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Synthesis of some new antimicrobial 5,6,7,8-tetrahydropyrimido[4,5-*b*]quinolone derivatives

Maher A. El-Hashash[a], Sherif M. Sherif[b], Azza A. E. Badawy[a] and Huda R. M. Rashdan[c*]

[a]*Department of Chemistry, Faculty of Science, Ain-Shams University, Cairo, Egypt*
[b]*Department of Chemistry, Faculty of Science, Cairo University, Giza, Egypt (Dean of Faculty of Science, Cairo University)*
[c]*Department of Chemistry of Natural and Microbial Products, Pharmaceutical and Drug Industries Research Division, National Research Center, Giza, Egypt*

ABSTRACT

*2-Amino-1-aryl-1,4,5,6,7,8-hexahydro-4-phenylquinoline-3-carbonitrile derivatives were synthesized by the reaction of cyclohexanone (**1**) with 2-benzylidinemalononitrile (**2**) and the appropriate of aniline derivatives. The reactivity of some of these newly synthesized derivatives toward carbon disulfide and further toward hydrazonoyl halides were also studied. In addition, the antimicrobial activity of the newly synthesized derivatives was reported.*

Keywords: Tetrahydroquinoline, Pyrimidoquinolines, Hydrazonoyl halides, Antimicrobial activity.

INTRODUCTION

The biological and pharmaceutical importance of pyrimidoquinoline derivatives [1-12] stimulated the recent interest in synthesis of these ring systems. These biological importance include antimalarial [13], anticancer[14], antimicrobial[15,16] and anti-inflammatory activities[17,18]. Recently, there has also been considerable interest in the synthesis of tetrahydroquinolinesand their fused derivatives [19-23]. The aim of the work presented herein was to synthesize pyrimido[4,5-*b*]quinolones using tetrahydroquinolinecarbonitriles as building blocks. Such a synthesis of condensed azines is of biological interest due to the isoelectronic releationship that exists between the pyrimidine ring and tetrahydroquinoline [24-35].

MATERIALS AND METHODS

1.1. Experimental Instrumentation

All melting points were determined on an electrothermal apparatus and are uncorrected. IR spectra were recorded (KBr discs) on shimadzu FT-IR 8201 PC spectrophotometer. H^1NMR and spectra was recorded in $CDCl_3$ and $(CD_3)_2SO$ solutions on a Varian Gemini 300 MHz FT-NMR system spectrometer and chemical shifts are expected in δ ppm units using TMS as an initial reference. Mass spectra were recorded on GC-MS QP1000 EX Shimadzu. Elemental analyses were carried out at the Microanalytical Center of Cairo University.Hydrazonoylhalides [43,44] were prepared as previously reported.

1.2. Synthesis

1.2.1. 2-amino-1-(2,6-dichlorophenyl)-1,4,5,6,7,8-hexahydro-4-phenylquinoline-3-carbonitrile (3).

A mixture of cyclohexanone (**1**) (1ml, 10 mmol), 2-benzylidinemalononitrile (**2**)(1,5gm, 10 mmol) and 2,6-dichloroaniline (1.6gm, 10 mmol) in absolute ethanol(20 ml) was heated under reflux for 10-12 hrs. Then the reaction mixture left to cool to room temperature overnight. The solid obtained was recrystallized from ethanol to

afford the corresponding compound **3** in a good yield. **Yield:** 84%; **MP:** 230-232°C; **FT-IR:** 3419, 3340(NH_2), 2933,2864(CH-aliphatic), 2210(CN), 1647(C=C); **H^1NMR(300MHz, DMSO-*d6*)**: 1.64-2.77(m, 8H, $4CH_2$), 4.5(s,1H, CH), 5.7(s, 2H, NH_2), 7.1-7.4(m, 8H, Ar-H); **C^{13}NMR(300MHz, DMSO-*d6*)**: **δ** =21.9, 24.2, 24.9, 26.9, 44.2, 57.6, 111.1, 117.3, 121.6, 125.8, 126.6, 126.8, 127.8, 127.9, 128.7, 128.8, 129.1,129.2, 140.7, 142.5, 147.2, 167.5; **MS(El, m/z(%)):** 397(M+2, 97%),396(M+1, 15%), 395(M^+, 100%); **Anal. Calcd.for$C_{22}H_{19}Cl_2N_3$ (395):** C,66.67; H,4.83; N,10.60**Found:** C,66.68; H,4.83; N,10.61%.

