Synthesis of Some Novel 4 (3H)-Quinazolinone Derivatives of Potential Antimicrobial Activity

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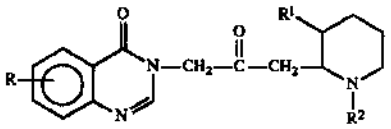
Summary: The reaction of 3-(chloroacetylamino)-2-methyl- 4(3H)-quinazolinone (3) with 2-substituted-5-mercapto-1,3,4- oxadiazoles (**4a**) and 2-substituted-5-mercapto-1,2,4-4 H-triazoles (**4b**) resulted in formation of 3-(5-substituted 1,3,4- oxadiazol-2-yl) thioacetylamino-2-methyl-4(3H)-quinazolinones and 3-(4-amino-5-substituted-1,2,4-4H-triazol-3-yl) thioacetylamino-2-methyl-4(3H)-quinazolinones (**5a-q**). The prepared compounds were evaluated for their antimicrobial activity. All the tested compounds containing 1,2,4-(4H) triazole ring showed antifungal activity.

Introduction

Considerable interest in the pharmacological activity of quinazolones was generated by the observation that fabrifugine, the antimalarial principal in an ancient Chinese herbal remedy, was a derivative of 4 (3H)-quinazolinone [1]. Subsequently, the quinazolinones have been shown to possess inter alia, CNS depressant [2], diuretic [3], anti-hypertensive [4], antiinflammatory [5] antifungal [6], herbicidal [7] and bactericidal [8] activity. It was also shown that compounds of the type (1) possess broad *in vitro* anti-bacterial activity against a variety of organisms [9].



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R = H, halogan or nitro, R^1 = H, R^2 = hydroxy, acetoxy or lower alkoxy.

On the other hand, 2-mercapto-1,3,4-oxadiazole derivatives are reported to have bactericidal and fungicidal properties [10]. Likewise it has been stated that certain s-triazole derivatives exhibit bactericidal [11] and fungicidal activities [12].

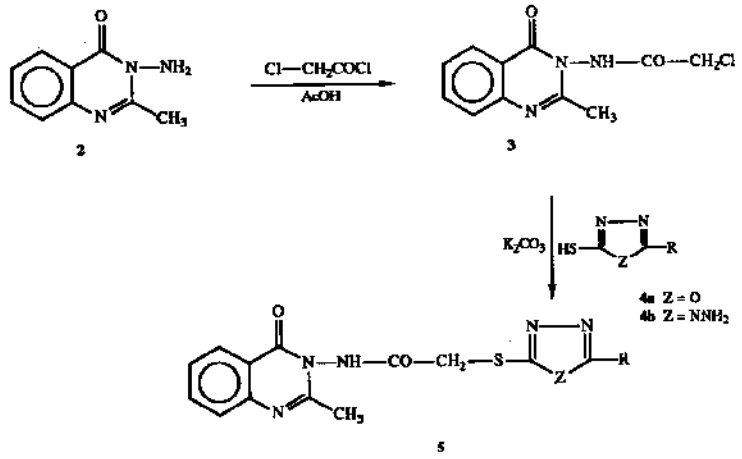
Keeping in view the wide spectrum activities of 4(3H)-quinazolinones and in continuation of our earlier work [13,14] on the synthesis of various heterocycles derived from 4(3H)-quinazolinone derivatives having pharmacological activities, it was considered worthwhile to synthesize some new 4 (3H)-quinazolinones incorporating 1,3,4-oxadia zole or s-triazole ring system to evaluate their antimicrobial activity.

Results and Discussion

The designed 3-(5-substituted-1,3,4-oxadiazol-2-yl)-thioacetylamino-2-methyl-4(3H)-quinazolinones and 3-(4-amino-5- substituted-1,2,4-4H triazol-3-yl)thioacetylamino-2-methyl-4(3H)-quinazolinones (**5a-q**) were prepared according to scheme 1.

