1 *Egypt. J. Chem.* **54**, No. 1, pp. 1-15 (2011)

Synthesis and Biological Activity of Some New Substituted Quinazolin-4(3H)-Ones

Nadia T.A. Dawood, Nahed F. Abdel-Ghaffar and Fekria M.A. Soliman*
Department of Chemistry, Faculty of Science "Girls", Al-Azhar University, Cairo, Egypt.

3 - (4-AMINOPHENYL)-2-benzyl-4-oxo-3,4-dihydroquinazoline 1a and 3 - (4 - aminophenyl) - 2 - benzyl - 6 - bromo - 4 - oxo - 3, 4 dihydroquinazoline 1b were prepared and diazotized by nitrous acid to give ″2a, b″. The diazonium chloride derivatives were converted to the corresponding 3-arylhydrazono derivatives on treatment with active methylene compounds namely acetylacetone, ethyl acetoacetate and/or ethyl cyanoacetate. The hydrazono derivatives were converted to the corresponding pyrimidino derivatives ″6a-f″, pyrazolo derivatives ″7a-d″ and pyrazoline derivatives ″8a-d″ and ″9a-f″ in order to study their antimicrobial activity. A significant level of activity of the new products was observed.

Keywords: 2- Benzyl - 4(3H) quinazolinone - 4 - (3H) - one, 6-Bromo derivative, Aryl hydrazones, β-Diketones and Biological activity.

Quinazolinone derivatives attract a widespread interest due to their biological activities (1). They are pharmaceutically important as antifibrillatory, choleretic, antiphlogistic(2), and anticonvulsant agents(3). They have also been successfully tested as inhibitors of the DNA repair enzyme poly (ADP-ribose) polymerase (4) and for their antineoplastic activity (5). It is well known that both pyrimidine(6-8) and pyrazole(9-11) moieties possess various therapeutic activities.

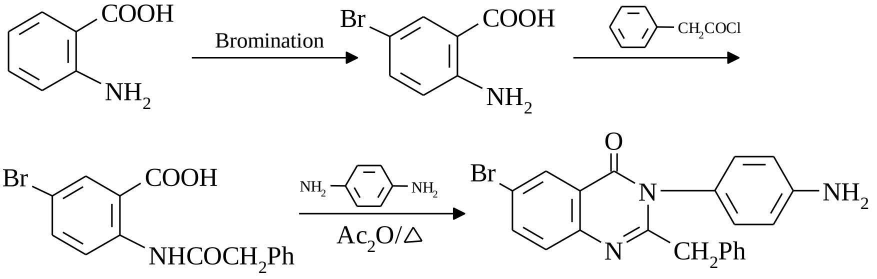
The formation of 2-alkyl-4 (3H) quinazolinones by condensation of anthranilic acid or substituted anthranilic acid and amides is designated as the Niementowski reaction (12). Ziegler, Steiger and Kappe(13) also demonstrated the formation of 2-alkyl, 2-aralkyl and 2-aryl-4(3H) quinazolinones in moderate yields from isatoic anhydride as the source of the anthraniloyl group and the corresponding carboxamide. In view of these and in continuation of our earlier work on substituted-quinazolin-4(3H)-ones (14-17), it was thought of interest to combine the pharmacophoric groups (pyrimidine, prazoline) as well as quinazoline moiety. The new compounds have been synthesized and screened for their antimicrobial activities.

---

*Author to whom correspondence should be addressed E-mail: kachef_hicham@yahoo.com

Results and Discussion

3- (4-aminophenyl) - 2 - benzyl -4 - oxo -3, 4- dihydroquinazoline″1a″ and 3-(4-aminophenyl) - 2 - benzyl - 6 - bromo - 4 - oxo - 3, 4-dihydroquinazoline ″1b″ were prepared according to the literature procedures (18-20). These derivatives which bear a bulky substituent at position-2 (14, 16). (*c.f.* Fig 1).



(1b)

Fig. 1.

Compounds ″1a, b″ were subjected to diazotization with nitrous acid ($NaNO_2$ and HCl) at 0-5°C to give 4-(2-benzyl-4-oxo-3, 4-dihydroquinazolin-3-yl) benzene diazonium chloride ″2a″ and 4-(2-benzyl-6-bromo-4-oxo-3, 4-dihydro-quinazolin-3-yl) benzene diazonium chloride ″2b″. Treatment of ″2a,b″ with β-diketones namely, acetylacetone, and ethylacetoacetate or active methylene compounds such as ethyl cyanoacetate in boiling ethanol containing fused sodium acetate afforded the corresponding 3-{4-(2-benzyl-4-oxo-3,4-dihydroquinazlin-3-yl) phenylhydrazono}pentane-2,4-diones ″3a″, 3-{4-(2-benzyl-6-bromo-4-oxo-3,4dihydroquinazlin-3-yl)phenyl hydrazono}pentane-2,4-diones″3b″,2-{4-(2-benzyl-4-oxo-3,4-dihydroquinazlin-3-yl) phenylhydrazono}-3-oxobutanoic acid ethyl esters ″4a,b″ and 2-{-4-(2-benzyl-4-oxo-3,4-dihydroquinazlin-3-yl)phenylhydrazono}-3-cyanoaceticc acid ethyl esters ″5a,b″, respectively. The IR spectrum of 3a agreed well with the proposed structure(18) The mass spectra of compounds which contain bromine atoms 3b, 4b and 5b showed fragments corresponding to the typical bromine isotopes (^{79}Br and ^{81}Br) patterns.

Interaction of the hydrazono derivatives ″3a, b″ with guanidine hydrochloride, thiourea and urea in refluxing ethanol afforded the cyclized products 2 - benzyl - 3 - {4-(2- amino-4,6-dimethyl} - 2, 5 - dihydropyrimidin-5-ylildine) hydrazinophenyl}- 4-oxoquinazolines ″6a,d″, 6-bromo-2-benzyl-3-{4-(2 - imino - 4, 6 - dimetyyl - 2 - thioxopyrimidin - 5 - ylildine) hydrazinophenyl}-4-oxoquinazolines ″6b-e″ and 2 - benzyl - 3 - {4 - (2 - imino - 4, 6 - dimetyyl -2-oxopyrimidin-5-ylildine) hydrazinophenyl}-4-oxoquinazolines ″6c,f″ .This is in agreement with the previous findings (21, 22).

Similarly, the hydrazonoquinazolone derivatives ″3a, b″ reacted with phenylhydrazine and 4-nitrophenyl hydrazine in boiling acetic acid containing sodium acetate giving the corresponding2-benzyl-3-{4-(3,5-dimethyl-1-phenyl-1-H-pyrazol-4-yl)azophenyl}-4-oxoquinazolines ″7a″, 2-benzyl-6-bromo-3-{4-(3,5-dimethyl-1-phenyl-1H-pyrazol-4-yl)-4-oxoquinazolines ″7b″ , 2-benzyl-3-{4-(3,5-dimethyl-1(-4-nitrophenyl-1H- pyrazol-4-yl)-4-oxoquinazolines ″7c″ and 2 - benzyl - 6-bromo - 3 -{4-(3,5-dimethyl - 1 (-4-nitrophenyl-1H- pyrazol-4-yl) - 4-oxoquinazolines ″7d″, respectively via thermal cyclization.

Interaction of the substituted hydrazono quinazolone derivatives ″4a,b″ with hydrazines, namely, hydrazine hydrate, phenyl hydrazine and 4-nitrophenylhydrazine in boiling ethanol afforded the corresponding 2-benzyl-3-{4- (3-methyl - 5 - oxo -4, 5- dihydro -1H- pyrazol- 4-ylidine) hydrazinophenyl}-4-oxoquinazolines ″8a-f″ ,respectively. Compounds ″8a-f″ was established by their correct analytical and spectral data.

