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Note

Synthesis of 1, 3, 4-oxadiazoles having nicotinamide moiety as potential antimicrobial agents

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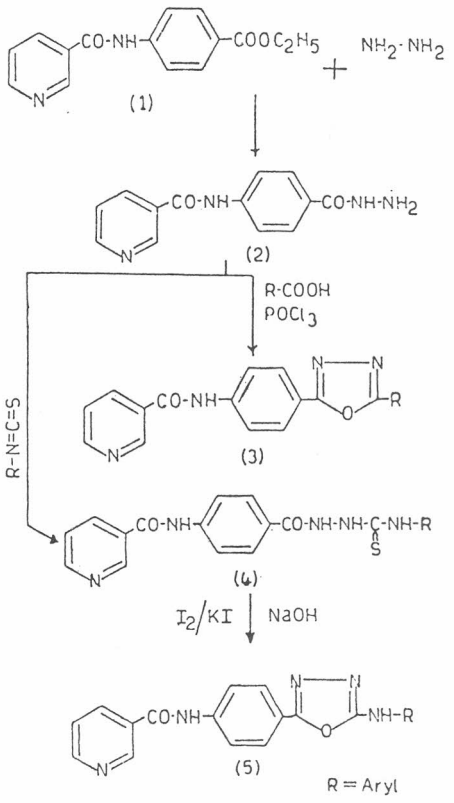
2-Arylamino-5-*p*-(nicotinamidophenyl)-1,3, 4-oxadiazoles (**5a-q**) have been synthesised starting from ethyl *p*-nicotinamidobenzoate (**1**) which in turn is obtained by treatment of nicotinic acid with thionyl chloride followed by reaction with ethyl *p*-aminobenzoate in pyridine.

Some new oxadiazoles have been synthesised having nicotinamide moiety to get better therapeutically active compounds. Nicotinamide and oxadiazole derivatives have been reported to have therapeutic activity[1-9].

The starting compound nicotinic acid on reaction with thionyl chloride gave nicotinoyl chloride, which on reaction with ethyl *p*-aminobenzoate in pyridine yielded ethyl *p*-nicotinamidobenzoate (**1**). Compound **1** on reaction with hydrazine hydrate furnished N-*p*-(nicotinamidobenzoyl)hydrazine (**2**) which on treatment with different aromatic acids in presence of $POCl_3$ underwent cyclisation to give corresponding oxadiazoles (**3a-o**). When **2** was reacted with different substituted aryl isothiocyanate, the corresponding N^1-*p*-(nicotinamidobenzoyl)-N^3-substituted aryl thiosemicarbazides (**4a-q**) were obtained which on cyclisation with iodine afforded respective 2-arylamino-5-*p*-(nicotinamidophenyl)-1, 3, 4-oxadiazoles (**5a-q**) (Table I; Scheme I).

The structure of the compounds synthesized were assigned on the basis of elemental analyses, IR, PMR and mass spectral data. The compounds were evaluated for antimicrobial screening.



Antimicrobial activity

The antimicrobial activity was determined using cup-plate agar diffusion method[10] by measuring the inhibition zones in mm. All the compounds were screened *in vitro* for their antimicrobial activity against a variety of bacterial strains such as *Escherichia coli*, *Salmonella typhosa*, *Staphylococcus citrus*, *Bacillus megaterium* and fungi such as *Aspergillus niger*. Compounds **3a-b, 3g, 3o, 4c, 4e, 4g-h, 4o, 5a, 5f, 5m** and **5p** showed highest activity (26-30 mm) against the above microbes (Cf. Table II).

Experimental

All the recorded melting points were determined in open capillary tubes and are uncorrected. IR spectra (ν_{max} in cm^{-1}) were recorded in KBr on Shimadzu-435-IR spectrophotometer, PMR spectra on Hitachi NMR-R-1200 (60 MHz) using TMS as internal standard (chemical shifts in δ, ppm) and mass spectra on Jeol d 300 e.V.

