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Synthesis, antimicrobial and antiinflammatory activities of 1,3,4-oxadiazoles linked to naphtho[2,1-*b*]furan

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Condensation of naphtho[2,1-*b*]furan-2-carboxyhydrazide **1** with different aromatic aldehydes affords the corresponding N^1-[(1*E*)-arylmethylene]-naphtho[2,1-*b*]furan-2-carboxyhydrazides **2a-h**. These compounds undergo cyclization with acetic anhydride and mercuric oxide to yield 3-acetyl-5-naphtho[2,1-*b*]furan-2-yl-2-aryl-2,3-dihydro-1,3,4-oxadiazoles **3a-h** and 2-naphtho[2,1-*b*]furan-2-yl-5-aryl-1,3,4-oxadiazoles **4a-h** respectively. The compound **1** on refluxing with carbon disulphide and ethanolic potassium hydroxide followed by acidification with hydrochloric acid furnishes 5-naphtho[2,1-*b*]furan-2-yl-1,3,4-oxadiazole-2(3*H*)-thione **5**. It is converted into Mannich bases 3-(anilinomethyl)-5-naphtho[2,1-*b*]furan-2-yl-1,3,4-oxadiazole-2(3*H*)-thiones **6a-h** on treatment with formaldehyde and appropriate aromatic amines. All the newly synthesized compounds are characterized by elemental analysis and spectral studies. The selected compounds have been screened for their antimicrobial and anti-inflammatory activities.

Keywords: 1,3,4-Oxadiazole, naphtho[2,1-*b*]furan, thione, Mannich base, antimicrobial activity, antiinflammatory activity

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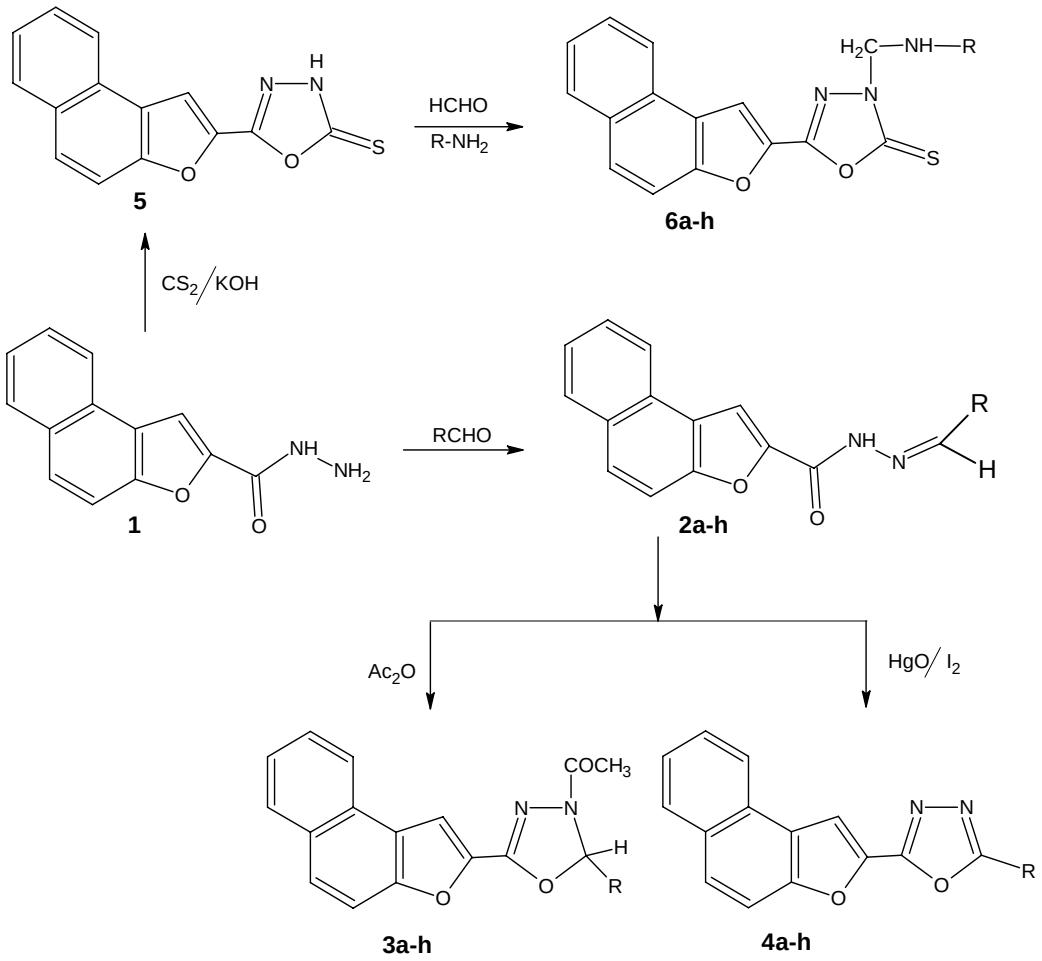
Among the wide variety of heterocycles that have been explored for developing pharmaceutically important molecules, 1,3,4-oxadiazole derivatives have played an vital role in the medicinal chemistry. There are large number of synthetic compounds with oxadiazole nucleus used for antibacterial[1-5], antifungal[6-9], analgesic and antiinflammatory[10-13] activities, when properly substituted in 2 and 5 positions. Various biological applications have been reported for naphtho[2,1-*b*]furan derivatives, such as antimicrobial, antiinflammatory, analgesic and anthelmintic activities[14-17]. The broad spectrum of therapeutic values of naphtho[2,1-*b*]furan and oxadiazole ring system prompted us to synthesize the title compounds and screen them for pharmacological activities. The sequence of reactions is as shown in **Scheme I**.

