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MICROWAVE INDUCED SYNTHESIS OF SOME NEW 3-SUBSTITUTED-1, 3-THIAZOLIDIN-4-ONES FOR THEIR POTENT ANTI MICROBIAL AND ANTITUBERCULAR ACTIVITIES

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Abstract : The ring system 2-[3-nitrophenyl-1-(pyridin-4-ylcarbonyl)-1H-pyrazol-4-yl]-3-substituted-1, 3-thiazolidin-4-one **3a-j** have been synthesized by the reaction of 3-(4-nitrophenyl)-1-(pyridin-4-ylcarbonyl)-1H-pyrazole-4-carbaldehyde **2** and different substituted aromatic amines in the presence of tolune. The structures of the compounds have been characterized by IR, ^{1}H NMR and Mass spectroscopy. The antibacterial activity of the newly synthesized compounds have been screened against Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Pseudomonas aureginosa; antifungal activity against Candida albicans and Aspergillus niger have been screened using the disc diffusion method. The antitubercular activity has also been screened.
Key words: Pyrazole, Vilsmeier Haack complex, 1, 3-thiazolidin-4-ones, antibacterial, antifungal, antitubercular

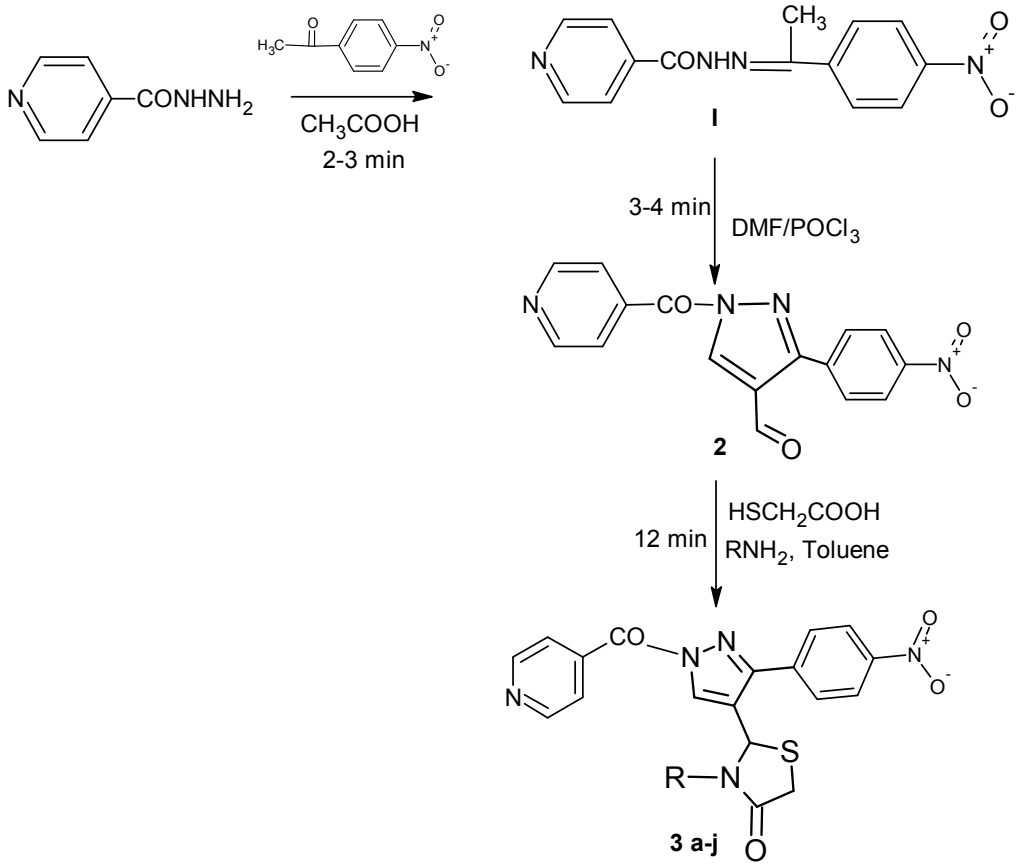
Introduction

The microwave induced activation and acceleration of various reactions has several advantages and is suitable for the use with the polar and thermolabile compounds[1-6]. The high irradiating efficiency in a short time gives rise to remarkable rate enhancement with the formation of cleaner products and is eco-friendly. In the last few years there has been an interest in the use of microwave heating in organic synthesis. Commercial microwave oven is used as a convenient source of heat in the laboratory. Pyrazole nucleus has wide applications in the medicinal chemistry. This ring system plays an important role in many biological processes, for example, some alkyl and aryl substituted pyrazoles have pronounced sedative action on the CNS[7] and have shown significant analgesic and antipyretic[8], bacteriostatic[9], bactericidal and fungicidal[10] activities.

