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QUINAZOLINONE DERIVATIVES OF BIOLOGICAL INTEREST II

Synthesis and Antibacterial Activity of Certain 3-Aryl-2-(β-arylsulphonylhydrazinomethy-4(3H)-quinazolinones

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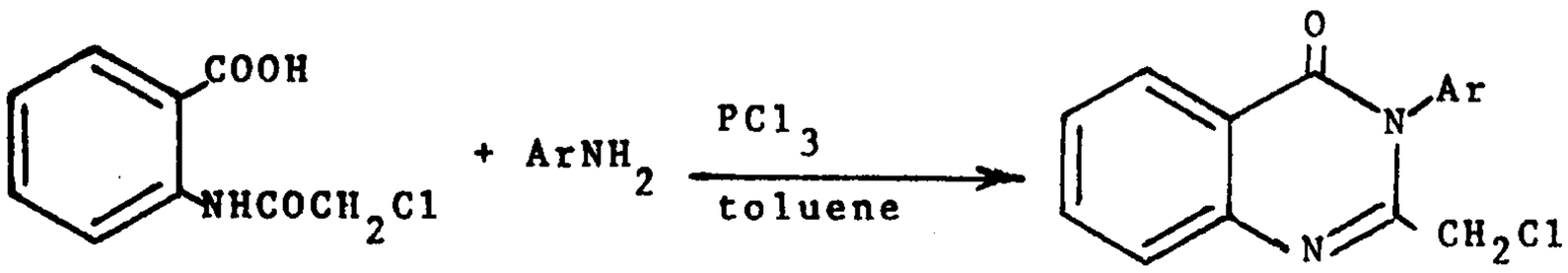
Twenty five new quinazolinone derivatives were synthesized. Structure of these compounds was established by microanalysis, uv and ir spectrometry, Antibacterial activity of the prepared compounds was determined in comparison to sulphanilamide against four microorganisms . Fifteen compounds exhibited measurable antibacterial activity especially towards Staph. aureus .

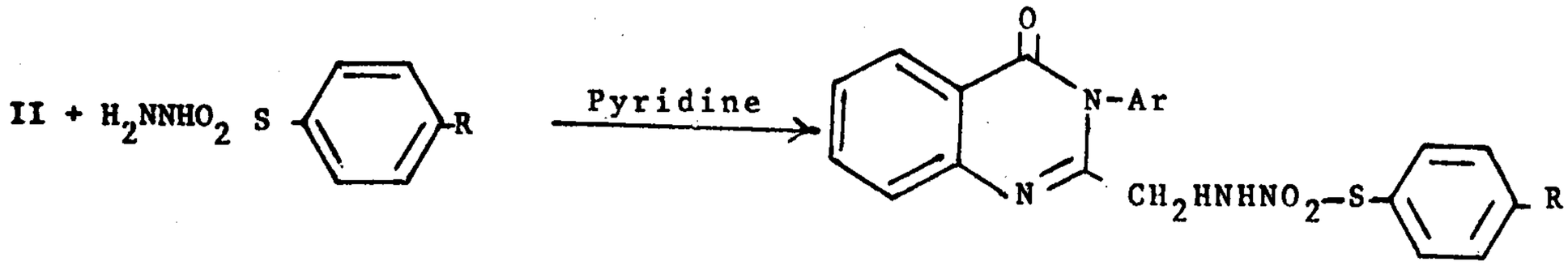
4-Quinazolones were reported to have antibacterial and antiviral properties[1,2]. Some 2-alkyl-3-aryl-4(3H)-quinazolinones have been shown to possess bactericidal as well as tuberculostatic activities[3,5]. Several 3-(p-alkoxyphenyl)-2-isoamylthio-4 (3H)-quinazolinone derivatives were also active against M. tuberculosis[6]. Recently, it has been observed that certain 3-aryl-2-{D-threo-(-)-1-(p-nitrophenyl)-1,3-dihydroxy-2-propylamino} methyl-4-(3H)-quinazolinones exerted bacteriostatic effect similar to that of sulphanilamide[7]. Accordingly, the synthesis of 3-aryl-2-(β-arylsulphonylhydrazinomethyl)-4-(3H)-quinazolinones as well as their screening for antibacterial activity seemed to be attractive.

