RESEARCH ARTICLE

Preparation with Biological Study for Pyrimidine Derivatives from Chalcone

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Received: 11th January, 2022; Revised: 13th February, 2022; Accepted: 21st February, 2022; Available Online: 25th March, 2022

ABSTRACT

Pyrimidine has been mentioned to present diverse biological activities such as antioxidant, anti-inflammatory, anti-tubercular, anti-bacterial, in additional to another biological activities, therefore, many medicine containing pyrimidine moiety have been observed. Due to the pharmacological importance of pyrimidine derivatives, the present work coms as attempt to synthesis of various pyrimidine derivatives by series of steps starting from chalcone, compounds (1 and 2) which were prepared by Cliesen-Schemidt condensation of acetophenone with (4-bromobenzaldehyde or 4-chlorobenzaldehyde). Then cyclization of compounds (1 or 2) with urea or thiourea to produce compounds (3 or 4 respectively). by another way, compound (1) was cyclized with thiourea to produce 4,5-Dihydropyrimidine-2(3*H*)-thione compound (5) which could be reacted with 3-cyanobenzyl chloride or benzyl chloride to give 2-Arylalkylthio-2,5-dihydropyrimidine derivatives compounds (6 or 7, respectively). These target compounds were confirmed on the basis FT-IR, and ^{1}H-NMR techniques. The biological study was evaluated against tow bacterial (*Staphylococcus aureus* as gram positive) and (*Klebsiella pneumonia* as gram negative) in concentration (50 and 100) µg/mL. It was found that derivatives have biological activity against growth these bacterial.

Keywords: Biological activity, Chalcones, Pyrimidine derivatives.

International Journal of Drug Delivery Technology (2022); DOI: 10.25258/ijddt.12.1.32

How to cite this article: Atiya RN, Salih NA, Adam RW. Preparation with Biological Study for Pyrimidine Derivatives from Chalcone. International Journal of Drug Delivery Technology. 2022;12(1):174-179.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Chalcone consider an important class for natural product natural products also precursors for biologically active compounds.[1] This class destination by wide range from pharmaceutical applications as antimicrobial,[2] anti-HIV,[3] anti-inflammatory,[4] antibacterial,[5] anticancer activities,[6] anti-diabetes[7] as potential treatment agents for Alzheimer's disease,[8] etc. Therefore many researchers have done many research studies on chalcones.[9-11]

Heterocyclic derivatives involved nitrogen atoms occupies role in chemistry according for pharmacological application and therefor there are spectrum from research about pyrrole, imidazole, pyridine, indole and pyrazine, which consider types important form heterocycles systems according to diverse pharmaceutical importance.[12] Pyrimidines are six heterocyclic containing nitrogen atoms at 1,3-positions within ring, are biologically active compounds.[13-15] Depending on the divers pharmaceutical applications of pyrimidine, we worked through this study on preparation of pyrimidine derivatives followed by a study of their biological activity (Scheme 1 and Table 1).

MATERIALS AND METHODS

Chemistry

All chemical materials were equipped by Fluka (Switzerland) and Sigma (USA), this was used without any additional purification. Melting ranges has been determined via Stuart apparatus SMP 30 melting point. The FT-IR spectra were collected on the use of KBr pellet on IR Prestige-21 SHIMADZE. On the VARIAN spectrometer, ^{1}H-NMR spectra were collected at 499.49 MH_Z using d_6-DMSO as solvent, shifts are recorded in ppm using TMS as the internal standard chemical. Thin layer chromatography (TLC) was used to monitor the reactions by 0.2 mm percolated plates of silica gel G60 F254 (Merck) using Benzene/methanol (4:1) as mobile phase and spots were examined by iodine vapor.

