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SYNTHESIS OF NOVEL SUBSTITUTED 2*H*-THIAZOLO [3,2-a] PYRIMIDINES USING WATER AS GREEN SOLVENT AND THEIR ANTIMICROBIAL EVALUATION

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ABSTRACT

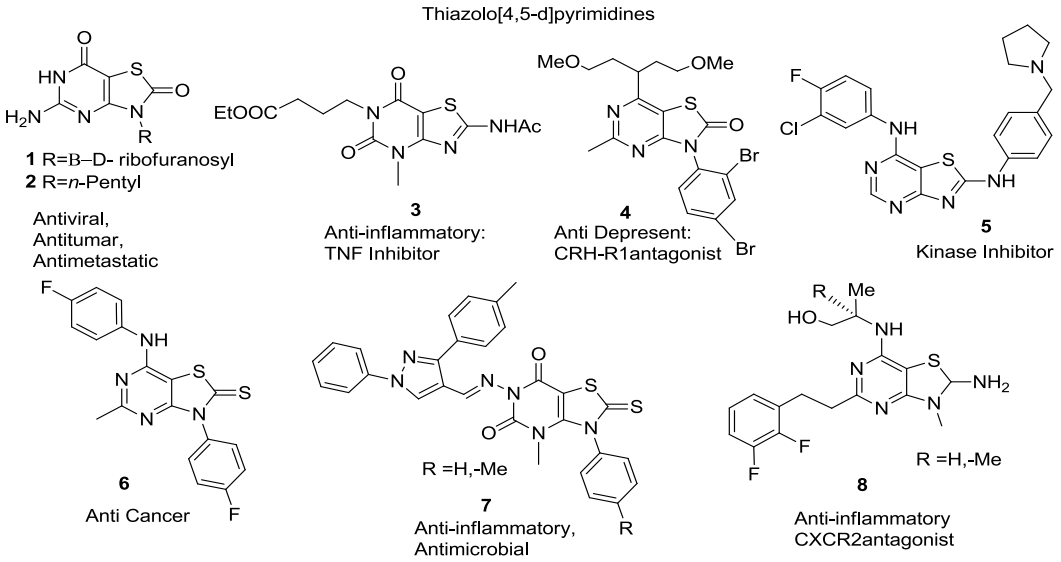
A novel series of *N*,5-bis(4-fluorophenyl)-3,5-dihydro-7-isopropyl-2*H*-thiazolo[3,2-*a*]pyrimidine -6-carboxamide has been prepared by reaction of *N*,4-bis(4-fluorophenyl)-1,2,3,4-tetrahydro-6-isopropyl-2-thioxopyrimidine-5-carboxamide with dibromoethane using basic catalysts TEA/ K_2CO_3, in the presence of TBAB/TEAB in water. We found water as an efficient and green solvent for the synthesis of novel thiazolo [3,2-a] pyrimidine scaffolds in good yields for biological interest. Among all compounds, **8c**, **8g**, **8i**, **8l** and **8o** shows good antimicrobial activity against bacterial strain compare to ciprofloxacin.

KEYWORDS: Thiazolo[3,2-*a*]pyrimidine, Pyrimidine, Alkylation Antimicrobial evaluation.

INTRODUCTION

The rapid development in new pharmacotherapies of bacterial drug resistance are growing into a global problem. Consequently, there is a pressing need to develop new antimicrobial drugs with potent activity in order to overcome the bacterial drug resistance. Electron-rich nitrogen heterocycles and sulfur compounds play an important role in diverse biological activities.[1-2] thiazolo[4,5-d] pyrimidine 1 (a guanosine analogue) exhibited in vivo activity against a variety of RNA and DNA viruses[3] and The guanine derivative 2 showed potent in vitro activity against human cytomegalovirus (HCMV).[4] Thiazole [4,5-d]pyrimidine-5,7-dione analogues (Compound 3) have been reported as having anti-inflammatory activities, due to TNF inhibition.[5] 2-Oxo-3-

aryl-thiazolo[4,5-d] pyrimidine analogues (compound 4) have been synthesized as antagonists of the corticotrophin releasing hormone (CRH) R1 receptor.[6] 2-Thio-3-aryl-thiazolo[4,5-d] pyrimidine derivatives have been described as having anticancer (compound 6)[6], anti-inflammatory and anti-microbial activity[7] (compound 7). 2-Aminothiazolo [4,5-d]pyrimidines (compound 8) which act as CXCR2 receptor antagonists[8-9] are also known. Recently, 2,7-substituted thiazolo[4,5-d] pyrimidines (compound 5) have been described as ATP-competitive inhibitors of protein kinase. Thiazolo [3,2-*a*] pyrimidine nucleus have been consistently regarded as structural analogs of biogenic purine bases and can be considered as potential purine antagonists.[10]