CHEMISTRY

The required quinazolinones IV were synthesized by the interaction of 3-aryl-2-chloromethyl-4-(3H)-quinazolinones , II , with various p-substituted arylsulphonylhydrazines , III , in pyridine as follows :



(I) (II)

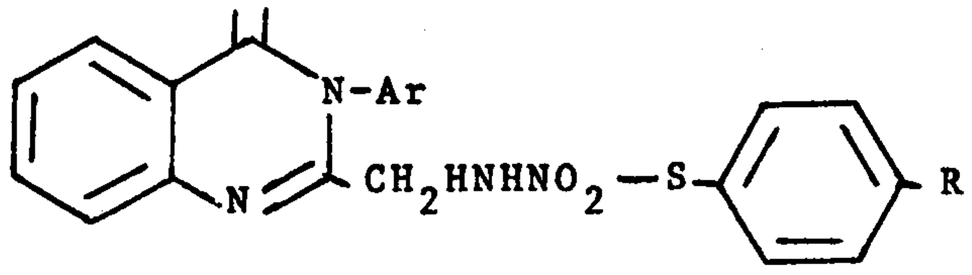


(III) (IV)

Intermediates II were prepared by cyclization of N-chloracetylanthranilic acid I with aromatic amines in presence of PCl_3 by analogy to a reported procedure[8] and were identified as reported[9]. Arylsulphonylhydrazines III were obtained by hydrazinolysis of the corresponding arylsulphonylchlorides in benzene[10] . The starting arylsulphonylchlorides were prepared from the appropriate anilines by a conventional procedure[11] .

Quinazolinones IV (Table 1) were crystallized from ethanol as white to pale-buff needles which are insoluble in water, ether. chloroform or benzene , but soluble in DMF and aqeous alkalies.

Table 1. 3-Aryl-2-(β-Arylsulphonylhydrazinomethyl)-4(3H)-Quinazolinones .



No	Ar	R	Yield %	M. P., ^0C	Molecular Formula	Microanalysis, % : Found/Calc. C	H
1	C_6H_5	H	53	256-7	$C_{21}H_{18}N_4O_3S$	62.20 62.07	4.50 4.43
2	m-$CH_3C_6H_4$	H	59	218-9	$C_{22}H_{20}N_4O_3S$	63.00 62.86	5.00 4.76
3	p-$CH_3C_6H_4$	H	59	261-2	$C_{22}H_{20}N_4O_3S$	62.80 62.86	4.50 4.76
4	m-$CH_3OC_6H_4$	H	56	220-2	$C_{22}H_{20}N_4O_4S$	60.70 60.55	4.60 4.59
5	p-$CH_3OC_6H_4$	H	60	203-4	$C_{22}H_{20}N_4O_4S$	60.20 60.55	4.50 4.59
6	p-BrC_6H_4	H	58	249-50	$C_{21}H_{17}BrN_4O_3S$	51.90 51.96	3.60 3.50
7	m-ClC_6H_4	H	45	247-8	$C_{21}H_{17}ClN_4O_3S$	57.20 57.21	3.90 3.86
8	p-ClC_6H_4	H	54	258-9	$C_{21}H_{17}ClN_4O_3S$	57.40 57.21	4.20 3.86
9	p-$EtOOCC_6H_4$	H	57	211-2	$C_{24}H_{22}N_4O_5S$	60.50 60.25	4.20 4.60
10	2-Pyridyl	H	49	222-3	$C_{20}H_{17}N_5O_3S$	59.00 58.97	4.20 4.18

