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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME NOVEL 2,3-DISUBSTITUTED QUINAZOLIN-4(3H)ONES

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يتناول هذا البحث تحضير بعض مشتقات ٣ امينو ٢ مستبدل – فينوكسى ميثيل / بروبيل كينازولين ٤(٣يد) اون (**4a-c**) كمركب وسيط لتشييد مركبات جديدة من ٣ مستبدل امينو كينازولينون. وقد تم ذلك عن طريق تكثيف مركب (**4**) مع ٥ نيترو ٢ فيورالدهيد و٤ نيتروبنزالدهيد وذلك للحصول على مستبدل الميثيليدين امينو (**5,6**) على التوالى. اما تفاعل (**4**)مع الايزاتين فقد نتج عنه مشتقات الاندوليليدين امينو (**7**). وقد تم ايضا تحضير مشتقات الكاربوكساميد (**8**) بتفاعل (**4**) مع كلوريد حمض الأوفلوكساسين. وقد تم تحضير مشتق ال ٣ كلورو استيل امينو ٢ [٣ (٢و٤ ثنائى كلورو فينوكسى) بروبيل] كينازولين ٤(٣يد) أون (**9**) بتفاعل (**4c**) مع كلوريد الكلورو استيل وقد استخدم هذا المركب فى التفاعل مع املاح بعض الاحماض المعروف لها نشاط مضاد للبكتريا وذلك للحصول على المركبات (**10a-c**). هذا وقد تم تقييم فعالية ستة عشر مركبا جديدا ضد بعض انواع ا لبكتريا الموجبة والسالبة الجرام و كذلك ضد فطر الكانديدا و مقارنة هذه المركبات ببعض العقاقير مثل السلفاديازين والنيتروفيورانتوين والأوفلوكساسين والكلوتريمازول كأدوية مرجعية. وقد اظهرت سبعة مركبات فعالية ملحوظة كمضاد للبكتريا (**4a, 4b, 6c, 8a, 8b, 8c, 10a**) اما المركبات (**5a, 5c, 6a, 6b, 7a, 7b**) فقد اظهرت فعالية متوسطة. كما أوضحت النتائج ايضا ان جميع المركبات المختبرة ليس لها اى نشاط مضاد للفطريات ماعدا المركب (**5a**) الذى اظهرفعالية متوسطةضد فطر الكانديدا.

*3-Amino-2-(substituted phenoxymethyl / propyl) quinazolin-4(3H)ones **4a-c** have been prepared. Refluxing **4** with 5-nitro-2-furaldehyde / 4-nitrobenzaldehyde afforded the corresponding substituted methylidene-amino derivatives **5** and **6** respectively. Reaction of **4** with isatin yielded the indolylideneamino derivatives **7**. Refluxing **4** with ofloxacin acid chloride furnished the corresponding carboxamides **8**. Reaction of chloroacetyl chloride*

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*with **4c** produced the 3-chloroacetylamino derivative **9** which upon further reaction with the potassium salts of some antibacterial acids gave the corresponding carboxylate derivatives **10.** Sixteen compounds were screened for their antibacterial and antifungal activities. Thirteen compounds were found to possess (high to moderate) activity against Pseudomonas aerugenosa and some of them were also active against Escherichia coli. Only one compound was found to exhibit moderate antifungal activity against Candida albicans.*

