Eurasian Journal of Analytical Chemistry
ISSN: 1306-3057 OPEN ACCESS 2018 13 (6): 19-30

Synthesis, Characterization and Biological Activity of new Pyran Derivatives of 8-Hydroxyquinoline

Mohamed Rbaa, Omar Bazdi, Younes Lakhrissi, Khadija Ounine, Brahim Lakhrissi*

Received 14 September 2018 ▪ Revised 23 October 2018 ▪ Accepted 24 November 2018

Abstract: We have synthesized a new pyran derivatives based on 8-hydroxyquinoline such as 2-Amino-4-phenyl-4H-pyrano [3,2-h] quinoline-3-carbonitrile (**QP-H**), 2-Amino-4-(4-chlorophenyl)-4H-pyrano-[3,2-h] quinoline-3-carbonitrile (**QP-Cl**), 2-Amino-4-(4-methoxyphenyl)-4H-pyrano-[3,2-h]quinoline-3-carbonitrile (**QP-OCH_3**) and 2-Amino-4-(4-nitrophenyl)-4H-pyrano[3,2-h]quinoline-3-carbonitrile (**QP-NO_2**). All the synthesized compounds were identified by elemental analysis data, IR, ^1H and ^{13}C NMR spectroscopy and were evaluated and screened "*in vitro*" by the disk diffusion technique against Gram-positive and Gram-negative bacterial strains (*E. coli (ATCC35218), S. aureus (ATCC29213), V. parahaemolyticus (ATCC17802),* and *P. aeruginosa (ATCC27853*)). The preliminary screening results showed that all the compounds displayed a potential antibacterial activity against all the tested four Gram bacteria. The results revealed that most of the tested compounds have a very good antibacterial activity compared to the standard antibiotic (Penicillin G).

Keywords: Synthesis, Quinolinol, Characterization, Antibacterial activity, Bacterial strains.

INTRODUCTION

The 8-hydroxyquinoline derivatives are of wide interest because of their diverse applications in wide-ranging fields, they have a remarkable biological importance [1-3] and a high therapeutic potential [4]. Some of these heterocycliques compounds have indeed been used in the treatment of inflammatory diseases [5], those related to antimalaria [6-8], infectious diseases [9], anti-cancer [10-12], anti-HIV agents [13], anti-tumor, anti-neurodegenerative, [14-21], DNA binding capacities, DNA intercalating agent, and chemotherapeutic agents for the treatment of malaria disease [22-27]. The preparation of these molecules plays a very important role in their organic synthesis [28-29]. The quinoline skeleton is thus an effective tool for the development of novel syntheses of biologically active heterocyclic compounds. The pyranquinoline carbonitrile derivatives were evaluated for their antitumor potency on four human tumor cell lines [30]. The quinolines bound with piperazines are potent antibacterial agents which act on several Gram-positive and Gram-negative bacteria. Recently, work on antibacterial activity has been carried out in our laboratory by four piperazinic compounds based on 8-hydroxyquinoline. Three of them exhibit significant antibacterial activity against Gram-positive and Gram-negative bacteria such as *E. coli*, *S. aureus*, *E. ludwigii*, *B. subtilis* [31, 32].

On the other hand, the pyran derivatives exhibits remarkable antibacterial properties towards standardized strains, Gram-positive and Gram-negative strains, as well as antioxidant activity such as

Mohamed Rbaa, Laboratory of Agro-resources, Polymers and Process Engineering, Department of Chemistry, Faculty of Science, Ibn Tofaïl University, PO Box 133, Kenitra, Morocco.

Omar Bazdi, Laboratory of Nutrition, Health and Environment, Department of Biology, Faculty of Science, Ibn Tofaïl University, PO Box 133, Kenitra, Morocco

Younes Lakhrissi, Laboratory of Agro-resources, Polymers and Process Engineering, Department of Chemistry, Faculty of Science, Ibn Tofaïl University, PO Box 133, Kenitra, Morocco.

Khadija Ounine, Laboratory of Nutrition, Health and Environment, Department of Biology, Faculty of Science, Ibn Tofaïl University, PO Box 133, Kenitra, Morocco

Brahim Lakhrissi*, Laboratory of Agro-resources, Polymers and Process Engineering, Department of Chemistry, Faculty of Science, Ibn Tofaïl University, PO Box 133, Kenitra, Morocco. E-mail: brahim.lakhrissi@uit.ac.ma (or) b.lakhrissi2012@gmail.com

pyranopyrimidines, pyranocar-bazoles, pyranopyrrole, 2-pyrone, 6-pentyl-α-pyrone and 3-methyl-γ-pyrone [33-37].

The purpose of the present work is to synthesize a series of new pyran based on 8-hydroxyquinoline and to investigate their biological activity against Gram-positive and Gram-negative bacteria. The synthesized compounds were characterized by elemental analysis data, IR, ^{1}H and ^{13}C NMR spectroscopy.

EXPERIMENTAL SECTION

Materials and Methods

All substances used in this study have been purchased from Sigma-Aldrich Chemical Company (Spain or France). Melting points were determined on Banc Kofler apparatus and are uncorrected. Infrared spectra were recorded in a FT-IR Nicolet 400D Spectrophotometer using KBr pellets. The recording of Nuclear Magnetic Resonance spectra was performed on a Bruker Advanced 300 WB at 300 MHz for solutions in Me_2SO-d_6 and chemical shifts are specified in δ_{ppm} with reference to tetramethylsilane (TMS) as an internal standard. The elemental composition (Carbon, hydrogen and nitrogen) was determined on a Perkin-Elmer Model 240 CHN Analyzer. The evolution of the reaction is followed by chromatography with thin layer of silica 60 F254 (E. Merck).

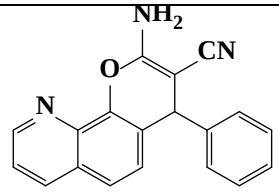
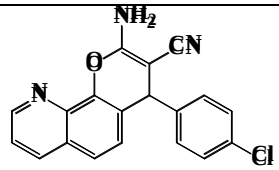
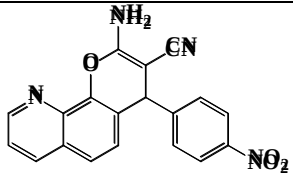
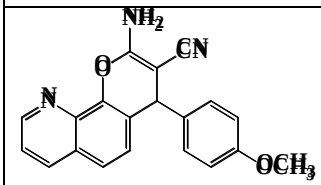
Chemical synthesis and characterization

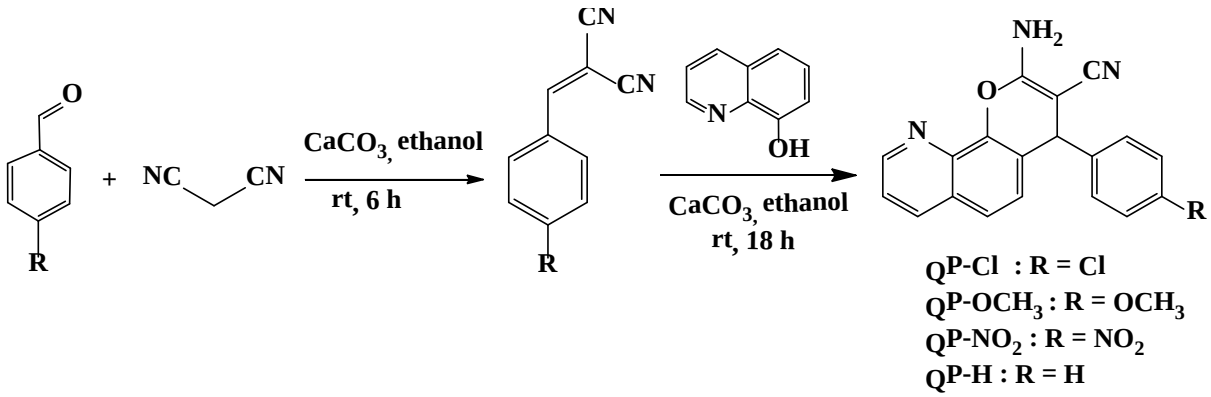
General Procedure for the Synthesis of Pyran Derivatives based on 8-Hydroxyquinoline