Reaction of ″5a, 5b″ with hydrazine hydrate and methyl hydrazine in refluxing ethanol afforded the corresponding 2-benzyl-3-{-4-(3-amino-5-oxo-4, 5-dihydro-1Hpyrazol-4-ylidine) hydrazinophenyl}-4-oxoquinazolines ″9a-d″, respectively. The structure of compounds ″9a-d″ was elucidated from correct analytical and spectral data.

Experimental

Melting points were determined (by using the open capillary tube method) using a Gallen-Kamp apparatus and are uncorrected. The IR spectra were measured by a unicam SP 1200 spectrophotometer using KBr discs. The ^{1}H-NMR as well as ^{13}C-NMR were recorded with a Bruker 250 MHz and 62.9 MHz, respectively using DMSO-d_6 as a solvent and TMS as internal reference, the chemical at 90°C inlet temperatures. Elemental analyses were carried out at the CMLS (Cairo University shifts δ are given in ppm. The mass spectra were run on a 7070 mass spectrometer at 70 eV). Purity of the compounds was checked on thin layer chromatography (TLC) plates (silica gel G) in the solvent system toluene ethyl formate/formic acid (5:4:1) and benzene-methanol (8:2), the spots were located under iodine vapors or UV light.

Synthesis of-3-(4-aminophenyl)-2-benzyl-4-oxo-3,4-dihydroquinazoline "1a" and 3-(4-aminophenyl)-2-benzyl-6-bromo-4-oxo-3,4-dihydroquinazoline "1b"(18-20)

General procedure

Diazotization of "1a, b". Formation of 4- (2- benzyl - 4 - oxo - 3, 4 - dihydroquinazolin - 3 - yl) benzene diazonium chloride "2a" and 4-(2-benzyl-6-bromo - 4 - oxo - 3, 4-dihydro-quinazolin -3-yl) benzene diazonium chloride "2b":

A well stirred cold solution of ″1a″ or ″1b″ (3.2g, 4.0g; 0.01 mol) in 3ml of conc. HCl and 5 ml of water was diazotized by a cold solution of $NaNO_2$ (0.7g; 0.01 mol, dissolved in 1.8mlof water) stirring was then continued for 30 min, then it was triturated with petroleum ether (b.p40-60°) to give ″2a ,b″, respectively.

Reaction of "2a, b" with acetyl acetone. Formation of 3-{4-(2-benzyl-4-oxo-3,4-dihydroquinazlin-3-yl) phenylhydrazono}pentane-2,4-diones "3a" and 3-{4-(2-benzyl-6-bromo-4-oxo-3,4dihydroquinazlin-3-yl)phenyl hydrazono}pentane - 2,4-diones "3b"

To a cold well stirred solution of acetyl acetone (1g; 0.01 mol) in 30 ml of ethanol containing sodium acetate (4.1g; 0.05 mol), the diazonium chloride ″2a″ (3.7g, 0.01 mol) and ″2b″ (4.5g; 0.01 mol) was added, dropwise while stirring during 30 min. Stirring was then continued at room temperature for 30 min and the solid that separated was filtered off, washed well with dilute ethanol and recrystallized from ethanol to give ″3a, b″. (*c.f.* Table 1).

3a: as yellow crystals IR, ″ υ/cm^{-1}″: 3422 (NH); 3058, 2928, 2822 (CH); 1717, 1658(C=O); 1606 (C=N); 1598 (C=C). ^{1}H-NMR; δ 11.01 (s, 1H, NH), 7.31-7.95 (m, 13H, Ar–H), 2.41 (2 x s, 2 x 3H, 2x $COCH_3$), 2.12 (s, 2H, $\underline{CH_2}$pH). ^{13}C-NMR, δ168.9 (2x CO acetyl), 160.9 (C–4), 154.6 (C–2), 148.2 (C–8a), 141.9 (C-1Ph), 134.9 (C–7), 133.7 (2C Ph, C–2,6), 132.2 (2C Ph, C–$1^{\backslash}$, $4^{\backslash}$), 130.1 (2CPh, C–$2^{\backslash}$,$6^{\backslash}$), 128.7 (C–5), 127.1 (C-8), 126.4 (2C Ph, C-3,5), 126.1 (C–6), 122.9, (C–4a), 120.9 (2C Ph, C–$3^{\backslash}$,$5^{\backslash}$), 119.9 (C-4Ph), 29.2 ($\underline{CH_2}$–Ph), 23.9 (2C, CH_3 acetyl). MS, m/z (%): 439(M^{+} +1) (19.7), 438 (M^{+}) (77.9), 395(42.1), 380(67.6), 352(52.2) 325(37.4), 225 (33.5), 148(100), 117(3.8), 91(15.1), 77 (11.3), 76 (4.4).

3b: crystallized as yellow needless IR, ″ υ/cm^{-1}″:3401 (NH); 3120, 2958, 2822 (CH), 1707, 1669 (C=O), 1610 (C=N), 1599 (C=C). ^{1}H-NMR: δ11.11 (s, 1H, NH), 7.19-8.01 (m, 12H, ArH), 2.59 (2x s, 2x3H, 2xCO$\underline{CH_3}$), 2.11 (s, 2H, $\underline{CH_2}$Ph). ^{13}C-NMR, δ 169.3 (2 x CO acetyl), 163.1 (C–4), 156.1 (C-2), 149.4 (C-8a), 143.2 (C–1 Ph), 137.3 (C-7), 133.7 (C-4a), 132.6 (C–5), 132.2 (2C Ph, C–$1^{\backslash}$,$4^{\backslash}$), 131.9 (2CPh, C-$2^{\backslash}$,$6^{\backslash}$), 130.1 (C-8), 128.7 (2CPh, C–3,5), 128.3 (C–6), 128.1 (2CPh, C-$3^{\backslash}$,$5^{\backslash}$), 125.9 (C-4 Ph), 34.4 ($\underline{CH_2}$–Ph), 29.2 (2C, CH_3 acetyl) MS, m/z (%) 521 (M^{+} + 4) (31.1), 519 (M^{+} +2) (30.9), 517 (M^{+}) (14.9), 431 (27.6), 404 (76.2), 314 (55.2), 237(31.4), 143(7.6), 90(11.3), 77 (12.9), 76 (14.4).

Reaction of "2a, b" with ethyl acetoacetate. Formation of 2-{4-(2-benzyl-4-oxo-3, 4- dihydroquinazlin-3-yl)phenylhydrazono}-3-oxobutanoic acid ethyl esters "4a,b"

To a cold, well stirred solution of ethyl acetoacetate (1.3g, 0.01 mol) in 30 ml of ethanol containing sodium acetate (4.1g, 0.05 mol) the diazonium chloride derivatives ″2a, b″ (3.7; 4.5g; 0.01 mol) was added drop wisely while stirring and the reaction was completed as usual to give ″4a, b″ ; (*c.f.* Table 1).