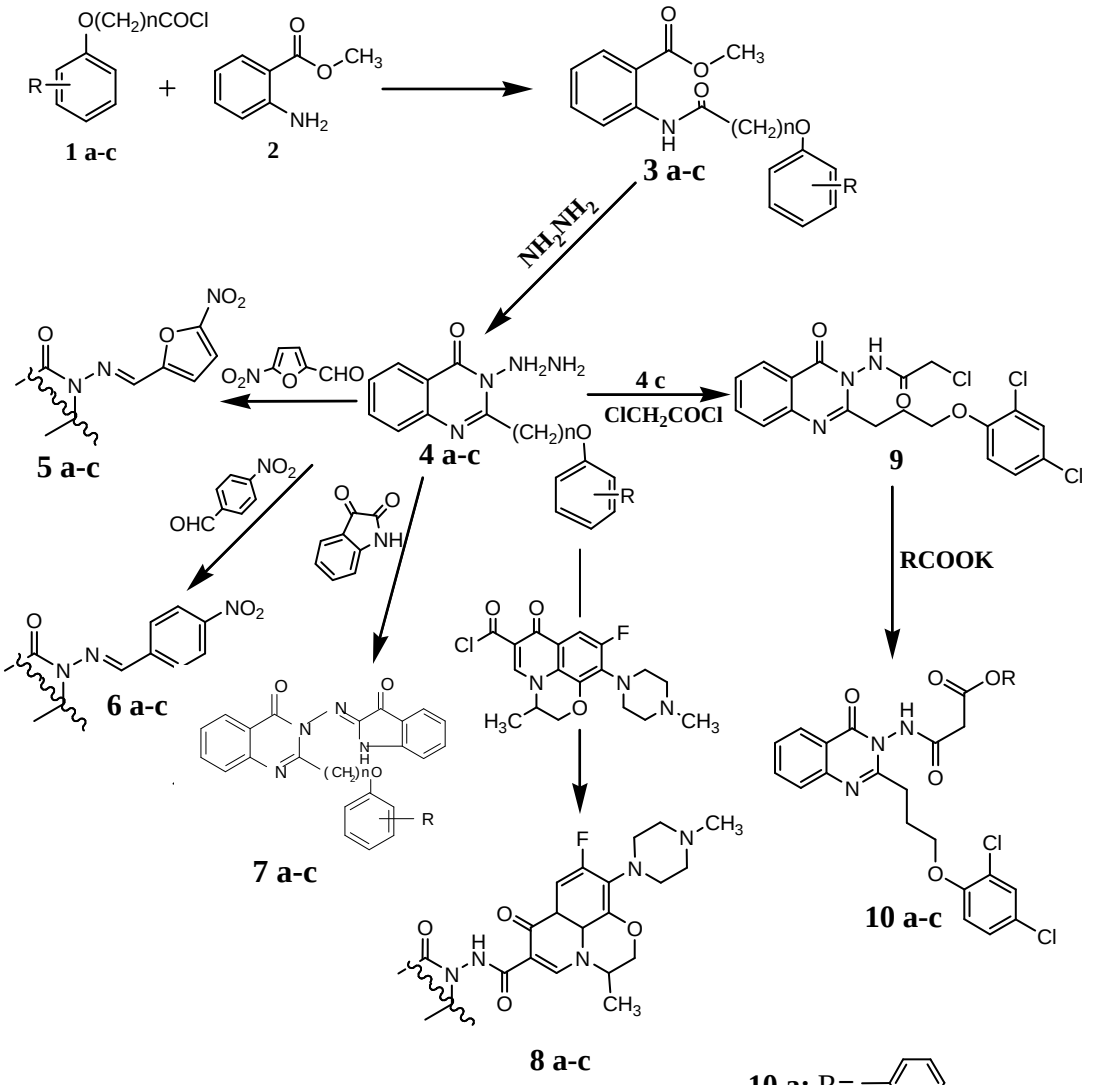
INTRODUCTION

The increasing importance of drug resistance bacterial pathogens is a major challenge for the medicinal chemists. Therefore, the search for novel antibacterial agents is one of the main targets nowadays. Quinazolinone represents one of the interesting nucleus in the field of antimicrobial agents[1-7], in addition to varied pharmacological properties as anti-inflammatory[8&9], analgesic[10], bronchodilator[11], antihyper-tensive[12&13], anticonvulsant[14&15], antidiabetic[16] and anti-HIV[17] agents.

Literature survey has shown that certain 5-nitro-2-furylidene derivatives[18], as well as Schiff bases of isatin[19] possessed marked antimicrobial activity. Also, some quinazolinone derivatives of nalidixic acid demonstrated antibacterial and antifungal activities[7]. Accordingly, the synthesis of quinazolinone derivatives bearing nitrofuran, isatin and ofloxacin moieties at position-3 was described. Also, 2-phenoxymethyl and 2- phenoxypropyl derivatives were prepared in order to investigate the effect of length of side chain at C-2 quinazolinone on the antibacterial activity. In addition, other carboxylate derivatives were prepared by reacting 3-chloroacetylamino quinazolinone with the potassium salts of some antibacterial acids hoping that the newly synthesized quinazolinones might show marked antimicrobial activity.