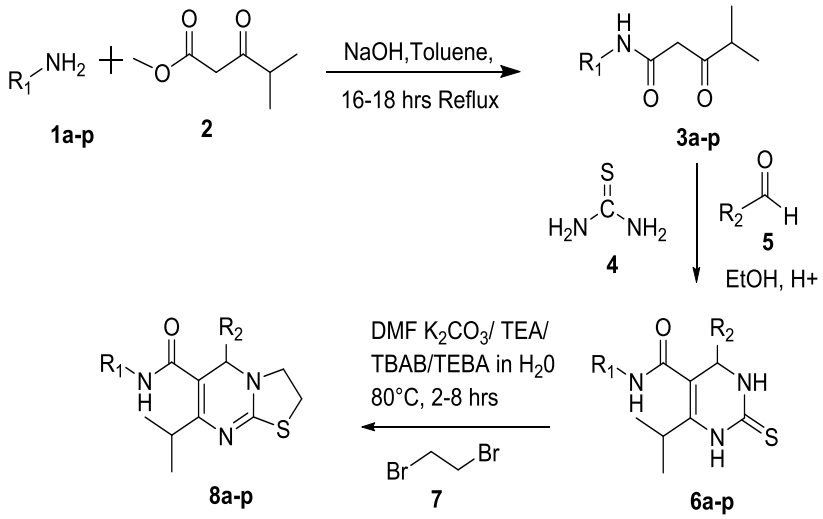


The -2*H*-Thiazolo [3,2-*a*]pyrimidine derivatives have considerable chemical and pharmacological importance because of a broad range of biological activities displayed by these classes of molecules. A series of 5*H*-thiazolo[3,2-*a*]pyrimidine derivatives **1** was studied with respect to the inhibition of IS, 3R--ACPD (10~tM)-stimulated GTP y35S binding on rat mGlu2 receptor transfected cell membranes.[11] Various methodologies have been described for the synthesis of substituted pyrimidine derivatives. However, the existing methods are suffer with some drawbacks, such as; yield, time, product isolation, purification. As we demonstrated, the tremendous biological potential of substituted pyrimidine derivatives and our ongoing interest[12,13] on application of ketene dithioacetals for the synthesis of various heterocyclic compounds encouraged us to synthesize some new highly functionalized substituted -2*H*-thiazolo[3,2-*a*]pyrimidine derivatives using ketene dithioacetal for their potent antimicrobial activity.

MATERIALS AND METHODS

Thin-layer chromatography was accomplished on 0.2-mm precoated plates of silica gel G60 F_{254} (Merck). Visualization was made with UV light (254 and 365nm) or with an iodine vapor. IR spectra were recorded on a SHIMADZUFTIR-8400 spectrophotometer using DRS prob. ^{1}H (400 MHz) and ^{13}C(100 MHz) NMR spectra were recorded on a BRUKER AVANCE II spectrometer in $CDCl_3$ and DMSO respectively ^{13}C and DMSO respectively[13] C NMR were recorded on 100 MHz spectrometer, referred to the internal solvent signals (77.0for $CDCl_3$ or 40.0 for DMSO-d_6). Chemical shifts are expressed in δ ppm downfield from TMS as an internal standard. Mass spectra were determined using direct inlet probe on a SHIMADZU GCMS-QP 2010 mass spectrometer. Solvents were evaporated with a BUCHI rotary evaporator. Melting points were measured in open capillaries and are uncorrected. The chemicals used in this work were purchased from Merck and Spectrochem Chemical Companies. All chemicals were reagent grade and used without further purification, and all solvents were freshly distilled before use.

EXPERIMENTAL SECTION



Where R_1= Substituted Amine R_2= Substituted Aldehyde

General process for the synthesis of 4-methyl-3-oxo-*N*- arylpentanamide 3a-p.

