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Synthesis of New 2-Derivatives of 3-(5,6,7,8-Tetrahydronaphthalen-2-yl)Quinoxaline

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Abstract. The known compound 3-(5,6,7,8-tetrahydronaphthalen 2-yl)-2-(1H)-quinoxalone was used to synthesize a new series of derivatives. Synthesis of a class of six quinoxaline derivatives, a new series of three hydrazinoquinoxaline-Schiff bases, and a corresponding Mannich base are described. The analytical data on the newly synthesized compounds reported in the paper include their melting points, percent yields, molecular formulae, molecular weights, and percent C, H, N calculated and experimental values. Also given are the IR, ^{1}H NMR, and mass spectral data of these new compounds.

Keywords: tetrahydronaphthalen, quinoxaline, heterocycles, triazines

Introduction

In continuation of our previous work in the drug discovery programme (Ebeid *et al.,* 2004; 1996; 1992; El-Zahar *et al.,* 1994; El-Wassimi *et al.,* 1983; Buu-Hoi *et al.,*1958), concerning the synthesis of anticipated biologically active 3-(5,6,7,8-tetrahydronaphthalen-2-yl)-heterocycles, such as, triazines (Ebeid *et al.*, 1992; Buu-Hoi *et al.,* 1958), thiazoles and thiazolidinones (Ebeid *et al.,* 2004; 1996; El-Zahar *et al.,* 1994; El-Wassimi *et al*., 1983), interest was focused to introduce another new series of this class of compounds incorporated into quinoxaline nucleus, which may be useful as key intermediates, using facile methods of preparation, starting with the known compound **I**, 3-(5,6,7,8-tetrahydronaphthalen -2-yl)-2-(1H)-quinoxalone (Nabih *et al*., 1984; Metri and Zoorob, 1982). From this compound **I**, new series of derivatives were synthesized, which included a class of six quinoxaline derivatives **II**-**VII** (Fig. 1), a new series of three hydrazinoquinoxaline-Schiff bases **VIII**-**X**, and a corresponding Mannich base **XI** (Fig. 2).

Materials and Methods

All melting points presented in Table 1 are uncorrected values and were taken in open capillaries using the Gallenkamp apparatus. Microanalyses were carried out at the Microanalytical Unit, National Research Centre and the Faculty of Science, Cairo University, Egypt. IR spectra were carried out on FT/IR 300E spectrophotometer Jasco, using KBr discs. ^{1}HNMR spectra were measured in DMSO or $CDCl_3$ using Joel EX-270 NMR spectrometer. Signals were measured with reference to TMS as the internal standard. The mass spectra were recorded on Finnigan SSQ-7000 spectrometer. All reactions were followed up by TLC, using $CHCl_3$/MeOH (9:1, v/v), and/or ethyl acetate/benzene (7:3,v/v) and detected by UV lamp. Analytical data and spectroscopic data of the newly synthesized compounds are respectively presented in Tables 1 and 2. A brief description of the procedure followed for the synthesis of new compounds is given below.

2-Chloro-3-(5,6,7,8-tetrahydronaphthalen-2-yl)quinoxaline; compound II). A mixture of compound **I** (1.4 g, 0.005 mole) in phosphorous oxychloride (4 ml) was heated in sandbath over the temperature range of 90-130 °C (Buu-Hoi *et al*., 1958). The solution was cooled by cautiously pouring ice/water and made slightly basic with 30% NaOH solution. If salts separated at this point, these were removed by filtration and the desired compound was extracted with chloroform, concentrated, and the brown residue was separated. The compound **II** was crystallized from methanol.

2-Hydrazino-3-(5,6,7,8-tetrahydronaphthalen-2-yl) quinoxaline; compound III. To a solution of compound **II** (1.5 g, 0.005 mole) in absolute ethanol, about 5-fold excess of hydrazine hydrate (1.3 g, 0.025 mole) was added. The solution mixture was refluxed for 3 h. Upon cooling, white precipitate was formed which was filtered off and recrystallized from ethanol to give compound **III**.

