_H 2.27 (s, 3H, $-CH_3$), 4.73 (s, 2H, $-OCH_2$), 4.91 (s, 2H, $-OCH_2$), 6.21 (s, 1H, =CH), 6.84-6.86 (d, 2H, J = 8.2 Hz, ArH), 7.07-7.09 (d, 2H, J = 8 Hz, ArH), 7.12-7.15 (dd, 1H, J = 4.7 Hz, 7.6 Hz, ArH), 7.24-7.27 (m, 2H, ArH), 7.46-7.50 (t, 1H, J = 7.2 Hz, ArH), 7.54-7.58 (t, 2H, J = 7.2 Hz, ArH), 8.23-8.25 (d, 1H, J = 7.6 Hz, ArH), 8.45 (d, 1H, J = 3 Hz, ArH); ms: (*m/z*) 397 (M^++H), 419 (M^++Na); *Anal.* Calcd for $C_{25}H_{20}N_2O_3$: C, 75.74; H, 5.08; N, 7.07%; Found C, 75.95; H, 5.11; N, 7.14%.

4-[(4-Phenoxy-2-butynyl)oxy]-1-phenyl-1,2-dihydro[1,8]-naphthyridin-2-one 3e. Yield: 1.91 g (50 %), solid, mp 132-134°; ir (KBr): ν_{max} 2921, 2226 (C≡C), 1663 (C=O), 1584, 1448 cm^{-1}; uv (EtOH): λ_{max} 241 (log ε 4.04), 264 (log ε 3.73), 271 (log ε 3.74), 278 (log ε 3.72), 321 (log ε 4.01), 333 (log ε 3.90) nm; ^{1}H nmr (500 MHz, $CDCl_3$): 4.77 (s, 2H, $-OCH_2$), 4.92 (s, 2H, $-OCH_2$), 6.22 (s, 1H, =CH), 6.95-7.00 (m, 3H, ArH), 7.13-7.15 (dd, 1H, J = 4.7 Hz, 7.8 Hz, ArH), 7.25-7.31 (m, 4H, ArH), 7.46-7.49 (t, 1H, J = 7.4 Hz, ArH), 7.55-7.58 (t, 2H, J = 7.8 Hz, ArH), 8.23-8.5 (dd, 1H, J = 1.7 Hz, 7.8 Hz, ArH), 8.45-8.46 (dd, 1H, J = 1.7 Hz, 4.6 Hz, ArH); ms: (*m/z*) 383 (M^++H), 405 (M^++Na); *Anal.* Calcd for $C_{24}H_{18}N_2O_3$: C, 75.38; H, 4.74; N, 7.33%; Found C, 75.64; H, 4.69; N, 7.48%.

4-[4-(2-Chlorophenoxy)-2-butynyl]oxy-1-phenyl-1,2-dihydro-[1,8]naphthyridin-2-one 3f. Yield: 2.08 g (50 %), solid, mp142-144°; ir (KBr): ν_{max} 2919, 2226 (C≡C), 1663 (C=O), 1583, 1448 cm^{-1}; uv (EtOH): λ_{max} 240 (log ε 3.99), 275 (log ε 3.68), 281 (log ε 3.65), 321 (log ε 3.96), 333 (log ε 3.85) nm; ^{1}H nmr (400 MHz, $CDCl_3$): δ_H 4.73 (s, 2H, $-OCH_2$), 4.92 (s, 2H, $-OCH_2$), 6.22 (s, 1H, =CH), 6.98-7.01 (d, 1H, J = 8.7 Hz, ArH), 7.15-7.17 (dd, 2H, J = 4.7 Hz, 7.7 Hz, ArH), 7.20-7.29 (m, 4H, ArH), 7.48-7.51 (t, 1H, J = 7.3 Hz, ArH), 7.56-7.59 (t, 2H, J = 7.5 Hz, ArH), 8.23-8.25 (d, 1H, J = 7.7 Hz, ArH), 8.47-8.48 (d, 1H, J = 3.4 Hz, ArH); ms: (m/z) 417 (M^++H), 439 (M^++Na); *Anal.* Calcd for $C_{24}H_{17}N_2O_3Cl$: C, 69.15; H, 4.11; N, 6.72%; Found C, 69.13; H, 4.21; N, 6.89%.

