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Microwave assisted synthesis of some 5-pyridyl-2-[(N-substituted phenyl) thioacetamido]-1,3,4-oxadiazoles as antibacterial and antioxidant agents

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Abstract

A series of some 5-pyridyll-2-[(N-substituted phenyl) thioacetamido]-1,3,4-oxadiazoles were synthesized by both conventional and microwave method and characterized on the basis of IR, NMR Mass Spectral and elemental analysis. The title compounds were subjected for antibacterial activity against both gram positive and gram negative organisms and *invitro* antioxidant activity by 1,1-diphenyl-2,2-picryl hydrazyl free radical (DPPH) method.

Key words: 1,3,4-oxadiazole; antibacterial; *invitro* antioxidant activity (DPPH).

Introduction

Several substituted 1,3,4-oxadiazole exhibit antibacterial [1], antimicrobial [2,3] pesticidal [4], anti-mycobacterial [5], anti-inflammatory [6] and anti-fungal [7] activities. Recently microwave assisted synthesis has attracted the researcher throughout the world for its less time consumption, minimum usage of solvents and increased yield of the compounds. The present investigation was to synthesize the title compounds 5-pyridyl-2-[(N-substituted phenyl) thioacetamido]-1,3,4-oxadiazoles (4a-g) by conventional and microwave methods and evaluate their antibacterial and antioxidant activities. It is well known that free radicals play an important role in the inflammatory process. Superoxide anion radicals, hydrogen peroxide and hydroxyl radicals, produced by activation of phagocytes, are considered to be involved in inflammation and tissue

destruction. Free radicals are also involved in the biosynthesis of prostaglandins, important mediators of inflammation. Compounds with antioxidant properties are generally expected to protect against inflammation. Several substituted chloroacetamide derivatives are reported to possess anti-inflammatory and/or antioxidant activities.

Hence in our investigation it was aimed to synthesize substituted oxadiazole derivatives and screen for their antibacterial and antioxidant activity.

Materials and methods

Experimental

Melting points were measured in open capillary tubes and are uncorrected IR (KBR) spectra were recorded in film or in potassium bromide disks on a Perkin-Elmer 398 spectrophotometer (υ max in cm^{-1}) and ^1H NMR spectra on a DPX 300 MHz Bruker FT-NMR spectrophotometer. The chemical shifts were reported as parts per million (δ ppm) tetramethyl silane (TMS) as internal standard. Mass spectra were obtained on a JEOL-SX-102 instrument using fast atom bombardment (FAB positive). Elemental analysis was performed on a Perkin–Elmer 2400 C,H,N analyzer. The progress of the reaction was monitored on a ready made silicagel plates (Merck) using n-hexane: ethyl acetate as a solvent system. Spectral data (IR, NMR and Mass spectra) confirmed the structure of the synthesized compounds and the purity of these compounds were ascertained by microanalysis. Elemental (C,H,N) analysis indicated that the calculated and observed values were within the acceptable limits (±0.4%). Physical data for the compounds are given in Table 1 and analytical data are given in Table II. Synthetic route is depicted in Scheme 1.

Table 1: Physical Data of the synthesized compounds

Compd Code	R	Mol.Formula	Reaction time		M.Pt. ^0C	%yield		TLC solvent x:y	R_f
			Conv	M.W		Conv	M.W		
2	--	$C_7H_5N_3SO$	--	--	256-58	--	--	1:1	0.28
4a	2-Methyl	$C_{16}H_{14}N_4O_2S$	22h	14min	208-10	40.3	61.6	1:1	0.26
4b	3-Methyl	$C_{16}H_{14}N_4O_2S$	26h	13min	202-05	28.7	58.8	1:1	0.46
4c	4-Methyl	$C_{16}H_{14}N_4O_2S$	18h	14min	208-10	36.6	63.6	1:1	0.49
4d	2-Chloro	$C_{15}H_{11}N_4O_2SCl$	19h	15min	195-98	31.8	69.4	1:1	0.57
4e	4-Chloro	$C_{15}H_{11}N_4O_2SCl$	21h	12min	220-22	32.8	67.9	1:1	0.67
4f	4-Bromo	$C_{15}H_{11}N_4O_2SBr$	17h	18min	225-27	38.7	67.8	1:1	0.46
4g	2,6-Dichloro	$C_{15}H_{11}N_4O_2SCl_2$	28h	17min	240-42	35.6	71.2	1:1	0.47

