Available online at www.joac.info

ISSN: 2278-1862

Journal of Applicable Chemistry

2013, 2 (3): 391-397

(International Peer Reviewed Journal)

Synthesis and antifungal evaluation of thiazolo[3,2-a]pyrimidine derivatives

Monika Bansal[1], Ramandeep Kaur[2], Balbir kaur[1*]

1. Department of Chemistry, Punjabi University, Patiala-147002, Punjab, INDIA
2. Department of Chemistry, S.U.S. Government College, Sunam-148028, Punjab, INDIA

Email: drbalbirkaur@gmail.com[1*], monika_singla79@yahoo.com[1], kaur2007_chem@yahoo.co.in[2]

Received on 11th April and finalized on 20th April 2013.

ABSTRACT

Heterocyclic compounds having nitrogen and sulfur in their skeleton are the most fascinated compounds, prepared by scientists, due to their diverse biological activities. Literature study reveals that, among the various heterocyclic compounds, pyrimidines along with thiazole moiety proves to be biologically very active substrates. Keeping this in view, a series of new thiazolo-pyrimidine derivatives were prepared through multi-component reaction of aromatic aldehydes, ethyl acetoacetate and 4-(4-bromophenyl)-1,3-thiazol-2-amine. The structure of the prepared compounds was elucidated through melting points, IR and PMR spectroscopy. Some of the compounds were tested for antifungal activities.

Keywords: Heterocyclic compounds, thiazolo-pyrimidine derivatives, Antifungal activities.

INTRODUCTION

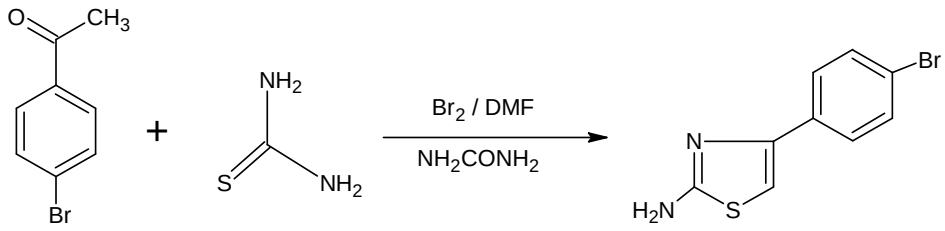
Heterocyclic nucleus imparts an important role in medicinal chemistry and serves as a key template for the development of various therapeutic agents. Nitrogen containing heterocyclic ring such as pyrimidine, is a promising structural moiety for drug design. Pyrimidines have been found to be associated with diverse biological activities[1]. Many detailed review, of the synthesis of substituted pyrimidines, have been appeard[2,3]. Pyrimidine derivatives are found in nucleic acid including uracil, thymine, cytosine, adenine, and guanine are fundamental building blocks for deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). Condensed pyrimidine derivatives have been reported as antimicrobial[4-6], analgesic[7,9]. anti-viral[8,9], anti-inflammatory[9], anti-HIV[10], anti-tubercular[11], anti-tumor[5-12], anti-neoplastic[13], anti-malarial[14], diuretic[15], antiplatelet[16], antifilarial[17], cardiovascular agents[18] and hypnotic drugs for the nervous system[19] and calcium-sensing receptor antagonists[20]. In addition, it has been observed for the years that thiazole nucleus possess different biological activities such as antihypertensive[21], anti-inflammatory[22], anti-schizophrenic[23], antibacterial[24], anti-HIV[25], hypnotic[26], anti-allergic[27], analgesic[28], fibrinogen receptor antagonists with antithrombotic activity[29]. It was envisaged that these two active pharmacophores, if linked together, would generate novel molecular templates which are likely to exhibit interesting biological properties. Thiazolo[4,5-*d*]pyrimidine derivatives have acquired a growing importance in the field of medicinal chemistry and considered as thia-analogues of the natural purine bases such as adenine and guanine, because of their biological potential while some thiazolo[3,2-*a*]pyrimidines have been demonstrated to be of pharmacological interest due to their anti-inflammatory[30,31], psychopharmacological[32],

bactericidal[33 and anti-viral[34] activity as inhibitors of HIV-1 reverse transcriptase. The above given applications prompted us to synthesize a series of new compounds.