The reaction of starting compound, naphtho[2,1-*b*]furan-2-carboxyhydrazide **1** (ref.18) with appropriate aldehydes afforded the corresponding N^1-[(1*E*)-arylmethylene]-naphtho[2, 1-*b*]furan-2-carboxyhydrazides **2a-h**. Their IR spectra showed carbonyl peak in the region 1644-1700 cm^{-1}. The structures were further confirmed by recording ^1H NMR spectra. Cyclization of these arylidene derivatives with acetic anhydride gave the desired 3-acetyl-5-naphtho-[2,1-*b*]furan-2-yl-2-aryl-2,3-dihydro-1, 3, 4-oxadiazoles **3a-h,** while oxidation of the arylidene derivatives with iodine and mercuric oxide afforded the 2-naphtho[2, 1-*b*]furan-2-yl-5-aryl-1, 3, 4-oxadiazoles **4a-h**. The assigned structures have been confirmed by the disappearance of carbonyl peak in the IR spectra and -NH proton in the ^1H NMR spectral studies.

The treatment of the acid hydrazide with carbon disulphide and potassium hydroxide in ethanol furnished 5-naphtho[2,1-*b*]furan-2-yl-1,3,4-oxadiazole-2(3*H*)-thione **5**. The IR spectrum of **5** revealed the presence of thiocarbonyl group at 1172 cm^{-1}, as well as -NH absorption at 3219 cm^{-1}. Reaction of **5** with formaldehyde and various aromatic amines gave the corresponding Mannich bases 3-(anilinomethyl)-5-naphtho[2, 1-*b*]furan-2-yl-1, 3, 4-oxadiazole-2(3*H*)-thiones **6a-h**. The structures of the above compounds were confirmed by ^1H NMR, ^{13}C NMR and mass spectral studies depicted in **Table I**. The characterization data of all the newly synthesized compounds are tabulated in **Table II**.

Antimicrobial activity

The antimicrobial activity of some selected compounds were determined using cup plate method[19]. The *in vitro* antibacterial activity was carried out against 24 hr old culture of *Escherichia coli*, *Micrococus luteus* and *Staphylococcus aureus*.



