

Synthesis and Bio-Evaluation of Novel N-(4-(8-Methoxy-2-Oxo-2H-Chromen-3-Yl) Thiazol-2-Yl) Amide Derivatives

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Abstract. In present work novel derivatives of substituted N-(4-(8-methoxy-2-oxo-2H-chromen-3-yl) thiazol-2-yl) amide have been synthesized. The solvent free reaction of 2-Hydroxy-3-methoxybenzaldehyde with Ethyl acetoacetate in presence of Piperidine catalyst produces 3-acetyl-8-methoxy-2H-chromen-2-one (C). Compound C was α - brominated using CuBr₂ and subsequently cyclized using Thiourea to produce 3-(2-aminothiazol-4-yl)-8-methoxy-2H-chromen-2-one as main scaffold (E). This scaffold E was finally reacted with different Acid chloride to isolate title compound derivatives. The chemical structures of synthesized compounds were confirmed by ¹H-NMR, FT-IR and Mass spectral/LCMS analysis. The synthesized compounds were screened for potential Antimicrobial, Antifungal and Antimalarial activity.

1. Introduction

Thiazoles are one of the important of Heterocyclic compounds. They are present in some of the natural resources and found to possess moderate to good pharmacological value [1]. Many researchers have made considerable progress on the synthesis of novel Thiazole derivatives and reported their important medicinal properties. Thiazole derivatives are known to exhibit a wide spectrum of biological activities including anesthetic[2], inhibitory activity on apoptosis[3], antibacterial[4,5], anti inflammatory[6], anti tubercular[7], hypolipidemic and hypoglycemic[8], anti cancer[9] and many other important medicinal activity. The widespread use of Thiazole compounds is also confirmed by their use in the medicinal sector, some of the 2-amino thiazole derivatives are well established drugs and widely prescribed by the medicinal practitioners. For example Talipexol and Pramipexole having 2-aminothiazole moiety are used as antiparkinsonian drugs and dopamine agonists.

Coumarin and its derivatives are also represent one of the most biologically active classes of medicinal compounds. Coumarin derivatives are well known to possess wide spectrum of biological activity [10, 11]. Many of such compounds have been proved to be active antibacterial [12] antifungal [13] agents. Coumarin is a flavonoids class compound and widely distributed in nature also. The synthetic and natural Coumarin is known to possess anti diabetic activity [14], anabolic and antioxidant properties [15], anti-Cancer [16], lipid lowering property [17], anti-coagulants [18] and anti-oxidant property [19].

Looking to the importance of both the nucleus we have incorporated both of them in a single moiety to enhance the activity. In this article we have reported 20 new synthetic molecules, which are well characterized to prove the structures. Also, we have shown the biological screening of the synthesized molecules against gram +ve and gram -ve bacteria. Some synthesized compounds have shown good biological activity.

