Synthesis And Evaluation of the Antimicrobial Activity of new Different Chalcones Derived From P-Amino Benzaldehyde Containing Thiozolidinone Ring

Shireen Nadhem Saleh[1], Muthanna saadi farhan[2]
[1] Department of Pharmaceutical Chemistry, College of Pharmacy, University of Tikrit, Salah-Aldin, Iraq
[2] Department of Pharmaceutical Chemistry, College of Pharmacy, University of Baghdad, Baghdad, Iraq
Emali: 07722164990sa@gmail.com

Abstract
In this article, we try to form a very quick, effective, three-component, the synthesis of N-substituted imino thiazolidin4one derivatives from chalcones via hard - soft acid-base reaction (Lewis). By utilizing reflux and agitation approach in alkali media. and evaluating the in vitro antimicrobial activity of these end-target compounds against Gram-positive and Gram-negative bacteria and fungi to avoid many resistance problems generation, especially in multidrug resistance (MDR). With exceptional yields, Claisen Schmidt condensation has been used to generate many new chalcones from substituted acetophenone and p-amino benzaldehydes. and use sodium hydroxide as a catalyst with excellent yield. The antimicrobial assessment was performed by well diffusion against selected microorganisms and used as standards, Amoxicillin, Ciprofloxacin, and Fluconazole. Melting point, TLC, FT-IR, 1H NMR and other physicochemical properties were used to characterize all the compounds produced.
Keywords: Chalcones, Thiozolidinone, Antimicrobial activity.

1. Introduction

Chalcones are a kind of open-chain flavone with a three-carbon linker across two benzyl rings. Furthermore, the bi-electrophilic keto-vinyl chain between the two rings is highly reactive and serves as a chemical synthon for constructing various four or five, six, and seven, membered hetero-aromatic scaffolds containing different heteroatoms such as N, O, and S atoms by abrogation with a range of different of bi-nucleophilic reagents. In the twenty-first century, scientists are still fascinated with chalcone chemistry., generating a wide range of interesting pharmacological actions, including, anti-inflammatory(1),anti-ulcer (2), antimicrobial(3), anticancer(4), anti-HIV(5),... etc.
Chalcone also has a good moiety, which allows for the construction of a variety of novel heterocyclic compounds with improved pharmacological activities (6) .The conjugated double bond also causes electron delocalization, lessening its electrophilic property and providing it an intermediary in the production of pyrazoline, oxazoline, oxazine, pyrimidine thiazine, and other physiologically relevant heterocycles. Thus, the synthesis of chalcones has piqued the curiosity of both organic and medicinal chemists (7) When it comes to the condensation of aryl ketones with aryl aldehydes in the presence of adequate condensing agents, the Claisen-Schmidt condensation tends to be the most attractive, and as a result, there are numeral approaches for the synthesis of chalcones are available. (8). The developing importance of thiazolidine-4-one analogs, a pharmacophore found in a variety of synthesized drugs with unique biological functions (9)such as: antimicrobial (10), anti-mycobacterial (11) ,antitumor (12) , anti-inflammatory and analgesic activities(13). This nucleus is being researched constantly supposing to develop and manufacture new molecules. Thiozolidine is a tetrahydro parent of thiazole and oxo derivative of thiazole, Itis referred to as thiozolidinone. On the 2, 3, and 5-positions, a wide range of replacements can be made, causing changes in compound features. It is also feasible to construct new derivatives by changing the substituents connected to the nitrogen and methylene carbon atoms..(14, 15) here for the design new chalcone derivative that's attached to thiozolidinone ring appears to be interesting for many chemical considerations and antimicrobial activity, such as fungal and bacterial illness have become prevalent and intricate in recent years, especially when directly linked research at the turn of the nineteenth century. As a result, the need for novel antifungal and antibacterial drugs has risen dramatically in recent years, particularly in light of the reported growth of multidrug-resistant (MDR) strains. (16)