1.2.2. 2-amino-1-(4-bromophenyl)-1,4,5,6,7,8-hexahydro-4-phenylquinoline-3-carbonitrile (4).

A mixture of cyclohexanone (**1**) (1ml, 10 mmol), 2-benzylidinemalononitrile (**2**) (1,5gm, 10 mmol) and 4-bromoaniline (1.7gm, 10 mmol) in absolute ethanol(20 ml) was heated under reflux for 10-12 hrs. Then the reaction mixture left to cool to room temperature overnight. The solid obtained was recrystallized from ethanol to afford the corresponding compound **4** in a good yield. **Yield:** 81%; **MP:**275-277°C; **FT-IR:** 3417,3339(NH_2), 2932,2864(CH-aliphatic), 2209(CN), 1647(C=C); **H^1NMR(300MHz, DMSO-*d6*): δ**=1.45-2.8(m, 8H, $4CH_2$), 4.5(s, 1H, CH), 5.74(s, 2H, NH_2), 7.3-7.5(m, 9H, Ar-H)**; MS(El, m/z(%)):** 407(M+2, 92%), 406 (M+1, 4%), 405 (M^+, 100%); **Anal. Calcd.for$C_{22}H_{20}BrN_3$(405):** C, 65.03 ; H, 4.96; N,10.34**Found:** C,65.01; H,4.95; N,10.34%.

1.2.3. 2-amino-1-(3-bromophenyl)-1,4,5,6,7,8-hexahydro-4-phenylquinoline-3-carbonitrile(5).

A mixture of cyclohexanone (**1**) (1ml, 10 mmol), 2-benzylidinemalononitrile (**2**) (1,5gm, 10 mmol) and 3-bromoaniline (1.7gm, 10 mmol) in absolute ethanol (20 ml) was heated under reflux for 10-12 hrs. Then the reaction mixture left to cool to room temperature overnight. The solid obtained was recrystallized from ethanol to afford the corresponding compound **5** in a good yield. **Yield:** 78%; **MP:**286-288°C ; **FT-IR:** 3418, 3339(NH_2), 2931, 2864(CH-aliphatic), 2212(CN), 1647(C=N); **H^1NMR(300MHz, DMSO-*d6*): δ**=1.45-2.8(m, 8H, $4CH_2$), 4.5(s, 1H, CH), 5.72(s, 2H, NH_2), 7.3-7.54(m, 9H, Ar-H)**; MS(El, m/z(%)):** 407(M+2, 32%), 406(M+1, 45%), 405(M^+, 34%); **Anal. Calcd.$C_{22}H_{20}BrN_3$(405):** C, 65.03; H, 4.96 ; N, 10.34**Found:** C, 65.00; H, 4.91; N, 10.32%.

1.2.4. 10-(2,6-dichlorophenyl)-6,7,8,9-tetrahydro-5-phenylpyrimido[4,5-b]quinoline-2,4(1H,3H,5H,10H)-dithione (8).

