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Synthesis and Antimicrobial Activity of Certain Novel Quinoxalines

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In this study, certain 3-methyl-2-[4-(substituted amino carbonyl)anilino] quinoxalines, (**2a-d**) and (**3a-d**), were synthesized from the new key compound 2-[4-(ethoxycarbonyl)anilino]-3-methyl quinoxaline (**1**). In addition, a series of 2-[4-(arylidene hydrazinocarbonyl)anilino]-3-methyl quinoxalines (**5a-e**), as well as their cyclized oxadiazolinyl derivatives (**6a-e**), and a series of 2-[4-N^2-acylhydrazinocarbonyl) anilino]-3-methyl quinoxalines (**7a-d**), as well as their cyclized oxadiazolyl derivatives (**8a-d**) were also prepared. Some of these derivatives were evaluated for antimicrobial activity *in vitro*. It was found that all the selected compounds exhibit antimicrobial activity and that compound **5b** had a broad spectrum of activity.

Key words: 2-[4-(Ethoxycarbonyl) anilino]-3-methylquinoxaline, Oxadiazolyl quinoxalines, Antimicrobial agents

INTRODUCTION

A literature survey revealed that quinoxaline derivatives display antibacterial (Badran *et al.*, 2003; Griffith *et al.*, 1992; El-Gendy *et al.*, 1995), antifungal (Reddy-Sastry *et al.*, 1990; El-Hawash *et al.*, 1999), antiviral (Westphal *et al.*, 1977), antimalarial (Crowther *et al.*, 1949), anticancer (Monge *et al.*, 1995) and antidepressant activities (Sarges *et al.*, 1990).

The versatile importance of oxadiazolyl quinoxalines is also expressed in their anticonvulsant and anxiolytic activities (TenBrink *et al.*, 1994), whereas the antimicrobial activity of arylhydrazinocarbonyl, oxadiazolyl and carboxamido quinoxalines is well documented (El-Kerdawy *et al.*, 1991; Kurasawa *et al.*, 1986a; Kurasawa *et al.*, 1986b; Dirlam and Presslitz, 1978). Therefore, substituted oxadiazolines, oxadiazoles and aryl carboxamides were incorporated into the quinoxaline nucleus, and their antimicrobial activities evaluated.

MATERIALS AND METHODS

The melting points of the synthesized compounds were obtained on a Griffin apparatus, and are uncorrected. Microanalyses for C, H and N were carried out at the Microanalytical center, Cairo University. IR spectra were recorded on a Shimadzu 435 spectrometer, Using KBr discs. ^{1}H-NMR spectra were obtained on a Joel NMR FXQ-200 MHZ Spectrometer, using TMS as the internal standard. Mass spectra were recorded on a GCMS-QP 1000 Ex. Mass spectrometer. The progress of the reactions was monitored by TLC, using aluminium sheets precoated with silica gel MERCK 60 F254, and visualized under UV illumination.

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2-[4-(Ethoxycarbonyl)anilino]-3-methyl quinoxaline (1)

A mixture of 2-chloro-3-methyl quinoxaline (50 mmol, 8.9 g) and ethyl 4-aminobenzoate (50 mmol, 8.25 g) in *n*-butanol (25 mL) was heated under reflux for 5 h. The solid obtained, after cooling, was collected by filtration, washed with water and recrystallized from ethanol (Tables I and II).

3-Methyl-2-[4-(substituted aminocarbonyl)anilino] quinoxalines (2a-d)

General procedure: A mixture of **1** (2 mmol, 0.6 g) and the respective amine (10 mmol) (Viz; 2-amino morpholine, 2-aminomethyl pyridine, 2-amino thiazole and 3-amino quinoline) in *n*-butanol (10 mL) was heated under reflux for 24 h. After cooling the reaction mixture, the solid was collected by filtration, washed

with diethyl ether and recrystallized from ethanol (Tables I and II).

3-Methyl-2-[4-(4-Substituted piperazin-1-ylcarbonyl) anilino] quinoxalines (3a-d)

General procedure: A mixture of **1** (2 mmol, 0.6 g) and the appropriate 4-substituted piperazines (10 mmol) (viz; 4-phenylpiperazine, 4(4-fluorophenyl)piperazine, 4(2-ethoxyphenyl)piperazine and 4(2-trifluoromethylphenethyl) piperazine) was heated under reflux for 48 h. The precipitated solid was filtered off, washed with diethyl ether and recrystallized from ethanol (Tables I and II).