Preparation 3-(4-bromophenyl)-1-phenyl-2-propenone (Compound 1)[16]

To a stirred mixture of acetophenone (0.005 mol, 0.06 gm) & *p*-bromobenzaldehyde (0.005 mol, 0.92 gm) in methanol (9.8 mL), add (1-mL) from 20% NaOH solution. The resulting

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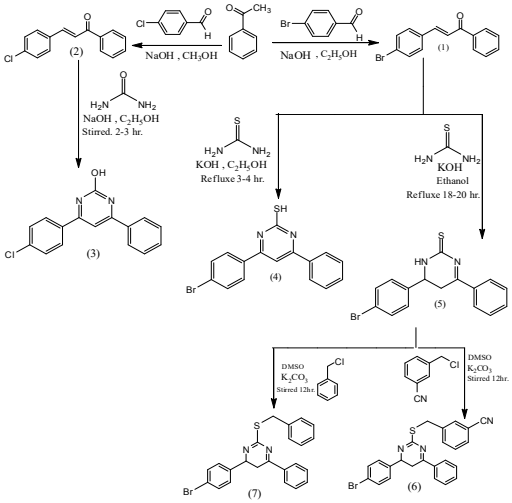
mixture was left overnight after being stirred at room temperature for 30 minutes. After the reaction was complete, the mixture was then placed into ice water, neutralized followed filtered. Crud product was re-crystallized from ethanol. FT-IR (KBr, cm^{-1}), Figure 1: γ 3059 (C-H Ar.str.); 3058,2996 (C-H alkene str.); 1658 (CO str. Of α, β-unsaturated ketone); 1606(C=C str. of alkene); 1485,1444 (C=C Ar.str.); 1012,977 (=C-Hoop); 686C-HAr.oop); 613(C-Br str.). ^{1}H-NMR (499.49 MHZ, DMSO-d_6, ppm): Figure (8), δ 7.5-8 (9H, m, Ar H), 8.1-8.2 (2H,d,Ar-CH=CH-CO-Ar).

3-(4-chlorophenyl)-1-phenyl-2-propenone (Compound 2)[16]

To a stirred mixture of acetophenone (0.005 mol, 0.06 gm) & *p*-chlorobenzaldehyde (0.005 mol, 1.21 gm) in methanol (9.8 mL), add (1-mL) from 20% NaOH solution. The resulting mixture was left over night after being stirred at room temperature for 30 minutes. After the reaction was complete, the mixture was then placed into ice water, neutralized followed by filtered. Crud product was re-crystallized from ethanol. FT-IR (KBr, Cm^{-1}), Figure 2: γ 3059 for stretching of aromatic C-H; 3028,2920 for stretching of alkene C-H; 1658 for stretching of CO;1598 stretching of alkene C=C; 1570,1487 for stretching of aromatic C=C; 1010,983 (=C-Hoop); 773(C-Cl str.); (686 C-HAr.oop.).



Scheme 1: Synthesis of target compounds

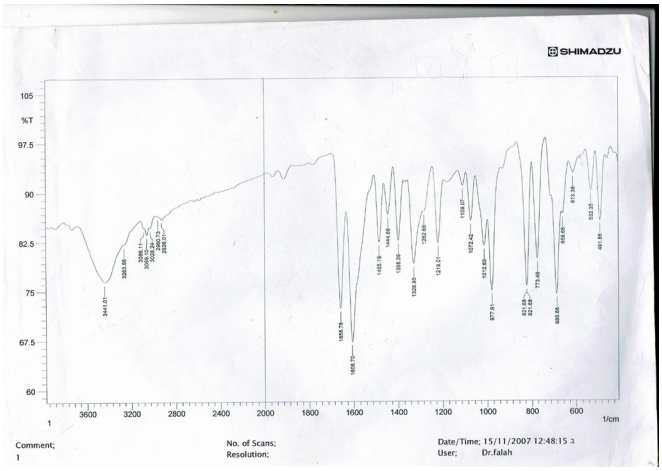


Figure 1: FT-IR for derivative [1]

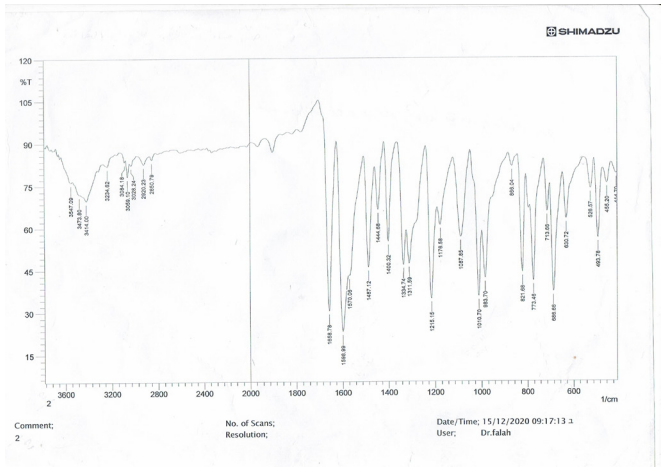


Figure 2: FT-IR for derivative [2]

