Research Journal of Chemical Sciences ISSN 2231-606X
Vol. **7(2),** 49-53, February **(2017)** *Res. J. Chem. Sci.*

Synthesis and Biological activity of 4-(3-bromophenyl)-N-(1-(4-(4-bromophenyl) thiazol-2-yl)-3-methyl-4-(2-phenylhydrazono)-4,5-dihydro-1H-pyrazol-5-ylidene)-6-(4-nitrophenyl)pyrimidin-2-amine derivatives

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Available online at: www.isca.in, www.isca.me
Received 28th December 2016, revised 7th Februry 2017, accepted 15th February 2017

Abstract

4-(3-bromophenyl) - N- (1- (4- (4-bromophenyl) thiazol-2-yl)-3-methyl-4-(2-phenylhydrazono)-4,5-dihydro-1H-pyrazol-5-ylidene) -6-(4-nitrophenyl)pyrimidin-2-amine derivatives (3a-h) have been synthesized using conventional method and microwave irradiation. The structure of the synthesized compounds have been confirmed by IR and NMR Spectroscopy. These compounds were evaluated for their biological efficacy.

Keywords: Pyrazole, Thiazole, Pyrimidine, Microwave assisted Synthesis, Biological efficacy.

Introduction

Compounds containing the thiazole ring system are known to possess pharmacological properties like antimicrobial[1], analgesic[2], antiinflammatory[2], anticancer[3], antitubercular[4] activities. Pyrazole exhibits pharmacological properties such as anticancer[5], analgesic[2], antiinflammatory[6] and antimicrobial[7] activities.

The literature survey indicated that a wide range of pharmacological activities are exhibited by the compounds encompassing pyrimidines nucleus. In addition to this, various analogs of pyrimidines have been found to posses antifungal[8], anti-inflammatory[9], analgesic[10], antiviral[11], anticonvulsant[12], and anticancer activities[13] and many of pyrimidines derivatives are reported to possess potential central nervous system (CNS) depressant properties[14] and also act as calcium channel blockers[15].

Earlier we have reported synthesis of heterocycles having thiazole, pyrazole and pyridine ring systems[16]. Synthesis of 1-Thiocarboxamido-3-methyl-4-(arylhydrazono)-2- pyrazolin-5-ones has been reported[17]. We treated this compound with *p*-bromo phenacyl bromide to obtain compounds 1(a-h). Derivatives of compound 1 are reported by one pot synthesis[18].

In continuation of our work on synthesis of new heterocyclic compounds and in view of the biological activities shown by thiazole, pyrazole and pyrimidine, we are hereby reporting synthesis of 4-(3-bromophenyl)-N-(1-(4-(4-bromophenyl) thiazol-2-yl)-3-methyl-4-(2-phenylhydrazono)-4,5-dihydro-1H-pyrazol -5-ylidene)-6- (4-nitrophenyl) pyrimidin-2-amine derivatives (3a-h).

Materials and methods

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded in KBr on Shimadzu Corporation, IR Affinity-I and PMR on a Agilant Technology 400/54 premium shielded using TMS as internal standard (chemical shift in δ ppm). The reactions were monitored on TLC.

Synthesis of 4-(3-bromophenyl)-N-(1-(4-(4-bromophenyl) thiazol-2-yl)-3-methyl-4-(2-(4-nitrophenyl)hydrazono)-4,5-dihydro-1H-pyrazol-5-ylidene)-6-(4-nitrophenyl)pyrimidin-2-amine (3g):

Conventional Method: 4-(4-bromophenyl)-2-[4-(4-nitrophenyl hydrazono)-3-methyl-5-oxo- 4,5-dihydro pyrazol-1-yl] -1,3-thiazole (1g) (0.001 mol) and 2-amino-4-(3-bromophenyl)-6-(4-nitrophenyl)-1,3-pyrimidine (2) (0.001 mol) were refluxed in 5 ml of glacial acetic acid and 10 ml of DMF for 8 hrs. After completion of reaction, the reaction mixture was then cooledand poured in to crushed ice with stirring. The solid obtained was filtered, washed with water and then recrystallized from toluene.

Microwave assisted synthesis: Compound 1g(0.001 mol) and Compound 2 (0.001 mol) were refluxed in 5 ml of glacial acetic acid and 10 ml of DMF for 18 minutes at 420 watt. After completion of reaction, the reaction mixture was cooled and poured in to crushed ice with stirring. The solid obtained was filtered, washed with water and then recrystallized from toluene.