11	m-$CH_3C_6H_4$	CH_3	53	258-9	$C_{23}H_{22}N_4O_3S$	63.40 63.59	5.10 5.07
12	m-$CH_3C_6H_4$	$NHCOCH_3$	65	228-9	$C_{24}H_{23}N_5O_4S$	60.40 60.38	5.00 4.82
13	m-$CH_3C_6H_4$	Br	61	232-3	$C_{22}H_{19}BrN_4O_3S$	53.20 52.90	4.00 3.81
14.	m-$CH_3C_6H_4$	Cl	56	235-6	$C_{22}H_{19}ClN_4O_3S$	58.20 58.08	4.20 4.18
15	m-$CH_3C_6H_4$	NO_2	54	220-1	$C_{22}H_{19}N_5O_5S$	56.90 56.77	4.50 4.09
16	p-$CH_3OC_6H_4$	CH_3	55	258-9	$C_{23}H_{22}N_4O_4S$	60.90 61.33	4.60 4.89
17	p-$CH_3OC_6H_4$	$NHCOCH_3$	55	254-5	$C_{24}H_{23}N_5O_5S$	58.40 58.42	5.00 4.67
18	p-$CH_3OC_6H_4$	Br	45	272-3	$C_{22}H_{19}BrN_4O_4S$	51.10 51.26	3.50 3.69
19	p-$CH_3OC_6H_4$	Cl	43	268-9	$C_{22}H_{19}ClN_4O_4S$	56.40 56.11	4.20 4.04
20	p-$CH_3OC_6H_4$	NO_2	50	247-8	$C_{22}H_{19}N_5O_6S$	54.70 54.88	3.90 3.95
21	p-ClC_6H_4	CH_3	66	265-9	$C_{22}H_{19}ClN_4O_3S$	57.80 58.08	4.20 4.18
22	p-ClC_6H_4	$NHCOCH_3$	58	264-5	$C_{23}H_{20}ClN_5O_4S$	55.40 55.48	4.30 4.02
23	p-ClC_6H_4	Br	54	272-3	$C_{21}H_{16}BrClN_4O_3S$	48.40 48.51	3.10 3.08
24	p-ClC_6H_4	Cl	48	260-1	$C_{21}H_{16}Cl_2N_4O_3S$	53.40 53.16	3.20 3.37
25	p-ClC_6H_4	NO_2	56	263-4	$C_{21}H_{16}ClN_5O_5S$	52.10 51.90	3.50 3.29

Structure of the quinazolinones IV was established by elementary analysis, uv and ir spectrometry. The obtained spectra have the same general characterististics as those of other reported quinazolinones[7,12,13]. The uv spectra are characterized by the presence of four peaks of maximum absorbance at 227, 265, 304 and 316 nm with corresponding log ϵ_{max} values of about 4.65 , 3.92 and 3.90 respectively. The ir spectra exhibited characteristic absorption bands at 1700 cm^{-1} (stretching vibrations of the quinazolinone carbonyl group)[14], 1620 cm^{-1}, 1595 cm^{-1} and at 1500 cm^{-1} (skeletal vibrations of quinazoline nucleus)[15]. A medium sharp band characteristic of the stretching vibrations of the C=N group appeared at 1645 cm^{-1}. A strong broad band of the NH group appeared at 3500 cm^{-1}, while the SO_2 group showed two sharp bands , an intense (ν asym.) at 1390 cm^{-1} and a weak (ν sym.) at 1125 cm^{-1}. The aromatic CH exhibited a medium broad band at 3080 cm^{-1} and very sharp intentse bands at 830 cm^{-1} and 800 cm^{-1}. The aliphatic CH_2 showed a weak broad ν band at 2990 cm^{-1} and intense sharp δ bands at 1480 cm^{-1} and 710 cm^{-1}.

MICROBIOLOGICAL SCREENING AND DISCUSSION.

The synthesized compounds were tested for antibacterial activity against four microorganisms ,Staph. aureus, E.coli, Pseud. pyocyaneus, and Prot. vulgaris. MICs of these compounds, in comparison to sulphanilamide, were determined by the serial dilution method using nutrient broth(pH 7.4) as the basal medium[16,17]. The screened compounds as well as the reference drug showed no antibacterial activity towards Pseud pyocyaneous . The other microorganisms were found to be sensitive to various degrees (Table 2).