MATERIALS AND METHODS

Melting points (°C uncorrected) were determined by open capillary tube method using Griffin apparatus. Elemental microanalyses were carried out at Microanalytical Center, Cairo University. Infrared spectra were recorded as KBr discs on JASCO FT / IR-460 Plus spectrophotometer and Bruker FT-IR spectrophotometer Vector 22. ^{1}H-NMR were scanned on Varian Mercury VX- 300-NMR Spectrometer, using TMS as internal standard at-NMR Lab., Department of Chemistry, Faculty of Science, Cairo University Mass spectra were performed on Fenningan MAT, SSQ 7000 GC/MS mass spectrophotometer at 70e V.



1, 3-8 a: n=1, R= 2-Cl

1, 3-8 b: n=1, R= 2, 4-diCl

1, 3-8 c: n=3, R= 2, 4-diCl

10 a: R=

10 b: R=

10 c: R=

Scheme

Chemistry

Methyl 2-(substituted phenoxy acetylamino) benzoate (3a,b)

Methyl 2-[3-(2,4-disubstituted phenoxy) propylcarbonylamino] benzoate (3c)

The appropriate acid chloride **1** (10 mmol) was added gradually to a stirred solution of methyl anthranilate **2** (15 mmol) in dry ether (200 ml). Stirring was continued overnight (20 hours) at room temperature (20-25°C). The ethereal layer was successively washed with 2 M hydrochloric acid (20 ml x 3), then with 2 M sodium hydroxide (20 ml x 3) and finally with water (30 ml). The ether extract was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The separated crystals were recrystallized from ethanol (Table I). **3a:** IR (KBr) 3250.3 (NH), 1705.7 and 1679.0 (CO). **3b**: (KBr) 3258.2 (NH), 1715.5 and 1684.9 (CO). **3c:** (KBr) 3267.0 (NH) and 1679.6 (CO). **3b**: ^{1}H-NMR ($CDCl_3$) δ: 3.91 (s, 3H, $COOCH_3$), 4.72 (s,2H, CH_2O), 6.98-8.76 (m, 7H, ArH), 11.81 (s, 1H, NH). **3c:** ^{1}H-NMR ($CDCl_3$) δ: 2.22-2.28 (m, 2H, $CH_2\underline{CH_2}CH_2O$), 2.70 (t, 2H, $\underline{CH_2}CH_2CH_2O$), 3.89 (s, 3H, $COOCH_3$), 4.13 (t, 2H, CH_2CH_2-$\underline{CH_2}O$), 6.83-8.70 (m, 7H, ArH), 11.10 (s, 1H, NH). **3b**: MS: m/z (%) = M-1: 353 (4.69), 318 (100).

3-Amino-2-(substituted phenoxy-methyl/propyl) quinazolin-4(3H)-ones (4a-c)

A mixture of **3a-c** (10 mmol) and hydrazine hydrate (1 ml, 20 mmol) in n-butanol (50 ml) was refluxed for 8-10 hours. The solvent was concentrated and the separated crystals were filtered, washed with aqueous ethanol and recrystallized from chloroform-ethanol (Table I). **4a**: IR (KBr) 3327, 3264.9 (NH_2), 1676.3 (CO). **4b**: IR (KBr) 3300, 3200 (NH_2), 1670 (CO). **4c:** IR (KBr) 3300, 3200 (NH_2), 1670 (CO). **4a:** ^{1}H-NMR ($CDCl_3$) δ: 5.37 (s, 2H, CH_2O), 5.46 (s, 2H, NH_2), 6.96-8.32 (m, 8H, ArH and quinazolinone H). **4c**: ^{1}H-NMR ($CDCl_3$) δ: 2.26-2.30 (m, 2H, $CH_2\underline{CH_2}CH_2O$), 3.15 (t, 2H, $\underline{CH_2}CH_2CH_2O$), 4.22 (t, 2H, $CH_2CH_2\underline{CH_2}O$), 5.72 (s, 2 H, NH_2), 7.19-8.12 (m, 7H, ArH and quinazolinone H). **4a:** MS: m/z (%) = M^+ 301 (5.42), 266(100).

3-[(5-Nitrofuran-2-yl)methyl-enamino]-2-[(substituted phenoxy) methyl/propyl] quinazolin-4(3H)-ones (5a-c)

3-[(4-Nitrobenzylidenamino)-2-(substituted phenoxy) methyl / propyl] quinazolin-4(3H)ones (6a-c)

A mixture of **4a-c** (1 mmol), 5-nitro-2-furaldehyde / 4-nitrobenz-aldehyde (1.1 mmol) in glacial acetic acid (20 ml) was heated under reflux for 4 hours. The solvent was evaporated under reduced pressure. The residue was washed with aqueous ethanol and recystallized from the appropriate solvent (Table I). **5a:** IR (KBr) 1680 (CO). **5b:** IR (KBr) 1680 (CO). **5c**: IR (KBr) 1673.5 (CO). **5a:** ^{1}H-NMR ($CDCl_3$) δ: 5.45 (s, 2H, CH_2O), 6.87-8.35 (m, 10 H, ArH, furyl H and quinazolinone H), 9.52

Table I: Physical and analytical data of the prepared compounds.