Other compounds were obtained by the same method.

Compound 3g: **IR (KBr):**1517 cm^{-1} (C=N), 1341 cm^{-1} (NO_2)

^{1}HNMR (CDCl$_3$, 400 MHz): 2.49 (s, 3H, -CH_3), 8.35 (s, 1H, -NH), 7.84 (s, 1H, thiazole 5-H), 7.2-7.58 (m, Ar-H, 17H).

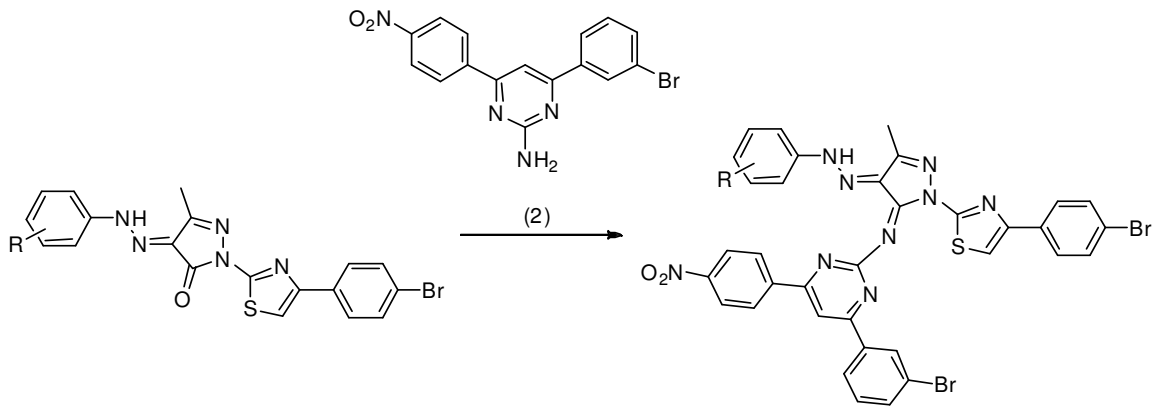
Results and discussion

Synthesis of 4-(3-bromophenyl)-N-(1-(4-(4-bromophenyl) thiazol-2-yl)-3-methyl-4-(2-phenylhydrazono)-4,5-dihydro-1H-pyrazol-5-ylidene)-6-(4-nitrophenyl)pyrimidin-2-amine derivatives (3a-h) was attempted. The IR Spectrum of compound 1 shows peak at 1676 cm^{-1} indicating the presence of >C=O group, whereas the IR spectrum of compound 3 does not shows peak at 1676 cm^{-1} indicating the absence of >C=O group confirming theformation of the product.

The synthesis has been carried out by conventional heating as well as by using microwave irradiation. The reaction rate is enhanced tremendously under microwave irradiation as compared to conventional method with improved yields.

The synthesised compounds were evalualed against *Staphylococcus aureus, Streptococcus pyogenes, Escherichia coli* and *Proteus vulgaris.* The activities exhibited by the synthesized compounds were compared with Co-Trimoxazole.

Biological activity: 25 mg of sample was dissolved in 1ml of DMSO and 50µl of the aliquot was added to agar well made in Muller Hinton Agar plates, which were previously seeded with 18 to 24hr old culture with 0.1 O.D. The plates were incubated at 37^{0}C.for 24 hrs and the zones of inhibition were measured in mm.



R = (a) H, (b) 2-OCH_3, (c) 4-OCH_3, (d) 4-Br, (e) 4-Cl, (f) 4-CH_3, (g) 4-NO_2, (h) 3-NO_2

Scheme-1: Synthesis of 4-(3-bromophenyl)-N-(1-(4-(4-bromophenyl) thiazol-2-yl)-3-methyl-4-(2-phenylhydrazono)-4,5-dihydro-1H-pyrazol-5-ylidene)-6-(4-nitrophenyl)pyrimidin-2-amine derivatives.

Table-1: Characterization data of 3(a-h).

Sr.No.	Compound No.	R	M.P.	Conventional Method		Microwave Irradiation	
				(Time in Hrs.)	% Yield	(Time in mins.)	% Yield
1	3a	H	168^{0}C	8	62	18	80
2	3b	2-OCH_3	110^{0}C	6	60	15	82
3	3c	4-OCH_3	118^{0}C	6	64	15	79
4	3d	4-Br	235^{0}C	9	66	18	82
5	3e	4-Cl	210^{0}C	9	65	18	77
6	3f	4-CH_3	160^{0}C	6	60	15	72
7	3g	4-NO_2	195^{0}C	8	65	18	78
8	3h	3-NO_2	200^{0}C	8	68	18	81

Table-2: Concentration: 25 mg/ml.