2,3 & 4	R	6	R
a	C_6H_5	**a**	C_6H_5
b	*m*-Cl C_6H_4	**b**	*m*-Cl C_6H_4
c	*p*-Cl C_6H_4	**c**	*p*-Cl C_6H_4
d	*m*-HO C_6H_4	**d**	*m*-H_3CO C_6H_4
e	*p*-HO C_6H_4	**e**	*p*-H_3CO C_6H_4
f	*p*-H_3CO C_6H_4	**f**	*p*-H_3C C_6H_4
g	*m*-O_2N C_6H_4	**g**	*m*-O_2N C_6H_4
h	*p*-O_2N C_6H_4	**h**	*p*-O_2N C_6H_4

Scheme I

The fungi used were *Aspergellius flavus*, *Aspergillus niger* and *Curvuliaria lunata*. The compounds were tested at a concentration of 0.001 mole/mL in dimethyl formamide against all the organisms. Chloramphenicol (0.001 mole/mL) and flucanazole (0.001 mole/mL) were used as standard for antibacterial and antifungal activity respectively.

Amongst the compounds tested for antimicrobial activity, the compound **4f** exhibited promising activity against all the six organisms. The compound **4c** was active against *S.aureus* and *E.coli*. The results showed that the activity was independent of nature of substituent on the compounds as it is depicted in **Table III**.

Antiinflammatory activity

Some selected compounds were screened for antiinflammatory activity by carragenin induced rat paw edema method[20] on albino rats (Wistar strain). Measurement of paw volume was carried by using plethysmometer. Ibuprofen in Tween-80 (0.1% per mL) at a dose of 40 mg/kg body weight served as standard. The test compounds at a dose of 30 mg/kg body weight in Tween-80 (0.1% per mL) solution

Table I — Characterization data of compounds

Compd	^{1}H NMR (δ, CDCl3/DMSO-*d*6)	^{13}C NMR (δ in ppm, $CDCl_3$/DMSO-d_6)	Mass (m/z)
2a	7.0-8.3 (m, 12H, ArH), 8.4 (s, 1H, CH=N), 9.65 (s, 1H, NH)	29.71 (CH), 151.68 (CO), 111.29-149.15 (other carbons)	315 (M^{+1})
2c	7.4-8.57 (m, 11H, ArH), 8.7 (s, 1H, CH=N), 12.6 (s, 1H, NH).		350 (M^{+1})
2f	4.3 (s, 3H, OCH_3), 7.6-8.5 (m, 11H, ArH), 8.65 (s, 1H, CH=N), 12.12 (s, 1H, NH)	18.49 (CH), 55.36 (OCH_3), 161.72 (CO), 110.10-160.16 (other carbons)	345 (M^{+1})
2g	7.59-8.64 (m, 12H, ArH & CH=N), 12.5 (s, 1H, NH)		358, 311, 194, 167, 154, 127, 77
3a	2.04 (s, 3H, $COCH_3$), 7.3-8.45 (m, 11H, ArH), 8.6 (s, 1H, CH)	16.12 (CH_3), 164.53 (CO), 110.24-157.54 (other carbons)	357 (M^{+1})
3c	2.15 (s, 3H, $COCH_3$), 7.2-8.52 (m, 11H, ArH), 8.62 (s, 1H, CH)		392 (M^{+1})
3f	2.1 (s, 3H, $COCH_3$), 3.88 (s, 3H, OCH_3), 7.2-8.5 (m, 11H, ArH), 8.6 (s, 1H, CH)	15.26 (CH_3), 55.54 (OCH_3), 163.66 (CO), 109.77-156.76 (other carbons)	386 (M^{+1})
3g	2.2 (s, 3H, $COCH_3$), 7.3-8.2 (m, 11H, ArH), 8.6 (s, 1H, CH)		359, 338, 211, 167, 154, 127, 77
4c	7.1-8.4 (m, 11H, ArH)	155.34, 156.53 (oxadiazol carbons C=N), 108.58-151.24 (other carbons)	348 (M^{+1})
4e	4.3 (b, 1H, OH), 7.2-8.7 (m, 11H, ArH)		329 (M^{+1})
4f	3.9 (s, 3H, OCH_3), 7.0-8.2 (m, 11H, ArH)	54.56 (OCH_3), 154.25, 155.31 (oxadiazol carbons C=N), 109.75-152.45 (other carbons)	343 (M^{+1})
4g	7.3-8.6 (m, 11H, ArH)		358 (M^{+1})
5	7.6-8.5 (m, 8H, NH & ArH)		269, 212, 167, 154, 127, 77
6c	2.4 (s, 2H, CH_2), 7.0-8.4 (m, 12H, NH & ArH)	56.01 (CH_2), 159.8 (CN), 166.71 (CS), 110.4-154.2 (other carbons)	
6e	2.44 (s, 2H, CH_2), 3.91 (s, 3H, OCH_3), 5.56 (s, 1H, NH), 7.0-8.4 (m, 11H, ArH)		
6f	2.5 (s, 2H, CH_2), 3.35 (m, 3H, CH_3), 7.0-8.4 (m, 12H, NH & ArH)		386, 372, 297, 267, 209, 167, 154, 127, 77
6h	2.49 (s, 2H, CH_2), 5.6 (s, 1H, NH), 7.0-8.4 (m, 11H, ArH)	55.23 (CH_2), 160.47 (CN), 166.71 (CS), 110.6-153.21 (other carbons)	417, 296, 267, 208, 167, 154, 127, 77