A mixture containing the primary amine (10 mmol), methyl isobutyrylacetate (10 mmol), and catalytic amount of sodium or potassium hydroxide (10 %) in Toluene was reflux at 110^{o}C for the approximately 15-20 h. The progress of reaction was monitored by TLC. After completion of reaction, the solvent was removed under *vaccuo* when the reaction was

completed. The solid or oil was crystallized from methanol to give pure product. The reaction also undergoes microwave irradiation in methanol/IPA the reaction is monitored by TLC.

General process for the synthesis of substituted *N*-(Aryl)-4-(4-Aryl)-1, 2, 3, 4-tetrahydro-6-isopropyl-2-thioxopyrimidine-5- carboxamide 6a-p.

To a solution of substituted benzaldehyde (1 mmol) (**5**), 4-methyl-3-oxo-*N*-arylpentanamide (1 mmol), thiourea (1.4 mmol)(**4**) were added to MeOH (10 mL) sequentially at room temperature. After the addition of HCl/etidronic acid (1.0 mmol), the mixture was stirred for 1 h at ambient temperature. Then reflux reaction mixture at 70-80°C. The progress of reaction was monitored by TLC. The crude product was collected by filtration and washed with hexane to give 0.55 g (91%) of THPM **(6a-p)** as brown solid.

General procedure for the synthesis of substituted *N*-(Aryl)-4-(4-Aryl)-1,2,3,4-tetrahydro-6-isopropyl-2-thioxopyrimidine-5-carboxamide 8a-p.

To a solution of the thioxopyrimidine**(6)** (1mmol, 1equiv.) in 2 ml of 1,2-dibromoethane (**7**) (1.5 mmol, 1equiv.) and (K_2CO_3/TEA) (1.4 mmol, 1equiv.), TBAB/TEAB (0.012mmol, 1equiv.) in H_2O, were dissolved in DMF(appropriative solvent in table 2) added slowly at ambient temperature. The resulted wine red solution was subjected to shaking until the disappearance of the color. The reaction mixture was heated to 75-80 °C for 2-10 hours. After completion of the reaction check by TLC, the solvent was evaporated under reduced pressure and the residue was treated with aqueous solution of saturated $NaHCO_3$ followed by extraction with10 ml The ethyl acetate evaporated in rotary evaporator. The resultant product was washed with 2 vol water. The organic extracts were dried over anhydrous Na_2SO_4. the product is extract in MDC After filtration the solvent was evaporated under reduced pressure and the crude product washed with (10/90, E.A/H mixtures) to obtain pure product 8a-p.

RESULT AND DISCUSSION

In order to optimize the reaction conditions, *N*,4-bis(4-fluorophenyl)-1,2,3,4-tetrahydro-6-isopropyl-2-thioxopyrimidine-5-carboxamide **6a** was used as the precursor for the synthesis of *N*,5-bis(4-fluorophenyl)-3,5-dihydro-7-isopropyl-2*H*-thiazolo[3,2-*a*]pyrimidine -6-carboxamide **8a** Initially we examined the reaction of K_2CO_3/ TEA(1.4 mmol), TBAB/TEAB (0.012 mmol) with **6a** (0.1 mmol). This potassium salt of THPM precursor by reacting with dibromoethane afforded desired compound In order to find suitable reaction conditions, various solvents were investigated (**Table 1**). Complete consumption of the bromine was indicated by the disappearance of the yellow-brown color and also check TLC input is nill

than reaction is complete from the reaction mixture, which takes about 5-10 minutes depending upon the solvent used. Only in the case of DMF (**Table 1**;) warming up of the reaction to 70-75°C for at least 2-4hrs was necessary to assure the complete consumption of bromine.

Table1: Catalyst and solvent for Thiazolo[3,2-*a*]pyrimidine compound 8a.

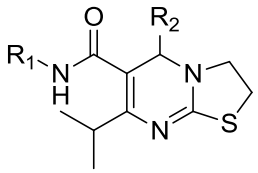
Sr No	Solvent	Catalyst	PTC	Temp °C	Reaction time	Yield
1.	Toluene	K_2CO_3/TEA	TBAB/TEAB in H_2O(2 vol)	95-100°C	6-8hrs	75%
2.	THF	K_2CO_3/TEA	TBAB/TEAB in H_2O(2 vol)	70-75°C	5-6hrs	65-70%
3.	DMF	K_2CO_3/TEA	TBAB/TEAB in H_2O(2 vol)	75-80 °C	2-4hrs	84-92%
4.	Ethanol	K_2CO_3/TEA	TBAB/TEAB in H_2O(2 vol)	75-78°C	4-5hrs	75-80%
5.	*i*Pr-OH	K_2CO_3/TEA	TBAB/TEAB in H_2O(2 vol)	75-78^{0}C	4-5hrs	70-72%
6.	*t*-BuOH	K_2CO_3/TEA	TBAB/TEAB in H_2O(2 vol)	80-82^{0}C	8-10 hrs	70-75%
7.	Chloroform	K_2CO_3/TEA	TBAB/TEAB in H_2O(2 vol)	65-70°C	4-6hrs	65-70%
8.	DCE	K_2CO_3/TEA	TBAB/TEAB in H_2O(2 vol)	65-70°C	5-6hrs	75%

