Synthesis and Antimicrobial Activity of Nove fused 4-(3H) Quinazolinone Derivatives

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Abstract: ***New antimicrobial compounds are of major importance because of growing problem of bacteria resistance and antimicrobial quinazoline have been gaining a lot of interest. Quinazolin-4(3H)-ones were synthesized and evaluated for antimicrobial activity against Gram positive and Gram negative microorganisms. Some of these derivatives exhibit better activity against Gram positive bacteria.***

Keywords: Antimicrobial Activity, Quinazoline, Heterocyclic**.**

1. Introduction

Drugs are the most valuable assets to fight against various diseases of human health. With respect to a variety of biological activities heterocyclic compounds occupy nearly the first place among the other classes of organic compounds. The great physiological importance of heterocyclic system is evident in view of the fact that these constitute the core structure of clinically very important antibiotics like penicillins, cephalosporins and thenamycins. A large number of heterocyclic compounds have been investigated for their various biological activities. The diverse pharmacological properties exhibited by quinazolone derivatives has been of much significance in recent years although there have been only scattered reports of the investigation of the medical properties of quninazolinone derivative.

2. Literature Review

Bacterial resistance to existing drugs is a constantly growing problem in the world that combined with a decline in the development of new antibiotics presents a significant threat to human health[1-4]. The identification of new antimicrobials agents is therefore of considerable importance. Quninazolinone compounds are class of compounds well known for a long time and still continue the object of considerable interest[5]**.** Quinazolines have been reported to be biologically versatile compounds posses variety of activity including anticancer, antifungal, antibacterial activities .The quninazolines have immense interest because of their broad spectrum of *in-vitro* activity and their *in-vivo* chemotherapeutic activity[6,7]**.**Being involved in a research program aiming at finding out new structure leads that would act as potent antimicrobial agents , we have reported the synthesis and anti microbial activities of some lead compounds comprising mainly the quinozoline moiety substituted with various functionalities and attached to different heterocyclic ring system through various linkage[8-13].

3. Results and Discussion

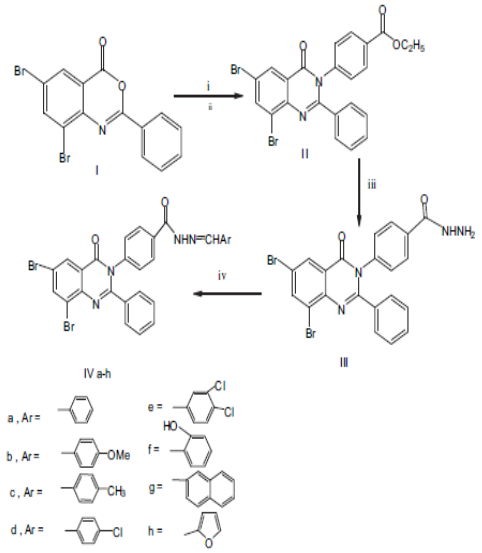
In this present work novel series of quinazolin-4(3*H*)-ones compounds were synthesized. Synthetic schemes as given below illustrate the way used for the synthesis of target compounds. All the synthesized compounds were screened for their anti-bacterial activity against *S. aureus*, *L. monocytogenes*, *B. cereus*, *E. coli*, *P. aeruginosa* and *S. typhimurium* The minimum inhibitory concentrations (MIC) of all compounds were also determined. The anti-bacterial Data Table 1 revealed that all tested compounds of this investigation are moderate to good in activity against all the tested pathogenic bacteria. As compared to the standard drug Ciprofloxacin with MICs 1.56, 0.39, 1.56, 1.56, 0.78 and 0.39 µg/ml against *E. coli*, *S. typhimurium*, *L. monocytogenes*, *S. aureus*, *P. aeruginosa*, and *B. cereus* respectively, Compound **II** show significant anti-microbial activity against *S. aureus*, *S. typhimurium* with MICs 1.56 µg/ml and 3.125 µg/ml respectively. Compound **IVe** show potent anti-microbial activity against *B. cereus* with MIC 1.56 µg/ml.

