AN EFFICIENT SYNTHESIS, BIOLOGICAL EVALUATION OF NOVEL THIAZOLOPYRIMIDINE DIHYDROPYRIMIDINE DERIVATIVES

Kundan Lal[a]*, L.J.Paliwal[a] and M.B.Bagade[b]
[a]Post Graduate Teaching Department of Chemistry, Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur- 440 033
[b]Post Graduate Teaching Department of Chemistry, Seth Kesarimal Porwal College, Kamptee- 441 002

A B S T R A C T

An environment friendly approach has been adopted for the synthesis of ethyl-6-methyl-4-(4-oxo-4H-benzo[h]chromen-3-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4) and (E)-ethyl-2-(substituted benzylidene)-7-methyl -3-oxo-5-(4-oxo-4H-benzo [h] chromen-3-yl)-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carboxylate 5(a-l). Compounds were characterized on the basis of elemental analysis and different spectroscopic methods like FTIR, MS, ^{1}H and ^{13}C NMR. The short reaction time, easy procedure and purity with high percentage yield are the major highlight of the current research work. Moreover the synthesized compounds have been screened against few bacterial species and found to possess moderate to good antibacterial properties. The biological properties of the synthesized compounds may be attributed due to the presence of active functional groups.

Keywords: Microwave Irradiation; Thiazolopyrimidine; Molecular Docking; Thiopyrimidine; Well Diffusion; Antimicrobial

1. Introduction

Diverse heterocyclic moieties serve an important part in medicinal chemistry and plays as a vital key model for the development of various therapeutic agents (Kumarasamy, D., Roy, B.G., Rocha-Pereira, J., et.al, 2016). Being an important moiety in the nucleic acid, pyrimidine and its derivative (Vanitha Ramachandran, V., Karthiga Arumugasamy, K., Singh, S.K., et.al., 2016) are consider being more vital compounds for the pharmaceutical companies for designing compounds having antimicrobial(Hemdan MM1, Abd El-Mawgoude HK., 2015; Salwa F. Mohamed, Eman M. Flefel, Abd El-Galil E. Amra, Dina N. Abd El-Shafy, 2010), antiviral(Babu, K.R., Rao, V.K., Kumar, Y.K., Kishore Polireddy, K., kata Subbaiah, K.V., Lokanatha, V., Chamarthi N. R.,2012) and anticancer(Mohamed AM, Al-Qalawi HR, El-Sayed WA, et.al., 2015; Kandeel M.M., Refaat H.M., Kassab A.E., Shahin I.G., Abdelghany T.M., 2015) properties. Among pyrimidine derivatives it has been observed that thiopyrimidine derivatives (Sari, O., Roy,V., Métifiot. M.,, Marchand, C.,, Pommier, Y.,, Bourg, S., Bonnet,P.,, Schinazi, R.F., Agrofoglio, L.A., 2015) like alkyl mercaptopyrimidine and substituted thiazole nucleus(Mohareb, R.M., Abdallah, A.E.M., Mohamed, A.A, 2018) possess immense biological activities(Chhabria M.T.,, Patel, S., Modi, P., Brahmkshatriya, P.S., 2016) such as anticancer (Varano, F., Catarzi, D., Squarcialupi, L., et.al., 2015), antibacterial(Batool, I., Saeed, A., Qureshi, I.Z., Kalsoom, S., Razzaq, A., 2016), hypnotic(Tabatabai, S.A., Zavareh, E. R., Reyhanfard, H., et.al.,2015), anti-allergic(Saleh A. Bahashwan, Ahmed A. Fayed, Mohamed A. Ramadan, et.al., 2014), antitumor(Hend N. Hafez, Abdel-Rahman B. A. El-Gazzar, 2009) and cytotoxic activities(Yousif, M.N.M., Wael A. El-Sayed,. Abbas, Hebat-Allah S, Hanem M. Awad Yousif, N.M.,2017; Rashid,M., Husain, A., Shaharyar, M., avinesh Mishra, R., Hussain, A Afzal, O., 2014). Due to the great potential of both the moiety, different

researcher has harnessed the thiopyrimidine derivatives extensively to evaluate their various pharmacological activities.

