Indian Journal of Chemistry
Vol. 56B, June 2017, pp. 670-676

Green synthesis, antibacterial and anti-inflammatory activities of 2-(2-substituted[1,8]naphthyridin-3-yl)-5-(substituted-2-thienyl)-1,3,4-oxadiazoles

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Received 5 January 2016; accepted (revised) 8 February 2017

An efficient and mild method for the synthesis of 2-(2-substituted[1,8]naphthyridin-3-yl)-5-(substituted-2-thienyl)-1,3,4-oxadiazoles **4** is reported by the oxidation of the corresponding N′3-[1-(substituted-2-thienyl)methylidene]-2-sustituted[1,8]naphthyridine-3-carbohydrazides **3** with iodobenzene diacetate($PhI(OAc)_2$) in solid state. The reaction proceeds efficiently giving the products in good yields and excellent purities. The structural assignments of compounds **3** and **4** are based on their elemental analyses and spectral (IR, ^1H NMR and MS) data. The compounds **4** have been screened for their antibacterial and anti-inflammatory activities.

Keywords: 1,8-Naphthyridines, 1,3,4-oxadiazoles, iodobenzene diacetate[$PhI(OAc)_2$] solid state, antibacterial activity, anti-inflammatory activity

1,3,4-Oxadiazoles derivatives represent one of the most active class of compounds possessing a wide spectrum of biological activity[1-3]. Various 1,8-naphthyridines[4-6] and thiophene[7,8] derivatives occupy an important place in medicinal chemistry as they show a variety of pharmacological and microbiological activities. With the increasing public concern over environmental degradation, one of the challenges for chemists is to come up with new approaches that are less hazardous to human health and the environment. The solvents used in organic synthesis are high on the list of environmental pollutants, because they are employed in large amounts and usually are volatile liquids. In recent years organic reactions in the solid state (solvent-free) by grinding have been attracting the synthetic organic chemists because of their simplicity and synthetic value[9,10]. Furthermore, the solid state reaction by grinding has many advantages; reduced pollution, low costs, and simplicity in process and handling. These factors are beneficial to industry as well as to environment. The versatile synthetic utility of organic hypervalent iodine reagents in general and iodobenzene diacetate [$PhI(OAc)_2$] in particular is of current interest[11-13].

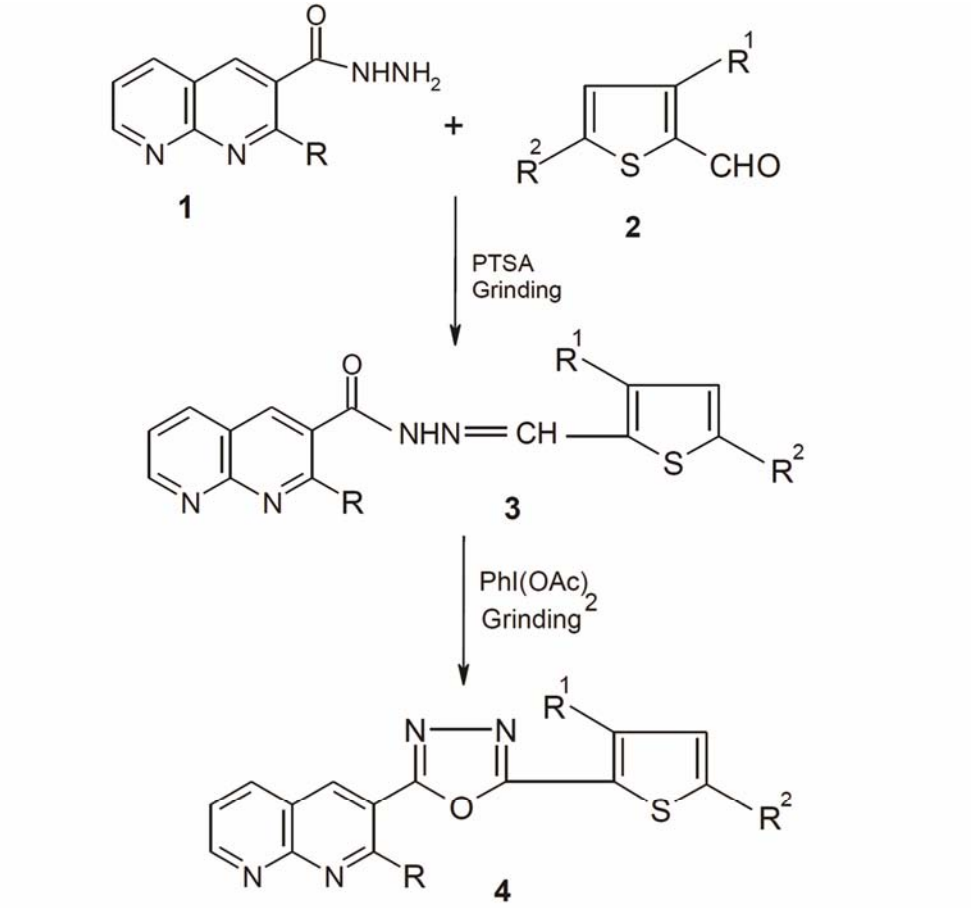
Prompted by these facts, and in continuation of the interest on solid state(solvent-free) organic trans-formations of 1,8-naphthyridine derivatives[14-16], herein is reported an efficient and convenient method for the synthesis of 2-(2-substituted [1,8]naphthyridin-3-yl)-5-(substituted-2-thienyl)-1,3,4-oxadiazoles using iodobenzene diacetate [$PhI(OAc)_2$] in solid state.

