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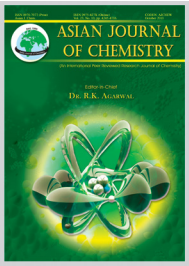

Synthesis, Antibacterial and Antifungal Activities of Some Novel Derivatives of Thiazolo[2,3-b]dihydropyrimidine Possessing 4-Pyrazolyl Moiety

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A series of new 2-arylidene-5-(5-chloro-3-methyl-1-*N*-phenyl-pyrazol-4-yl)-6-carbethoxy-7-methyl-5*H*-thiazolo[2,3-b]pyrimidin-3(1*H*)-ones have been synthesized by a three component (MCR) reaction involving 4-(5-chloro-3-methyl-1-*N*-phenyl- pyrazol-4-yl)-5-carbethoxy-6-methyl-3,4-dihydropyrimidin-2(1*H*)-thione, monochloroacetyl chloride and aryl aldehydes. The newly synthesized compounds were well characterized by elemental analysis, IR, ^{1}H NMR and mass spectral studies. The newly synthesized compounds were screened for their antibacterial and antifungal activities and have exhibited moderate to excellent growth inhibition of bacteria and fungi.

Key Words: Pyrazolyl aldehyde, Thiazolo[2,3-b]dihydropyrimidine, Antimicrobial activity.

INTRODUCTION

The 3,4-dihydropyrimidin-2(1*H*)-ones have recently emerged as important target molecules due to their therapeutic and pharmacological properties[1] such as antiviral[2], antimitotic[3], anticarcinogenic[4], antihypertensive[5] and as calcium channel modulators[6]. Additionally, their particular structure has been found in natural marine alkaloid batzelladine A and B which are the first low molecular weight natural products reported in the literature to inhibit the binding of HIV gp-120 to CD4 cells, so disclosing a new field towards the development of AIDS therapy[7]. Thiazoles and their derivatives are also found to be associated with various biological activities such as antibacterial, antifungal and antiinflammatory[8-11]. Prompted by the chemotherapeutic importance of pyrimidine derivatives and in a view to synthesize bioactive molecules[12], it was contemplated to synthesize a series of novel fused pyrimidine derivatives possessing 5-(5-chloro-3-methyl-1-*N*-phenyl-pyrazol-4-yl) moiety and study their biological properties.

EXPERIMENTAL

Melting points were determined by open capillary method and are uncorrected. Completion of reaction was routinely checked by TLC on silica gel-G plates of 0.5 mm thickness and the spot were located in UV chamber and by iodine chamber. The IR spectra (KBr pellets) were recorded on a Shimadzu FT-IR 8400 spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker DRX-300MHz spectrophotometer using TMS as an internal standard. The mass spectra were recorded on GCMS-QP200 mass spectrometer. The purity of the compounds was checked by thin layer chromatography on silica gel plate using *n*-hexane and ethyl acetate (4:1, v/v).

Synthesis of 2-arylidene-5-(5-chloro-3-methyl-1-*N*-phenyl-pyrazol-4-yl)-6-carbethoxy-7-methyl-5*H*-thiazolo[2,3-b]pyrimidin-3(1*H*)-ones (IIIa-j)

(1) Synthesis of 5-chloro-3-methyl-1-*N*-phenyl-pyrazol-4-carboxaldehyde 5-chloro-3-methyl-1-*N*-phenyl-pyrazol-4-carboxaldehyde (**I**) has been synthesized according to reported method[13].

(2) Synthesis of 4-(5-chloro-3-methyl-1-*N*-phenyl-pyrazol-4-yl)-5-carbethoxy-6-methyl-3,4-dihydropyrimidin-2(1*H*)-thione (II): A mixture of 5-chloro-3-methyl-1-*N*-phenyl-pyrazol-4-carboxaldehyde (3 mmol), ethyl aceto-acetate (3 mmol), thiourea (3.6 mmol) and HCl (0.5 mL) in ethanol medium were heated to reflux for 6 h. The resulting solution was cooled to room temperature and poured into cold water with vigorous stirring. The resulting solid was filtered under suction, washed with cold ethanol and recrystallized from hot ethanol. This compound was obtained as dark yellow coloured crystals. Yield: 90 %, m.p. 161-162 ºC, IR (KBr, ν_{max}, cm^{-1}): 3311 (N-H), 3185 (N-H), 2985 (C-H), 1706 (C=O), 1571 (C=C), 1274 (C=S), 1178 (C=O); ^{1}H NMR ($CDCl_3$) δ:1.22 (t, 3H, *J* = 7.12 Hz, ester-CH_3), 4.12 (q, 2H, *J* = 7.12 Hz, ester-CH_2), 2.45 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 5.42 (s, 1H, CH),