2-[4-(Hydrazinocarbonyl) anilino]-3-methyl quinoxaline (4)

A mixture of **1** (20 mmol, 6 g) and hydrazine hydrate 99% (100 mmol, 5 g) in absolute ethanol (50 mL) was refluxed for 5 h. The precipitate, which separated out on cooling, was filtered off, washed with water and recrystallized from ethanol (Tables I and II).

2-[4-(Arylidenehydrazinocarbonyl)anilino]-3-methyl quinoxalines (5a-e)

General procedure: A mixture of **4** (5 mmol, 1.5 g) and the respective aromatic aldehydes (10 mmol) (Viz; 4-fluorobenzaldehyde, 4-bromobenzaldehyde, 4-chlorobenzaldehyde, thiophene-2-carboxaldehyde and pyridyl-4-carboxaldehyde) was refluxed in ethanol (20 mL) for 6 h. The solution obtained was concentrated by evaporation, under reduced pressure, to one forth of its original volume and then allowed to cool. The precipitated solid was filtered off, washed with ether and recrystallized from ethanol (Tables I and II).

2-[*N*-Acetyl 4-(4-acetyl-5-aryl-1,3,4-Oxadiazolin-2-yl) anilino]-3-methyl quinoxalines (6a-e)

General Procedure: The appropriate arylidene hydrazide (**5a-e**) (2 mmol) was refluxed with acetic anhydride (3 mL) for 1 h. The excess acetic anhydride was distilled off under reduced pressure, the residue triturated with ice, filtered off and recrystallized from benzene/pet ether (60-80) (Tables I and II).

2-[4-(N^2-Acyl hydrazinocarbonyl)anilino]-3-methyl quinoxalines (7a-d)

Method A: To a stirred solution of **4** (5 mmol, 1.5 g) in dry benzene (20 mL), the respective acid chlorides (5 mmol) (Viz; 3-bromobenzoyl chloride, 4-bromobenzolyl chloride and 4-nitrobenzoyl chloride) and anhydrous potassium carbonate (0.5 g) were added, and the mixture refluxed for 4 h. The precipitate formed upon cooling, was filtered off, washed with water and recrystallized from ethanol (Table I, II).

