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Synthesis of Some Quinoxaline Derivatives Containing Indoline-2,3-dione or Thiazolidinone Residue as Potential Antimicrobial Agents

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The synthesis of some quinoxaline derivatives containing indoline-2,3-dione or thiazolidinone residue is described. The synthesized derivatives were screened *in vitro* for their growth inhibitory activity against six species of bacteria, viz. *Staphylococcus aureus, Streptococcus faecalis, Escherichia coli, Pseudomonas aeruginosa, Serratia marcescens* and *Mycobacterium semegmatis*. Most of the compounds exhibited antimicrobial activity especially those having indoline-2,3-dione moiety.

Key words: Quinoxalines, Indoline-2,3-diones, Thiazolidinones, Antimicrobial activity

INTRODUCTION

In a program directed towards the preparation of new quinoxalines of superior biological activity, we reported herein the synthesis of certain compounds where a number of quinoxaline derivatives are reported (Shindle and Pai, 1989; Loriga *et al.*, 1990; Awad, 1991) to possess anti-bacterial activity. Also, several isatin (Varma and Nobles, 1967, 1975; Tinland, 1976) and thiazolidinone (Mousseron, 1972; Akerblom, 1974; Hassan *et al.*, 1978; Mehta *et al.*, 1978) derivatives are useful antibacterial agents. In view of this it was thought worthwhile to synthesize some biologically active compounds, with the expectation that the combined biological effect of quinoxaline and isatin or thiazolidinone moieties might impart enhanced antibacterial potency of these compounds. The synthetic route followed is depicted in Scheme 1.

The key intermediate 2-hydrazino-3-methylquinoxaline (**2**) was prepared (Shino and Tagami, 1960) by halogenation of 2-hydroxy-3-methylquinoxaline (**1**) using phosphorus oxychloride followed by hydrazinolysis of the chloro compound using hydrazine hydrate. Condensation of **2** with various indoline-2,3-diones (Marvel and Hires, 1941; Wahl and Fericean, 1928) **3-5** in the presence of ethanol, containing traces of glacial acetic acid, afforded the hydrazones **6-8**. Mannich condensation of the latters with formalin and piperidine in DMF afforded the Mannich bases **9-11** in reasonable yields. Once more, heating of **1** with **3-5** in glacial acetic acid under reflux furnished the expected condensation products **12-14**. The 1-(3-methyl-2-quinoxalinonyl) acetic acid ethyl ester (**15**), previously obtained by the reaction of **1** with ethyl chloroacetate, and its hydrazide **16** were recognised from the coincidece of the m.p., IR and ^{1}H-NMR data of the products obtained herein with that reported (Badr *et al.*, 1990). Moreover, ^{13}C-NMR for **15** was performed to confirm the N-substitution rather than the O-substitution derivative (δc for 2 C=O at 157.199 and 167.243 ppm). Condensation of **16** with **3-5** in ethanol gave the hydrazones **17-19**. Again, treatment of **17-19** with formalin and piperidine in ethanol afforded the Mannich bases **20-22**. The electrophilic attack of **16** with different aryl or alkyl isothiocyanates proceeds smoothly leading to the thiosemicarbazides **23-25** which on cyclization (Aspelund, 1964) with chloroacetyl chloride in chloroform yielded the corresponding thiazolidinones **26-28**. All the newly synthesized compounds have been characterized by correct elemental analyses as well as IR, ^{1}H-NMR and mass spectral data.

MICROBIOLOGICAL SCREENING

All synthesized compounds were screened *in vitro* against representatives of gram positive bacteria (*Staphylococcus aureus* and *Staphylococcus faecalis*), gram negative bacteria (*Escherichia coli, Pseudomonas aeru-*