Compd. No.	Yield %	M.P.°C Solvent of crystallization	Molecular formula (Mol. Wt)	Microanalysis Calculated / Found		
				C%	H%	N%
3a	93	98-99 a	$C_{16}H_{14}ClNO_4$ (319.74)	60.10 59.99	4.41 4.92	4.38 4.35
3b	90	120-22 a	$C_{16}H_{13}Cl_2NO_4$ (354.19)	54.26 54.10	3.70 3.90	3.95 3.95
3c	80	86-8 a	$C_{18}H_{17}Cl_2NO_4$ (382.24)	56.56 56.60	4.48 4.70	3.66 3.36
4a	85	198-200 b	$C_{15}H_{12}ClN_3O_2$ (301.73)	59.71 59.40	4.01 4.00	13.93 13.95
4b	88	200-02 b	$C_{15}H_{11}Cl_2N_3O_2$ (336.18)	53.59 53.76	3.30 3.52	12.50 12.47
4c	86	128-30 b	$C_{17}H_{15}Cl_2N_3O_2$ (364.23)	56.06 56.38	4.15 4.24	11.54 11.50
5a	70	170-72 c	$C_{20}H_{13}ClN_4O_5$ (424.80)	56.55 56.72	3.08 3.14	13.19 12.99
5b	73	202-04 b	$C_{20}H_{12}Cl_2N_4O_5$ (459.25)	52.31 52.27	2.63 2.48	12.20 12.27
5c	70	138-40 b	$C_{22}H_{16}Cl_2N_4O_5$ (487.30)	54.23 54.30	3.31 3.40	11.50 11.47
6a	72	210-12 d	$C_{22}H_{15}ClN_4O_4$ (434.84)	60.77 60.80	3.48 3.50	12.88 12.81
6b	72	242-44 d	$C_{22}H_{14}Cl_2N_4O_4$ (469.28)	56.31 56.62	3.01 3.20	11.94 11.21
6c	75	200-02 b	$C_{24}H_{18}Cl_2N_4O_4$ (497.34)	57.96 58.14	3.65 3.82	11.27 11.22
7a	75	290-92 d	$C_{23}H_{15}ClN_4O_3$ (430.85)	64.12 64.42	3.51 3.12	13.00 13.21
7b	72	202-04 d	$C_{23}H_{14}Cl_2N_4O_3$ (465.30)	59.37 58.70	3.03 3.88	12.04 12.14
7c	70	210-12 d	$C_{25}H_{18}Cl_2N_4O_3$ (493.35)	60.85 60.81	3.65 3.66	11.36 11.26
8a	65	190-92 a	$C_{33}H_{29}FClN_6O_5$ (644.08)	61.54 61.33	4.54 4.42	13.05 12.98
8b	70	192-94 a	$C_{33}H_{28}FCl_2N_6O_5$ (678.53)	58.42 58.00	4.16 4.30	12.39 12.45
8c	70	122-24 a	$C_{35}H_{32}FCl_2N_6O_5$ (706.58)	59.50 59.30	4.56 4.40	11.89 11.87
9	80	130-32 c	$C_{19}H_{16}Cl_3N_3O_3$ (440.71)	51.78 52.09	3.66 3.79	9.53 9.51

Table I: Continue.

Compd. No.	Yield %	M.P.°C Solvent of crystallization	Molecular formula (Mol. Wt)	Microanalysis Calculated / Found		
				C%	H%	N%
10a	75	87-9 c	$C_{26}H_{21}Cl_2N_3O_5$ (526.38)	59.33 59.39	4.02 3.97	7.98 7.68
10b	75	160-62 c	$C_{26}H_{21}Cl_2N_3O_6$ (542.38)	57.58 57.40	3.90 4.00	7.75 7.72
10c	70	158-60 c	$C_{37}H_{34}FCl_2N_6O_7$ (763.61)	58.20 57.60	4.36 4.80	11.01 11.80

a= Ethanol; b= Chloroform-ethanol; c= Aqueous ethanol and d= DMF.