4a: as yellow crystals. IR, ″ υ/cm^{-1}″: 3343 (NH), 3103, 3050, 2928 (CH), 1769, 1701, 1654 (C=O), 1601 (C=N), 1589 (C=C). ^{1}H–NMR δ: 10.59 (s, 1H, NH), 7.39 7.85 (m, 13H, Ar–H), 3.49 (q, 2H, $\underline{CH_2}CH_3$), 2.45 (s, 3H, CO$\underline{CH_3}$), 2.15 (s, 2H, CH_2Ph), 1.39 (t, 3H, $CH_2\underline{CH_3}$). ^{13}C-NMR δ:168.6 (CO acetyl), 164.9 (C=O ester), 161.9 (C–4), 158.1 (C-2), 156.2 (C–8a), 146.8 (C-1 Ph), 141.9 (C-7), 137.2 (C-4a), 133.7 (C-5), 133.1 (2C Ph, C-1$^{\backslash}$,4$^{\backslash}$), 132.2 (2C Ph, C–2$^{\backslash}$,6$^{\backslash}$), 131.9 (C-8), 130.1 (2C Ph, C-3$^{\backslash}$,5$^{\backslash}$), 128.1 (C-6), 126.3 (2C Ph, C-3$^{\backslash}$,5$^{\backslash}$), 125.9 (C–4 Ph), 29.2 (CH_2– Ph), 24.1 (CH_3 acetyl), 21.3 (CH_3 ester). MS, m/z (9%): 468 (M^+) (32.4), 423 ($M^+–C_2H_5$), (19.1), 395 (M^+–CO) (7.3), 352 ($M^+–COCH_3$), 219 (40.1), 118 (85.7), 81(100), 77(50.5).

4b: as yellow crystals. IR, ″ υ/cm^{-1}″ :(3419 (NH), 3069, 3005, 2929 (CH), 1774, 1701, 1660 (C=O), 1605 (C=N), 1590 (C=C). ^{1}H-NMR δ: 11.09 (s, 1H, NH), 7.23-8.01 (m, 12H, Ar–H), 4.03 (q, 2H, $\underline{CH_2}CH_3$), 2.59 (s, 3H, $COCH_3$), 2.19 (s, 2H, $\underline{CH_2}Ph$), 1.40 (t, 3H, $CH_2\underline{CH_3}$). MS, m/z (40): 548/ 507/546(40) for (M^+, ^{81}Br, ^{80Br}, ^{79}Br), 314 (49), 298 (13.6), 210/209/208 ($C_8H_5N_2$, ^{81}Br,$C_8H_5N_2{}^{80}$Br, $C_8H_5N_2{}^{79}$Br(85), 158/157/156($C_6H_5{}^{81}$Br, C_6H_5 ^{80}Br, $C_6H_5{}^{79}$Br), 81(100), 77(55.1).

Reaction of diazonium chloride salts "2a, b" with ethylcyanoacetate. Formation of: 2-{-4-(2-benzyl-4-oxo-3, 4- dihydroquinazlin-3-yl)phenylhydrazono}-3-cyanoaceticc acid ethyl esters "5a, b"

It was prepared as for ″4a, b″, using ethyl cyanoacetate as the active methylene compound (1.1g, 0.01 mol) to give ″5a, b″ (*c.f.* Table 1).

5a: as yellow crystals. IR, ″ υ/cm^{-1}″: 3338 (NH), 3105, 3009, 2958 (CH), 2242 (C≡N), 1719, 1658(C=O), 1601(C=N), 1598 (C=C), 1429 (N=N–). ^{1}H-NMR δ 11.01 (s, 1H, NH), 7.18-7.95 (m, 13H, Ar–H), 3.79 (q, 2H, $\underline{CH_2}CH_3$), 2.20 (s, 2H, $\underline{CH_2}$ Ph), 1.36 (t, 3H, $CH_2\underline{CH_3}$) MS, m/z(%) 452 (M^+ +1), 19.4), 451 (M^+), 78.9), 406 (42.1), 378(31.4), 351 (20.9) 145(100), 102 (4.7), 77(7.1).

5b: as yellow crystals. IR, ″ υ/cm^{-1}″: 3432 (NH), 3108, 3008, 2958 (CH), 2245 (C≡N), 1721, 1659(C=O), 1607(C=N), 1589(C=C), 1278 (–N–N=). ^{1}H-NMR δ: 10.95 (s, 1H, NH), 7.09-7.99 (m, 12H, Ar–H), 4.01 (q, 2H, $\underline{CH_2}CH_3$), 2.57 (s, 2H, $\underline{CH_2}Ph$), 1.38 (t, 3H, $CH_2\underline{CH_3}$). ^{13}C–NMR δ: 164.7 (C=O, ester), 163.2 (C–4), 159.1 (C-2), 143.1 (C–8a), 141.9 (C-1Ph), 137.3 (C-7), 135.2 (2C, C-2, 6 Ph), 133.7, 132.2, 130.1, 128.8 (4C, C–1$^{\backslash}$,2$^{\backslash}$, 3$^{\backslash}$,4$^{\backslash}$, Ph), 128.1 (C-4, Ph), 127.9 (C-5), 126.3 (C-5$^{\backslash}$ Ph), 125.9 (C-8), 125.4 (2C, C-3,5 Ph) 125.51 (C-6), 122.2 (C-4a), 119.5 (C≡N), 59.2 (CH_2), 29.6 (CH_2–Ph), 15.8 (CH_3 ester) MS, m/z (%): 532/531/530/529 (M^+ + 2, M^++1, M^+, M^+-1) (14.6, 14.7, 14.5, 14.3).

Reaction of "3a, b" with guanidine hydrochloride, thiourea and urea, Formation of: 2- benzyl -3- {4-(2-amino -4, 6- dimethyl} - 2, 5 –dihydropyrimidin -5-ylildine) hydrazinophenyl} -4-oxoquinazolines "6a,d", 6-bromo-2-benzyl-3-{4-(2-imino-4, 6-dimetyyl-2-thioxopyrimidin-5-ylildine) hydrazinophenyl} - 4 - oxoquinazolines "6b-e" and 2- benzyl - 3 - {4- (2-imino - 4, 6 - dimetyyl - 2 - oxopyrimidin - 5 -ylildine) hydrazinophenyl} - 4 - oxoquinazolines "6c, f"

A mixture of ″3a″ or ″3b″ (0.01 mol) and guanidine hydrochloride (0.59g, 0.01 mol), thiourea (076g, 0.01 mol) or urea (0.6g, 0.01 mol) in 30 ml of absolute ethanol was refluxed for 6h. After concentration and cooling, the solid that separated was collected, washed well with cold dilute ethanol and recrystallized from the proper solvent as ″6a- f″ (*c.f.* Table. 1).

TABLE 1. Analytical data of the newly prepared compounds.