Various substituted thiazolidinones[11] derivatives have been reported to possess various pharmacological properties. 4-thiazolidinones are known to exhibit antitubercular[12], antibacterial and antifungal[13], anticonvulsant[14],antitumour[15,16],antidiabetic[17], antiparkinsons[18],antiviral[19],anthelmintic[20] and analgesic[21] activities. Prompted by these observations and in continuation of our interest to synthesize new heterocyclic compound having both pyrazoles and 4-thiazolidinones, we have synthesized 2-[3-nitrophenyl-1-(pyridin-4-ylcarbonyl)-1H-pyrazol-4-yl]-3-substituted-1, 3-thiazolidin-4-one.

The literature review shows that the Vilsmeier reaction of acetophenone phenyl hydrazones resulted in the formation of pyrazole-4-carbaldehyde[22]. This inspired the synthesis of 3-(4-nitrophenyl)-1-(pyridin-4-ylcarbonyl)-1*H*-pyrazole-4-carbaldehyde **2** using Vilsmeier haack complex from *N*'-[1-(4-nitrophenyl) ethylidene] benzohydrazide **1**. In the literature it was shown that new 1, 3-thiazolidin-4-one[23] derivatives are formed, when a carbaldehydes were treated with different amines and thioglycolic acid. In this work, in line with literature findings, 3-(4-nitrophenyl)-1-(pyridin-4-yl carbonyl)-1*H*-pyrazole-4-carbaldehyde **2**, when reacted with different substituted amines and thioglycolic acid in the presence of toluene afforded the desired 3-substituted -1, 3-thiazolidin-4-ones **3a-j (Scheme I)**.

Scheme I



Experimental

General procedures. Melting points were determined in open capillaries and are uncorrected. TLC was performed on the silica gel G and spotting was found using iodine vapours. IR spectra were recorded on JASCO FT IR-40 spectrophotometer (cm^{-1}) using KBr disc. ^1H NMR spectra were recorded on a Perkin Elmer (model RB-12) spectrometer using $CDCl_3$ as solvent and TMS as an internal standard. All chemical shift values are recorded in δ scale downfield from TMS. Mass spectra were recorded on Joel D-300 spectrometer.

Synthesis of *N*'-[1-(4-nitrophenyl) ethylidene] benzohydrazide 1. A solution of isoniazid (0.01mol) and nitro acetophenone (0.01mol) in ethanol (20ml) with few drops of glacial acetic acid in a 100ml beaker was subjected to microwave irradiation for 2-3 mins and the reaction mixture was cooled. The solid that separated on cooling was filtered, washed with cold ethanol, dried and recrystallised from suitable solvent. Yield 91%, m.p. 214^0C. IR (KBr, cm^{-1}) spectra of the compounds showed bands at 3441 (N-H str), 2968 (C-H str), 1682 (C=O str), 1592 (C=N str), 1348 (C-NO_2 str). ^1H NMR:δ 9.7 (brs, 1H, NH), 3.3 (s, 3H, N=C-CH_3), 7.2-7.7 (m, 8H, ArH). Mass spectra of the compound exhibited molecular ion peak at m/z 284 (M^+).

Synthesis of 3-(4-nitrophenyl)-1-(pyridin-4-yl carbonyl)-1*H*-pyrazole-4-carbaldehyde 2. To the Vilsmeier haack complex prepared from dimethyl formamide (10ml) and phosphorus oxychloride (0.012 mole) at 0^0C, **1** (0.004 mole) was added and the reaction mixture was subjected to microwave irradiation for 3-4 mins. The reaction mixture was cooled and poured into ice cold water. The product which separated on neutralization with sodium bicarbonate was filtered and recrystallised from a suitable solvent. Yield 60%, m.p. $245\text{-}247^0$C. IR (KBr, cm^{-1}) spectra of the compounds showed bands at 2870 (C-H str), 1710 (C=O), 1591 (C=N str), 1350 (C-NO_2 str). ^1H NMR:δ 7.4-7.9 (m, 8H, ArH), 9.6 (s, 1H, CHO), 8.7 (s, 1H, 5- CH of pyrazole). Mass spectra of the compound exhibited molecular ion peak at m/z 322 (M^+).

Synthesis of 2-[3-(4-nitrophenyl)-1-(pyridin-4-ylcarbonyl) - 1*H*-pyrazol-4-yl] - 3-substituted 1, 3-thiazolidin-4-one 3a-h. A mixture of 2-mercaptoacetic acid (2 mmol), **2** (1mmol), aromatic amine (1m mol) in dry toluene (3 ml) were stirred and irradiated in a microwave oven for 12 min. After cooling, ethyl acetate (30 ml) was added. The resultant product was dried using anhydrous sodium sulphate. After the removal of solvent under reduced pressure, the oily residue was treated with diethyl ether to afford a solid, which was recrystallised from suitable solvent. **3d.** Yield 77%, m.p.$148\text{-}150^0$C. IR (KBr, cm^{-1}) spectra of the compounds showed bands at 2995 (C-H str), 1730 (C=O str), 690 (C-S str). ^1H NMR:δ 7.5-8.1 (m, 16H, ArH), 8.7 (s, 1H, 5- CH of pyrazole), 3.4 (s, 2H, CH_2S), 3.1 (s, 1H, -CH-N-). Mass spectra of

the compound exhibited molecular ion peak at m/z 502 (M^+).

