Modern Organic Chemistry Research, Vol. 5, No. 1, August 2020
https://dx.doi.org/10.22606/mocr.2020.51002

Synthesis of Some Coumarin and Diazepine Derivatives and Evaluation of Their Antibacterial Activities

Hussniya A. Al-Difar, Khalid M. Darwish*, Amera AL-Hijazy, Noor EL-Barassi and Haneen Al-Difar

Chemistry Department, Science Faculty, University of Benghazi, Benghazi, Libya
Email: kdarwish1962@gmail.com

Abstract. In preparations of some coumarin derivatives, salicylaldehyde was reacted with ethyl acetoacetate in a catalytic amount of piperidine to produce 3-acetylcoumarin 3 through a reaction like Pechmann condensation. The product was then condensed with aromatic aldehydes to produce coumarinyl derivatives as chalcones **5a-b**. These, in turn, were reacted with *o*-phenylene diamine to obtain the corresponding diazepines **7a-b**. On the other hand, the synthesized products were examined for their antibacterial activity. Structures of the synthesized products were confirmed with the help of their melting points, TLC analysis and spectral data.

Keyword: Salicylaldehyde, 3-Acetyl coumarin, OPDA

1 Introduction

Coumarins are well known naturally occurring heterocyclic compounds isolated from various plants. They belong to the family of lactones having 1-benzopyran-2-one skeleton that can be isolated from plants as well as synthesized in the laboratory[1]. On the other hand, coumarin is a versatile pharmacophore which shows antimicrobial activity[2-4]. As a class of compounds which have a special role in nature, they belong to the flavonoid class of plant secondary metabolite, which exhibit a variety of biological activities usually associated with low toxicity and they have raised considerable interest because of their potential beneficial effect on human health. Their wide use in food additives fragrances, pharmaceuticals, and biochemical properties. Their therapeutic applications depend upon the pattern of substitution. Coumarin derivatives have been reported as anticoagulant[14], anti-inflammatory[14], antimicrobial[6], anti HIV[15], antioxidation[8], anti-allergic[16], anticancer[5,9], anti-proliferative[17] and antiviral[10].