Compd. No	**Yield (%)**	**M.P.°C solvent of cryst.**	**Molecular formula (Mol. w.t)**	**Elemental analysis cacld/found (%)**				
				C	H	N	S	Br
3a	78	158-160	$C_{26}H_{22}N_4O_3$	71.23	5.02	12.79		
		EtOH	(438)	71.2	5.0	12.8		
3b	80	174-176	$C_{26}H_{21}N_4O_3Br$	60.35	4.06	10.83		15.47
		EtOH	(517)	60.3	4.1	10.8		15.5
4a	72	200-202	$C_{27}H_{24}N_4O_4$	69.23	5.13	11.97		
		EtOH	(468)	69.2	5.1	12.0		
4b	82	262-264	$C_{27}H_{23}N_4O_4Br$	59.23	4.20	10.24		14.62
		AcOH	(547)	59.2	4.2	10.2		14.6
5a	75	148-150	$C_{26}H_{21}N_5O_3$	69.17	4.65	15.52		
		EtOH	(451)	69.2	4.7	15.5		
5b	81	184-186	$C_{26}H_{20}N_5O_3Br$	58.86	3.77	13.207		15.09
		AcOH	(530)	58.9	3.8	13.2		15.1
6a	65	290-291	$C_{27}H_{23}N_7O$	70.28	4.98	21.25		
		AcOH	(461)	70.3	5.0	21.3		
6b	62	210-212	$C_{27}H_{22}N_6OS$	67.78	4.602	17.57	6.69	
		EtOH		67.8	4.6	17.6	6.7	
6c	60	284-286	$C_{27}H_{22}N_6O_2$	70.12	4.76	18.18		
		AcOH	(462)	70.1	4.8	18.2		
6d	68	263-265	$C_{27}H_{22}N_7OBr$	60.0	4.07	18.14		14.81
		AcOH	(540)	60.0	4.1	18.1		14.8
6e	61	217-219	$C_{27}H_{21}N_6OSBr$	58.16	3.77	15.08	5.74	14.36
		EtOH	(557)	58.2	3.8	15.1	5.7	14.4
6f	73	234-236	$C_{27}H_{21}N_6O_2Br$	59.88	3.88	15.53		14.78
		AcOH	(541)	59.9	3.9	15.5		14.8
7a	60	217-219	$C_{32}H_{26}N_6O$	75.29	5.09	16.47		
		EtOH	(510)	75.3	5.1	16.5		
7b	64	233-235	$C_{32}H_{25}N_6OBr$	65.19	4.24	14.601		13.58
		AcOH	(589)	65.2	4.2	14.6		13.6
7c	59	263-265	$C_{32}H_{25}N_7O_3$	69.18	4.504	17.65		
		AcOH	(555)	69.2	4.5	17.7		
7d	61	289-290	$C_{32}H_{24}N_7O_3Br$	60.56	3.78	15.45		12.61
		AcOH	(634)	60.6	3.8	15.5		12.6
8a	50	161-163	$C_{25}H_{20}N_6O_2$	68.807	4.58	19.27		
		EtOH	(436)	68.8	4.6	19.3		
8b	55	213-215	$C_{31}H_{24}N_6O_2$	72.65	4.68	16.406		
		EtOH	(512)	72.7	4.7	16.4		
8c	60	265-267	$C_{31}H_{23}N_7O_4$	66.78	4.12	17.59		
		AcOH	(557)	66.8	4.1	17.6		
8d	53	257-259	$C_{25}H_{19}N_6O_2Br$	58.25	3.63	16.31		15.53
		AcOH	(515)	58.3	3.7	16.3		15.5
8e	60	273-275	$C_{31}H_{23}N_6O_2Br$	62.94	3.89	14.21		13.53
		EtOH	(591)	62.9	3.9	14.2		13.5
8f	65	263-265	$C_{31}H_{22}N_7O_4Br$	58.49	3.45	15.408		12.57
		AcOH	(636)	58.5	3.5	15.4		12.6
9a	60	179-181	$C_{24}H_{19}N_7O_2$	65.90	4.35	22.43		
		EtOH	(437)	65.9	4.3	22.4		
9b	65	243-245	$C_{24}H_{18}N_7O_2Br$	55.81	3.48	18.99		15.503
		AcOH	(516)	55.8	3.5	19.0		15.5
9c	63	187-189	$C_{25}H_{21}N_7O_2$	66.51	4.65	21.72		
		EtOH	(451)	66.5	4.7	21.7		
9d	65	269-271	$C_{25}H_{20}N_7O_2Br$	56.603	3.77	18.49		15.09
		AcOH	(530)	56.6	3.8	18.5		15.1

where EtoH = ethanol and AcoH = Acetic acid.

6a: as yellow crystals. IR, ″ υ/cm^{-1}″: 3420 (NH), 3058, 2982 (CH), 1671(CO), 1614 (C=N), 1601 (C=C). ^{1}H-NMR δ: 11.01 (s, 1H, NH–Ph), 10.91 (s, 1H, C=NH), 7.01-7.95 (m, 13 H, Ar–H), 3.14 (s, 2H, CH_2-pH), 2.13 (s, 6H, 2x CH_3). ^{13}C–NMR δ: 162.7 (C–4 quinazolinone), 155.2 (C–2, quinazolinone), 153.1 (C–2, pyrimidine), 152.8 (C-6, pyrimidine), 151.9 (C–4, pyrimidine), 150.2 (C-5, pyrimidine), 149.8 (C-8a), 148.1 (C-1, Ph), 147.3 (C-4, Ph), 145.2 (C–7), 142.7 (2C, C–2,6 Ph), 140.7 (C-8), 138.1 (C-5), 133.1, 132.8, 130.9, 129.3 (4C, C-1$^{\backslash}$,2$^{\backslash}$,3$^{\backslash}$, Ph), 128.6 (C-4, Ph), 128.1 (C-8), 127.4 (C-5), 126.6 (2C C-3,5 Ph), 126.3 (C-6), 125.9 (C-4a), 126.3 (4C, C-2$^{\backslash}$,3$^{\backslash}$,5$^{\backslash}$,6$^{\backslash}$), 125.9 (C–4$^{\backslash}$ Ph), 122.2 (C–1$^{\backslash}$ Ph), 26.9 (CH_2-Ph), 21.3 (2C, 2 x pyrimidine CH_3).

6b: as dark yellow crystals, IR, ″ υ/cm^{-1}″: 3437(NH), 3093, 2921, 2852 (CH), 1673 (C=O), 1608 (C=N), 1598 (C=C), 1279 (–N–N=), 1218 (C=S). ^{1}H-NMR δ: 11.09 (s, 1H, NH-Ph), 7.18-8.31 (m, 13H, Ar–H), 2.95 (s, 2H, CH_2 Ph), 2.11 (2xs, 6H, 2xCH_3). MS, m/z (%): 479 (M^{+} + 1) (14.6), 478 (M^{+}), (14.6), 348 (20.9), 243 (23.9), 152 (100), 145 (67.1), 105 (16.1), 92 (12.3), 77(7.5), 76 (4.9).

6c: as dark yellow crystals, IR, ″ υ/cm^{-1}″:3443 (NH), 30 95, 2958, 2922 (CH), 1679, 1668 (C=O), 1601, (C=N), 1595(C=C), 1425($-\overset{|}{N}-\overset{|}{N}-$). ^{1}H-NMR δ 11.4 (s, 1H, NH-Ph) , 7.09-8.19 (m, 13H, Ar–H), 3.14 (s, 2H, CH_2Ph), 2.25 (s, 6H, 2 x CH_3). ^{13}C-NMR δ: 168.2 (C-2, pyrimidinone), 166.8 (C–4, quinazolinone), 163.8 (C-6, pyrimidinone), 162.4 (C-4, pyrimidinone),157.1 (C-5, pyrimidin-2-one), 155.9 (C-2, quinazolinone), 149.8 (C-8a), 145.3 (C-1, Ph), 136.1 (C-7), 133.5 (2C, C-2, 6 Ph), 132.6 (2C, C-3,5 Ph), 131.9 (C-4Ph) 130.1 (C-8), 128.3 (C-5), 128.1 (C-6), 126.6 (C-4a), 126.3 (C-1$^{\backslash}$), 125.9 (2C, C-2$^{\backslash}$,6$^{\backslash}$Ph), 125.4 (2C, C-3$^{\backslash}$,5$^{\backslash}$ Ph), 125.1 (C-4$^{\backslash}$), 29.3 (CH_2. Ph) , 21.4 (2C, 2x pyrimidin-2-one –CH_3).

6d: as yellowish orange crystals. IR, ″ υ/cm^{-1}″:3444 (NH), 3090, 2982, 2858 (CH), 1678 (C=O), 1607 (C=N), 1595 (C=C), 1278 (–N–N=). ^{1}H-NMR δ: 10.99 (s, 1H, NH, Ph), 7.12-8.23 (m, 12H, Ar–H), 3.18 (s, 2H, CH_2 Ph), 2.53 (2 x s, 6H, 2x CH_3). MS, m/z (%): 542 (M^{+} + 2) (17.6), 540 (M^{+}) (17.8), 539 (M^{+}-1) (17.6), 314 (19.6), 234 (12.7), 218 (37.9), 150 (67.2), 134(100), 92 (37.1), 77(4.9), 76(3.8).