General procedure for the preparation of compounds 4a-f. Compounds **3(a-f)** (1 mmol) were refluxed in chlorobenzene (5 ml) for 4-6 h. The reaction was monitored by TLC. The

chlorobenzene was removed at reduced pressure and the residual mass was chromatographed over silica gel. Elution of the column with petroleum ether removed residual chlorobenzene and the rearranged products **(4a-f)** were obtained by eluting the column with petroleum ether: ethyl acetate (4:1).

3-[(4-Chlorophenoxy)methyl]-6-phenyl-5,6-dihydro-4*H*-pyrano[3,2-*c*][1,8]naphthyridin-5-one 4a. Yield: 0.32 g (78 %), solid, mp 224-226°; ir (KBr): ν_{max} 2918, 1662 (C=O), 1641, 1582 cm^{-1}; uv (EtOH): λ_{max} 240 (log ε 4.11), 344 (log ε 3.88), 353 (log ε 3.89) nm; ^{1}H nmr (500 MHz, $CDCl_3$): δ_H 5.05 (d, 2H, *J* = 2 Hz, -OCH_2), 5.20 (d, 2H, *J* = 2 Hz, -OCH_2), 5.93-5.95 (m, 1H, =CH), 6.89-6.91 (d, 2H, *J* = 8.9 Hz, ArH), 7.14-7.16 (dd, 1H, *J* = 4.6 Hz, 7.9 Hz, ArH), 7.18-7.20 (d, 2H, *J* = 8.9 Hz, ArH), 7.25-7.28 (m, 2H, ArH), 7.47-7.50 (t, 1H, *J* = 7.4 Hz, ArH), 7.56-7.59 (t, 2H, *J* = 7.5 Hz, ArH), 8.22-8.24 (dd, 1H, *J* = 1.6 Hz, 7.8 Hz, ArH), 8.44-8.47 (dd, 1H, *J* = 1.6 Hz, 4.6 Hz, ArH); ^{13}C NMR (125 MHz, $CDCl_3$): 67.20, 67.96, 108.43, 111.15, 113.99, 116.58, 118.60, 118.90, 126.03, 128.98, 129.37, 129.52, 129.66, 129.99, 130.01, 130.95, 132.29, 137.41, 150.70, 151.50, 157.50, 158.16, 162.17; ms: (m/z) 417 (M^++H), 439 (M^++Na); *Anal.* Calcd for $C_{24}H_{17}N_2O_3Cl$: C, 69.15; H, 4.11; N, 6.72%; Found C, 69.30; H, 4.24; N, 6.81%.

3-[(4-Methoxyphenoxy)methyl]-6-phenyl-5,6-dihydro-4*H*-pyrano[3,2-*c*][1,8]naphthyridin-5-one 4b. Yield: 0.32 g (78 %), solid, mp 222-224°; ir (KBr): ν_{max} 2922, 1662 (C=O), 1638, 1583 cm^{-1}; uv (EtOH): λ_{max} 240 (log ε 4.10), 341 (log ε 3.87), 357 (log ε 3.92) nm; ^{1}H nmr (400MHz, $CDCl_3$): δ_H 3.74 (s, 3H, -OCH_3), 5.05 (d, 2H, *J* = 2 Hz, -OCH_2), 5.16 (d, 2H, *J* = 2 Hz, -OCH_2), 5.98-6.00 (m, 1H, =CH), 6.77-6.79 (m, 2H, ArH), 6.89-6.92 (m, 2H, ArH), 7.13-7.16 (dd, 2H, *J* = 4.6 Hz, 7.8 Hz, ArH), 7.25-7.27 (m, 1H, ArH), 7.46-7.50 (t, 1H, *J* = 7.4 Hz, ArH), 7.55-7.59 (t, 2H, *J* = 7.3 Hz, ArH), 8.22-8.24 (dd, 1H, *J* = 1.5 Hz, 7.8 Hz, ArH), 8.43-8.44 (dd, 1H, *J* = 1.6 Hz, 4.5 Hz, ArH); ms: (*m/z*) 413 (M^++H), 435 (M^++Na); *Anal.* Calcd for $C_{25}H_{20}N_2O_4$: C, 72.80; H, 4.89; N, 6.79%; Found C, 72.98; H, 4.97; N, 6.91%.