2. Experimental

3. Materials and Methods

All ketones, aldehydes, and phenylisothio-cyanate

doi.org/10.31838/hiv23.02.128 Reaceived: 14.10.22, Revised: 24.11.22, Accepted: 27.12.22.

derivatives were bought from Hyper Chem. Company (China). Solvent and other reagents that were used through reaction were bought from commercial sources. The purity of products and monitoring of the reactions were done by thin layer chromatography TLC (GF254, merk-Germany) under UV light (254nm) two solvent systems were used A: n-hexane: ethyl acetate: glacial acetic acid (3.5:1.5:1) and B: ethyl acetate: petroleum ether (1:4). Melting points exist uncorrected and recognize by u tilizing Stuart SMP3 point at which something melts equipment with a purpose in open capillary tube. IR spectra were done by thin-film technique (õ, cm-1), (Shimadzu FT-IR spectrophotometer, Japan). 1H-NMR was done recorder using Brucker ultra-shield model 300 MHz using DMSO as a solvent.

General procedure for the Synthesis chalcones: (17, 18).

4-aminobenzaldehyde and p-methoxy, bromo, Fluoro acetophenone were combined and dissolved in 12 mL of ethanol in an equimolar amount (0.001mol). At room temperature, add a 40% sodium hydroxide solution (3-5 mL) gently and stir occasionally for 5 hours. TLC utilizing Silica gel-G was used to confirm the reaction's completion. From hot 100% ethanol, the solvent was evaporated, and the precipitate was recrystallized

1-(E)-3-(4-aminophenyl)-1-(4-methoxyphenyl) prop-2-en-1-one (compound a)

Yellowish crystal, yield80%, M.P: (158-160), FT-IR (νcm-1) = 3437, 3329 (NH2, str),2985,2839 (C-H) asym and sym. 1635 (C=O, str), 1580 (C=C, str),1253(c-o-c) ether cm-1. 1H-NMR (400 MHz, DMSO-d6) δ:5.87 (2H, s, NH2), 6.61-8.13(8H, m, ArH) 7.76 (1H, d, CH=CH), 3.87 (3H, s, OCH3),8.10 (1H, d, CH=CH) ppm. 2. (E)-3-(4-aminophenyl)-1-(4-bromophenyl) prop-2-en-1-one (compound b):

Orang crystal, Yield: 75%, M.P.:(153-155), FT-IR (νcm-1)= 1643 (C=O) ketone,1570(C=C, str), 3425-3336 (-NH2), 3093(-CH) alkenes,510-690(C-Br str) cm-1.1H-NMR (400 MHz, DMSO-d6) δ:5.96(2H, s, NH2),6.61-8.05(8H, m,Ar-H),7.55(1H,d, CH=CH)7.79(1H,d, CH=CH)ppm.

3.(E)-3-(4-aminophenyl)-1-(4-fluorophenyl) prop-2-en-1-one (compound c)

Orange crystallize, yield 77%, M.P.: (138-140), FT-IR (νcm-1) = 1651 (C=O, str) ketone,1597(C=C, str,),3406-3332(-NH2),3093(-CH, str) alkenes,1037-1300(C-F, str) cm-1.

1H-NMR (400MHz, DMSO-d6) δ:5.93(2H, s, NH2),6.62-8.21(8H, m, ArH)7.59(1H, d, CH=CH),8.18(1H, d, CH=CH) ppm.

General procedure for the Synthesis thiourea group: (19-21)

Each compound (a-c) (0.0012mole) was mixed with (0.0016 mole) of various phenyl-isothio-cyanate derivatives in absolute ethanol (25ml) and refluxed for 8 hours at 600c. TLC with Silica gel-G was used to observe the response. From hot 100% ethanol, the solvent was evaporated and the precipitate was recrystallized.