The reaction performance under different solvent conditions at room temperature has been monitored by TLC analysis. It was found that in all other solvents the reactions were not completed. Additionally it was observed that prolonged reaction time at room temperature did not yield the desired cyclized thiazolo pyrimidine **8a**. The reaction temperature was therefore elevated. It was observed that open chain intermediate **6a** gets converted into the desired thiazolo pyrimidine **8a** at 70-80°C. The progress of the reaction was monitored by TLC After heating the reactions for 2-6 hours the best yields were obtained in case of DMF (84-92%). Physical properties of all compounds are given in table 2.

Table 2: Physical properties of Thiazolo[3,2-*a*]pyrimidine compounds 8a-p.

Entry	R^1	R^2	Yield %	Time h.
8a	4-FC_6H_4	4-FC_6H_4	92	6-8
8b	4-ClC_6H_4	3,4-$(OCH_3)_2C_6H_3$	90	6-8
8c	4-BrC_6H_4	3,4-$(OCH_3)_2C_6H_3$	92	8-10
8d	4-BrC_6H_4	2,5-$(OCH_3)_2C_6H_3$	86	6-8
8e	4-BrC_6H_4	4-$(OH)C_6H_4$	90	4-6
8f	4-BrC_6H_4	3-$NO_2C_6H_4$	72	8-10
8g	4-BrC_6H_4	4-ClC_6H_4	88	2-4
8h	3-Cl,4-F,C_6H_3	3,4-$(OCH_3)_2C_6H_3$	84	6-8
8i	4-$CH_3C_6H_4$	4-FC_6H_4	88	2-4
8j	4-$CH_3C_6H_4$	3-BrC_6H_4	68	2-4
8k	4-$CH_3C_6H_4$	4-ClC_6H_4	84	4-6
8l	4-$OCH_3C_6H_4$	4-ClC_6H_4	90	4-6
8m	4-$OCH_3C_6H_4$	3,4-$(OCH_3)_2C_6H_3$	84	4-6
8n	4-ClC_6H_4	3,5-$(OCH_3)_2C_6H_3$	88	6-8
8o	3-Cl,4-F,C_6H_3	4-$OCH_3C_6H_4$	84	4-6
8p	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	86	2-4

Table: 3 Antimicrobial activity of thiazolo[3,2-*a*]pyrimidines.



Antimicrobial activity

The solvent DMSO was also purified before use by standard method (37). All the synthesized compounds were recrystallized prior to use. For all the compounds, agar well diffusion method was used to evaluate antimicrobial activity.

Preparation of test compounds

The stoke solutions were prepared at a concentration of 1 mg/mL (Stock Solution) and further diluted to 0.1 mg/mL and 0.05 mg/mL for all the compounds.

Preparation of the plates and microbiological assay

The antibacterial evaluation was done by agar well diffusion method (38, 39) using Mueller Hinton Agar No.2 as the nutrient medium. The agar well diffusion method was preferred to be used in this study because it was found to be better than the disc diffusion method (39).The agar well diffusion method was preferred to be used in this study because it was found to be better than the disc diffusion method (39). The bacterial strains were activated by inoculating a loop full of test strain in 25 mL of N-broth and the same was incubated for 24 h in an incubator at 37ºC. 0.2 mL of the activated strain was inoculated in Mueller Hinton Agar. Mueller Hinton Agar kept at 45ºC was then poured in the Petri dishes and allowed to solidify. After solidification of the media, 0.85 cm ditch was made in the plates using a sterile cork borer and these were completely filled with the test solution. The plates were incubated for 24 h at 37ºC. The mean value obtained for the three wells was used to calculate the zone of growth inhibition of each sample. The controls were maintained for each bacterial strain and each solvent. The inhibition zone formed by these compounds against the particular test bacterial strain determined the antibacterial activities of these synthesized compounds.