(s, 1H, N=CH). **5c**: ^{1}H-NMR ($CDCl_3$) δ: 2.41-2.45 (m, 2H, $CH_2\underline{CH_2}CH_2O$), 3.28 (t, 2H, $\underline{CH_2}CH_2CH_2O$), 4.24 (t, 2H, $CH_2CH_2\underline{CH_2}O$), 6.88-8.29 (m, 9H, ArH, furyl H and quinazolinone H), 9.60 (s, 1H, N=CH). **6b:** IR (KBr) 1676.6 (CO). **6c:** IR (KBr) 1675.4 (CO). **6b**: ^{1}H-NMR (DMSO-d6) δ: 5.49 (s, 2H, CH_2O), 7.30-8.32 (m, 11H, ArH and quinazolinone H), 9.42 (s, 1H, N=CH). **6c:** ^{1}H-NMR (DMSO-d_6) δ: 2.24-2.28 (m, 2H, $CH_2\underline{CH_2}CH_2O$), 3.11 (t, 2H, $\underline{CH_2}CH_2$-CH_2O), 4.22 (t, 2H, $CH_2CH_2\underline{CH_2}O$), 7.15-8.26 (m, 11H, ArH and quinazolinone H), 9.26 (s, 1H, N=CH). **5a:** MS: m/z (%)= M^+ 424 (2.54), 389 (100). **5c:** MS: m/z (%) = M^+ 487 (0.20), 187 (100). **6c**: MS: m/z(%)= M^+ 497 (1.15), 187 (100).

3-(2-Oxo-3-indolinylideneamino)-2-[(substituted phenoxy) methyl / propyl]quinazolin-4 (3H)ones (7a-c)

A mixture of **4 a-c** (2 mmol) and isatin (2 mmol) in glacial acetic acid (20 ml) was refluxed for 4-6 hours. The separated crystals were filtered, washed with ethanol and recrystallized from DMF (Table I). **7a**: IR (KBr) 3211 (NH), 1696.0, 1660.5 (CO). **7b**: IR 3199.9 (NH), 1699, 1677.0 (CO). **7c**: IR (KBr) 3231.3 (NH), 1651.9, 1739.0 (CO). **7a:** ^{1}H-NMR (DMSO-d_6) δ: 4.81(s, 2H,CH_2 O), 6.85-8.38 (m, 12H, ArH and quinazolinone H), 11.86 (s,1H,NH). **7c**: ^{1}H-NMR (DMSO-d_6) δ: 2.51-2.53 (m, 2H, $CH_2\underline{CH_2}CH_2O$), 3.18 (t, 2H, $\underline{CH_2}CH_2CH_2O$), 4.08 (t, 2H,$CH_2CH_2\underline{CH_2}O$), 7.22-8.38 (m, 11H, ArH and quinazolinone H), 11.81 (s, 1H, NH). **7a:** MS: M^+ 430 (20), 76 (100).

N-{2-[-2-(Substituted phenoxy) methyl / propyl]-4-oxo-3,4-dihydro-quinazolin-3-yl)}-9-fluoro-3-methyl-10-(4-methylpiperazin-1-yl)-7-oxo-3,5,7,7a-tetrahydro-2H-[1,4]oxazino [2,3,4-*ij*]quinoline-6-carboxamide (8a-c)

A mixture of **4a-c** (1 mmol), ofloxacin acid chloride (0.38 g, 1 mmol) and anhydrous potassium carbonate (0.14 g, 1 mmol) in dry

benzene (30 ml) was refluxed for 6 hours. The reaction mixture was filtered while hot and the solvent was evaporated under reduced pressure. The residual mass was solidified by trituration with aqueous ethanol and recrystallized from ethanol (Table I). **8c**: IR (KBr) 3283.9 (NH), 1740.2, 1653.1 (CO). **8b**: ^{1}H-NMR ($CDCl_3$) δ: 1.23 (d, 3H, oxazine -C_3-CH_3), 2.60 (S, 3H, N-CH_3 piperazine), 2.80-3.00 (br, 4H, 2 x CH_2 piperazine), 3.60-3.70 (br, 4H, 2xCH_2 piperazine), 4.70 (d, 2H, oxazine- C_2-H), 5.20-5.40 (m, 1H, oxazine- C_3-H), 5.33 (S, 2H, CH_2O quinazolinone-C_2), 7.07 - 8.31 (m, 9H, ArH and quinazolinone H), 8.60 (s, 1H, NHCO). **8c:** MS: m/z (%)= M +1: 707 (0.72), 360 (100).

