RJC
http://www.rasayanjournal.com

RASĀYAN *J. Chem.*
Vol.4, No.3 (2011), 605-608
ISSN: 0974-1496
CODEN: RJCABP

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME NOVEL DERIVATIVES OF THIAZOLO[2,3-b] DIHYDROPYRIMIDINE CONTAINING 4-PYRAZOLYL MOIETY

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ABSTRACT

A series of new 7-amino 2-arylidene-5-(5-Chloro-3-methyl-1-N-phenyl-pyrazol-4-yl) -6-carb-ethoxy-5H-thiazolo[2,3-b]pyrimidin-3-ones have been synthesized by a three component (MCR) reaction involving 6-amino 4-(5- Chloro-3- methyl- 1-N-phenyl- pyrazol-4-yl)-5-carbethoxy-3,4-dihydropyrimidin-2(1H)-thione, monochloroacetylchlo- ride and arylaldehydes. The newly synthesized compounds were well characterized by elemental analysis, IR, 1H NMR and mass spectral studies. The newly synthesized compounds were also screened for their antibacterial and antifungal activities and have exhibited moderate to excellent growth inhibition of bacteria and fungi. The results of such studies have been discussed in this paper.

Keywords: Cyclocondensation, Pyrazolyl aldehyde, Thiazolo [2,3-b] dihydro pyrimi- dinone, antimicrobial activity.

INTRODUCTION

The 3,4-dihydropyrimidin-2(1H)-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 noteworthy,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 anti-inflammatory [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. Results of such studies are discussed in this paper.

Chemistry

4-(5-Chloro-3-methyl-1-N-phenyl-pyrazol-4-yl)-5-carbethoxy-6-methyl-3,4-dihydro pyrimidin-2(1H)-thione II was synthesized in a one pot Biginelli reaction involving 5-chloro-3-methyl-1-phenyl-pyrazole-4-carbaldehyde, ethyl cyanoacetate and thiourea in presence of HCl catalyst according to the procedure reported in the literature [13]. This compound was used further in order to synthesize a series of novel N-bridged heterocycles. The title compounds i.e. 7-amino, 2-arylidene- 5-(5-Chloro-3-methyl-1-N-phenyl-pyrazol-4-yl)-6-carbethoxy-5H-thiazolo[2,3-b]-pyrimidin-3-onesIIIa-j have been synthesized in a one pot multi-component reaction involving II, monochloro acetylchloride and the corresponding arylaldehyde in presence of anhydrous sodium acetate in DMF (Scheme 1). The structures of some of the newly synthesized compounds have been established on the basis of elemental analysis, IR, 1H NMR and mass spectral studies. The results of such studies have been discussed in this paper (Table 1).

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.

Table-1 : Physical constant of Synthesized compounds IIIa-j

Compd. No.	*R*	*Molecular* Formula	M.P. ^{0}C	*Yield* %	*Rf* Value	% of Nitrogen *Calcd / Found*
IIIa	C_6H_5	$C_{26}H_{22}ClN_5O_3S$	161	76	0.53	13.46 / 13.51
IIIb	2-Cl-C_6H_4	$C_{26}H_{21}Cl_2N_5O_3S$	139	71	0.48	12.63 / 12.71
IIIc	4-Cl-C_6H_4	$C_{26}H_{21}Cl_2N_5O_3S$	213	78	0.51	12.63 / 12.71
IIId	3- NO_2 -C_6H_4	$C_{26}H_{21}ClN_6O_5S$	225	73	0.49	14.86 / 14.90
IIIe	4- CH_3O -C_6H_4	$C_{27}H_{24}ClN_5O_4S$	196	75	0.51	12.72 / 12.76
IIIf	2-OH-C_6H_4	$C_{26}H_{22}ClN_5O_4S$	130	72	0.55	13.05 / 13.10
IIIg	4-OH-C_6H_4	$C_{26}H_{22}ClN_5O_4S$	219	79	0.47	13.05 / 13.10
IIIh	C_6H_5-CH=CH	$C_{28}H_{23}ClN_5O_3S$	178	70	0.52	12.84 / 12.89
IIIi	4-CH_3S-C_6H_4	$C_{27}H_{24}ClN_5O_3S_2$	153	71	0.50	12.36 / 12.41
IIIj	4-F-C_6H_4	$C_{26}H_{21}ClFN_5O_3S$	186	76	0.58	13.02 / 13.07

Table-2: Antimicrobial Activity of Synthesized compounds IIIa-j

Compd. No.	R	Antibacterial activity Zones of inhibition in m.m.				Antifungal activity Zones of inhibition In m.m.	
		S. pyogens	S. aureus	E. coli	B. subtilis	C. albicans	A. niger
IIIa	C_6H_5	15	15	16	18	17	13
IIIb	2-Cl-C_6H_4	14	15	16	19	17	19
IIIc	4-Cl-C_6H_4	16	17	19	20	20	21
IIId	3- NO_2 –C_6H_4	11	13	15	16	21	20
IIIe	4- CH_3O -C_6H_4	20	21	22	23	23	16
IIIf	2-OH-C_6H_4	16	17	18	20	16	19
IIIg	4-OH-C_6H_4	14	16	18	20	17	19
IIIh	C_6H_5-CH=CH	14	16	17	19	19	20
IIIi	4-CH_3S-C_6H_4	17	18	19	20	17	21
IIIj	4-F-C_4H_3O	19	20	22	23	18	22
Antimicrobial activity (Highest and Comparable) of compounds (IIIa-j)with choosen 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

The IR spectra (in KBr pellets) were recorded on a Shimadzu FT-IR 8400 spectrophotometer. 1H 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 (TLC) on silica gel plate using n-hexane and ethyl acetate (4:1, v/v).