Results and Discussion

Condensation of 2-substituted-1,8-naphthyridine-3-carboxylic acid hydrazides **1** with substituted thiophene-2-aldehydes **2** in the presence of catalytic amount of PTSA in solvent-free grinding conditions at RT resulted in the formation of corresponding *N*′3-[1-(substituted-2-thienyl)methylidene]-2-sustituted[1,8] naphthyridine-3-carbohydrazides **3** in excellent yields.

Oxidative cyclization of **3** with $PhI(OAc)_2$ in solid state at RT afforded the respective 2-(2-substituted [1,8]naphthyridin-3-yl)-5-(substituted-2-thienyl)-1,3,4-oxadiazoles **4** in good yields (Scheme I). The oxidative transformation is very clean and rapid. The reaction conditions and work-up procedures are mild, convenient and efficient. Furthermore, it is to be noted that highly pure products were obtained using this procedure and in most cases no further purification was needed. The process is environmentally benign. The experimental procedure is very simple and avoids sophistication.

In a typical case, a mixture of **3a** ($R=CH_3$; $R^1=R^2=H$) and $PhI(OAc)_2$ was ground in a mortar by



	R	R^1	R^2
a:	CH_3	H	H
b:	CH_3	CH_3	H
c:	CH_3	H	NO_2
d:	CF_3	H	H
e:	CF_3	CH_3	H
f:	CF_3	H	NO_2

	R	R^1	R^2
g:	C_6H_5	H	H
h:	C_6H_5	CH_3	H
i:	C_6H_5	H	NO_2
j:	4-$NO_2C_6H_4$	H	H
k:	4-$NO_2C_6H_4$	CH_3	H
l:	4-$NO_2C_6H_4$	H	NO_2

Scheme I

pestle at RT for 6.0 min. After completion of the reaction as indicated by TLC, the reaction mixture is treated with cold water followed by simple processing afforded 2-(2-methyl[1,8]naphthyridin-3-yl)-5-(2-thienyl)-1,3,4-oxadiazole **4a** (R=CH_3; R^1=R^2=H) in 87% yield. The generality of the facile oxidative transformation was established by treating other hydrazones **3b-l** with $PhI(OAc)_2$ under solid state grinding conditions to get the corresponding 2-(2-substituted[1,8]naphthyridin-3-yl)-5-(substituted-2-thienyl) -1,3,4-oxadiazoles **4b-l** (Table I).

The structures of the compounds **3** and **4** were determined by their elemental analyses and spectral (IR, ^{1}H NMR and MS) data. The significant advantages of this procedure are: experimental simplicity, good yields of the products, short reaction times, non-toxicity of the reagent, mild reaction conditions, excellent purity and minimum environmental impact.