TABLE-1
PHYSICAL CONSTANT OF SYNTHESIZED COMPOUNDS(**IIIa-j**)

Compound no.	R	Molecular formula	m.p. (°C)	Yield (%)	R_f value	% of Nitrogen (calcd./found)
IIIa	C_6H_5	$C_{27}H_{23}N_4O_3SCl$	152	74	0.51	10.78 / 10.75
IIIb	2-Cl-C_6H_4	$C_{27}H_{22}N_4O_3SCl_2$	170	76	0.46	10.12 / 10.08
IIIc	4-Cl-C_6H_4	$C_{27}H_{22}N_4O_3SCl_2$	186	71	0.53	10.12 / 10.08
IIId	3- NO_2 -C_6H_4	$C_{27}H_{22}N_5O_5SCl$	210	78	0.49	12.41 / 12.38
IIIe	4- CH_3O -C_6H_4	$C_{28}H_{25}N_4O_4SCl$	202	71	0.55	10.20 / 10.15
IIIf	2-OH-C_6H_4	$C_{27}H_{23}N_4O_4SCl$	192	77	0.56	10.46 / 10.42
IIIg	4-OH-C_6H_4	$C_{27}H_{23}N_4O_4SCl$	208	72	0.48	10.46 / 10.42
IIIh	C_6H_5-CH=CH	$C_{29}H_{24}N_4O_3SCl$	161	71	0.53	10.27 / 10.23
IIIi	4-CH_3S-C_6H_4	$C_{28}H_{25}N_4O_3S_2Cl$	142	70	0.52	09.91 / 09.87
IIIj	4-F-C_6H_4	$C_{27}H_{22}N_4O_3SClF$	141	75	0.59	10.42 / 10.37

7.34 7.65 (s, 1H, NH), 8.25 (s, 1H, NH); MS (m/z, %): 323 (M^+ +1, 100), 322 (M^+, 18), 199 (31), 177 (20), 154 (36), 137 (22), 136 (37), 77 (19). 6.2.

(3) Synthesis of 2-arylidene-5-(5-chloro-3-methyl-1-*N*-phenyl-pyrazol-4-yl)-6-carbe-thoxy-7-methyl-5*H*-thiazolo[2,3-b]pyrimidin-3(1*H*)-ones (IIIa-j): A mixture of thione (2) (10 mmol), monochloroacetyl chloride (15 mmol), anhydrous sodium acetate (2 g), glacial acetic acid (20 mL), acetic anhydride (15 mL) and aryl aldehyde (10 mmol) were heated to reflux for 3 h. The reaction mixture was cooled to room temperature and poured into crushed ice with vigorous stirring. The precipitated solid was filtered under suction, washed with cold water and recrystallized from glacial acetic acid. The characterization data of these compounds are given in Table-1.

Compound IIIa: IR (KBr, ν_{max}, cm^{-1}) : 2976 (C-H), 1710 (C=O), 1606 (C=N), 1541 (C=C), 1159 (C=O), 774 (C-Cl); ^{1}H NMR ($CDCl_3$) δ: 1.22 (t, 3H, *J* = 7.10 Hz, ester-CH_3), 4.10 (q, 2H, *J* = 7.14 Hz, ester-CH_2), 2.44 (s, 3H, CH_3), 2.51 (s, 3H, SCH_3), 3.62 (s, 3H, CH_3), 6.18 (s, 1H, CH), 7.17 (d, 2H, *J* = 8.06 Hz, phenyl), 7.33 (δ, 2H, *J* = 8.16 Hz, 4-phenyl), 7.64 (δ, 2H, *J* = 8.36 Hz, 4-phenyl), 7.71 (s, 1H, exocyclic CH); MS (m/z, %): 518 (M^+), 441 (M^+), 332, 305, 253, 196, 189, 127, 73, 67.