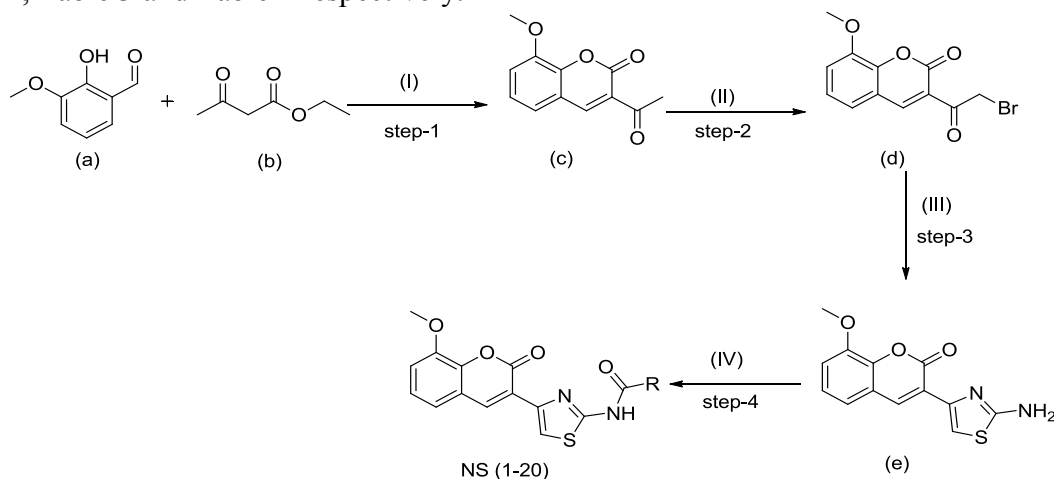
2. Experimental

2.1 Material

All key raw materials, reagents and solvents were of commercial grade and used after further purification. All melting points were measured using open capillaries in a liquid paraffin bath and were uncorrected. The completion of reaction was monitored by thin layer chromatography using silica gel-G as absorbent and Methylene dichloride: Methanol was employed as mobile phase. The visualization of TLC was accomplished by UV light and Iodine. IR spectra (KBr pallet) were recorded on FT-IR, Perkin Elmer RX1 spectrophotometer and $^1\text{H-NMR}$ was determined in $\text{CDCl}_3/\text{DMSO-d}_6$ solution on a Bruker Ac 400 MHz spectrometer data using TMS as internal standard (chemical shifts in δ ppm). Mass spectra were recorded on Shimadzu GCMS-QP-2010 model using Direct Injection Probe technique.

Methods

In the present work, novel caumarine derivatives were prepared by following general reaction scheme as shown in Scheme 1. The physical constants of synthesized compounds are mentioned in Table 1. Synthesized compounds were screened for antibacterial, antifungal and Antimalarial activity. The results of antibacterial, antifungal and Antimalarial activity are depicted in Table 2, Table 3 and Table 4 respectively.



(I) Cat. Piperidine, solvent free reaction. (II) CuBr_2 , CHCl_3 , EtOAc reflux. (III) Thiourea, Ethanol reflux, (IV) Acid chloride derivatives, Pyridine, 25°C .

2.2 General Procedure for Synthesis of Novel N-(4-(8-methoxy-2-oxo-2H-chromen-3-yl)thiazol-2-yl) amide derivatives.

Step-1: 3-acetyl-8-methoxy-2H-chromen-2-one [20] (C)

2-hydroxy-3-methoxybenzaldehyde (a, 10.00 g, 65.76 mmol), Ethyl acetoacetate (b, 8.55 g, 65.76 mmol) and a few drops of Piperidine were mixed and grinded well for 5 min at room temperature. Reaction progress was monitored by TLC using Methylene dichloride as mobile phase. After completion of reaction, the reaction mass was diluted with water and neutralized with dilute Hydrochloric acid. The obtained crude product was filtered and purified in Ethanol to produce pure crystals of 3-acetyl-8-methoxy-2H-chromen-2-one (C, 13.5 g) in 94% yield.

Step-2: 3-(2-bromoacetyl)-8-methoxy-2H-chromen-2-one [21] (D)

3-acetyl-8-methoxy-2H-chromen-2-one (C) 13.5g (61.86 mmol) was dissolved in Chloroform and this solution was added to a suspension of Copper (II) bromide (27.65 g, 123.8 mmol) in 270 ml Ethyl acetate. The resulting reaction mixture was refluxed with vigorous stirring until the reaction was complete. After completion of reaction, the reaction mass was filtered to remove suspended Copper (I) bromide. The filtrate was cooled and resultant solids were filtered to isolate 3-(2-bromoacetyl)-2H-chromen-2-ones (D, 11.91g) in 65% yield.