Table 1: The physicochemical properties of the synthesized analogous (1-7)

Compound	*M.F.*	*M. Wt.*	*M. P. (°C)*	*Description*	*Yield%*	*R_f value*
1	$C_{15}H_{11}BrO$	286	122–123	yellow	61	0.85
2	$C_{15}H_{11}ClO$	242	104–105	Pale yellow	90	0.87
3	$C_{16}H_{11}ClN_2O$	282	138–140	Pink	75	0.88
4	$C_{16}H_{11}BrN_2S$	343	164–165	yellow	72	0.71
5	$C_{16}H_{13}BrN_2S$	345	153–154	yellow	64	0.82
6	$C_{24}H_{18}BrN_3S$	460	192–193	yellow	50	0.71
7	$C_{23}H_{19}BrN_2S$	435	172–173	yellow	78	0.76

Table 2: Antibacterial activity of synthesized compounds

	Gram positive Bacterial		*Gram positive Bacterial*	
	S. aureus		*K. pneumonia*	
Compound	*50 µg/mL*	*100 µg/mL*	*50 µg/mL*	*100 µg/mL*
3	No bacterial growth	No bacterial growth	Bacterial growth	No bacterial growth
4	Bacterial growth	Bacterial growth	No bacterial growth	No bacterial growth
5	No bacterial growth	No bacterial growth	No bacterial growth	No bacterial growth

4-(4-chlorophenyl)-6-phenylpyrimidin-2-ol (Compound 3)[17]

A solution of chalcone (0.4 g, 0.001 mol) and urea (0.001 mol, 0. 06 g) was dissolved in ethanolic sodium hydroxide (0.7 g NaOH and 10 mL ethanol) and stirred with a magnetic stirrer for around 2–3 hours. The mixture was then placed into 400 cc of cold water and stirred continuously for an hour then refrigerated for 24 hours. The resulting precipitate was filtered. FT-IR (KBr,Cm^{-1}), Figure (3): γ 3437 stretching for hydroxyl group; 3061 stretching for aromatic C-H; 1672,1591 stretching for C=N; 1521,1489 stretching for aromatic C=C; 1409 (C-O-H bending); 1220 (C-Ostr.);1093(C-Nstr.); 696 (C-H Ar.oop); 540 (C-Br str.).

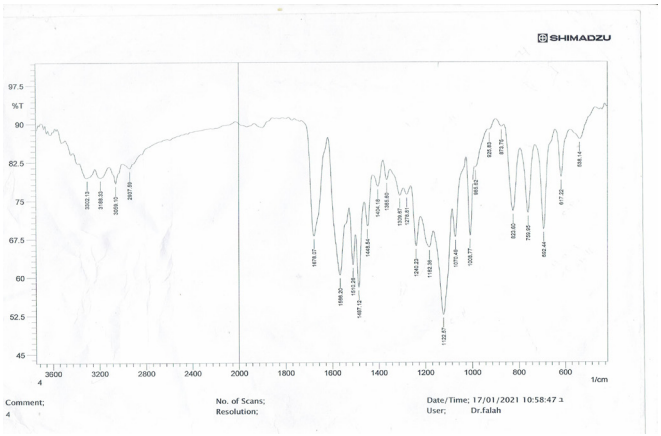


Figure 3: FT-IR for derivative [3]