To a solution of **3**(2 gm, 5 mmol) in dry pyridine (30 ml) carbon disulfide (5mmol) was added and the reaction mixture was refluxed on water bath for 6 hrs. then left to cool to room temperature, poured onto ice-cold water and neutralized with diluted hydrochloric acid to complete precipitation. The solid obtained was filtered off, washed, dried well and recrystallized from methanol to give **8** as orange crystals.**Yield:** 78%; **MP:**207-209°C ; **FT-IR:** 3300(NH), 2931, 2864(CH-aliphatic); **H^1NMR(300MHz, DMSO-*d6*): δ=** 1.45-2.8(m, 8H, $4CH_2$), 4.5(s, 1H, CH), 7.32-7.54(m, 8H, Ar-H), 11.0(s, 2H, NH)**;C^{13}NMR(300MHz, DMSO-*d6*): δ=** 21.9, 24.2, 26.6, 26.9, 38, 90.7, 111.1, 121.6,124.2, 125.8, 126.6, 126.7 127.8, 127.9, 128.8, 128.8,129.1, 129.2, 140.7, 147.5, 160.3, 173, 195; **MS(El, m/z(%)):** 473(M+2, 98%), 472(M+1, 21%), 471(M^+, 100%); **Anal. Calcd.$C_{23}H_{19}Cl_2N_3S$(471):** C, 58.47; H, 4.05; N, 8.89**Found:** C, 58.46; H, 4.03; N, 8.88%.

1.2.5. *General Method for synthesis of 9a-c, 10, 11a and 11b.*

A mixture of **8**(4.7 gm, 10 mmol)and the appropriate of hydrazonoylhalides (10 mmol) was boiled under reflux in chloroform (30 ml) containing catalytic amount of triethyl amine(10 drops) for 12-15 hrs. the reaction mixture was left overnight for cooling, the solid collected and recrystallized from the proper solvent to give the corresponding**9a-c**, **10**, **11a** and **11b** respectively.

1.2.5.1. Ethyl(6,10-diphenyl-1-(2,6-dichlorophenyl)-7-thio-1,2,3,4,5,6-hexahydro-1,7a,9,10,11-pentaazacyclopenta[a]anthracene)acetate(9a).

Yellow crystals from ethanol.**Yield:** 72%; **MP:**194-196°C ; **FT-IR:** 1735(C=O), 2937, 2868(CH-aliphatic); **H^1NMR(300MHz, DMSO-*d6*): δ**=1.22-2.89(m, 11H, $4CH_2$, 3H-CH_2**CH_3**), 4.3-4.35(q, 2H, **CH_2**CH_3), 4.7(s, 1H, CH), 7.30-7.54(m, 13H, Ar-H)**; MS(El, m/z(%)):** 629(M+2, 73%), 628(M+1, 34%), 627(M^+, 70%); **Anal. Calcd.$C_{33}H_{27}Cl_2N_5O_2S$(627):** C, 63.06; H, 4.33; N, 11.14 **Found:** C, 63.06; H, 4.33; N, 11.12%.

1.2.5.2. Ethyl(6-phenyl-10-(p-chlorophenyl)-1-(2,6-dichlorophenyl)-7-thio-1,2,3,4,5,6-hexahydro-1,7a,9,10,11-pentaazacyclopenta[a]anthracene)acetate(9b).

Yellow crystals from ethanol.**Yield:** 74%; **MP:** 187-189°C ; **FT-IR:** 1739(C=O), 2939, 2878(CH-aliphatic); **H^1NMR(300MHz, DMSO-*d6*): δ**=1.20-2.87(m, 11H, $4CH_2$, 3H-CH_2**CH_3**), 4.31-4.35(q, 2H, **CH_2**CH_3), 4.7(s, 1H, CH), 7.33-7.52(m, 12H, Ar-H)**; MS (El, m/z(%)):** 665(M+2, 3%), 664(M+1, 70%), 663(M^+, 4%); **Anal. Calcd. $C_{33}H_{26}Cl_3N_5O_2S$(663):** C, 59.78; H, 3.95; N, 10.56**Found:** C, 59.78; H, 3.95; N, 10.56%.