Table 3 In vitro antibacterial activity (MIC lg/mL)

Compound Code	Bacterial strain								
	E. coli			P aurogenosa			B. Circulance		
	50µ /gm	100µ /gm	1000µ /gm	50µ /gm	100µ /gm	1000µ /gm	50µ /gm	100µ /gm	1000µ /gm
8c	2	3	5	-	-	-	-	-	-
8g	2	3	5	-	-	-	-	-	2
8i	-	1	2	-	3	5	-	2	4
8l	-	-	3	-	1	2	-	-	2
8o	1	2	3	-	-	-	-	-	-
CIP	2	3	32	2	3	29	2	4	35

WHERE= – = no inhibition. CIP = ciprofloxacin as antibacterial standard.

The newly synthesized compounds were tested to evaluate antimicrobial study using FDA-approved drugs: ciprofloxacin as reference compounds. Compounds showing antibacterial activities are described in table 3. Compound **8g**, showed good activity aginst *E. coli*. Compound **8i** showed good activity against *B. Circulance*, Compound **8l** showed good activity against *P aurogenosa***.** The results of the antimicrobial screening of selected new compounds are summarized in **Table 3**.

Analytical data of Thiazolo[3,2-*a*]pyrimidine compounds 8a-p.

1,2,3,4-tetrahydro-6-isopropyl-2-thioxo-*N*,4-di*p*-tolylpyrimidine-5-carboxamide 6a: White solid; R_f 0.60 (6:4 hexane-EtOAc); mp 150-153°C IR (KBr): 3373, 3072, 2895, 2828, 1694, 1635, 1482, 1343, 1298 cm^1;^{1}H NMR: δ ppm 1.45-1.62 (d, 6H, 2 x ^{i}prCH$_3$), 2.24 - 2.26 (s, 6H, 2 x CH_3), 3.85 (m, 1H, ^{i}prCH), 4.76 - 4.77 (s, 1H, -CH),7.10 - 7.48 (m, 8H, Ar-H), 8.86 - 8.87 (s, 1H, -NH),8.93 (s, 1H, -NH), 9.73 (br, s, 1H, -CONH); ^{13}C NMR : 15.08, 19.28, 30.56, 31.27, 43.26, 54.35, 64.96, 116.38, 116.59, 119.13, 119.77, 121.15, 127.50, 128.48, 132.74, 135.67, 137.97, 148.89, 152.11, 154.53, 168.04, 169.67; MS (*m/z*): 379 (M^+); Anal. Calcd for $C_{22}H_{25}N_3OS$: C, 69.62; H, 6.64; N, 11.07; Found: C, 69.58; H, 6.55; N, 11.05

***N*,5-bis(4-fluorophenyl)-3,5-dihydro-7-isopropyl-2*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxamide (8a):** Light brown solid; R_f 0.65 (7:3 H-EA); mp 241-243°C; IR (KBr): 3439, 3200, 3144, 3047, 2982, 2929, 2874,1678, 1645, 1614, 1552, 1535, 1506, 1450, 1410, 1334, 1301, 1220, 1159, 1101, 1047, 1012, 962, 835,788,704, cm^{-1}; ^{1}H NMR: (400 MHz, DMSO): δ_H1.24 (s, 6H, 2 X ^{i}prCH$_3$), 2.28 (m, 1H, -^{i}prCH), 3.24-3.26 (m, 2H, -CH_2), 3.78-3.85 (m, 2H, -CH_2), 5.16 (s, 1H, -ArCH), 7.02-7.06 (s, 4H, ArH), 7.22-7.25 (t, 2H, ArH), 7.60-7.63 (t, 2H, ArH), 10.17 (s, 1H, -ArCONH); ^{13}C NMR: (100 MHz, DMSO) δ_C13.83, 18.85, 20.09, 22.10, 26.28, 28.73, 29.06, 31.31, 45.45, 53.01, 61.45, 114.13, 114.34, 114.76, 114.98, 121.12,

121.19, 127.96, 128.04, 134.97, 165.49; MS *m/z*: 413.48(M^+); Anal. Calcd. for$C_{22}H_{21}F_2N_3OS$: C, 63.90; H, 5.12; N, 10.16%.Found: C, 63.78; H, 5.02; N, 10.27%.