The precursor 2-methyl-3-(chloroacetylamino)-4(3H)-quinazolinone [15] (3) was prepared through the reaction of 2-methyl-3-amino- 4(3H)-quinazolinone [16] (2) and chloroacetic acid in presence of $POCl_3$ adopting the method of Klosa [15]. Likewise, the same compound (3) was prepared by refluxing chloroacetylchloride and compound (2) in dry benzene adopting the method for Buyuktimkin [17]. Adopting the method of Klosa and also the method of Buyktimkin gave (3) in a very low yield (10%). In an attempt to increase the yield, compound (2) was stirred with chloroacetylchloride in acetic acid for 3 hours, then neutralization with ammonia gave (3) in a quantitative yield (90%). The structure of compound (3) was verified from its correct elemental analysis and also from IR spectral data which showed bands in the region 3230-3020 characteristic of NH, in the region 1730 and 1665 cm^{-1} characterististic of C = O, and in the region 780 cm^{-1} characteristic of CH_2-Cl. (ν_{max} in cm^{-1}).

Compounds of interest, 3-(5-substituted 1,3,4-oxa-diazol-2-yl) thioacetylamino-2-methyl-4(3H)-



SCHEME 1

quinazolinones and 3-(4-amino-5-substituted- 1,2, 4-4H-triazol-3-yl) thioacetylamino-2-methyl- 4(3H) quinazolinones (**5a-q**) were prepared via the reaction of the aforementioned 3 with 2-substituted-5-mercapto-1,3,4-oxadiazoles [18] or 2-substituted-5-mercapto-1,2,4-4H-triazoles [19,20] in acetone in presence of anhydrous potassium carbonate. The structure of **5a-q** were dedu ced on the basis of spectral data and microanalysis.

IR spectrum (KBr ν_{max} in cm^{-1}) of **5a-e** in which 4(3H)-quinazolinones incorporating 1,3,4-oxadiazole ring systems exhibited peaks at 3250-3200 (NH) and 1680, 1650 (C=O). ^{1}H-NMR spectrum (DMSO d_6, chemical shift in δ ppm) gave more evidence to support the structures of (**5a-e**). ^{1}H-NMR of (**5b**) showed resonance at 2.5 (s, 3H, methylprotons of quinazolinone ring), 3.95 - 4.02 (d, 2H, the -$COCH_2$ group), 7.0-8.5 (m, 9H, aromatic protons) and 11.25 (s, 1H, the secondary amide proton exchangeable with D_2O). The chemical shifts of different carbon atoms in ^{13}C-NMR of compound (**5b**) (δ ppm) showed: 171.0 (C), 164.86 (C), 164.60 (C), 159.35 (C), 140.58 (C), 133.0 (CH) 132 (CH), 129 (CH), 128 (CH), 127.5 (CH), 127 (C), 126.6 (C), 125.5 (C), 125 (CH), 124 (CH), 123.5 (CH), 123 (CH), 30.55 (CH_2) and 20.70 (CH_3). (**5a-e**) were also identified depending on their mass spectra. The mass spectrum of (**5b**) established the molecular formula $C_{19}H_{15}N_5O_3S$ m/z 393 (M^+).

Compound (**5f-j**) in which 4(3H)-quinazolinones incorporating 4-amino-5-substituted phenyl-1,2,4-4H triazole ring systems exhibited IR peaks at 3300-3250 (NH and NH_2), 1690, 1660 (C=O) and 1600-1590 (C=N). ^{1}H-NMR of (**5g**) showed resonances at 2.5 (s, 3H, methyl protons of quinazolinone ring), 3.80-3.95 (d, 2H, $COCH_2$ group), 6.0 (s, 2H, the amino group of triazole ring), 7.0- 8.0 (m, 9H, aromatic protons) and 11.5 (s, 1H, NH). The mass spectrum of 5 g established the molecular formula $C_{19}H_{17}N_2O_2S$ m/z 407 (M^+). Compound **5k-q** in which 4(3H)-quinazolinones incorporating 4-amino-5-substituted phenoxymethyl-1,2,4-4H triazole ring systems exhibited IR peaks at 3290-3200 cm^{-1} (NH, NH_2), and 1700-1680 (C=O). ^{1}H-NMR of **5k** showed resonances at 2.5 (s, 3H, methyl protons of quinazolinone ring), 3.90-4.1 (d., 2H, $COCH_2$ group), 5.1 (s, 2H, -O-CH_2-group), 5.6 (s, 2H, amino group of triazole ring), 7.0-8.2 (m, 9H, aromatic protons) and 11.8 (s, 1H, NH).