Table I. Physical and analytical data for the prepared compounds

Compd. No.	Yield %	m.p. °C	Formula (Mol. Wt.)	Analysis % calcd/found		
				C	H	N
1	92	235-237	$C_{18}H_{17}N_3O_2$ (307)	70.35 70.31	5.53 5.55	13.68 13.70
2a	73	160-162	$C_{20}H_{21}N_5O_2$ (363)	66.11 66.23	5.78 5.81	19.28 19.35
2b	68	165-167	$C_{22}H_{19}N_5O$ (369)	71.54 71.48	5.14 5.09	18.97 19.05
2c	56	145-147	$C_{19}H_{15}N_5OS$ (361)	63.15 63.14	4.15 4.17	19.39 19.40
2d	70	132-135	$C_{25}H_{18}N_5O$ (404)	74.25 74.30	4.45 4.48	17.32 17.34
3a	82	178-180	$C_{26}H_{25}N_5O$ (423)	73.76 73.80	5.91 5.87	16.54 16.47
3b	78	190-192	$C_{26}H_{24}FN_5O$ (441)	70.74 70.68	5.44 5.45	15.87 15.82
3c	80	170-172	$C_{28}H_{29}N_5O_2$ (467)	71.94 72.00	6.20 6.19	14.98 14.87
3d	85	200-202	$C_{29}H_{28}F_3N_5O$ (519)	67.05 67.00	5.39 5.36	13.48 13.51
4	75	185-187	$C_{16}H_{15}N_5O$ (293)	65.52 65.62	5.11 5.17	23.89 23.92
5a	90	123-125	$C_{23}H_{18}FN_5O$ (399)	69.17 69.21	4.51 4.49	17.54 17.48
5b	92	118-120	$C_{23}H_{18}BrN_5O$ (460)	60.00 60.02	3.91 3.95	15.21 15.15
5c	89	125-127	$C_{23}H_{18}ClN_5O$ (415.5)	66.42 66.38	4.33 4.30	16.84 16.80
5d	85	135-137	$C_{21}H_{17}N_5OS$ (387)	65.11 65.00	4.39 4.40	18.08 18.12
5e	87	150-152	$C_{22}H_{18}N_6O$ (382)	69.10 69.07	4.71 4.74	21.98 22.01
6a	72	118-120	$C_{27}H_{22}FN_5O_3$ (483)	67.08 67.11	4.55 4.56	14.49 14.48
6b	75	152-154	$C_{27}H_{22}BrN_5O_3$ (544)	59.56 59.60	4.04 4.06	12.86 12.88
6c	78	108-110	$C_{27}H_{22}ClN_5O_3$ (499.5)	64.86 64.90	4.40 4.42	14.01 14.03
6d	66	125-127	$C_{25}H_{21}N_5O_3S$ (471)	63.69 63.71	4.45 4.48	14.86 14.92
6e	60	131-133	$C_{26}H_{22}N_6O_3$ (466)	66.95 66.90	4.72 4.76	18.02 18.00
7a	81	188-190	$C_{23}H_{18}BrN_5O_2$ (476)	57.98 58.01	3.78 3.82	14.70 14.71
7b	79	227-230	$C_{23}H_{18}BrN_5O_2$ (476)	57.98 57.96	3.78 3.76	14.70 14.70
7c	90	210-212	$C_{23}H_{18}N_6O_4$ (442)	62.44 62.48	4.07 4.10	19.00 19.01
7d	64	158-160	$C_{22}H_{18}N_6O_2$ (398)	66.33 66.34	4.52 4.52	21.10 21.11
8a	54	205-207	$C_{23}H_{16}BrN_5O$ (458)	60.26 60.28	3.49 3.50	15.28 15.27
8b	45	212-215	$C_{23}H_{16}BrN_5O$ (458)	60.26 60.30	3.49 3.51	15.28 15.30
8c	60	227-230	$C_{23}H_{16}N_6O_3$ (424)	65.09 65.10	3.77 3.77	19.81 19.81
8d	58	258-260	$C_{22}H_{16}N_6O$ (380)	69.47 69.50	4.21 4.22	22.10 22.00