1.2.5.3. Ethyl(6-phenyl-10-(p-methylphenyl)-1-(2,6-dichlorophenyl)-7-thio-1,2,3,4,5,6-hexahydro-1,7a,9,10,11-pentaazacyclopenta[a]anthracene)acetate(9c).
Yellow crystals from ethanol.**Yield:** 71%; **MP:** 190-192°C ; **FT-IR:** 1737(C=O), 2939, 2878(CH-aliphatic); **H^{1}NMR(300MHz, DMSO-*d6*): δ=**1.20-2.87(m, 14H, 4CH_2, 3H-CH_3, 3H-CH_2**CH_3**), 4.31-4.35(q, 2H, **CH_2**CH_3), 4.7(s, 1H, CH), 7.33-7.54(m, 12H, Ar-H)**; MS (El, m/z(%)):** 643(M+2, 81%), 642(M+1, 27%), 641(M^+, 80%); **Anal. Calcd. $C_{34}H_{29}Cl_2N_5O_2S$(641):** C, 63.55; H, 4.55; N, 10.90**Found:** C, 63.53; H, 4.55; N, 10.89%.

1.2.5.4. 6,10-diphenyl-8-benzoyl-1-(2,6-dichlorophenyl)-7-thio-1,2,3,4,5,6-hexaahydro-1,7a,9,10,11-pentaazacyclopenta[a]anthracene(10).
Pale yellow crystals from ethanol.**Yield:** 79%; **MP:** 150-152°C ; **FT-IR:** 1680(C=O), 2936, 2871(CH-aliphatic); **H^{1}NMR(300MHz, DMSO-*d6*):δ=**1.40-2.81(m, 8H, 4CH_2), 4.67(s, 1H, CH), 7.13-7.59(m, 18H, Ar-H)**; MS (El, m/z(%)):** 661(M+2, 14%), 660(M+1, 27%), 659(M^+, 13%); **Anal. Calcd. $C_{37}H_{27}Cl_2N_5OS$(659):** C, 67.27; H, 4.12; N, 10.60 **Found:** C, 67.27; H, 4.12; N, 10.61%.

1.2.5.5. ***6,10-diphenyl-8-acetyl-1-(2,6-dichlorophenyl)-7-thio-1,2,3,4,5,6-hexaahydro-1,7a,9,10,11-pentaazacyclopenta[a]anthracene(11a).***
Yellow crystals from ethanol.**Yield:** 73%; **MP:** 163-165°C ; **FT-IR:** 1690(C=O), 2935, 2879(CH-aliphatic); **H^{1}NMR(300MHz, DMSO-*d6*): δ=**1.43-2.89(m, 11H, 4CH_2, 3H-CH_3), 4.7(s, 1H, CH), 7.33-7.54(m, 13H, Ar-H)**; MS (El, m/z(%)):** 600(M+2, 9%), 599(M+1, 12%), 598(M^+, 11%); **Anal. Calcd. $C_{32}H_{25}Cl_2N_5OS$(598):** C, 64.21; H, 4.21; N, 11.70**Found:** C, 64.21; H, 4.22; N, 11.68%.