Experimental

Microanalyses and IR spectra were carried out in the microanalytical centre, Cairo University. IR (KBr) was carried out using a Pye Unicam spectrophotometer. The NMR spectra were recorded on a Varian T-60 NMR spectrophotometer and a Bruker WH 90 spectrophotometer. The mass spectra were recorded on a Kratos- D_s-50 spectrophotometer. All NMR experiments were done in DMSO-d_6 using TMS as internal standard. The NH and OH protons could be exchanged with D_2O. NMR data are reported in δ ppm; s = singlet, d = doublet, t = triplet, q = quaterted and m = multiplet.

Tablle 1: 2-Methyl-3-(5-substituted-1,3,4-oxadiazol-2- yl)thioacetylamino-4(3H) quinazolinones (5 a-e) and 2-methyl-3-(5-substituted-4-amino-1,2,4-4H-triazol-3-yl) thioacetyl-amino-4(3H) quinazolinones (5 f-q).

Comp.	Z	R	Yield %	m.p. °C	M.F. M.wt.	Analysis (Cal/F) %C	%H	%N
5a	0	4-Pyridyl	50	118-20	$C_{18}H_{14}N_6O_3S$	54.8	3.5	21.3
					(394)	54.7	3.4	21.5
5b	0	C_6H_5	70	88-90	$C_{19}H_{15}N_5O_3S$	58.1	3.8	17.8
					(393)	58.0	3.6	17.4
5c	0	4-BrC_6H_4	50	136-8	$C_{19}H_{14}BrN_5O_3S$	48.3	2.9	14.8
					(472)	48.2	2.8	14.7
5d	0	4-ClC_6H_4	80	163-5	$C_{19}H_{14}ClN_5O_3S$	53.3	3.2	16.3
					(427.5)	53.5	3.5	16.8
5e	0	2-ClC_6H_4	60	above	$C_{19}H_{14}ClN_5O_3S$	53.3	3.2	16.3
				350	(427.5)	53.4	3.4	16.5
5f	NNH_2	4-pyridyl	50	276-8	$C_{18}H_{16}N_8O_2S$	52.9	3.9	27.4
					(408)	52.8	3.8	27.2
5g	NNH_2	C_6H_5	70	220-1	$C_{19}H_{17}N_7O_2S$	56.0	4.1	24.0
					(407)	56.2	4.3	24.5
5h	NNH_2	4-BrC_6H_4	40	230-2	$C_{19}H_{16}BrN_7O_2S$	46.9	3.2	20.1
					(486)	46.8	3.0	20.5
5i	NNH_2	4-ClC_6H_4	50	159-60	$C_{19}H_{16}ClN_7O_2S$	51.6	3.6	22.1
					(441.5)	51.5	3.8	22.7
5j	NNH_2	2-ClC_6H_4	40	168-70	$C_{19}H_{16}ClN_7O_2S$	51.6	3.6	22.1
					(441.5)	51.2	3.5	22.4
5k	NNH2	$CH_2OC_6H_5$	40	106-8	$C_{20}H_{19}N_7O_3S$	549	4.3	22.4
					(437)	54.6	4.8	22.7
5l	NNH_2	$CH_2OC_6H_4$-(2Cl3)	50	90-2	$C_{21}H_{21}N_7O_3S$	55.8	4.6	21.7
					(451)	55.6	4.4	21.3
5m	NNH_2	$CH_2OC_6H_4$-(2-CH_3)	40	118-20	$C_{21}H_{21}N_7O_3S$	558	4.6	21.7
					(451)	55.4	4.2	21.6
5n	NNH_2	$CH_2OC_6H_4$-(4-CH_3)	60	86-8	$C_{21}H_{21}N_7O_3S$	55.8	4.6	21.7
					(451)	55.5	4.5	21.3
5o	NNH_2	$CH_2OC_6H_4$-(2-Cl)	50	94-6	$C_{20}H_{18}ClN_7O_3S$	50.9	3.8	20.7
					(471.5)	50.6	3.6	20.3
5p	NNH_2	$CH_2OC_6H_4$-(3-Cl)	40	96-8	$C_{20}H_{18}ClN_7O_3S$	50.9	3.8	20.7
					(471.5)	50.7	4.0	20.4
5q	NNH_2	$CH_2OC_6H_4$-(4-Cl)	80	120-2	$C_{20}H_{18}ClN_7O_3S$	50.9	3.8	20.7
					(471.5)	50.6	4.2	20.9