Similarly, Compounds **3a-j** were prepared by the treatment of 3-(4-nitrophenyl)-1-(pyridin-4-yl carbonyl)-1*H*-pyrazole-4-carbaldehyde **2** with mercapto acetic acid and different substituted amines. The the physical data of the synthesized compounds were listed in **Table 1**.

Antimicrobial activity

The antimicrobial activity was assayed by using the cup plate agar diffusion method[24] by measuring the zone of inhibition in mm. All the compounds were screened *in vitro* for their antimicrobial activity against variety of bacterial strains such as *Bacillus subtilis* NCIM 2063, *Staphylococcus aureus* NCIM 2079, *Escherichia coli* NCIM 2118, *Pseudomonas aureginosa* NCIM 2036, and fungi strains such as *Aspergillus niger* NCIM 3102, *Candida albicans* NCIM 596. Standards like Ciprofloxacin for antibacterial activity and Fluconazole for antifungal activity were used for the comparison purpose (**Table II**).

Table I - Physical characterization data of the compounds 3a-j

Compd	R	Molecular formula	Molecular weight	% weight	Melting point(^{0}C)
3a	C_6H_5	$C_{24}H_{17}N_5O_4S$	471.487	76	139
3b	4-$C_6H_4NO_2$	$C_{24}H_{16}N_6O_6S$	516.487	85	157
3c	4-C_6H_4Cl	$C_{24}H_{16}N_5O_4SCl$	505.934	66	170
3d	4-C_7H_7O	$C_{25}H_{19}N_5O_5S$	501.515	80	149
3e	4-C_7H_7	$C_{25}H_{19}N_5O_4S$	485.516	74	146
3f	4-C_8H_7O	$C_{25}H_{17}N_5O_6S$	515.497	67	151
3g	4-$C_7H_5O_2$	$C_{26}H_{19}N_5O_5S$	513.525	75	150
3h	3-$C_6H_4NO_2$	$C_{24}H_{16}N_6O_6S$	516.487	81	160
3i	4-C_6H_4F	$C_{24}H_{16}FN_5O_4S$	489.478	52	140
3j	4-C_6H_4Br	$C_{24}H_{16}BrN_5O_4S$	550.384	59	172

Table II –Antimicrobial activities

Compd	Antibacterial activity				Antifungal activity	
	B.subtilis	*S.aureous*	*E.coli*	*P. aureginosa*	*C.albicans*	*A.niger*
2	17	22	18	16	14	11
3a	10	15	11	14	11	12
3b	12	14	10	12	12	10
3c	00	17	12	12	10	12
3d	11	13	13	13	15	12
3e	12	18	12	10	10	16
3f	15	12	12	10	12	11
3g	14	10	15	14	13	13
3h	12	13	14	12	10	11
3i	14	10	12	12	14	10
3j	10	15	13	15	10	12
Ciproflo xacin	21	24	22	21	--	--
Fluconaz ole	--	--	--	--	25	18

Antitubercular activity

The compounds were screened for the antitubercular activity against *Mycobacterium tuberculosis H37Rv* using Resazurin microplate assay[25] (REMA) at the concentration of 1, 10, 50µg/ml. All the compounds have given mild activity at 50µg/ml especially **3d** have given a good activity at 1 and 10 µg/ml.

Results and discussion

The synthesis of 2-[3-nitrophenyl-1-(pyridin-4-ylcarbonyl)-1H-pyrazol-4-yl]-3-substituted-1, 3-thiazolidin-4-one **3a-j** was carried out in three steps, first by the condensation of isoniazid with 4-nitroacetophenone in the presence of glacial acetic acid to give *N*'-[1-(4-nitrophenyl) ethylidene] benzohydrazide **1,** secondly Vilsmeier Haack complex was treated with it to

give 3-(4-nitrophenyl)-1-(pyridin-4-yl carbonyl)-1*H*-pyrazole-4-carbaldehyde **2**, which on treatment with different substituted aromatic amines and thioglycolic acid in the presence of toluene afforded the title compound.

The structures were determined from IR, ^{1}H NMR and mass spectra. The IR spectra of the compounds displayed their characteristic stretching vibrations. The ^{1}H NMR spectra of a few selected compounds gave characteristic peaks in the expected regions. Mass spectra of all the compounds showed the molecular ion peak (M^+) with low intensity. All the compounds have shown mild to moderate antibacterial and antifungal activities. Only a few compounds have shown the antitubercular activity.

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