Sys Rev Pharm 2020; 11(2): 679 – 684
A multifaceted review journal in the field of pharmacy
E-ISSN 0976-2779 P-ISSN 0975-8453

Pharmaceutical and Biological Application of New Synthetic Compounds of Pyranone, Pyridine, Pyrmidine, Pyrazole and Isoxazole Incorporating on 2-Flouroquinoline Moieties

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Article History: *Submitted: 20.02.2020* *Revised: 18.03.2020* *Accepted: 02.05.2020*

ABSTRACT
Cyclization condensation between 2-Flouroquinoline-3-carbaldehyde and substituted ketone to Produced chalcone, the derivative (3) was adopted as chalcone to react with different compound such as ethyl cyanoacetate, ammonia, urea, thiourea, phenylthiosemicarbazide, and hydroxyl amine hydrochloride to produced new ring of pyranone, pyridine, pyrmidine, pyrazole and isoxazole compounds (4,5,6,7,8,9) respectively, were identified their structure by infrared spectroscopy, Nuclear magnetic and elemental analysis. Pharmaceutical applications have been studied for the prepared compound and achievement with different drugs.

Keywords: Polycyclic fluoroquinolones, pyrimidines, pyridine, pyranone, isoxazole
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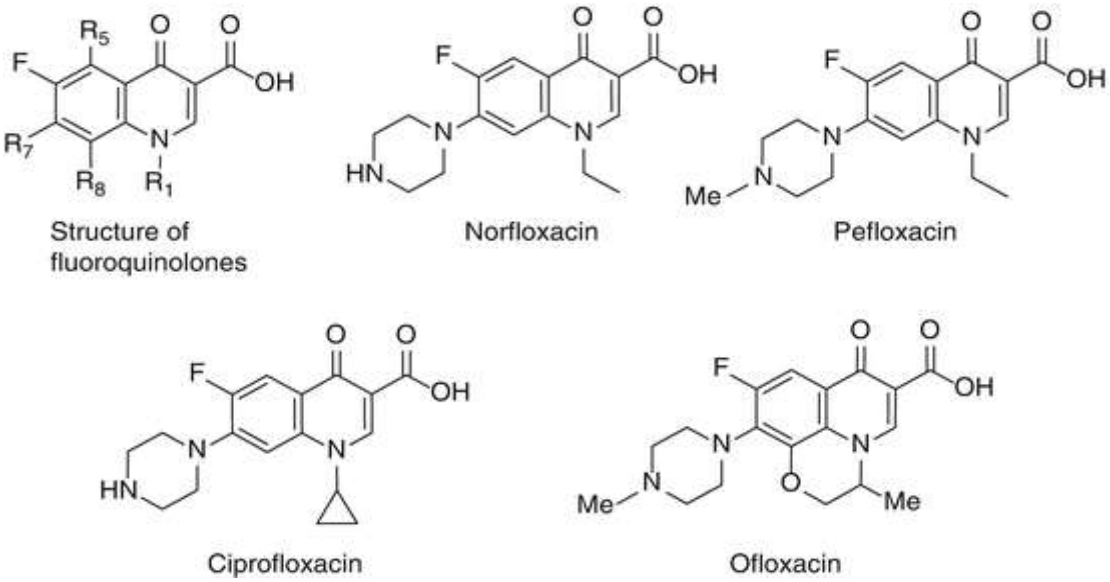
DOI: 10.5530/srp.2020.2.98