3-Chloroacetylamino-2-[3-(2,4-dichlorophenoxy)propyl]quinazolin-4(3H)one (9)

Chloroacetyl chloride (1.2 ml, 10 mmol) was added portionwise to a solution of **4c** (3.6 g, 10 mmol) in dimethylformamide (20 ml). The mixture was stirred at room temperature for 2-3 hours and poured onto ice. The separated solid was filtered, washed with water, dried and recrystallized from aqueous ethanol (Table I). IR (KBr) 3174.0 (NH), 1708.0, 1674.0 (CO). ^{1}H-NMR ($CDCl_3$) δ: 2.36-2.41 (m, 2H, CH_2-$\underline{CH_2}CH_2O$), 2.99 (t, 2H, $\underline{CH_2}CH_2$-CH_2O), 4.18 (t, 2H, $CH_2CH_2\underline{CH_2}O$), 4.85 (s, 2H, $COCH_2$), 6.85-8.22 (m, 7H, ArH and quinazolinone H), 8.86 (s, 1H, NHCO). MS: m/z (%)= M^+ 441 (0.26), 187 (100).

2-[3-(2,4-Dichlorophenoxypropyl)-4-oxoquinazolin-3(4H)-yl carbamoyl] methyl benzoate and salicylate (10a and b)

2-[3-(2,4-Dichlorophenoxypropyl)-4-oxoquinazolin-3-(4H)-yl carbamoyl] methyl-9-fluoro-3,7-dihydro-3-methyl-10-(4-methylpiperazin-1-yl)-7-oxo-2H-[1,4]oxazino[2,3,4-ij] quinoline 6-carboxylate 10c

A mixture of **9** (0.44 g, 1 mmol) and the potassium salt of the appropriate acid (1 mmol) in DMF (20 ml) was heated in a water-bath for 4-6 hours. The reaction mixture was poured onto ice-cold water, the separated solid was filtered, washed with water, dried and recrystallized from aqueous ethanol (Table I). **10a**: IR (KBr) 3284.2(NH), 1717.5, 1677.2 (CO). **10b**: IR (KBr) 3284.6 (NH), 1681.4, (CO). **10c:** IR (KBr) 3284.5 (NH), 1717.5, 1655.2 (CO). **10a:** ^{1}H-NMR ($CDCl_3$) δ: 2.37-2.47 (m, 2H, $CH_2\underline{CH_2}CH_2O$), 3.28, (t, 2H, $\underline{CH_2}$-CH_2CH_2O),4.21 (t, 2H, CH_2CH_2-$\underline{CH_2}O$), 4.87 (s, 2H, $COCH_2$), 6.83-8.25 (m, 12H, ArH and quinazolinone H), 8.57 (s, 1H, NHCO). **10b:** ^{1}H-NMR ($CDCl_3$) δ: 2.41-2.45 (m, 2H, $CH_2\underline{CH_2}CH_2O$), 3.08 (t, 2H, $\underline{CH_2}CH_2$-CH_2O), 4.22 (t, 2H, $CH_2CH_2\underline{CH_2}O$**),** 5.10 (s, 2H, $COCH_2$), 6.83-8.26 (m, 11H, ArH and quinazolinone H), 8.61 (s, 1H, NHCO), 10.28 (s, 1H, OH). **10b**: MS: m/z (%) = M +1: 543 (0.20), 187 (100).

Antimicrobial Activity

Sixteen compounds were evaluated for their *in vitro* antibacterial and antifungal activity by the MIC method[20]. The

microbiological screening was carried out against *Staphylococcus aureus* and *Bacillus subtilis* as examples of Gram positive bacteria, *Escherichia coli*, and *Pseudomonas aeruginosa* as examples of Gram negative bacteria, in addition to *Candida albicans* as an example of fungi.

Materials and Methods

A stock solution of the tested compounds was prepared in a concentration of (1000 µg/ml) in DMF and two folds serial dilution were made in the same solvent. Each dilution was added to 20 ml nutrient agar medium to yield the final test concentrations in the range of 12.5-400 µg/ml. Controls were prepared using the same quantities of DMF as blank. The mixtures were mixed, poured into sterile petri dishes and allowed to harden at room temperature. The agar surface was inoculated with 10 ml of a standardized suspension of the test organisms (10^6 cell/ml) and incubated at 37°C for 24-48 hours. Standard plates containing nitrofurantoin, ofloxacin, sulfadiazine and clotrimazole as reference drugs were examined side by side (Table II).

