Int. J. Chem. Sci.: 7(4), 2009, 2508-2512

SYNTHESIS OF SOME 1, 3, 4-OXADIAZOLE DERIVATIVES AS POTENTIAL BIOLOGICAL AGENTS

B. C. REVANASIDDAPPA* and E. V. S. SUBRAHMANYAM

Department of Pharmaceutical Chemistry, NGSM Institute of Pharmaceutical Sciences, Paneer, DERALAKATEE – 574160, Dist. Mangalore (K.S.) INDIA

ABSTRACT

A new series of INH containing 1, 3, 4-oxadiazole **(3a-3j)** were synthesized by $POCl_3$ cyclization of INH with different substituted aromatic acids. IR, ^1H NMR, and mass spectral data support the structures of newly synthesized compounds. All the newly synthesized compounds have been tested for their *in vitro* antibacterial and antifungal activity. Most of the compounds showed very good activity against all the organisms.

Key words: 1, 3, 4-Oxadiazoles, $POCl_3$ Cyclization, Antibacterial, Antifungal.

INTRODUCTION

The recent literature is enriched with the progressive findings about the synthesis and biological activities of 1, 3, 4-oxadiazole moiety. It was observed from the review of literature that these five membered heterocyclic compounds possess interesting biological and pharmacological activities. The synthesis of 1, 3, 4-oxadiazoles is of considerable interest due to their various biological activities. Reported among these activities are: antimirobial[1], analgesic[2], antiviral[3], anticonvulsant[4], antiproliferative[5] and anti-inflammatory[6]. In view of the above mentioned facts and prompted by the biological activities of 1, 3, 4-oxadiazole, it was contemplated to synthesize a new series of oxadiazoles containing INH moiety and to pursue *in vitro* antibacterial and antifungal activity. The results of the antibacterial and antifungal activities are discussed in this paper. The reaction sequence for the synthesis of the title compounds is outlined (**Scheme 1).**

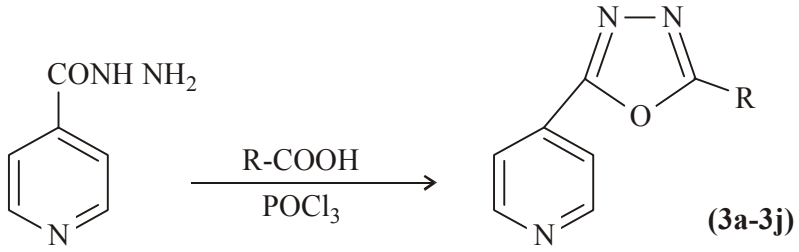
EXPERIMENTAL

*Author for correspondence; Ph.: +91-0824-2203991-93; Fax No.: +91- 0824-2203992
E-mail: evergreen_revan@rediffmail.com

Melting points were determined by open capillary method and are uncorrected. Silica gel G plates were used for TLC and spots were located by UV or in iodine chamber. The IR spectrum (in KBr pellets) was recorded by using Shimadzu 8201 PC IR Spectrometer and frequencies are expressed in cm^{-1}. The PMR spectra were recorded on Bruker Avance II 400 NMR Spectrometer in $CDCl_3$ and DMSO with TMS as an internal standard and values are expressed in δ ppm. The FAB mass spectra were recorded on JEOL SX-102/DA-6000 Mass spectrometer operating at 70 eV.

General procedure for the synthesis of 1, 3, 4-oxadiazoles

A mixture of hydrazide (0.01 mol), aromatic acids (0.01 mol) and $POCl_3$ (10 mL) was refluxed on a water bath for 9 hrs (as monitored by TLC). The excess of $POCl_3$ was removed under reduced pressure. The reaction mixture was cooled and poured into crushed ice with stirring and neutralized with $NaHCO_3$. The resulting solid is washed with water and recrystallized from alcohol. The physical data of the compounds are given in Table 1.



Scheme 1

Table 1: Physical data of the compounds

Comp.	R-COOH	MP (°C)	Yield (%)
3a	C_6H_5	109	66
3b	o-OH	149	58
3c	p-OH	154	68
3d	3,5-$(NO_2)_2$	102	60
3e	p-NO_2	134	70
3f	p-Cl	142	66

Cont…

Comp.	R-COOH	MP (°C)	Yield (%)
3g	2,4-$(Cl)_2$	121	58
3h	2-Br	168	64
3i	2-Cl-4-NO_2	186	61
3j	p-OCH_3	176	51

Spectral data

(3g): IR: 1602 (C=N), 1553 (C=C), 1087 (C-O-C) and 694 (C-Cl) cm^{-1}; **NMR**: 7.50-8.12 δ (ppm) (m,7H, Ar-H)**; Mass:** 302 [M^+].