In view of the above findings and as an extension of our studies aiming to the some new thiazolopyrimidine has been synthesized under microwave irradiation. All the synthesized compounds were characterized using FTIR, ESI-MS, ^{1}H and ^{13}C NMR and they were also screened for the invitro antibacterial properties and were found to be of possess potential pharmaceutical interest.

2. Experimental

The progress of reaction was monitored by thin layer chromatography (TLC) using Silica Coated Aluminium TLC plates (TLC Silica Gel 60F254, Merck, Germany) by different eluent systems. The spots were visualized by keeping the dry plates in iodine vapors and in UV light. IR spectra were recorded on Perkin-Elmer Spectrometer (RX-IFTIR) scanned in KBr discs and wave numbers were expressed in cm-1.^{1}H NMR spectra were recorded in DMSO-d6 on a Bruker Avance II 400 MHz NMR spectrometer and chemical shift (δ) values are given in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard. ^{13}C NMR spectra were recorded in DMSO-d_6 on a Bruker Avance II 100 MHz NMR spectrometer and chemical shift (δ) values are given in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard. Mass spectra were recorded on JMS-T100 LC and Expression CMS (ESI) mass spectrometer. Elemental analyses were carried out with Elementar Vario EL III elemental analyzer. All the melting points were determined by open capillary method and are uncorrected. Microwave reactions were performed at 300 W in the CEM Focused Microwave™ Synthesis System.

2.1 Synthesis of Ethyl-6-methyl-4-(4-oxo-4H-benzo[h]chromen-3-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4)

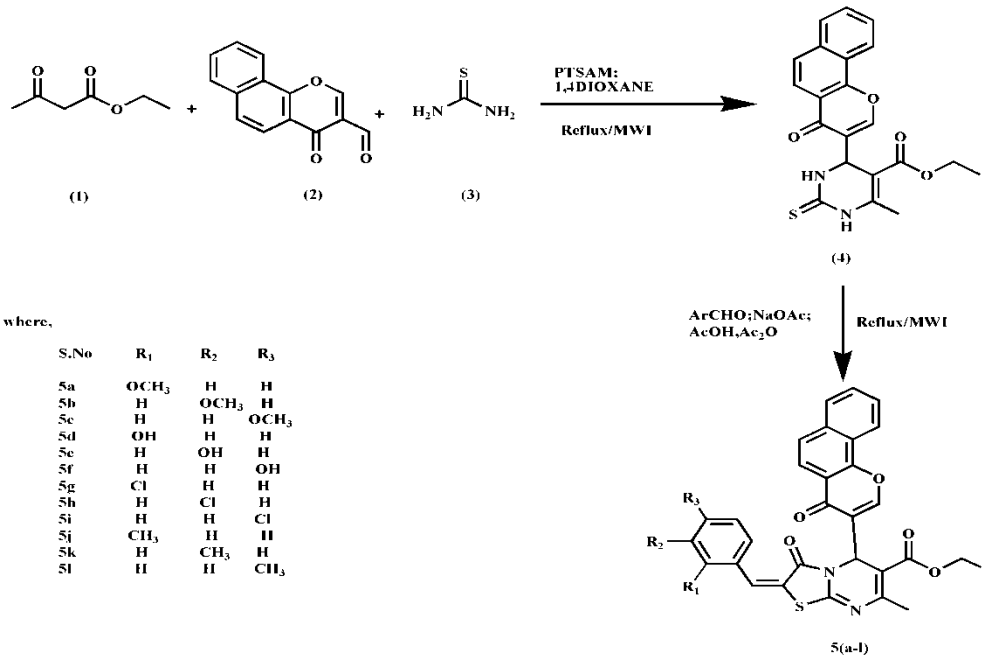
Conventional Method: Ethylacetoacetate (1mmol) (**1**), 4-Oxo-4-H-benzo[h]chromene-3-carbaldehyde(0.01 mol) (**2**) was reacted with thiourea (0.01mol) (**3**) and in presence of p-toulene sulphonic acid monohydrate (PTSAM) (7 mol %) as catalyst in 1,4 dioxane 30(mL) was refluxed for 4 h. Obtained product was poured into the cold water, filtered, washed with water and was recrystallized using ethanol.