Step-3: 3-(2-aminothiazol-4-yl)-8-methoxy-2H-chromen-2-one [22] (E)

Thiourea (2.95 g, 38.75 mmol) was added to the solution of 3-(2-bromoacetyl)-8-methoxy-2H-chromen-2-one (d, 11.50 g, 38.75 mmol) in Ethanol (100 ml) and the mixture was refluxed for 1 hour. Reaction progress was monitored by TLC using Methylene dichloride: Methanol (9.5:0.5) as Mobil phase. After completion of reaction, the mass was poured in water and neutralized with aqueous Ammonia. The precipitated product was filtered, washed with water and Ethanol to isolate the solid product (E, 8.5g) having 80% yield.

Step-4: General procedure for amide derivative N-(4-(8-methoxy-2-oxo-2H-chromen-3-yl)thiazol-2-yl) benzamide (NS 1-20)

To solution of 3-(2-aminothiazol-4-yl)-8-methoxy-2H-chromen-2-one (E) (0.250 g 0.91 mmol) in 5 ml Pyridine was added appropriate Acid chloride (1.36 mmol) and the reaction mixture was stirred for 30 minutes at 25-35°C for completion. Reaction progress was monitored by TLC using Methylene dichloride: Methanol (9.5:0.5) as Mobil phase. After completion of reaction, the Pyridine was distilled out under reduced pressure and the residual mass was treated with 2N Sodium hydroxide solution. The precipitated mass was filtered, washed with water to isolate the crude product. The crude product was dried and then purified in Ethanol to isolation pure product derivatives as mentioned in Table-1.

2.3 The spectral data**NS-1**

LCMS (ESI) m/z (M+H): 379. IR (cm⁻¹): 3066 (N-H stretching of secondary amine), 2974 (C-H stretching of aromatic ring), 1718 Coumarin carbonyl moiety stretching, 1577 amide –NH stretching 1541 and 1439 (C=C stretching of aromatic ring). ¹H-NMR (CDCl₃) δ: 4.00 (s, 3H), 7.11 (d, J=8.0 Hz, 1H), 7.17 (d, J=6.8 Hz, 1H), 7.25 (d, J=8.0 Hz, 1H), 7.55 (m, 2H), 7.64 (d, J=7.2 Hz, 1H), 7.97 (d, J=7.2 Hz, 1H), 8.23 (s, 1H), 8.51 (s, 1H), 9.68 (s, 1H), mp 192-199°C.

NS-5

LCMS (ESI) m/z (M+H): 359.2. IR (cm⁻¹): 3244 (N-H stretching of secondary amine), 2968 (C-H stretching of aromatic ring), 1704 Coumarin carbonyl moiety stretching, 1544 amide –NH stretching, 1477 and 1444 (C=C stretching of aromatic ring). ¹H-NMR (DMSO-d₆) δ: 1.28 (s, 9H), 3.94 (s, 3H), 7.33-7.36 (m, 3H), 8.00 (s, 1H), 8.64 (s, 1H), 11.97 (s, 1H), mp 201-205°C.