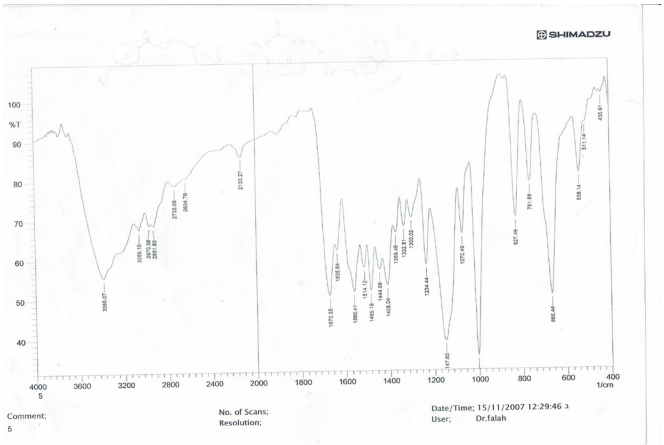


Figure 4: FT-IR for derivative [4]

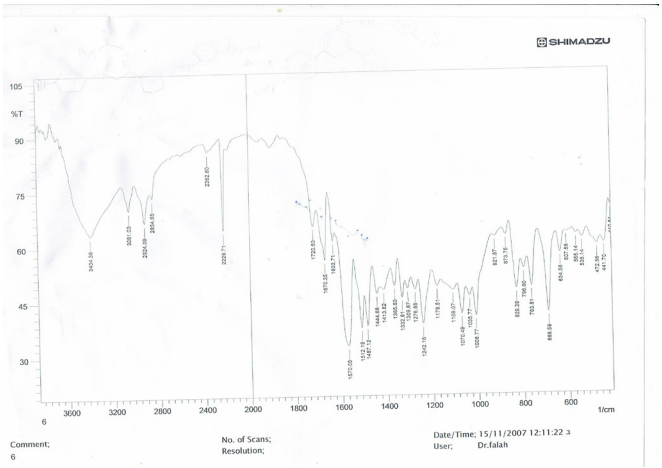


Figure 5: FT-IR for derivative [5]

4-(4-bromophenyl)-6-phenylpyrimidine-2-thiol (Compound 4)[18]

The solution of substituted chalcone compound (1) (0.001 mol, 0.24 g) in methanol (4 mL) was added with potassium hydroxide (0.001 mol, 0.056g) and thiourea (0.001M, 0.076g) for 3-4 was refluxed, then was cooled followed by acidification by few drops from HCl (5 cc in concentrated 0.5M).The precipitate was then isolated and dried. After that recrystallized by ethanol. FT-IR (KBr, Cm^{-1}), Figure 4: γ 3188,3059 (C-H Ar.str.); 2937 (SHstr.); 1678,1566 (C=Nstr.); 1510,1487 stretching for C=C; 1122 stretching for C-N; 692(C-H Ar.oop); 617 (C-Br str.).

6-(4-bromophenyl)-4-phenyl-(1H)-5,6-dihydro-2-pyrimidinthione (Compound5)[19]

The reaction mixture was prepared from synthesized chalcone, compound (1) (0.01 mol, 2.8 gm), thioura (0.01 mole, 0.76gm.) and KOH (0.017 moL, 0.95 gm) in solvent ethanol and for 18–20 hours was reflexed then was placed into ice followed by collected the product then recrystallized via ethanol. FT-IR (KBr,Cm^{-1}) Figure (5): γ 3385 (N-H); 3059 stretching of aromatic C-H; 2931 stretching aliphatic C-H; 2133(C=Sstr.); 1670,1760(C=Nstr.); 1514,1485 stretching of aromatic C=C; 1000 stretching for C-N; 665(C-H Ar.oop);538(C-Brstr.). ^{1}H-NMR (499.49 MHZ, DMSO-d_6, ppm): Figure 9: δ 1-1.5 (2H, *d*, CH_2); 3-3.5 (1H,tr.,CH); 6-9(9H,m,Ar-H), 10-10.5 (1H,s,NH).

General Procedure for the Syntheses of Compounds (6 and 7)[20,21]

Compound (5) (0.47 mmol) and (0.94 mmol) of K_2CO_3 were dissolved by 2 mL from DMSO. The Mixture and at room temperature was stirred then added (0.47 mmoL) from substituted alkyl halide (3-cyanobenzylchloride or benzyl chloride) respectively and for 12 hours. was stirred the mixture and (7 mL) of H_2O was added and pH to 3 was adjusted with 2Naq HCl. (10 mL) of Ethyl acetate was added and stirred for 15 min. To extract the aqueous layer, ethyl acetate (20 mL x 3) was added and organic layers were combined, dried via anhydrous magnesium sulfate and recrystallized from EtOAc–petroleum ether.