N-*p*-(Nicotinamidobenzoyl)hydrazine (2). A mixture of ethyl *p*-nicotinamidobenzoate (**1**) (0.01 mole, 2.7 g) and excess of hydrazine hydrate (0.04 mole, 2.0 mL) in absolute ethanol was refluxed for 5 hr. The solution was then poured into ice-water, filtered and washed with water. The resulting solid was recrystallised from ethanol to give **2**, yield 68%, m.p. 221°C (Found: C,

Table I—Physical data of **3a-o, 4a-q** and **5a-q**

Compd	R	Yield (%)	m.p. °C	Mol. formula	N (%) Found	N (%) Calc.
3a	C_6H_5	78	129	$C_{20}H_{14}O_2N_4$	16.25	16.37
3b	$2\text{-}OCOCH_3-C_6H_4$	71	194	$C_{22}H_{16}O_4N_4$	14.21	14.00
3c	$2-Cl-C_6H_4$	73	178	$C_{20}H_{13}O_2N_4Cl$	14.81	14.87
3d	$3-Cl-C_6H_4$	70	>320	$C_{20}H_{13}O_2N_4Cl$	14.91	14.87
3e	$4-Cl-C_6H_4$	77	>320	$C_{20}H_{13}O_2N_4Cl$	14.76	14.87
3f	$3,4-(OCH_3)_2-C_6H_3$	72	305	$C_{22}H_{18}O_4N_4$	13.82	13.93
3g	$2-OH-C_6H_4$	68	>320	$C_{20}H_{14}O_3N_4$	15.77	15.64
3h	$3-OH-C_6H_4$	74	114	$C_{20}H_{14}O_3N_4$	15.56	15.64
3i	$4-OH-C_6H_4$	76	132	$C_{20}H_{14}O_3N_4$	15.81	15.64
3j	$2-OCH_3-C_6H_4$	71	239	$C_{21}H_{16}O_3N_4$	15.12	15.05
3k	$4-OCH_3-C_6H_4$	69	165	$C_{21}H_{16}O_3N_4$	15.01	15.05
3l	$2-CH_3-C_6H_4$	74	>320	$C_{21}H_{16}O_2N_4$	15.67	15.73
3m	$3-CH_3-C_6H_4$	70	156	$C_{21}H_{16}O_2N_4$	15.74	15.73
3n	$4-CH_3-C_6H_4$	69	169	$C_{21}H_{16}O_2N_4$	15.81	15.73
3o	$-CH=CH-C_6H_4$	73	156	$C_{22}H_{14}O_2N_4$	15.52	15.57
4a	C_6H_4	65	183	$C_{20}H_{17}O_2N_5S$	17.85	17.90
4b	$3-Cl-C_6H_4$	65	177	$C_{20}H_{16}O_2N_5SCl$	16.40	16.45
4c	$4-Cl-C_6H_4$	60	192	$C_{20}H_{16}O_2N_5SCl$	16.32	16.45
4d	$2,4-Cl_2-C_6H_3$	62	222	$C_{20}H_{15}O_2N_5SCl_2$	15.25	15.18
4e	$2,5-Cl_2-C_6H_3$	61	208	$C_{20}H_{15}O_2N_5SCl_2$	15.11	15.18
4f	$2,3-(CH_3)_2-C_6H_3$	68	176	$C_{22}H_{21}O_2N_5S$	16.79	16.71
