Synthesis of Some New Heterocycles of Pharmaceutical Interest: Pyridinyl and Isoxazolyl Quinoxaline Derivatives

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3-(*p*-Acetyl-anilinomethyl)quinoxalin-2(1*H*)-one (**3**) was prepared by the reaction of 3-bromomethylquinoxalin-2(1*H*)-one (**1**) with *p*-aminoacetophenone (**2**) in pyridine. Reaction of *p*-acetylcompound (**3**) with aromatic aldehydes yield the corresponding chalcones (**4a-c**). Condensation of latter chalcones with malononitrile afforded cyanopyridines (**5a-c**). Also, the reaction of chalcones (**4a-c**) with hydroxylamine hydrochloride furnished isoxazoles (**6a-c**). The reaction of bromo compound (**1**) with *p*-aminobenzophenone yield (**8**) which was condenced with hydrazine hydrate to get the corresponding hydrazone derivatives (**9**). Some of the synthesized compounds have been screened for their antimicrobial activity against various strains of bacteria and fungi .

Keywords: Quinoxaline; Isoxazoles; Antimicrobial activity.

INTRODUCTION

Quinoxaline derivatives are known to possess interesting biological properties which show antibacterial, fungicidal, insecticidal, anthelmic and cytotoxic activities.[1] Recently, that some quinoxaline derivatives inhibit selectively the platelet-derived growth factor (PDGF) receptor kinase, PDGF-dependent DNA synthesis in cells[2] and its unique inhibitory activity against a panel of human cancer cell lines.[3] On the other hand, a quinonimine system (napthooxazinoquinoxalinone derivative)[4] is of interest because this system constitutes the structure of several antitumor antibiotics such as actionmycin D,[5] questiomycin A,[6] and glycosylquestiomycin.[7] Also, among the wide variety of heterocycles that have been explored for the viral and antifungal activities of developing pharmaceutically important molecules, cyanopyridines,[8-10] isoxazoles[11-13] have been similarly investigated. The present investigation, and in continuation of our work on quinoxaline moiety;[14-18] is concerned with the use of 3-bromomethylquinoxalin-2(1*H*)-one for the synthesis of many heterocycles systems of a new type with the aim of investigating their antimicrobial properties.

RESULTS AND DISCUSSION

The starting compound 3-bromomethylquinoxalin-2(1*H*)-one **1** was reacted with *p*-aminoacetophenone **2** in the presence of pyridine as a basic catalyst to get 3-(*p*-acetyl-anilinomethyl)quinoxalin-2(1*H*)-one **3** which was treated with virous aromatic aldehydes to give chalcones **4a-c** (the IR spectra of these compounds showed two absorption bands at 970 , 730 cm^{-1} duo to the presence of these compounds as a mixture their trans and cis forms, respeceivally;[21] the latter compounds on treatment with malononitrile in the presence of ammonium acetate gave cyanopyridinylquinoxalinones **5a-c** through Michael reaction[22] with the elimination of water and hydrogen (Scheme I).

Reaction of chalcones **4a-c** with hydroxylamine hydrochloride in the presence of sodium acetate in acetic acid furnished isoxazolylquinoxalinone derivatives **6a-c** (Scheme II).[18b,23]

Also the bromo compound **1** was reacted with *p*-aminobenzophenone **7** in basic medium to afford 3-(4-benzoyl-anilinomethyl)quinoxalin-2(1*H*)-one **8**; hydrazinolysis of the latter compound with hydrazine hydrate afforded the corresponding hydrazone **9** (Scheme III).

ANTIMICROBIAL ACTIVITY

The newly synthesized compounds were screened for their antibacterial activity aganist three species of different bacteria: Gram postive, *Bacillus subtillus, Micrococcus luteus* and Gram negative; *Serration rhodenil* and three species of fungi: *Aspergillus fumigatus*, *Penicllum chrysogen*,