-((4-(4-bromophenyl)-6-phenyl-4,5-dihydropyrimidin-2-ylthio)methyl)benzonitrile (6): 3

FT-IR (KBr,Cm^{-1}) Figure (6): γ 3061 stretching for aromatic C-H; 2924, 2854 stretching for aliphatic C-H; 2229 stretching (CN, cyano); 1670, 1633,1570 stretching for C=N; 1008 stretching C-N; 688(C-H Ar. oop);634(C-Br str.). ^{1}H-NMR(499.49 MHZ, DMSO-d_6, ppm): Figure 10: δ 1-1.5(2H,d,CH_2), 2.5 (1H,CH), 4.5-5.6 (2H,S-CH_2),6-9.5(Ar.C-H).

2-(benzylthio)-4-(4-bromophenyl)-6-phenyl-4,5-dihydropyrimidine (7): FT-IR (KBr,Cm^{-1}) Figure 7: γ

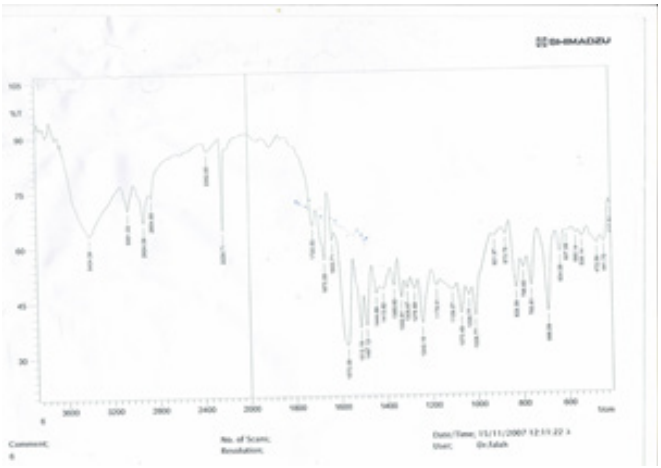


Figure 6: FT-IR for derivative [6]

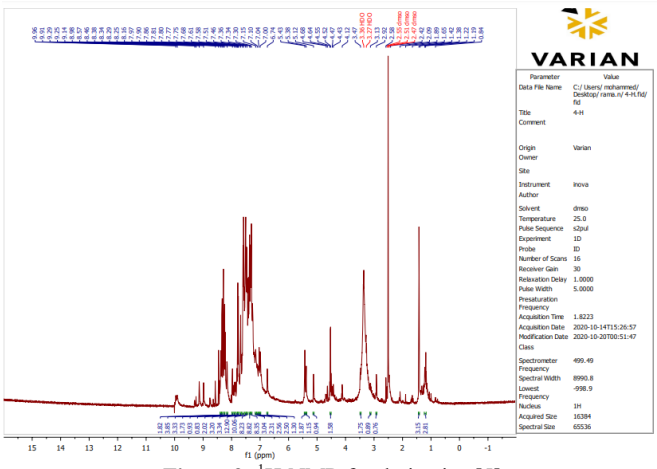


Figure 9: ^{1}H-NMR for derivative [5]

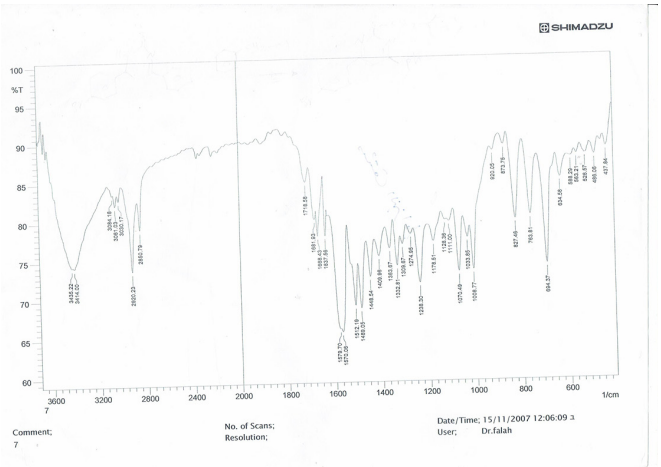


Figure 7: FT-IR for derivative [7]