Antibacterial activity

All the title compounds **4** were evaluated *in vitro* for their antibacterial activity against the Gram-negative *Escherichia coli* and Gram-positive *Bacillus subtilis* by filter paper disc technique of Vincent and Vincent[17] at 250 and 500 µg/disc concentrations. Gentamycin was used as standard for

Table I — Physical and analytical data of compounds **3** and **4**

Compd	R	R^1	R^2	Reaction Time (min)	m.p. °C	Yield (%)	Mol. formula	Found (%) (Calcd) C	H	N
3a	CH_3	H	H	2.5	242	93	$C_{15}H_{12}N_4OS$	60.92 (60.80	4.10 4.08	18.96 18.91)
3b	CH_3	CH_3	H	2.0	234	96	$C_{16}H_{14}N_4OS$	62.03 (61.92	4.56 4.55	18.09 18.05)
3c	CH_3	H	NO_2	2.0	235	94	$C_{15}H_{11}N_5O_3S$	52.92 (52.78	3.27 3.25	20.58 20.52)
3d	CF_3	H	H	2.5	237	93	$C_{15}H_9F_3N_4OS$	51.55 (51.43	2.60 2.59	16.03 15.99)
3e	CF_3	CH_3	H	2.0	240	95	$C_{16}H_{11}F_3N_4OS$	52.89 (52.75	3.06 3.04	15.43 15.38)
3f	CF_3	H	NO_2	2.0	272	92	$C_{15}H_8F_3N_5O_3S$	45.71 (45.58	2.06 2.04	17.76 17.72)
3g	C_6H_5	H	H	3.0	248	93	$C_{20}H_{14}N_4OS$	67.16 (67.02	3.97 3.94	15.67 15.63)
3h **6a**	C_6H_5	CH_3	H	2.5	215	94	$C_{21}H_{16}N_4OS$	67.85 (67.72	4.35 4.33	15.09 15.04)
3i	C_6H_5	H	NO_2	2.0	252	92	$C_{20}H_{13}N_5O_3S$	59.69 (59.55	3.27 3.25	17.41 17.36)
3j	4-$NO_2C_6H_4$	H	H	3.5	305	92	$C_{20}H_{13}N_5O_3S$	59.68 (59.55	3.27 3.25	17.40 17.36)
3k	4-$NO_2C_6H_4$	CH_3	H	2.5	282	93	$C_{21}H_{15}N_5O_3S$	60.54 (60.42	3.64 3.62	16.83 16.78)
3l **6a**	4-$NO_2C_6H_4$	H	NO_2	2.0	288	90	$C_{20}H_{12}N_6O_5S$	53.70 (53.57	2.72 2.70	18.79 18.74)
4a	CH_3	H	H	6.0	188	87	$C_{15}H_{10}N_4OS$	61.32 (61.21	3.44 3.42	19.08 19.04)
4b	CH_3	CH_3	H	5.5	203	88	$C_{16}H_{12}N_4OS$	62.45 (62.32	3.94 3.92	18.22 18.17)
4c	CH_3	H	NO_2	6.5	223	85	$C_{15}H_9N_5O_3S$	53.22 (53.09	2.69 2.67	20.68 20.64)
4d	CF_3	H	H	6.0	168	86	$C_{15}H_7F_3N_4OS$	51.85 (51.73	2.05 2.03	16.14 16.09)
4e	CF_3	CH_3	H	5.5	196	87	$C_{16}H_9F_3N_4OS$	53.17 (53.04	2.52 2.50	15.50 15.46)
4f	CF_3	H	NO_2	5.0	240	84	$C_{15}H_6F_3N_5O_3S$	45.93 (45.81	1.55 1.54	17.86 17.81)
4g	C_6H_5	H	H	6.5	200	85	$C_{20}H_{12}N_4OS$	67.53 (67.40	3.41 3.39	15.76 15.72)