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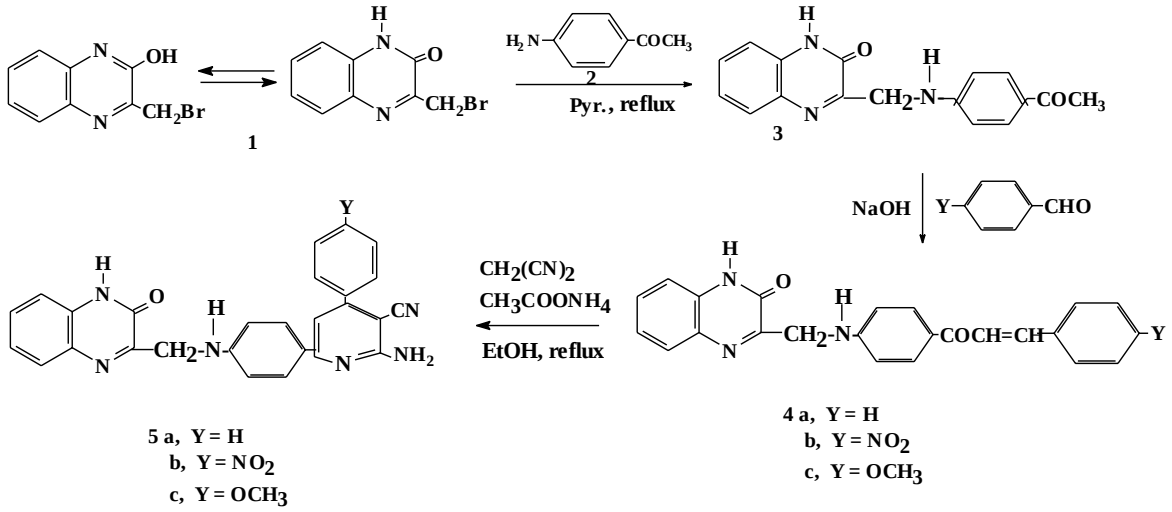
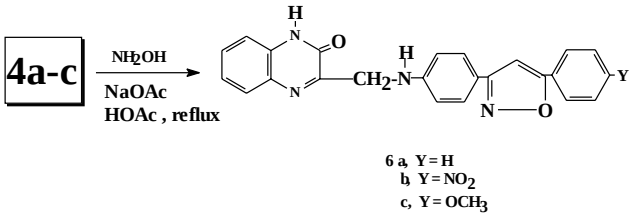
Scheme I



Scheme II



and *Fusarium equiseti* using the filter paper technique[19,20] measuring the zone of inhibition in mm at 25 μg concentration. The screening results summerized in Table 1 indicated that among of tested compounds, the new compounds showed good growth inhibition against Gram postive bacteria, but only two compounds **3** and **5a** showed good growth inhibition against Gram negative bacteria. However, concerning the antifungal activities only two compounds **3** and **6a** were active against fungi. The results of the antimicrobial activity tests are summarized in Table 1.

EXPERIMENTAL

Melting points were determined on a Gallen Kamp melting point apparatus and are uncorrected. IR spectra were recorded on a Pye-Unicam SP^3-100 spectrophotometer using KBr wafer technique.^{1}H NMR spectra were measured on a Varian 390-90 MHz NMR spectrometer in the suitable deuterated solvent, using TMS as internal standard. Elemental analyses were performed on a Perkin-Elmer 240 C microanalyzer and all compounds gave results in an acceptable range. Spectroscopic data are listed in Table 2.

3-Bromomethylquinoxalin-2(1*H*)-one (1) was prepared according to the literature[14] mp. 245 °C.

3-(*p*-Acetylanilinomethyl)quinoxalin-2(1*H*)-one (3)
Method A:

To a mixture of *p*-aminoacetophenone **2** (1.35 g, 0.01 mol) in pyridine (2.3 mL, 0.025 mol), 3-bromomethylquino-

Scheme III

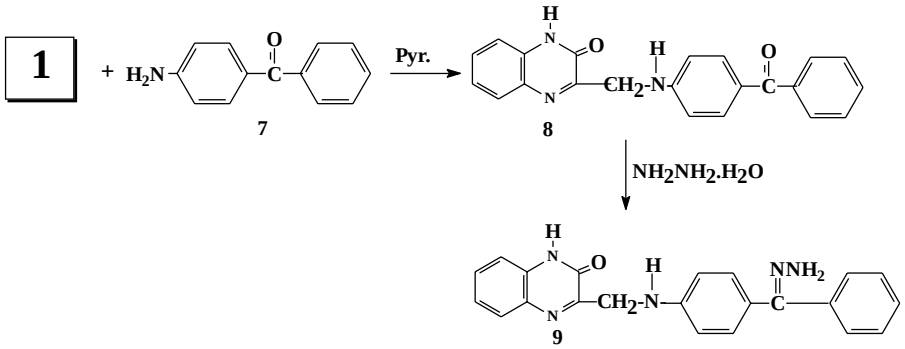


Table 1. Antimicrobial Activity of Some Synthesized Compounds [zone of inhibition in mm]