A mixture of substituted benzaldehyde ou *para*-benzaldehyde (0.01 mol), malononitrile (0.01 mol) and calcium carbonate ($CaCO_3$) (0.01 mol) in absolute ethanol (30 mL) was stirred for 6 h. 8-hydroxyquinoline (0.01 mol) dissolved in absolute ethanol (10 mL) was then added to this mixture, which is then refluxed under magnetic stirring for 18 h. The progress of the reaction was monitored by TLC using hexane-acetone (4:6, v/v) as the mobile phase. The reaction mixture was filtered while hot and the filtrate was allowed to cool for 30 minutes until the expected product was precipitated. The formed solid was collected by filtration, washed with hexane and recrystallized from ethanol to afford the desired compound (Scheme 1).

The chemical structures, names and abbreviations of the products have been given in **Table 1**.

Table 1: Chemical structures, names and abbreviations of the *synthesized compounds*

Structure	Name	Abbreviation
	2-Amino-4-phenyl-4*H*-pyrano [3,2-*h*] quinoline-3-carbonitrile	**QP-H**
	2-Amino-4-(4-chlorophenyl)-4*H*-pyrano [3,2-*h*] quinoline-3-carbonitrile	**QP-Cl**
	2-Amino-4-(4-nitrophenyl)-4*H*-pyrano [3,2-*h*] quinoline-3-carbonitrile	**QP-NO_2**
	2-Amino-4-(4-methoxyphenyl)-4*H*-pyrano [3,2-*h*] quinoline-3-carbonitrile	**QP-OCH_3**



Scheme 1: Synthetic route for the preparation of pyran derivatives based on 8-hydroxyquinoline

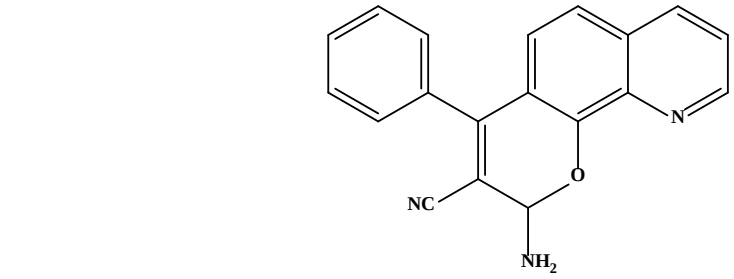
Synthesis of 2-Amino-4-Phenyl-4H-Pyrano [3, 2-h] Quinoline-3-Carbonitrile (QP-H)

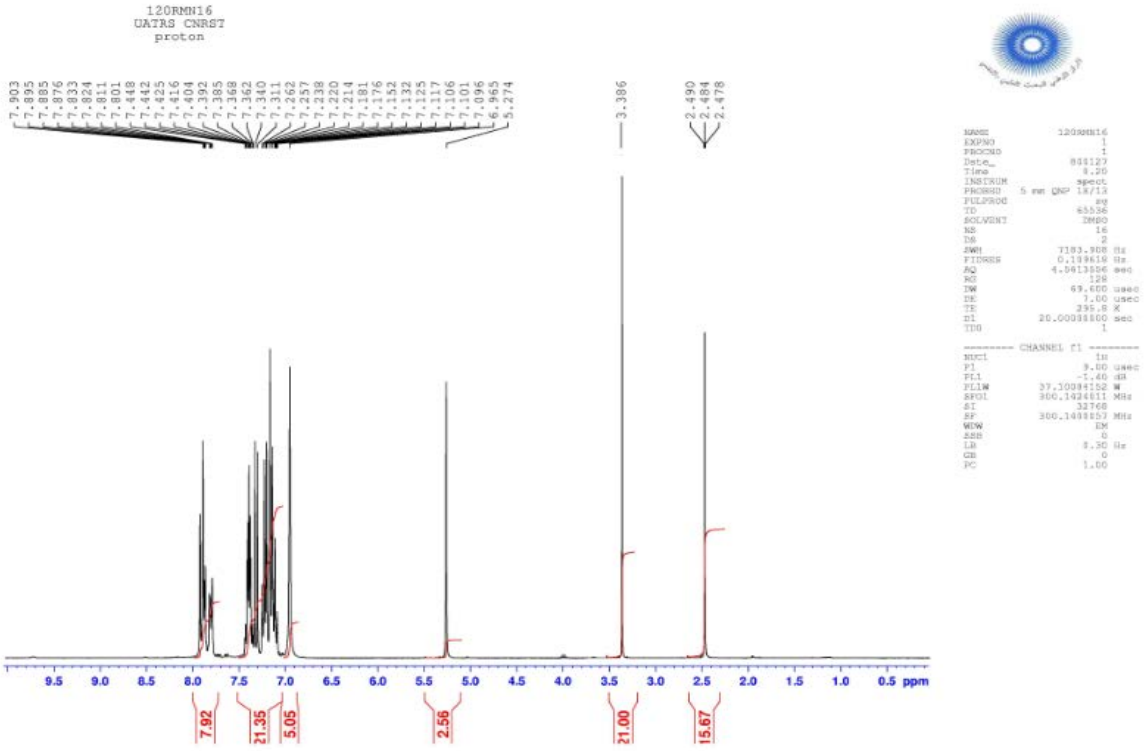
It was synthesized from benzaldehyde, malononitrile and 8-hydroxyquinoline following the general procedure: Yield 92 %, aspect: white solid, m.p. = 169-171 °C, R_f value = 0.76 (n-hexane/dichloromethane: 5/5 (v/v)).

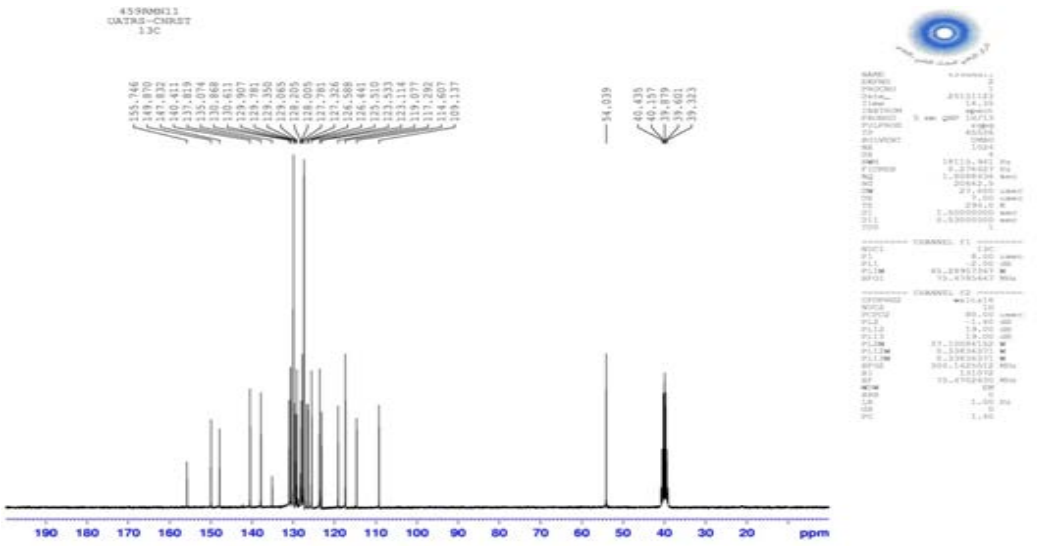
^{1}H (DSMO-d_6): δ_{ppm} = 6.96 (S, 2H, NH_2), 5.27 (S, 1H, CH_{pyran}), 7.31-7.90 (m, 10 H, aromatic protons)

^{13}C (DSMO-d_6): δ_{ppm} = 54.03 (C-NH_2), 109.13 (CN), 155.74 (C-CN), 117.29-123.53-130.61-135.07-147.83 (ArCH of quinoline), 129.90-140.41 (ArC of quinoline), 128.20-129.60-130.86- (ArCH of benzene ring), 130.61(ArC of benzene ring).