Table II: The minimum inhibitory concentration (MIC) of the tested compounds.

Compd. No.	MIC µg/ml				
	Staph.aureus	*Bacillus subtilis*	*E.coli*	*Pseudomonas aeroginosa*	*Candida albicans*
4a	>400	>400	400	<12.5	<400
4b	>400	>400	>400	<12.5	200
4c	400	200	>400	100	100
5a	<12.5	400	25	25	50
5b	200	>400	25	400	200
5c	50	400	400	50	100
6a	>400	>400	>400	50	400
6b	>400	>400	>400	50	400
6c	400	>400	.400	<12.5	>400
7a	400	>400	400	25	>400
7b	>400	400	>400	25	400
8a	400	100	<12.5	<12.5	400
8b	>400	400	400	<12.5	100
8c	200	200	50	<12.5	>400
9	>400	>400	>400	>400	200
10a	>400	200	100	<12.5	100
Sulfadiazine	400	<12.5	50	100	>400
Nitrofurantoin	<12.5	<12.5	<12.5	<12.5	>400
Ofloxacin	<12.5	<12.5	<12.5	<12.5	>400
Clotrimazole	>400	>400	>400	>400	<12.5

RESULTS AND DISCUSSION

Methyl N-substituted phenoxy-methyl / propyl anthranilate derivatives **3a-c** were prepared according to a method reported for the synthesis of certain 2-substituted quinazolinones[21].

Reacting the appropriate substituted phenoxyacetyl / butyryl chloride **1** with methyl anthranilate **2** in dry ether afforded methyl N-substituted anthranilate derivatives **3a-c**. IR spectrum of **3a** showed the presence of a band at 3250.5 cm^{-1} attributed to (NH) and two bands at 1750.7 and 1679.8 cm^{-1} due to the (COs) of the ester and amide. ^{1}H-NMR of **3b** revealed three singlets at δ 3.91, 4.72 and 11.81 assigned for $COOCH_3$, CH_2O and NHCO protons respectively. Mass spectrum of **3b** indicated M-1: 353.

Refluxing **3a-c** with hydrazine hydrate in n-butanol yielded the 3-aminoquinazolinones **4a-c.** IR spectrum of **4a** showed the presence of a forked band at 3327.0 and 3264.9 cm^{-1} due to (NH_2) and a band at 1676.3 cm^{-1} corresponding to (CO) of the quinazolinone. ^{1}H-NMR ($CDCl_3$) of **4**a showed two singlets at δ 5.37 and 5.46 due to the two protons of (CH_2O) and (NH_2) respectively. ^{1}H-NMR of **4c** demonstrated the signals of the propyl moiety: multiplet at δ 2.26-2.30 and two triplets at δ 3.15 and 4.22 corresponding to the methylene protons of the propyl chain. Mass spectrum of **4a** showed M^+ 301.

5-Nitro-2-furylidenes **5a-c** and 4-nitrobenzylidenes **6a-c** were obtained by refluxing **4** with 5-nitro-2-furaldehyde and 4-nitrobenzaldehyde respectively in glacial acetic acid. IR spectrum of **5a** lacked the bands attributed to (NH_2) and showed a band at 1680.0 cm^{-1} corresponding to the (CO). ^{1}H-NMR of **5a** revealed the disappearance of the singlet at δ 5.46 corresponding to the(NH_2) protons and showed a new singlet at δ 9.52 assigned to the (CH=N) proton. Mass spectrum of **5a** showed a molecular ion peak at M^+ 424. Also, IR spectrum of **6c** showed the disappearance of the (NH_2) bands and the presence of the band at 1675.4 cm^{-1} due to the (CO).

^{1}H-NMR of **6b** lacked the singlet at δ 5.70 of the (NH_2) protons and showed an increase in the integration of aromatic protons (7 to 11Hs), in addition to a singlet at δ 9.42 due to the (CH=N) proton. Mass spectrum of **6c** demonstrated M^+ 497.

Similarly, the indolylideneamino derivatives **7a-c** were achieved by refluxing **4** with isatin in glacial acetic acid. IR spectrum of **7a** showed the disappearance of the (NH_2) bands and the presence of a band at 3211.0 cm^{-1} due to (NH) and two bands at 1696.0 and 1660.5 cm^{-1} attributed to the (COs). ^{1}H-NMR of **7a** revealed the absence of the singlet at δ 5.46 due to the (NH_2) protons and showed an increase in the integration of the aromatic protons (8-12Hs). Mass spectrum of **7a** revealed M^+ 430.