MATERIALS AND METHODS

Multiple reactions are combined into one synthetic operation, have been used extensively to form carbon-carbon bonds in synthetic chemistry[35].. Such reactions offer a wide range of possibilities for the efficient construction of highly complex molecules in a single procedural step, avoid the complicate purification operations and allow savings of both solvents and reagents. The need to reduce the amount of toxic waste and by-product arising from chemical processes requires increasing emphasis on the use of less toxic and environmentally compatible materials in the design of new synthetic methods.

At first, we synthesize the starting material i.e. 4-(4-bromophenyl)-1,3-thiazol-2-amine which is a two step synthesis. In the first step there is selective bromination of ketone in DMF in the presence of urea and in the second step intermediate α-bromoketone was reacted with thiourea to form resulting thiazole (Scheme 1).

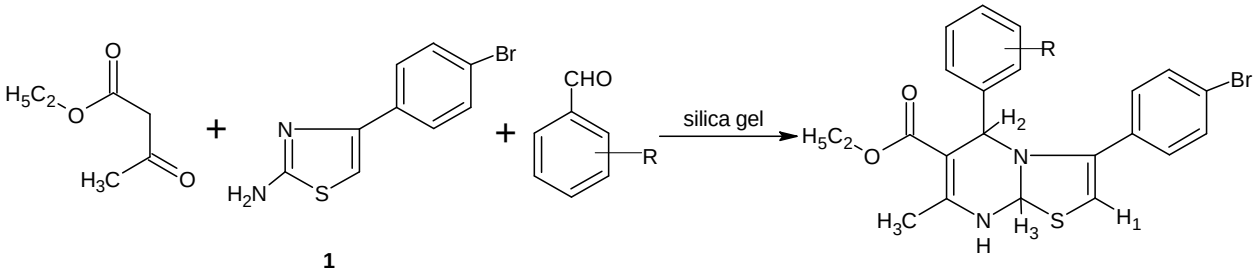


1

Scheme 1

The structure of this heterocyclic compound was confirmed by melting point, IR & PMR data as given below: **Melting point:** 177-178^0 C .**Yield:** 80%. IR: 3429.8, 3282.5, 3112.4, 1534.3,1473.5, 1396.2
NMR: 6.53(s,2H,NH_2), 6.74(s,1H,CH), 7.47(d,2H,haro),7.66(d, 2H,haro)

During this period, 4-(4-bromophenyl)-1,3-thiazol-2-amine is reacted with ethylacetoacetate and aromatic aldehydes, under microwave irradiation (Scheme 2) to form derivatives (2a-m).



1 **2a-m**

Scheme 2

RESULTS AND DISCUSSION

The Characterization data of Ethyl 3-(4-bromophenyl)-7-methyl-5-phenyl-8,8a-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-6-carboxylate derivatives (2a-m) are presented in table1.

Table 1: Characterization data of Ethyl 3-(4-bromophenyl)-7-methyl-5-phenyl-8, 8a-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-6-carboxylate derivatives (2a-m)

Entry	R	Time (min.)	Product	M.Pt (^{0}C)	Molecular Formula	Yield (%)
1.	H	7	1a	231-232	$C_{22}H_{21}BrN_2O_2S$	50
2.	4-OCH_3	10	1b	186-187	$C_{23}H_{23}BrN_2O_3S$	62
3.	2-NO_2	3.20	1c	231-232	$C_{22}H_{20}BrN_3O_4S$	60
4.	4-OH,3-OCH_3	8	1d	215-216	$C_{23}H_{23}BrN_2O_4S$	80
5.	3-OH	4	1e	226-227	$C_{22}H_{21}BrN_2O_3S$	59
6.	2,3-(O-CH_2-O)	4	1f	221-222	$C_{23}H_{21}BrN_2O_4S$	46
7.	4-NO_2	4	1g	228-230	$C_{22}H_{20}BrN_3O_4S$	30
8.	2,4-(Cl)	4	1h	227-228	$C_{22}H_{19}BrCl_2N_2O_2S$	63
9.	3-NO_2	4.30	1i	240-241	$C_{22}H_{20}BrN_3O_4S$	51
10.	2-Cl	5	1j	220-221	$C_{22}H_{20}BrClN_2O_2S$	26
11.	3,4(OCH_3)	6	1k	182-183	$C_{24}H_{25}BrN_2O_4S$	35
12.	4-$N(CH_3)_2$	4.30	1l	210-211	$C_{24}H_{26}BrN_3O_2S$	76
13.	4-Cl	8	1m	209-210	$C_{22}H_{20}BrClN_2O_2S$	27
14.	4-OH	4	lo	192-193	$C_{22}H_{21}BrN_2O_3S$	40

The spectral data is given in table2.