2-Amino-4-Phényl-2H-Pyrano[3,2-h]Quinolin-3-Carbonitrile (QP-H)







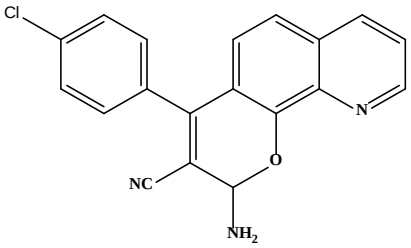
Synthesis of 2-Amino-4-(4-chlorophenyl)-4H-Pyrano [3, 2-h] Quinoline-3-Carbonitrile (QP-Cl)

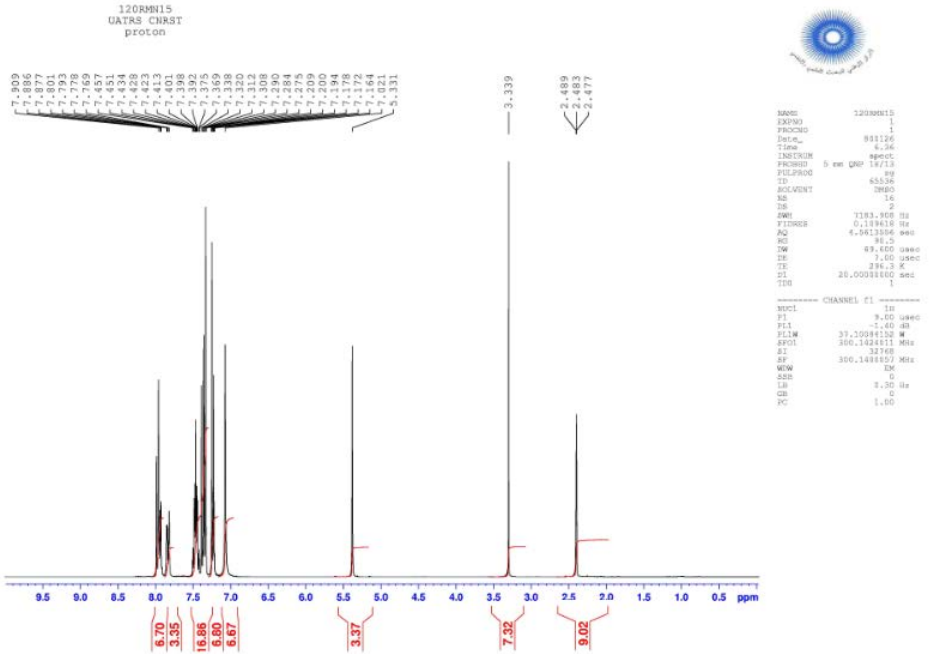
It was synthesized from *p*-chlorobenzaldehyde, malononitrile and 8-hydroxyquinoline following the general procedure: Yield 90 %, aspect: white solid, m.p. = 162-164 °C, R_f value = 0.78 (n-hexane/dichloromethane: 5/5 (v/v)).

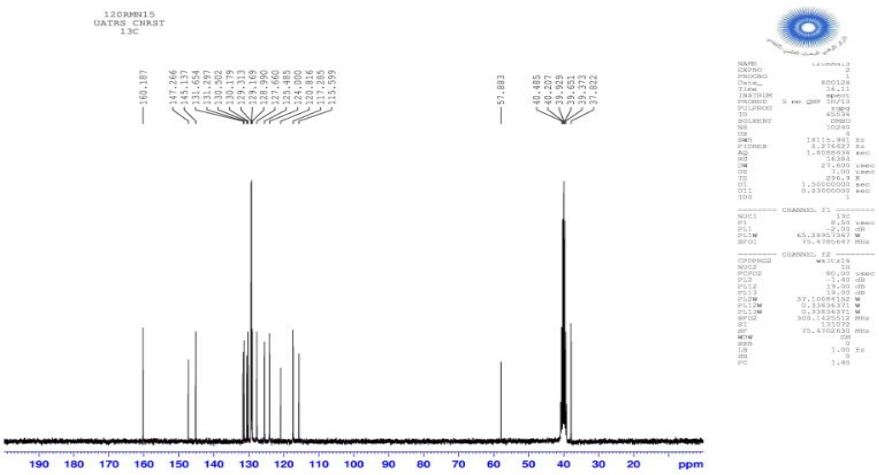
^{1}H (DSMO-d6): δ_{ppm} = 7.02 (S, 2H, NH_2), 5.33(S, 1H, CH_{pyran}), 7.32-7.90 (m, 9 H, Aromatics).

^{13}C (DSMO-d_6): δ_{ppm} = 117.28 (CN), 160.18 (C_{pyran}), 57.88(C-NH_2), 130.5 (C-Cl), 120.81-124.00-125.48-129.31-147.26 (ArCH of quinoline), 115.59-129.66-130.50-145.13 (ArC of quinoline), 127.66-128.99-131.65 (ArCH of benzene ring), 130.17-131.29 (ArC of benzene ring).

2-Amino-4-(4-Chlorophényl)-2H-Pyrano[3,2-h]Quinolin-3-Carbonitrile (QP-Cl)







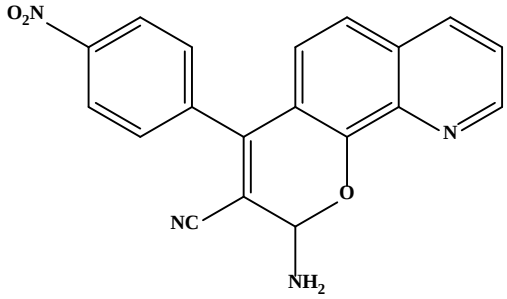
Synthesis of 2-Amino-4-(4-Nitrophenyl)-4H-Pyrano [3,2-h] Quinoline-3-Carbonitrile (QP-NO_2)