x= n-Hexane y= Ethyl acetate

Table II: IR and ^{1}H NMR data of the newly synthesized compounds

Compd. Code	IR νmax (cm^{-1})	^{1}HNMR (δ, ppm)
4a	3276 (-NH Str), 3108, 2985 (Ar-CH Str),1687 (-C=O Str),1569 (C=N Str) 1504,1409 (Ar-C=C Str), 1295 (C-O Str), 1112 (C-S-C Str)	10.39 (s, NH, 1H), 7.11-8.83 (m, ArH, 8H), 4.38 (s, CH_2, 2H), 2.55 (s,CH_3,1H)
4b	3326 (-NH Str), 3029 (Ar-CH Str), 1660 (-C=O,Str), 1598 (C=N Str),1567,1455(Ar-C=C Str), 1186 (C-S-C Str)	10.42 (s, NH, 1H), 7.34-8.14 (m, ArH, 8H), 4.23 (s, CH_2, 2H), 2.46 (s,CH_3,1H)
4c	3255 (-NH Str), 3050 (Ar-CH Str),1685 (-C=O,Str), 1610 (C=N Str),1548,1513 (Ar-C=C Str), 1081 (C-S-C Str)	10.12 (s, NH, 1H), 7.43-8.19 (m, ArH, 8H), 4.23 (s, CH_2, 2H), 2.50 (s,CH_3,1H)
4d	3249 (-NH Str), 3054 (Ar-CH Str),1681 (-C=O Str), 1590 (C=N Str),1519, 1490 (Ar-C=C Str) ,1245 (-C-O Str), 1072 (C-Br Str), 1008 (C-S-C, Str)	10.65 (s, NH, 1H), 7.87-8.65 (m, ArH, 8H), 4.11 (s, CH_2, 2H)
4e	3251 (-NH Str), 3058 (Ar-CH Str),1678 (-C=O Str), 1585 (C=N Str),1521, 1486 (Ar-C=C Str) ,1249 (-C-O Str), 1081 (C-Br Str), 1010 (C-S-C, Str)	10.54 (s, NH, 1H), 7.98-8.34 (m, ArH, 8H), 4.87 (s, CH_2, 2H)
4f	3249(-NH Str), 3054 (Ar-CH Str),1681 (-C=O Str), 1590 (C=N Str),1519, 1490 (Ar-C=C Str),1245 (-C-O Str), 1072 (C-Br Str), 1008 (C-S-C Str)	10.31 (s, NH, 1H), 7.61-8.77 (m, ArH, 8H), 4.75 (s, CH_2, 2H)
4g	3762 (-NH Str), 3075 (Ar-CH Str),1693 (-C=O Str), 1589 (C=N Str),1461 (Ar-C=C Str),1251 (-C-O Str), 1199 (C-S-C Str), 1103 (C-Cl Str)	10.29 (s, NH, 1H), 7.22-8.81 (m, ArH, 7H), 4.16 (s, CH_2, 2H)

Solvent: $^a CDCl_3$

Procedure:

5-Pyridyl-1,3,4-oxadiazole-2-thiol (2)

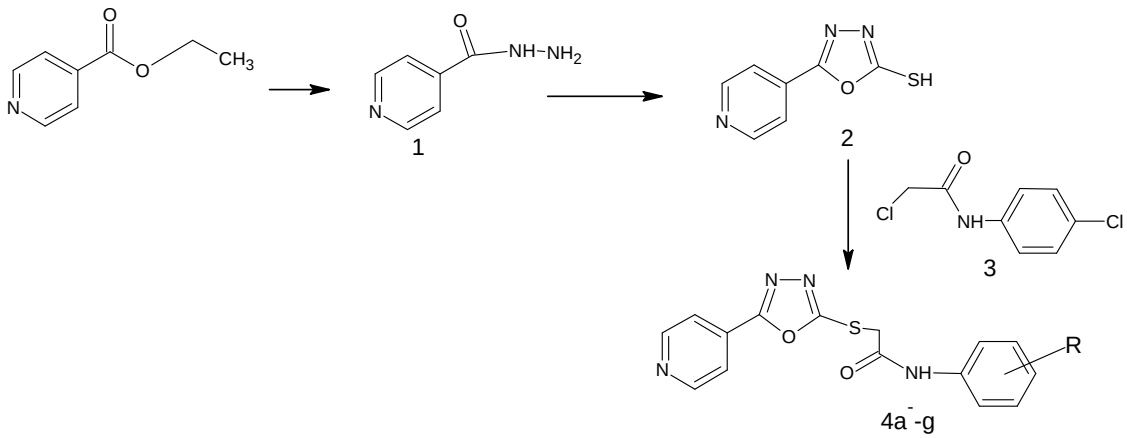
To a solution of isonicotinic acid hydrazide (1.36g, 0.01 mol) in alcohol (20 ml) was added potassium hydroxide (0.56g, 0.01mol) and carbon disulphide (0.76g, 0.01mol) with shaking. The mixture was then refluxed for 7h until the H_2S ceased. The contents were poured in to a beaker containing crushed ice and acidified with glacial acetic acid. The solid obtained was filtered, washed with water and recrystallised from alcohol to get needle shaped crystals.

Synthesis of 5-pyridyl-2-[(N-4-chlorophenyl) thioacetamido]-1,3,4-oxadiazoles (4e)

A mixture of 5-Pyridyll-1,3,4-oxadiazole-2-thiol (1.79g, 0.01 mol) and 4-chlorophenyl chloro acetamide (0.243g, 0.012 mol) were refluxed in dry pyridine (20 ml) for 21h. The reaction mixture was then poured in to a beaker containing ice cold water, the solid obtained was filtered, washed with water and recrystallised from alcohol to yield yellow coloured crystals of 5-pyridyll-2-[(N-4-chlorophenyl) thioacetamido]-1,3,4-oxadiazoles (4e).