Contd—

Table I — Physical and analytical data of compounds **3** and **4** —*Contd*

Compd	R	R^1	R^2	Reaction Time (min)	m.p. °C	Yield (%)	Mol. formula	Found (%) (Calcd) C	H	N
4i	C_6H_5	H	NO_2	5.5	241	84	$C_{20}H_{11}N_5O_3S$	59.98	2.78	17.49
6a					195			(59.85	2.76	17.45)
								67.70	3.43	12.65
								(67.57	3.40	12.61)
4j	4-$NO_2C_6H_4$	H	H	7.0	176	84	$C_{20}H_{11}N_5O_3S$	59.97	2.78	17.50
6a					195			(59.85	2.76	17.45)
								67.70	3.43	12.65
								(67.57	3.40	12.61)
4k	4-$NO_2C_6H_4$	CH_3	H	6.5	210	85	$C_{21}H_{13}N_5O_3S$	60.85	3.17	16.90
6a					195			(60.72	3.15	16.86)
								67.70	3.43	12.65
								(67.57	3.40	12.61)
4l	4-$NO_2C_6H_4$	H	NO_2	6.0	273	83	$C_{20}H_{10}N_6O_5S$	53.95	2.28	18.88
6a					195			(53.81	2.26	18.83)
								67.70	3.43	12.65
								(67.57	3.40	12.61)

comparison. The results are presented in Table II. A notable observation being that all the compounds **4** showed antibacterial activity against both the test bacteria at 250 µg/disc concentration. Compounds **4a**, **4b**, **4e**, **4f** and **4h** exhibited significant antibacterial activity. Rest of the compounds displayed moderate activity. Compound **4e** exhibited antibacterial activity comparable to the standard drug Gentamycin.

Anti-inflammatory

The anti-inflammatory activity of the compounds **4** was carried out using the carrageenan induced rat paw edema method[18], using Diclofenac sodium as reference drug for comparison. The results are summarized in Table III. The screening data of the compounds **4** indicate that all the compounds exhibited anti-inflammatory activity. Compounds **4b**, **4d**, **4e** and **4k** have displayed promising anti-inflammatory activity. Other compounds showed moderate anti-inflammatory activity.

Experimental Section

Melting points were determined on a Cintex melting point apparatus and are uncorrected. Homogeneity of the compounds was checked using precoated TLC plates (Merk, 60F-254). IR spectra (KBr) were recorded on a Perkin-Elmer FT-IR spectrophotometer, ^{1}H NMR spectra on a Varian Gemini 300 MHz spectrometer (Chemical shifts in δ, ppm) using TMS as internal standard and mass spectra on a PE-SCIEX API 3000 LC/MS/MS instrument. Elemental analyses were performed on a Perkin-Elmer 240 CHN analyzer.

Table II — Antibacterial activity data of compounds **4**

Compd	Inhibition zone (in mm)			
	E. coli at		*B. subtilis* at	
	250 µg/disc	500 µg/disc	250 µg/disc	500 µg/disc
4a	9.0	13.5	6.5	11.5
4b	9.5	15.0	7.0	12.0
4c	8.5	12.0	6.0	11.0
4d	11.0	20.5	7.0	13.5
4e	11.5	21.5	7.5	14.5
4f	9.5	16.5	6.5	13.0
4g	8.5	12.5	6.0	11.5
4h	9.0	14.0	6.5	12.0
4i	8.0	11.5	5.5	10.0
4j	7.5	11.0	5.0	8.5
6a				
4k	8.5	13.0	6.0	10.5
6a				
4l	8.0	12.0	5.5	9.0
Gentamycin	12.0	22.0	8.0	15.0

General procedure for the synthesis of N′3-[1-(substituted -2-thienyl)methylidene]-2-substituted [1,8]naphthyridine-3-carbohydrazides, 3

A mixture of **1** (0.01 mol), substituted thiophene-2-aldehyde **2** (0.01 mol) and PTSA (0.015 mol) was ground by pestle and mortar at RT for specified time (Table I). On completion of the reaction (monitored by TLC), the reaction-mixture was treated with

Table III — Anti-inflammatory screening data of compounds **4** (Carrageenan-induced paw edema test in rats) Rat paw edema in mL[b]