Sample No.	Zone of inhibition in mm			
	Test cultures used			
	Escherichia coli	*Proteus vulgaris*	*Staphylococcus aureus*	*Streptococcus pyogenes*
3a	-------	-------	10mm	11mm
3b	-------	-------	12mm	11mm
3c	-------	-------	12mm	11mm
3d	-------	-------	10mm	12mm
3e	-------	-------	--------	16mm
3f	-------	-------	12mm	14mm
3g	-------	-------	-------	15mm
3h	-------	-------	11mm	--------
Co-Trimoxazole	25mm	10mm	26mm	25mm

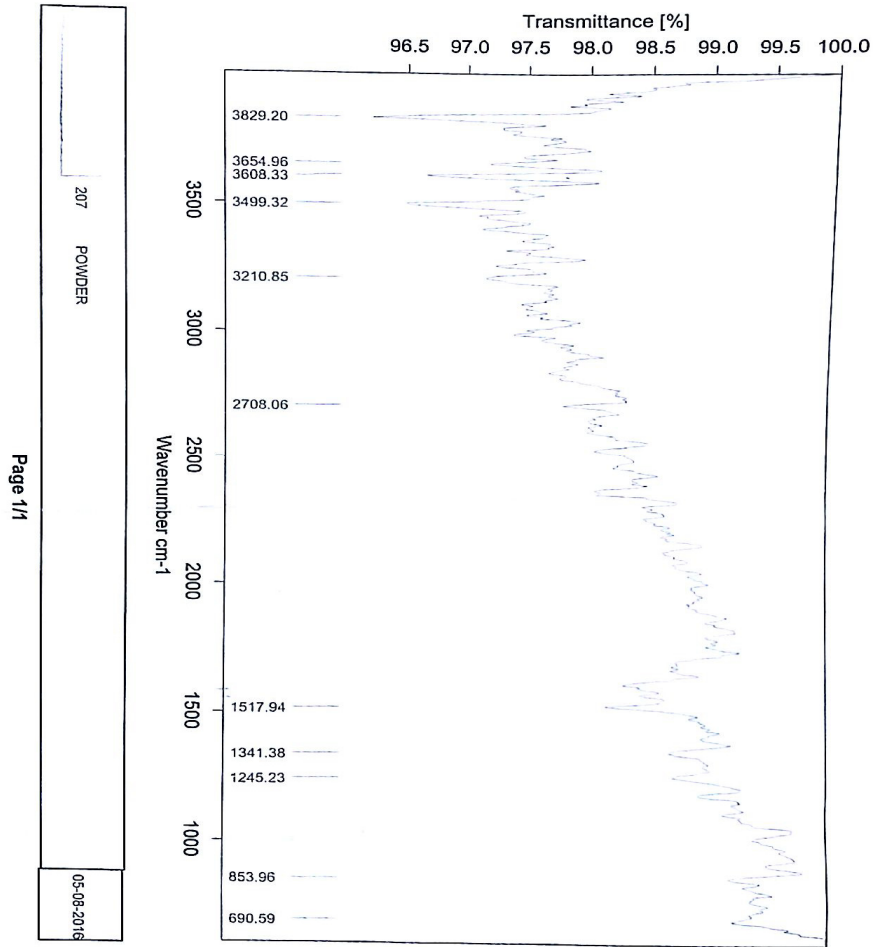


Figure-1: IR of 4-(3-bromophenyl)-N-(1-(4-(4-bromophenyl)thiazol-2-yl)-3-methyl-4-(2-(4-nitrophenyl)hydrazono)-4,5-dihydro-1H-pyrazol-5-ylidene)-6-(4-nitrophenyl)pyrimidin-2-amine (3g).