Table 2: Spectral data of the synthesized compounds

Comp	^{1}H(δ,ppm); IR spectral data
1c	IR (KBr,cm^{-1}) : 3373.1,3267.6,3112,1628.8,1571.9,1490.3,1395.6
1b	IR:3382.4,3267.2,3192.6,3058.5,2924.3,1634.5,1510.6,1395, 1256.5
1d	PMR (δ,ppm): 9.35(s,1H, OH); 7.90 (s, 1H, NH); 6.79-7.33 (m, 9H, Ar-H & H_1); 5.68 (s, 1H, H_3) ; 3.75(s,3H,OCH_3)3.48(q, 2H,-O$\underline{CH_2}CH_3$); 2.32 (s, 3H, CH_3); 2.54 (s, 1H, H_2); 1.10 (t, 3H, $OCH_2\underline{CH_3}$). IR (KBr,cm^{-1}) **:** 3361, 3275, 1635.8, 1519, 1462
1e	PMR (δ,ppm): 9.16(s,1H, OH); 7.53 (s, 1H, NH); 6.69-7.45 (m, 9H, Ar-H & H_1); 5.70 (s, 1H, H_3) ; 3.25(q, 2H,-O$\underline{CH_2}CH_3$); 2.23 (s, 3H, CH_3); 2.58 (s, 1H, H_2); 1.25 (t, 3H, $OCH_2\underline{CH_3}$). IR (KBr,cm^{-1}) **:**3423; 2962; 2840; 1634; 1562.1; 1495
1f	PMR (δ,ppm): 9.59 (s, 1H, NH); 6.77-7.40 (m, 8H, Ar-H & H_1); 5.57 (s, 1H, H_3); 6.05(s, 2H, O-CH_2-O ; 3.56(q, 2H,-O$\underline{CH_2}CH_3$); 2.20 (s, 3H, CH_3); 2.57 (s, 1H, H_2); 1.16 (t, 3H, $OCH_2\underline{CH_3}$). IR (KBr,cm^{-1})**:** 3345.2,2999.8, 1639.9, 1537.7,1485.6, 1298.6
1h	PMR (δ,ppm): 9.15(s, 1H, NH); 7.62-8.18(m, 7H, Ar-H); 7.27(s,1H,H1); 5.87 (s, 1H, H_3) ; 3.26(q, 2H,-O$\underline{CH_2}CH_3$); 2.21 (s, 3H, CH_3); 2.54(s, 1H, H_2); 1.20 (t, 3H, $OCH_2\underline{CH_3}$).
1i	PMR (δ,ppm): 8.06 (s, 1H, NH); 8.06-7.12 (m, 9H, Ar-H & H_1); 5.80 (s, 1H, H_3) ; 3.26(q, 2H,-O$\underline{CH_2}CH_3$); 2.21(s, 3H, CH_3); 2.50 (s, 1H, H_2); 1.20 (t, 3H, $OCH_2\underline{CH_3}$). IR (KBr,cm^{-1}): 3287.8, 3120.5, 1626.5, 1524.1, 1353.6
1j	IR (KBr,cm^{-1}) **:**3436.5; 2924.3; 2857; 1637; 1590.5; 1489
1k	PMR (δ,ppm): 9.50(s, 1H, NH); 6.88-7.71(m, 7H, Ar-H); 6.82(s,1H,H1); 5.62 (s, 1H, H_3) ; 3.90(s,3H,OCH_3); 3.82(s,3H,CH_3)3.26(q, 2H,-O$\underline{CH_2}CH_3$); 2.21 (s, 3H, CH_3); 2.54 (s, 1H, H_2);1.20 (t, 3H, $OCH_2\underline{CH_3}$).
1l	PMR (δ,ppm) : 7.81 (s, 1H, NH): 7.10-7.42 (m, 8H, Ar-H); 6.81(s,1H,H1); 5.51 (s, 1H, H_3) ; 3.34(q, 2H,O$\underline{CH_2}CH_3$); 2.91 (s, 6H, $N(CH_3)_2$);2.34 (s, 3H, CH_3); 2.49 (s, 1H, H_2); 1.04 (t, 3H, $OCH_2\underline{CH_3}$). IR: 3393.9, 3162.9, 2915.7, 1641.8, 1580.6, 1513.2, 1487.6
1o	PMR (δ,ppm): 9.01(s,1H, OH); 7.59 (s, 1H, NH); 6.79-7.33 (m, 9H, Ar-H & H_1); 5.68 (s, 1H, H_3) ; 3.31(q, 2H,-O$\underline{CH_2}CH_3$); 2.29 (s, 3H, CH_3); 2.57 (s, 1H, H_2); 1.29 (t, 3H, $OCH_2\underline{CH_3}$).