Microwave Irradiation Method : Ethylacetoacetate (1mmol) (**1**), 4-Oxo-4H-benzo[h]chromene-3-carbaldehyde (1mmol) (**2**) was reacted with thiourea(1mmol) (**3**) in presence of p-toulene sulphonic acid monohydrate (PTSAM) (1-3mmol %) as catalyst in minimum amount of 1,4 dioxane was irradiated at 300 W for 10-12 min. Obtained product was poured into the cold water, filtered, washed with water and was recrystallized using ethanol.

2.2 Synthesis of (E)-ethyl 2-(substituted benzylidene)-7-methyl-3-oxo-5-(4-oxo-4H-benzo[h]chromen-3-yl)-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carboxylate 5(a-l)

Conventional Method: Ethyl-6-methyl-4-(4-oxo-4H-benzo[h]chromen-3-yl)-2-thioxo-1,2,3,4 tetrahydropyrimidine-5-carboxylate (**4**) (0.01 mol) was reacted with the fused sodium acetate(2 g), glacial acetic acid (20 mL),chloroacetic acid(0.015 mol), acetic anhydride(15 mL) and substituted aromatic aldehydes(0.01 mol). The reaction mixture was refluxed for 6 h. Obtained product was poured into the cold water, filtered, washed with water and was recrystallized using acetic acid. Similarly, 4(E)-ethyl 2-(substituted benzylidene)-7-methyl-3-oxo-5-(4-oxo-4H-benzo[h]chromen-3-yl)-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carboxylate 5(b-l) have been prepared by following the above procedure.

Microwave Irradiation Method: Ethyl-6-methyl-4-(4-oxo-4H-benzo[h]chromen-3-yl)-2-thioxo-1,2,3,4 tetrahydropyrimidine-5-carboxylate (4) (1 mmol) was added to the mixture of fused sodium acetate(0.5 g), glacial acetic acid(2 mL), chloroacetic acid(1 mmol), acetic anhydride(1.5 mL) and substituted aromatic aldehydes(1 mmol). The mixture was then transferred in reaction vessel and was irradiated at 300 W for 50-55 min. Obtained product was poured into the cold water, filtered, washed with water and was recrystallized using acetic acid. Similarly, 4(E)-ethyl 2-(substituted benzylidene)-7-methyl-3-oxo-5-(4-oxo-4H-benzo[h]chromen-3-yl)-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carboxylate **5(b-l)** have been prepared by following the above procedure.



where,

S.No	R_1	R_2	R_3
5a	OCH_3	H	H
5b	H	OCH_3	H
5c	H	H	OCH_3
5d	OH	H	H
5e	H	OH	H
5f	H	H	OH
5g	Cl	H	H
5h	H	Cl	H
5i	H	H	Cl
5j	CH_3	H	H
5k	H	CH_3	H
5l	H	H	CH_3

