Original Article

Environmentally favorable Synthesis and Characterization of series of 2-hydrazinyl-3- substituted [1,8] naphthyridines

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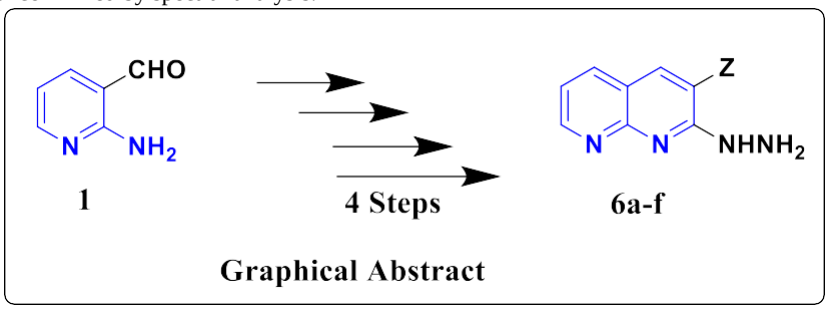
DOI: 10.47750/pnr.2023.14.S02.230

Abstract

A mixture of 2-aminonicotinaldehyde 1 (0.01 mol), various acetonitrile 2a-f and in the presence of KOH with MW irradiation at 200 W intermittently at 30 sec for 2.0 min to furnish 3a-f and cooled further more mixture of HCl and were added $NaNO_2$ solution were added and stirred at RT for 5 min to afford 4a-f.This is mixed with $POCl_3$ was exposed to MW irradiation at 200 W intermittently at 30 sec intervals for 5 min. The reaction mixture was cooled and poured onto a mixture of crushed ice and $NaHCO_3$. The solid thus obtained was filtered, washed with water and purified by recrystallization from ethanol to give 5a-f. To this hydrazine hydrate in ethanol was refluxed on a water bath for 0.5 hr. resulting solid product was filtered, washed with water and purified by recrystallization from ethanol to afford 6a-f shown in Scheme-I. The products were further confirmed by spectral analysis.



Graphical Abstract

Keywords: 1,8-Naphthyridines, acetonitrile, $NaNO_2$, $POCl_3$, MWI.

INTRODUCTION

1,8-Naphthyridines have emerged as an important class of heterocyclic compounds due to their diverse biological activities [1] and photochemical properties.[2] Gemifloxacin, a compound containing 1,8-naphthyridine core has reached drug market for the treatment of bacterial infections.[3] Due to the wide applicability in medicinal chemistry and materials science, the development of methods for the synthesis of 1,8-naphthyridines has been of considerable interest to synthetic community including attemptsto develop more ecofriendly, safe, and atom economical approaches.[4–5]

The medicinal properties of naphthyridines and their derivatives are the major driving forces to synthesize them on a large scale. Among naphthyridines, 1,8-naphthyridines (1) and their derivatives are used as drugs for antimicrobial activities (nalidixic acid, 2),[6–9] antibacterial activities (gemifloxacin, 3),[10-11] shown in below as Fig.I.