1: (E)-1-(4-bromophenyl)-3-(4-(3-(4-methoxyphenyl)-3-oxoprop-1-en-1-yl) phenyl) thiourea (compound 1a):

Yellowish powder, Yield: 70%, M.P.: (156-159 0C), FT- IR (ν cm-1): 3313.7 (N–H) 3005 aomatic (C-H),1643 (C=O, str) 1597 (C=C, str) 1219 (C=S) 644 (Ar-Br) 1029 (C-O-C). (1H- NMR (400 MHz, DMSO-d6) δ:3.75(1H, s, OCH3), 9.80 (1H, s, NHCS),9.87 (1H, s, CNH),6.92-8.24 (12H, m, Ar-H),7.57(1H, d, CH=CH) 7.88 (1H, d, CH=CH) ppm.

2-(E)-1-(4-(3-(4-methoxyphenyl)-3-oxoprop-1-en-1-yl) phenyl)-3-(4-nitrophenyl) thiourea:(compound 2a)

Pale-yellow powder, Yield: 80%, M.P.: (157-159), (ν cm-1): 3294 (N–H) 3009 aromatic (C-H),1647 (C=O, str) 1577 (C=C, str) 1219 (C=S) 1504-1566 (Ar-NO2) 1022 (C-O-C) cm-1.

(1H- NMR (400 MHz, DMSO-d6) δ:3.88(1H, s, OCH3), 10.07 (1H, s, NHCS),10.14 (1H, s, CNH),7.05-8.2 (12H, m, Ar-H),7.57(H, s, CH=CH) 7.93 (1H, s, CH=CH) ppm.

3-(E)-1-(4-(3-(4-bromophenyl)-3-oxoprop-1-en-1-yl) phenyl)-3-(4-methoxyphenyl) thiourea:(compound 1b)

Pale-yellow powder, Yield: 76%, M.P.: (188-190), FT-IR(νcm-1): 3329 (N–H) 3001aromatic (C-H),1639 (C=O, str) 1589 (C=C, str) 1219 (C=S) 686 (Ar-Br) 1029(C-O-C) cm-1. (1H- NMR (400 MHz, DMSO-d6) δ:3.77(1H, s, OCH3), 9.95 (1H, s, NHCS),10.0 (1H, s, CNH),6.98-8.28 (12H, m, Ar-H),7.55(1H, d, CH=CH) 7.92 (1H, d, CH=CH) ppm.

4-(E)-1-(4-(3-(4-bromophenyl)-3-oxoprop-1-en-1-yl) phenyl)-3-(4-chlorophenyl) thiourea:(compound 2b)

Yellowish powder, Yield: 75%, M.P.: (175-178), FT-IR (ν cm-1): 3302 (N–H) 3043 aromatic (C-H),1654 (C=O, str) 1581 (C=C, str) 1219 (C=S) 663 (Ar-Br), 1086-1091(Ar-Cl) cm-1. (1H- NMR) (400 MHz, DMSO-d6) δ: 10.08 (1H, s, NHCS),10.14 (1H, s, CNH),7.47-8.11 (12H, m, Ar-H),7.53(1H, d, CH=CH)7.96 (1H, d, CH=CH) ppm.

5-(E)-1-(4-bromophenyl)-3-(4-(3-(4-fluorophenyl)-3-oxoprop-1-en-1-yl) phenyl) thiourea: (compound 1c)

Orange to yellow powder, Yield: 70%, M.P.: (166-169), FT- IR (ν cm-1): 3305 (N–H) 3101aromatic (C-H),1639(C=O, str) 1593 (C=C, str) 1219 (C=S) 671(Ar-Br), 1303(Ar-F) cm.

(1H- NMR)400 MHz, DMSO-d6)) δ: 10.06 (1H, s, NHCS),10.13(1H, s, CNH),7.47-8.26 (12H, m, Ar-H),7.54(1H, d, CH=CH)7.89 (1H, d, CH=CH) ppm.