Table II. Spectral data for prepared compounds

Compd. No.	IR (KBr cm^{-1}), ^{1}H-NMR (DMSO-d_6, δ ppm) MS m/z (% relative abundance)	
1	IR: ^{1}H-NMR:	3350 (NH), 2900-2800 (CH aliph.), 1710 (C=O) 1.13 (t, 3H, $OCH_2\underline{CH_3}$), 2.52 (s, 3H, CH_3) 4.11 (q, 2H, $O\underline{CH_2}CH_3$), 7.24-7.72 (m, 8H, ArH), 12.30 (br, NH, D_2O exchangeable)
2a	IR:	3350 (NH), 2850-2800 (CH aliph.), 1690 (C=O)
2b	IR:	3300 (NH), 2900-2850 (CH aliph.), 1700 (C=O)
2c	IR: ^{1}H-NMR:	3400 (NH), 2900-2850 (CH aliph.), 1700 (C=O) 2.77 (s,3H, CH_3), 7.20-8.24 (m, 10H, ArH) 8.70 (s, 1H, NH, D_2O exchangeable), 8.97 (s, 1H, NH, D_2O exchangeable)
2d	IR:	3300 (NH), 1690 (C=O)
3a	IR:	3400 (NH), 2900 (CH aliph.), 1690 (C=O)
3b	IR: ^{1}H-NMR:	3350 (NH), 2900 (CH aliph.), 1700 (C=O) 2.77 (s,3H, CH_3), 3.29 (br, 4H, $2CH_2$, piperazine), 4.31 (br, 4H, $2CH_2$, piperazine), 7.4-8.20 (m, 12H, ArH), 8.99 (s,1H, NH, D_2O exchangeable)
3c	IR:	3450 (NH), 2900 (CH aliph.), 1695 (C=O)
3d	IR:	3400 (NH), 2900 (CH aliph.), 1700 (C=O)
4	IR: ^{1}H-NMR:	3350,3200 (NH, NH_2), 2900 (CH aliph.)1700 (C=O) 2.76 (s, 3H, CH_3), 4.46 (s, 2H, NH_2, D_2O exchangeable), 7.49-8.10 (m, 8H, ArH), 8.82 (s, 1H, NH, D_2O exchangeable), 9.66 (s, 1H, NH, D_2O exchangeable).
5a	IR:	3350 (NH), 1650 (C=O)
5b	IR:	3400 (NH), 1640 (C=O)
	^{1}H-NMR:	2.78 (s, 3H, CH_3), 7.47-8.19 (m, 12H, ArH), 8.46 (s, 1H, N=CH), 8.92 (s, 1H, NH, D_2O exchangeable), 11.82 (s, 1H, NH, D_2O exchangeable)
5c	IR:	3300 (NH), 1640 (C=O)
5d	IR:	3300 (NH), 1630 (C=O)
5e	IR: MS:	3350 (NH), 1650 (C=O) 383 (M+1, 2.51%), 382 (M^+, 8.50), 262 (100%)
6a	IR:	2900 (CH aliph.), 1670 (-$COCH_3$)
6b	IR: MS:	2950 (CH aliph.), 1670 (-$COCH_3$) 545 (M+2, 6.70%), 544 (M^+1, 4.23) 543 (M^+, 7.23%), 502 (3.35%), 501 (5.47%), 458 (2.82%), 459 (4.00), 260 (100%)
6c	IR: ^{1}H-NMR:	2900 (CH aliph.), 1670 (-$COCH_3$) 2.15 (s, 3H, -$COCH_3$), 2.32 (s, 3H, -$COCH_3$), 2.81 (s, 3H, -CH_3), 7.14-8.09 (m, 13H, 12 ArH and one oxadiazoline proton)
6d	IR:	2900 (CH aliph.), 1680 (-$COCH_3$)
6e	IR:	2850 (CH aliph.), 1660 (-$COCH_3$)
7a	IR:	3350 (NH), 1700, 1680 (2C=O)
7b	IR:	3350 (NH), 1710, 1680 (2C=O)
7c	IR: ^{1}H-NMR:	3300 (NH), 1710, 1690 (2C=O), 1530, 1320 (NO_2) 2.76 (s, 3H, CH_3), 7.70-8.36 (m, 12H, ArH), 8.90 (s, 2H, 2NH, D_2O exchangeable), 11.41 (s, 1H, NH, D_2O exchangeable)
7d	IR:	3350 (NH), 1710, 1680 (2C=O)
8a	IR:	3300 (NH), 1600 (C=N)
8b	IR:	3350 (NH), 1620 (C=N)
8c	IR: MS:	3400 (NH), 1620 (C=N) 426 (M+2, 3.25%), 425 (M+1, 21.73%), 424 (M+, 90.55) 423 (100%)
8d	IR:	3350 (NH), 1620 (C=N)

Method B: To a stirred solution of **1** (5 mmol, 1.5 g) in ethanol (20 mL), isonicotinic acid hydrazide (5 mmol, 0.5 g) was added, and the mixture refluxed for 5 h. After cooling, the precipitate formed was filtered off and recrystallized from ethanol (Table I).

2-[4-(5-Aryl-1,3,4-oxadiazol-2-yl)anilino]-3-methyl quinoxalines (8a-d)

General procedure: Phosphorus oxychloride (5 mL) was added to the appropriate compounds (**7a-d**) (2 mmol), and the mixture heated under reflux for 6 h. The

excess phosphorus oxychloride was distilled under reduced pressure, the residue triturated with ice, filtered off and recrystallized from ethanol (Tables I and II).