***N*-(4-chlorophenyl)-3,5-dihydro-7-isopropyl-5-(3,4-dimethoxyphenyl)-2*H*-thiazolo[3,2-*a*] pyrimidine-6-carboxamide (8b):** Light brown solid; R_f 0.62 (7:3 H-EA); mp 255-257°C; IR (KBr): 3460, 3107, 3034, 2924, 2852, 1672, 1606, 1548, 1516, 1498, 1462, 1392, 1257, 1211, 1145, 1026, 877, 815, 767, 740, cm^{-1}; ^{1}H NMR: (400 MHz, DMSO): δ_H1.45 (s, 6H, 2 × -^{i}prCH$_3$), 2.52 (m, 1H, -^{i}prCH), 3.26 (s, 2H, -CH_2), 3.80 (s, 2H, -CH_2), 5.29(s, 1H, -ArCH), 6.70-6.89 (m, 4H, ArH), 7.02 (s, 1H, ArH), 7.38-7.42 (s, 1H, ArH), 7.95 (s, 1H, ArH), 10.63 (s, 1H, -ArCONH); ^{13}C NMR: δ_C(100MHz, DMSO) 19.24, 20.39, 29.02, 55.39, 55.57, 110.12, 110.69, 116.57, 118.38, 119.62, 121.18, 124.27, 127.48, 148.35, 159.58; MS *m/z*: 472(M^+); Anal. Calcd. for $C_{24}H_{26}ClN_3O_3S$: C, 61.07; H, 5.55; N, 8.90%.Found: C, 61.28; H, 5.35; N, 8.82%.

***N*-(4-bromophenyl)-3,5-dihydro-7-isopropyl-5-(3,4-dimethoxyphenyl)-2*H*-thiazolo[3,2-*a*] pyrimidine-6-carboxamide (8c)**

Light brown solid; R_f 0.62 (7:3 H-EA); mp 246-248°C; IR (KBr): 3446, 3054, 2978, 2839, 1606, 1546, 1516, 1494, 1472, 1392, 815, 725, 538, cm^{-1}; MS *m/z*: 516.45(M^+); Anal. Calcd. for $C_{24}H_{26}BrN_3O_3S$: C, 55.81; H, 5.07; N, 8.14%. Found: C, 55.27; H, 4.99; N, 8.07%.

***N*-(4-bromophenyl)-3,5-dihydro-7-isopropyl-5-(2,5-dimethoxyphenyl)-2*H*-thiazolo[3,2-*a*] pyrimidine-6-carboxamide (8d)**

Light brown solid; R_f 0.62 (7:3 H-EA); mp 250-252°C; IR (KBr): 3462, 3067, 2963, 2812, 1606, 1546, 1516,1499, 1472, 1389, 817,716, 528, cm^{-1}; MS *m/z*: 516.45(M^+); Anal. Calcd. for $C_{24}H_{26}BrN_3O_3S$: C, 55.81; H, 5.07; N, 8.14%.Found: C, 55.26; H, 5.14; N, 8.77%.

***N*-(4-bromophenyl)-3,5-dihydro-5-(4-hydroxyphenyl)-7-isopropyl-2*H*-thiazolo[3,2-*a*] pyrimidine-6-carboxamide (8e)**

Light brown solid; R_f 0.58 (7:3 H-EA); mp 255-257°C; IR (KBr): 3457, 3062, 2957, 2838, 1606, 1546, 1518,1502, 1472, 1393, 817,709, 535, cm^{-1}; MS *m/z*: 472.4(M^+); Anal. Calcd. for $C_{22}H_{22}BrN_3O_2S$: C, 55.93; H, 4.69; N, 8.90%. Found: C, 55.78; H, 4.58; N, 8.37%.

_N_-(4-bromophenyl)-3,5-dihydro-7-isopropyl-5-(3-nitrophenyl)-2_H_-thiazolo[3,2-_a_]pyrimidi -ne-6-carboxamide (8f)

Yellow solid; R_f 0.62 (7:3 H-EA); mp 262-264°C; IR (KBr): 3446, 3075, 2946, 2852, 1618, 1595, 1546, 1518, 1506, 1472, 1399, 835, 804, 729, 514, cm^{-1}; MS *m/z*: 501.4(M^+); Anal. Calcd. for $C_{22}H_{21}BrN_4O_3S$: C, 52.70; H, 4.22; N, 11.17%. Found: C, 52.49; H, 4.87; N, 11.47%.