Scheme 1

3. Results & Discussion

Here in we are reporting the microwave assisted synthesis of Ethyl 6-methyl-4-(4-Oxo-4H-benzo[h]chromen-3-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate **(4)** using 4-Oxo-4-H-benzo[h]chromene-3-carbaldehyde (**2)**, thiourea (**3)** and ethylacetoacetate(**1)** in presence of p-toulene sulphonic acid monohydrate (PTSA) as catalyst in minimum amount of 1,4 dioxane was irradiated under MWI at 300 W at 120 °C for 10 min to get 6-Methyl-4-(4-oxo-4H-benzo[h]chromen-3-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate **(4)**. Further mixture of Ethyl 6-methyl-4-(4-oxo-4H-benzo[h]chromen-3-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate **(4)**, sodium acetate, chloroacetic acid, acetic anhydride and substituted aromatic aldehydes was irradiated under MWI at 300 W at 140 °C to get (E)-ethyl 2-(substituted benzylidene)-7-methyl-3-oxo-5-(4-oxo-4H-benzo[h]chromen-3-yl)-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carboxylate **5(a-l)**. This synthesis has been done by using both conventional and microwave irradiation **Scheme 1**. In both of the reactions the time along with the % yield has been changes drastically. In case (**4)** time has been decreased from 4 h to 4 min also the % yield has been increased from 72% to 95%. Same occur with the **5(a-l)** where the reaction time has been decreased from 6 h to 4-5 min and % yield has been increased from 60% to 95% **Table 1**. The obtained products were further characterized on the basis of spectral data (IR, MS, ^{1}H and ^{13}C NMR). FTIR Spectra of 3-(6-Ethyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-4-yl)-4H-benzo[h]chromen-4-one **4** showed characteristic bands at 1700, 1643 and 1116 cm^{-1} due to –C=O (chromone), –C=O (ester) and –C=S (pyrimidine) stretching vibration respectively. A broad peak at 3384 cm^{-1} was observed due to NH groups of pyrimidine ring. Molecular ion peak at m/z 395.1 [M+1] also lend credence to the structure. The ^{1}H NMR spectrum recorded in DMSO-d_6 showed broad peak at δ8.3 ppm and doublet at δ9.3 ppm due to NH protons of pyrimidine. Active methylene protons for CH appeared at δ4.0 ppm as doublet of coupling constant of 7.5Hz. The aromatic protons have been appeared as multiplet around δ7.8-7.5 ppm. Similarly, ^{13}C NMR showed characteristic peak at δ165.7 and δ162.66 due to –C=O (chromone) and –C=O (pyrimidine) respectively. The peaks depicted in the region δ137.4-124.0 ppm are assigned to aromatic carbon. The peaks at δ89.12 and δ55.29 ppm are due to –CH and -C=CH- of pyrimidine ring respectively. Compounds like (E)-Ethyl 2-(4-methoxybenzylidene)-7-methyl-3-oxo-5-(4-oxo-4H-benzo[h]chromen-3-yl)-3,5-dihydro-2H-thiazolo [3,2-a] pyrimidine-6-carboxylate 5(a) gives a sharp peak at 1700 and 1644 cm^{-1} confirms the presence of (-C=O; Chromone) and (-C=O;ester) respectively. Peak appears at 1186 cm^{-1} assigned for -C-S-C- of thiazole

ring. ^{1}H NMR spectrum reveal appearance of singlet at δ8.8, δ2.1 and δ1.2 ppm assigned to benzylidene linkage -C=CH linkage of thiazole ring to methoxy benzene $–CH_3$ and $–O-CH_3$ respectively. Multiplets have been observed around δ 4.1 and δ 7.0 for $–OCH_2$ and aromatic hydrogen. In ^{13}C NMR spectra peaks observed at δ179.7, δ175.3 and δ166.3 are assigned for the presence of –C=O of chromone, ester and thiazole ring respectively. Peaks observed around δ137.8-127.9 ppm were assigned for the aromatic carbon. Similarly peaks observed at δ79.03, δ60.9, δ20.4 and δ13.9 ppm assigned for the $–CH_2$-, $-O-CH_3$, $-CH_3$ (Pyrimidine ring) and $–CH_3$ (ester) respectively. All compounds **4** and **5(a-l)** gave satisfactory elemental analysis and their physicochemical analysis has been incorporated in **Table 2**.