Table II — Characterization data of synthesized compounds

Compd	R	Mol formula	m.p. °C	Yield (%)	Found % (Calcd) C	H	N
2a	C_6H_5	$C_{20}H_{14}N_2O_2$	186	91	76.22 (76.42	4.37 4.49	8.73 8.91)
2b	C_6H_4-3-Cl	$C_{20}H_{13}N_2O_2Cl$	195	84	68.45 (68.87	3.33 3.76	8.91 8.03)
2c	C_6H_4-4-Cl	$C_{20}H_{13}N_2O_2Cl$	204	89	68.43 (68.87	3.49 3.76	7.91 8.03)
2d	C_6H_4-3-OH	$C_{20}H_{14}N_2O_3$	188	79	72.43 (72.72	4.19 4.27	8.11 8.48)
2e	C_6H_4-4-OH	$C_{20}H_{14}N_2O_3$	179	74	72.39 (72.72	4.09 4.27	8.19 8.48)
2f	C_6H_4-4-OCH_3	$C_{21}H_{16}N_2O_3$	214	85	73.03 (73.24	4.49 4.68	7.95 8.13)
2g	C_6H_4-3-NO_2	$C_{20}H_{13}N_3O_4$	189	81	66.44 (66.85	3.24 3.65	10.88 11.69)