6-(E)-1-(4-chlorophenyl)-3-(4-(3-(4-fluorophenyl)-3-oxoprop-1-en-1-yl) phenyl) thiourea :(compound 2c)

Orange powder, Yield: 80%, M.P.: (188-190), FT-IR) (ν cm-1): 3336 (N–H) 3101-3066aromatic (C-H),1639(C=O) 1593 (C=C) 1219 (C=S) 1064-1086(Ar-Cl), 1319(Ar-F) cm-1. (1H NMR (400 MHz, DMSO-d6) δ: 10.47 (1H, s, NHCS),10.52(1H, s, CNH),7.35-8.26 (12H, m, Ar-H),7.65(1H, d, CH=CH) 7.90 (1H, d, CH=CH) ppm.

general procedure for the synthesis thiozoldinone from chalcones:(22, 23)

Ethyl-bromoacetate (0.0012 mole) and anhydrous sodium acetate (0.003 mole) were added to a solution of the appropriate distinct thiourea derivative (1a-2c) (0.001 mole) in absolute ethanol (20 mL) and the reaction mixture was heated under reflux for 4–6 h. From hot 100% ethanol, the precipitated material was filtered, washed with water, dried, and recrystallized.

1-(Z)-3-(4-bromophenyl)-2-((4-((E)-3-(4-methoxyphenyl)-3-oxoprop-1-en-1-yl) phenyl) imino) thiazolidin-4-one:(compound 3a)

Yellowish powder, Yield: 70%, M.P.: (170-173 0C), FT- IR (ν cm-1): 1728 (thiazolidinone, C=O),1689 (chalcone C=O, str), 1654.9 (C=N, str), 1581(C=C, str). (1H NMR) (400 MHz, DMSO-d6):3.88 (3H, s, -OCH3), 4.20(2H, s, -CH2), 6.83-8.20(12H, complex m, Ar -H) 7.57-7.88(1H, d, α – β H of chalcone) ppm.

2 - (Z)-2-((4-((E)-3-(4-methoxyphenyl)-3-oxoprop-1-en-1-yl) phenyl) imino)-3-(4-nitrophenyl) thiazolidin-4-one:(compound 4a)

Pale yellow powder, Yield: 70%, M.P.: (196-198 0C), IR (v cm 1): 1732 (thiazolidinone, C=O),1658 (chalcone C=O, str), 1624 (C=N), 1581(C=C, str). (1H- NMR) (400 MHz, DMSO-d6) δ:3.89 (3H, s, -OCH3), 4.27(2H, s, -CH2), 7.00-8.26(12H, complex m, Ar –H) 7.57-7.93(1H, d, α – β H of chalcone) ppm.

3-(Z)-2-((4-((E)-3-(4-bromophenyl)-3-oxoprop-1-en-1-yl) phenyl) imino)-3-(4-chlorophenyl) thiazolidin-4-one: (compound 3b)

white powder, Yield: 70%, M.P.: (184-186 0C), FT- IR (v cm-1): 1724 (thiazolidinone, C=O),1658(chalcone C=O, str), 1631 (C=N), 1585(C=C, str). (1H NMR) (400 MHz, DMSO-d6) δ: 4.21(2H, s, -CH2), 6.88-8.12(12H, complex m, Ar –H)7.51-7.93(1H, d, α – β H of chalcone) ppm.

4: (Z)-2-((4-((E)-3-(4-bromophenyl)-3-oxoprop-1-en-1-yl) phenyl) imino)-3-(4-methoxyphenyl) thiazolidin-4-one (compound 4b)

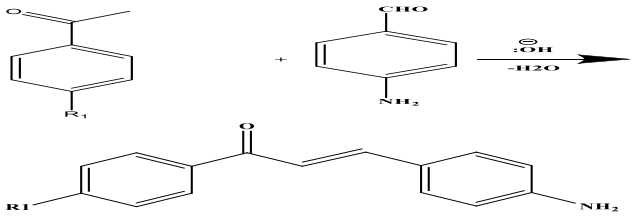
yellowish powder, Yield: 75%, M.P.: (166-169 0C), FT-IR (v cm-1): 1732 (thiazolidinone, C=O),1654(chalcone C=O, str), 1635 (C=N),1585(C=C, str). (1H-NMR) (400 MHz, DMSO-d6) δ: 3.81(3H, s, - OCH3), 4.19(2H, s, -CH2), 6.97-8.11(12H, complex m, Ar –H)7.52-7.90(1H, d, α – β H of chalcone) ppm.