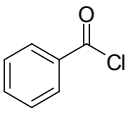
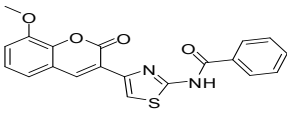
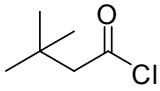
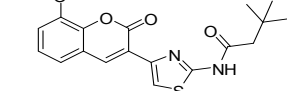
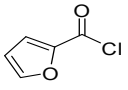
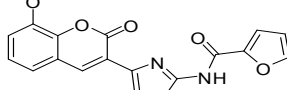
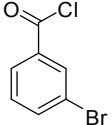
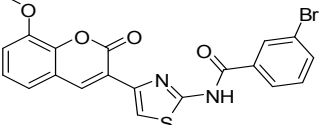
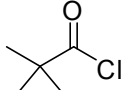
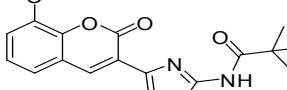
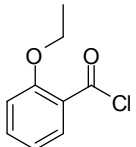
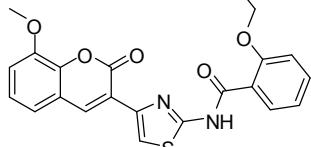
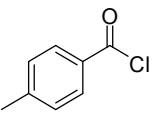
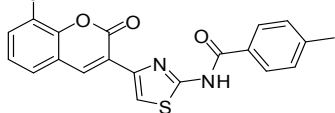
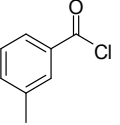
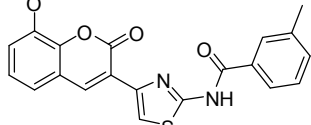
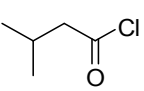
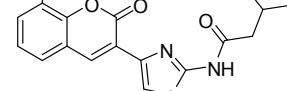
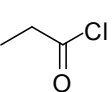
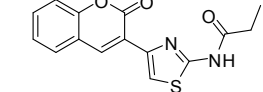
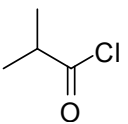
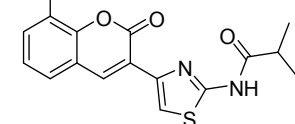
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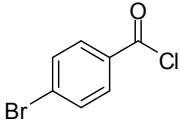
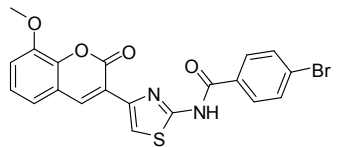
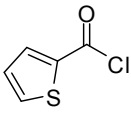
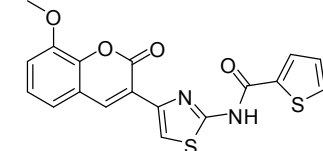
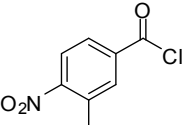
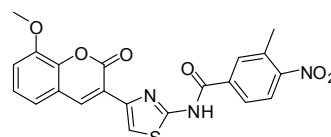
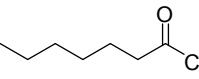
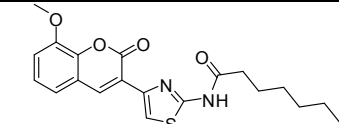
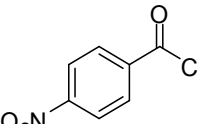
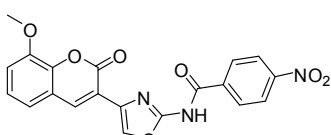
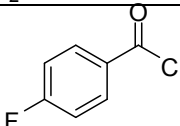
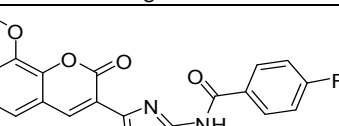
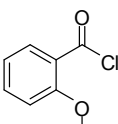
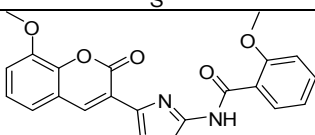
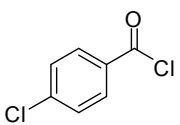
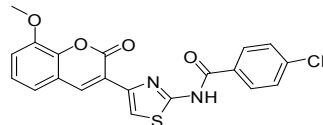
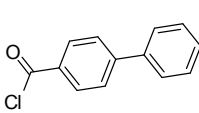
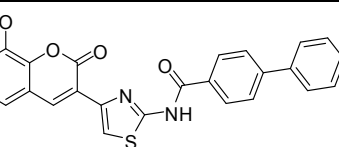
Mass (ESI) m/z (M+H): 384.8. IR (cm⁻¹): 3155 (N-H stretching of secondary amine), 3088 (C-H stretching of aromatic ring), 1707 Coumarin carbonyl moiety stretching, 1575 amide –NH stretching, 1508 and 1466 (C=C stretching of aromatic ring). ¹H-NMR (DMSO-d₆) δ: 3.94 (s, 3H), 7.28-7.30 (m, 1H), 7.34-7.40 (m, 3H), 8.01 (d, J=4.0 Hz, 1H), 7.08 (s, 1H), 7.32 (d, J=3.6 Hz, 1H), 8.65 (s, 1H). 12.94 (s, 1H), mp 209-210°C