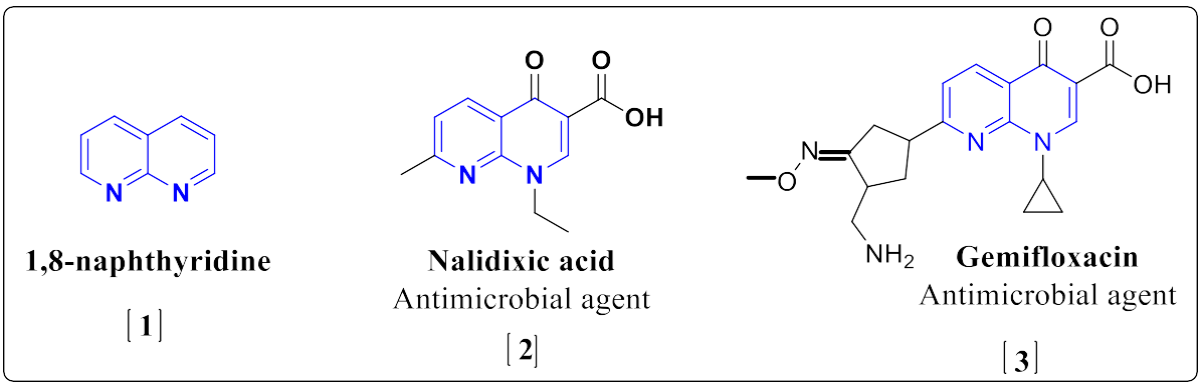


Fig. I Biologically potent 1,8-naphthyridines

1,8-Naphthyridine derivatives constitute an important class of compounds possessing diverse biological and pharmacological activities.[12-14] Use of MW activation in organic synthesis has become a standard tool for organic chemists because of enhancement in rate of reaction, higher yields and improved selectivity in comparison to conventional reactions.[15-17]

Experimental section

Melting points were determined using a Cintex melting point apparatus and are uncorrected. Thin-layer chromatography (TLC) was performed by using Merck silica gel 60F254 precoated plates (0.25 mm) and column chromatography was performed by using Silica gel (particle size 100-200 mesh). Proton nuclear Magnetic Resonance (400 MHz) and Carbon Nuclear Magnetic Resonance (100 MHz) spectrums were logged on Bruker AC-300 spectrophotometer in DMSO-d_6 with TMS as reference. Mass spectrum was documented on JEOL SX-102 spectrophotometer. All the chemicals and reagents used in present investigation were purchased from Sigma- Aldrich Chemical Company.

Results and discussions

Synthesis of series of 2-Hydrazino- [1,8] naphthyridine 6a-f depicted below.

(a) Various [1,8]naphthyridin-2-amine 3a-f:

A mixture of 2-aminonicotinaldehyde 1 (0.01 mol), various acetonitrile 2a-f (0.01 mol) and 10% KOH (5 drops) was subjected to MW irradiation at 200 W intermittently at 30 sec for 2.0 min. After completion of the reaction, as monitored by TLC, the reaction mixture was cooled, the separated solid filtered, washed with water and purified by recrystallization from methanol to furnish 3a-f.

(b) Substituted -1,2-dihydro[1,8]naphthyridin-2-ones 4a-f:

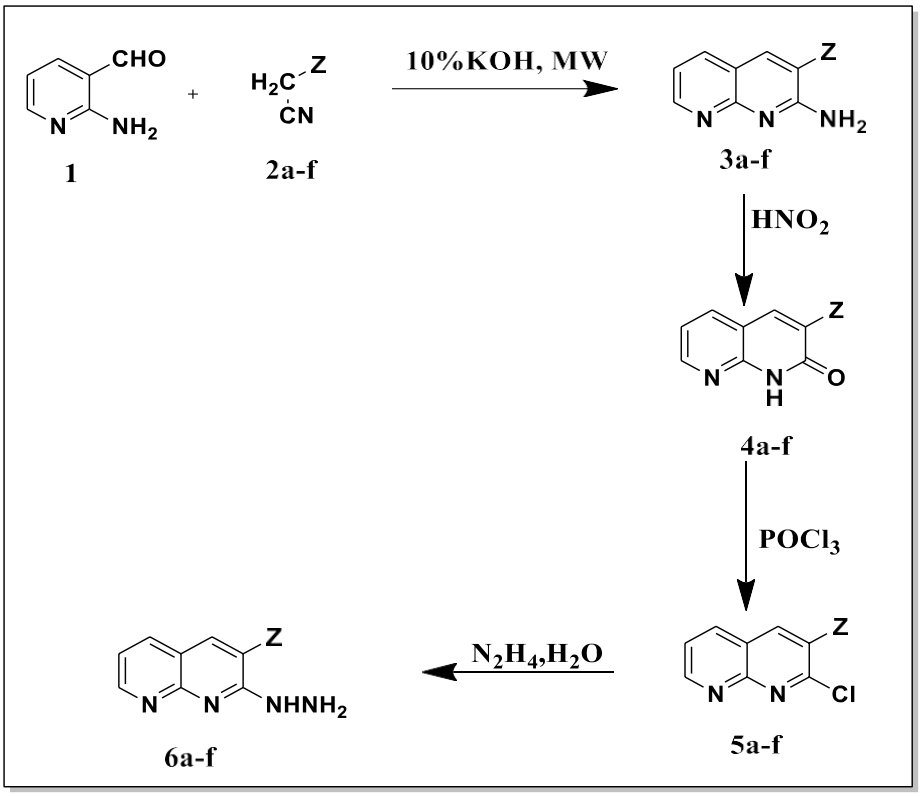
To a cold solution containing 3a-f (0.01 mol) in 2 M HCl (25 mL) was added $NaNO_2$ solution (0.01 mole in 25 mL water) and the reaction mixture was stirred at RT for 0.5 hr and treated with cold water. The solid that separated was filtered, washed with water and purified by recrystallization from methanol to afford 4a-f.