3-(5,6,7,8-Tetrahydronaphthalen-2-yl)-2-(3,5-disubstituted pyrazolines and/or pyrazol-1-yl)quinoxalines; compounds IV-VI. To a solution of compound **II** (0.3 g, 0.001 mole) in 30 ml of absolute ethanol, about 0.001 mole of different β-diketones, namely, ethyl acetoacetate, diethyl malonate and acetyl acetone, respectively, were seperately added and refluxed for 3 h. The solvent was evaporated on rotary evaporator and the precipitate formed was recrystallized from acetone/cyclohexane to give the compounds **IV**-**VI**, respectively.

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2-(Alicyclic or aromatic amino)-3-(5,6,7,8-tetrahydronaphthalen-2-yl)quinoxaline; compounds VIIa-c. A mixture of compound **II** (1.5 g, 0.005 mole) and 0.005 mole of different amines, namely morpholine, N-methylpiprazine and *p*-toluidine in 20 ml absolute ethanol was refluxed with stirring for 15-20 h. The reaction mixture was concentrated and cooled. The precipitate formed was seperated by filtration and recrystallized from chloroform/petroleum ether to give compound **VIIa-c**, respectively.

2-Hydrazino-3-(5,6,7,8-tetrahydronaphthalen-2-yl) quinoxaline-Schiff bases; compounds VIIIa-e. A mixture of compound **III** (2.9 g, 0.01 mole) and the appropriate aromatic aldehydes, namely, benzaldehyde, *p*-dimethylaminobenzaldehyde, *p*-nitrobenzaldehyde, thiophene-2-carbaldehyde and cinnamaldehyde (0.01 mole) in absolute ethanol, with 3 drops of acetic acid, was refluxed for 10 h. The solvent was evaporated on rotary evaporator and the precipitate formed was seperated by crystallizing from dilute ethanol to give compounds **VIIIa-e**, respectively.

3-(5,6,7,8-Tetrahydronaphthalen-2-yl)-2-[(3-chloro-4-aryl-2-oxo-azetidin-1-yl)amino]quinoxalines; compounds IXa, b. To a solution of the appropriate hydrazone compound **VIIIb, e** (0.01 mole) in 20 ml dioxane, few drops of triethylamine were added and chloroacetyl chloride (1.13 g, 0.01 mole) was added to the solution dropwise for 1 h at room temperature. The solution was then refluxed for 3 h. Upon cooling the reaction mixture, the precipitate formed was removed by crystallizing from dioxane to give compounds **IXa, b,** respectively.

3-(5,6,7,8-Tetrahydronaphthalen-2-yl)-2-[(2-aryl-4-oxo-thiazolidin-3-yl)amino]quinoxalines; compounds Xa-c. A solution of thioglycolic acid (0.5 ml, 0.005 mole) in 5 ml of dry benzene was added to a stirred solution of compounds **VIIIa, c, d** (0.005 mole) in 30 ml of dry benzene. The reaction mixture