Antibacterial activity: The purified products were screened for their antibacterial activity. The nutrient agar bath prepared by the usual method was inoculated specially with 0.5 mL for 24 h, old subculture of *Sreptococcus pyogens* MTCC-442, *Staphylococcus aureus* supsp. *aureus* MTCC-96, *Bacillus subtilius* MTCC-441, *Escherichia coli* MTCC-443 were taken in separate conical flask at 40º-50 ºC and mix well by gentle shaking. About 25 mL of the contents of the flask were poured and evenly spread in a petridish (13 mm in diameter) and allowed to settle down for 2 h. The cups (10 mm in diameter) were formed by the help of borer in agar medium and filled with 0.04 mL (40 µg/mL) solution of a sample in DMF. The plate were incubated at 37 ºC for 24 h and the control was maintained with 0.04 mL of DMF in similar manner and the zones of inhibition of the bacterial growth were measured in mm. The antibacterial activity of the compounds (**IIIa-j**) ware compared with known standard reference drugs like ampicillin, ciprofloxacin, chloramphenicol and griseofulvin at same concentration.

Antifungal activity: *Aspergillus niger* MTCC-282 and *Candida albicans* MTCC-227 were employed for testing fungicidal activity using cup plate method. The cultures were maintained on Sabouraud's agar slants. Sterilized Saboraud's agar medium was inoculated with 72 h old, 0.5 mL suspension of fungal spores, in a separate flask. About 25 mL of the inoculated medium was evenly spread in a sterilized petri dish and allowed to settle down for 2 h. The cups (10 m in diameter) were punched in petri dish and loaded with 0.04 mL (40 µg/mL) of solution of a sample in DMF. The plates were incubated at room temperature (30 ºC) for 48 h. After the completion of the incubation period, the zones of inhibition of growth of compounds, **(IIIa-j)** in the form of diameter in mm was measured. Along the test solution in each petri dish, one cup was filled with solvent, which acted as control. The antifungal activity of compounds (**IIIa-J**) are compared with known standard drugs.

RESULTS AND DISCUSSION

4-(5-Chloro-3-methyl-1-*N*-phenyl-pyrazol-4-yl)-5-carbethoxy-6-methyl-3,4-dihydro pyrimidin- 2(1*H*)-thione (**II**) was synthesized in a one pot Biginelli reaction involving 5-chloro-3-methyl-1-phenyl-pyrazole-4-carbaldehyde, ethyl acetoacetate and thiourea in presence of HCl catalyst according to the procedure reported in the literature[14]. The characterization data of the above synthesized compound is given Table-1. This compound was used further in order to synthesize a series of novel *N*-bridged heterocycles. The title compounds *i.e.* 2-arylidene-5-(5-chloro-3-methyl-1-*N*-phenyl-pyrazol-4-yl)-6-carbethoxy-7-methyl-5*H*-thiazolo[2,3-b]-pyrimidin-3-ones (**IIIa-j**) have been synthesized in a one pot multi-component reaction involving 2, monochloro acetylchloride and the corresponding arylaldehyde in presence of anhydrous sodium acetate in acetic acid:acetic anhydride medium (**Scheme-I**). The newly synthesized compounds were screened for their antibacterial and antifungal activities and have exhibited moderate to excellent growth inhibition of bacteria and fungi (Table-2).