	(Treatment in hours)			
	1 h	2 h	3 h	4 h
4a	2.31±0.324 15.69	2.06±0.312** 28.22	1.60±0.260** 48.71	0.89±0.258*** 71.74
4b	2.12±0.251 22.62	1.92±0.365*** 33.10	1.27±0.367*** 59.29	0.60±0.273*** 80.95
4c	2.14±0.334 21.89	1.63±0.376*** 43.20	1.10±0.271*** 64.74	0.63±0.292*** 80.00
4d	2.24±0.328 18.24	1.82±0.340*** 36.58	1.31±0.275*** 58.01	0.61±0.308*** 80.63
4e	2.01±0.348 26.64	1.54±0.361*** 46.34	1.02±0.278*** 67.30	0.56±0.254*** 82.22
4f	2.04±0.324 25.54	1.81±0.352*** 36.93	1.12±0.274*** 64.10	0.67±0.284*** 78.73
4g	2.30±0.327 16.05	2.02±0.354** 29.61	1.32±0.281*** 57.69	0.91±0.254*** 71.11
4h	2.17±0.327 20.80	1.92±0.312*** 33.10	1.29±0.274*** 58.65 6	0.68±0.347*** 78.41
4i	2.21±0.372 19.34	1.98±0.312*** 31.10	1.31±0.387*** 58.01	0.74±0.354*** 76.50
4j	2.43±0.384 11.31	2.27±0.382* 20.90	1.60±0.383** 48.71	1.02±0.318*** 67.61
4k **6a**	2.15±0.318 21.53 34.	1.88±0.394*** 34.49	1.25±0.278*** 59.93	0.62±0.284*** 80.32
4l	2.18±0.321 20.43	1.84±0.382*** 35.88	1.28±0.264*** 58.97	0.64±0.276*** 79.68
control	2.74±0.242 NA	2.87±0.254 NA	3.12±0.289 NA	3.15±0.291 NA
Diclofenac sodium	1.84±0.251*** 32.84	1.32±0.251*** 54.01	0.91±0.257*** 70.83	0.52±0.309*** 83.49

[a] Dose level: test compounds (100mg/kg b.wt), Diclofenac sodium (10mg/kg b.wt)
[b] Values are expressed as mean± SD (number of animals N= 6 rats)
Statistically significant compared to respective control values, ***P<0.001, **P<0.01, *P<0.05 (Dunnet's test)

ice-cold water. The resulting solid product was filtered, washed with water and purified by recrystallization from ethanol to afford **3** (Table I).

3a: IR (KBr): 3169 (NH), 1672 (C=O), 1604 cm^{-1} (C=N); ^1H NMR (300 MHz, $CDCl_3$): δ 2.62 (s, 3H, CH_3), 7.71 (m, 1H, C_6-H), 8.50 (m, 2H, C_4-H, C_5-H), 9.11 (m, 1H, C_7-H), 8.60 (s, 1H, N=CH), 7.16-7.72 (m, 3H, C_3-H, C_4-H, C_5-H of thiophene), 12.02 (s, 1H, NH); LC-MS: *m/z* 297.1 $[M+H]^+$.

3b: IR (KBr): 3195 (NH), 1642 (C=O), 1595 cm^{-1} (C=N); ^1H NMR (300 MHz, $CDCl_3$): δ 2.32 (s, 3H, CH_3), 2.65 (s, 3H, CH_3), 7.67 (m, 1H, C_6-H), 8.52 (m, 2H, C_4-H, C_5-H), 9.12 (m, 1H, C_7-H), 8.59 (s, 1H, N=CH), 7.00 (d, 1H, C_4-H of thiophene), 7.62 (d, 1H, C_5-H of thiophene), 11.93 (s, 1H, NH); LC-MS: *m/z* 311.18 $[M+H]^+$.

3c: IR (KBr): 3162 (NH), 1683 (C=O), 1607 cm^{-1} (C=N); ^1H NMR (300 MHz, $CDCl_3$): δ 2.63 (s, 3H, CH_3), 8.15 (m, 1H, C_6-H), 8.52 (m, 2H, C_4-H, C_5-H), 9.13

(m, 1H, C_7-H), 8.64 (s, 1H, N=CH), 7.65 (d, 1H, C_3-H of thiophene), 8.03 (d, 1H, C_4-H of thiophene), 12.40 (s, 1H, NH); LC-MS: *m/z* 342.06 $[M+H]^+$.

3d: IR (KBr): 3157 (NH), 1658 (C=O), 1603 cm^{-1} (C=N); ^1H NMR (300 MHz, $CDCl_3$): δ 7.89 (m, 1H, C_6-H), 8.51 (m, 2H, C_4-H, C_5-H), 9.33 (m, 1H, C_7-H), 9.03 (s, 1H, N=CH), 7.42-7.68 (m, 3H, C_3-H, C_4-H, C_5-H of thiophene), 12.01 (s, 1H, NH); LC-MS: *m/z* 351.17 $[M+H]^+$.