Table 1- The physicochemical characterization data of ethyl 6-methyl-4-(4-oxo-4H-benzo[h]chromen-3-yl)-2-thioxo-1, 2,3,4-tetrahydropyrimidine-5-carboxylate (4) and (E)-ethyl 2-(substituted benzylidene)-7-methyl-3-oxo-5-(4-oxo-4H-benzo[h]chromen-3-yl)-3,5-dihydro-2H-thiazolo[3,2-a] pyrimidine-6-carboxylate 5(a-l)

Compound	R_1	R_2	R_3	m.p. °C	Yield (%)	
					Reflux	MWI
4	-	-	-	180-182	72	95
5(a)	-OCH3	H	H	148-150	58	86
5(b)	H	$-OCH_3$	H	222-224	62	90
5(c)	H	H	$-OCH_3$	260-262	60	95
5(d)	OH	H	H	230-232	55	90
5(e)	H	OH	H	240-242	62	92
5(f)	H	H	OH	230-232	60	90
5(g)	Cl	H	H	178-180	58	85
5(h)	H	Cl	H	220-222	60	90
5(i)	H	H	Cl	200-202	52	88
5(j)	$-CH_3$	H	H	186-188	62	95
5(k)	H	$-CH_3$	H	202-204	64	92
5(l)	H	H	$-CH_3$	210-212	68	95

Table 2- The elemental analysis of ethyl 6-methyl-4-(4-oxo-4H-benzo[h]chromen-3-yl)-2-thioxo-1, 2,3,4-tetrahydropyrimidine-5-carboxylate (4) and (E)-ethyl 2-(substituted benzylidene)-7-methyl-3-oxo-5-(4-oxo-4H-benzo[h]chromen-3-yl)-3,5-dihydro-2H-thiazolo[3,2-a] pyrimidine-6-carboxylate 5(a-l)

Compound	R_1	R_2	R_3	Elemental composition Calculated(Observed)			
				C	H	N	S
4	-	-	-	63.94(63.80)	4.60(4.45)	7.10(7.03)	8.13(8.10)
5(a)	-OCH_3	H	H	67.38(67.35)	4.38 (4.30)	5.07 (5.10)	5.80(5.87)
5(b)	H	-OCH_3	H	67.38(67.40)	4.38 (4.30)	5.07 (5.10)	5.80(5.87)
5(c)	H	H	-OCH_3	67.38(67.32)	4.38 (4.30)	5.07 (5.10)	5.80(5.72)
5(d)	OH	H	H	66.90(66.82	4.12(4.	5.20(5.1	5.95(5.9

				)	10)	7)	0)
5(e)	H	OH	H	66.90(66.85)	4.12(4. 11)	5.20(5.1 1)	5.95(5.9 3)
5(f)	H	H	OH	66.90(66.89)	4.12(4. 13)	5.20(5.1 8)	5.95(5.9 4)
5(g)	Cl	H	H	64.69 (64.65)	3.80 (3.75)	5.03 (5.02)	5.76(5.7 3)
5(h)	H	Cl	H	64.69(64.67)	3.80 (3.78)	5.03 (5.00)	5.76(5.7 4)
5(i)	H	H	Cl	64.69(64.65)	3.80 (3.73)	5.03 (5.01)	5.76(5.7 2)
5(j)	$-CH_3$	H	H	69.39(69.37)	4.51(4. 49)	5.22(5.2 0)	5.98(5.9 2)
5(k)	H	$-CH_3$	H	69.39(69.34)	4.51(4. 48)	5.22(5.2 0)	5.98(5.9 4)
5(l)	H	H	$-CH_3$	69.39(69.36)	4.51(4. 49)	5.22(5.2 0)	5.98(5.9 4)