6e: as light orange crystals. IR, ″ υ/cm^{-1}″:3358 (NH), 3093, 2928, 2852 (CH), 1671 (C=O), 1605 (C=N), 1598 (C=C), 1258 (C=S). ^{1}H-NMR δ: 10.95 (s, 1H, NH.Ph) 7.19-8.30 (m, 12H, Ar-H), 3.21 (s, 2H, CH_2Ph), 2.59 (2x5, 6H, 2 x CH_3). ^{13}C-NMR δ: 162.7 (C-4, quinazolinone), 159.5 (C-2, Pyrimidine-2-thione), 157.4 (C-5, pyrimidine-2-thione), 155.9 (C-6, pyrimidin-2-thione), 155.3 (C-2, quinazolinone), 150.3 (C-8a), 145.6 (C–1, Ph), 136.3 (C–7), 133.3 (2C, C-3,6 Ph), 132.2 (2C, C3,5 Ph), 131.9 (C-4 Ph), 130.1 (C-8), 128.6 (C-5), 128.1 (C-6), 126.3 (C-4a), 125.9 (C-1$^{\backslash}$), 125.4 (2C, C-2$^{\backslash}$,6$^{\backslash}$ Ph), 122.2 (2C, 3$^{\backslash}$,5$^{\backslash}$Ph), 121.7 (C–4$^{\backslash}$Ph), 29.1 (CH_2.Ph), 21.3 (2C, 2x pyrimidin-2-thione CH_3).

6f: as orange crystals. IR, ″ υ/cm^{-1}″:3448 (NH), 3098, 2954, 2851 (C-H), 1679, 1666 (C=O), 1608 (C=N), 1578 (C=C), 1262 (N-N=). ^{1}H-NMR δ: 11.01 (s, 1H, NH), 7.23-8.01 (m, 12H, Ar-H), 2.45 (2 x s , 6H, 2 x CH_3 pyrimidin-2-one). MS, m/z (%): 543 (M^++2), (19.6), 542(M^+ +1) (19.6), 541 (M^+) (19.6), 316, 314 (26.1). 227, 225 (47), 170 (18), 151 (66), 89(38), 76(23), 75(13), 62(100).

Reaction of "3a, b" with hydrazines. Formation of 2-benzyl-3-{4-(3,5-dimethyl-1-phenyl-1-H-pyrazol-4-yl) azophenyl}- 4-oxoquinazolines "7a", 2-benzyl-6-bromo-3-{4-(3,5-dimethyl-1-phenyl-1H-pyrazol-4-yl)-4-oxoquinazolines "7b" , 2-benzyl-3-{4- (3,5- dimethyl-1(-4-nitrophenyl -1H-pyrazol-4-yl)-4 oxoquinazolines "7c" and 2- benzy l- 6- bromo -3- {4-(3,5-dimethyl-1(-4-nitrophenyl-1H-pyrazol-4-yl)-4-oxoquinazolines "7d"

A mixture of ″3a,b″ (0.01 mol), phenyl hydrazine (1g, 0.01 mol), 4-nitrophenyl hydrazine (1.5g, 0.01 mol) and freshly fused sodium acetate (0.8g, 0.01 mol) in 30 ml of acetic acid was refluxed for 6hrs. After cooling, the excess solvent was evaporated (under pressure), and the product that separated was collected, washed with ether, then with dilute alcohol and recrystallized from the proper solvent to give ″7a-d″ (*c.f.* Table 1).

7a: as yellow orange crystals. IR, ″υ/cm^{-1}″:3064, 3016, 2954, 2921, 2851 (CH), 1667(C=O,quinazolinone), 1608 (C=N), 1424 (-N=N-). ^{1}H-NMR δ: 7.73-7.98 (m, 18H, Ar-H), 2.82-2.83 (2x s, 2 x 3H, 2x CH_3-pyrazole ring, 2.35 (s, 2H, $\underline{CH_2}$. Ph). ^{13}C-NMR δ: 163.7 (C-4 quinazolinone), 159.5 (C-2, quinazolinone, 154.7 (C-8a quinazolinone), 153.9 (C-4a quinazolinone, 153.1 (C-4 pyrazole), 144.8 (2C, C-1,4 Ph), 142.7 (2C, C-3,5 pyrazole), 133.6 (2C, C-2,6 Ph), 132.6 (2C, C-3,5 Ph), 132.2 (Cl-phenyl pyrazole), 130.1 (2C, C-2,6 phenyl pyrazole), 128.3 (C-4 phenyl pyrazole), 126.6 (2C, C-3,5 phenyl pyrazole), 126.3 (C-1$^{\backslash}$ Ph), 125.9 (C-4$^{\backslash}$ Ph), 125.4 (2C, C-2$^{\backslash}$,6$^{\backslash}$ Ph), 122.2 (2C,C–3$^{\backslash}$,5$^{\backslash}$ Ph), 29.6 ($\underline{CH_2}$–Ph), 21.6 (2C, 2x CH_3 pyrazole).

7b: as dark orange crystals. IR, ″ υ/cm^{-1}″:3103, 3090, 2984, 2921, 2823 (CH), 1671 (C=O, quinazolinone), 1609, 1598 (C=N and C=C), 1428 (–N=N–). ^{1}H–NMR δ: 7.79-8.09 (m, 17H, Ar-H), 2.91, 2.95 (2xs, 2x3H, 2x CH_3-pyrazole ring), 2.49 (s, 2H, $\underline{CH_2}$-Ph). MS, m/z(%): 593 (M^+ + 4) (4.5), 591 (M^++2) (4.5), 589 (M^+) (27.7), 418(11.1), 224(37.1) 171 (3.5), 199 (19.1), 144 (15.7), 129 (23), 96 (11.1), 77(23.3), 76(9.1), 55(100).

7c: as reddish crystals. IR, ″ υ/cm^{-1}″:3080, 3005, 2955, 2922, 2825 (CH), 1676 (C=O, quinazoline), 1601 (C=N), 1588 (C=C), 1523 (N=O), 1419 (-N=N). ^{1}H-NMR δ: 7.46-8.13 (m, 17H, Ar-H), 2.61, 2.54 (2 x s, 2 x 3H, 2 x CH_3-pyrazole ring), 2.51 (s, 2H, $\underline{CH_2}$. Ph) .

7d: as dark red crystals. IR, ″ υ/cm^{-1}″:3103, 3080, 2958, 2921, 2852 (CH), 1674 (C=O, quinazolinone), 1605 (C=N), 1591 (C=C), 1523 (N=O), 1414 (–N=N–). MS, m/z(%): 635(M^++1) (16.7), 634(M^+) (19.2), 633 (M^+–1) (19.2), 554 (7.2), 320 (33.6), 215(17.1), 122(9.3), 96(100).

Reaction of "4a, b" with hydrazines. Formation of: 2-benzyl-3-{4-(3-methyl-5-oxo-4, 5-dihydro-1H- pyrazol-4-ylidine)hydrazinophenyl}-4-oxoquinazolines "8a-f"

A mixture of ″4a ,b″ (0.01 mol), and hydrazine hydrate (0.5g, 0.01 mol),or 4-nitrophenylhydrazine (1.0g, 0.01 mol) in 15 ml of acetic acid containing sodium acetate (0.41 g, 0.005 mol) was refluxed for 6hr. After concentration and cooling, the excess solvent was removed (reduced pressure) and the product was collected washed well with dilute alcohol and recrystallized from the proper solvent to give ″8a-f″ (*cf.* Table 1).