3e: IR (KBr): 3160 (NH), 1675 (C=O), 1605 cm^{-1} (C=N); ^1H NMR (300 MHz, $CDCl_3$): δ 2.31 (s, 3H, CH_3), 7.68 (m, 1H, C_6-H), 8.53 (m, 2H, C_4-H, C_5-H), 9.11 (m, 1H, C_7-H), 8.60 (s, 1H, N=CH), 7.00 (d, 1H, C_4-H of thiophene), 7.62 (d, 1H, C_5-H of thiophene), 11.95 (s, 1H, NH); LC-MS: *m/z* 365.14 $[M+H]^+$.

3f: IR (KBr): 3172 (NH), 1668 (C=O), 1606 cm^{-1} (C=N); ^1H NMR (300 MHz, $CDCl_3$): δ 8.02 (m, 1H, C_6-H), 8.53 (m, 2H, C_4-H, C_5-H), 9.12 (m, 1H, C_7-H), 8.64 (s, 1H, N=CH), 7.68 (d, 1H, C_3-H of thiophene), 8.15 (d, 1H, C_4-H of thiophene), 12.42 (s, 1H, NH); LC-MS: *m/z* 396.0 $[M+H]^+$.

3g: IR (KBr): 3159 (NH), 1659 (C=O), 1603 cm^{-1} (C=N); ^1H NMR (300 MHz, $CDCl_3$): δ 7.80 (m, 1H, C_6-H), 8.59 (m, 2H, C_4-H, C_5-H), 9.18 (m, 1H, C_7-H), 8.77 (s, 1H, N=CH), 6.97-7.23 (m, 3H, C_3-H, C_4-H, C_5-H of thiophene), 7.41-7.52 (m, 5H, Ar-H), 12.03 (s, 1H, NH); LC-MS: *m/z* 359.16 $[M+H]^+$.

3h: IR (KBr): 3158 (NH), 1652 (C=O), 1601 cm^{-1} (C=N); ^1H NMR (300 MHz, $CDCl_3$): δ 2.26 (s, 3H, CH_3), 7.82 (m, 1H, C_6-H), 8.57 (m, 2H, C_4-H, C_5-H), 9.17 (m, 1H, C_7-H), 8.76 (s, 1H, N=CH), 6.81 (d, 1H, C_4-H of thiophene), 7.03 (d, 1H, C_5-H of thiophene), 7.44-7.68 (m, 5H, Ar-H), 12.00 (s, 1H, NH); LC-MS: *m/z* 373.05 $[M+H]^+$.

3i: IR (KBr): 3163 (NH), 1680 (C=O), 1604 cm^{-1} (C=N); ^1H NMR (300 MHz, $CDCl_3$): δ 7.90 (m, 1H, C_6-H), 8.30 (m, 2H, C_4-H, C_5-H), 9.24 (m, 1H, C_7-H), 8.48 (s, 1H, N=CH), 6.99 (d, 1H, C_3-H of thiophene), 7.51 (d, 1H, C_4-H of thiophene), 7.57-7.69 (m, 5H, Ar-H), 12.02 (s, 1H, NH); LC-MS: *m/z* 404.23 $[M+H]^+$.

3j: IR (KBr): 3159 (NH), 1659 (C=O), 1605 cm^{-1} (C=N); ^1H NMR (300 MHz, $CDCl_3$): δ 8.02 (m, 1H, C_6-H), 8.63 (m, 2H, C_4-H, C_5-H), 9.23 (m, 1H, C_7-H), 8.88 (s, 1H, N=CH), 6.99-7.50 (m, 3H, C_3-H, C_4-H, C_5-H of thiophene), 7.70-7.81 (m, 4H, Ar-H), 12.15 (s, 1H, NH); LC-MS: *m/z* 404.19 $[M+H]^+$.