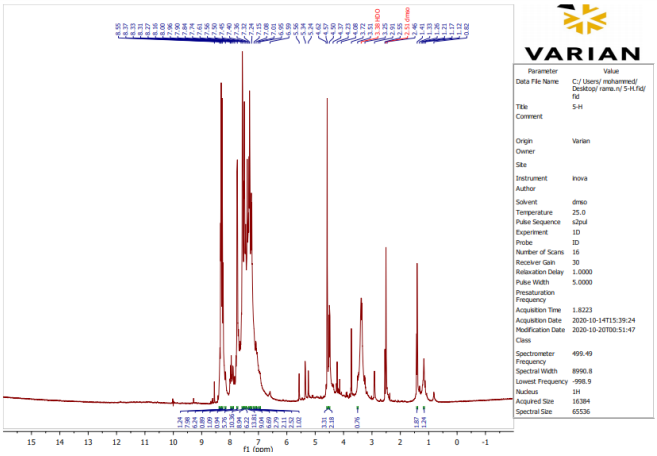


Figure 10: ^{1}H-NMR Spectra of Compound (6) (1)

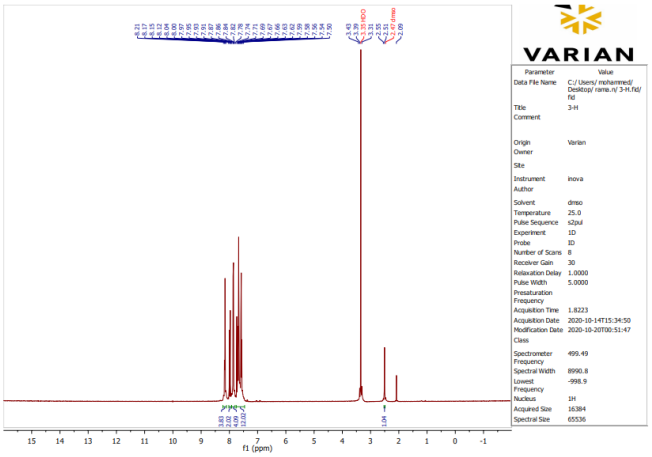


Figure 8: ^{1}H-NMR for derivative [1]

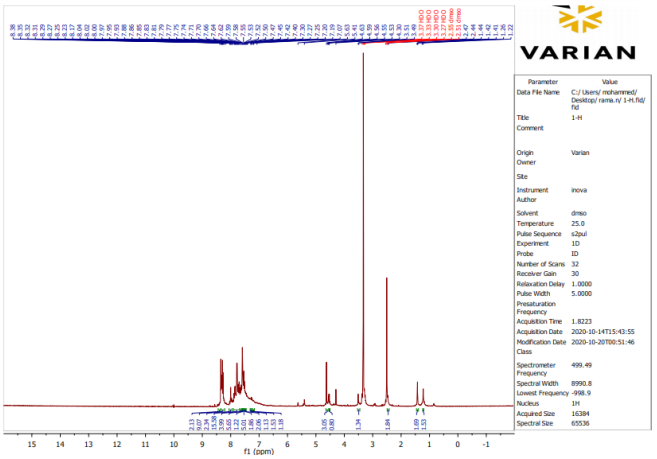
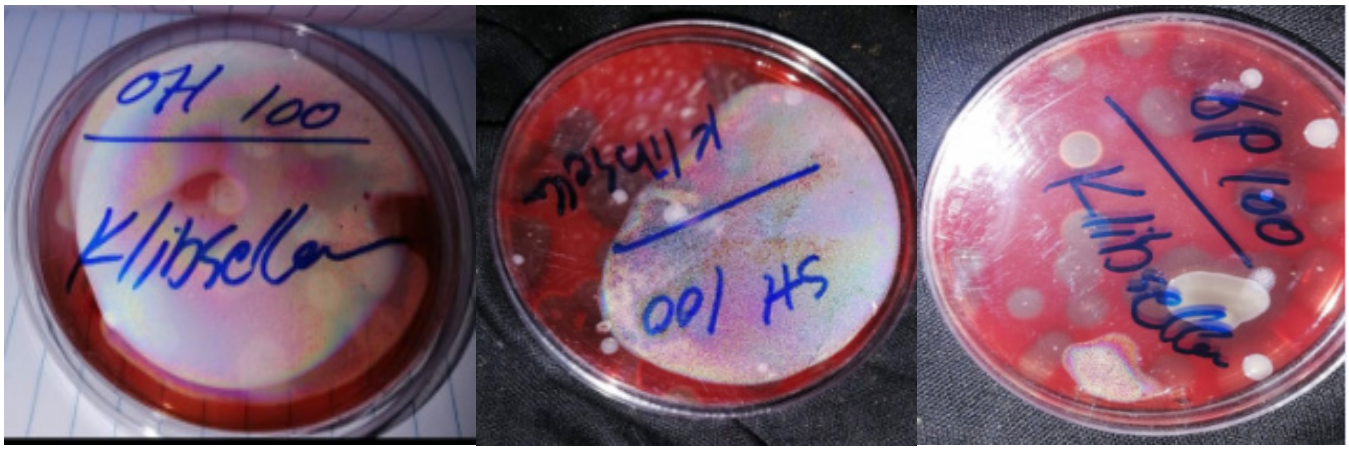