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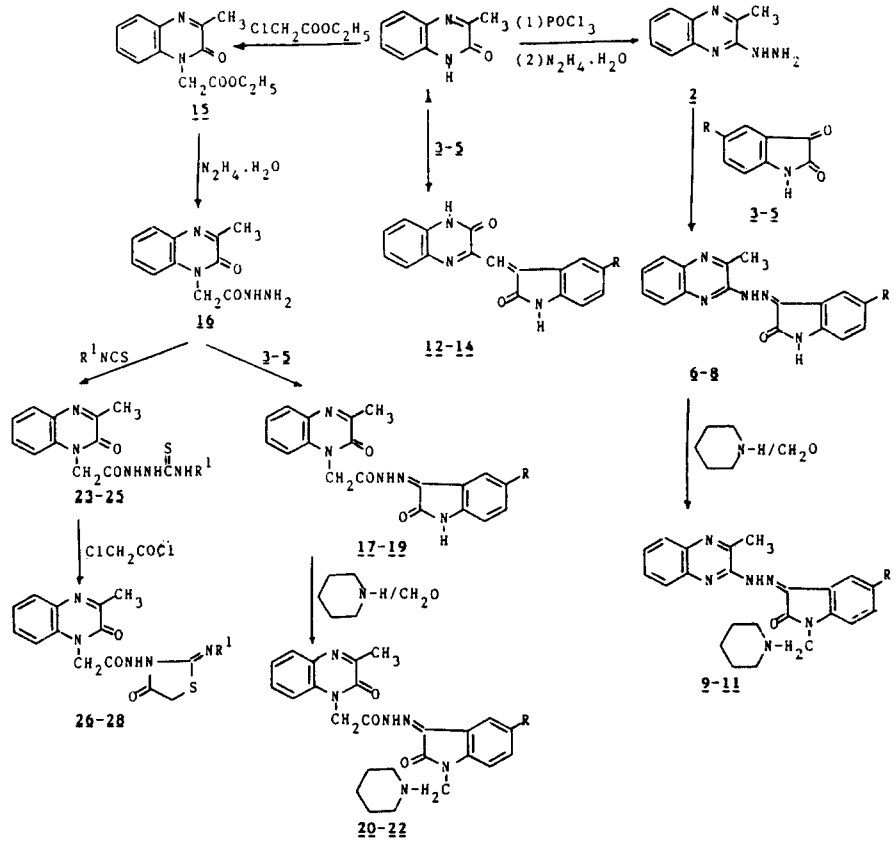

Scheme 1

ginosa and *Serratia marcescens*) and acid fast bacilli (*Mycobacterium semegmatis*). The antimicrobial activity was tested by agar diffusion method (Blain *et al.*, 1970). Test compounds were dissolved in DMSO at concentration of 5 mg/ml, then 50 µl were transferred onto sterile discs of Whatman filter paper (5 mm diameter). The discs were then placed onto the surface of the previously prepared inoculated plates. A disc impregnated with 50 µl of tetracylcine hydrochloride is used as a control for each microorganism. The plates were incubated at 37°C for 24-48 h. After incubation, the zone of inhibition were recorded in mm.

EXPERIMENTAL METHODS

Purity of the compounds was routinely checked by TLC. Melting points were determined in open capillary tubes and are uncorrected. Elemental analyses were carried out at the Microanalytical Unit, University of Cairo. IR spectra were recorded in KBr using Shimadzu IR 435 Spectrophotometer (ν in cm $^{-1}$). ^{1}H- and ^{13}C-NMR were meausred on Jeol FX 90Q Spectrometer using TMS as internal standard and DMSO-d_6 as a solvent (Chemical shift in δ, ppm). Melting points, yield percentages, molecular formulae and anti-bacterial activity of the newly synthesized compounds are listed in Table I.

2-(5-Substituted oxindol-3-ylidenehydrazino)-3-methyl-quinoxalines (6-8)

The appropriate isatin **3-5** (10 mmol) was added to a solution of 2-hydrazino-3-methylquinoxaline (10 mmol, 1.7 g) in ethanol (20 ml) containing two drops of acetic acid. The mixture was heated under reflux for 4 h. On cooling, the solid separated was crystallized from DMF/ethanol. IR: 3400-2800 (N-H association), 1715-1695 (C=O) and 1615 (C=N). ^{1}H-NMR: **8**; 2.6 (s, 3H, CH_3), 7.3-8.7 (m, 7H, Ar-H), 12.1 (br.s., 1H, heteroring NH) and 13.7 (s, 1H, hydrazone NH). MS: **6**; m/z 303.7 (M^+, 16.9% intensitty).