3-[(2-Methylphenoxy)methyl]-6-phenyl-5,6-dihydro-4*H*-pyrano[3,2-*c*][1,8]naphthyridin-5-one 4c. Yield: 0.28 g (72 %), solid, mp 224-226°; ir (KBr): ν_{max} 2918, 1662 (C=O), 1641, 1582 cm^{-1}; uv (EtOH): λ_{max} 240 (log ε 4.08), 343 (log ε 3.87), 357 (log ε 3.91) nm; ^{1}H nmr (500 MHz, $CDCl_3$): δ_H 2.29 (s, 3H, -CH_3), 5.08 (d, 2H, *J* = 2 Hz, -OCH_2), 5.22 (d, 2H, *J* = 2 Hz, -OCH_2), 6.03-6.05 (m, 1H, =CH), 6.82-6.85 (t, 1H, *J* = 7.2 Hz, ArH), 6.92-6.94 (t, 1H, *J* = 8 Hz, ArH), 7.04-7.16 (m, 3H, ArH), 7.27-7.29 (m, 2H, ArH), 7.48-7.51 (t, 1H, *J* = 7.4 Hz, ArH), 7.56-7.59 (t, 2H, *J* = 7.4 Hz, ArH), 8.24-8.25 (dd, 1H, *J* = 1.7 Hz, 7.8 Hz, ArH), 8.44-8.45 (dd, 1H, *J* = 1.7 Hz, 4.6 Hz, ArH); ms: (*m/z*) 397 (M^++H), 419 (M^++Na); *Anal.* Calcd for $C_{25}H_{20}N_2O_3$: C, 75.74; H, 5.08; N, 7.07%; Found C, 75.99; H, 5.21; N, 7.12 %.

3-[(4-Methylphenoxy)methyl]-6-phenyl-5,6-dihydro-4*H*-pyrano[3,2-*c*][1,8]naphthyridin-5-one 4d. Yield: 0.29 g (74 %), solid, mp 216-218°; ir (KBr): ν_{max} 2923, 1665 (C=O), 1644, 1583 cm^{-1}; uv (EtOH): λ_{max} 242 (log ε 4.06), 344 (log ε 3.92), 354 (log ε 3.90) nm; ^{1}H nmr (400 MHz, $CDCl_3$): δ_H 2.26 (s, 3H, -CH_3) 5.04 (d, 2H, *J* = 2 Hz, -OCH_2), 5.19 (d, 2H, *J* = 2 Hz, -OCH_2), 5.97-5.99 (m, 1H, =CH), 6.86-6.88 (d, 2H, *J* = 8.4 Hz, ArH), 7.03-7.05 (d, 2H, *J* = 8.4 Hz, ArH), 7.13-7.16 (dd, 1H, *J* = 4.8 Hz, 8.4 Hz, ArH), 7.25-7.29 (m, 2H, ArH), 7.36-7.50 (t, 1H, *J* = 7.6 Hz, ArH), 7.55-7.59 (t, 2H, *J* = 7.6 Hz, ArH), 8.22-8.24 (dd, 1H, *J* = 1.6 Hz, 7.6 Hz, ArH), 8.43-8.44 (dd, 1H, *J* = 1.6 Hz, 4.4 Hz, ArH). ms: (*m/z*) 397 (M^++H), 419 (M^++Na); *Anal.* Calcd for $C_{25}H_{20}N_2O_3$: C, 75.74; H, 5.08; N, 7.07%; Found C, 75.82; H, 5.04; N, 7.20%.