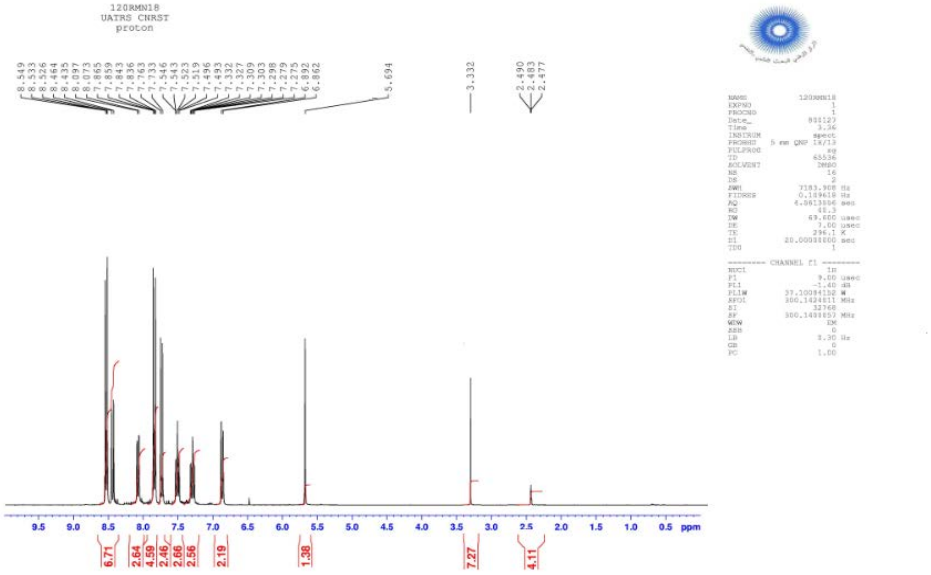
It was synthesized from *p*-nitrobenzaldehyde, malononitrile and 8-hydroxyquinoline following the general procedure: Yield 80 %, aspect: yellow solid, m.p. = 149-151 °C, R_f value = 0.80 (n-hexane/dichloromethane: 5/5, (v/v)).

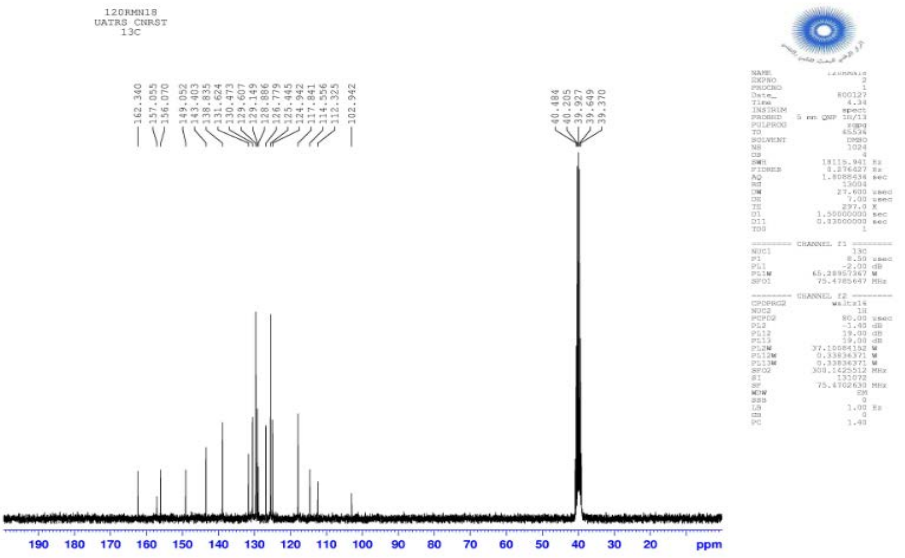
^{1}H (DSMO-d_6): δ_{ppm} = 5.69 (S, 2H, NH_2), 6.86 (S, 1H, CH_{pyran}), 7.33-7.56-7.73-8.43-8.54 (m, 5H, Ar-quinoline), 7.83-8.07 (m, 4H, benzene ring).

^{13}C (DSMO-d_6): δ_{ppm} = 114.55 (CN), 162.34 (C-CN), 102.94 (C-NH_2), 149.05 (C-NO_2), 117.84-124.94-126.77-138.83-162.34 (ArCH of quinoline), 112.32-157.05 (ArC of quinoline), 129.60-125.44 (ArCH of benzene ring), 130.47-156.07 (ArC of benzene ring).

2-Amino-4-(4-Nitrophenyl)-2H-Pyrano [3,2-h] Quinolin-3-Carbonitrile (QP-NO_2)







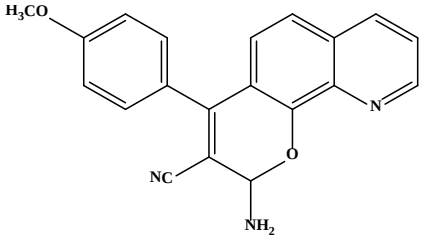
Synthesis of 2-Amino-4-(4-Methoxyphenyl)-4H-Pyrano [3,2-h] Quinoline-3-Carbonitrile (QP-OCH$_3$)

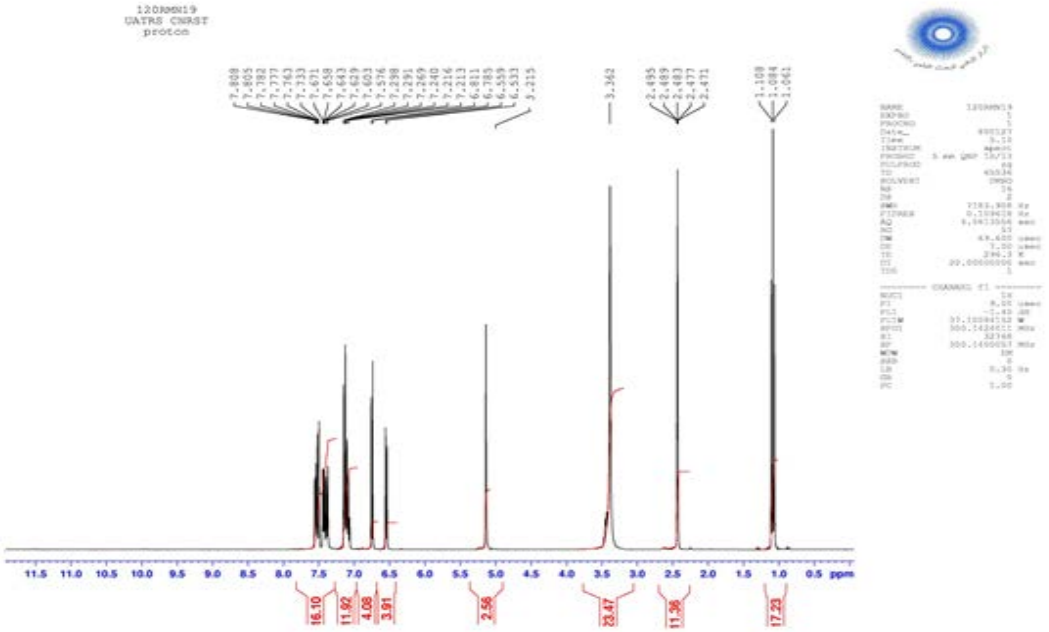
It was synthesized from *p*-methoxybenzaldehyde, malononitrile and 8-hydroxyquinoline following the general procedure: Yield 93 %, aspect: Red solid, m.p. = 142-144 °C, R_f value = 0.72 (n-hexane/dichloromethane: 5/5, (v/v)).