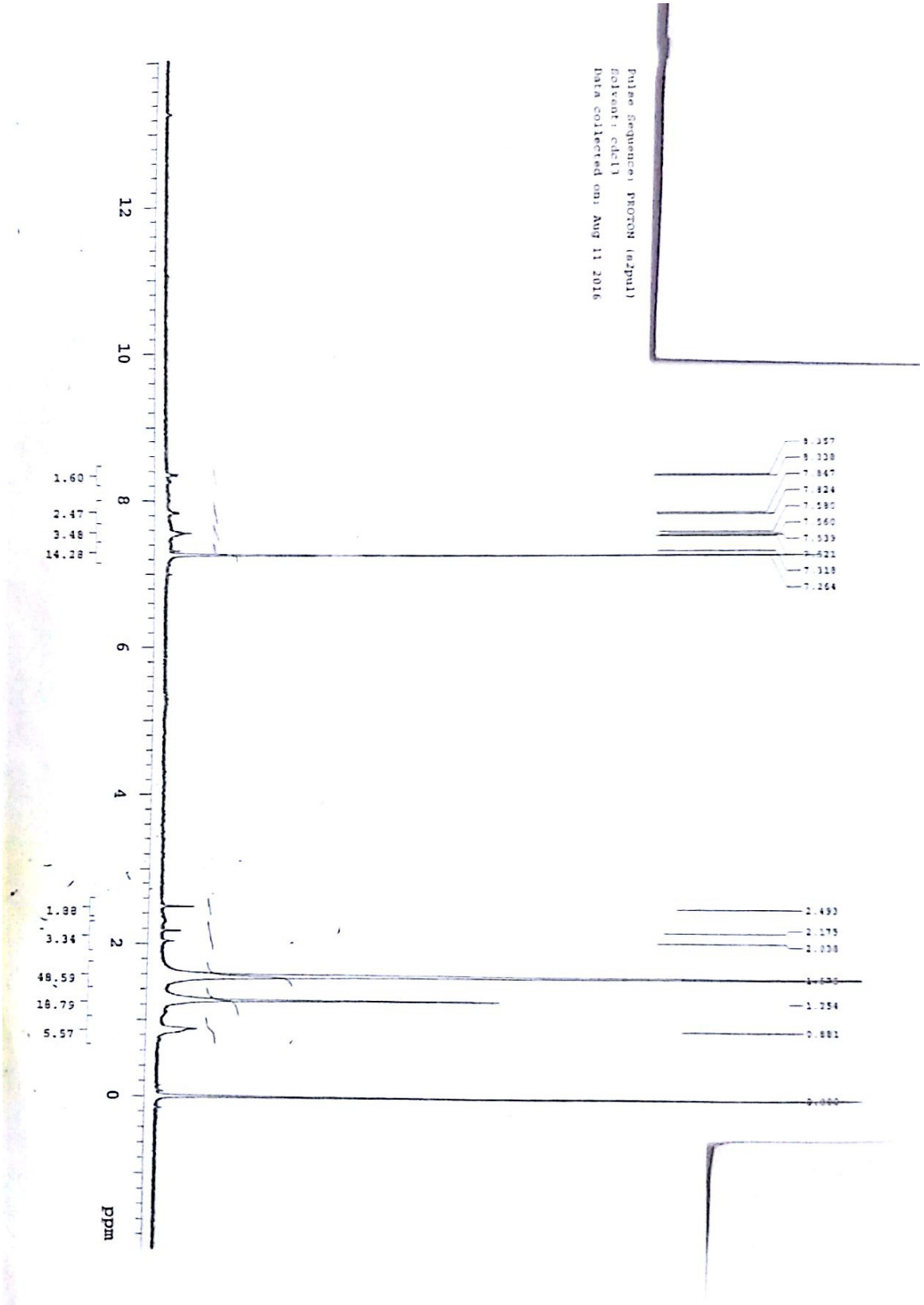


Figure-2: [1]HNMR of 4-(3-bromophenyl)-N-(1-(4-(4-bromophenyl)thiazol-2-yl)-3-methyl-4-(2-(4-nitrophenyl)hydrazono)-4,5-dihydro-1H-pyrazol-5-ylidene)-6-(4-nitrophenyl)pyrimidin-2-amine (3g).

Conclusion

Synthesis of 4-(3-bromophenyl)-N-(1-(4-(4-bromophenyl) thiazol-2-yl)-3-methyl-4-(2-phenylhydrazono)-4,5-dihydro-1H-pyrazol-5-ylidene)-6-(4-nitrophenyl)pyrimidin-2-amine derivatives (3a-h) has been successfully achieved by conventional method as well as by using microwave irradiation. Higher yields of compounds (3a-h) in a short reaction time were obtained when the reactions were carried out by using microwave irradiation. The evaluation of biological efficacy of the synthesized compounds in comparison with standard Co-Trimoxazole showed that the *Staphylococcus aureus, Streptococcus pyogenes* (Gram positive organisms) were sensitive to some extent to all these compounds whereas *Escherichia coli, Proteus vulgaris* (Gram negative organisms) were not at all sensitive to these compounds.

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