3k: IR (KBr): 3165 (NH), 1662 (C=O), 1607 cm^{-1} (C=N); ^1H NMR (300 MHz, $CDCl_3$): δ 2.25 (s, 3H, CH_3), 8.03 (m, 1H, C_6-H), 8.64 (m, 2H, C_4-H, C_5-H), 9.23 (m, 1H, C_7-H), 8.86 (s, 1H, N=CH), 6.99 (d, 1H, C_4-H of thiophene), 7.38 (d, 1H, C_5-H of thiophene), 7.76-7.81 (m, 4H, Ar-H), 12.04 (s, 1H, NH); LC-MS: *m/z* 418.23 $[M+H]^+$.

3l: IR (KBr): 3179 (NH), 1665 (C=O), 1598 cm^{-1} (C=N); ^1H NMR (300 MHz, $CDCl_3$): δ 8.00 (m, 1H, C_6-H), 8.66 (m, 2H, C_4-H, C_5-H), 9.25 (m, 1H, C_7-H), 8.93 (s, 1H, N=CH), 7.35 (d, 1H, C_3-H of thiophene), 7.62 (d, 1H, C_4-H of thiophene), 7.78-7.82 (m, 4H, Ar-H), 12.35 (s, 1H, NH); LC-MS: *m/z* 449.23 $[M+H]^+$.

General procedure for the synthesis of 2-(2-substituted [1,8]naphthyridin-3-yl)-5-(substituted-2-thienyl)-1,3,4-oxadiazoles, 4

A mixture of appropriate hydrazone **3** (0.01 mol) and $PhI(OAc)_2$ (0.01 mol) was ground in a mortar by pestle at RT for the period indicated in Table I. After complete conversion as indicated by TLC, the reaction mixture was treated with cold water. The solid thus obtained was filtered, washed with water and purified by recrystallization from ethanol to give **4** (Table I).

4a: IR (KBr): 1602cm^{-1} (C=N); ^1H NMR (300 MHz, $CDCl_3$): δ 3.10 (s, 3H, CH_3), 8.05 (m, 1H, C_6-H), 8.65 (m, 1H, C_5-H), 8.83 (s, 1H, C_4-H), 9.17 (m, 1H, C_7-H), 7.35-8.02 (m, 3H, C_3-H, C_4-H, C_5-H of thiophene); LC-MS: *m/z* 295.0 $[M+H]^+$.

4b: IR (KBr): 1606 cm^{-1} (C=N); ^1H NMR (300 MHz, $CDCl_3$): δ 2.68 (s, 3H, CH_3), 3.08 (s, 3H, CH_3), 7.71 (m, 1H, C_6-H), 8.68 (m, 1H, C_5-H), 9.12 (s, 1H, C_4-H), 9.16 (m, 1H, C_7-H), 7.22 (d, 1H, C_4-H of thiophene), 7.90 (d, 1H, C_5-H of thiophene); LC-MS: *m/z* 309.20 $[M+H]^+$.

4c: IR (KBr): 1604 cm^{-1} (C=N); ^1H NMR (300 MHz, $CDCl_3$): δ 3.09 (s, 3H, CH_3), 8.33 (m, 1H, C_6-H), 8.64 (m, 1H, C_5-H), 9.25 (s, 1H, C_4-H), 9.18 (m, 1H, C_7-H), 7.37 (d, 1H, C_3-H of thiophene), 8.08 (d, 1H, C_4-H of thiophene); LC-MS: *m/z* 340.16 $[M+H]^+$.

4d: IR (KBr): 1596 cm^{-1} (C=N); ^1H NMR (300 MHz, $CDCl_3$): δ 8.03 (m, 1H, C_6-H), 8.65 (m, 1H, C_5-H), 9.19 (s, 1H, C_4-H), 9.16 (m, 1H, C_7-H), 7.33-8.03 (m, 3H, C_3-H, C_4-H, C_5-H of thiophene); LC-MS: *m/z* 349.4 $[M+H]^+$.

4e: IR (KBr): 1603 cm^{-1} (C=N); ^1H NMR (300 MHz, $CDCl_3$): δ 2.67 (s, 3H, CH_3), 7.89 (m, 1H, C_6-H), 8.70 (m, 1H, C_5-H), 9.11 (s, 1H, C_4-H), 9.16 (m, 1H, C_7-H), 7.22 (d, 1H, C_4-H of thiophene), 7.90 (d, 1H, C_5-H of thiophene); LC-MS: *m/z* 363.19 $[M+H]^+$.