As previously reported, the amide of nalidixic acid bearing a quinazolinyl nucleus was prepared[7] via reaction of nalidixic acid hydrazide with 4*H*-3,1-benzoxazin-4-one. In the present work, the carboxamide derivatives **8a-c** were synthesized by reacting **4** with ofloxacin acid chloride in dry benzene and in presence of anhydrous potassium carbonate. IR spectrum of **8c** showed the disappearance of the bands characteristic for the (NH_2) and showed a band at 3283.9 cm^{-1} due to (NH), in addition to two bands at 1740.2 and 1653.1 cm^{-1} corresponding to (COs). ^{1}H-NMR of **8b** showed three singlets at δ 1.23, 2.60 and 8.60 assigned for C_3-CH_3 oxazine, N-CH_3 piperazine and NHCO protons respectively, in addition to the characteristic signals of the piperazine. Mass spectrum of **8c** showed M+1: 707.

A simple method was performed to synthesize the 3-chloroacetylamino derivative **9**, this was achieved by stirring **4c** with chloroacetyl chloride at room temperature in DMF. IR spectrum lacked the bands of the (NH_2) and showed a band at 3174.0 cm^{-1} related to (NH) and at 1708.0, 1674.0 cm^{-1} due to the (COs). ^{1}H-NMR demonstrated the characteristic signals of the propyl moiety, in addition to two singlets at δ 4.85 and 8.86 related to $COCH_2Cl$ and NHCO protons respectively.

Heating **9** with the appropriate potassium salts of some antibacterial acids in DMF gave the corresponding carboxylate derivatives **10a-c.** IR spectrum of **10a** showed a band at 3284.2 cm^{-1} due to (NH) and two bands at 1717.5, 1677.2 cm^{-1} attributed to (COs). ^{1}H-NMR of **10b** revealed the presence of the characteristic signals of the propyl moiety and three singlets at δ 5.10, 8.61 and 10.28 assigned for $COCH_2$, NHCO and ArOH protons respectively, in addition to an increase in the integration of the aromatic protons (7-11Hs). **10b** Mass spectrum indicated M+1: 543.

Microbiological Evaluation

The antimicrobial screening of the sixteen representative compounds indicated that the 3-aminoquinazolinones **4a** and **4b** having substituted phenoxymethyl moiety at C-2 exhibited marked antibacterial activity against *Pseudomonas aeruginosa*, while increasing length of the side chain to phenoxypropyl **4c** decreased the antimicrobial activity. Also, the Schiff bases **5a**, **5b**, **5c** bearing the 5-nitrofurylidene moiety and **6a, 6b** including the 4-nitrobenzylidene as their isosters, in addition to the isatin derivatives **7a**,**7b** displayed moderate antibacterial activity against *E. coli* and *Pseudomonas aeruginosa*, except **5a** and **6c** that demonstrated marked activity against *Staphylococcus aureus* and *Pseudomonas aeruginosa* respectively. Hybridization of the quinazolinone derivatives **4a-c** with ofloxacin moiety through an amide linkage afforded the carboxamide derivatives **8a**, **8b** and **8c** that revealed a potent antibacterial activity

against *Pdeudomonas aeruginosa*. Additionally compound **8a** possessed a pronounced antibacterial activity against *E. coli*. Substitution of the 3-amino functionality of **4c** to 3-chloroacetylamino **9** produced a compound with no antimicrobial activity, whereas further substitution to the carbamoyl methylbenzoate **10a** increased the activity against *Pseudomonas aeruginosa*.

Conclusion

The antimicrobial screening of the tested compounds showed that seven compounds **4a**, **4b**, **6c**, **8a**, **8b**, **8c** and **10a** exhibited marked antibacterial activity against *Pseudomonas aeruginosa*. Also, compounds **5a** and **8a** demonstrated pronounced activity against *Staphylococcus aureus* and *E. coli* respectively. In addition, compounds **5a**, **5c**, **6a**, **6b**,**7a** and **7b** showed moderate antibacterial activity against *Pseudomonas aeruginosa*. All the tested compounds showed no antifungal activity, except **5a** which displayed a moderate activity against *Candida albicans*.

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