3.1. Biological Evaluation

Antimicrobial Activity

All the newly synthesized compounds were screened for their anti-microbial activities by paper disc diffusion technique against *Staphlococcus aureus, Legionella monocylogens, Bacillus cereus, Escherichia coli, Pseudomonas aeruginosa* and *Salmonella typhimurium*. The anti-bacterial activity of the synthesized compounds was tested against strains isolated from animal byproducts and were accused of being a direct cause of food intoxication in human. The strains include three Gram-positive bacteria (*S. aureus*, *Legionella monocytogenes* and *Bacillus cereus*) and three Gram-negative bacteria (*Escherichia coli,*

Pseudomonas aeruginosa and *Salmonella typhimurium*) using Muller Hinton agar medium (Oxoid). The result were recorded for each tested compound as the average diameter of Inhibition Zones(IZ) of bacterial growth around the disc in mm. The observed data on the anti-microbial activity of the synthesized compounds and standard drugs are given in table 1.



Scheme

Tested chemical	*In vitro activity-zone of inhibition in mm (MIC in μg/ml)*					
	Tested strains					
	E. coli O157 (F)	S.Ttyphimurium (3)	L.Monocytogenes (A)	S. Aureu	P.Aaeruginosa c	B.Cereus (E)
II	11 (50)	16 (3.125)	14 (25)	17 (1.56)	12 (50)	9 (50)
III	10 (>50)	11 (50)	11 (50)	10 (>50)	13 (25)	12 (25)
IVa	11(45)	10 (>50)	13 (35)	12 (25)	12 (50)	12 (30)
IVb	8 (>50)	10 (>50)	12 (50)	11 (50)	11(>50)	13 (35.5)
IVc	11(40)	15 (5)	13 (30)	12 (25)	15 (2.5)	11 (35)
IVd	12 (20)	10 (>50)	14 (30)	12 (25)	12 (20)	16 (5.5)
IVe	14 (25)	11(50)	13 (25)	14 (25)	14 (25)	17 (1.56)
IVf	10 (50)	13 (30)	11 (50)	15 (12.5)	11(>50)	13 (25.5)
IVg	13 (25)	12 (50)	16 (3.125)	14 (25)	13 (25)	12 50)
IVh	9 (>50)	16 (5)	11 (>50)	13 (20)	8 (>50)	12 (50)

3.2. Chemistry

All melting points are uncorrected, elemental analyses were carried out in the micro analytical units of National Research Centre and Cairo University, Egypt. IR spectra were recorded on FT. IR spectrophotometer-Nexus 670-Nicolet, USA and Perkin Elmer-9712 spectrophotometer. ^{1}H NMR spectra were determined on a Varian-Gemmi-300 MHz and Joel-Ex270 MHz NMR spectrometer using TMS as an internal standard. Mass spectra were recorded on Finnegan Mat SSQ 7000 mode EI 70 ev (Thermo Inst. Sys. Inc., USA). Thin layer chromatography was carried out on silica gel 60 F254 (Merck) thin layer chromatography plates using a chloroform, petroleum ether, methanol mixture (7:4:1 v/v) as the mobile phase.

2-Phenyl-6, 8-dibromo-(4H)-3, 1-benzoxazin-4-one (I)

This compound was prepared according to a reported method [14]. m.p. 178 °C.

Ethyl 4-(2-phenyl-6, 8-dibromo-4-oxo-(4H) quinazolin-3-yl) benzoate (II)