(c) 2-Chloro [1,8]naphthyridines 5a-f:

A mixture of 4a-f (0.01 mol) and $POCl_3$ (10 mL) was exposed to MW irradiation at 200 W intermittently at 30 sec intervals for 1.5 min. After finishing the reaction, as directed by TLC, the reaction mixture was cooled and poured onto a mixture of crushed ice and $NaHCO_3$. The solid thus obtained was filtered, washed with water and purified by recrystallization from ethanol to give 5a-f.

(d) 2-Hydrazino-3-substituted [1,8]naphthyridines 6a-f:

A mixture of 5a-f (0.01 mol) and hydrazine hydrate (0.015 mol) in ethanol (20 mL) was refluxed on a water bath for 3.5 hr. The reaction mixture was cooled and treated with cold water. The resulting solid product was filtered, eroded with water and purified by recrystallization from ethanol to afford desired products 6a-f.



Scheme I

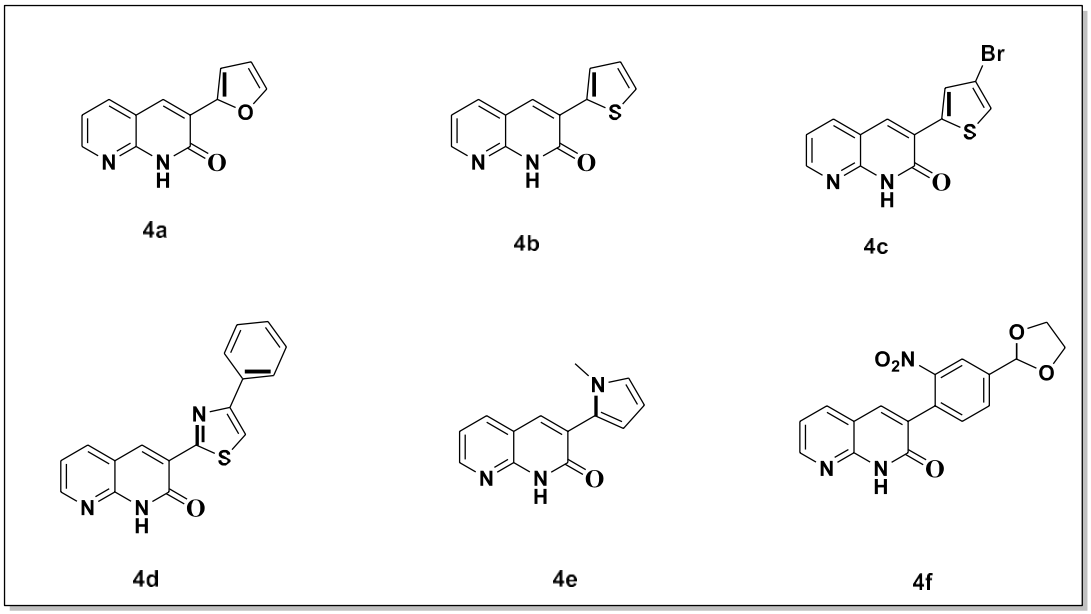


Fig. II Structures of compounds 4a-f

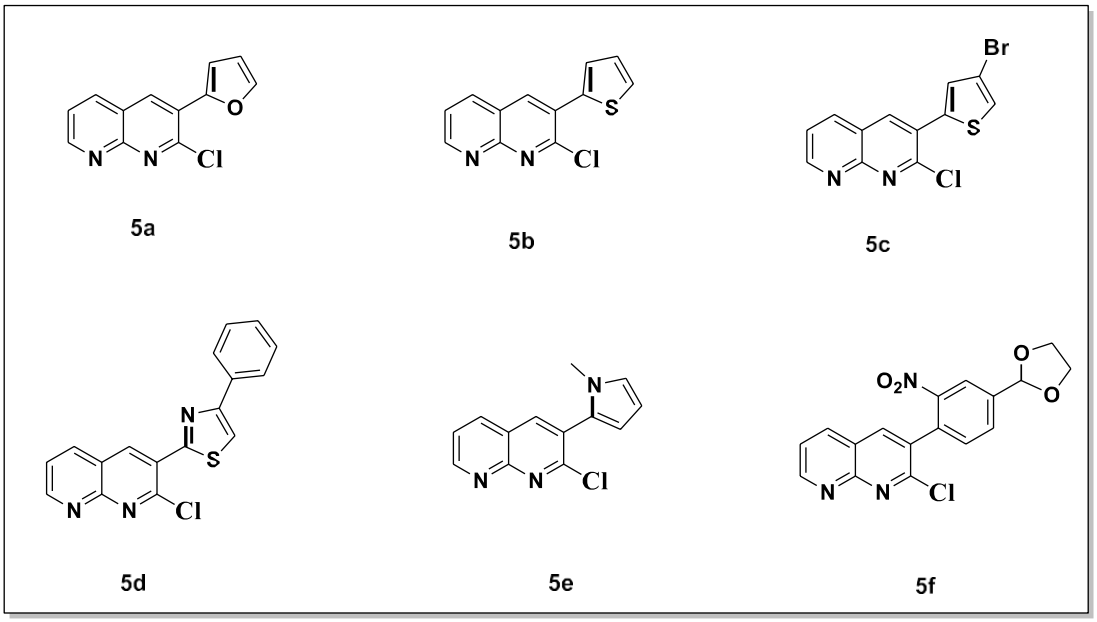


Fig. III Structures of compounds 5a-f

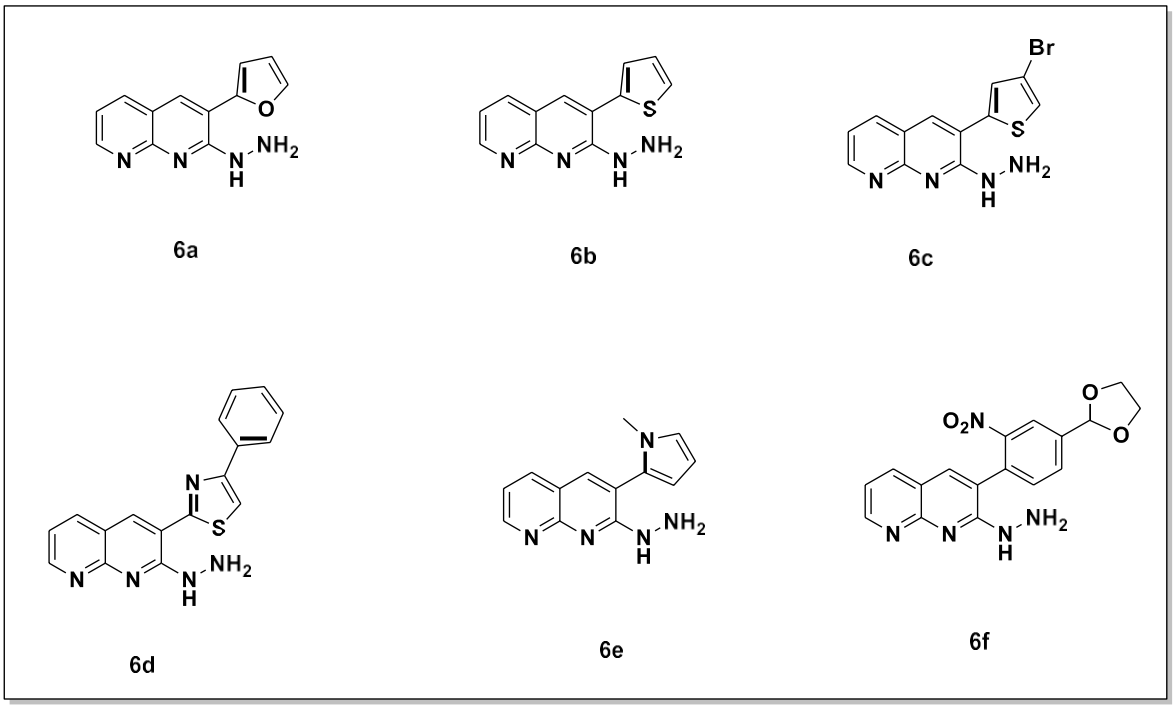


Fig. IV Structures of 3- substituted title compounds 6a-f

Table I List of purchased reactants are depicted below

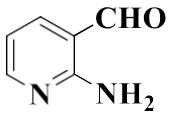
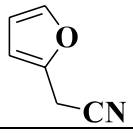
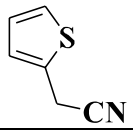
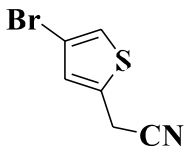
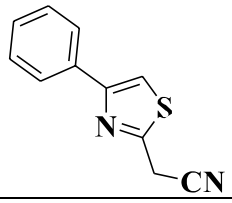
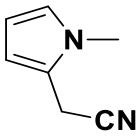
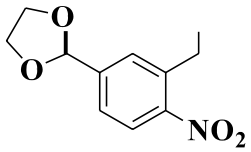
Entry	Name	Structure	Sigma- Aldrich CAS number
1	2-aminonicotinaldehyde		639109
2a	2-(furan-2-yl)acetonitrile		2745-25-7
2b	2-(thiophen-2-yl)acetonitrile		20893-30-5
2c	2-(4-bromothiophen-2-yl)acetonitrile		CDS003130