The above reaction was also carried out by microwave method for 12-20 min to obtain the title compounds 4a-g and the formation of compounds was confirmed by spectral data. All other derivatives of the series have been synthesized following the similar procedure.

Scheme 1

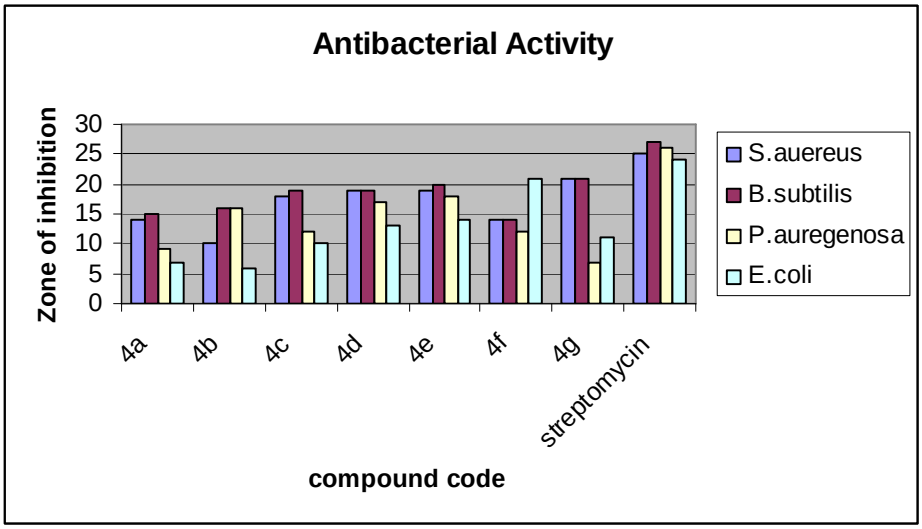


Biological Activity:

Antibacterial Activity

The antibacterial activity of the test compounds 4a-g were determined by agar cup plate [8] method using four organisms such as *Bacillus subtilis* (NCIM 2063), *Staphylococcus aureus* (NCIM 2079), *Escherichia coli* (NCIM 2065*) and Pseudomonas aeuroginosa* (NCIM 2200) using Ampicillin as the standard drug at a concentration of 10 µg ml^{-1} . DMSO as a solvent showed no zone of inhibition. The graphical presentation of antibacterial activity shown in Fig I. Results are shown in Table III.

Fig I: Antibacterial Activity of the synthesized compounds



Antioxidant Activity

The model of scavenging of the stable DPPH radical is extensively applied to evaluate antioxidant activities in less time than that is required by other methods. DPPH is stable free radical that can accept an electron or hydrogen radical and must thus be converted to a stable, diamagnetic molecule. DPPH has an odd electron and so has a strong absorption band at 517 nm when this electron becomes paired off, the absorption decreases stoichiometrically with respect

to the number of electrons or hydrogen atoms taken up, such change in the absorbance by this reaction has been extensively adopted to test the capacity of several molecules to act as free radical scavengers. Various concentrations of the test compound in methanol were added to a 1.5 ml (0.2mM) solution of DPPH radical in methanol [9]. The mixture was shaken vigorously and allowed to stand for 30 min; the absorbance of the resulting solution at 517 nm was measured using shimadzu UV spectrophotometer. Compounds such as 4d and 4g have shown significant activity compared with other compounds of the series and the standard drug. The values are summarized as IC_{50}. (Table III).

Table III: Antioxidant and Antibacterial Activity of the synthesized compounds

Comp. Code	**Antioxidant Activity**	**Antibacterial Activity (zone of inhibition in mm)**			
	IC_{50} (μg/ml)	**S.aureus** NCIM 2079	**B.subtilis** NCIM 2063	**P.aeruginosa** NCIM 2200	**E.coli** NCIM 2065
4a	45.53	14	15	09	07
4b	47.23	10	16	16	06
4c	40.08	18	19	12	10
4d	33.57	19	19	17	13
4e	39.65	19	20	18	17
4f	38.72	14	14	12	15
4g	53.28	21	21	07	11
Ascorbic Acid	25.84	---	---	---	---
Streptomycin	-----	25	27	26	24

Results and Discussion

The compound 4g (possessing a dichloro substitution on the phenyl ring) has shown promising antibacterial activity against gram positive organism while the compound 4e (possessing a chloro substitution on the phenyl ring has shown good antibacterial activity against gram negative organism). The compound 4d (possessing a chloro substitution on the phenyl ring) has inhibited the DPPH radical at a lower concentration and was found to be a comparatively better than other compounds of the series. Hence, these compounds can be further exploited for arriving at a pharmacophore exclusively with antibacterial and antioxidant activity.

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