INTRODUCTION

A quinolone antibiotics a member of a large groups of broad bands spectrum bacteriocidals and fungicidal that contain a bicyclic cores in structure (Pankaj *et al*., 2013). Flouroquinoline nucleous is incopporated in varous and a large class of broad spectrum bacteriocidals that used to treatment or prevent certain bacterial diseases (Eswaran *et al*., 2009). Flouroquinoline nucleous has various biological activities, such as antituberculosis(Mahamoud *et al* ., 2006), tyro-kinase PDGFRTK inhibiting as agents , anticancer (Cortegiani *et al* ., 2020) , antimalarial (Babar *et al* ., 2013), antihypertensive (Bingul *et al*., 2016), antibiotic, antimicrobial (Aldred, 2014), anti-inflammatory, anti-HIV (Heeb, 2011). Moreover recently, in this year Hydroxychloroquine is being studied to prevent and treatment coronavirus diseases 2019 (COVID-19) In various strains (Meyerowitz *et al*., 2020; Juurlink, 2020), High quality indicaties of benefit for such used. Approximately all quinolones antibiotics that which contain a fluorine (F) atom in their chemical Formula and are effective versus bacteria and fungi (Johnson *et al*., 2007). One example from Flouroquinoline drugs ciprofloxacin, one of the most widely used in antibiotics worldwide (Sung *et al*., 2012; Rosanova *et al*., 2010). The fluoroquinolones antibiotic includes levofloxacin (Levaquin), moxifloxacin (Avelox), gemifloxacin (Factive), ofloxacin (Floxin) (Lilienkampf *et al*., 2009), and ciprofloxacin (Cipro) and for example for the drugs and its structure as the following that shown in structure in the Fig (1):



Difference literatures is indicates with progressive findings with the synthesis and pharmacological and biological activities of pyranone, pyridine, pyrmidine, pyrazole and isoxazole derivtives. Pyrazoles have been found to used

perfect as antimicrobial, antitubercular, anti-inflammatory, anti-tumor and antiviral activities.

MATERIALS AND SYNTHETIC METHODS

All materials (chemicals and solvent) that used in research from Fluke, BDH, and Sigma-Aldrich. The Synthesis of carbaldehyde and modification of starting materials according to repleacement of chlorine atom to produced 2-Flouroquinoline according the lit. (Abdel-Wahab and Khidre, (2013).

3-(2-Flouroquinolin-3--yl)-1-(2,4-dimethoxyphenyl)-2-propenone (3)

To the stirring mixture of 2-Flouroquinoline-3-carbaldehyde (870 mg, 5 mmole), 25 cm^3 Absolute C_2H_5OH and 2,4-dimethoxyphenyl acetophenone (800 mg, 5 mmole) at room temperature. Sodium hydroxide (40 %) was added drop wise and the reaction mixture was stirred for 5 hr. the reaction mixture neutralized with HCl and filtered to recrystallization the precipitate washed with C_2H_5OH to give compound (3) in 78 % m.p (146-148 °); FT-IR (in KBr): C-F (1260),C-$H_{aroma.}$ (3055 cm^{-1}), carbonyl conjugated (1634) $^1HNMR_{DMSO-d6}$ (400 MHz) (3.66 δ, s, 6H) $2OCH_3$; (7.11-7.23 δ, m, Aromatic-H), (8.23-8.45 δ, 5H, Quinoline protons), (7.55-7.98 δ, d, 1H, J= 11.90 H_z for protons of α, β-unsaturatedketone) Analytical calculation for compound (3) $C_{20}H_{16}NO_3F$ calculated. C (74.43), H (4.76), N (4.17); finding, C (74.45), H (4.66), N (4.56)

4-(2-Flouroquinolin-3-yl)-6-(2,4-dimethoxyphenyl)-2-oxo-pyran-2H-3-carbonitrile (4)

Compound (3) (500 mg, 1.5 mmole) was dissolved in absolute C_2H_5OH (25 cm^3), ethyl cyanoacetate (151 mg, 1.5 mmole) in ethanol, and (C_2H_5ONa / C_2H_5OH solution) that prepared currently was added to the mixture was refluxed overnight. The resulting sold product was cooled, filtered, and recrystallized to give (4) as solid crystal in 73% m.p (123-125°); FT-IR (in KBr): O-C=O (1695 cyclic ester), C-$H_{aromatic}$ (3030 cm^{-1}), cyanide (2210 cm^{-1}), $^1HNMR_{DMSO-d6}$ (400 MHz) (3.74 δ, s, 6H) $2OCH_3$; (7.13-7.28 δ, m, Aromatic-H), (8.45-8.78 δ, 5H, Quinolineprotons). Analytical calculation for compound (4) MF=$C_{23}H_{15}N_2O_4F$, calculated. C 68.83, H 3.74, N 6.98; finding, C 68.39, H 3.65, N 6.22

1,2-Dihydro-4-(2-Flouroquinolin-3-yl)-6-(2,4-dimethoxyphenyl)-2-oxo-pyridine-3-carbonitrile (5)