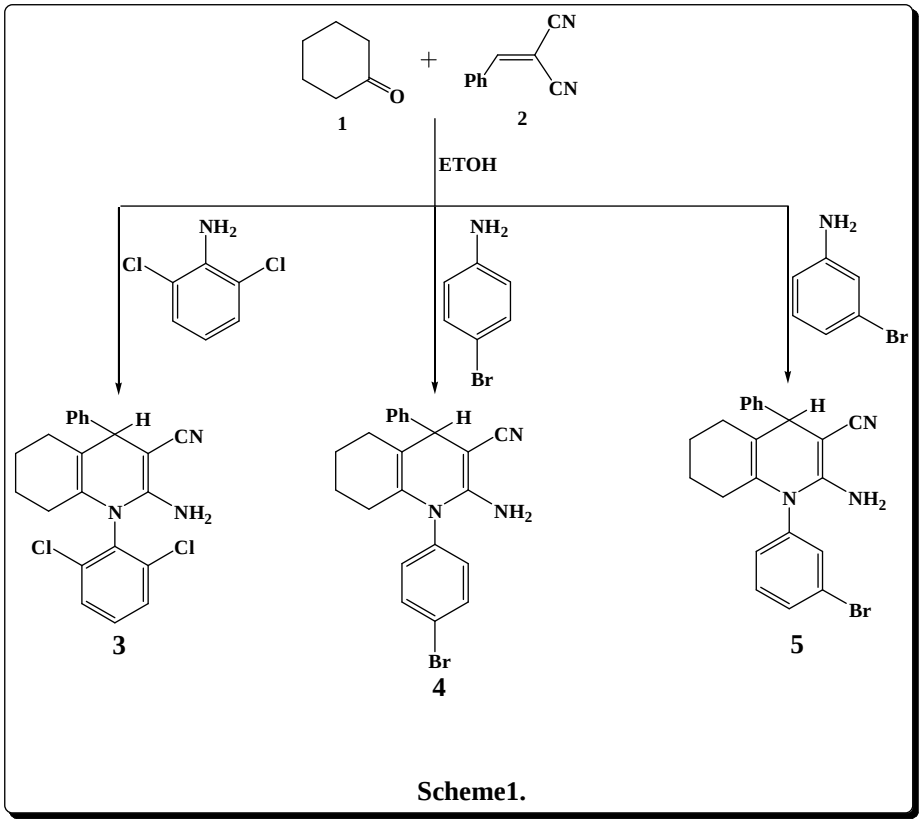
1.2.5.6. ***6-phenyl-10-(p-chlorophenyl)-8-acetl-1-(2,6-dichlorophenyl)-7-thio-1,2,3,4,5,6-hexahydro-1,7a,9,10,11-pentaazacyclopenta[a]anthracene(11b).***
Yellow crystals from ethanol.**Yield:** 75%; **MP:**171-173°C ; **FT-IR:** 1689(C=O), 2935, 2883(CH-aliphatic); **H^{1}NMR(300MHz, DMSO-*d6*): δ=**1.42-2.88(m, 11H, 4CH_2, 3H-CH_3), 4.7(s, 1H, CH), 7.33-7.54(m, 12H, Ar-H)**; MS (El, m/z(%)):** 633(M+2, 75%), 632(M+1, 6%), 631(M^+, 80%); **Anal. Calcd. $C_{32}H_{24}Cl_3N_5OS$(631):** C,60.72; H,3.82; N,11.06**Found:** C,60.71; H, 3.81; N,11.04%.