A mixture of the benzoxazine I (3.8 g, 10 mmol) and ethyl-*p*-aminobenzoate (1.65 g; 10 mmol) was heated together upon fusion at 140 °C on sand bath for 1 h. After cooling, the crude mass was crystallized from ethanol twice to give white crystals of **II**. M.p. 194 °C, in 75% yield. Analysis for $C_{23}H_{16}Br_2N_2O_3$, M.wt (528.2) Calcd.: %C, 52.30; H, 3.05; N, 5.30. Found: % C, 52.50; H, 2.95; N, 5.10, IR (KBr, cm^{-1}): 3059(CH, aromatic), and 1700, 1684 (2CO). ^{1}H NMR (DMSO-d_6, δ ppm): 1.3 (t, J = 7.1 Hz, 3H, CH3, ethyl group), 4.18 (q, J = 7.13 Hz, 2H, CH_2, ethyl group), 7.26–7.73 (m, 9H, aromatic-H), 7.8 (s, 1H, H-7, Ar-H), and 8.2 (s, 1H, H-5, Ar-H).MS (*m*/*z*, R.I.): M^+ 525.95, 527.95, 529.95 (10.1%, 20.4%, 10.4%) and at *m*/*z* 108.2 (100%).

4-(2-Phenyl-6,8-dibromo-4-oxo-(4H)quinazolin-3-yl)-benzoic acid hydrazide(III)

A solution of the ester derivative **II** (5.28 g; 10 mmol) and hydrazine hydrate 98% (1.6 g; 50 mmol) in absolute ethanol (20 mL) was refluxed for 6 h. Upon cooling, the formed precipitate was filtered off and recrystalized from ethanol to give the hydrazide derivative **III**. m.p. 240 °C, in 85% yield. Analysis for $C_{21}H_{14}Br_2N_4O_2$, M.wt. (514.17). Calcd.: %C, 49.05; H, 2.74; N, 10.90. Found: %C, 49.00; H, 2.69; N, 10.80. IR (KBr, cm^{-1}): 3312, 3132 (NH, NH_2), 3056 (CH, aromatic), 1712 (CO, quinazoline ring) and 1640 (CO, amide). ^{1}H NMR (DMSO-d_6, δ ppm): 4.9 (s, 2H, NH_2, exchangeable with D_2O), 7.40–7.8 (m, 9H, aromatic-H), 7.9 (s, 1H, H-7, Ar-H), 8.2 (s, 1H, H-5, Ar-H) and 10.00 (s, 1H, NH, exchangeable with D_2O). ^{13}C NMR (DMSO-d_6, δ ppm): 113.5 (C-5), 122.4 (C-7), 124.1 (C-2 ,6), 125.3 (C-3), 127.8 (C-4) 128.2 (C-2 and C-6), 129.3 (C-3 andC-5), 129.7(C-1 ,3 , 5),), 131.3 (C-8), 132.9 (C-6)137.6 (C-1), 139 (C-6), 154 (C-4), 156 (C-1), 160 (C-2), and 167.8 (CO). MS (*m*/*z*, R.I.): M^+ 512.2, 514.24, 516.2 (49%, 100%, 50%).

4-(2-Phenyl-6,8-dibromo-4-oxo-(4H)quinazolin-3-yl)benzoic acid (1-substituted meth(E)ylidene) hydrazides (IVa–h)

General method: A mixture of compound **III** (5.14 g; 10 mmol) and the appropriate aldehyde, namely: benzaldehyde, *p*-anisaldehyde, *p*-tolualdehyde, *p*-chlorobenzaldehyde, 3,4-dichlorobenzaldehde, 2-hydroxybenzaldehyde, naphthalene-2-carboxaldehyde and/or furan-2-carboxaldehyde (20 mmol) in glacial acetic acid (30 mL), was refluxed for 5 h. The reaction mixture was cooled and adding ice water the formed precipitate was

filtered off, washed with water and crystallized from the proper solvent to obtain the desired Schiff bases (**IVa–h**) respectively.