Comp. No.	Antibacterial activity			Antifungal activity		
	Bacillus subtillus	Micrococcus luteus	Serration rhodenil	Aspergillus fumigatus	Penicillium chrysogen	Fusarium equiseti
3	7	-	16	-	-	12
4b	-	-	-	-	-	-
5a	7	-	19	-	-	-
5b	-	-	-	-	-	-
6a	7	-	-	-	-	13
6b	11	-	-	-	-	-
8	-	-	-	-	-	-
9	7	-	-	-	-	-

Table 2. Spectroscopic Data of Compounds **3-9**

Comp. No	IR (ν cm^{-1}) / ^{1}H NMR δ (ppm)
3	3400, 3200 (2NH), 1710, 1670 (2CO), 1610 (C=N); (DMSO-d_6): δ 2.4 (s, 3H, CH_3), 4.2 (s, 2H, CH_2), 7.2-7.9 (m, 8H, Ar-H), 10.5, 11.4 (2s, 2H, 2NH).
4a	3300, 3150 (2NH), 2960 (CH-alph.), 1700, 1670 (2CO), 1600 (C=N); (CF_3COOD): δ 4.3 (s, 2H, CH_2), 7.4-8.2 (m, 15H, Ar-H and CH=CH).
4b	3350-3100 (2NH), 2950 (CH-alph.), 1700, 1670 (2CO), 1610 (C=N); (CF_3COOD): δ 4.2 (s, 2H, CH_2), 7.4-8.1 (m, 14H, Ar-H and CH=CH).
4c	3400-3180 (2NH), 2960 (CH-alph.), 1705, 1670 (2CO), 1620 (C=N); ($CDCl_3$): δ 3.58 (s, 3H, OCH_3), 4.35 (s, 2H, CH_2), 7.5-8.0 (m, 14H, Ar-H and CH=CH), 10.5, 11.1 (2s, 2H, 2NH).
5a	3450, 3200 (NH, NH_2), 2220 (CN), 1670 (CO), (DMSO-d_6): δ 2.6 (s, 2H, NH_2), 4.35 (s, 2H, CH_2), 7.5-8.2 (m, 14H, Ar-H and CH, pyr.), 10.4, 11.0 (2s, 2H, 2NH).
5b	3330 (NH, NH_2), 2220 (CN), 1670 (CO); (DMSO-d_6): δ 2.45 (s, 2H, NH_2), δ 4.2 (s, 2H, CH_2), 7.2-8.1 (m, 13H, Ar-H and CH, pyr), 10.5, 11.2 (s, 2H, 2NH).
5c	3180-3420 (NH, NH_2), 2220 (CN); 1670 (CO), (DMSO-d_6): δ 2.6 (s, 2H, NH_2), 3.58 (s, 3H, OCH_3), 4.25 (s, 2H, CH_2), 7.3-7.9 (m, 13H, Ar-H), 11.3 (s, 1H, NH).
6a	3200 (NH), 1670 (CO), 1620 (C=N); (DMSO-d_6): δ 4.4 (s, 2H, CH_2), 7.4 -8.2 (m, 14H, Ar-H), 10.5, 11.3 (s, 2H, 2NH).
6b	3200-3300 (NH), 1670 (CO), (DMSO-d_6): δ 4.45 (s, 2H, CH_2), 7.3-8.1 (m, 13H, Ar-H), 10.7 (s, 1H, NH).
6c	3240 (NH), 1670 (CO), 1620 (C=N); (DMSO-d_6): δ 4.50 (s, 2H, CH_2), 7.4-8.2 (m, 13H, Ar-H), 10.85 (s, 1H, NH).
8	3220, 3500 (NH), 1720, 1670 (2CO); ($CDCl_3$): δ 4.3 (s, 2H, CH_2), 7.4-8.0 (m, 13H, Ar-H). 11.2 (s, 1H, NH).
9	3250-3420 (NH, NH_2), 1670 (CO); 1600 (C=N); (CF_3COOD): δ 4.4 (s, 2H, CH_2), 7.6-8.2 (m, 13H, Ar-H).

xalin-2(1*H*)-one **1** (2.39 g, 0.01 mol) was added portionwise with constant stirring. The mixture was refluxed for 3 h in 20 mL of ethanol; the contents were poured into a crushed ice (60 g) and conc. HCl (5 mL) mixture. The product thus separated was filtered and crystallized from ethanol, 67% yield, as yellow crystals mp: 261-262 °C, [$C_{17}H_{15}N_3O_2$; 293].