RESULTS AND DISCUSSION

Chemistry

The starting material, 2-chloro-3-methyl quinoxaline, was prepared from 1, 2-phenylene diamine and ethyl pyruvate (Westphal, 1977) followed by chlorination of the product with phosphorus oxychloride (Shiho and Tagami, 1959). The reaction of 2-chloro-3-methyl quinoxaline with ethyl 4-aminobenzoate afforded the key intermediate **1**. Amination of **1**, with certain amines and substituted piperazines in *n*-butanol, gave the 3-methyl-2-[4-(Substituted aminocarbonyl) anilino] quinoxalines (**2a-d**) and the 3-methyl-2-[4-(4-substituted piperazin-1-ylcarbonyl)anilino] quinoxalines (**3a-d**), respectively. Conversely, hydrazinolysis of **1** afforded 2-[4-(hydrazinocarbonyl)anilino]-3-methyl quinoxaline (**4**). Compound **4** was allowed to react with certain aromatic aldehydes to give the corresponding arylidene hydrazides (**5a-e**), which underwent acetylation with concomitant cyclization using acetic anhydride to give oxadiazolines (**6a-e**). The ^{1}H-NHR of compound **6c** revealed the absence of the singlet signals corresponding to the azomethine (CH=N) of its precursor. Also, the disappearance of the signals corresponding to the 2NH, and the presence of signals at 2.15 and 2.31, corresponding to 2acetyl groups, were indicative of successful oxadiazoline ring formation and acetylation of the 2NH. The structure was also substantiated by the mass spectrum of compound **6b**, which showed successive loss of the two acetyl groups of the parent compound. Attempts to prepare compounds 8a-d from compound **4** and acid chloride by refluxing in pyridine led only to benzoylation of the hydrazino moiety. Therefore, the hydrazide, **4**, was reacted with the respective acid chloride in dry benzene to give the 2-[4-(*N*^{2}-acylhydrazino carbonyl) anilino]-3-methyl quinoxalines (**7a-c**). Conversely, compound **7b** was prepared via the reaction of the ester **1** with isonicotic acid hydrazide in ethanol. Finally, cyclization of compounds **7a-d** was achieved using phosphorus oxychloride, to the give oxadiazoles **8a-d**.

Antimicrobial activity

The preliminary antibacterial and antifungal activities were obtained for selected compounds against various bacteria and fungi, namely:

1-Staphylococcus aureus (Gram positive bacteria).
2-Bacillus subtilis (Gram positive spore-forming bacteria).
3-Sarcina lutea (Gram positive bacteria).
4-Escherichia coli (Gram negative bacteria).
5-Candida albicans (representative of fungi).

Table III. Results of antimicrobial activity, zones of inhibition (in mm)

Compd No.	*S. aureus*	*Sar. lutea*	*B. subtilis*	*E. coli*	*C. albicans*
1	11	-	10	13	15
2c	12	-	10	14	-
3c	14	-	-	12	-
4	13	-	10	11	-
5b	10	12	10	13	13
6e	15	-	-	15	14
7c	13	14	10	11	-
8b	25	13	12	11	-
T	30	26	28	22	-
N	-	-	-	-	26

T : Tetacycline standard disc.
N : Nystatin standard disc.
- : Inactive, inhibition zone < 7 mm.

Materials

Culture media

Nutrient broth, Sabouraud's broth and nutrient agar were the products of Oxoid Ltd, England.

Methodology

The agar plate disc-diffusion technique (Collins, 1964).

Sterilized filter papers (6mm in diameter) were wetted with 10 µL of a solution of each compound to be tested, containing 10 mg/mL in DMF, and the discs were allowed to air dry. The discs were then placed onto the surface of agar plates (nutrient agar for bacteria and Sabouraud's dextrose agar for fungi) seeded with the test organism. Each plate contained 15 mL of the agar medium, previously seeded with 0.2 mL of the broth culture of each organism for 18 h. The plates were incubated at 37°C for 48 h, and the inhibition zones measured in mm. Discs impregnated with DMF were used as a control. The antibacterial and antifungal references, tetracycline and nystatin, discs were tested concurrently as a standard.

Results of antimicrobial activity

The results of antimicrobial testing revealed compounds **5b**, **7c**, and **8b** to have little antimicrobial activity against both Gram positive and Gram negative bacteria, while compound **8b** was comparable to the standard against S. aureus. Compounds **1**, **2c**, **3c**, and **4** possessed little or no activity against Gram positive and Gram negative bacteria. Compound **6e** showed moderate activity, which was more active on Gram negative bacteria. As for the antifungal activity, only compounds **1**, **5b**, and **6e** showed moderate activities against C. albicans. The other tested compounds showed no activity.