2-(1-Piperidinomethyl-5-substituted oxindol-3-ylidene-hydrazino)-3-methylquinoxalines (9-11)

To a suspension of the appropriate **6-8** (2.5 mmol) and aqueous formalin (1 ml, 37%) in warm DMF (20 ml), piperidine (2.5 mmol, 0.25 ml) was added with constant stirring and the mixture was heated on a water-bath for 30 min. The reaction mixture was allowed to stand at room temperature for 24 h. After cooling, the separated solid was filtered, washed well with pet. ether (60-80°C), dried and crystallized from ethyl ace-

Table I. Melting points, yield percentages, molecular formulae and antibacterial activity of the newly synthesized compounds

Compd. No.	R or R[1]	mp °C	Yield %	Molecular Formula[b]	Mean area inhibition[c] A	B	C	D	E	F
6	H	284-286	92	$C_{17}H_{13}N_5O$	++	+++	++	++	+	+
7	CH_3	270-272	85	$C_{18}H_{15}N_5O$	+++	++	++	++	+	+
8	Cl	276-278	85	$C_{17}H_{12}ClN_5O$	+	+	+	++	+	−
9	H	202-204	72	$C_{23}H_{24}N_6O$	+++	++	++	++	+	+
10	CH_3	238-240	80	$C_{24}H_{26}N_6O$	++	++	++	+	+	+
11	Cl	249-251	85	$C_{23}H_{23}ClN_6O$	++	+	++	+	+	+
12	H	317-319	90	$C_{17}H_{11}N_3O_2$	++	++	++	+	+	−
13	CH_3	322-324	85	$C_{18}H_{13}N_3O_2$	++	++	+	+	+	−
14	Cl	328-330	81	$C_{17}H_{10}ClN_3O_2$	+	+	−	−	−	−
17	H	301-303	80	$C_{19}H_{15}N_5N_3$	+++	++	++	++	++	+
18	CH_3	279-281	75	$C_{20}H_{17}N_5O_3$	++	++	++	+	+	+
19	Cl	282-284	82	$C_{19}H_{14}ClN_5O_3$	+	+	+	+	−	−
20	H	177-179	77	$C_{25}H_{26}N_6O_3$	+++	++	++	+	+	+
21	CH_3	178-180	72	$C_{26}H_{28}N_6O_3$	+	++	+	+	−	−
22	Cl	216-218	60	$C_{25}H_{25}ClN_6O_3$	+	−	−	−	−	−
23	C_2H_5	212-213	55	$C_{14}H_{17}N_5O_2S$	+	+	+	−	−	−
24	$CH_2CH{=}CH_2$	217-218	60	$C_{15}H_{17}N_5O_2S$	+	−	+	+	+	−
25[a]	C_6H_5	258-259	72	$C_{18}H_{17}N_5O_2S$	+	+	+	+	−	−
26	C_2H_5	230-232	42	$C_{16}H_{17}N_5O_3S$	+	−	−	−	−	−
27	$CH_2CH{=}CH_2$	195-197	50	$C_{17}H_{17}N_5O_3S$	−	+	−	−	+	−
28	C_6H_5	138-140	50	$C_{20}H_{17}N_5O_3S$	+	+	+	−	+	−
Control: Tetracycline HCl					>+++	>+++	>+++	>+++	>+++	>+++

[a] Reported mp 210°C (Badr *et al.*, 1990); [b] Satisfactory elemental analyses for C, H and N within ± 0.4% of the theoretical values were obtained for all compounds; [c] A=*Staphylococcus aureus*, B=*Streptococcus faecalis*, C=*Essherechia coli*, D=*Pseudomonas eruginosa*, E=*Serratia marcescens*, F=*Mycobacterium semegmatis*, (−) no inhibition, (+) zone size 7-9 mm, (++) zone size 10-12 mm, (+++) zone size 13-16 mm and (>+++) zone size >16 mm.

tate. IR: 3300 (N-H), 2900-2800 (C-H), 1695-1680 (C=O) and 1615-1610 (C=N). ^{1}H-NMR: **11**; 1.4-1.8 (m, 6H, $(CH_2)_3$), 2.4-2.8 (m, 7H, CH_3 and $N(CH_2)_2$), 4.6 (s, 2H, NCH_2N), 7.5-8.2 (m, 7H, Ar-H) and 13.6 (s, 1H, hydrazone NH).