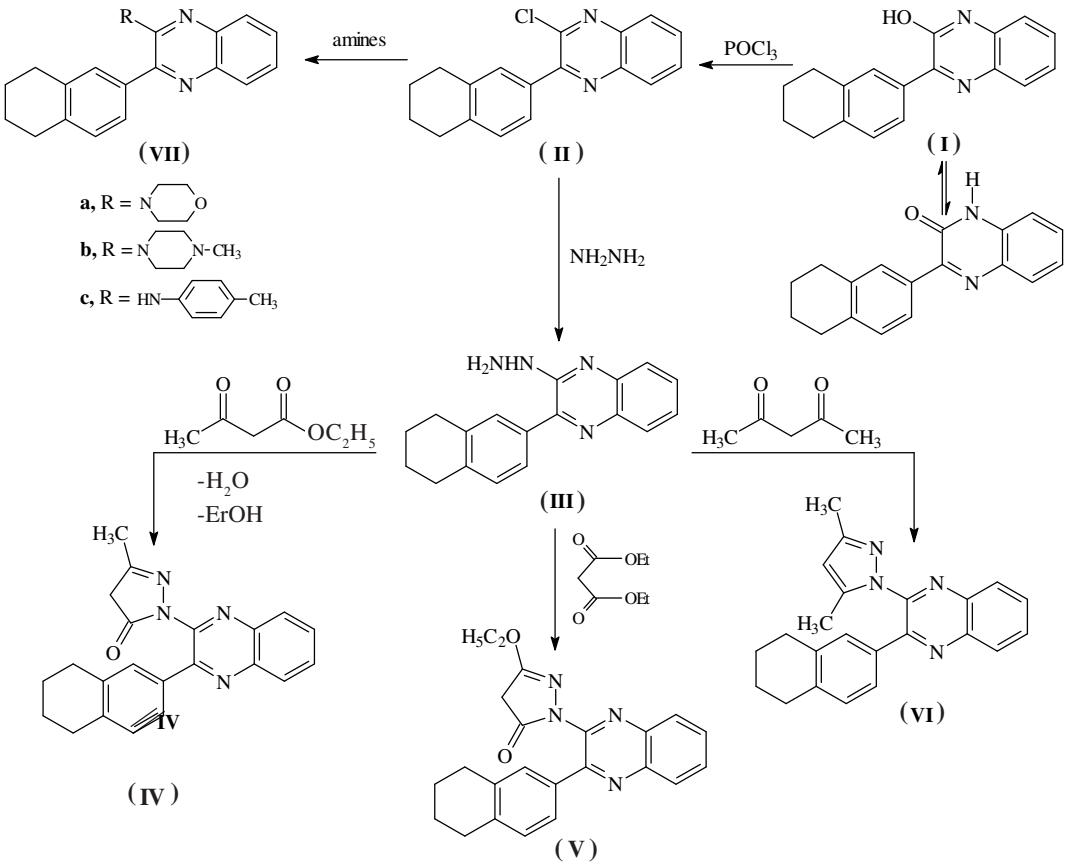

Fig 1. Conversion of quinoxalone drivative **(I)** into derivatives: 3-(5,6,7,8-tetrahydronaphthalen-2-yl)-2-chloroquinoxaline **(II)**, 2-hydrazino-3-(5,6,7,8-tetrahydronaphthalen-2-yl)quinexaline **(III)**, 3-5,6,7,8-tetrahydronaphthalen-2-yl)-2-(3-methyl-5-oxopyrazolin-1-yl)quinoxaline **(IV)**, 3-(5,6,7,8-naphthalen-2-yl)-2-(3-ethoxy-5-oxopyrazolin-1-yl)quinoxaline **(V)**, 3-(5,6,7,8-tetrahydronaphathalen-2-yl-2-(3,5-dimethylpyrazol-1-yl)quinoxaline **(VI),** 2-morpholono-2-(N-methylpiprazino) and/or 2-*p*-toluidino)-3-(5,6,7,8-tetrahydronaphthalen-2-yl) quinoxalines **(VIIa-c)**.

was refluxed for 10 h. After evaporation of the volatile solvent under reduced pressure, the residue was triturated with petroleum ether. The obtained material was removed and crystallized from ethanol to give compounds **Xa-c**, respectively.

3-(5,6,7,8-Tetrahydronaphthalen-2-yl)-2-[2-(4-nitrophenyl-5-diethyl-aminomethyl-4-oxo-thiazolidin-3-yl)amino] quinoxaline; compound XI. A mixture of paraformaldehyde (0.9 g, 0.001 mole) and diethylamine (1.0 g, 0.015 mole) was refluxed for 30 min in 10 ml of absolute ethanol till complete solubility of paraformaldehyde. A solution of compound **Xa** (2 g, 0.04 mole) in 10 ml absolute ethanol was added to the reaction mixture and refluxed for 48 h. The reaction mixture was concentrated and the separated product was recrystallized from ethanol to give compound **XI**.