3-(Phenoxymethyl)-6-phenyl-5,6-dihydro-4*H*-pyrano[3,2-*c*]-[1,8]naphthyridin-5-one 4e. Yield: 0.28 g (75 %), solid, mp 222-224°; ir (KBr): ν_{max} 2919, 1663 (C=O), 1644, 1583 cm^{-1}; uv (EtOH): λ_{max} 240 (log ε 3.96), 344 (log ε 3.88), 357 (log ε 3.83) nm; ^{1}H nmr (500 MHz, $CDCl_3$): δ_H 5.06 (d, 2H, *J* = 2 Hz, -OCH_2), 5.23 (d, 2H, *J* = 2 Hz, -OCH_2), 5.98-6.00 (m, 1H, =CH), 6.91-6.93 (t, 1H, *J* = 7.3 Hz, ArH), 6.98-6.99 (d, 2H, *J* = 7.9 Hz, ArH), 7.13-7.16 (dd, 1H, *J* = 4.6 Hz, 7.8 Hz, ArH), 7.23-7.28 (m, 4H, ArH), 7.47-7.50 (t, 1H, *J* = 7.4 Hz, ArH), 7.56-7.59 (t, 2H, *J* = 7.5 Hz, ArH), 8.23-8.25 (dd, 1H, *J* = 1.7 Hz, 7.8 Hz, ArH), 8.44-8.45 (dd, 1H, *J* = 1.7 Hz, 4.6 Hz, ArH); ms: (*m/z*) 383 (M^+ + H), 405 (M^+ + Na); *Anal.* Calcd for $C_{24}H_{18}N_2O_3$: C, 75.38; H, 4.74; N, 7.33%; Found C, 75.56; H, 4.96; N, 7.37%.

3-[(2-Chlorophenoxy)methyl]-6-phenyl-5,6-dihydro-4*H*-pyrano[3,2-*c*][1,8]naphthyridin-5-one 4f. Yield: 0.31 g (75 %), solid, mp 218-220°; ir (KBr): ν_{max} 2921, 1663 (C=O), 1644, 1583 cm^{-1}; uv (EtOH): λ_{max} 240 (log ε 4.06), 347 (log ε 3.83), 357 (log ε 3.87) nm; ^{1}H nmr (500 MHz, $CDCl_3$): δ_H 5.07 (d, 2H, *J* = 2 Hz, -OCH_2), 5.19 (d, 2H, *J* = 2 Hz, -OCH_2), 6.00-6.02 (m, 1H, =CH), 6.96-6.98 (m, 1H, ArH), 7.11-7.17 (m, 2H, ArH), 7.25-7.28 (m, 4H, ArH), 7.48-7.51 (t, 1H, *J* = 7.5 Hz, ArH), 7.56-7.59 (t, 2H, *J* = 7.4 Hz, ArH), 8.24-8.25 (dd, 1H, *J* = 1.6 Hz, 7.8 Hz, ArH), 8.44-8.46 (dd, 1H, *J* = 1.7 Hz, 4.6 Hz, ArH); ms: (*m/z*) 417 (M^++H), 439 (M^++Na); *Anal.* Calcd for $C_{24}H_{17}N_2O_3Cl$: C, 69.15; H, 4.11; N, 6.72%; Found C, 69.28; H, 4.16; N, 6.80%.

General procedure for the preparation of 5a-f. Compounds (**4a-f**) (0.5 mmol) were dissolved in dry dichloromethane (10 ml) and anhydrous $AlCl_3$ (0.06 g, 0.5 mmol) was added to it. The reaction mixture was stirred at room temperature for 0.5-2.0 h. Crushed ice was added to the reaction mixture after which the mixture was extracted with dichloromethane. The combined extracts were washed with water (20 ml), brine (20 ml) and dried (Na_2SO_4). The solvent was removed and the residual viscous mass was chromatographed over silica gel using petroleum ether: ethyl acetate (3:1) as eluant to afford the products **5(a-f)**.