_N_-(4-bromophenyl)-5-(4-chlorophenyl)-3,5-dihydro-7-isopropyl-2_H_-thiazolo[3,2-_a_]pyrimidi -ne-6-carboxamide (8g)

Yellow solid; R_f 0.56 (7:3 H-EA); mp 248-250°C; IR (KBr): 3455, 3069, 2953, 2841, 1609, 1548, 1515,1503, 1467, 1384, 847, 719, 503, cm^{-1}; MS *m/z*: 490.84(M^+); Anal. Calcd. for $C_{22}H_{21}BrClN_3OS$ C, 53.83; H, 4.31; N, 8.56%. Found: C, 53.16; H, 4.75; N, 8.17%.

_N_-(3-chloro-4-fluorophenyl)-3,5-dihydro-7-isopropyl-5-(3,4-dimethoxyphenyl)-2_H_-thiazolo[3,2-_a_]pyrimidine-6-carboxamide (8h)

Light brown solid; R_f 0.60 (7:3 H-EA); mp 248-250°C; IR (KBr): 3460, 3107, 3034, 2924, 2852, 1680, 1606, 1552, 1498, 1465, 1392, 1332, 1257, 1184, 1143, 1111, 1031, 877, 829, 802, 767, cm^{-1}; ^{1}H NMR: (400 MHz, DMSO) δ_H1.61 (s, 3H, -^{i}prCH**3**), 1.89 (s, 3H, -^{i}prCH**3**), 2.52 (m, 1H, -^{i}prCH), 3.79-3.81 (s, 6H, -2X-OCH**3**), 3.27-3.32 (m, 2H, -CH_2), 3.43-3.50 (m, 2H, -CH_2), 5.51 (s, 1H, -ArCH), 6.71-6.73 (d, 1H *J* =8 *Hz*, ArH), 6.79-6.81 (d, 1H *J* =8 *Hz*,ArH), 6.87 (m, 1H, ArH), 7.14-7.19 (t, 1H, ArH), 7.51-7.53 (s, 1H, ArH), 7.95-7.97 (d, 1H *J* =8 Hz, ArH), 10.49 (s, 1H, -ArCONH); ^{13}C NMR: (100 MHz, DMSO) δ_C 19.06, 20.25, 22.10, 26.48, 28.31, 29.03, 29.23, 31.37, 45.23, 53.32, 54.03, 55.35, 55.69, 61.25, 110.17, 110.50, 115.99, 116.20, 118.46, 119.26, 119.45, 121.16, 123.79, 125.03, 133.73, 135.68, 135.71, 147.83, 148.17, 152.09, 154.52, 162.48, 168.80: MS *m/z*: 489.99(M^+); Anal. Calcd. for $C_{24}H_{25}ClFN_3O_3S$: C, 58.83; H, 5.14; N, 8.58%. Found: C, 58.97; H, 5.75; N, 8.47%.

5-(4-fluorophenyl)-3,5-dihydro-7-isopropyl-_N_-p-tolyl-2_H_-thiazolo[3,2-_a_] pyrimidine-6-carb -oxamide(8i)

Light brownsolid; R_f 0.58 (7:3 H-EA); mp 268-270°C; IR (KBr): 3428, 3048, 2927, 2849, 1654, 1541, 1509,1435, 1254, 862, 705, cm^{-1}; MS *m/z*: 409.52(M^+); Anal. Calcd. for $C_{23}H_{24}FN_3OS$: C, 67.46; H, 5.91; N, 10.26%. Found: C, 67.87; H, 5.58; N, 10.07%.

5-(3-bromophenyl)-3,5-dihydro-7-isopropyl-*N*-*p*-tolyl-2*H*-thiazolo[3,2-*a*]pyrimidine-6-carb -oxamide(VBA-8j)

Yellow solid; R_f 0.58 (7:3 H-EA); mp 247-249°C; IR (KBr): 3435, 3039, 2947, 2838, 1663, 1547, 1517,1443, 1259, 857, 735, 540, cm^{-1}; MS *m/z*: 470.43(M^+); Anal. Calcd. for $C_{23}H_{24}BrN_3OS$: C, 58.72; H, 5.14; N, 8.93%. Found: C, 58.58; H, 5.25; N, 8.72%.