General procedure for the synthesis of 7-amino, 2-arylidene-5-(5-Chloro-3- methyl -1-N-phenyl-pyrazol-4-yl)-6-carbethoxy-l-5H-thiazolo[2,3-b]pyrimidin-3(1H)-ones (IIIa-j)

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 the reported procedure of D. Russowsky et.al. [14]

Synthesis of 6-amino-4-(5- Chloro-3-methyl-1-N-phenyl-pyrazol-4-yl) -5-carbethoxy- 3,4-dihydropyrimidin-2(1H)-thione(II)

A mixture of 5-Chloro-3-methyl-1-N-phenyl-pyrazol-4-carboxaldehyde (3.0 mmol), ethyl cyanoacetate (3.0 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 colored crystals. Yield: 90%, m.p. 171-172 ^{0}C, IR (KBr) ν/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), 5.42 (s, 1H, CH), 7.34 7.65 (s, 1H, NH), 8.25 (s, 1H, NH), 9.53 (s, 2H, NH_2); MS (m/z, %): 390 (M^{+1}, 100), 322 (M^+, 18), 199 (31), 177 (20), 154 (36), 137 (22), 136 (37), 77 (19). 6.2.

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

A mixture of thione (II) (10 mmol), monochloroacetyl chloride (15 mmol), arylaldehyde (10 mmol), anhydrous sodium acetate (1 g) and DMF (20 ml), and were heated to reflux for 8-6 h. The reaction mixture was cooled to room temperature and poured into cold water with vigorous stirring. The precipitated solid was filtered under suction, washed with cold water and recrystallized from DMF. The physical properties of the synthesized compounds(IIIa-j)are given in Table 1.

Compound IIIa: IR (KBr) ν/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 (δ, 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, %): 519 (M^{+1}), 442 (M^{+1}), 333, 306, 254, 197, 190, 128, 74, 68.

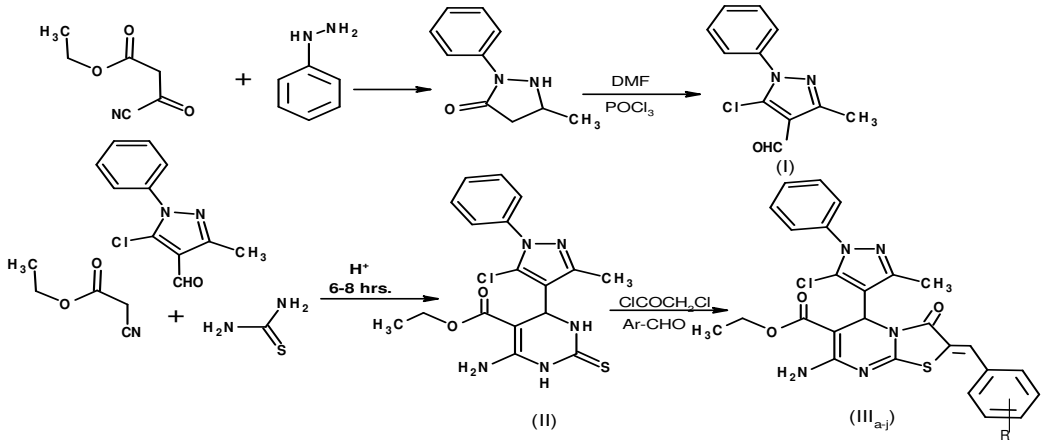
Antibacterial activity

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 hrs, 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 40°-50°C 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 two hours. 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°c for 24 hours 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, Griseofulvin, at same concentration. The moderate and comparable antibacterial activities of compounds are recorded in Table 2.

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 hours 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 petridish and allowed to settle down for two hours. The cups (10 m in diameter) were punched in petridish and loaded with 0.04 ml (40 ug /ml) of solution of a sample in DMF. The plates were incubated at room temperature

(30°C) for 48 hours. 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 petridish, one cup was filled with solvent, which acted as control. The antifungal activity of compounds (IIIa-J) are compared with known standard drugs mentioned above, which are recorded in Table 2.



Scheme-1

ACKNOWLEDGEMENTS

The authors are thankful to Department of Chemistry, Saurashtra University, Rajkot for providing laboratory facilities, CDRI lucknow for providing ^{1}HNMR and Mass spectral facilities

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[RJC-796/2011]