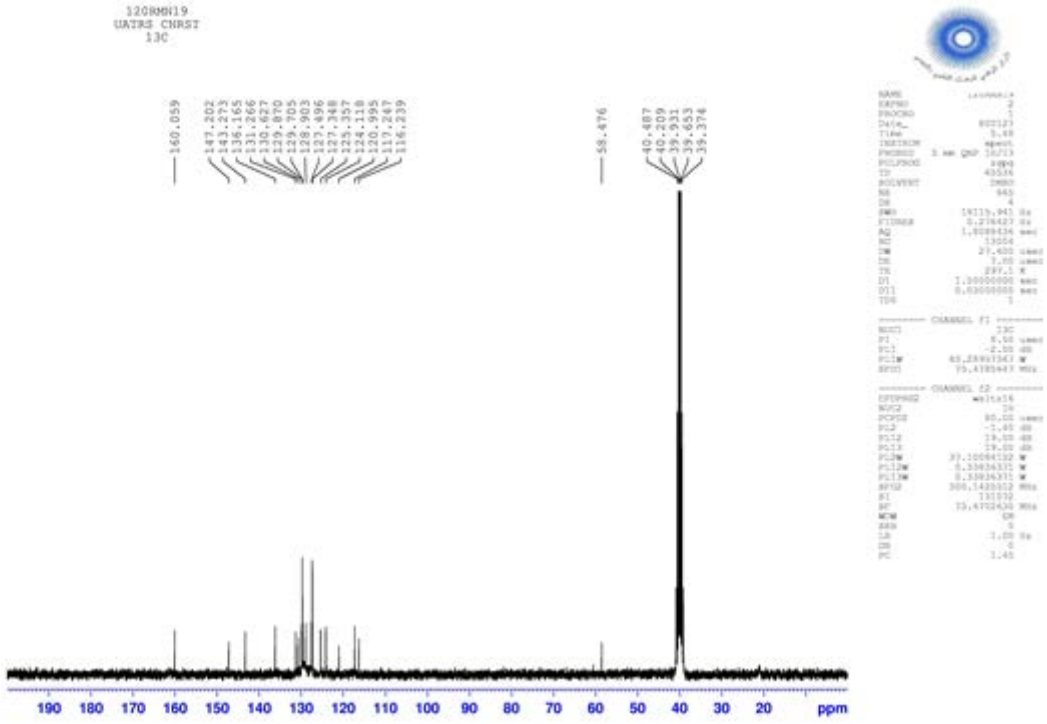
^{1}H (DSMO-d$_6$): δ_{ppm} = 5.21 (S, 2H, NH_2), 6.53(S, 1H, CH_{pyran}), 1.06 (S, 3H, CH_3) 7.57-7.62-7.63-7.80-7.81 (m, 5H, Ar-quinoline), 6.81-7.29 (m, 4H, benzene ring).

^{13}C (DSMO-d$_6$): δ_{ppm} = 117.24 (CN), 160.05 (C-CN), 116.23 (C-NH_2), 58.47 (CH_3)125.35-127.49-127.49-143.27-147.20 (ArCH of quinoline), 124.11-154.80 (ArC of quinoline), 120.99-136.16 (ArCH of benzene ring), 131.26-160.05 (ArC of benzene ring).

2-Amino-4-(4-Methoxyphenyl)-2H-Pyrano [3,2-h] Quinolin-3-Carbonitrile (QP-OCH$_3$)







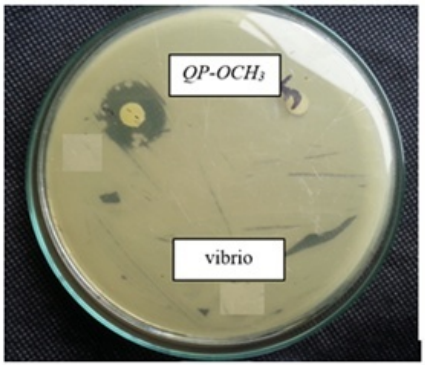
Antibacterial Activity

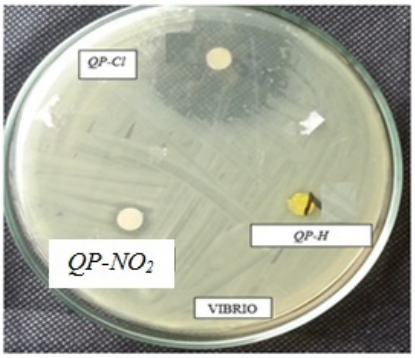
Microorganisms

We chose four different bacteria to test the antibacterial activity of the synthesized products. The bacteria selected for this study are *E. coli* responsible for food poisoning and infections [38], *S. aureus* caused serious life-threatening complications such as infection of the blood bones or lungs [39], *P. aeruginosa* is considered a human pathogen more often responsible for nosocomial infections [40] and *V. parahaemolyticus* represent a serious and global threat to human health [41]. They were all provided by the Laboratory of Nutrition, Health and Environment, Faculty of Science, Ibn Tofail University, Kenitra Morocco. Each bacterium was inoculated onto the Mueller-Hinton agar culture medium. The bacterial isolates *E. coli*, *S. aureus* and *P. aeruginosa* are of clinical origin. However, *V. parahaemolyticus* apart from food poisoning.

Antibacterial Test

The antibacterial activity was determined by using the agar disk diffusion assay. A bacterial culture of 24 hours was spread on the surface of the Muller-Hinton agar plate. A disc of sterile 6 mm whatmann paper was saturated with 10 µl of solution of the quinoline compounds under investigation in dimethylsulfoxide (DMSO). After 1 h of diffusion, the Petri dishes were incubated at 37 °C for 24 hours and the zones of inhibition of the development were measured and compared with those of the reference discs of penicillin G (**Figures 1 and 2**).





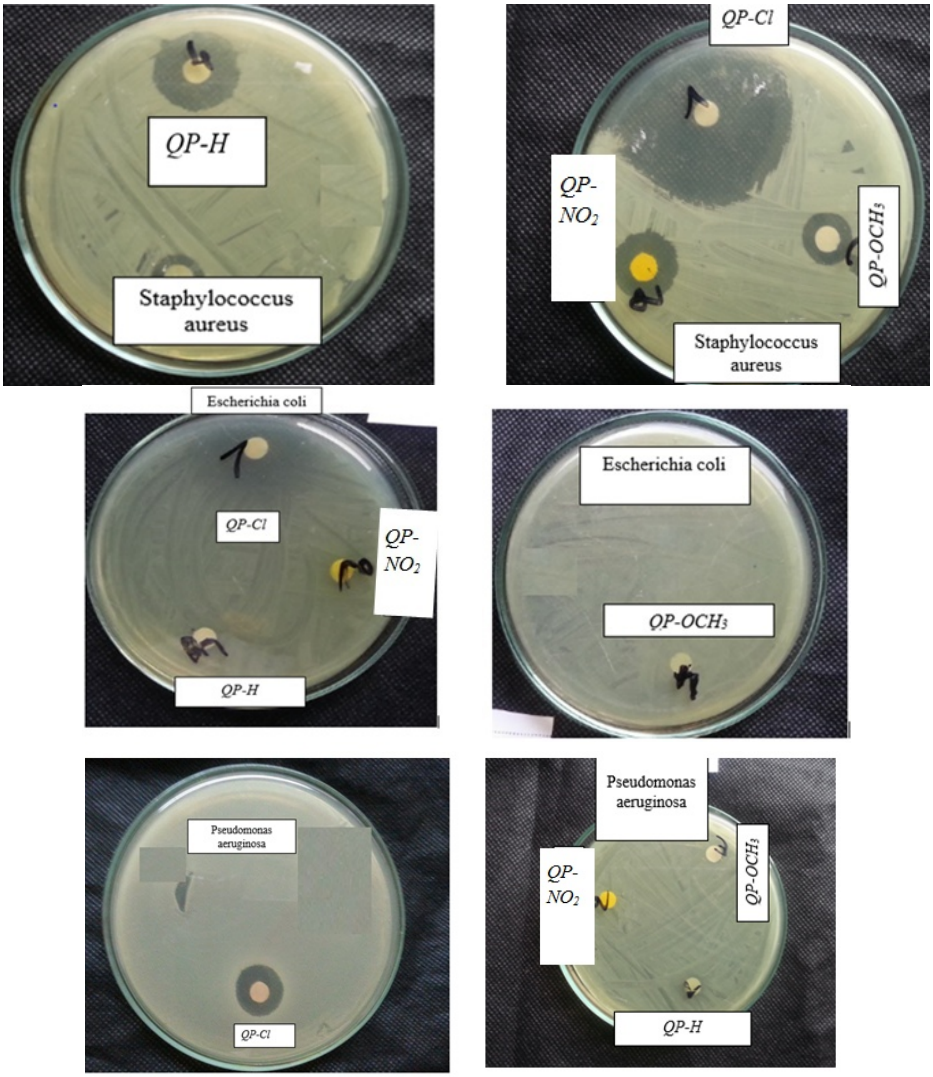


Figure 1: Antibacterial activity of the synthesized compounds against bacteria after 24 h incubation at 37 °C