4g	$2,4-(CH_3)_2-C_6H_3$	66	178	$C_{22}H_{21}O_2N_5S$	16.68	16.71
4h	$3,4-(CH_3)_2-C_6H_3$	64	154	$C_{22}H_{21}O_2N_5S$	16.85	16.71
4i	$3,5-(CH_3)_2-C_6H_3$	60	186	$C_{22}H_{21}O_2N_5S$	16.81	16.71
4j	$2-CH_3-C_6H_4$	62	174	$C_{21}H_{19}O_2N_5S$	17.19	17.28
4k	$3-CH_3-C_6H_4$	60	173	$C_{21}H_{19}O_2N_5S$	17.21	17.28
4l	$4-CH_3-C_6H_4$	60	174	$C_{21}H_{19}O_2N_5$	17.31	17.28
4m	$2-OCH_3-C_6H_4$	62	183	$C_{21}H_{19}O_3N_5S$	16.71	16.63
4n	$3-OCH_3-C_6H_4$	66	169	$C_{21}H_{19}O_3N_5S$	16.59	16.63
4o	$4-OCH_3-C_6H_4$	64	169	$C_{21}H_{19}O_3N_5S$	16.57	16.63
4p	$2-C_2H_5-C_6H_4$	68	206	$C_{22}H_{21}O_2N_5S$	16.79	16.71
4q	$4-C_2H_5-C_6H_4$	61	164	$C_{22}H_{21}O_2N_5S$	16.82	16.71
5a	C_6H_4	67	277	$C_{20}H_{15}O_2N_5$	19.49	19.61
5b	$3-Cl-C_6H_4$	66	194	$C_{20}H_{14}O_2N_5Cl$	17.79	17.88
5c	$4-Cl-C_6H_4$	72	>320	$C_{20}H_{14}O_2N_5Cl$	17.92	17.88
5d	$2,4-Cl_2-C_6H_3$	71	>320	$C_{20}H_{13}O_2N_5Cl_2$	16.48	16.39
5e	$2,5-Cl_2-C_6H_3$	70	>320	$C_{20}H_{13}O_2N_5Cl_2$	16.28	16.39
5f	$2,3-(CH_3)_2-C_6H_3$	70	193	$C_{22}H_{19}O_2N_5$	18.30	18.18
5g	$2,4-(CH_3)_2-C_6H_3$	66	236	$C_{22}H_{19}O_2N_5$	18.31	18.18
5h	$3,4-(CH_3)_2-C_6H_3$	70	254	$C_{22}H_{19}O_2N_5$	18.21	18.18
5i	$3,5-(CH_3)_2-C_6H_3$	72	259	$C_{22}H_{19}O_2N_5$	18.78	18.18
5j	$2-CH_3-C_6H_4$	72	172	$C_{21}H_{17}O_2N_5$	18.76	18.87
5k	$3-CH_3-C_6H_4$	70	260	$C_{21}H_{17}O_2N_5$	18.79	18.87
5l	$4-CH_3-C_6H_4$	67	>320	$C_{21}H_{17}O_2N_5$	18.94	18.87
5m	$2-OCH_3-C_6H_4$	72	283	$C_{21}H_{17}O_3N_5$	18.16	18.09
5n	$3-OCH_3-C_6H_4$	70	222	$C_{21}H_{17}O_3N_5$	18.21	18.09
5o	$4-OCH_3-C_6H_4$	70	203	$C_{21}H_{17}O_3N_5$	18.17	18.09
5p	$2-C_2H_5-C_6H_4$	65	278	$C_{22}H_{19}O_2N_5$	18.26	18.18
5q	$4-C_2H_5-C_6H_4$	72	>320	$C_{22}H_{19}O_2N_5$	18.02	18.18