3-(Chloroacetylamino)-2-methyl-4(3H) quinazolinone

To 15 g (857 mmol) of 2-methyl-3-amino-4(3H)-quinazolinone [16] in 30 ml glacial acetic acid was added 20 ml (181 mmol) chloroacetylchloride dropwise with stirring. The addition was done in 10 minutes, and stirring continued for 3 hours. On stranding, a heavy precipitate was obtained, neutralized with ammonia in presence of ice and filtered. Crystallization from ethanol afforded 2-methyl-3 (chloroacetylamino)-4-

(3H)- quinazolinone in 90% yield, m.p. 210° (reported 162-164° [17] and 240-2° [15]). Anal.Calcd. for $C_{12}H_{12}Cl\ N_3O_2$ (265.7): C, 54.3; H. 4.5, N 15.8; Found: C, 54.0; H 4.2: N 15.7. IR (cm^{-1}): 3230 and 3020 (NH); 1730 and 1665 (C=O), 1510 (δ NH), 780 (CH_2-Cl).

2-Methyl-3(5-substituted-1,3,4-oxadiazol-2-yl)-thioacetyl- amino-4(3H) quinazolinones (**5 a-e**) *and 2-Methyl-3(5-substituted-4-amino-1,2,4-4H-triazol-3-yl) thioacetylamino-4(3H)-quinazolinones* (**5f-q**).

A mixture of the respective 2-substituted-5-mercapto-1,3,4- oxadiazole [18], 3-substituted-5-mercapto-4-amino-1,2,4-4H triazole [19] or 4-amino-3-aryloxymethyl-5-mercapto 1,2,4-4H triazole [20] and 3-(chloroacetylamino)-2-methyl-4-(3H)-quinazolinone in equimolar amounts (5 mmol.) was heated in dry acetone in presence of anhydrous potassium carbonate (10 mmol) for 21 h. The mixture was cooled, treated with water, dried and crystallized from ethanol (Table 1).

Anbtimicrobial Testing

The antimicrobial activity of 2-methyl-3(5-substituted-1,3,4- oxadiazol-2-yl) thioacetylamino-4(3H)-quinazolinones (**5a-e**) and 2-methyl-3 (5-substituted-4-amino-1,2,4,-4H-triazol-3-yl) thio acetyl amino-4(3H) quinazolinones (**5f-q**) was deter -mined by agar diffusion method [21] against gram-positive bacteria (*Staphylococcus aureus*), gram-negative bacteria (*Escherichia coli*) and fungi (*Candida albicans*).

The agar media were inoculated with the test organisms by 1 ml of a 24 hour broth culture to 100 ml of the media. The solution of the compounds to be tested in propylene glycol (1 mg/ml) was placed separately in cups (8 mm diameter) cut into the agar medium. The plates were incubated at 37°C for 24 hours.

All the tested compounds were inactive against *Escherichia coli* excpet compounds (**5c**) and (**5d**) whereas compounds (**5a**) and (**5e**) showed equal activity against Staphylococcus aureus. All the tested compounds containing the triazole ring (**5f-q**) were active against fungi but the maximum activity was shown by compounds (**5k**), (**5n**), (**5o**), (**5p**) and (**5q**).

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