Method B:

To a solution of *p*-aminoacetophenone **2** (1.35 g, 0.01 mol) in 10 mL of pyridine, 3-bromomethylquinoxalin-2(1*H*)-one **1** (2.39 g, 0.01 mol) was added portionwise with constast stirring. The mixture was stirred for 30 min. at 0 °C; the contents were poured into a crushed ice (60 g) and conc. HCl (5 mL) was added. The product thus separated was filtered and crystallized from ethanol, 71% yield.

Condensation of (3) with aromatic aldehydes

A mixture of acetyl compound **3** (3.25 g, 0.01 mol) and aromatic aldehydes (0.01 mol) in ethanol (20 mL), and NaOH (40%, 5 mL) was stirred for 5 h. The contents were poured into a crushed ice; the product was isolated by acidifaction (HCl, 5 mL) and crystallized from ethanol.

4a: 72% yield, as reddish crystals mp: 251-252 °C

[$C_{24}H_{19}N_3O_2$; 381].

4b: 65% yield; as red crystals mp: 280-281 °C [$C_{24}H_{18}N_4O_4$; 426].

4c: 69% yield, as pale brown crystals mp: 272-274 °C [$C_{25}H_{21}N_3O_3$; 411].

Reactions of chalcones (4a-c) with malononitrile

A mixture of chalcone **4** (0.1 mol), malononitrile (0.66 g, 0.1 mol) and ammonium acetate (6.16 g, 0.8 mol) was refluxed in ethanol (30 mL) for 6 h on a water-bath; the cooled contents were then poured into crushed ice with constant stirring, and the resulting solid was washed with water and the residue was crystallized from ethanol to give **5a-c**.

5a: 72% yield, as yellowish crystals mp: 222-224 °C [$C_{27}H_{20}N_6O$; 444].

5b: 72% yield, as pale orange crystals mp: 259-260 °C [$C_{27}H_{19}N_7O_3$; 489].

5c: 72% yield, as yellow crystals mp: 227-238 °C [$C_{28}H_{22}N_6O_2$; 474].

Reactions of chalcones (4a-c) with hydroxylamine hydrochloride

Anhydrous sodium acetate (0.73 g, 0.01 mol) dissolved in a minimum amount of hot acetic acid was added to the solution of hydroxylamine hydrochloride (0.7 g, 0.01 mol) in ethanol (20 mL). This solution was added to a solution of chalcones **4a-c** (0.01 mol) in ethanol (20 mL). The mixture was refluxed for 6 h, concentrated and neutralized with NaOH. The product thus isolated was filtered and crystallized from ethanol to yield **6a-c**.

6a: 78% yield, as pale yellow crystals mp: 219-220 °C [$C_{24}H_{18}N_4O_2$; 394].

6b: 70% yield, as yellowish crystals mp: 230-232 °C [$C_{24}H_{17}N_5O_4$; 439].

6c: 69% yield, as yellow crystals mp: 227-228 °C [$C_{25}H_{20}N_4O_3$; 424].

3-(4-Benzoylanilinomethyl)quinoxalin-2(1*H*)-one (8)

was prepared from **1** (2.39 g, 0.01 mol) and *p*-aminobenzophenone (1.97 g, 0.01 mol) to give **8**, 77% yield, as white crystals mp: 120-122 °C [$C_{22}H_{17}N_3O_2$; 355].

3-(4-Benzoylhydrazoneanilinomethyl)quinoxalin-2(1*H*)-one (9)

A solution of ketone compound **8** (3.55 g, 0.01 mol) and hydrazine hydrate (0.01 mol) in ethanol (30 mL) was heated under reflux for one h; the reaction mixture was cooled, the solid separated was filtered and crystallized from ethanol to give 65% yield of **9**, as yellowish crystals mp: 154-155 °C [$C_{22}H_{19}N_5O$; 369].

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