5- (Z)-3-(4-bromophenyl)-2-((4-((E)-3-(4-fluorophenyl)-3-oxoprop-1-en-1-yl) phenyl) imino) thiazolidin-4-one: (compound3c)

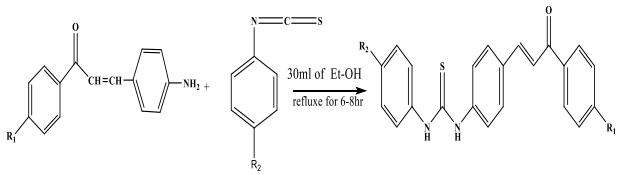
Pale white powder, Yield: 76%, M.P: (198-200 0C), FT- IR (v cm-1): 1728 (thiazolidinone, C=O),1645(chalcone C=O, str), 1627 (C=N), 1581(C=C, str). (1H- NMR) (400 MHz, DMSO-d6) δ: 4.22(2H, s, -CH2), 6.95-8.28(12H, complex m, Ar–H) 7.56- 7,94(1H, d, α – β H of chalcone) ppm.

6-:(Z)-3-(4-chlorophenyl)-2-((4-((E)-3-(4-fluorophenyl)-3-oxoprop-1-en-1-yl) phenyl) imino) thiazolidin-4-one (compound 4c)

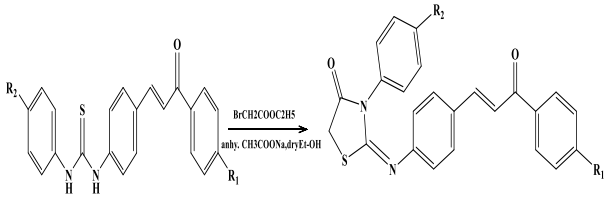
Pale yellow powder, Yield: 77%, M.P.: (194-197 0C), FT-IR (v cm-1): 1732 (thiazolidinone, C=O),1658(chalcone C=O, str), 1627 (C=N), 1581(C=C, str). (1H NMR (400 MHz, DMSO-d6) δ: 4.50(2H, s, -CH2), 7.13-8.08(12H, complex m, Ar –H) 7.65-7.90(1H, d, α – β H of chalcone) ppm.



R1-acetophenone p-aminobenzaldehyde chalcone(a-c)

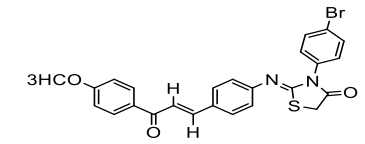


Chalcone(a-c) R2-phenylisothiocynate (1a,2a,1b,2b,1c,2c)

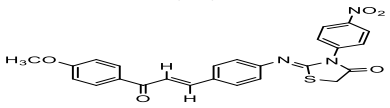


(1a,2a,1b,2b,1c,2c) Final target compound(3a,4a,3b,4b,3c,4c)

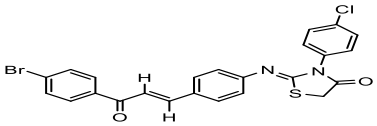
Chalcones	A	b	C
R1	OCH3	Br	F
R2	(Br,NO2)	(Cl,OCH3)	(Cl, Br)



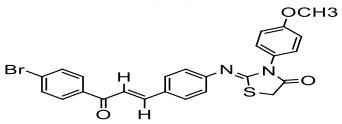
(3a)



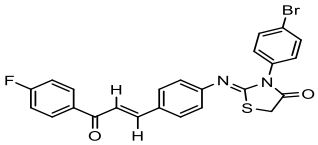
(4a)



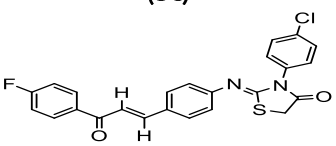
(3b)



(4b)



(3c)



(4c)

Final compounds

Scheme 1: General scheme and path away for synthesis.