Compound (4) (800 mg, 2 mmole) in absolute C_2H_5OH (25 cm^3) , dry NH_3 was used . The solution was refluxed for 10 hr, The resulting sold collected and cooled, then filtration, and recrystallization in C_2H_5OH to give compound (5) as solid crystal in 70% m.p (153--154°) ;FT-IR (in KBr): N-H (3223 cm^{-1}) C-F (1395),C-$H_{aromatic}$ (3035), N-Carbonyl (1688 cm^{-1}) cyanide (2257 cm^{-1}), $^1HNMR_{DMSO-d6}$ (400 MHz) (3.55 δ , s,6H) $2OCH_3$; (7.32-7.35 δ, m , Aromatic-H) , (8.11-8.23 δ, 5H , Quinolineprotons).

Analytical calculation for compound (5) MF= $C_{23}H_{16}N_3O_3F$ calculated. C 69.00, H 4.00, N 12.00; finding, C 68.82, H 4.33, N 12.36

1-(4,5-dihydro-5-(2-Flouroquinolin-3--yl)-3-(2,4-dimethoxyphenyl pyrimidin-2(1H)-one) (6)

Compound (3) (500 mg , 1.5 mmole) was added to (C_2H_5ONa / C_2H_5OH solution) that prepared from Na Metal (36 mg , 1.5 mmole)in absolute C_2H_5OH (25 cm^3) and then added urea (90 mg , 1.5 mmole) . The solution mixture was refluxed for 24 hr. The resulting sold collected, cooled, and recrystallization after filtration with DMF/ C_2H_5OH and cooled, then filtration, and recrystallization in C_2H_5OH to give compound (5) as solid crystal in 70% to give (6) as solid crystal in 73% m.p (184-185°); FT-IR (in KBr) : N-H (3250 cm^{-1}) , C-F (1366),C-$H_{aromatic}$ (3031) , HN-carbonyl (1685 cm^{-1}) imine (1620 cm^{-1}), $^1HNMR_{DMSO-d6}$ (400 MHz) (3.54 δ , s,6H) $2OCH_3$; (7.34-7.37 δ, m , Aromatic-H) , (8.17-8.22 δ, 5H , Quinolineprotons).Analytical calculation for compound (6) MF= $C_{21}H_{16}N_3O_3F$ calculated C 67.02, H 4.26, N 11.17; finding, C 67.25, H 4.45, N 11.47

1-(4,5-dihydro-5-(2-Flouroquinolin-3--yl)-3--(2,4-dimethoxyphenyl)pyrazol-1-ylpyrimidine-2(1H)-thione) (7)

Compound (3) (500 mg , 1.5 mmole) was added to (C_2H_5ONa / C_2H_5OH solution) that prepared from Na Metal (36 mg , 1.5 mmole) in absolute C_2H_5OH (25 cm^3) and then added thiourea (114 mg , 1.5 mmole) . The solution mixture was refluxed for 24 hr. The resulting sold product was cooled, filtered, and recrystallized with C_2H_5OH/DMF to give (6) as solid crystal in 73% m.p (178-179°)

FT-IR (in KBr) : N-$H_{aromatic}$ (3265 cm^{-1}) florine (1345 cm^{-1}),C- $H_{aromatic}$(3038 cm^{-1}) , HN-C=S (1385) imine(1622), $^1HNMR_{DMSO-d6}$ (400 MHz) (3.57 δ , s,6H) $2OCH_3$; (7.30-7.36 δ, m , Aromatic-H) , (8.13-8.24 δ, 5H , Quinolineprotons).Analytical calculation for compound (7) MF= $C_{21}H_{16}N_3O_2SF$ calculated C 64.29, H 4.08, N 10.71; finding, C 64.98, H 3.93, N 10.88

4,5-dihydro-5-(2-Flouroquinolin-3--yl)-3--(2,4-dimethoxyphenyl)pyrazole-1-phenylthioamide (8)