Contd —

Table II — Characterization data of synthesized compounds — *Contd*

Compd	R	Mol formula	m.p. °C	Yield (%)	Found % (Calcd) C	H	N
2h	C_6H_4-4-NO_2	$C_{20}H_{13}N_3O_4$	194	86	66.49 (66.85	3.36 3.65	11.91 11.69)
3a	C_6H_5	$C_{22}H_{16}N_2O_3$	226	68	74.06 (74.15	4.37 4.53	7.65 7.86)
3b	C_6H_4-3-Cl	$C_{22}H_{15}N_2O_3Cl$	235	62	67.35 (67.61	3.77 3.87	7.02 7.17)
3c	C_6H_4-4-Cl	$C_{22}H_{15}N_2O_3Cl$	228	69	67.34 (67.61	3.56 3.87	6.91 7.17)
3d	C_6H_4-3-OH	$C_{22}H_{16}N_2O_4$	214	63	70.56 (70.96	4.25 4.33	7.22 7.52)
3e	C_6H_4-4-OH	$C_{22}H_{16}N_2O_4$	205	58	70.42 (70.96	4.11 4.33	7.41 7.52)
3f	C_6H_4-4-OCH_3	$C_{23}H_{18}N_2O_4$	219	64	71.35 (71.49	4.38 4.70	7.07 7.25)
3g	C_6H_4-3-NO_2	$C_{22}H_{15}N_3O_5$	228	61	65.75 (65.83	3.42 3.77	10.21 10.47)
3h	C_6H_4-4-NO_2	$C_{22}H_{15}N_3O$	231	59	65.69 (65.83	3.56 3.77	10.39 10.47)
4a	C_6H_5	$C_{20}H_{12}N_2O_2$	214	63	76.78 (76.91	3.82 3.87	8.88 8.97)
4b	C_6H_4-3-Cl	$C_{20}H_{11}N_2O_2Cl$	228	56	68.97 (69.27	3.11 3.20	8.05 8.08)
4c	C_6H_4-4-Cl	$C_{20}H_{11}N_2O_2Cl$	239	59	69.21 (69.27	3.17 3.20	7.91 8.08)
4d	C_6H_4-3-OH	$C_{20}H_{12}N_2O_3$	235	52	73.02 (73.16	3.52 3.68	8.49 8.53)
4e	C_6H_4-4-OH	$C_{20}H_{12}N_2O_3$	227	57	72.12 (73.16	3.49 3.68	8.36 8.53)
4f	C_6H_4-4-OCH_3	$C_{21}H_{14}N_2O_3$	238	58	73.66 (73.68	4.03 4.12	7.95 8.18)
4g	C_6H_4-3-NO_2	$C_{20}H_{11}N_3O_4$	243	62	67.05 (67.23	3.01 3.10	11.68 11.76)
4h	C_6H_4-4-NO_2	$C_{20}H_{11}N_3O_4$	236	67	67.21 (67.23	3.00 3.10	11.65 11.76)
5	-	$C_{14}H_8N_2O_2S$	233	74	62.11 (62.67	3.56 3.01	10.32 10.44)
6a	C_6H_5	$C_{21}H_{15}N_3O_2S$	224	63	67.52 (67.54	4.01 4.05	11.14 11.25)
6b	C_6H_4-3-Cl	$C_{21}H_{14}N_3O_2SCl$	240	55	61.79 (61.84	3.37 3.46	10.19 10.30)
6c	C_6H_4-4-Cl	$C_{21}H_{14}N_3O_2SCl$	246	59	61.67 (61.84	3.39 3.46	10.26 10.30)
6d	C_6H_4-3-OCH_3	$C_{22}H_{17}N_3O_3S$	229	49	65.18 (65.49	4.23 4.25	10.29 10.42)
6e	C_6H_4-4-OCH_3	$C_{22}H_{17}N_3O_3S$	214	57	65.42 (65.49	4.18 4.25	10.41 10.42)
6f	C_6H_4-4-CH_3	$C_{22}H_{17}N_3O_2S$	232	65	68.13 (68.20	4.36 4.42	10.56 10.85)
6g	C_6H_4-3-NO_2	$C_{21}H_{14}N_4O_4S$	247	60	60.25 (60.28	3.19 3.37	13.23 13.39)
6h	C_6H_4-4-NO_2	$C_{21}H_{14}N_4O_4S$	256	67	60.17 (60.28	3.33 3.37	13.28 13.39)

Table III — Antimicrobial activity of the some selected compounds

Compd	Antibacterial activity Zone of inhibition in mm			Antifungal activity Zone of inhibition in mm		
	E.coli	*M.luteus*	*S.aureus*	*A.flaves*	*A.niger*	*C.lunata*
2a	-	-	-	05	-	-
2c	16	15	15	22	10	15
2e	18	15	14	14	09	09
2f	12	12	20	05	10	12
2h	12	09	11	09	-	08
3c	22	20	22	11	12	11
3e	20	22	20	10	12	09
3f	10	06	13	15	09	12
3h	19	17	09	17	09	10
4c	29	27	26	05	-	-
4f	40	36	35	17	12	15
4h	08	16	12	-	06	10
5	11	09	14	09	11	15
6a	23	19	12	12	08	10
6f	13	16	21	13	12	05
6h	26	22	13	15	09	11
Standard	38	37	44	16	19	16
DMF	+ve	+ve	+ve	+ve	+ve	+ve

+ve indicates growth of microbes
DMF used as control.