Figure [11]: ^{1}H-NMR for derivative [7]

3061 stretching for aromatic C-H; 2920,2850 stretching for aliphatic C-H; 1668,1637;1579 (C=Nstr.);1512,1489 stretching for aromatic C=C;1008 (C-N); 694 (C-H Ar. oop); 634 (C-Br str.). ^{1}H-NMR (499.49 MHZ, DMSO-d_6, ppm): Figure (10): δ 1-1.4(2H,d,CH_2), 3.5 (1H,CH), 4-4.5 (2H,S-CH_2),6-9.5(Ar.C-H).

Spectra of Synthesized Compounds



5 4 3
Gram negative (*K. pneumonia*)

3 4 5
Gram positive (*S. aureus*)

CONCLUSION

In conclusion, chalcone compounds were synthesized in this study in excellent to good yield, as good intermediate for synthesis series of various pyrimidine derivatives **(3-7)** (Figure 3 to 11. These derivatives also were synthesized in good yield. All pyrimidine derivatives have high melting point, that refer to their stability. The pyrimidine derivatives, compounds (3-5) were evaluated their biological activity as antibacterial by using two types from bacterial (*S. aureus* as positive bacterial) and (*K. pneumonia* as negative bacterial), Compound (3) show biological activity against growth of *S. aureus* and with an increase in its concentration is observed activity of compound against *K. pneumonia*. Compound (4) doesn't biological activity against growth of *S. aureus* while show activity against growth of *K. pneumonia*. Compound (5) show biological activity against growth of *S. aureus* and *K. pneumonia* (Table 1).

REFERENCES

1. Arif R, Rana M, Yasmeen S, Khan MS, Abid M, Khan MS. Facile synthesis of chalcone derivatives as antibacterial agents: synthesis, DNA binding, molecular docking, DFT and antioxidant studies. J Mol Struct. 2020;1208:127905.
2. Lal K, Yadav P, Kumar A, Kumar A, Paul AK. Design, synthesis, characterization, antimicrobial evaluation and molecular modeling studies of some dehydroacetic acid-chalcone-1, 2, 3-triazole hybrids. Bioorg Chem. 2018;77: 236–44.
3. Wu J-H, Wang X-H, Yi Y-H, Lee K-H. Anti-AIDS agents 54. A potent anti-HIV chalcone and flavonoids from genus Desmos. Bioorg Med Chem Lett. 2003;13(10):1813–5.
4. Li J, Li D, Xu Y, Guo Z, Liu X, Yang H, et al. Design, synthesis, biological evaluation, and molecular docking of chalcone derivatives as anti-inflammatory agents. Bioorg Med Chem Lett. 2017;27(3):602–6.
5. Xu M, Wu P, Shen F, Ji J, Rakesh KP. Chalcone derivatives and their antibacterial activities: Current development. Bioorg Chem. 2019;91:103133.
6. Sultana F, Bonam SR, Reddy VG, Nayak VL, Akunuri R, Routhu SR, et al. Synthesis of benzo [d] imidazo [2, 1-b] thiazole-chalcone conjugates as microtubule targeting and apoptosis inducing agents. Bioorg Chem. 2018;76:1–12.
7. Cai C-Y, Rao L, Rao Y, Guo J-X, Xiao Z-Z, Cao J-Y, et al. Analogues of xanthones——Chalcones and bis-chalcones as α-glucosidase inhibitors and anti-diabetes candidates. Eur J Med Chem. 2017;130:51–9.