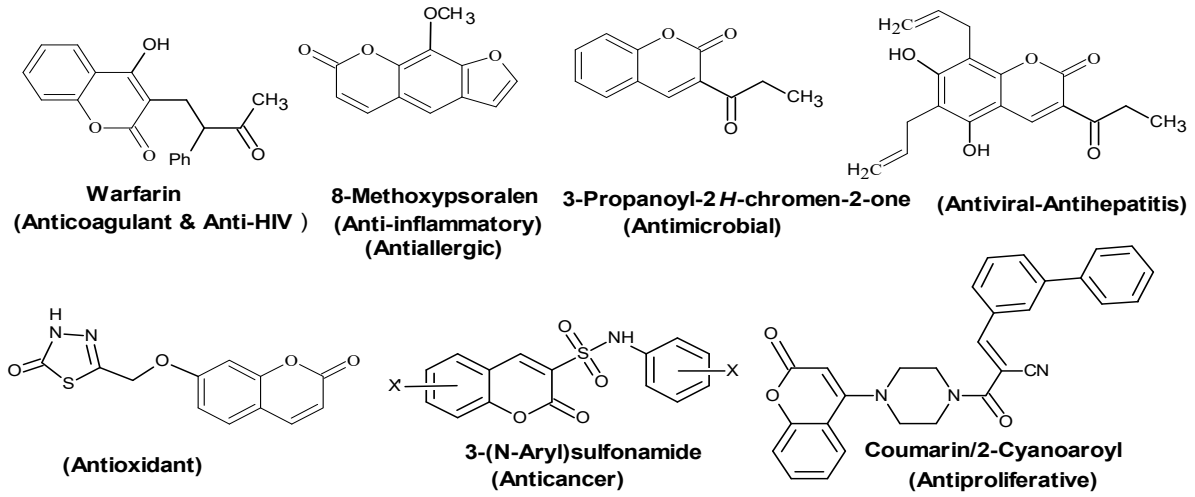


Chart 1. Some biologically active coumarins

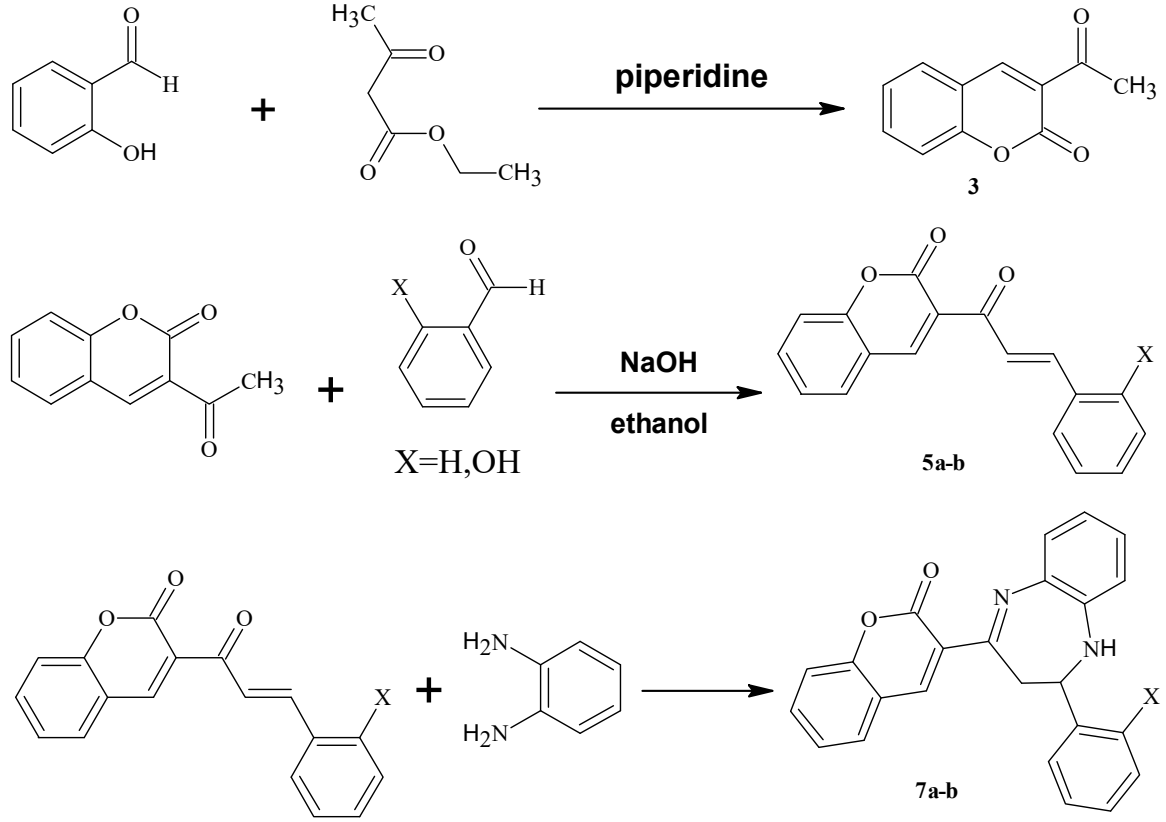
Chalcones, precursors of open chain flavonoids and isoflavonoids, are present in edible plants, and their derivatives have attracted increasing attention. Due to numerous potential pharmacological application, they have displayed a broad spectrum of pharmacological activities changes in their

structure and have offered a high degree of diversity that are useful for development of new medicinal agents having improved potency and lesser toxicity.

The Pechmann condensation involves the synthesis of coumarins starting from a reaction of a phenol derivative with either a carboxylic acid (or an ester) having a β-carbonyl group under acidic condition.

In our work, salicylic acid was reacted with ethyl acetoacetate in piperidine affording the 3-acetylcoumarin **3**. This reaction was followed with another condensation of involving reaction the acetyl group of **3** with some aldehyde derivatives to give the relevant chalcone derivatives **5a-b**. In an interesting cyclization reaction, the obtained chalcones were reacted with *o*-phenylenediamine to give diazepine **7a-b**. The following representation describes the referred reactions.

Graphical Abstract



Structures of compounds **3**, **5a-b**, and **7a-b** were approved and confirmed with the help of their physical, analytical and spectral data and then have been tested for antibacterial activity through their effect on gram positive and gram negative bacteria.

2 Experimental Section

Melting point of the synthesized compound were determined in capillary tubes using griffin apparatus and were uncorrected.