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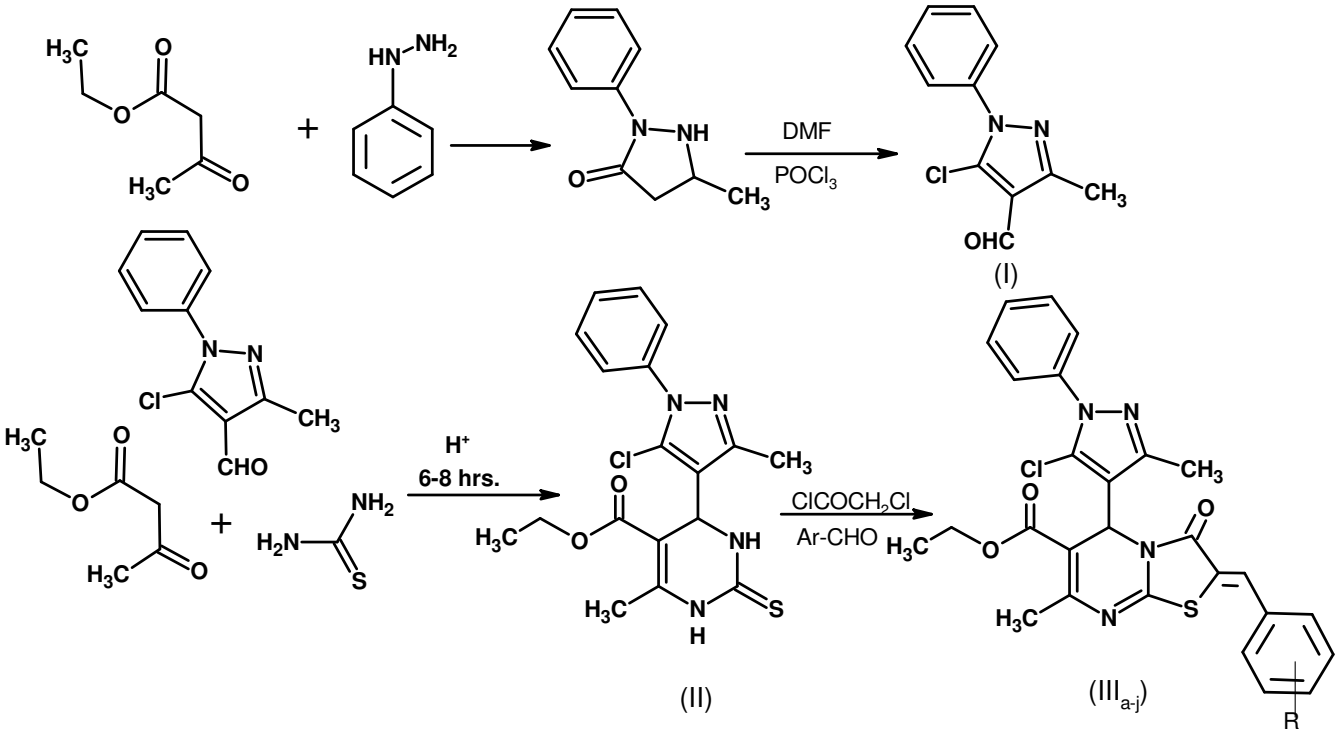

Scheme-I

TABLE-2
ANTIMICROBIAL ACTIVITY OF SYNTHESIZED COMPOUNDS **IIIa-j**

Compd. No.	R	Zones of inhibition (mm)					
		Antibacterial activity				Antifungal activity	
		S. pyogens	*S. aureus*	*E. coli*	*B. subtilis*	*C. albicans*	*A. niger*
IIIa	C_6H_5	14	12	10	16	18	12
IIIb	2-Cl-C_6H_4	13	11	14	18	16	18
IIIc	4-Cl-C_6H_4	15	16	22	14	20	22
IIId	3-NO_2-C_6H_4	10	10	20	15	22	19
IIIe	4- CH_3O-C_6H_4	19	14	16	17	24	14
IIIf	2-OH-C_6H_4	17	17	14	20	15	21
IIIg	4-OH-C_6H_4	15	18	12	19	17	16
IIIh	C_6H_5-CH=CH	14	19	15	12	19	11
IIIi	4-CH_3S-C_6H_4	12	12	17	16	16	21
IIIj	4-F-C_4H_3O	16	17	19	21	14	17
Antimicrobial activity (highest and comparable) of compounds **IIIa-j** with chosen standard drugs:							
Ampicillin		16	17	23	19	–	–
Chloramphenicol		19	22	23	25	–	–
Amoxycillin		17	20	21	25	–	–
Ciprofloxacin		21	22	28	22	–	–
Norfloxacin		20	25	26	23	–	–
Griseofulvin		–	–	–	–	25	22

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