(200 mg, 5 mmole) from NaOH and (330 mg from 2 mmole) phenyl thiosemicarbazide added to Compound (3) (500 mg, 1.5 mmole) in absolute C_2H_5OH (25 cm^3) . The solution mixture was refluxed for overnight . The resulting sold product was cooled, filtered, and recrystallized with C_2H_5OH to give (8) as colure crystal in 70% m.p (204-205°) FT-IR (in KBr) : N-H (3360 cm^{-1}) florine (1343 cm^{-1}),C-$H_{aromatic}$ (3041 cm^{-1}) , N-C=S (1392 cm^{-1}) C=N(1642 cm^{-1}), $^1HNMR_{DMSO-d6}$ (400 MHz) (3.64 δ , s,6H) $2OCH_3$; (7.16-7.28 δ, m , phenyl protons) , (7.31-7.33 δ, m , pyrazole protons), (8.45-8.67 δ, 5H , Quinolineprotons).Analytical calculation for compound (8) MF= $C_{27}H_{23}N_4O_2SF$ calculated, C 65.72, H 4.67, N 12.98; finding, C 65.44, H 4.64, N 12.22

3-(4,5-dihydro-3-(2,4-dimethoxyphenyl)isoxazol-5-yl)- 2-Flouroquinoline (9)

(105 mg , 1.5 mmole) from $NH_2OH.HCl$ and (210 mg from 1.5 mmole) K_2CO_3 that anhydrous added to Compound (3) (500 mg , 1.5 mmole) in absolute C_2H_5OH (25 cm^3) . The solution mixture was refluxed for over night . The resulting sold product was cooled in water, filtered, and

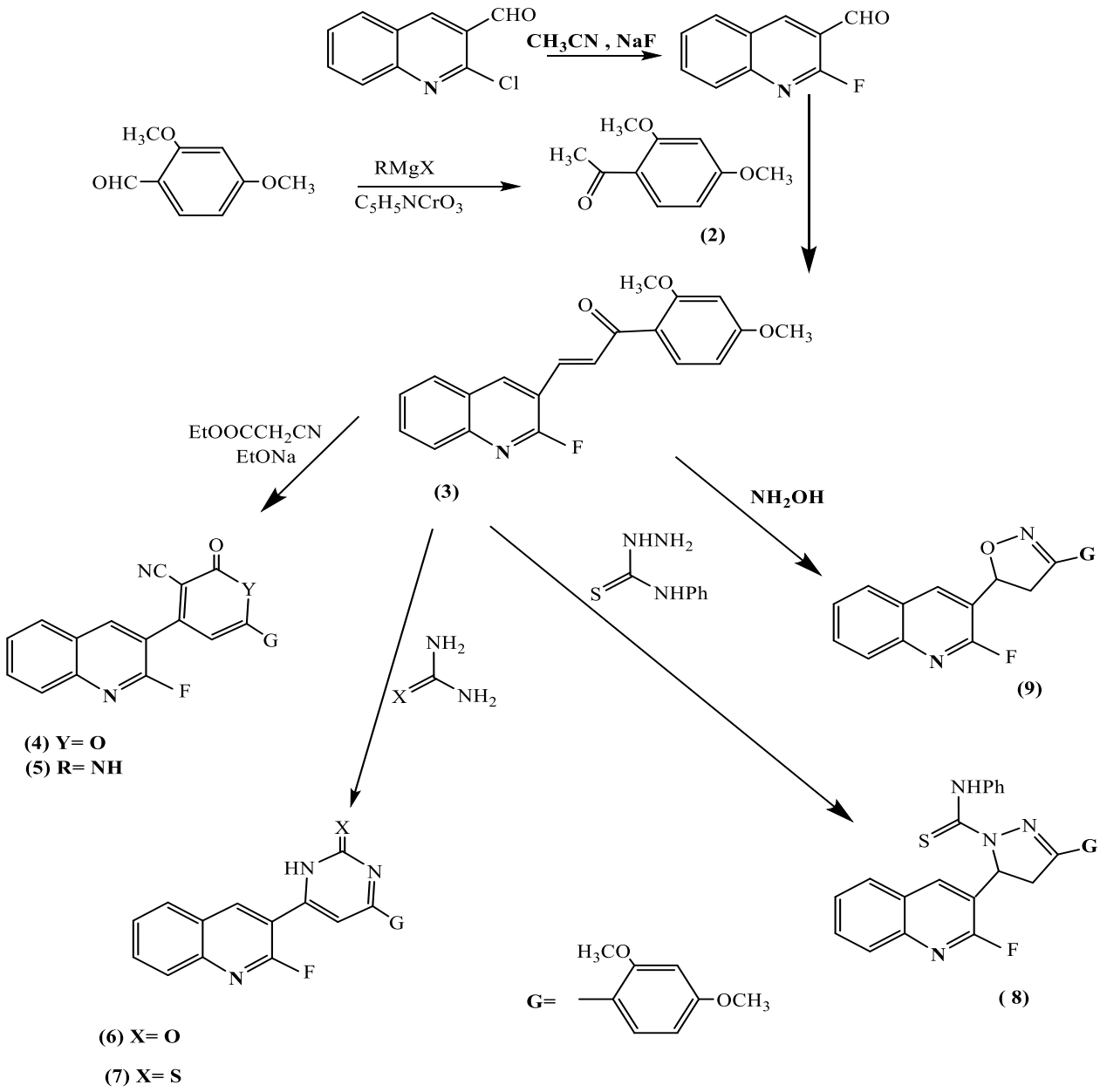
recrystallized with C_2H_5OH to give (9) as sold crystal in 73% m.p (137-138°)