3-(5-Substituted oxindol-3-ylmethylidene)-1H-quinoxalin-2-ones (12-14)

A mixture of 2-hydroxy-3-methylquinoxaline (5 mmol, 0.8 g) and the appropriate isatin (5 mmol) in glacial acetic acid (5 ml) was heated under reflux for 6 h. After cooling, the resulting crystalline solid was filtered, washed with ethanol and recrystallized from DMF. IR: 3200-2800 (O-H/N-H association), 1700 and 1655-1600 (C=O) and 1605-1600 (C=C). MS: **12**; m/z 289.4 (M^+, 12.2% intensity).

1-(5-Substituted oxindol-3-ylidenehydrazioncarbonylmethyl)-3-methyl-1H-quinoxalin-2-ones (17-19)

The appropriate isatin (5 mmol) was added to a solution of **16** (5 mmol, 1.16 g) in ethanol (10 ml) containing one drop of acetic acid. The mixture was heated under reflux for 3 h. On cooling, the separated solid was crystallized from ethanol. IR: 3300-2800 (N-H association) and 1720-1700, 1680-1675 and 1645-1640 (C=O). ^{1}H-NMR: **19**; 2.6 (s, 3H, CH_3), 5.7 (s, 2H, NCH_2), 7.1-8.8 (m, 7H, Ar-H), 11.4 (s, 1H, CONH) and 12.3 (br.s., 1H, heteroring NH).

1-(1-Piperidinomethyl-5-substituted oxindol-3-ylidenehydrazioncarbonylmethyl)-3-methyl-1H-quinoxalin-2-ones (20-22)

To a suspension of the appropriate **17-19** (2.5 mmol) and aqueous formalin (1 ml, 37%) in warm ethanol (10 ml), piperidine (2.5 mmol, 0.25 ml) was added and continued as mentioned under compounds **9-11**. IR: 3200 (N-H), 2900-2800 (C-H) and 1690-1685, 1680-1675 and 1660-1645 (C=O). ^{1}H-NMR; **22**; 1.5-1.8 (m, 6H, $(CH_2)_3$), 2.4-2.8 (m, 7H, CH_3 and $N(CH_2)_2$), 4.7 (s, 2H, NCH_2N), 5.8 (s, 2H, NCH_2 CO), 7.6-8.4 (m, 7H, Ar-H) and 11.3 (s, 1H, CONH).

N[1]-(3-Methyl-2-oxoquinoxalin-1-ylmethylcarbonyl)-N[4]-substituted thiosemicarbazides (23-25)

A solution of the hydrazide **16** (1 mmol, 0.2 g) and the appropriate isothiocyanate (1 mmol) in ethanol (10 ml) was heated under reflux with stirring for 1 h. On cooling, the separated solid was filtered and crystallized from ethanol. IR: 3300-3200 (N-H), 1700-1680 and 1675-1640 (C=O) and 1210-1190 (C=S). ^{1}H-NMR: **25**; 2.6 (s, 3H, CH_3), 5.3 (s, 2H, NCH_2), 7.3-8.2 (m, 9H, Ar-H), 10.1 (br.s., 2H, 2 NH) and 11.0 (s, 1H, CONH). MS: **25**; m/z 367 (M^+, 8.1% intensity).

1-(2-N-Substituted imino-4-oxothiazolidin-3-ylaminocarbonylmethyl)-3-methyl-1H-quinoxalin-2-ones (26-28)

A mixture of the appropriate thiosemicarbazides **23-25** (1 mmol) and chloroacetyl chloride (1 mmol, 0.11 g) in chloroform (50 ml) containing three drops of triethylamine was heated under reflux for 6 h. The solvent was then distilled in vacuo and the residue triturated with ether. The solid was crystallized from aqueous ethanol. IR: 3450-3350 (N-H), 1760-1720, 1720-1680 and 1650-1640 (C=O) and 1620 (C=N).

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