NS-17

Mass (ESI) m/z (M+H): 396.9. IR (cm⁻¹): 3088 (N-H stretching of secondary amine), 3058 (C-H stretching of aromatic ring), 1701 Coumarin carbonyl moiety stretching, 1508 amide –NH stretching, 1508 and 1475 (C=C stretching of aromatic ring), 568 (C-Br). ¹H-NMR (DMSO-d₆) δ: 3.94 (s, 3H), 7.35-7.41 (m, 5H), 8.09 (s, 1H), 8.22 (s, 2H), 8.65 (s, 1H), 12.87 (s, 1H), mp 248-250°C.

Table 1. Synthesized derivative of N-(4-(8-methoxy-2-oxo-2H-chromen-3-yl) thiazol-2-yl) amide.

Sr No	Name	Acid chloride	Structure	Mol. wt	Qty-(mg)	Yield (%)
1	NS-1			378.4	155	44.9%
2	NS -2			372.4	175	51.5%
3	NS -3			368.4	90	26.8%
4	NS -4			457.3	82	16.4%
5	NS -5			358.4	280	85.6%
6	NS -6			422.5	50	12.9%
7	NS -7			392.4	135	37.7%
8	NS -8			392.4	45	12.6%
9	NS -9			358.4	80	24.5%
10	NS -10			330.4	180	59.7%
11	NS -11			344.4	75	23.9%

Sr No	Name	Acid chloride	Structure	Mol. wt	Qty-(mg)	Yield (%)
12	NS -12			457.3	300	71.9%
13	NS -13			384.4	305	86.9%
14	NS -14			437.4	253	63.4%
15	NS -15			386.5	260	73.7%
16	NS -16			423.4	100	25.9%
17	NS -17			396.4	210	58.1%
18	NS -18			408.4	90	24.2%
19	NS -19			412.9	100	33.3%
20	NS -20			454.5	120	36.2%

2.4 Biological evaluation

Antimicrobial Activity

All the synthesized compounds NS1-20 were evaluated in-vitro for antibacterial activity against gram positive *Bacillus subtilis* (MCMB-310) and gram negative *Escherichia coli* (MCMB- 301) bacterial strains at the concentrations of 100µg/ml by bore plate method using DMF solvent and nutrient agar was employed as culture media. After 48 hrs of incubation at 37 °C, the results were obtained in the form of cleared zone and were noted after the period of incubation was over. Correspondingly these compounds were evaluated for antifungal potencies against fungal strains *Candida albicans* (NCIM-3471) and *Aspergillus niger* (NCIM- 545) at the concentration 100µg/ml per disc by paper disc diffusion method using DMSO solvent. The yeast *Candida albicans* cultured using a malt extract, glucose yeast extract peptone agar medium (MGYP medium) and for fungi *Aspergillus niger* potato dextrose agar medium was used. After 3-7 days of incubation at 30°C,

Antifungal Activity

All the synthesized compounds NS1-20 were evaluated making it difficult to extract a clear structure-activity relationship analysis, some broad conclusions can still be drawn. These compounds were noticeably more active against *Botrytis cinerea* and *Colletotrichum capsici*, but lacked potency against *Alternaria solani*, *Alternaria mali* and *Rhizoctonia solani*, as illustrated by the absence of activity against these three kinds of fungi. Compounds NS-3, NS-4, NS-6 and NS-11 showed equivalent activity with the positive control Azoxystrobin against *Alternaria mali*. Secondly, the spectrum of antifungal activity is generally improved.

Anti malarial Activity

In this research work, firstly, all the derivatives were subjected to the susceptibility assay for *Plasmodium falciparum* to find out whether the synthesized derivatives possess anti-malarial activity. In this point of view, schizonticidal testing method was selected based on the ease of the test, less time consumption, robust, and economical. Compound NS-2, NS-6, NS-11 and NS-12 found good activity. Further to support the selection of schizonticidal as the test assay for the synthesized derivatives, schizonticidal possess the anti-malarial susceptibility of the derivatives.