RESULTS AND DISCUSSION

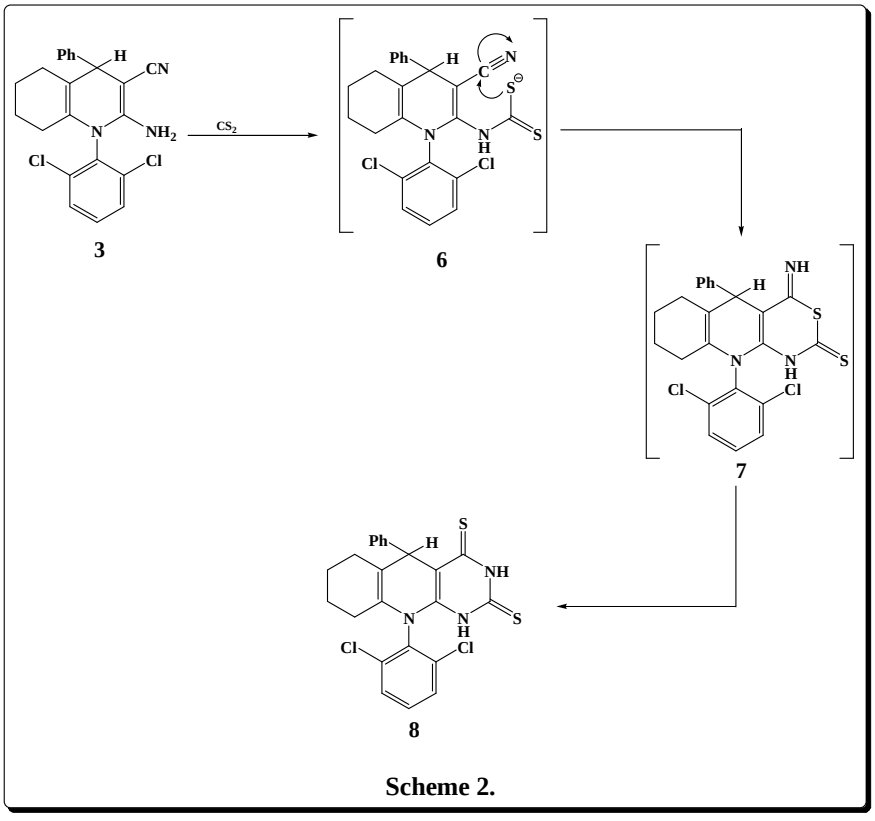
The reaction of cyclohexanone (**1**) with 2-benzylidinemalononitrile (**2**) and the appropriate of 2,6-dichloro aniline, *p*-chloroaniline or 3-chloroaniline in absolute ethanol afforded 2-amino-1-(2,6-dichlorophenyl)-1,4,5,6,7,8-hexahydro-4-phenylquinoline-3-carbonitrile (**3**),2-amino-1-(4-bromophenyl)-1,4,5,6,7,8-hexahydro-4-phenylquinoline-3-carbonitrile(**4**) and 2-amino-1-(3-bromophenyl)-1,4,5,6,7,8-hexahydro-4-phenylquinoline-3-carbonitrile(**5**), respectively the structures of the newly synthesized compounds **3**, **4** and **5** were illustrated by spectral data (IR, H^{1}NMR and Mass) and elemental analysis (Scheme 1).

Compound **3** reacted with carbon disulfide to yield the target ring system **8** through the intermediates **6** and **7**, whose subsequent rearrangement leads to the fused pyrimidinedithione**8**(Scheme 2).

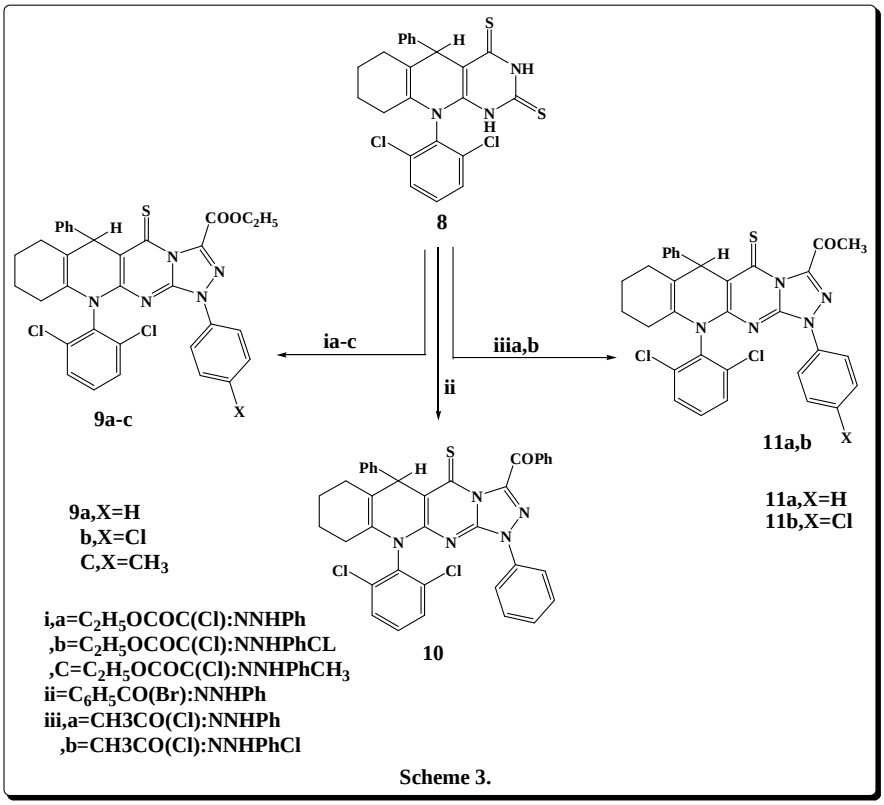
Compound **8** reacted with the appropriate of hydrazonoyl halides in chloroform in the presence of catalytic amount of triethyl amine under reflux to give the corresponding derivatives **9a-c**, **10** and **11a**,**b**the structure of these compounds confirmed by elemental analysis, spectral data (IR, H^{1}NMR, Mass) where, compound **9a**showed IRsignals at1735(C=O), 2937, 2868(CH-aliphatic) and showed H^{1}NMR signals at 1.22-2.89(m, 11H, 4CH_2, 3H-CH_2**CH_3**), 4.3-4.35(q, 2H, **CH_2**CH_3), 4.7(s, 1H, CH), 7.30-7.54(m, 13H, Ar-H). Also, compound 10 showed IR signals at 1680(C=O), 2936, 2871(CH-aliphatic)and H^{1}NMR signals at1.40-2.81(m, 8H, 4CH_2), 4.67(s, 1H, CH), 7.13-7.59(m, 18H, Ar-H)(Scheme 3).