4. 2. Results and Discussion

Chemistry

Currently, our research is focused on developing an easier method for the entire synthesis of various thiozoldinone analogs. Despite this, p-amino chalcones were produced and serve as important targets precursors. As a result, several of them, including the target molecule, were produced (a-c). To get a satisfactory yield of compound (a-c), equimolar quantities of p-amino benzaldehyde and various acetophenone analogues were utilized via a Claisen–Schmidt condensation reaction, which also used ethanol as a solvent and NaOH as a catalyst in producer synthesis, as illustrated in Scheme 1. After 25 minutes of heating, the starting material dissolved and was kept on stirrer for 5 hours at 0°C in an ice bath (TLC control), and the precipitate was filtered and recrystallized with ethanol to get an orange to yellow crystal with a crystalline structure. spectroscopic characterization of compounds (a-c) would be worthwhile. FT-IR, HNMR techniques, and elemental analysis were used. The most relevant spectroscopic (FT-IR) features for compounds (a-c) are the NH2 and C=O absorption bands at (3468, 3321) and 1643 cm-1, respectively. In the 1H-NMR spectrum, two doublets at 7.59 (α H) and 7.99 (β 1H) ppm, assigned to the α, β unsaturated ketone protons in trans configuration related with the new C=C bond, formed. A broad singlet at 5.89 ppm (2H) was assigned to the NH2 functional group. A new method for the synthesis of symmetrical and asymmetrical thiourea, using di and mono-analogous alkyl and aryl amines. so, the reaction proceeds through dissolved different p- amino chalcone with several phenyl-iso-thiocyanate derivatives in ethanol solvent and still reflux for 8hr and then obtained compounds (1a-2c). (Z)-2-((4-((E)-3-(4-substituted phenyl)-3-oxoprop-1-en-1-yl) phenyl) imino)-3-(4-substituted phenyl) thiazolidin-4-one derivatives(3a-4c) obtained through were synthesized by the reaction of ethyl α-bromoacetate and anhydrous sodium acetate in dry ethanol with the thiourea groups (1a-2c). by using essential analysis was decided the pureness of the synthesized products. Structures of these compounds were characterized using 1H-NMR, FT-IR spectral data. The1H-NMR spectra of compounds(1a-2c) displayed singlets at 9.08–10.09 ppm for the (NHCSNH). And signal at 4.21-4.53 ppm for compound (3a-4c) due to -S–CH2- confirms the formation of the thiazolidinone ring. The FT-IR spectra of the thiourea products (1a-2c) showed characteristic absorption bands in the thiocarbonyl frequency region at 1125–1136 cm-1 and 3321-3225 absorption band for secondary amine and 1645 – 1590 cm-1 for the (α – β conjected system of chalcone) these data is agreement with the suggested structures.

Biological activities

Our major purpose and objective in the research study were to find, synthesize, and develop effective drugs for a variety of pharmacological functions with minimal side effects. Thiazolidinone is one of the most well-known physiologically active heterocyclic agents in the literature, and as a result, it has been the focus of several research investigations.

Sensitivity assay

Well, diffusion assay was carried out by utilizing abacterial suspension of nearly (1.5×108CFU/ml) obtained from McFarland turbidity standard (number 0.5). This was applied to vaccinated by swabbing the exterior area of MHA plates. The excess liquid was dried by air under a sterile hood. In each agar plate of examined bacteria and fungi, four wells were made, and (80µl) of each concentration (1000µg) (of the synthesized compound) was poured in to. The plates were incubated at 30 °C for (24 hr). (fungi species) or 37 °C for (24 hr). (bacterial species). The evaluation of antibacterial and antifungal activity was based on the measurement of the diameter of the inhibition zone formed around the well.