Table 2. Antibacterial Activity, Minimum Inhibition Concentration (MIC^a).

Compound Name	MIC ^a			
	E. Coli MTCC 443	P. Aeruginosa MTCC 1688	S.Aureus MTCC 96	S.Pyogenus MTCC 442
NS-1	500	500	200	200
NS -2	100	200	250	250
NS -3	250	250	500	500
NS -4	200	200	500	250
NS -5	125	125	500	500
NS -6	200	200	250	250
NS -7	250	200	250	250
NS -8	250	200	500	500
NS -9	500	250	500	500
NS -10	250	250	125	200
NS -11	200	200	250	250
NS -12	250	200	250	500
NS -13	62.5	100	500	500
NS -14	100	125	500	500
NS -15	250	125	125	125
NS -16	200	200	100	200
NS -17	500	250	500	500
NS -18	500	500	250	250
NS -19	250	500	200	200
NS -20	100	250	500	250
Gentamycine	0.05	1	0.25	0.5
Ampicillin	100	100	250	100
Chloramphenicol	50	50	50	50
Ciprofloxacin	25	25	50	50
Norfloracin	10	10	10	10

(MIC)^a: Minimum Inhibitory concentration in µg/ml

Table 3. Antifungal activity, Minimum Fungicidal Concentration (MIC^b).

Compound Name	MIC ^b		
	C.Albicans MTCC 227	A.Niger MTCC 282	A.Clavatus MTCC 1323
NS-1	500	1000	1000
NS -2	500	1000	1000
NS -3	>1000	500	1000
NS -4	>1000	1000	1000
NS -5	1000	250	250
NS -6	>1000	500	500
NS -7	250	1000	>1000
NS -8	1000	1000	>1000
NS -9	500	500	500
NS -10	500	500	500
NS -11	>1000	250	250
NS -12	1000	1000	1000
NS -13	250	1000	1000
NS -14	1000	500	500
NS -15	1000	500	500
NS -16	500	>1000	>1000
NS -17	250	>1000	>1000
NS -18	250	>1000	>1000
NS -19	250	500	500
NS -20	1000	1000	1000
Nystatin	100	100	100
Greseofulvin	500	100	100

(MIC)^b: Minimum Inhibitory concentration in µg/ml

3. Results and discussion

Aiming to adopt simpler reaction conditions for syntheses of new biologically active heterocyclic compounds. We have established convenient and practical methodology for the preparation of a variety N-(4-(8-methoxy-2-oxo-2H-chromen-3-yl)thiazol-2-yl) amide derivatives. The commercial available 2-hydroxy-3-methoxybenzaldehyde was reacted with Ethyl acetoacetate in presence of Piperidine catalyst under solvent free condition to produce 3-acetyl-8-methoxy-2H-chromen-2-one, which was then α - brominated using CuBr₂ and cyclized using Thiourea to produce 3-(2-aminothiazol-4-yl)-8-methoxy-2H-chromen-2-one as main scaffold (E). This scaffold (E) was further reacted with different acid chloride to result in novel series of amide compounds as listed in Table-1.

All the new synthesized compounds were characterized by ¹H NMR, IR and LCMS/Mass spectra analysis. The presence of characteristics absorptions at 3250 and 3050 cm⁻¹ in the infrared spectra confirms the presence of NH of amide derivative. The presence of absorbance band at 1710 cm⁻¹ in IR spectra confirms the presence of Carbonyl moiety of Coumarin heterocyclic. In addition to these, presence of characteristics bands in ¹H NMR, IR and LCMS/Mass spectra confirm the structure of synthesized compounds.