8. Zhang X, Rakesh KP, Bukhari SNA, Balakrishna M, Manukumar HM, Qin H-L. Multi-targetable chalcone analogs to treat deadly Alzheimer's disease: current view and upcoming advice. Bioorg Chem. 2018;80:86–93.
9. Siddiqui ZN, Asad M, Praveen S. Synthesis and biological activity of heterocycles from chalcone. Med Chem Res. 2008;17(2):318–25.
10. Kurt BZ, Kandas NO, Dag A, Sonmez F, Kucukislamoglu M. Synthesis and biological evaluation of novel coumarin-chalcone derivatives containing urea moiety as potential anticancer agents. Arab J Chem. 2020;13(1):1120–9.
11. Huo P-C, Guan X-Q, Liu P, Song Y-Q, Sun M-R, He R-J, et al. Design, synthesis and biological evaluation of indanone–chalcone hybrids as potent and selective hCES2A inhibitors. Eur J Med Chem. 2021;209:112856.
12. Al-Mulla A. A review: biological importance of heterocyclic compounds. Der Pharma Chem. 2017;9(13):141–7.
13. Wang R, Yu S, Zhao X, Chen Y, Yang B, Wu T, et al. Design, synthesis, biological evaluation and molecular docking study of novel thieno [3, 2-d] pyrimidine derivatives as potent FAK inhibitors. Eur J Med Chem. 2020;188:112024.
14. Zhang L, Tang X, Cao Y, Wu S, Zhang Y, Zhao J, et al. Synthesis and biological evaluation of novel 2-arylalkylthio-5-iodine-6-substituted-benzyl-pyrimidine-4 (3H)-ones as potent HIV-1 non-nucleoside reverse transcriptase inhibitors. Molecules. 2014;19(6):7104–21.
15. Kerru N, Gummidi L, Maddila S, Gangu KK, Jonnalagadda SB. A review on recent advances in nitrogen-containing molecules and their biological applications. Molecules. 2020;25(8):1909.
16. Naik TA, Chikhalia KH. Studies on synthesis of pyrimidine derivatives and their pharmacological evaluation. E-Journal Chem. 2007;4(1):60–6.
17. Abd El-Sattar NEA, Badawy EHK, Abdel-Mottaleb MSA. Synthesis of Some Pyrimidine, Pyrazole, and Pyridine Derivatives and Their Reactivity Descriptors. J Chem. 2018;2018.
18. Narwal S, Kumar S, Verma PK. Design, synthesis and antimicrobial evaluation of pyrimidin-2-ol/thiol/amine analogues. Chem Cent J. 2017;11(1):1–9.
19. Sahu M, Siddiqui N, Sharma V, Wakode S. 5, 6-Dihydropyrimidine-1 (2H)-carbothioamides: Synthesis, in vitro GABA-AT screening, anticonvulsant activity and molecular modelling study. Bioorg Chem. 2018;77:56–67.
20. Manetti F, Esté JA, Clotet-Codina I, Armand-Ugón M, Maga G, Crespan E, et al. Parallel solution-phase and microwave-assisted synthesis of new S-DABO derivatives endowed with subnanomolar anti-HIV-1 activity. J Med Chem. 2005;48(25):8000–8.
21. Qin H, Liu C, Zhang J, Guo Y, Zhang S, Zhang Z, et al. Synthesis and biological evaluation of novel 2-arylalkylthio-4-amino-6-benzyl pyrimidines as potent HIV-1 non-nucleoside reverse transcriptase inhibitors. Bioorg Med Chem Lett. 2010;20(9):3003–5.