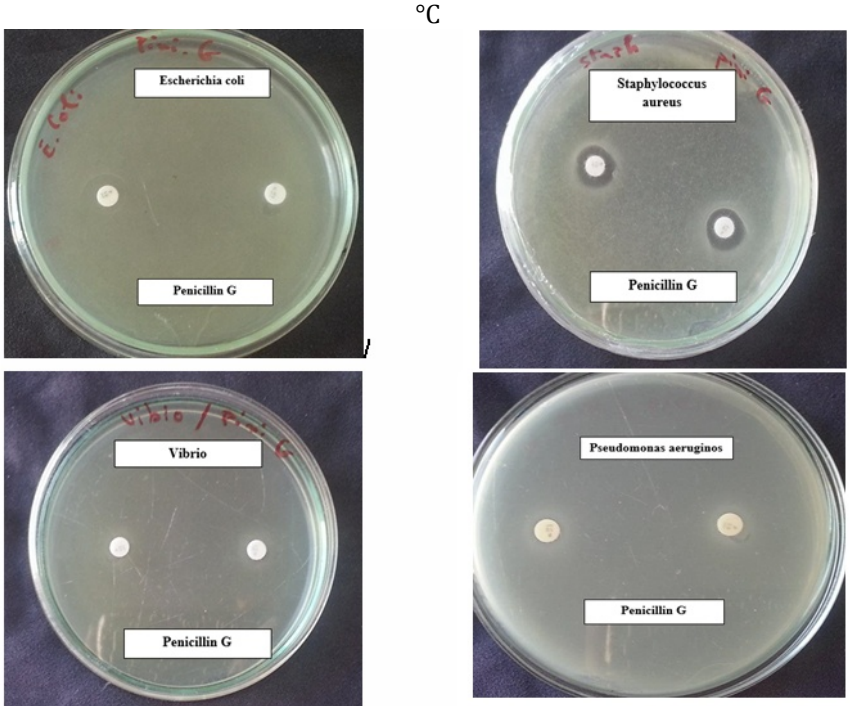


Figure 2: Antibacterial control activity (Penicillin G) against bacteria after 24 h of incubation at 37 °C

Minimal Inhibitory Concentration

In this study, the minimum inhibitory concentration (MIC) was determined by the agar diffusion method [42]. Disk diffusion refers to the diffusion of an antimicrobial agent of a specific concentration using filter paper discs, in the solid culture medium inoculated with the bacterial strains. Disk diffusion is based on the determination of a zone of inhibition proportional to the bacterial sensitivity to the antimicrobial present in the filter paper disc. The diameters of the zones of inhibition are measured after 24 hours of incubation at 37 °C.

RESULTS AND DISCUSSIONS

In this study, the synthesis of pyran derivatives based on 8-hydroxyquinoline was carried out by condensation of methyl-2-cyanoacetate with benzaldehyde and substituted benzaldehydes and 8-hydroxyquinoline. These products were identified by elemental analysis data, IR, ^{1}H and ^{13}C NMR spectroscopy, the data spectral obtained show good coherence with the assigned structures. All these compounds have been evaluated and screened "*in vitro"* by the disk diffusion technique against Gram-negative bacterial strains *(E. coli)*, and Gram-positive bacterial strains (*S. aureus, V. parahaemolyticus* and *P. aeruginosa*).

We found in the literature that the pyranic compounds had a good antibacterial activity against *Klebsiella aerogenes* and *E. coli* [43]. According to V. Tets, and others, the pyran-based substance exhibiting a remarkable antimicrobial activity with respect to the substances which carry the groups: NH, N-Alkyl, OH, halogen, *O*-Alkyl, NH_2, NH-Alkyl, NH-Ar, N-$(Alkyl)_2$, SH, *S*-Alkyl and *S*-Ar [44].

For all the tested compounds, the pH is between 7.5 and 8.0 while the results of the antimicrobial activity compared with the standard antibiotic *penicillin G* are given in **Table 2** and **Figures 1 and 2**.

Table 2: Inhibition zone in (mm) of the synthesized compounds compared with standard antibiotic penicillin G against Gram positive and Gram negative bacteria at 10^{-3} g/ml

Compound	Inhibition zone diameter (mm)			
	Gram-positive bacteria	Gram-negative bacteria		
	S. aureus	*V. parahaemolyticus*	*E. coli*	*P.aeruginosa*
QP-Cl	40	35	30	17
QP-NO_2	12	08	-	-
QP-OCH_3	14	17	-	-
QP-H	19	-	-	-
Penicillin G	11	5	12	9

(-) No Zone

In the light of the results obtained in Table 2 and Figures 1 and 2, we notice that all the tested compounds which have the zones of inhibition at different diameters depending on the type of bacterium. The three products **QP-OCH_3, QP-NO_2 and QP-Cl** show antibacterial activity against the Gram-positive and Gram-negative strains compared to the standard antibiotic penicillin G except the **QP-H** compound which has no effect against the strains. These differences in inhibitory activity are due to the nature of the substituent and the structures of the tested molecules [45].

The molecules that have electron with drawing substituents (acid function, nitro, etc.) have shown a lower activity against Gram-positive and Gram-negative bacteria than those having electron-donating substituents (*O*-alkyl, *O*-aryl, chlorophenyl, etc.) [46]; this suggests that the three products are substituted by donor groups such as **QP-OCH_3**, and **QP-Cl** which affect the inhibitory activity.

It is clear in this series, that the **QP-Cl** have the most important antibacterial activity once compared to the control (penicillin G). For this we tested this product at a concentration range in order to determine the minimum concentration of inhibition (MIC).

Determination of Minimum Inhibitory Concentration (MIC)

MIC: Minimum inhibitory concentration being the lowest concentration of antibiotic that inhibits any visible culture of a bacterial strain after 24 hours of incubation at 37 °C, this value characterizes the bacteriostatic effect of an antibiotic.

We have adopted the agar diffusion method to determine the minimum inhibitory concentration at a concentration range of 10^{-3} to 10^{-7} (g/ml). The obtained results are illustrated in **Table 3**. The zones of inhibition are varied in view of the concentration of the compound **QP-Cl** (**Figure 6**).

Table 3: Variation of the inhibition zones in view of the concentration of **QP-Cl** compound in the pathogenic strains at 37 °C for 24 hours of incubation

Compound	Inhibition zone diameter (mm)			
QP-Cl	Gram-positive bacteria	Gram-negative bacteria		
	S. aureus	*V. parahaemolyticus*	*E. coli*	*P.aeruginosa*
Conc. (g/ml)				
10^{-3}	40	35	30	17
10^{-4}	30	28	17	15
10^{-5}	22	22	13	11
10^{-6}	17	13	11	-
10^{-7}	-	-	-	-

(-) No zone

From the results of this table we notice that the inhibition zones after 24 hours of incubation at 37 °C, decrease with the decrease in the concentrations of compound **QP-Cl** (**Figure 3**), until the disappearance of the latter at a concentration of 10^{-7} g/ml in the case of *S. aureus*, *V. parahaemolyticus* and *E. coli*. We could say that the minimum inhibitory concentration is 10^{-6} g/ml. In the other hander, the minimum inhibitory concentration (MIC) of *P. aeruginosa* is 10^{-5} g/ml.