4. InvitroAntimicrobial Activity

The antimicrobial activities were determined by using well diffusion method[32] by measuring zone of inhibition in mm. The microbial strains were obtained from the microbiology laboratory, S.K.Porwal College, Kamptee. MHA (Mueller-Hinton Agar) was used as microbial growth medium. The media were prepared according to the instructions given by the manufacturer. A loopful of culture was inoculated from the stock culture in 5 ml of MHA broth and the broth was incubated at 35 °C in incubator for 6-8 h. After incubation, this culture was used for the inoculation of MH test agar plates. Medium was autoclaved and was maintained at 45-50 °C in constant temperature water bath. 0.5 ml of 6-8 h old test organism was transferred to petridish of 100 mm size (sterilized in oven at 180 °C for 1 h) using sterile micropipette. MH test agar medium maintained at 45-50 °C was poured and mixed properly. Petri plates were allowed to set at room temperature. A 10 mm borer was used to prepare wells in agar plates. By using micropipette 10 µl of the test sample was transferred to each well. Plates were immediately kept at 4 °C in refrigerator for 1 h for diffusion of the samples and then shifted to 35 °C in incubator. The zone of inhibition was measured in millimetres by the end of the incubation period of 24 h at 35 ^{o}C in incubator. Amoxicillin was used as a standard drug for antibacterial screening. DMSO was used as control as it does not show any inhibition. All newly synthesized compounds **5(a-l)** were screened to check their antimicrobial activities at concentration of 10 µl. The results have been summarized in **Table 3**.

mTable-3: Invitro Antibacterial activity of Ethyl 6-methyl-4-(4-oxo-4H-benzo[h]chromen-3-yl)-2-thioxo-1, 2,3,4-tetrahydropyrimidine-5-carboxylate **(4),** (E)-ethyl 2-(substituted benzylidene)-7-methyl-3-oxo-5-(4-oxo-4H-benzo[h]chromen-3-yl)-3,5-dihydro-2H-thiazolo[3,2-a] pyrimidine-6-carboxylate **5(a-l)**

Compound	**R_1**	**R_2**	**R_3**	S.aureus	B.subtilis	E.coli	K.aerogenes
4	-	-	-	20	12	18	16
5(a)	$-OCH_3$	-H	-H	23	10	20	15
5(b)	-H	$-OCH_3$	-H	20	18	18	19
5(c)	-H	-H	$-OCH_3$	23	10	24	16
5(d)	-OH	-H	-H	22	15	22	12
5(e)	NO_2	-OH	-H	20	18	18	19
5(f)	-H	-H	- OH	20	13	20	10
5(g)	-Cl	-H	-H	18	20	18	19
5(h)	-H	-Cl	-H	12	18	18	19
5(i)	-H	-H	-Cl	18	10	18	16
5(j)	- CH_3	-H	-H	18	10	18	19

5(k)	-H	- CH_3	-H	15	12	21	10
5(l)	-H	-H	- CH_3	20	10	18	10
Ciprofloxacin				22	22	20	22
DMSO	-	-	-	00	00	00	00

5. Conclusions

Microwave irradiation method proved to be an environmental friendly approach, high yields with good purity in a very less time makes this process highly useful for the synthesis of Ethyl -6-methyl-4-(4-oxo-4H-benzo[h]chromen-3-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate **(4)** and (E)-ethyl 2-(substituted benzylidene)-7-methyl-3-oxo-5-(4-oxo-4H-benzo[h]chromen-3-yl)-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carboxylate **5(a-l**). Besides the green chemistry process synthesized molecules were evaluated for their antimicrobial properties using well diffusion method. Most of the compounds show their efficacy against *S.aureus and B.subtilis* (Gram +ve) bacteria and *E.coli* (Gram-ve) bacterial species. Apart from them compounds **4**, **5a**, **5c**, **5d** and **5f** shows good antibacterial properties at the very low concentration of 10 µl in comparison of the standard drug Ciprofloxacin. Enhanced antimicrobial properties of the synthesized compounds may be attributed due to the presence of electron donating group like – OCH_3, Cl and CH_3.

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