60.85; H, 4.64; N, 21.93. $C_{13}H_{12}O_2N_4$ requires C, 60.94; H, 4.69; N, 21.88%).

2-(*p*-Methoxyphenyl)-5-*p*-(nicotinamido phenyl)-1, 3, 4-oxadiazole (3a-o). A mixture of N-*p*-(Nicotinamidobenzoyl)hydrazine (**2**) (0.01 mole, 2.56 g) and *p*-methoxybenzoic acid (0.01 mole, 1.52 g) in phosphorus oxychloride (5 mL) were refluxed for 5-6 hr. The content was cooled and poured onto crushed ice, made basic by sodium bicarbonate solution and the resulting solid was filtered, dried and recrystallised from chloroform to give **3k**, yield 67%, m.p. 165°C (Found : C, 67.75; H, 4.28; N, 15.01. $C_{21}H_{16}O_3N_4$ requires C, 67.74; H, 4.30; N, 15.05%); IR : 2975, 2875 (C−H str.), 1630 (C=N str. pyridine), 1115 (C−O−C str. oxadiazole), 1040

Table II—Antimicrobial screening results of those compounds which exhibited highest activity (inhibition zone = 19-30 mm) at 50 μg concentration

E. coli	*S. typhosa*	*S. citrus*	*B. mega.*	*A. niger*
3b, 3e, 3o, 4g, 4h, 4p, 5f, 5m, 5p	**5b**	**3a, 3b, 3c, 3e, 3f, 3g, 3h, 3i, 3o, 4c, 4c, 4o, 5a, 5m**	**3h, 4p, 5b, 5c**	**3, 3m, 4k, 5e, 5q**

Standard antibiotics: Ampicillin 17-24 mm; Chloramphenicol 24-26 mm; Norfloxacin 23-33 mm; Griseofulvin 20-23 mm

(N−N str. oxadiazole), 1680 (C=O str.) and 3280 (N−H str.); PMR (TFA) : 4.05 (s, 3H, $-OCH_3$), 7.04-7.98 (m, 8H, Ar-H), 8.02 (s, 1H, NH), 8.1-8.52(m, 4H, Ar-H pyridine).

Similarly other members of **3** were prepared and their physical data are recorded in Table I.

N^1 -*p*-(Nicotinamidobenzoyl)-N^3 -(*p*-methoxyphenyl)thiosemicarbazide (4a-q). An ethanolic solution of N-*p*-(Nicotinamidobenzoyl) hydrazine (**2**) (0.01 mole, 2.56g) and *p*-methoxyphenyl-isothiocyanate (0.01 mole, 1.65 g) was refluxed for 4 hr. The resulting solution was then cooled and the solid was crystallised from DMF to give **4o**, yield 63%, m.p. 169°C (Found : C, 59.81; H, 4.55; N, 16.57. $C_{12}H_{19}O_3N_5S$ requires C, 59.86; H, 4.51; N, 16.63%); IR : 2970, 2875 (C−H str.), 3070 (C−H str.), 1595 (C=N str. pyridine), 750 (C=S str.) and 1675 (C=O str.); PMR (TFA) : 3.99 (s, 3H, $-OCH_3$), 7.1-8.2 (m, 8H, Ar-H), 8.4 (s, 3H, NH−NH−C−NH), 8.5 (s, 1H, −CO−NH), 9.0-9.3 (m, 4H, Ar-H pyridine); Mass: 421 (M^+), 356, 342, 313, 311, 298, 255, 240, 224, 120, 105, 78 (Base Peak).

Similarly other members of **4** were prepared and their physical data are recorded in Table I.

2-(*p*-Methoxyphenyl)amino-5-*p*-(nicotinamidophenyl)-1, 3, 4-oxadiazole (5a-q). To the N^1-*p*-(Nicotinamidobenzoyl)-N^3-(*p*-methoxyphenyl)thiosemicarbazide (**4o**) (0.01 mole, 4.21g) dissolved in minimum quantity of ethanol, 6*N* NaOH (15 mL) was added. A 10% solution of iodine in KI was then added dropwise and the reaction mixture was kept at 10°C. The addition of iodine was continued till the colour of iodine persisted and the reaction mixture was refluxed for 4 hr at 70-80°C. On cooling, the separated solid was washed thoroughly with water and recrystallised from DMSO to give **5o**, yield 70%, m.p. 203°C (Found : C, 65.19; H, 4.4; N, 18.17. $C_{21}H_{17}O_3N_5$ requires C, 65.12; H, 4.4; N, 18.09%); IR: 2975, 2875 (C−H str. $-OCH_3$), 3070 (C−H str. Ar), 1565 (C=C str.), 1630 (C=N pyridine), 1140 (C−O−C str. oxadiazole), 1665 (C=O str.) and 3375 (N−H str.); PMR (TFA): 4.0(s, 3H, $-OCH_3$), 7.1-7.65 (m, 8H, Ar-H), 7.7 (s, 1H, −NH), 7.82 (s, 1H, −CONH), 8.16-8.25 (m, 4H, Ar-H pyridine); Mass : 387 (M^+), 309, 281, 280, 264, 252, 223, 132, 112 (Base Peak).

Similarly other members of **5** were prepared and their physical data are recorded in Table I.

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