APPLICATIONS

Antifungal studies: The antifungal screening studies of some compounds were performed by the standard Agar diffusion Method. The fungi analyzed were Aspergillus niger, Neurospora crassa, Cladosporium oxysporum, Candida albicans. The standard antibiotic and the solvent used were Amphotericin and Dimethyl sulfoxide respectively. The different concentrations of compounds taken was 25, 50, 100, 200, 400, 800 µg. Sample preparation: 10 mg sample was dissolved in 1 ml of DMSO.Stock Sample Concentration: 10 mg ml^{-1}. Media Used: Potato Dextrose Agar (PDA). 250 g of peeled potato

were boiled for 20 min and squeezed and filtered. To this filtrate 20 g of dextrose was added and the volume was made up to 1000ml by distilled water.

Initially, the stock cultures of were revived by inoculating in broth media and grown at 27^0C for48 hrs.

The agar plates of the above media were prepared and wells were made in the plate. Each plate was inoculated with 48 h old cultures (100 µl 10^{-4} CFU) and spread evenly on the plate. After 20 min, the wells were filled with of compound at different concentrations. The control plates with antibiotic were also prepared. All the plates were incubated at 27^0C for 48 h and the diameter of inhibition zone were noted.The results are presented in following table as diameter of inhibition zones in cm

A. Niger

Sample	25 µg	50 µg	100 µg	200 µg	400 µg	800 µg	MIC µg
EAA 1b	0	0	0	0	0	0.4	800
EAA 1g	0	0	0	0	0	0	>800
EAA 1d	0	0	0	0	0	0	>800
EAA 1h	0	0	0	0	0	0.1	800
EAA 1i	0	0	0	0	0	0.1	800
EAA 1o	0	0	0	0	0	0	>800
Amphotericin	0	0	0.2	0.3	0.5	0.7	100

N. crassa

Sample	25 µg	50 µg	100 µg	200 µg	400 µg	800 µg	MIC µg
EAA 1b	0	0	0	0	0	0	>800
EAA 1g	0	0	0	0	0	0	>800
EAA 1d	0	0	0	0	0	0.1	800
EAA 1h	0	0	0	0	0.9	1	400
EAA 1i	0	0	0	0	0	0.4	800
EAA 1o	0	0	0	0	0	0.5	800
Amphotericin	0	0	0	0	0.7	0.9	400

C.oxysporum

Sample	25 µg	50 µg	100 µg	200 µg	400 µg	800 µg	MIC µg
EAA 1b	0	0	0	0	0	0	>800
EAA 1g	0	0	0	0	0	0	>800
EAA 1d	0	0	0	0	0	0.6	800
EAA 1h	0	0	0	0	0	0	>800
EAA 1i	0	0	0	0	0	0.8	800
EAA 1o	0	0	0	0	0.4	0.5	400
Amphotericin	0	0.2	0.7	0.9	1.3	1.5	50

C.albicans

Sample	25 µg	50 µg	100 µg	200 µg	400 µg	800 µg	MIC µg
EAA 1b	0	0	0	0	0	0.7	800
EAA 1g	0	0	0	0	0	0.3	800
EAA 1d	0	0	0	0	0	0	>800
EAA 1h	0	0	0	0	0.5	1	400
EAA 1i	0	0	0	0	0	0.1	800
EAA 1o	0	0	0	0	0	0.2	800
Amphotericin	0	0.2	0.7	0.9	1.3	1.5	50

ACKNOWLEDGEMENT

We are thankful to Punjabi University, Patiala, for providing Lab and spectroscopy facilities.

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