8-Chloro-11a-methyl-13-phenyl-6a,11a,12,13-tetrahydro-6*H*-benzo[4',5']furo[2',3':4,5]pyrano[3,2-*c*][1,8]naphthyridin-12-one 5a. Yield: 0.17 g (82 %), solid, mp 145-147° (decomposed); ir (KBr): ν_{max} 2923, 1657 (C=O), 1623, 1589, 1475 cm^{-1}; uv (EtOH): λ_{max} 240 (log ε 3.99), 282 (log ε 3.67), 325 (log ε 3.85), 337 (log ε 3.81) nm; ^{1}H nmr (400 MHz, $CDCl_3$): δ_H 2.01 (s, 3H, -CH_3) 3.54-3.57 (dd, 1H, *J* = 4 Hz, 8 Hz, ring juncture H), 4.23-4.28 (dd, 1H, *J* = 8 Hz, 11 Hz, -OCH_2), 4.49-4.53 (dd, 1H, *J* = 4 Hz, 11 Hz, -OCH_2), 6.83-6.85 (d, 1H, *J* = 8.4 Hz, ArH), 7.11-7.14 (m, 2H, ArH), 7.23-7.28 (m, 3H, ArH), 7.43-7.47 (t, 1H, *J* = 7.2 Hz, ArH), 7.49- 7.53 (m, 2H, ArH), 8.21-8.23 (dd, 1H, *J* = 1.3 Hz, 7.8 Hz, ArH), 8.44 (d, 1H, *J* = 3 Hz, ArH); ^{13}C NMR (125 MHz, $CDCl_3$): 24.24, 49.13, 66.56, 84.21, 110.31, 111.03, 112.68, 118.36, 124.83, 125.72, 127.56, 128.75, 129.70, 129.77, 132.86, 137.20, 150.71, 151.69, 157.97, 158.50, 162.55; ms: (m/z) 417 (M^++H), 439 (M^++Na); *Anal.* Calcd for $C_{24}H_{17}N_2O_3Cl$: C, 69.15; H, 4.11; N, 6.72%; Found C, 69.11; H, 4.19; N, 6.77%.

8-Methoxy-11a-methyl-13-phenyl-6a,11a,12,13-tetrahydro-6*H*-benzo[4',5']furo[2',3':4,5]pyrano[3,2-*c*][1,8]naphthyridin-12-one 5b. Yield: 0.17 g (84%), solid, mp 148-150° (decomposed); ir (KBr): ν_{max} 2921, 1655 (C=O), 1587, 1486 cm^{-1}; uv (EtOH): λ_{max} 240 (log ε 4.00), 282 (log ε 3.61), 325

(log ε 3.90), 337 (log ε 3.77) nm; ^{1}H nmr (500 MHz, $CDCl_3$): δ_H 1.99 (s, 3H, -CH_3) 3.51-3.54 (dd, 1H, *J* = 4 Hz, 8 Hz, ring juncture H) 3.77 (s, 3H, -OCH_3) 4.24-4.28 (dd, 1H, *J* = 8 Hz, 11 Hz, -OCH_2), 4.50-4.54 (dd, 1H, *J* = 4 Hz, 11 Hz, -OCH_2), 6.71-6.72 (d, 1H, *J* = 8.3 Hz, ArH), 6.83-6.85 (m, 2H, ArH), 7.10-7.13 (dd, 1H, *J* = 4.7 Hz, 7.5 Hz, ArH), 7.25-7.36 (m, 2H, ArH), 7.44-7.47 (t, 1H, *J* = 7.1 Hz, ArH), 7.53-7.55 (m, 2H, ArH), 8.21-8.23 (d, 1H, *J* = 7.6 Hz, ArH), 8.43-8.44 (d, 1H, *J* = 3.2 Hz, ArH); ms: (*m/z*) 413 (M^++H), 435 (M^++Na); *Anal.* Calcd for $C_{25}H_{20}N_2O_4$: C, 72.80; H, 4.89; N, 6.79%; Found C, 72.87; H, 5.10; N, 6.70 %.