CONCLUSION

In summary, we have described the synthesis and characterization a series of a new pyran derivatives based on 8-hydroxyquinoline. From the screening results, we conclude that the antibacterial activity of the synthesized compounds clearly indicates that the nature of the substituent group (R) on the benzene ring significantly affects the "*in vitro*" antibacterial activity. Furthermore, we note that the synthesized compounds showed antibacterial activity, especially for the **QP-Cl** which exhibits particularly potent antibacterial activity against all the tested bacteria compared to antibiotic penicillin G.

References

[1] Mladenova, R., Ignatova, M., Manolova, N., Petrova, T., & Rashkov, I. (2002). Preparation, characterization and biological activity of Schiff base compounds derived from 8-hydroxyquinoline-2-carboxaldehyde and Jeffamines ED®. *European polymer journal*, *38*(5), 989-999.

[2] Kenawy, E. R. (2001). Biologically active polymers. IV. Synthesis and antimicrobial activity of polymers containing 8-hydroxyquinoline moiety. *Journal of Applied Polymer Science*, *82*(6), 1364-1374.

[3] Benard, C., Zouhiri, F., Normand-Bayle, M., Danet, M., Desmaële, D., Leh, H., & Le Bret, M. (2004). Linker-modified quinoline derivatives targeting HIV-1 integrase: synthesis and biological activity. *Bioorganic & medicinal chemistry letters*, *14*(10), 2473-2476.

[4] Suwanjang, W., Prachayasittikul, S., & Prachayasittikul, V. (2016). Effect of 8-hydroxyquinoline and derivatives on human neuroblastoma SH-SY5Y cells under high glucose. *PeerJ*, *4*, e2389.

[5] Klingenstein, R., Melnyk, P., Leliveld, S. R., Ryckebusch, A., & Korth, C. (2006). Similar structure–activity relationships of quinoline derivatives for antiprion and antimalarial effects. *Journal of medicinal chemistry*, *49*(17), 5300-5308.

[6] Kaur, K., Jain, M., Reddy, R. P., & Jain, R. (2010). Quinolines and structurally related heterocycles as antimalarials. *European journal of medicinal chemistry*, *45*(8), 3245-3264.

[7] Foley, M., & Tilley, L. (1998). Protein trafficking in malaria-infected erythrocytes. *Int J Parasitol., 28*, 1671-1680.

[8] Vlahov, R., Vlahov, J., Nickel, P., & Snatzke, G. (1990). Synthesis of some new quinoline derivatives-potential antimalarial drugs. *Pure and applied chemistry*, *62*(7), 1303-1306..

[9] El-Gaby, M. S. A., Abdel-Gawad, S. M., Ghorab, M. M., Heiba, H. I., & Aly, H. M. (2006). Synthesis and biological activity of some novel thieno [2, 3-b] quinoline, quinolino [3′, 2′: 4, 5] thieno [3, 2-d] pyrimidine and pyrido [2′, 3′: 4, 5] thieno [2, 3-b] quinoline derivatives. *Phosphorus, Sulfur, and Silicon and the Related Elements*, *181*(2), 279-297.

[10] Jiang, H., Taggart, J. E., Zhang, X., Benbrook, D. M., Lind, S. E., & Ding, W. Q. (2011). Nitroxoline (8-hydroxy-5-nitroquinoline) is more a potent anti-cancer agent than clioquinol (5-chloro-7-iodo-8-quinoline). *Cancer letters*, *312*(1), 11-17.

[11] Ott, I., & Gust, R. (2007). Non platinum metal complexes as anti-cancer drugs. *Archiv der Pharmazie: An International Journal Pharmaceutical and Medicinal Chemistry*, *340*(3), 117-126.

[12] SHEN, A. Y., WU, S. N., & CHIU, C. T. (1999). Synthesis and cytotoxicity evaluation of some 8-hydroxyquinoline derivatives. *Journal of pharmacy and pharmacology*, *51*(5), 543-548.

[13] Guenfoud, F., Direm, A., Laabassi, M., & Benali-Cherif, N. (2012). Synthesis of New Cyano-Quinoline Derivatives by the Baylis–Hillman Reaction. *Journal of Chemical Crystallography*, *42*(10), 989-996.

[14] Shaw, A. Y., Chang, C. Y., Hsu, M. Y., Lu, P. J., Yang, C. N., Chen, H. L., & Chern, M. K. (2010). Synthesis and structure-activity relationship study of 8-hydroxyquinoline-derived Mannich bases as anticancer agents. *European journal of medicinal chemistry*, *45*(7), 2860-2867.

[15] Parups, E. V., & Peterson, E. A. (1973). Inhibition of ethylene production in plant tissues by 8-hydroxyquinoline. *Canadian Journal of Plant Science*, *53*(2), 351-353.

[16] Cherny, R. A., Atwood, C. S., Xilinas, M. E., Gray, D. N., Jones, W. D., McLean, C. A., & Huang, X. (2001). Treatment with a copper-zinc chelator markedly and rapidly inhibits β-amyloid accumulation in Alzheimer's disease transgenic mice. *Neuron*, *30*(3), 665-676.

[17] Ashok, M., Athar, F., Aubert, G., Awasthi, A., Azas, N., Aziz, M., & Baldasso, P. (2009). Eur. J. Med. Chem., 44.

[18] Biegel, A., Gebauer, S., Hartrodt, B., Brandsch, M., Neubert, K., & Thondorf, I. (2005). Three-Dimensional Quantitative Structure−Activity Relationship Analyses of β-Lactam Antibiotics and Tripeptides as Substrates of the Mammalian H+/Peptide Cotransporter PEPT1Eur. *J. Med. Chem., 48*(13), 4410–4419.

[19] Atwell, G. J., Baguley, B. C., & Denny, W. A. (1989). Potential antitumor agents. 2-Phenylquinoline-8-carboxamides as minimal DNA-intercalating antitumor agents with in vivo solid tumor activity. *Journal of medicinal chemistry*, *32*(2), 396-401.

[20] Xia, Y., Yang, Z. Y., Xia, P., Bastow, K. F., Tachibana, Y., Kuo, S. C., & Lee, K. H. (1998). Antitumor agents. 181. Synthesis and biological evaluation of 6, 7, 2 ‘, 3 ‘, 4 ‘-substituted-1, 2, 3 4-tetrahydro-2-phenyl-4-quinolones as a new class of antimitotic antitumor agents. *Journal of medicinal chemistry*, *41*(7), 1155-1162.

[21] Domagala, J. M. (1994). Structure-activity and structure-side-effect relationships for the quinolone antibacterials. *Journal of Antimicrobial Chemotherapy*, *33*(4), 685-706.

[22] Baguley, B. C., Denny, W. A., Atwell, G. J., & Cain, B. F. (1981). Potential antitumor agents. 34. Quantitative relationships between DNA binding and molecular structure for 9-anilinoacridines substituted in the anilino ring. *Journal of medicinal chemistry*, *24*(2), 170-177.