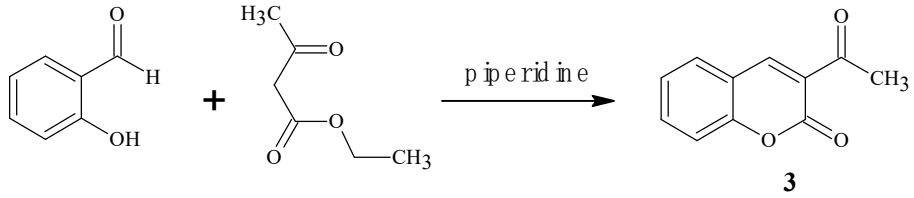
Chromatography: Analytical glass plates were used with kites legal GF245 (Merck). The plates were run in the following system:

Table 1. Material for synthesis

Material	Boiling Point (°C)	Company	Purity
Salicylaldehyde	194-196	Merk	98%
ethylacetoacetate	180.8	Merk	99%
Ethanol	78.39	Merk	99.9%
Sodium Hydroxide	1338	RDH	98%
o-phenylenediamine	102-104	Merk	99%
Acetone	56-57	Merk	99.5%

Synthesis of 3-Acetyl coumarin 3

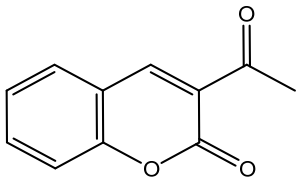
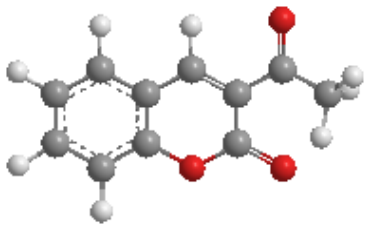
A mixture of salicylaldehyde (0.1 mol, 6.01 g) and ethyl acetoacetate (0.1 mol, 12.31 g) and piperidine (2 ml) was prepared with rapid stirring for 20 min. The yellowish solid separated was filtered off, subsequently washed with ethanol and recrystalized from water and ethanol.



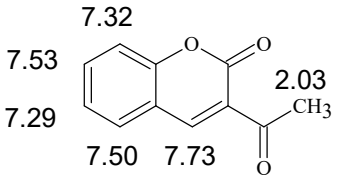
3

Scheme 1. Synthesis of 3-Acetyl coumarin

Compound No.	Molecular weight	Molecular formula	Yield %	Melting Point °C	Reaction time	Color precipitate
3	188	$C_{11}H_8O_3$	94 %	120-123 ^{0}C	20 min	yellow

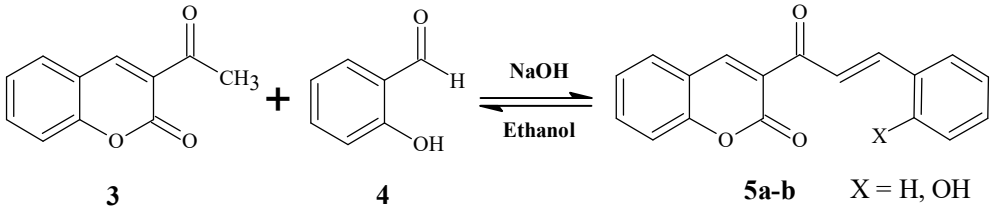
IUPAC name	Structure	3D
3-acetyl-2*H*-chromen-2-one		

3-Acetyl-2H-chromen-2-one (**3**): Yellow crystals from ethanol; m.p. 120-123 °C; yield 94 %; Anal. For $C_{11}H_8O_3$ (m.w. 188): Found: C, 70.21; H, 4.29; O, 25.51; Calc: C, 70.21; H, 4.26; O, 25.53; MS: *m/z*: 188.05 (100 %), 189.05 (11.9 %); ^{1}H-NMR (DMSO-d_6): δ2.03 (s, 3H; -CO*CH3*), 7.29-7.53 (m, 4 H; *Ar-H*), 7.73 (s, 1 H; C4 of chromene).