2d	2-(4-phenylthiazol-2-yl)acetonitrile		41381-89-9
2e	2-(1-methyl-1H-pyrrol-2-yl)acetonitrile		24437-41-0
2f	2-(5-(1,3-dioxolan-2-yl)-2-nitrophenyl)acetonitrile		882864-44-0

Table II Physical and analytical data of -1,8-naphthyridin-2(1H)-one 4

Entry	Reaction Time (min)	m.p. °C	Yield (%)	Mol. Formula	Found (%) (Calcd)		
					C	H	N
4a	3.5	186	92	$C_{12}H_8N_2O_2$	68.04 (67.92	3.81 3.80	13.34 13.20)
4b	3.5	178	90	$C_{12}H_8N_2OS$	63.26 (63.14	3.54 3.53	12.41 12.27)
4c	4.0	190	93	$C_{12}H_7BrN_2OS$	47.02 (46.92	2.32 2.30	9.26 9.12)
4d	3.5	178	92	$C_{17}H_{11}N_3OS$	66.99 (66.87	3.65 3.63	13.90 13.76)
4e	4.0	184	90	$C_{13}H_{11}N_3O$	69.44	4.94	18.78

					(69.32	4.92	18.66)
4f	4.0	168	92	$C_{17}H_{13}N_3O5$	60.26 (60.18	3.88 3.86	12.42 12.38)

Table III Physical and analytical data of 2-chloro-3-substituted-1,8-naphthyridine 5