10,11a-Dimethyl-13-phenyl-6a,11a,12,13-tetrahydro-6*H*-benzo[4',5']furo[2',3':4,5]pyrano[3,2-*c*][1,8]naphthyridin-12-one 5c. Yield: 0.15 g (80%), solid, mp 238-240°; ir (KBr): ν_{max} 2925, 1655 (C=O), 1622, 1588, 1475 cm^{-1}; uv (EtOH): λ_{max} 240 (log ε 4.00), 280 (log ε 3.67), 325 (log ε 3.88), 337 (log ε 3.76) nm; ^{1}H nmr (500 MHz, $CDCl_3$): δ_H 1.99 (s, 3H, -CH_3) 2.21 (s, 3H, -CH_3) 3.51-3.54(dd, 1H, *J*= 4 Hz, 8 Hz, ring juncture H) 4.20-4.24 (dd, 1H, *J* = 8 Hz, 11 Hz, -OCH_2) 4.50-4.54 (dd, 1H, *J* = 4 Hz, 11 Hz, -OCH_2), 6.79-6.82 (t, 1H, *J* = 7.4 Hz, ArH), 6.99-7.01 (d, 1H, *J* = 7.4 Hz, ArH), 7.09-7.11 (m, 2H, ArH), 7.25-7.29 (m, 2H, ArH), 7.44-7.47 (t, 1H, *J* = 7.4 Hz, ArH), 7.54-7.57 (t, 2H, *J* = 7.6 Hz, ArH), 8.21-8.22 (dd, 1H, *J* = 1.2 Hz, 7.7 Hz, ArH), 8.42-8.43 (d, 1H, *J* = 3.1 Hz, ArH); ms: (*m/z*) 397 (M^++H), 419 (M^++Na); *Anal.* Calcd for $C_{25}H_{20}N_2O_3$: C, 75.74; H, 5.08; N, 7.07%; Found C, 75.80; H, 4.98; N, 7.10%.

8,11a-Dimethyl-13-phenyl-6a,11a,12,13-tetrahydro-6*H*-benzo[4',5']furo[2',3':4,5]pyrano[3,2-*c*][1,8]naphthyridin-12-one 5d. Yield: 0.15 g (78%), solid, mp 200-202°; ir (KBr): ν_{max} 2924, 1656 (C=O), 1620, 1586, 1488 cm^{-1}; uv (EtOH): λ_{max} 240 (log ε 4.03), 286 (log ε 3.64), 296 (log ε 3.62), 325 (log ε 3.89), 337 (log ε 3.80) nm; ^{1}H nmr (500 MHz, $CDCl_3$): δ_H 1.99 (s, 3H, -CH_3), 2.30 (s, 3H, -CH_3), 3.50-3.52 (dd, 1H, *J* = 4 Hz, 8 Hz, ring juncture H) 4.21-4.25 (dd, 1H, *J* = 8Hz, 11 Hz), 4.50-4.53 (dd, 1H, *J* = 4 Hz, 11 Hz), 6.81-6.83 (d, 1H, *J* = 8.1 Hz, ArH), 6.96-6.97 (d, 1H, *J* = 3.2 Hz, ArH), 7.07 (s, 1H, ArH), 7.10-7.12 (dd, 1H, *J* = 4.8 Hz, 7.8 Hz, ArH), 7.25-7.29 (m, 2H, ArH), 7.44-7.47 (t, 1H, *J* = 7.4 Hz, ArH), 7.48-7.54 (m, 2H, ArH), 8.21-8.23 (d, 1H, *J* = 7.8 Hz, ArH), 8.43-8.44 (d, 1H, *J* = 4 Hz, ArH); ms: (*m/z*) 397 (M^++H), 419 (M^++Na); *Anal.* Calcd for $C_{25}H_{20}N_2O_3$: C, 75.74; H, 5.08; N, 7.07%; Found C, 76.01; H, 5.22; N, 7.15%.