4-(2-Phenyl-6,8-dibromo-4-oxo-(4H)quinazolin-3-yl) benzoic acid (phenyl meth(E) ylidene) hydrazide (IVa)

Crystallized from ethanol to give white crystals, m.p. 220 °C, in 70% yield. Analysis for $C_{28}H_{18}Br_2N_4O_2$, M.wt. (602.28). Calcd.: %C, 55.84; H, 3.01; N, 9.30. Found: 55.75; H, 2.98; N, 9.1. IR (KBr, cm^{-1}): 3360 (NH), 1710, 1683 (2CO) and 1594 (CN). ^{1}H NMR (DMSO-d_6, δ ppm): 7.2–7.74(m, 14H, aromatic-H), 7.8 (s, 1H, H-7, Ar-H), 8.2 (s, 1H, H-5, Ar-H), 8.66(s, 1H, CHN) and 12.00 (s, 1H, NH, exchangeable with D_2O). MS (*m*/*z*, R.I.): M^+ 599.95, 601.95, 603.95 (3.1%, 6.4%, 3.4%) and at *m*/*z* 323.4 (100%).

4-(2-Phenyl-6,8-dibromo-4-oxo-(4H)*quinazolin-3-yl) benzoic acid (4-methoxy phenyl meth(*E*)ylidene) hydrazide (IVb)

Crystallized from ethanol to give yellowish white crystals, m.p. 160 °C, in 79% yield. Analysis for $C_{29}H_{20}Br_2N_4O_3$, M.wt. (632.30). Calcd.: %C, 55.09; H, 3.19; N, 8.86. Found, %C, 54.97; H, 3.00; N, 8.56. IR (KBr, cm^{-1}): 3350 (NH), 1714, 1683 (2CO) and 1594 (CN). ^{1}H NMR (DMSO-d_6, δ ppm): 3.7(3H, s, OCH_3), 7.2–7.6 (m, 13H, aromatic-H), 7.8 (s, 1H, H-7, Ar-H), 8.2 (s, 1H, H-5, Ar-H), 8.66(s, 1H, CHN), and 12.07 (s, 1H, NH, exchangeable with D_2O).

4-(2-Phenyl-6,8-dibromo-4-oxo-(4H)quinazolin-3-yl)benzoic acid (4-methyl phenyl meth(E)ylidene) hydrazide (IVc)

Crystallized from ethanol to give white crystals, m.p. 200 °C, in 80% yield (Analysis for $C_{29}H_{20}Br_2N_4O_2$, M.wt. (616.30). Calcd.: %C, 56.52; H, 3.27; N, 9.09. Found, %C, 56.49; H, 3.30; N, 8.97. IR (KBr, cm^{-1}): 3313 (NH), 1715, 1679 (2CO) and 1595 (CN). ^{1}H NMR (DMSO-d_6, δ ppm): 2.5(3H, s, CH_3), 7.03–7.75 (m, 13H, aromatic-H), 7.8 (s, 1H, H-7, Ar-H), 8.2 (s, 1H, H-5, Ar-H), 8.8(s, 1H, CHN), and 11.2 (s, 1H, NH, exchangeable with D_2O). ^{13}C NMR (DMSO-d_6, δ ppm): 20.5 (CH_3), 113.5 (C-5), 124.2 (C-7), 125.3 (C-2 ,6), 126.4 (C-2 and C-6), 127.3 (C-3), 127.9 (C-4) 128.2 (C-2 and C-6), 129.5 (C-3 andC-5), 129.7(C-1 ,3 , 5),), 130.1 (C-3 and C-5), 130.4 (C-1) 131.3 (C-8), 132.8 (C-6)137.6 (C-1), 139 (C-6), 144.2 (C-4). 147.8 (-N=CH)., 154 (C-4), 156 (C-1), 160 (C-2), 162.8 (CO), MS (*m*/*z*, R.I.): M^+ 613.99, 615.99, 617.99 (5.1%, 10.3%, 5.4%) and at *m*/*z* 498.7 (100%).

4-(2-Phenyl-6,8-dibromo-4-oxo-(4H)quinazolin-3-yl)benzoic acid (4-chloro phenyl meth(E)ylidene) hydrazide (IVd)

Crystallized from ethanol to give white crystals, m.p. 180 °C, in 82% yield. Analysis for $C_{28}H_{17}Br_2ClN_4O_2$, M.wt. (636.72). Calcd.: %C, 52.82; H, 2.69; N, 8.80. Found, %C, 52.79; H, 2.60; N, 8.60. IR (KBr, cm^{-1}): 3415 (NH), 1710, 1680 (2CO) and 1600 (CN). ^{1}H NMR (DMSO-d_6, δ ppm): 7.3–7.76 (m, 13H, aromatic-H), 7.8 (s, 1H, H-7, Ar-H), 8.2 (s, 1H, H-5, Ar-H), 8.8(s, 1H, CHN), and 11.7 (s, 1H, NH, exchangeable with D_2O).