Table 2. Antibacterial Activities of Quinazolinones IV

NO	MIC * against		
	Staph. aureus	*E. coli*	*Prot vulagaris*
1	250.00	500.00	250.00
2	62.50	125.00	62.50
3	125.00	125.00	62.50
4	------	------	-----
5	------	31.25	31.25
6	------	------	-----
7	250.00	500.00	500.00
8	125.00	62.50	62.50
9	------	------	------
10	62.50	125.00	125.00
11	250.00	125.00	125.00
12	125.00	250.00	250.00
13.	125.00	125.00	125.00
14	125.00	------	------
15	------	------	------
16	------	------	------
17	------	------	------
18	250.00	250.00	250.00
19	250.00	125.00	125.00
20	------	------	------
21	250.00	500.00	500.00
22	125.00	62.50	125.00
23	------	------	------
24	------	125.00	125.00
25	62.50	250.00	125.00
Sulphanil-amide	125.00	62.5o	62.50

* MIC is the lowest concentration (μg/ml) preventing visual turbidity after 18-24 hrs. incubation at 37°C.

The screened compounds embody certain groups which are capable of discriminating between the electronic σ, lipophilic ¶ as well as the E_s parameters [8].

Data of Table 2 revealed that compound 5 exhibited twice the antibacterial activity of sulphanilamide against E. coli and Prot. vulgaris, while the other active compounds possessed either equal or lower activity than the reference drug. On the other hand, Staph . aureus was found to be most sensitive towards the screened compounds. Compounds 3, 8, 12, 13, 14 and 22 were equally as effective as the reference drug, while compounds 2, 10 and 25 were twice as active.

EXPERIMENTAL:

Melting points were determined in capillary tubes in Electrothermal Melting Point Apparatus and are uncorrected. Microanalyses were carried out at Microanalytical Centre, Cairo University, ARE. Ultraviolet and infrared spectra were run on Pye-Unicam SP 1750 and SP 1000 Spectrophotometers in absolute ethanol and potassium bromide discs respectively.

3-Aryl-2-(β-arylsulphonylhydrazinomethyl)-4 (3H)-quinazolinones, General Procedure : Proper molar equivalents of 3-aryl-2-chloromethyl-4-(3H)-quinazolinones II and required arylsulphonylhydrazide III were heated in pyridine on a steem bath for 1 hour. Most of pyridine was distilled in *vacuo* and the residue was allowed to cool. The precipitated quinazolinones IV were filtered, drained well, washed successively with water and ether and recrystallized from ethanol.

MICROBIOLOGICAL SCREENING :

MICS of the prepared compounds were determined by the serial dilution method. Each of the screened compounds was dissolved in DMF at a concentration of 1 mg/ml and the solutions were then doubly diluted with sterile broth in Wassermann tubes to obtain the appropriate concentrations. To all tubes 0.2 ml of a bacterial suspension from each strain was added. With each group of tests tubes of uninoculated medium with and without the tested compounds were included to act as control to ensure sterility and clarity of the medium. A third control tube containing inoculated medium was also included to ascertain the ability of growth of strains in the medium. All tubes were incubated at 37°C for 18-24 hrs. and examined for turbidity as an indication for bacterial growth.

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تخليق بعض مشتقات ٣ـ أريل ٢ـ بيتا أريل سلفونيل عمد رازينو ميثيل (٤ ـ أوكسي) الكينازولين ذات الفاعلية البكتريولوجيه

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تم فى هذا البحث تخليق خمسة وعشرين مركبا جديدا ، وأثبتت تركيبها الكيميائى بالتحليل الدقى للعناصر والتحليل الطيفى بالاشعة تحت الحمراء وفوق البنفسجية ، كما درست خواصها البكتريولوجية تجاه أربعة أنواع من البكتريا بالمقارنة مع مركب السلفانيل أميد ٠

وقد اسفرت هذه الدراسة عن أن لخمسة عشر مركبا منها تأثير ملموس ضد البكتريا خاصة تجاه البكتريا العنقودية الذهبية ٠