11a-Methyl-13-phenyl-6a,11a,12,13-tetrahydro-6*H*-benzo-[4',5']furo[2',3':4,5]pyrano[3,2-*c*][1,8]naphthyridin-12-one 5e. Yield: 0.15 g (82%), solid, mp 242-244°; ir (KBr): ν_{max} 2927, 1654 (C=O), 1621, 1587, 1477 cm^{-1}; uv (EtOH): λ_{max} 240 (log ε 3.79), 281 (log ε 3.43), 325 (log ε 3.65), 337 (log ε 3.56) nm; ^{1}H nmr (400 MHz, $CDCl_3$): δ_H 1.99 (s, 3H, -CH_3) 3.54-3.57 (dd, 1H, *J* = 4 Hz, 8Hz, ring juncture H), 4.21-4.26 (dd, 1H, *J* = 8 Hz, 11 Hz, -OCH_2), 4.51-4.55 (dd, 1H, *J* = 4 Hz, 11 Hz, -OCH_2), 6.89-6.94 (m, 2H, ArH), 7.09-7.12 (m, 1H, ArH), 7.15-7.19 (t, 1H, *J* = 7.6 Hz, ArH), 7.24-7.29 (m, 3H, ArH), 7.45-7.53 (m, 3H, ArH), 8.20-8.23 (dd, 1H, *J* = 1.4 Hz, 7.8 Hz, ArH), 8.42-8.44 (dd, 1H, *J* = 1.4 Hz, 4.4 Hz, ArH); ms: (*m/z*) 383 (M^++H), 405 (M^++Na); *Anal.* Calcd for $C_{24}H_{18}N_2O_3$: C, 75.38; H, 4.74; N, 7.33%; Found C, 75.44; H, 4.85; N, 7.40%.

10-Chloro-11a-methyl-13-phenyl-6a,11a,12,13-tetrahydro-6*H*-benzo[4',5']furo[2',3':4,5]pyrano[3,2-*c*][1,8]naphthyridin-12-one 5f. Yield: 0.17 g (85%), solid, mp 250-252°; ir (KBr): ν_{max} 2923, 1659 (C=O), 1622, 1588, 1455 cm^{-1}; uv (EtOH): λ_{max} 240 (log ε 3.97), 282 (log ε 3.67), 325 (log ε 3.90), 337 (log ε 3.82) nm; ^{1}H nmr (500 MHz, $CDCl_3$): δ_H 2.04 (s, 3H, -CH_3), 3.59-3.62 (dd, 1H, *J* = 4 Hz, 8 Hz, ring juncture H), 4.23-4.27 (dd, 1H, *J* = 8Hz, 11 Hz, -OCH_2), 4.51-4.54 (dd, 1H, *J* = 4 Hz, 11 Hz, -OCH_2), 6.82-6.85 (t, 1H, *J* = 7.7 Hz, ArH), 7.10-7.12 (dd, 1H, *J* = 4.6 Hz, 7.8 Hz, ArH), 7.14-7.20 (m, 2H, ArH), 7.28-7.30 (d, 2H, *J* = 7.3 Hz, ArH), 7.44-7.47 (t, 1H, *J* = 7.4 Hz, ArH), 7.53-7.58 (t, 2H, *J* = 7.5 Hz, ArH), 8.20-8.22 (dd, 1H, *J* = 1.7 Hz,7.8 Hz, ArH), 8.43-8.45 (dd, 1H, *J* = 1.7 Hz, 4.6 Hz, ArH); ms: (*m/z*) 417 (M^++H), 439 (M^++Na); *Anal.* Calcd for $C_{24}H_{17}N_2O_3Cl$: C, 69.15; H, 4.11; N, 6.72%; Found C, 69.31; H, 4.09; N, 6.83%.

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* Corresponding author. Tel.: +91-33-2582-7521, fax: +91-33-25828282; e-mail: kcm_ku@yahoo.co.in

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