FT-IR (in KBr) : $C_{aromatic}$-F (1348),C- $H_{aromatic}$(3048 cm^{-1}) , imine (1649 cm^{-1}), $^1HNMR_{DMSO\text{-}d6}$ (400 MHz) (3.67 δ , s,6H) $2OCH_3$; (7.15-7.46 δ, m , Aromatic-H) , (8.33-8.52 δ, 5H , Quinolineprotons).Analytical calculation for compound (9) MF= $C_{20}H_{23}N_4O_2SF$ calculated. C 68.61, H 4.57, N 13.71; finding, C 68.48, H 4.43, N 13.58

RESULTS AND DISCUSSION

Cyclization of 3-(2-Flouroquinolin-3--yl)-1-(2,4-dimethoxyphenyl)-2-propenone (3) as chalcone with ethylcyanoacetate in solution sodium ethoxide to produced pyranone compound (4) under refluxed for 12 hr (scheme 1) .The spectro data that identify its structure (Pavia *et al* ., 2009) ; FT-IR (in KBr) : conjugated cyclicO-C=O (1695 cm^{-1}) , $C_{armatic}$-F (1365 cm^{-1}) ,C-$H_{aromatic}$ (3030 cm^{-1}) , weak band of C≡N(2210 cm^{-1}), $^1HNMR_{DMSO\text{-}d6}$ (3.74 δ , s,6H) refer to methoxy $2OCH_3$; (7.13-7.28 δ, m , Aromatic-H) , (8.45-8.78 δ, 5H , as signals of Quinolineprotons. Pyranone compound (4) led to produced corresponding's pyridinone (5) by condensation with NH_3 The spectro data that identify its structure FT-IR (in KBr) : N-H (3223 cm^{-1}) refer the replacement of ammonia ,C-$H_{aromatic}$ (3035 cm^{-1}) , conjugated N-carbonyl (1688 cm^{-1}) weak band of cyanide(2257 cm^{-1}), $^1HNMR_{DMSO\text{-}d6}$ (3.55 δ , s,6H) $2OCH_3$; (7.32-7.35 δ, m , Aromatic-H) , (8.11-8.23 δ, 5H , as signals of Quinolineprotons). ; . Reaction of compound (3) with urea or use thiourea in the presence of C_2H_5ONa / C_2H_5OH to produced the pyrimidine derivative (6,7) respectively for compound (6) The spectro data that identify its structure. FT-IR (in KBr) : N-$H_{aromatic}$ (3250) , $HN_{pyrimidine}$-Carbonyl (1685) imineC=N(1620 cm^{-1}), $^1HNMR_{DMSO\text{-}d6}$ (3.54 δ , s,6H) $2OCH_3$; (7.34-7.37 δ, m , Aromatic-H) , (8.17-8.22 δ, 5H , Quinolineprotons).and for compound (7) spectro data of spectro data IR (in KBr) : HN-C=S (1385 cm^{-1}) C=N_{cyclic}(1622 cm^{-1}),N-$H_{aromatic}$ (3265 cm^{-1}), $^1HNMR_{DMSO\text{-}d6}$ (3.57 δ , s,6H) $2OCH_3$; (7.30-7.36 δ, m , Aromatic-H) , Reaction of compound (3) with phenylthiosemicarbazide and sodium hydroxide in C_2H_5OH to produced pyrazole (8) spectro data of spectro data of compound (8) FT-IR (in KBr):N-$H_{aromatic}$ (3360 cm^{-1}) N-C=S (1392 cm^{-1}) C=N(1642 cm^{-1}), $^1HNMR_{DMSO\text{-}d6}$ (3.64 δ , s,6H) $2OCH_3$; (7.16-7.28 δ, m , phenyl protons) , (7.31-7.33 δ, m , pyrazole protons), (8.45-8.67 δ, 5H , Quinolineprotons).