(3i): IR: 1590 (C=N), 1533 (C=C), 1097 (C-O-C) and 739 (C-Cl) cm^{-1}; **NMR**: 7.49-8.86 δ (m, 7H, Ar-H); **Mass:** 292 [M^+].

(3j): IR: 1573 (C=N), 1523 (C=C), 1116 (C-O-C) and 769(C-Cl) cm^{-1}; **NMR**: 3.91 (s,3H, OCH_3) and 7.05-8.84 δ (ppm) (m, 8H, Ar-H); **Mass:** 253 [M^+].

Other compounds were also synthesized similarly.

Antimicrobial activity

The antibacterial activity of all the newly synthesized compounds was determined by *in vitro* cup-plate method[7] against variety of pathogenic micro-organisms like *P.aeruginosa, E. coli* (gram negative), B. subtilis*, S. aureus* (gram-positive) 100 µg/mL concentrations, in the nutrient agar media by measuring the zone of inhibition in mm. Streptomycin was used as standard drug for comparison and DMF was used as a solvent control. Similarly, the antifungal screening of the compounds was carried out against two fungi, *C. albicans* and *A. Niger* using griseofulvin as standard. Most of the synthesized compounds showed very good activities against both the bacterial and fungi organisms. The biological data of the compounds is given in Table 2.

RESULTS AND DISCUSSION

In the present work, a new series of 1, 3, 4-oxadiazoles were synthesized by reacting INH and aromatic acids in presence of phosphorous oxychloride as cyclization agent.

The compounds resulted in good yields. All the newly synthesized compounds were screened for their antibacterial and antifungal activity.

In the antibacterial activity, the compounds **3a, 3b, 3e** and **3j** showed highest activity against both; the gram positive and gram negative organisms. But most of the compounds also show good activity against all the organisms. Similarly, in the antifungal study the compounds **3e, 3f, 3g** and **3j** showed highest activity against both the fungal organisms. The rest of the compounds also showed good activity.

Table 2: Antimicrobial activity data of compounds

Comp.	Diameter of zone of inhibition (mm) at 10 µg/mL concentration					
	S.aureus	***B.subtilis***	***E.coli***	***P.aeruginosa***	***C.albicans***	***A.niger***
3a	14	13	12	13	11	10
3b	13	14	13	12	12	09
3c	11	13	13	12	11	10
3d	10	12	13	11	10	11
3e	13	14	11	11	11	12
3f	12	12	11	12	13	12
3g	10	12	12	11	12	11
3h	12	10	13	11	11	10
3i	12	12	12	11	12	10
3j	13	13	12	11	12	11
Streptomycin	22	22	22	21	-	-
Griseofulvin	-	-	-	-	22	21
Control (DMF)	-	-	-	-	-	-

ACKNOWLEDGEMENT

The authors are thankful to NITTE Education Trust for the financial support. The authors are also grateful to the Directors, RSIC, Chandigarh and CDRI, Lucknow for providing IR, NMR and Mass spectra.

REFERENCES

1. A. A. El-Emam, O. A. Al-Deeb, M. Al-Omar and Lehmann, Bioorg. Med. Chem., **12**, 5107 (2004).

2. M. Santagati, M. Modica, A. Santagati, F. Russo, A. Caruso, V. Cutuli, E. Dipietro, and Amico Roxas, Pharmazie, **49**, 880 (1994).

3. T. M. C. Tan, Y. Chen, K. H. Kong, J. Bai, Y. Li, S. G. Lim, T. H. Ang and Y. Lam, Antiviral Res., **71**, 7 (2006).

4. S. A. Almasirad, M. Tabatabai, A. Faizi, N. Kebriaeezadeh, A. Mehrabi and Shafiee, Bioorg. Med. Chem. Lett., **14,** 6057 (2004)

5. L. Jin, J. Chen, B. Song, Z. Chen, S. Yang, Q. Li, D. Hu and R. Xu, Bioorg. Med. Chem. Lett., **16,** 5036 (2006).

6. M. M. Burbuliene, V. Jakubkiene, G. Mekuskiene, E. Udrenaite, R. Smicius and P. Vainilavicius, IL Farmaco, **59,** 767 (2004).

7. R. Cruichshank, J. P. Duguid, B. P. Marmoin and H. A. Swan, The Practice of Medical Microbiology, Vol. 2, 12th Edn**,** Churchill Livingstone, London (1975) p. 190.

Accepted : 10.08.2009