All newly synthesized compounds were screened for their potential antibacterial, antifungal and antimalarial activity. Among all, NS- 2, 13, 14 and 20 are found to possess equipotent activity to Ampicillin (MIC=100 µg/mL) against E.Coli and P.Aeruginosa (gram -ve strains). NS- 2, 6, 11, 12, 18, 19 are found to be equipotent to Ampicillin against S.Aureus (gram +ve) while compound

NS-10, 15 and 16 were found to be more efficient than Ampicillin (MIC=250 $\mu\text{g}/\text{mL}$) against gram +ve bacteria. All the newly synthesized compounds are not showed good antibacterial activity against *S.Pyogenus* (gram +ve). Overall, compound NS-13 possessed moderate to good antibacterial activity against gram negative bacterial strain. On the antifungal activity side, compound NS-1, 2, 9, 10, 16 are found equipotent to Griseofulvin (MIC=500 $\mu\text{g}/\text{mL}$) and compound NS 7, 13, 17, 18 and 19 are found to be more potent against *C.Albicans*; rest other synthesized compounds are not showed good antifungal activity and less potent than standard drugs. It was also found that all synthesized compounds possessed less antimalarial activity potential than standard drugs available in the market.

Table 4. Antimalarial activity, Minimum Inhibition Concentration.

Plasmodium faclparum	
Minimum Inhibition Concentration (MIC^c)	
Compound Name	MEAN IC150 IN ($\mu\text{g}/\text{ml}$)
NS-1	0.8
NS -2	1.46
NS -3	0.94
NS -4	0.79
NS -5	1.07
NS -6	1.12
NS -7	1.08
NS -8	0.6
NS -9	0.85
NS -10	0.73
NS -11	1.25
NS -12	1.56
NS -13	0.92
NS -14	0.62
NS -15	0.71
NS -16	0.68
NS -17	1.02
NS -18	1.15
NS -19	1.03
NS -20	0.83
Chloroquine	IC50: 0.20 ($\mu\text{g}/\text{ml}$)
Quinine	IC50: 0.268 ($\mu\text{g}/\text{ml}$)

(MIC)^c: Minimum Inhibitory concentration in $\mu\text{g}/\text{ml}$

4. Conclusions

The novel series of amide derivatives of N-(4-(8-methoxy-2-oxo-2H-chromen-3-yl) thiazol-2-yl) have been synthesized in reasonably good yield by following simpler synthesis route using commercially available raw materials. The structure of all synthesized compounds are confirmed by FT-IR, Mass/LCMS and ¹H-NMR spectral study. The synthesized compounds were evaluated for potential biological property. Among all synthesized compounds, some of the compounds are found to possess reasonably good antimicrobial activity.