8a: crystallized as yellow crystals. IR, ″ υ/cm^{-1}″:3466, 3324 (NH), 3030, 3005, 2958 (CH), 1665, 1672(C=O), 1601(C=N), 1589(C=C). ^{1}H–NMR δ: 11.11 (s, 1H, Ph. NH.N=), 10.09 (s, 1H, NH-pyrazolone), 7.23-8.01 (m, 13H, Ar–H), 2.49 (s, 2H, CH$_2$ Ph), 2.13 (s, 3H, CH$_3$-pyrazolone). ^{13}C–NMR δ: 159.1 (C-4 quinazolinone), 158.4 (C-5 pyrazolone), 156.1 (C-4 pyrazolone), 155.2 (C-2 quinazolone), 152.4 (C-3 pyrazolone), 149.7 (C-8a), 148.1 (C-1, Ph), 147.3 (C-4 Ph), 145.3 (C-7), 149.7 (C-8a), 148.1 (C-1, Ph), 147.3 (C-4 Ph), 145.3 (C-7), 142.6 (2C, C-2,6 Ph), 140.5 (C-8), 138.2 (C-5), 133.7, 132.6, 132.2, 130.1 (4C, C-1$^{\backslash}$, 2$^{\backslash}$,3$^{\backslash}$,4$^{\backslash}$Ph), 128.1 (C-8), 126.3 (2C, C-3,5 Ph), 125.9 (C-6), 125.4 (C-4a), 122.2 (2C, 5$^{\backslash}$,6$^{\backslash}$), 24.1 (CH$_2$.Ph), 23.9 (CH$_3$, pyrazolone).

8b: light orange crystals. IR, ″ υ/cm^{-1}″:3442 (NH), 3130, 3005, 2928, 2828 (C–H), 1664, 1679 (C=O), 1605, 1599 (C=N, C=C). ^{1}H-NMRδ: 11.12 (s, 1H, NH-N-Ph) 7.21-8.09 (m, 18H, Ar-H), 2.48 (s, 2H, CH$_2$Ph) 2.135 (s, 3H, CH$_3$–pyrazolinone). MS, m/z (%), 513 (M^{+} + 1, 73.2), 512 (M^{+}, 41.5).

8c: dark orange crystals. IR, ″ υ/cm^{-1}″: 3440.9 (NH), 3090, 3005, 2982, 2928, 2828 (C–H), 1669, 1678 (C=O), 1604, 1598 (C=N, C=C). ^{1}H-NMRδ: 11.39 (s, 1H, NH-N-Ph), 7.38-8.13 (m, 23H, Ar–H), 2.51 (s, 2H, CH$_2$Ph), 2.35 (s, 3H, CH$_3$– pyrazolinone). MS, m/z (%): 558 (M^{+}+1, 78.9), 557 (M^{+}, 52.1) 232 (37.6), 205(100), 109 (87.1), 84(37.4), 76 (71.13), 54(57.3).

8d: yellowish orange crystals. IR, ″ υ/cm^{-1}″: 3451.1 (N H), 3110, 3030, 3005, 2928, 2852 (C–H), 1668, 1674 (C=O), 1601, 1599 (C=N, C=C). ^{1}H-NMRδ: 11.31 (s, 1H, NH–N–Ph), 7.39-8.35 (m, 19H, Ar–H), 2.601 (s, 2H, CH$_2$Ph), 2.36 (s, 3H, CH$_3$–pyrazolone). MS, m/z (%): 516(M^{+}1 for ^{81}Br, 19.37), 515(M^{+} for ^{80}Br, 19.37) 514 (M^{+} for ^{79}Br, 63.1), 146 (C$_8$H$_6$N$_2$O^{+}, 73.1), (C$_6$H$_6$N^{+}, 100) 52(76).

8e: Dark orange crystals. IR, ″ υ/cm^{-1}″: 3450 (NH), 3151, 3030, 3008, 2982, 2928, 2822 (C–H), 1669, 1680 (C=O), 1605, 1603, 1590 (υC=N), C=C). ^{1}H-NMRδ: 11.321 (s, 1H, NH-NPh), 7.41-8.34 (m, 23H, Ar-H), 2.61 (s, 2H, CH$_2$Ph), 2.51 (s, 3H, CH$_3$–pyrazolinone), MS, m/z (%) 592 (M^{+} +1, for ^{81}Br, 19.2), 591 (M^{+} for ^{80}Br, 20.1), 590 (M^{+}–1 for ^{79}Br, 20.1)

8f: Reddish crystals. IR, ″ υ/cm^{-1}″: 455 (NH), 3051, 3030, 3009, 2982, 2928, 2828 (C–H), 1673, 1680(C=O), 1605, 1601, 1590(C=N, C=C). ^{1}H-NMRδ: 11.68 (s, 1H, NH–N–Ph), 7.41-8.26 (m, 16H, Ar–H), 2.62 (s, 2H, CH$_2$ Ph), 2.49 (s, 3H, CH$_3$-pyrazolinone). MS, m/z (%): 627 (M^{+}+1 for ^{81}Br, 11,2), 636 (M^{+} for ^{80}Br, 70.9), 635 (M^{+}-1 ^{79}Br, 71.1).

Reaction of "5a, b" with hydrazines. Formation of: 2-benzyl-3-{-4-(3-amino-5-oxo-4, 5-dihydro-1Hpyrazol-4-ylidine) hydrazinophenyl}-4-oxoquinazolines "9a-d"

A mixture of ″5a, b″ (0.01 mol) and hydrazines namely hydrazine hydrate or methyl hydrazine (1.0gm, 0.01mol) in 30ml of ethanol was refluxed for 6 hr. After concentration and cooling, the excess of solvent was removed and the product was collected and recrystalized from the proper solvent to give ″9a-d″ (*c.f.* Table 1).

9a: yellowish orange crystals. IR, ″ υ/cm^{-1}″: 430, 3452(NH), 3310(NH_2), 3156, 2928 (CH), 1679, 1669 (C=O), 1605, 1589, 1509 (C=N, C=C). ^{1}H-NMR δ: 11.67(s, ^{1}HNH-N=), 10.01 (s, 1H, $\underline{NH}$–pyrazolinone), 7.41-8.13(m, 13H, Ar–H), 5.05 (s, 2H, $\underline{NH_2}$–pyrazolinone), 2.61(s, 2H, $\underline{CH_2}$–Ph). MS, m/z (%), 438(M^++1) (14.3), 437 (M^+) (37.25), 327 ($C_{21}H{=}17O^+N_3$) (71.1), 312 ($C_{21}H_{16}O^+N_2$), 236 ($C_{15}H_{12}O^+N_2$) (100), 160 ($C_9H_8O^+N_2$) (41.1), 146($C_8H_6O^+N_2$) (27.5), 104 ($C_7H_4O^+$) (2.7), 77(83.3), 76(18.3), 55(71.4).

9b: Orange crystals. IR, ″ υ/cm^{-1}″:434, 3451 (NH), 3316 (NH_2), 3159, 2952,2928, 2882, 2826 (VH), 1678, 1666 (C=O), 1604, 1601, 1561 (C=N, C=C) ^{1}H-NMR δ: 11.69 (s, ^{1}H-NM–N=), 10.12(s, 1H, $\underline{NH}$-pyrazolinone), 7.52-8.21 (m, 12H, Ar–H), 5.13 (s, 2H, $\underline{NH_2}$-Pyrazolinone), 2.63 (s, 2H, $\underline{CH_2}$Ph).