Scheme1.



Scheme 2.



Scheme 3.

2. Biological Activity

Screening of antimicrobial activity was performed at a Microbiology Lab in Faculty of Agriculture, El-Azhar University, Cairo, Egypt. All the tested microorganisms were chosen on bases of their pathogenicity. Where,***Aspergillus*** caused a broad spectrum of disease in the human host, ranging from hypersensitivity reactions to direct angioinvasion. ***Aspergillus*** primarily affects the lungs, causing four main syndromes, including allergic bronchopulmonaryaspergillosis (ABPA), chronic necrotizingAspergilluspneumonia (or chronic necrotizing pulmonary aspergillosis [CNPA]), aspergilloma, and invasive aspergillosis. However, in patients who are severely immunocompromised, ***Aspergillus*** may hematogenously disseminate beyond the lung, potentially causing endophthalmitis, endocarditis, and abscesses in the myocardium, kidney, liver, spleen, soft tissue, and bone. On the other hand, ***Candida albicans*** is a diploidfungus that grows both as yeast and filamentous cells and a causal agent of opportunisticoral and genital infections in humans.[36,37]. ***C. albicans*** have emerged as important causes of morbidity and mortality in immunocompromised patients (e.g., AIDS, cancer chemotherapy, organ or bone marrow transplantation). Also,***Staphlococcusaureus***can cause a range of illnesses, from minor skin infections, such as pimples, impetigo, boils (furuncles), cellulitis folliculitis, carbuncles, scalded skin syndrome, and abscesses, to life-threatening diseases such as pneumonia, meningitis, osteomyelitis, endocarditis, toxic shock syndrome (TSS), bacteremia, and sepsis. Its incidence ranges from skin, soft tissue, respiratory, bone, joint, endovascular to wound infections. It is still one of the five most common causes of nosocomial infections and is often the cause of postsurgical wound infections. Each year, some 500,000 patients in American hospitals contract a staphylococcal infection [38]. In addition, some ***Bacillus*** species can cause food poisoning; ***Bacillus***can result in two different kinds of intoxications. It can either cause nausea, vomiting, and abdominal cramps for 1-6 hours, or diarrhea and abdominal cramps for 8-16 hours. The food poisoning usually occurs from eating rice that is contaminated with ***Bacillussubtilis*** (EMBL EBI), some ***Bacillus*** organisms can cause more severe illnesses, for example causes Anthrax. Also, ***Salmonellatyphimurium*** is a pathogenic Gram-negative bacteria predominately found in the intestinal lumen. Its toxicity is due to an outer membrane consisting largely of lipopolysaccharides (LPS) which protect the bacteria from the environment. ***Salmonella typhimurium*** causes gastroenteritis in humans and other mammals. And finally, pathogenic strains of ***E.coli*** are responsible for three types of infections in humans: urinary tract infections (UTI), neonatal meningitis, and intestinal diseases (gastroenteritis).Representative derivatives **3, 4, 5, 8, 9a, 9b, 9c, 10, 11a** and **11b** were selected and tested for their antimicrobial activity against two gram(+) bacteria (*Staphlococcusaureus,Bacillussubtilis*),two gram(-) bacteria (*Escherichia coli, salmonellatyphimurium*) and a filamentous fungus (*Asperigillusfumigatus*) and a diploid fungus (*Candida albicans*).using the modified Kirby-Bauer disc diffusion method [39,40,41]. For the disc diffusion, the zone diameters were measured with slipping calipers of the national committee for clinical laboratory standards [42].