Entry	Reaction Time (min)	m.p. °C	Yield (%)	Mol. Formula	Found (%) (Calcd)		
					C	H	N
5a	4.5	181	90	$C_{12}H_7ClN_2O$	62.61 (62.49	3.09 3.06	12.21 12.15)
5b	3.5	174	89	$C_{12}H_7ClN_2S$	58.54 (58.42	3.89 2.86	11.40 11.35)
5c	4.0	193	94	$C_{12}H_6BrClN_2S$	44.39 (44.27	1.88 1.86	8.30 8.06)
5d	3.5	179	92	$C_{17}H_{10}ClN_3S$	63.18 (63.06	3.13 3.11	13.12 12.98)
5e	4.5	185	90	$C_{13}H_{10}ClN_3$	64.19 (64.07	3.15 4.14	17.38 17.24)
5f	4.0	166	92	$C_{17}H_{12}ClN_3O_4$	57.20 (57.08	3.40 3.38	12.03 11.89)

Table IV Physical and analytical data of series of 3-substituted-2-hydrazinyl-1,8-naphthyridine 6a-f

Entry	Reaction Time (min)	m.p. °C	Yield (%)	Mol. Formula	Found (%) (Calcd)		
					C	H	N
6a	20.0	189	92	$C_{12}H_{10}N_4O$	63.81 (63.71	3.49 4.46	19.79 24.76)
6b	15.0	183	94	$C_{12}H_{10}N_4S$	59.60 (59.48	4.18 4.16	23.16 23.12)
6c	14.0	191	93	$C_{12}H_9BrN_4S$	44.99 (44.87	2.84 2.82	17.46 17.44)
6d	14.5	187	90	$C_{17}H_{13}N_5S$	63.98 (63.83	4.13 4.10	22.00 21.93)
6e	15.5	184	92	$C_{13}H_{13}N_5$	65.35 (65.25	5.50 5.48	29.30 29.27)
6f	20.0	178	90	$C_{17}H_{15}N_5O_4$	57.91 (57.79	4.31 4.28	19.87 19.82)

Table V Mass spectral data of compounds 4a-f

Entry	MS(LC-MSD) $[M+H]^+$: *m/z*
4a	213.2
4b	229.3
4c	306.2
4d	306.3
4e	226.2
4f	340.3

Table VI Mass spectral data of compounds 5a-f

Entry	MS(LC-MSD) $[M+H]^+$: *m/z*
5a	231.2
5b	247.3
5c	324.2
5d	323.2
5e	244.3
5f	358.2

Table VII Mass spectral data of compounds 6a-f

Entry	MS(LC-MSD) $[M+H]^+$: *m/z*
6a	227.2
6b	243.2
6c	320.2
6d	319.3
6e	240.2
6f	354.3

Table VIII ^{1}H NMR & ^{13}C NMR data of compounds 4a-f

Entry	^{1}H NMR data (400 MHz, DMSO-d_6) (δ, ppm)	^{13}C NMR data (100 MHz, DMSO-d_6) (δ, ppm)
4a	8.49 (s, 1H), 8.05 (s, 1H), 7.69 (d, *J* = 8.9 Hz, 1H), 7.62 – 7.31 (m, 2H), 7.07 (d, *J* = 7.5 Hz, 1H), 6.47 (t, *J* = 7.5 Hz, 1H), 5.74 (s, 1H)	163.20, 150.13, 145.95, 145.43, 144.04, 137.32, 135.64, 124.51, 117.45, 112.60, 107.12.
4b	8.49 (s, 1H), 8.05 (s, 1H), 7.69 (d, *J* = 8.9 Hz, 1H), 7.62 – 7.32 (m, 2H), 7.07 (d, *J* = 7.5 Hz, 1H), 6.47 (t, *J* = 7.5 Hz, 1H), 5.74 (s, 1H)	163.20, 150.13, 145.97, 145.41, 144.04, 137.32, 135.6, 124.51, 117.45, 112.60, 107.12.
4c	8.52 (s, 1H), 8.06 (s, 1H), 7.77 (s, 1H), 7.58 (s, 1H), 7.42 (d, *J* = 7.5 Hz, 1H), 7.06 (s, 1H), 5.77 (s, 1H).	163.06, 150.13, 145.95, 138.03, 137.32, 133.02, 129.08, 128.27, 122.34, 117.20, 112.02.
4d	8.77 (d, *J* = 8.9 Hz, 1H), 8.16 (d, *J* = 9.1 Hz, 1H), 7.99 – 7.22 (m, 8H), 5.85 (s, 1H).	164.64, 161.81, 154.89, 150.13, 145.95, 137.32, 134.62, 129.65, 127.65, 127.06, 125.25, 117.86, 117.20.