9c: golden yellow crystals. IR, ″ υ/cm^{-1}″:3438 (NH), 3312(NH_2), 3030, 2928, 2882, 2828(CH), 1674, 1666 (C_2O), 1605, 1601, 1588 (C=N, C=C). ^{1}H–NMR δ: 11.59 (s, 1H, NH–N=), 7.43-8.21 (m, 13H, Ar–H), 5.11 (s, 2H, NH_2–pyrazolinone), 2.39 (s, 2H, $\underline{CH_2}$.Ph), 1.31 (s, 3H, $\underline{CH_3}$–N)

9d: light orange crystals. IR, ″ υ/cm^{-1}″:3438 (NH), 3321 (NH_2), 3150, 3050, 3003, 2928, 2828 (CH), 1679, 1669 (C=O), 1606, 1602, 1580 (C=N, C=C). ^{1}H–NMR δ: 11.61 (s, 1H, $\underline{NH}$–N=), 7.45-8.31 (m, 12H, Ar–H), 5.14 (s, 2H, NH_2–pyrazolinone), 2.63 (s, 2H, CH_2Ph), 1.37 (s, 3H, CH_3–N).

Biological evaluation

Antimicrobial activity

The antimicrobial activity was evaluated by filter paper disc agar diffusion method (23). For antibacterial studies Hi-media bacteriological nutrient broth (24) and bacteriological nutrient agar were used against Gram-positive *Bacillus subtilis, Staphylococcus aureus* and Gram-negative *Salmonella typhi* and *Escherichia coli.* Antifungal studies were carried out using *Sabouraud's dextrose* broth and dextrose agar against *Aspergillus fumigatus, Aspergillus niger*, *Alternaria alternate* and *Penicillum chrysogenum*. Dimethyl formamide was used as solvent and also for control studies. The concentration of the compounds taken was 1mg ml^{-1}. Norfloxaxin (1mg ml^{-1}) and clotrimazole (1mg ml^{-1}) were used as standards for bacterial and fungal studies respectively. The sensitivity of microorganisms to the compounds is identified in the flowing table (Table 2).

Electron-rich nitrogen heterocycles play an important role in diverse biological activities. Introducing a pyrazolone ring (25-26) in place of the β-lactam ring in penicillins and cephalosporins(27) results in enhanced activity. Second nitrogen in the five-membered ring also influences the antibacterial or pharmacokinetic properties (28-30).

The antimicrobial activity of some newly synthesized compounds (3a,b; 4a,b; 5a,b; 6a-e; 7a,d; 8b,c; 9a-c) were tested and the results are shown in Table 2. Evaluation of the new compounds established that compounds 6a, 6d, 7a, 9a, and 9c have shown the highest inhibitory activity against Gram-positive bacterium *"B. subtilis"*, while compounds 5b, 6a, 6d, 7a, d, 8c, 9a,c have shown the same highest inhibitory activity against Gram-positive bacterium *"S. aureus"*. It was also noticed that compounds 5b, 6b,c, 6e, 7d, 8b and 8b and compounds 4b, 5a, 6b,c,e, 8b, and 9b as well demonstrated antibacterial activity less effective towards Gram-positive bacterium *"B. subtilis"* and *"S. aureus,"* respectively. Compounds 3a, 4a,b, 5a, 8b and 9b were slightly active against the same bacterium, while compounds 3b was inactive. For the Gram-negative bacterium. *"S. typhi"* and *"E. coli"*, compounds 3a, 6a-d, 7a, 8b, 9a revealed the highest inhibitory activity, while compounds 3b, 4a,b, 5a,b, 6d, 7d, 8c, 9b,c were moderately sensitive against those two organisms, and compound 6a, demonstrated no sensitivity against *E. coli* for the fungi used, *A. fumigatus*, *A. nigen*, *A. alternata* and *P. chynsogenum* compounds 3a,b, 4a,b, 6b revealed no activity towards all of them while compound 9c was more effective than the other tested compounds. Compounds 6a, c, 7a, d, were slightly active against the tested fungi (*c.f.* Table 2).

TABLE 2. *In vitro* antimicrobial activity of some newly synthesized heterocyclic compounds.

Compd.	**Gram-positive**		**Gram-negative**		**Fungi**			
	Bacillus subtilis	*Staphylococcus aureus*	*Salmonella typhi*	*Escherichia coli*	*Aspergillus fumigatus*	*Aspergillus niger*	*Alternaria alternate*	*Penicillium chrysogenum*
3a	5	5	16	16	0	0	0	0
3b	0	0	14	12	0	0	0	0
4a	5	5	10	10	0	0	0	0
4b	10	10	14	12	0	0	0	0
5a	10	10	10	10	0	5	5	5
5b	14	15	14	12	5	5	12	12
6a	18	15	18	0	0	12	12	12
6b	12	13	16	16	0	0	0	0
6c	14	12	18	16	12	12	13	12
6d	18	18	16	12	12	0	0	12
6e	14	14	12	14	12	12	10	10
7a	18	15	16	16	12	10	12	10
7d	14	17	14	14	12	12	0	12
8b	10	10	18	18	10	10	10	12
8c	15	18	10	10	12	10	10	10
9a	15	15	15	15	10	10	10	6
9b	10	10	10	10	10	10	10	0
9c	17	17	13	12	18	18	17	10

where: highly sensitive = 15-20mm; moderately sensitive = 10-15 mm; slightly sensitive 5-15 mm; slightly sensitive 5-10mm and not sensitive = o mm.

References

1. **Lopez, S.E., Rosales, M.E., Canelon, C.E., Valverode, E.A., Narvaez, R.C., Charris, J.E., Giannini, F.A., Enriz, R.D., Carrasco, M., and Zacchino, S.,** Synthesis and preliminary cytotoxic and antifungal evaluation of some 6-N,N-dialkyl 2-Aryl-4(3H)-quinazolinone derivatives. *Heterocycl. Commun*, **7**(5), 473-480 (2001).

2. **Bekhit, A.A., Habbib, N.S. and Bekhit, El.A.,** Synthesis and antimicrobial evaluation of chalcone and syndrome derivatives of 4(3H)-quinazolinone. *Boll. Chim. Farm*. **140**(5), 297-301 (2001).

3. **Usifoh, C.O. and Scriba, G.K.E.,** Synthesis and anticonvulsant activity of acetylenic quinazolinone derivatives. *Arch. Pharm. (Weinheim),* **333**, 261 (2000).

4. **Kulcsar, G., Kalai, T., Osz, E., Sar, C.P., Jeko, J., Sumegi, B. and Hideg, K.**, "The role of akt and mitogen-activated protein kinase systems in the protective effect of poly(ADP-sibose) polymerase inhibition in langendorff perfused and in isoproterenol-damaged rat hearts. *Arkivoc*, **121** (2003).

5. **Raffa, D., Daidone, G., Schillaci, D., Maggio, B. and Plescia. F.,** Synthesis of new 3-(3-Phenyl-isoxazol-5-yl) or 3-[(3-Phenyl-isoxazol-5-yl) amino] Substituted 4(3H)-quinazolinone derivatives with antineoplastic activity. *Pharmazie,* **54**, 251 (1999).

6. **Ahluwalia, V.K. and Chandra, R.J.** *Miniprint;* A convenient synthesis of novel pyrimidine analogues of o-hydroxy chalcones and pyrano [2,3-*d*] pyrimidines and their biological activities. *Chem. Res.* **4**, 162-163 (2000).

7. **Flefel, E.M., Salama, M.A., El-Stahat, M., El-Hashash, M.A. and El-Farargy, A.F.**, A novel synthesis of some new pyrimidine and thiazolopyrimidine derivatives for anticancer evaluation. *Phosphorus, Sulphur and Silicon*, **182**(8), 1739 (2007).