***4-(2-Phenyl-6,8-dibromo-4-oxo-(4H)*quinazolin-3-yl)benzoic acid (3,4-dichloro phenyl meth(E)ylidene) hydrazide (IVe)**

Crystallized from ethanol to give white crystals, m.p. 140 °C, in 82% yield. Analysis for $C_{28}H_{16}Br_2Cl_2N_4O_2$, M.wt. (671.17). Calcd.: %C, 52.82; H, 2.69; N, 8.80. Found, %C, 52.79; H, 2.60; N, 8.60. IR (KBr, cm^{-1}): 3320 (2NH), 1712, 1685 (2CO) and 1605 (CN).

4-(2-Phenyl-6,8-dibromo-4-oxo-(4H)quinazolin-3-yl)benzoic acid (2-hydroxy phenyl meth(E)ylidene) hydrazide (IVf)

Crystallized from ethanol to give yellowish white crystals, m.p. 154 °C, in 80% yield. Analysis for $C_{28}H_{18}Br_2N_4O_3$, M.wt. (618.28). Calcd.: %C, 54.39; H, 2.93; N, 9.06. Found, %C, 54.30; H, 2.70; N, 8.96. IR (KBr, cm^{-1}): 3310 (NH), 1710, 1680 (2CO) and 1600 (CN). MS (*m*/*z*, R.I.): M^+ 615.97, 617.97, 619.97 (4.1%, 8.3%, 4.4%) and at *m*/*z* 500.3 (100%).

4-(2-Phenyl-6,8-dibromo-4-oxo-(4H)quinazolin-3-yl)-benzoic acid (naphthalene-2-yl meth(E)ylidene) hydrazide (IVg)

Crystallized from ethanol to give white crystals, m.p. 145 °C, in 80% yield. Analysis for $C_{32}H_{20}Br_2N_4O_2$, M.wt. (652.33). Calcd.: %C, 58.92; H, 3.09; N, 8.59. Found, %C, 58.81; H, 3.00; N, 8.50. IR (KBr, cm^{-1}): 3400 (NH), 1712, 1681 (2CO) and 1595 (CN). ^{1}H NMR (DMSO-d_6, δ ppm): 7.3–7.72 (m, 16H, aromatic-H), 7.8 (s, 1H, H-7, Ar-H), 8.2 (s, 1H, H-5, Ar-H), 8.7(s, 1H, CHN), and 11.8 (s, 1H, NH, exchangeable with D_2O).

4-(2-Phenyl-6,8-dibromo-4-oxo-(4H)quinazolin-3-yl)-benzoic acid (furan-2-yl meth(E) ylidene) hydrazide (IVh)

Crystallized from ethanol to give white crystals, m.p. 160 °C, in 75% yield. Analysis for $C_{26}H_{16}Br_2N_4O_3$, M.wt. (592.24). Calcd.: %C, 56.52; H, 3.27; N, 9.09. Found, %C, 56.49; H, 3.30; N, 8.97. IR (KBr, cm^{-1}): 3410 (NH), 1715, 1681 (2CO) and 1605 (CN).

4. Conclusion

The objective of the present study was to synthesize and investigate the antimicrobial activity of new quinzoline compound with hope of discovering new structure leads serving as antimicrobial agents.We have synthesized novel series of quinazolin-4(3*H*)-ones compounds to evaluate them on anti-microbial screen. The anti-microbial activity of the synthesized compounds may be due the presence of the versatile pharmacophores and bromine which might increase the lipophilic character of the molecule, which facilitate the crossing through the biological membrane of the micro-organism and thereby inhibit their growth.

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