4e	8.51 (s, 1H), 8.05 (s, 1H), 7.62 – 7.26 (m, 2H), 6.74 (d, *J* = 8.9 Hz, 1H), 6.43 (d, *J* = 8.9 Hz, 1H), 6.06 (t, *J* = 7.5 Hz, 1H), 5.73 (s, 1H), 3.61 (s, 3H).	162.94, 150.13, 145.95, 137.32, 136.46, 132.70, 126.24, 122.19, 117.45, 110.76, 105.78, 36.41.
4f	8.63 (d, *J* = 7.5 Hz, 1H), 8.24 (s, 1H), 7.91 (d, *J* = 7.5 Hz, 1H), 7.55 (dt, *J* = 17.4, 7.5 Hz, 3H), 6.86 (s, 1H), 6.04 (s, 1H), 4.30 – 3.92 (m, 5H).	158.75, 150.13, 145.95, 140.68, 137.32, 132.97, 131.05, 130.61, 129.89, 129.41, 124.43, 117.20, 104.60, 67.28.

Table IX ^{1}H NMR & ^{13}C NMR data of compounds 5a-f

Entry	**^{1}H NMR data (400 MHz, DMSO-d_6) (δ, ppm)**	**^{13}C NMR data (100 MHz, DMSO-d_6) (δ, ppm)**
5a	8.67 (d, *J* = 63.6 Hz, 2H), 8.13 (s, 1H), 7.72 (d, *J* = 7.5 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.20 – 6.98 (m, 1H), 6.51 (t, *J* = 7.5 Hz, 1H).	160.38, 152.86, 147.74, 145.04, 140.98, 137.99, 129.60, 126.98, 119.93, 114.41, 113.35, 104.26.
5b	8.88 – 8.57 (m, 2H), 8.15 (d, *J* = 8.9 Hz, 1H), 7.75 (s, 1H), 7.58 – 7.26 (m, 2H), 7.19 (t, *J* = 7.5 Hz, 1H).	160.37, 152.86, 150.12, 137.99, 132.02, 131.56, 129.63, 128.79, 126.12, 119.93, 114.41.
5c	8.88 – 8.57 (m, 2H), 8.15 (dt, *J* = 7.5, 1.4 Hz, 1H), 7.80 (d, *J* = 1.4 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.10 (s, 1H).	160.37, 152.86, 150.78, 137.99, 134.23, 132.09, 128.45, 124.05, 119.93, 114.41, 113.10.
5d	9.14 – 8.76 (m, 2H), 8.27 (d, *J* = 7.5 Hz, 1H), 7.99 – 7.58 (m, 3H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.43 (t, *J* = 7.4 Hz, 2H), 7.35 (t, *J* = 7.5 Hz, 1H).	160.37, 157.59, 154.34, 152.86, 151.29, 138.38, 134.62, 129.65, 128.01, 127.65, 127.06, 119.95, 114.41.
5e	8.76 (s, 1H), 8.60 (s, 1H), 8.16 (s, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 6.82 (dd, *J* = 52.0, 8.9 Hz, 2H), 6.28 (t, *J* = 7.5 Hz, 1H), 3.60 (s, 3H).	160.37, 152.86, 150.77, 137.99, 129.29, 128.81, 125.93, 124.60, 113.77, 110.09, 36.99.
5f	8.87 (s, 1H), 8.60 (s, 1H), 8.47 (s, 1H), 8.23 (s, 1H), 7.91 (s, 2H), 7.49 (s, 1H), 6.04 (s, 1H), 4.33 – 3.97 (m, 4H).	160.37, 152.86, 146.54, 145.81, 133.61, 132.62, 132.35, 130.59, 129.63, 129.10, 126.82, 119.93, 114.41, 104.60, 67.28.