8. **Farag A.M., Ali. K. A.K., Taha M.A.; Abdelrahman S. M.; Abdel-Galil E. and Mohamed, M.,** "Design, synthesis and structure–activity relationship study of novel pyrazole-based heterocycles as potential antitumor agents. *Eur.J. Med. Chem*, **45**(12), 5887-5989 (2010).

9. P**ropsavin, M., Torovic, L., Spaic, S., Stankov, S., Kapor, A., Tomic, Z. and Popsavin, V.,** Synthesis and biological evaluation of new pyrazole- and tetrazole-related *C*-nucleosides with modified sugar moieties. *Tetrahedron*, **58**(3), 569-580 (2002).

10. **Turan-Zitouni, G., Özdemir, A. and Güven, K.,** Synthesis of some 1-[(N, N-disubstituted thiocarbamoylthio) acetyl] -3- (2-thienyl) -5- aryl -2-pyrazoline derivatives and investigation of their antibacterial and antifungal activities. *Arch Pharm. Med. Chem.* **338**, 96-104 (2005).

11. **Turan-Zitouni, G., Ozdemir. A., Kaplancikli, Z.A., Chevallet, P. and Tunali. Y.**, Synthesis and antimicrobial activities of some 1-[(N, N-disubstitutedthiocarbamoylthio) acetyl] - 3,5 - diaryl - 2 - pyrazolines. *Phosphorus Sulfur, Silicon Relat. Elem* **180**, 2717-24 (2005).

12. **Niementowski, V.,** Reaction of anthranilic acid with amide to form 4-oxo- 3, 4-dihydro quinazoline. *J. Prakt, Chem.* **51,** 564, *Beilestein* **24**, 143 (1895).

13. **Ziegler, E., Steiger, W. and Kappe**, *Th. Monatsh. Chem.* **100**, 150-152 (1969).

14. **Kaur, R., Bansal, M. and Kaur., B.,** Synthesis of some new quinazoline derivatives and theoritical studies of their geometrics. *Chemical Sciences J.* 18 (2011).

15. **Murugesan, D., Periyaswamy, S., Erik, D. and Seshaiah, K.S.,** Synthesis, antiviral and Cytotoxic Activity of 6- Bromo-2, 3- disubstituted-4(3H) quinazolinones. *Biol. Pharm. Bull.* **26** (9), 1278-1282 (2003).

16. **Soliman, F.M., Eslam, I.E., Kassab, R.R.,Souka, L.M. and El-Kady, M.Y.,** Chem Inform Abstract: A new approach for the synthesis of some benzoxazinone and quinazolinone derivatives. *Rev. Roum. Chim.* **39**(4), 405-411 (1994).

17. **Hamidian, H., Tikdari, A.M., and Khabazzadeh, H;** Synthesis of new 4(3H)-quinazolinone derivatives using -5(4H)-oxazolones. *Molecules,* **11**, 377-382 (2006).

18. **Chavadad. B. N., Patel, R. and Vanpuria., S.** Study on the antimicrobial activity for normal and multidrug resistant strains for 3-benzensulfonamide substituted quinazolinone derivatives in *in-vitro* condition. *I J PA S,* **1** (1), 70-73 (2010).

19. **Mosaad, S.M., Mohsen, M. M. and Kassem, N.A.,** Novel 6,8-dibromo-4 (3H) quinazolinone derivatives of antibacterial and antifungal activities. *Eur. J. Med. Chem.* **45**, 3311-3319 (2010).

20. **Misra, R.S., Dwivedi, C. and Parmar, S.S.**, Synthesis of 2-substituted styryl-6-bromo-4-quinazolone 3-(4-benzhydrazides) as possible monoamine oxidase inhibitors. *J. Heterocycl. Chem.* **17**(6), 1337 (1980).

21. **Singh, S.P., Parmer, S.S. and Stenberg, V.I., T.K.**, Carbon-13 nuclear magnetic resonance spectrum of methaqualone. *J. Heterocycl. Chem.* **15**(1), 53 (1978).

22. **Still, J.W., Plavac, N., McKinnon, D.M. and Chauhan, M.S.**, *Can. J. Chem.* **56**, 725 (1978).

23. **Marruzella, J.C. and Henry, P.A.,** synthesis and antibacterial of some 2- amino -4,6-diaryl pyrimidine. *J. Am. Pharm. Assoc.* **47**, 471 (1958).

24. **National committee for clinical laboratory standard**, References method for broth dilution antifungal susceptibility testing of yeast, approval standard. Document M27-A National Committee for Clinical Laboratory Standard, Wayne, PA, USA (1997).

25. **Junghein, L.N., Sigmund, S.K. and Fisher, J.W.,** Bicyclic pyrazolidinones, a new class of antibacterial agent based on the β-lactam model. *Tetrahedron Lett.* **28**(3), 285-92 (1987).

26. **Jungheim, L.N., Sigmund, S.K., Jones, N.D and Swartendruber, J.K.**, Bicyclic pyrazolidinones, steric and electronic effects on antibacterial activity. *Tetrahedron Lett.* **28**(3), 289-92 (1987).

27. **Boyd, D.B.**, *Theoretical and Physicochemical Studies on β-lactam Antibiotics In β-lactam Antibiotics, Chemistry and Biology,* In: R.B. Morin, and Gorman (Ed.), Vol. 1, Academic Press, New York, pp. 437-45 (1982).

28. **Jungheim, L.N., Holmes, R.E., OH, J.L., Ternasky, R.J., Draheim, S.E., Neel, D.A., Stepherd, T.A. and Sigmund, S.K.**, *Abstracts of 26th Interscience Conf. on Antimicrobial Agents & Chemotherapy Oct. 1988, 23-26, Los Angels, C.A.,* Paper 240.

29. **Ternanskym, R.J. and Draheim, S.E.**, An efficient synthesis of a new class of synthetic antibacterial agents. *Tetrahedron Lett.* **31**(20), 2805-08 (1990).

30. **Ilango., K, Valentina, N. and Been, K.P.,** Eco-benign mediated versatile synthesis of newer quinazolin-4-(3H)-one clubbed isatin derivatives as potent antimicrobial agents. *Int.J.Res.Pharm.Sci.* **1**(2), 133-138 (2010).

(*Received* 13/7/2010;
accepted 3 / 5/2011)

تخليق والنشاط البيولوجى لبعض مشتقات الكوينازولينون الجديدة

نادية طه علي داوود ، ناهد فتح الله عبد الغفار و فكرية محمد احمد سليمان
قسم الكيمياء – كلية العلوم (بنات) - جامعة الأزهر – القاهرة – مصر.

تم تحضيرمركبات ٣- -(٤- امينوفينيل)- ٢- بنزيل -٤- اوكسو-٣،٤-ثنائي هيدروكوينازولين (1a) و ٣-(٤-امينوفينيل)-٢-بنزيل-٦-برومو-٤-اوكسو-٣،٤ – ثنائي هيدروكوينازولين (1b) ثم تحويلهم الى مركبات الآزو(2a,b) . تم تحويل مشتقات الديازونيوم كلوريد الى مشتقات- ٣-اريل هيدرازونو(3a,b) (4a,b) (5a,b) عن طريق تفاعلهم مع المركبات المحتوية على مجموعة الميثيلين النشطة مثل استيل اسيتون، ايثيل اسيتو اسيتات ، ايثيل سيانو اسيتات. كذلك تم تحويل مشتقات الهيدرازونو الى مشتقات البيريميدين (٦a-f) ، مشتقات البيرازولو(٧a-d) ، مشتقات البيرازولين (٨a-d) (٩a-f) لدراسة نشاطهم الميكروبي.