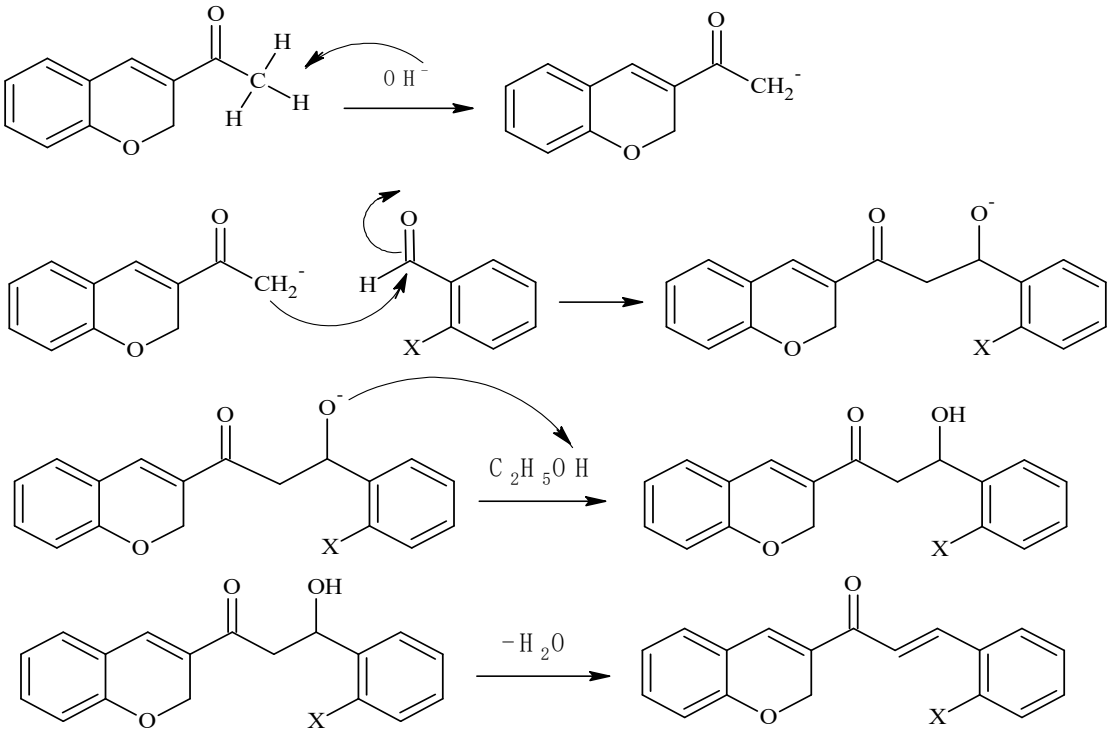
Synthesis of *E*-3-(3-(2-Hydroxyphenyl)acrytoyl-2*H*-chromen-2-one 5a-b

Salicylaldehyde (0.02 mol, 3.16 g) and 3-acetyl coumarin (0.01 mol, 1.66 g) were dissolved in ethanol (10 ml). Dilute sodium hydroxide (4 ml) was added to the former solution. The mixture was shaken vigorously for 15 minutes then cooled in ice for 10 minutes. The obtained chalcone was then recrystallized from ethanol.



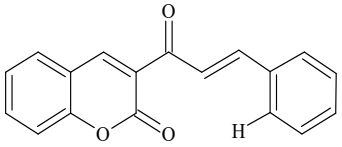
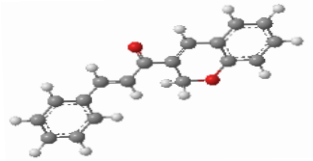
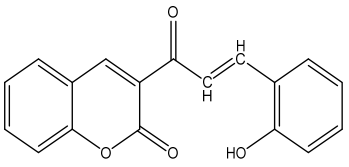
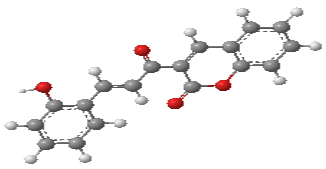
Scheme 2. Synthesis of chalcone

The following mechanism explains chalcone formation.



Scheme 3. Mechanism of chalcone formation

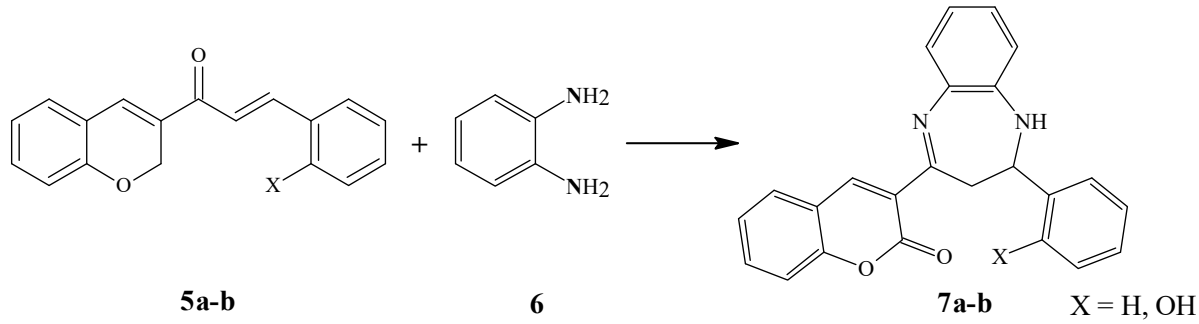
Compound No.	Molecular Weight	Molecular formula	Yield %	Melting Point °C	Reaction time	Color precipitate
5-a	276	$C_{18}H_{12}O_3$	80 %	120-122	3 hrs	yellow
5-b	292	$C_{18}H_{12}O_4$	74 %	130-132	4 hrs	dark Yellow