Table X ^{1}H NMR & ^{13}C NMR data of title compounds 6a-f

Entry	**^{1}H NMR data (400 MHz, DMSO-d_6) (δ, ppm)**	**^{13}C NMR data (100 MHz, DMSO-d_6) (δ, ppm)**
6a	8.72 – 8.66 (m, 1H), 8.28 (s, 1H), 8.13 (s, 1H), 7.66 (s, 1H), 7.36 (s, 1H), 7.05 (d, *J* = 8.9 Hz, 1H), 6.48 (d, *J* = 15.0 Hz, 1H), 4.29 (s, 1H), 2.55 (s, 1H), 2.02 (s, 1H).	155.24, 153.41, 145.04, 141.18, 135.79, 132.39, 118.61, 115.65, 113.35, 102.26.
6b	8.72 (s, 1H), 8.36 (s, 1H), 8.17 (s, 1H), 7.71 (s, 1H), 7.39 (d, *J* = 33.7 Hz, 2H), 7.15 (s, 1H), 2.27 (s, 1H), 2.01 (s, 1H), 1.82 (s, 1H).	155.24, 153.41, 144.09, 135.79, 132.02, 128.79, 121.01, 118.61, 117.83, 117.47, 115.65.
6c	8.70 (dd, *J* = 7.5, 1.4 Hz, 1H), 8.36 (d, *J* = 1.4 Hz, 1H), 8.15 (dt, *J* = 7.5, 1.4 Hz, 1H), 7.58 – 7.26 (m, 2H), 7.04 (d, *J* = 1.4 Hz, 1H), 2.84 (d, *J* = 71.1 Hz, 2H), 1.92 (s, 1H).	155.24, 153.41, 144.75, 135.79, 134.23, 132.93, 126.09, 118.63, 116.59, 115.58, 113.10.
6d	8.85 (s, 1H), 8.54 (s, 1H), 8.26 (s, 1H), 7.91 (s, 1H), 7.83 – 7.59 (m, 3H), 7.42 (dd, *J* = 44.2, 24.2, 7.5 Hz, 4H), 2.83 (s, 1H), 2.36 (s, 1H).	155.24, 154.34, 153.41, 146.95, 143.58, 140.59, 135.79, 134.62, 129.65, 127.65, 119.95, 118.61, 115.65, 113.24.
6e	8.71 (s, 1H), 8.19 (d, *J* = 62.1 Hz, 2H), 7.36 (d, *J* = 14.8 Hz, 1H), 6.69 (dd, *J* = 46.7, 8.2 Hz, 2H), 6.25 (t, *J* = 7.5 Hz, 1H), 3.60 (s, 3H), 2.58 (s, 1H), 2.37 (s, 1H), 2.06 (s, 1H).	155.24, 153.41, 144.36, 135.79, 130.03, 125.93, 124.83, 118.61, 115.63, 112.24, 110.09, 103.45, 37.00.

6f	8.79 (s, 1H), 8.41 (s, 1H), 8.07 (s, 1H), 7.87 (d, *J* = 22.6 Hz, 2H), 7.65 (s, 1H), 7.46 (t, *J* = 7.5 Hz, 1H), 6.04 (s, 1H), 4.40 – 3.95 (m, 4H), 1.99 (s, 1H), 1.35 (d, *J* = 56.0 Hz, 2H).	155.24, 153.41, 146.70, 145.04, 136.49, 135.79, 133.82, 133.34, 128.23, 127.66, 126.57, 118.61, 115.65, 114.03, 104.62, 67.28.

Conclusion

Four step synthesis of 3-substituted 2-hydrazinyl-1,8-naphthyridines with good yields were depicted and analytical and physical data shown inrespective tables.

Acknowledgements

We, the authors, express our sincere gratitude to Department of Chemistry, Chaitanya (Deemed to be University), Hanamkonda for the laboratory facilities provided to conduct this research work.

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