Antimicrobial evaluation

The antibacterial activities of the synthesized derivatives (3a,4a,3b,4b,3c,4c) were measured using a well diffusion technique with G(+ve) and G(-ve) bacteria and compared to Ciprofloxacin and Amoxicillin. Fluconazole was used as an antifungal standard to test for the antifungal activity of the final compounds. As stated in table 1, DMSO was employed as a solvent and a control. The antibacterial activity of 4b and 3c was shown to be the most effective and broadest activity, containing both gram-positive and gram-negative bacteria, whereas 3a and 4b have moderate activity and 4a with 4c were have selectivity for gram negative bacteria and gram positive bacteria.

Table 1: In vitro antimicrobial activities of the synthesized fluorinated compounds tested at 1 mg/mL by well diffusion agar assay and expressed as inhibition zone diameter (mm).

Compound No.	Inhibition zone (IZ) in mm				
	Escherichia coli (G-ve)	Pseudomonas aeruginosa (G-ve)	Staphylococcus aureus (G+ve)	Streptococcus pyogenes (G+ve)	Candida ablicans
Amoxicillin*	20	10	23	18	-
Ciprofloxacin*	19	-	19	17	--
Fluconazole**					22
DMSO	-	-	-	-	-
3a	12	10	14	15	13
4a	-	-	18	16	-
3b	10.5	11	16	13	-
4b	10	13.5	15	18	17
3c	12	19	20	17	15
4c	14	11	-	-	5

(-)= No activity, slightly active: (Inhibition zone in between 5-10 mm), moderately

Also, compounds 3a, 4b, 3c, and 4c showed a strong-weak inhibition zone against C. Albicans, similar to fluconazole, which has a high inhibitory impact, but other target compounds exhibited no antifungal activity against C. Albicans.
active: (Inhibition zone in betwe en 10-15 mm), and highly active (Inhibition zone more
than15mm) (24, 25)

Conclusion

Synthesis of novel drugs with effective outcomes using current ingredients and is procedures the focus of this study. Their chemical structures were confirmed by using FT-IR spectroscopy and 1HNMR. As a consequence, it offered medium results in the microbiological investigation for positive bacteria are better than negative bacteria with moderate - little against fungus species.