[23] Xia, Y., Yang, Z. Y., Xia, P., Bastow, K. F., Tachibana, Y., Kuo, S. C., & Lee, K. H. (1998). Antitumor agents. 181. Synthesis and biological evaluation of 6, 7, 2 ‘, 3 ‘, 4 ‘-substituted-1, 2, 3, 4-tetrahydro-2-phenyl-4-quinolones as a new class of antimitotic antitumor agents. *Journal of medicinal chemistry*, *41*(7), 1155-1162.

[24] Chen, Y. L., Chen, I. L., Tzeng, C. C., & Wang, T. C. (2000). Synthesis and Cytotoxicity Evaluation of Certain α-Methylidene-γ-butyrolactones Bearing Coumarin, Flavone, Xanthone, Carbazole, and Dibenzofuran Moieties. *Helvetica Chimica Acta*, *83*(5), 989-994.

[25] Loiseau, P. M., Gupta, S., Verma, A., Srivastava, S., Puri, S. K., Sliman, F., & Desmaele, D. (2011). In vitro activities of new 2-substituted quinolines against Leishmania donovani. *Antimicrobial agents and chemotherapy*, *55*(4), 1777-1780.

[26] Stanley, M. A., & Turner, S. M. (1995). Current status of pharmacological and behavioral treatment of obsessive-compulsive disorder. *Behavior therapy*, *26*(1), 163-186.

[27] Farruggia, G., Iotti, S., Lombardo, M., Marraccini, C., Petruzziello, D., Prodi, L., & Zaccheroni, N. (2010). Microwave assisted synthesis of a small library of substituted N, N′-bis ((8-hydroxy-7-quinolinyl) methyl)-1, 10-diaza-18-crown-6 ethers. *The Journal of organic chemistry*, *75*(18), 6275-6278.

[28] Madonna, S., Béclin, C., Laras, Y., Moret, V., Marcowycz, A., Lamoral-Theys, D., & Cresteil, T. (2010). Structure–activity relationships and mechanism of action of antitumor bis 8-hydroxyquinoline substituted benzylamines. *European journal of medicinal chemistry*, *45*(2), 623-638.

[29] Musser, J. H., Jones, H., Sciortino, S., Bailey, K., Coutts, S. M., Khandwala, A., ... & Neiss, E. S. (1985). Synthesis and antiallergic activities of 1, 3-oxazolo [4, 5-h] quinolines. *Journal of medicinal chemistry*, *28*(9), 1255-1259..

[30] Hammoudaa, M. A., EL-Haga, F. A. A., El-Serwya, W. S., & MAb, E. M. Research Journal of Pharmaceutical, Biological and Chemical Sciences. (2015). Res. J. Pharm. Biol. Chem. Sci 6:208.

[31] El Faydy, M., Dahaief, N., Rbaa, M., Ounine, K., & Lakhrissi, B. (2016). Synthesis, Characterization and Biological Activity of Some Novel 5-((4-Alkyl piperazin-1-yl) methyl) quinolin-8-ol Derivatives. *chemistry*, *17*, 18.7:356.

[32] El Faydy, M., Djassinra, T., Haida, S., Rbaa, M., Ounine, K., Kribii, A., & Lakhrissi, B. (2017). Synthesis and investigation of antibacterial and antioxidants properties of some new 5-subsituted-8-hydroxyquinoline derivatives. *J. Mater. Environ. Sci 8*, 3863.

[33] EL-AGRODY, A. M., EL-HAKIM, M. H., El-Latif, M. A., FAKERY, A. H., El-Sayed, E. S., & EL-GHAREAB, K. A. (2000). Synthesis of pyrano [2, 3-d] pyrimidine and pyrano [3, 2-e][1, 2, 4] triazolo [2, 3-c] pyrimidine derivatives with promising antibacterial activities. *Acta pharmaceutica*, *50*(2), 111-120..

[34] Bedair, A. H., Emam, H. A., El-Hady, N. A., Ahmed, K. A., & El-Agrody, A. M. (2001). Synthesis and antimicrobial activities of novel naphtho [2, 1-b] pyran, pyrano [2, 3-d] pyrimidine and pyrano [3, 2-e][1, 2, 4] triazolo [2, 3-c]-pyrimidine derivatives. *Il Farmaco*, *56*(12), 965-973.

[35] Kumar, D., Reddy, V. B., Sharad, S., Dube, U., & Kapur, S. (2009). A facile one-pot green synthesis and antibacterial activity of 2-amino-4H-pyrans and 2-amino-5-oxo-5, 6, 7, 8-tetrahydro-4H-chromenes. *European Journal of Medicinal Chemistry*, *44*(9), 3805-3809.

[36] Ghorab, M. M., & Hassan, A. Y. (1998). Synthesis and antibacterial properties of new dithienyl containing pyran, pyrano [2, 3-b] pyridine, pyrano [2, 3-d] pyrimidine and pyridine derivatives. *Phosphorus, Sulfur, and Silicon and the Related Elements*, *141*(1), 251-261..

[37] Li, H. H., Qi, F. M., Dong, L. L., Fan, G. X., Che, J. M., Guo, D. D., & Fei, D. Q. (2014). Cytotoxic and antibacterial pyran-2-one derivatives from Croton crassifolius. *Phytochemistry Letters*, *10*, 304-308.

[38] Tada, Y., Shikishima, Y., Takaishi, Y., Shibata, H., Higuti, T., Honda, G., & Ohmoto, Y. (2002). Coumarins and γ-pyrone derivatives from Prangos pabularia: antibacterial activity and inhibition of cytokine release. *Phytochemistry*, *59*(6), 649-654.

[39] Reddy, P. V. L., Kavitha, B., Reddy, P. A. K., & Kim, K. H. (2017). TiO2-based photocatalytic disinfection of microbes in aqueous media: a review. *Environmental research*, *154*, 296-303.

[40] Klevens, R. M., Morrison, M. A., Nadle, J., Petit, S., Gershman, K., Ray, S., & Craig, A. S. (2007). Invasive methicillin-resistant Staphylococcus aureus infections in the United States. *Jama*, *298*(15), 1763-1771.

[41] Lodise Jr, T. P., Lomaestro, B., & Drusano, G. L. (2007). Piperacillin-tazobactam for Pseudomonas aeruginosa infection: clinical implications of an extended-infusion dosing strategy. *Clinical Infectious Diseases*, *44*(3), 357-363.

[42] Eloff, J. N. (1998). A sensitive and quick microplate method to determine the minimal inhibitory concentration of plant extracts for bacteria. *Planta medica*, *64*(08), 711-713.

[43] Dechet, A. M., Yu, P. A., Koram, N., & Painter, J. (2008). Nonfoodborne Vibrio infections: an important cause of morbidity and mortality in the United States, 1997–2006. *Clinical Infectious Diseases*, *46*(7), 970-976.

[44] Kidwai, M., Bhushan, K. R., Sapra, P., Saxena, R. K., & Gupta, R. (2000). Alumina-supported synthesis of antibacterial quinolines using microwaves. *Bioorganic & medicinal chemistry*, *8*(1), 69-72.

[45] Higaki, N., & Shiba, K. (2010). Analysis of Specific Absorption Rate and Current Density in Biological Tissues Surrounding Energy Transmission Transformer for an Artificial Heart: Using Magnetic Resonance Imaging-based Human Body Model. *Artificial organs*, *34*(1), E1-E9.

[46] Vaghasiya, Y. K., Nair, R., Soni, M., Baluja, S., & Shanda, S. (2004). Synthesis, structural determination and antibacterial activity of compounds derived from vanillin and 4-aminoantipyrine. *Journal of the Serbian Chemical Society*, *69*(12), 991-998.