IUPAC name	Structure	3D
(*E*)-1-(2*H*-chromen-3-yl)-3-phenylprop-2-en-1-one		
(*E*)-3-(3-(2-hydroxyphenyl)acryloyl)-2H-chromen-2-one		

E-3-(3-(phenyl)acryloyl-2H-chromen-2-one (**5a**): Yellow crystals from ethanol; m.p. 120-122 °C; yield 80 %; Anal. For $C_{18}H_{12}O_3$ (m.w. 276): Found: C, 70.21; H, 4.29; O, 25.51; Calc: C, 78.26; H, 4.35; O, 17.39; MS: *m/z*: 276.05 (100 %), 277.05 (19.2 %); ^{1}H-NMR (DMSO-d_6): δ 6.82 (d, 1 H; H_α); 7.49 (d, 1 H; H_β); 7.43-7.50 (m, 5 H; Ph-*H*); 7.33-7.90 (m, 4 H; chromene-*H*), 8.60 (s, 1 H; C4 of chromene).
E-3-(3-(2-Hydroxyphenyl)acryloyl-2H-chromen-2-one (**5b**): Dark yellow crystals from ethanol; m.p. 130-132 °C; yield 74 %; Anal. For $C_{18}H_{12}O_4$ (m.w. 292): Found: C, 73.21; H, 4.19; O, 21.51; Calc: C, 73.97; H, 4.10; O, 21.91; MS: *m/z*: 292.07 (100 %), 293.08 (19.5 %), 294.08 (1.8 %).^{1}H-NMR (DMSO-d_6): δ 6.73 (d, 1 H; H_α); 7.44 (d, 1 H; H_β); 6.90-7.70 (m, 4 H; Ph-*H*); 7.32-7.90 (m, 4 H; chromene-*H*), 8.57 (s, 1 H; C4 of chromene).

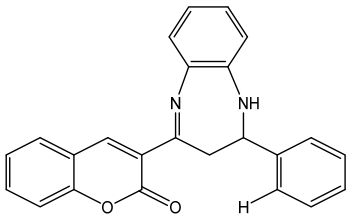
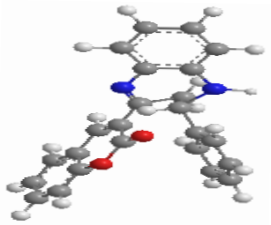
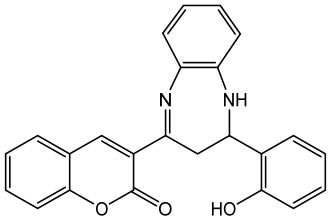
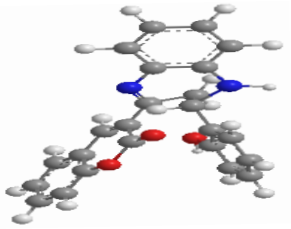
Synthesis of 3-(2-(2-hydroxypheyl)-2,3-dihydro-1*H*-benzo-1[*H*][1,4]diazepin-4-yl)-2*H*-chromen-2-one 7a-b

In absence of sunlight, a solution of chalcone (**5a-b**) (0.01 mol), 1,2-diazobenzene (1.08 g, 0.01 mol), ethanol (15 ml) and triethylamine (3 ml) was refluxed for 15 hrs. The reaction mixture was cooled to 0 °C, left over night, filtered and recrystallized from water and ethanol.