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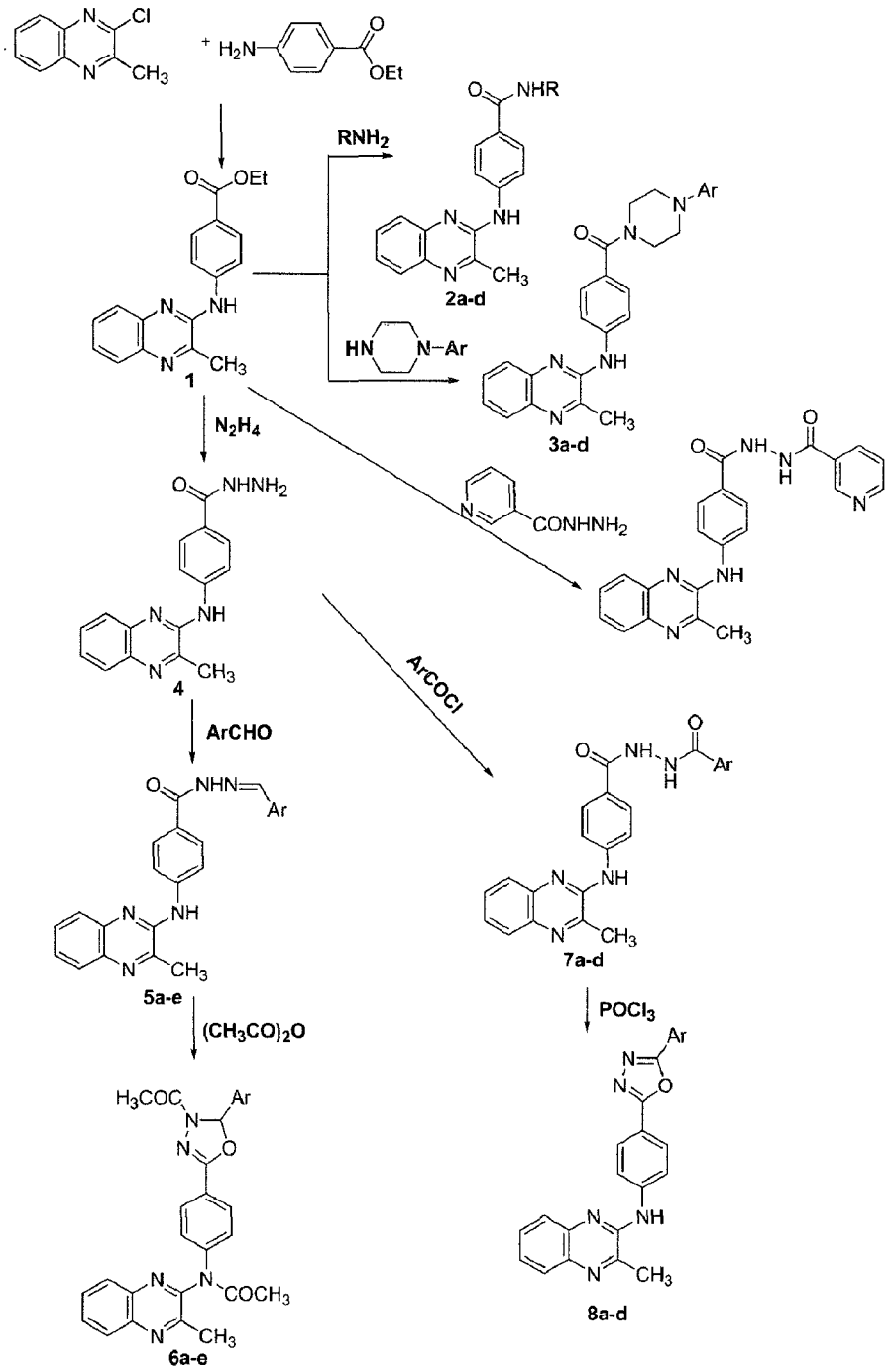

2a R = 2-morpholinyl **2b** R = 2-pyridyl methyl
2c R = 2-thiazolyl **2d** R = 3-quinolyl
3a Ar = C_6H_5 **3b** Ar = 4-F-C_6H_4
3c Ar = 2-OC_2H_5-C_6H_4 **3d** Ar = CH_2CH_2-C_6H_4(2-CF_3)
5a, 6a Ar = 4-F-C_6H_4 **5b, 6b** Ar = 4-Br-C_6H_4
5c, 6c Ar = 4-Cl-C_6H_4 **5d, 6d** Ar = 2-thienyl
5e, 6e Ar = 4-pyridyl
7a, 8a Ar = 3-Br-C_6H_4 **7b, 8b** Ar = 4-Br-C_6H_4
7c, 8c Ar = 4-NO_2-C_6H_4 **7d, 8d** Ar = 3-pyridyl

Scheme 1. Synthesis of oxadiazolyl quinoxalines

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