4f: IR (KBr): 1601 cm^{-1} (C=N); ^1H NMR (300 MHz, $CDCl_3$): δ 8.33 (m, 1H, C_6-H), 8.65 (m, 1H, C_5-H), 9.26 (s, 1H, C_4-H), 9.41 (m, 1H, C_7-H), 7.36 (d, 1H,

C_3-H of thiophene), 8.08 (d, 1H, C_4-H of thiophene); LC-MS: *m/z* 394.0 $[M+H]^+$.

4g: IR (KBr): 1599 cm^{-1} (C=N); ^1H NMR (300 MHz, $CDCl_3$): δ 7.95 (m, 1H, C_6-H), 8.74 (m, 1H, C_5-H), 9.28 (s, 1H, C_4-H), 9.23 (m, 1H, C_7-H), 7.25-7.61 (m, 3H, C_3-H, C_4-H, C_5-H of thiophene), 7.66-7.81 (m, 5H, Ar-H); LC-MS: *m/z* 357.14 $[M+H]^+$.

4h: IR (KBr): 1600 cm^{-1} (C=N); ^1H NMR (300 MHz, $CDCl_3$): δ 2.16 (s, 3H, CH_3), 7.78 (m, 1H, C_6-H), 8.75 (m, 1H, C_5-H), 9.23 (s, 1H, C_4-H), 9.25 (m, 1H, C_7-H), 7.07 (d, 1H, C_4-H of thiophene), 7.50 (d, 1H, C_5-H of thiophene), 7.54-7.60 (m, 5H, Ar-H); LC-MS: *m/z* 371.4 $[M+H]^+$.

4i: IR (KBr): 1602 cm^{-1} (C=N); ^1H NMR (300 MHz, $CDCl_3$): δ 8.23 (m, 1H, C_6-H), 8.76 (m, 1H, C_5-H), 9.34 (s, 1H, C_4-H), 9.27 (m, 1H, C_7-H), 7.37 (d, 1H, C_3-H of thiophene), 7.69 (d, 1H, C_4-H of thiophene), 7.75-7.82 (m, 5H, Ar-H); LC-MS: *m/z* 402.18 $[M+H]^+$.

4j: IR (KBr): 1599 cm^{-1} (C=N); ^1H NMR (300 MHz, $CDCl_3$): δ 8.36 (m, 1H, C_6-H), 8.76 (m, 1H, C_5-H), 9.39 (s, 1H, C_4-H), 9.28 (m, 1H, C_7-H), 7.26-7.69 (m, 3H, C_3-H, C_4-H, C_5-H of thiophene), 7.71-7.95 (m, 4H, Ar-H); LC-MS: *m/z* 402.3 $[M+H]^+$.

4k: IR (KBr): 1605 cm^{-1} (C=N); ^1H NMR (300 MHz, $CDCl_3$): δ 2.28 (s, 3H, CH_3), 8.37 (m, 1H, C_6-H), 8.78 (m, 1H, C_5-H), 9.36 (s, 1H, C_4-H), 9.26 (m, 1H, C_7-H), 6.81 (d, 1H, C_4-H of thiophene), 7.26 (d, 1H, C_5-H of thiophene), 7.42-7.50 (m, 4H, Ar-H); LC-MS: *m/z* 416.03 $[M+H]^+$.

4l: IR (KBr): 1603 cm^{-1} (C=N); ^1H NMR (300 MHz, $CDCl_3$): δ 8.36 (m, 1H, C_6-H), 8.79 (m, 1H, C_5-H), 9.44 (s, 1H, C_4-H), 9.30 (m, 1H, C_7-H), 7.23 (d, 1H, C_3-H of thiophene), 7.72 (d, 1H, C_4-H of thiophene), 7.78-7.91 (m, 4H, Ar-H); LC-MS: *m/z* 447.0 $[M+H]^+$.

Acknowledgement

The authors are thankful to the Director, IICT Hyderabad for providing ^1H NMR and mass spectra. Two of them (ChV and ANR) are grateful to UGC and CSIR, New Delhi for the award of BSR-RFSMS Fellowship and Senior Research Fellowship, respectively.

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