Scheme 4. Synthesis of Diazepine

Compound No.	Molecular Weight	Molecular formula	Yield %	Melting Point °C	Reaction time	Color precipitate
7-a	366	$C_{24}H_{18}N_2O_2$	80 %	134-136	15 hrs	Light yellow
7-b	382	$C_{24}H_{18}N_2O_3$	76 %	142-144	16 hrs	Light Yellow

IUPAC name	structure	3D
3-(2-phenyl-2,3-dihydro-1*H*-benzo[b][1,4]diazepin-4-yl)-2*H*-chromen-2-one		
3-(2-(2-hydroxyphenyl)-2,3-dihydro-1*H*-benzo[b][1,4]diazepin-4-yl)-2*H*-chromen-2-one		

3-(2-(2-Phenyl)-2,3-dihydro-1H-benzo-1[H][1,4]diazepin-4-yl)-2H-chromen-2-one (**7a**): Light yellow crystals from ethanol; m.p. 134-136 °C; yield 80 %; Anal. For $C_{24}H_{18}N_2O_2$ (m.w. 366): Found: C, 78.66; H, 4.89; N, 7.62; O, 8.77; Calc: C, 78.68; H, 4.91; N, 7.65; O, 8.74. MS: *m/z*: 366.41 (100 %), 367.42

(28.0 %), 368.43 (2.7 %); ^{1}H-NMR (DMSO-d_6): δ 7.02-7.75 (m, 13 H, Ar-*H*), 7.86 (s, 1 H, C4 of chromene).

3-(2-(2-Hydroxypheyl)-2,3-dihydro-1H-benzo-1[H][1,4]diazepin-4-yl)-2H-chromen-2-one (**7b**): Light yellow crystals from ethanol; m.p. 142-144 °C; yield 76 %; Anal. For $C_{24}H_{18}N_2O_3$ (m.w. 382): Found: C, 75.38; H, 4.74; N, 7.33; O, 12.55; Calc: C, 75.39; H, 4.71; N, 7.33; O, 12.56; MS: *m/z*: 382.13 (100 %), 383.14 (26.0 %), 384.14 (2.7 %); ^{1}H-NMR (DMSO-d_6): δ 7.18-8.25 (m, 12 H, Ar-*H*), 5.55 (s, H; OH), 10.5 (s, NH, exchangeable).

3 Antibacterial Activity

The *in vitro* antibacterial activity against different strains of gram positive bacteria (s. aureus and p. aeruginosa) gram negative bacteria (E. coli, K. pneumoniea). The bacterial activity against all the bacterial strains was significant compared with standard DMSO. The antibacterial activity was determined by measuring the diameter of the inhibition zone in (mm) the tested samples (100 µg/mL, 10 µg/mL) were loaded into the wells of the plates. All compounds were prepared in dimethyl sulfoxide (DMSO) loaded as control. The plates were kept for in caption at 37 °C for 24 hr and then were examined for the formation of zone inhibition. Each zone inhibition was measured three times by caliper to get an average value. The test was performed three times for each bacterium culture, where penicillin and streptomycin were used as antibacterial standards (Table 2).

Table 2. Results of antibacterial screening with zone inhibition (in mm)

Compound	Gram positive		Gram negative	
	S. Aureus	***P. Aeruginosa***	***E. coli***	***K. Pneumoniea***
3	**12**	**13**	**14**	**15**
5a	**11**	**12**	**15**	**10**
5b	**16**	**18**	**14**	**14**
7a	**17**	**19**	**17**	**16**
7b	**16**	**17**	**14**	**12**
Std	**15**	**13**	**16**	**14**