Reference

1. Kim JY, Garcia-Carbonell R, Yamachika S, Zhao P, Dhar D, Loomba R, et al. ER stress drives lipogenesis and steatohepatitis via caspase-2 activation of S1P. Cell. 2018;175(1):133-45. e15.
2. K Sahu N, S Balbhadra S, Choudhary J, V Kohli D. Exploring pharmacological significance of chalcone scaffold: a review. Current medicinal chemistry. 2012;19(2):209-25.
3. Mohammed M, Aljamali NM, Shubber WA, Abdalrahman SA. New Azomethine-Azo heterocyclic ligands via cyclization of ester. Research Journal of Pharmacy and Technology. 2018;11(6):2555-60.
4. Page P, Orchard M, Fioraso-Cartier L, Mottironi B. Tetrahydroindole derivatives as NADPH oxidase inhibitors. Google Patents; 2012.
5. Mukhlif MK. Review on Chalcone.
6. Goyal K, Kaur R, Goyal A, Awasthi R. Chalcones: A review on synthesis and pharmacological activities. J Appl Pharmaceut Sci. 2021;11:1-14.
7. Jaiswal P, Pathak D, Bansal H, Agarwal U. Chalcone and their heterocyclic analogue: A review article. J Chem Pharm Res. 2018;10:160-73.
8. Hasan SA, Elias AN, Farhan MS. Synthesis, characterization and antimicrobial evaluation of a series of chalcone derivatives. Der Pharma Chem. 2015;7:39-42.
9. Verma A, Saraf SK. 4-Thiazolidinone–A biologically active scaffold. European journal of medicinal chemistry. 2008;43(5):897-905.
10. Omar K, Geronikaki A, Zoumpoulakis P, Camoutsis C, Soković M, Ćirić A, et al. Novel 4-thiazolidinone derivatives as potential antifungal and antibacterial drugs. Bioorganic & medicinal chemistry. 2010;18(1):426-32.
11. Havrylyuk D, Zimenkovsky B, Vasylenko O, Gzella A, Lesyk R. Synthesis of new 4-thiazolidinone-, pyrazoline-, and isatin-based conjugates with promising antitumor activity. Journal of Medicinal Chemistry. 2012;55(20):8630-41.
12. Srivastava T, Gaikwad AK, Haq W, Sinha S, Katti SB. Synthesis and biological evaluation of 4-thiazolidinone derivatives as potential antimycobacterial agents. Arkivoc. 2005;2:120-30.
13. Malhotra M. Aakash Deep, Sandeep Jain, Prabodh Chander Sharma, Priyanka Phogat &. Med Chem Res. 2012;21:1652-9.
14. Tripathi AC, Gupta SJ, Fatima GN, Sonar PK, Verma A, Saraf SK. 4-Thiazolidinones: the advances continue…. European Journal of Medicinal Chemistry. 2014;72:52-77.
15. Alsafi MHA, Farhan MS. Synthesis, Characterization and Acute Anti-inflammatory Evaluation of New Mefenamic Acid Derivatives Having 4-Thiazolidinone Nucleus. Iraqi Journal of Pharmaceutical Sciences (PISSN: 1683-3597, E-ISSN: 2521-3512). 2019;28(1):138-46.
16. Patil M, Noonikara-Poyil A, Joshi SD, Patil SA, Patil SA, Bugarin A. New urea derivatives as potential antimicrobial agents: Synthesis, biological evaluation, and molecular docking studies. Antibiotics. 2019;8(4):178.
17. Adam RW, Al-Labban HMY, Kadhim IN, Aljanaby AAJ. Synthesis, characterization, and antibacterial activity of some new pyrimidine derivatives from chalcone derivatives. Drug Invention Today. 2019;11(7):1732-9.
18. Hasan SA, Elias AN. Synthesis of new diclofenac derivatives by coupling with chalcone derivatives as possible mutual prodrugs. International Journal of Pharmacy and Pharmaceutical Sciences. 2014;6(1):239-45.
19. Sharabiyani SK, Foroughifar N, Khajeh-Amiri A. Using of some novel derivatives of thiourea for Synthesis of pharmaceutical compounds of 5-Arylidine-2-imino-4-thiazolidinones and their medicinal properties study as anti-inflammatory agents. International Journal of Advanced Engineering Research and Science.4(10):237281.
20. Küçükgüzel G, Kocatepe A, De Clercq E, Şahin F, Güllüce M. Synthesis and biological activity of 4-thiazolidinones, thiosemicarbazides derived from diflunisal hydrazide. European journal of medicinal chemistry. 2006;41(3):353-9.
21. Güzel-Akdemir Ö, Angeli A, Demir K, Supuran CT, Akdemir A. Novel thiazolidinone-containing compounds, without the well-known sulphonamide zinc-binding group acting as human carbonic anhydrase IX inhibitors. Journal of enzyme inhibition and medicinal chemistry. 2018;33(1):1299-308.
22. Küçükgüzel ŞG, Coşkun İ, Aydın S, Aktay G, Gürsoy Ş, Çevik Ö, et al. Synthesis and characterization of celecoxib derivatives as possible anti-inflammatory, analgesic, antioxidant, anticancer and anti-HCV agents. Molecules. 2013;18(3):3595-614.
23. Alheety KA, Jamel NM, Tomma JH, Alheety KA. Synthesis and biological activity of some new thiazolidinone derivatives. Sys Rev Pharm. 2020;11:490-4.
24. Tegeder I, Niederberger E, Israr E, Guhring H, Brune K, Euchenhofer C, et al. Inhibition of NF-kappaB and AP-1 activation by R-and S-flurbiprofen.

FASEB JOURNAL. 2001;15(3):595-7.
25. Koeberle A, Werz O. Natural products as inhibitors of prostaglandin E2 and pro-inflammatory 5-lipoxygenase-derived lipid mediator biosynthesis. Biotechnology advances. 2018;36(6):1709-23.