Refluxing compound (3) with $NH_2OH.HCl$ in C_2H_5OH to produced Oxazoline (9) spectro data of spectro data of compound (9) FT-IR (in KBr) : $C_{aromatic}$-F (1348 cm^{-1}),C-$H_{aromatic}$ (3048 cm^{-1}) , C=$N_{oxazo.}$(1649 cm^{-1}), $^1HNMR_{DMSO\text{-}d6}$ (400 MHz) (3.67 δ , s,6H) $2OCH_3$; (7.15-7.46 δ, m , Aromatic-H) , (8.33-8.52 δ, 5H , Quinolineprotons).



Scheme 1: Show preparation the Heterocyclic compounds (4-9)

Antibacterial and Antifungals activity

Five and six membered heterocyclic compounds show different various of bactericidal activity (Rouveix , 2006) a fungicidal activity among them 2-Flouroquinoline Moieties which are associated with same condition's diverse of biological activity such as antimicrobial (Basu *et al* ., 2011; Mann *et al* ., 2007) .In the present work, six newly synthetic heterocyclic compounds were tested against bacteria (-ve) *Shigella , Escherichia coli , Enterobacter and Streptococcus , Bacillus , and Clostridium* as (+ve) for concentration (10,20,30) µg/cm^3 as shown in Table (A) and also fungi *Aspergillus flavus* and *Penicillium* at the same concentrations as in Table (B)

Table A: Pharmaceutical activity of new synthesis compounds

Comp. No.	Conc. g/ml µ	Gram negative bacteria			Gram positive bacteria		
		E.coli	*Enterobacter*	*Shigella*	*Streptococcus*	*Bacillus*	*Clostridium*
4	30	12	6	9	-	-	4
	20	10	9	8	11	7	13
	10	-	3	5	1	2	4
5	30	6	16	-	-	-	11
	20	3	9	7	5	3	9

	10	-	-	-	-	-	-
6	30	9	7	10	13	8	9
	20	8	5	4	9	7	3
	10	2	4	2	6	5	-
7	30	11	8	14	9	15	5
	20	7	9	4	5	6	10
	10	-	3	6	2	-	7
8	30	12	9	10	13	9	15
	20	11	8	7	10	8	9
	10	1	3	-	-	-	5
9	30	15	10	14	9	12	10
	20	10	9	12	8	11	13
	10	-	3	-	2	-	-
Ciprofloxacin		10	5	10	9	10	12

Table B: Antifungal activity of new synthesized compounds

Comp. No.	Conc. g/ml**µ**	*Aspergillus flavus*	*Penicillium*
4	30	9	11
	20	8	10
	10	-	1
5	30	10	7
	20	5	4
	10	2	-
6	30	10	12
	20	7	9
	10	5	3
7	30	13	7
	20	9	10
	10	6	-
8	30	15	8
	20	12	9
	-	-	5
9	30	13	9
	20	-	6
	10	-	-
Clotrimazole		10	8

CONCLUSION

New synthesized compounds was testing on Gram negative and positive bacteria, as well as fungi, in this study conclude that these compounds are effective and can be developed in the future as a treatment for such microbes as they were compared with Ciprofloxacin and Clotrimazole that used to treat these microorganisms and the percentage of the prepared compounds was higher as an effective treatment.

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