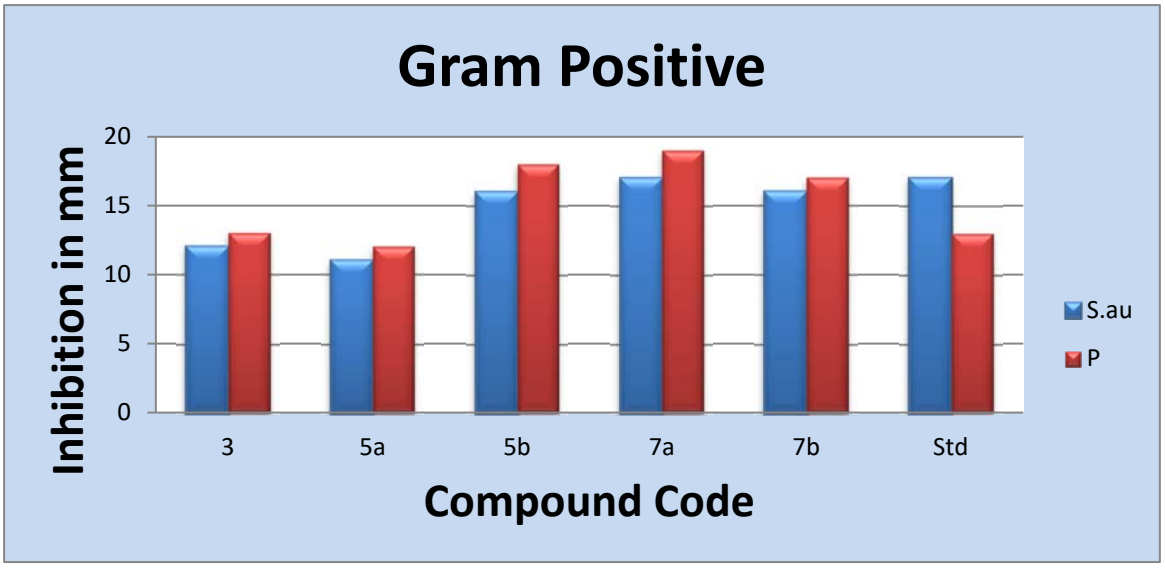


Figure 1. Zone inhibition of compounds an gram positive microorganisms (in mm)

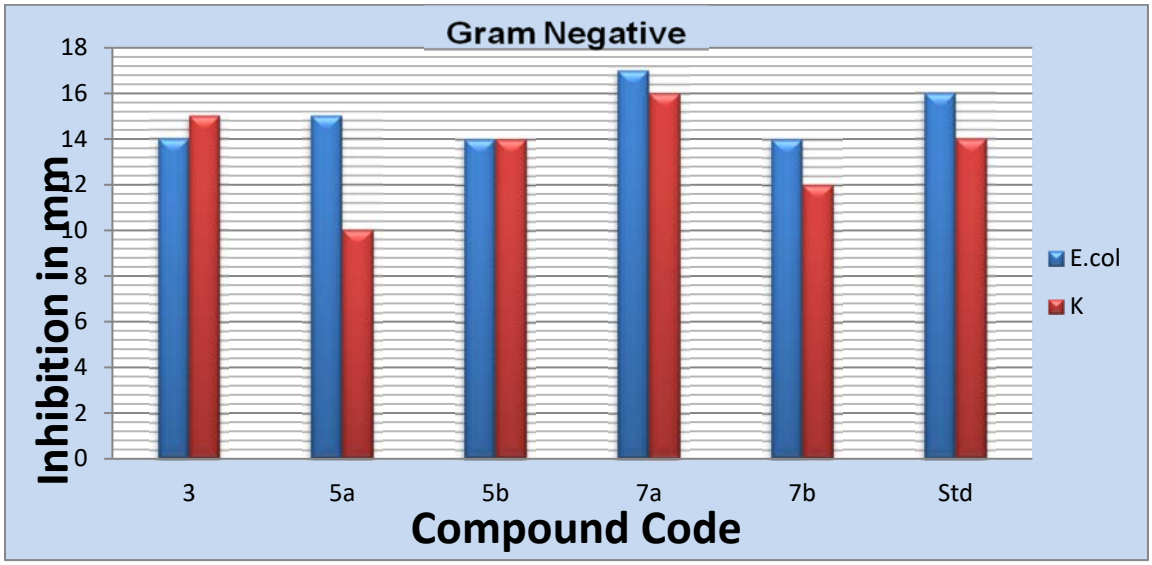


Figure 2. Zone inhibition of compounds an gram negative microorganisms (in mm)

4 Future Plan

There is a plan for synthesis of further coumarin derivatives by cyclization mechanism similar to that proceeded in diazepine synthesis accompanied by biological evaluation.