5-(4-chlorophenyl)-3,5-dihydro-7-isopropyl-*N*-*p*-tolyl-2*H*-thiazolo[3,2-*a*] pyrimidine-6-carb -oxamide(8k)

light brown solid; R_f 0.58 (7:3 H-EA); mp 237-239°C; IR (KBr): 3414, 3029, 2956, 2823, 1659, 1552, 1519,1452, 1262, 838, 718, cm^{-1}; MS *m/z*: 425.97(M^+); Anal. Calcd. for $C_{23}H_{24}ClN_3OS$: C, 64.85; H, 5.68; N, 9.86%. Found: C, 64.97; H, 5.39; N, 9.02%.

5-(4-chlorophenyl)-3,5-dihydro-7-isopropyl-*N*-(4-methoxyphenyl)-2*H*-thiazolo [3,2-*a*] pyrimidine-6-carboxamide (8l)

light brown solid; R_f 0.60 (7:3 H-EA); mp 244-246°C; IR (KBr): 3510, 3045, 2927, 2823, 1652, 1563, 1516,1447, 1278, 849, 723, cm^{-1}; MS *m/z*: 441.97(M^+); Anal. Calcd. for $C_{23}H_{24}ClN_3O_2S$: C, 62.50; H, 5.47; N, 9.51%. Found: C, 62.28; H, 5.76; N, 9.23%.

3,5-dihydro-7-isopropyl-5-(3,4-dimethoxyphenyl)-*N*-(4-methoxyphenyl)-2*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxamide (8m)

light brown solid; R_f 0.64 (7:3 H-EA); mp 255-257°C; IR (KBr): 3485, 3032, 2957, 2848, 1645, 1557, 1508, 1447, 1264, 1104, 878, 756, cm^{-1}; MS *m/z*: 467.58(M^+); Anal. Calcd. for $C_{25}H_{29}N_3O_4S$: C, 64.22; H, 6.25; N, 8.99%. Found: C, 64.65; H, 6.07; N, 8.45%.

3,5-dihydro-7-isopropyl-5-(3,4-dimethoxyphenyl)-*N*-*p*-tolyl-2*H*-thiazolo[3,2-*a*] pyrimidine-6-carboxamide (8n)

light brown solid; R_f 0.66 (7:3 H-EA); mp 262-264°C; IR (KBr): 3485, 3354, 3073, 2968, 2875, 1645, 1542, 1516,1457, 1218, 1115, 863, 738, cm^{-1}; MS *m/z*: 451.58(M^+); Anal. Calcd. for $C_{25}H_{29}N_3O_3S$: C, 66.49; H, 6.47; N, 9.31%. Found: C, 66.58; H, 6.23; N, 9.62%.

***N*-(3-chloro-4-fluorophenyl)-5-(4-chlorophenyl)-3,5-dihydro-7-isopropyl-2*H*-thiazolo[3,2-*a*] pyrimidine-6-carboxamide (8o)**

light brown solid; R_f 0.58 (7:3 H-EA); mp 262-264°C; IR (KBr): 3494, 3342, 3078, 2974, 2867, 1645, 1542, 1522, 1459, 1205, 1138, 854, 715, cm^{-1}; MS *m/z*: 456.32(M^+); Anal.

Calcd. for $C_{22}H_{12}Cl_2FN_3OS$: C, 57.91; H, 2.65; N, 9.21%. Found: C, 57.09; H, 2.73; N, 9.37%.

7-isopropyl-N,5-dip-tolyl-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carboxamide(8p)

Light brown solid; R_f 0.67 (7:3 H-EA); mp 246-248°C; IR (KBr): 3446, 3054, 2927, 2978, 2839, 2849,1606, 1546, 1516, 1494, 1472, 1392, 815, 725, 538, cm^{-1}; MS *m/z*: 405.56(M^+); Anal. Calcd. for $C_{24}H_{27}N_3OS$: C, 71.08; H, 6.71; N, 10.36; O, 3.95; S, 7.91%. Found: C, 71.02; H, 6.63; N, 10.31; O, 3.99; S, 7.84%.

CONCLUSION

We have demonstrated an easy and green process for the synthesis of highly substituted Thiazolofused pyrimidines staring from acetoacetanilide.TBAB and TEAB were utilized as PTC in the presence of base under aqueous medium for the synthesis of desired compounds for biological interest. Among all compounds, five compounds exhibits moderate to potent antimicrobial activity.

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