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References

- [1] D. Davyt, G. Serra, Thiazole and oxazole alkaloids: Isolation and synthesis, *Mar. Drugs*. 8 (2010) 2755–2780.
- [2] A. Geronikakil, G. Theophilidis, Synthesis of 2-(aminoacetyl-amino) thiazole derivatives and comparison of their local anaesthetic activity by the method of action potential, *European journal of medicinal chemistry*. 2 (1992) 709–716.
- [3] M. Li, Y. Sim, S.W. Ham, Discovery of 2-aminothiazole derivatives as antitumor agents, *Bull. Korean Chem. Soc.* 31 (2010) 1463–1464.
- [4] N. Singh et al., Synthesis and antimicrobial activity of some novel 2-amino thiazole derivatives, *J. Chem. Pharm. Res.* 2(3) (2010) 691–698.
- [5] K. Prakasha, Design, synthesis and antimicrobial screening of amino acids conjugated 2-amino-4-arylthiazole derivatives, *Int. J. Pharm. Pharm. Sci.* 3 (2011) 120-125.
- [6] C.A. Kontogiorgis, D.J. Hadjipavlou-Litina, Synthesis and antiinflammatory activity of coumarin derivatives, *J. Med. Chem.* 48 (2005) 6400–6408.
- [7] M. Pieroni et al., Design, synthesis and investigation on the structure-activity relationships of N-substituted 2-aminothiazole derivatives as antitubercular agents, *Eur. J. Med. Chem.* 72 (2014) 26–34.
- [8] S.N. Mokale et al., Bioorganic & Medicinal Chemistry Letters Synthesis, hypolipidemic and hypoglycemic activity of some novel propanoic acid derivatives, *Bioorg. Med. Chem. Lett.* 21 (2011) 682–685.
- [9] C.-Y. Tsai et al., Synthesis and Evaluation of Aminothiazole-Paeonol Derivatives as Potential Anticancer Agents, *Molecules*. 21 (2016) 2–9.
- [10] Z.M. Nofal, M.I. El-Zahar, S.S. Abd El-Karim, Novel coumarin derivatives with expected biological activity, *Molecules*. 5 (2000) 99–113.
- [11] A.M. El-Agrody et al., Heteroaromatization with 4-Hydroxycoumarin Part II: Synthesis of Some New Pyrano [2, 3-d] pyrimidines, [1, 2, 4] triazolo [1, 5-c] pyrimidines and Pyrimido [1, 6-b]-[1, 2, 4] triazine Derivatives, *Molecules*. 6(6) (2001) 519-527.
- [12] A.A. Al-Amiery, A.A.H. Kadhum, A.B. Mohamad, Antifungal activities of new coumarins, *Molecules*. 17 (2012) 5713–5723.
- [13] P. Sharma, S. Pritmani, Note Synthesis, characterization and antimicrobial studies of some novel 3-aryloxy-7-hydroxy-4-methylcoumarins, *Indian J. Chem. B.* 38 (1999) 1139–1142.
- [14] S.O. Lee et al., Antidiabetic Coumarin and Cyclitol Compounds from *Peucedanum japonicum*, *Archives of pharmacal research*. 27(2) (2004) 1207–1210.
- [15] A.A.H. Kadhum et al., The antioxidant activity of new coumarin derivatives, *Int. J. Mol. Sci.* 12 (2011) 5747–5761.
- [16] I. Kostova, G. Momekov, New cerium(III) complexes of coumarins- Synthesis, characterization and cytotoxicity evaluation, *Eur. J. Med. Chem.* 43 (2008) 178–188.

-
- [17] M.A. Musa, J.S. Cooperwood, M.O.F. Khan, A review of coumarin derivatives in pharmacotherapy of breast cancer, *Curr. Med. Chem.* 15 (2008) 2664–2679.
- [18] J. Jung, Y. Jung, O. Park, A convenient one-pot synthesis of 4-hydroxythiocoumarin and 4-hydroxyquinolin-2(1H)-one, *Synth. Commun.* 31 (2001) 1195–1200.
- [19] R.K. Arora et al., Novel coumarin–benzimidazole derivatives as antioxidants and safer anti-inflammatory agents, *Acta Pharm. Sin. B.* 4 (2014) 368–375.
- [20] T. Sugino, K. Tanaka, Solvent-Free Coumarin Synthesis, *Chem. Lett.* 2 (2001) 110–111.
- [21] V. La Pietra et al., Identification of novel molecular scaffolds for the design of MMP-13 inhibitors: A first round of lead optimization, *Eur. J. Med. Chem.* 47 (2012) 143–152.
- [22] J. Heinicke, E. Nietzschmann, A. Tzschach, Synthese von o-Halogenphenoxy-, o-Halogenphenylthio- und o-Halogen-methylanilinoderivaten der IVb- und Vb-Elemente, *Journal für Praktische Chemie.* 325(3) (1983) 511–516.
- [23] B.Z. Kurt et al., Synthesis, antioxidant and anticholinesterase activities of novel coumarylthiazole derivatives, *Bioorganic chemistry.* 59 (2015) 80-90.
- [24] B. Naik, K.R. Desai, Novel approach for the rapid and efficient synthesis of heterocyclic Schiff bases and azetidinones under microwave irradiation, *Indian J. Chem.* 45 (2006) 267–271.