References

1. Batra Nikhil, Batra Shikha, Pareek Anil, Nagori Badri Prakash. (2012), "Diverse pharmacological activities of 3-substituted coumarins: A review", Int. Res. Journal of Pharm, vol. 3(7), pp. 24-29.
2. Sengupta AK, Sen S, Srivastava V. (1989), "Synthesis of Coumarin Derivatives as Possible Antifungal and Antibacterial Agents." J. Indian Chem. Soc., vol. 66, pp. 710-716.
3. R Sastry Shridhar, Reddy CV, Vaidya NK, Moorty SR, Reddy GS, Thapar GS, et al. (1978), "Antimicrobial agents: Synthesis and antibacterial activity of some new 4-[2-(heteroaryl) vinyl] coumarins," Indian J. Chem, vol. 16B, pp. 704-708.
4. Gadaginmath, S Guru, Joshi, G Raghvendra, et al. (1995), "Synthesis and antimicrobial activity of benzimidazolyl / coumarinylmethoxyindoles," Indian J. Chem, vol. 34B: 120-124.
5. Koneni V Sashidhara, Kumar Abdhesh, Kumar Manoj, Sarkar Jayanta B and Sinha Sudhir (2010), "Synthesis and in vitro evaluation of novel coumarinchalcone hybrids as potential Anticancer agents," Bioorganic and Medicinal Chemistry Letters, vol. 20 (24), pp. 7205-7211.
6. Olayinka O Ajania and Obinna C Nwinyi (2010), "Microwave-Assisted Synthesis and Evaluation of Antimicrobial Activity of 3-{3-(s-Aryl and s-Heteroaromatic) acryloyl}-2Hchromen-2-one Derivatives," J. Heterocyclic Chem, vol. 47, pp. 179-187.
7. Gummudavelly Sandeep, Y Sri Ranganath, S Bhasker and N Rajkumar (2009), "Synthesis and Biological Screening of Some Novel Coumarin Derivatives," Asian J. Research Chem, vol. 2(1). pp. 46-48.
8. Mulwad VV and Shirodkhar JM. (2002), "Synthesis of some of the antibacterial compounds from 4-hydroxycoumarins: Part II," Indian Journal of Chemistry, vol. 41B, pp. 1263-1267.
9. Raviraj K, Manjunath G, Manohar K. (2004), "Synthesis and biological activities of some substituted 4-{4-(1,5-Diphenyl-1H-pyrazol-3 yl) phenoxymethyl} coumarins," Indian J Chem, vol. 13, pp. 201-204.
10. Rao Rajeshwar V, Srimanth K and Kumar Vijaya P. (2004), "Synthesis of 3-[3- substituted thio]-7H-1,2,4-triazolo [3,4-b] [1,3,4]thiadiazin-6-yl]-2H-1-benzopyran-2-ones and 3-[3-amino aryl/heterocyclyl]-7H-1,2,4-triazolo[3,4-b][1,3,4]thiadiazin-6-yl]-2H-1-benzopyran-2-ones," Indian Journal of Heterocyclic chemistry, vol. 14, pp. 141-144.

11. Sadhu, S.K.; Okuyama, E.; Fujimoto, H.; Ishibashi, M. (2003), "Separation of Leucas Aspera, a Medicinal Plant of Bangladesh, Guided by Prostaglandin Inhibitory and Antioxidant Activities," Chem. Pharm. Bull., vol. 51, pp. 595–598.
12. Mohamed N Ibrahim, Hussniya-Al-Difar (2013), "synthesis and biological activity study of some heterocyclic's derived from dibenzalacetone," Ijesm Journal, vol. 2 (3), pp. 1-7.
13. Seranthimata Samshuddin, Badiadka Narayana, Balladka Kunhanna sarojini Hemmigs. Yathirajan and Ramappa Raghavendra (2012), "Synthesis, characterization and biological evaluation of functionalized derivatives of versatile synthon 4, 4'-difluoro chalcone," Der pharma chemical, vol. 4(4), pp. 1445-1457.
14. Ali Irfan, Laila Rubab, Mishbah Ur Rehman, Rukhsana Anjum, Sami Ullah, Mahwish Marjana, Saba Qadeer and Sadia Sana (2020), "Coumarin sulfonamide derivatives: An emerging class of therapeutic agents," Heterocycl. Commun., vol. 26, pp. 46–59.
15. Irena Kostova, Jan Mojzis. (2007), "Biologically active coumarins as inhibitors of HIV-1," Future HIV Ther., vol. 1(3), pp. 315–329.
16. Gnerre C, Catto M, Leonetti F, Weber P, Carrupt PA, Altomare C, et al. (2000), "Inhibition of monoamine oxidases by functionalized coumarin derivatives: biological activities, QSARs, and 3D-QSARs," J Med Chem., vol. 43, pp. 4747–58.
17. Musiliyu A. Musa, M. Omar F. Khan, and John S. Cooperwood (2009), "Synthesis and antiproliferative activity of coumarin-estrogen conjugates against breast cancer cell lines," Lett Drug Des Discov., vol. 6(2), pp. 133–138.