The results are given in Table 1.

Table 1: Response of various microorganisms to some synthesized compounds in *in vitro* culture

Inhibition zone diameter (mm/mg sample) Antimicrobial activity%						
Sample	*A.fumigatus*	*C.albicans*	*S.aureus*	*B.subtilis*	*E.coli*	*S.typhimurium*
DMSO (positive control)	0.00	0.00	0.00	0.00	0.00	0.00
Tetracycline (Antibacterial agent)	--	--	30	29	31	30
Clotrimazole (Antifungal Agent)	24	22	--	--	--	--
3	22 92%	16 73%	23 77%	22 76%	24 77%	27 90%
4	14 58%	8 36%	17 57%	16 55%	17 55%	14 47%
5	16 67%	7 32%	15 50%	10 34%	12 50%	15 50%
8	9 38%	0.00 0.00	21 70%	12 41%	5 16%	0.00 0.00
9a	12 50%	9 41%	5 17%	12 41%	19 61%	14 47
9b	19 79%	18 82%	9 30%	23 79%	25 81%	23 77%
9c	15 63%	5 23%	3 10%	14 48%	11 35%	10 33%
10	10 42%	12 55%	14 47%	0.00 0.00	0.00 0.00	0.00 0.00
11a	4 17%	0.00 0.00	12 40%	14 48%	14 45%	12 40%
11b	14 58%	0.00 0.00	23 77%	22 76%	23 74%	25 83%

$$\text{Antimicrobial activity \%} = \frac{\text{Inhibition zone diameter of the tested sample}}{\text{Inhibition zone diameter of the standard}} \times 100$$

Strong effect means: antimicrobial activity% ≥ 60%
Moderate effect means: 60%>antimicrobial activity%≥40%
Weak effect means: 40%>antimicrobial activity%≥ 1%
No effect means: antimicrobial activity%=0.00%

CONCLUSION

The varied biological activities of the newly synthesized compounds promoted us to synthesize some new derivatives of these ring systems and study their antimicrobial activities, their biological activities depended mainly on the nature and the position of the substituents. The antifungal activity studies revealed that compounds **3**, **5**,**9b** and **9c** show strong effects against*Asperigillusfumigatus.*Also, compounds **3** and **9b** show strong effects against *Candida albicans*. On the other hand compounds **3, 8** and **11b**display strong effects against*Staphlococcusaureus*. Compounds**3, 9b** and **11b**give strong effects against *Bacillus subtilis.*Compounds**3, 9a, 9b** and **11b**show strong effects against *Escherichia coli*. And finally compounds**3, 9b**and **11b**afford strong effects against *salmonella typhimurium.* All the other compounds show effects against different types of tested microorganisms ranged from negative effects to moderate effects.So we can say that synthesis of new derivatives of these compounds is still an active area of research. Where, synthesis and study of the antimicrobial activities of new analogous of these compounds will be helpful for medicinal chemist to focus design of novel chemical entities containing pyrimidoquinoline derivatives as a part of antimicrobial drugs.

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