Table IV — Antiinflammatory activity of some selected compounds

Compd	Dose mg / kg	Paw volume ± S.E.M. after 3 hr	Inhibition (%) of edema after 3 hr
Control	-	5.26 ± 0.2880	-
Ibuprofen	40	1.76 ± 0.3209	66.54
2c	30	2.18 ± 0.2683	58.55
2f	30	2.52 ± 0.5937	51.16
3c	30	2.30 ± 0.1581	56.27
3f	30	3.50 ± 0.1923	33.46
4c	30	1.50 ± 0.1581	71.48
4f	30	3.18 ± 0.1200	39.50

S.E.M.= Standard Error Mean

were administered orally. Statistical analysis was carried out to determine the percentage protection and the results are presented in **Table IV**. Compound **4c** was found to exhibit higher activity when compared to standard drug.

Experimental Section

Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded in KBr on FT-IR (Research spectrophotometer series) and Perkin-Elmer FT-IR (spectrum 1000); ^{1}H NMR and ^{13}C NMR spectra on a Bruker AMX (500 MHz) spectrophotometer using DMSO-d_6 or $CDCl_3$ as solvent and TMS as an internal standard (chemical shifts in δ) and mass spectra on a GC-MS instrument. Compounds were checked for their purity by TLC on silica gel G plates and spots were located by iodine vapours. Satisfactory C, H, N analyses were obtained for all the compounds.

***N*^{1}-[(1*E*)-Arylmethylene]-naphtho[2,1-*b*]furan-2-carbohydrazides 2a-h**. A solution of benzaldehyde (0.001 mole) in ethanol (15 mL) was added to a solution of naphtho[2,1-*b*]furan-2-carboxyhydrazide **1** (0.001 mole) in DMF (20 mL). The reaction mixture was refluxed for 2 hr cooled to room temp. and poured into crushed ice to yield **2a**. The crude product that separated out was filtered and recrystallized from ethanol. Similarly, the compounds **2b-h** were prepared by reacting **1** with different aromatic aldehydes.

3-Acetyl-5-naphtho[2, 1-*b*]furan-2-yl-2-aryl-2, 3-dihydro-1,3,4-oxadiazoles 3a-h. A mixture of the arylidene **2a** (0.001 mole) and acetic anhydride (5 mL) was refluxed for 3 hr on water-bath. It was cooled to room temp., poured into ice-cold water and the solid separated was recrystallized from ethanol to yield **3a**. Similarly, the compounds **3b-h** were synthesized from **2b-h**.

2-Naphtho[2,1-*b*]furan-2-yl-5-aryl-1,3,4-oxadiazoles 4a-h. A solution of the **2a** (0.001 mole) in DMF (40 mL) was stirred with yellow mercuric oxide (3 g) and iodine (1.5 g) at room temp. for 48 hr under

anhydrous condition. The reaction mixture was filtered and the filtrate was poured into crushed ice. The solid separated out was washed with water and recrystallized from ethanol to yield **4a**. Compounds **4b-h** were prepared similarly from **2b-h**.

5-Naphtho[2,1-*b*]furan-2-yl-1,3,4-oxadiazole-2(3*H*)-thione 5 (**ref. 17**). To a cold stirred solution of **1** (0.001 mole) in ethanol (50 mL) containing potassium hydroxide (0.01 mole), carbon disulphide (0.05 mole) was added gradually. The reaction mixture was heated under reflux on a steam-bath until hydrogen sulphide evolution ceased. Ethanol was removed by distillation under reduced pressure and the residue was stirred with water, filtered and the filtrate was neutralized with dilute hydrochloric acid. The product was filtered, washed with water and recrystallized from ethanol to get the compound **5**.

3-(Anilinomethyl)-5-naphtho[2,1-*b*]furan-2-yl-1,3,4-oxadiazole-2(3*H*)-thiones 6a-h. A solution of the appropriate amine (0.001 mole) in ethanol (5 mL) was added drop-wise to a stirred solution of **5** (0.001 mole) in ethanol (10 mL) containing formaldehyde (2 mL) and the reaction mixture was stirred for 24 hr at room temperature. The separated product was filtered, washed with cold ethanol, dried and recrystallized from ethanol-DMF to yield **6a-h**.

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