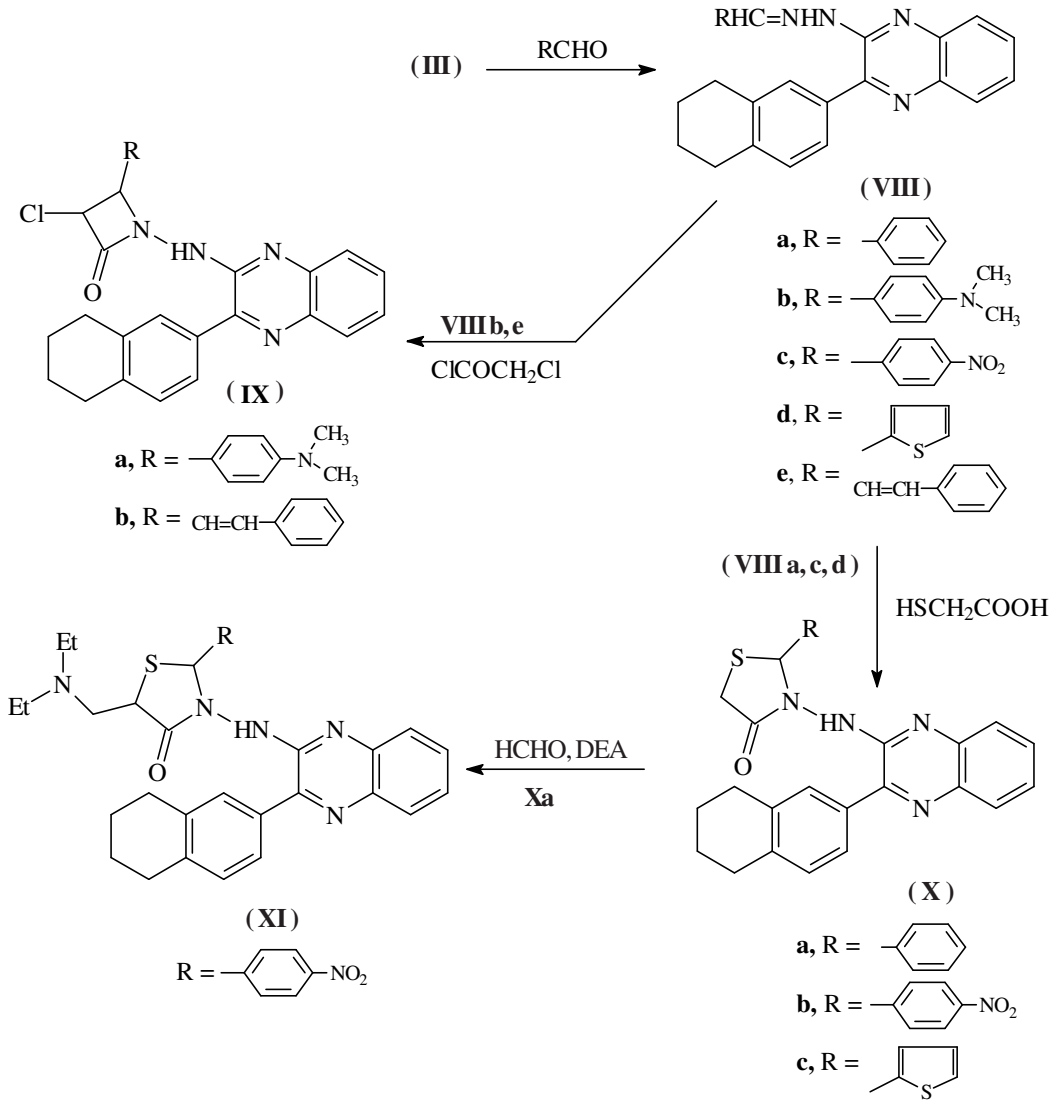

Fig. 2. Synthesis of a new series of hydrazino-quinoxaline Schiff bases from 2-hydrazino-quinoxaline derivative **(III)** to yield 2-hydrazino-quinoxaline derivative with different aromatic aldehydes to the corresponding Schiff bases **(VIIIa-e)**; cyclocondensation with chloroacetylchloride of the Shiff bases **(VIIIb)** and / or **(VIIIe)** to the corresponding 3-(5,6,7, 8-tetrahydronaphthalen-2-yl)-2-[(-3-chloro-4-aryl-2-oxo-azetidin-1-yl)-amino] quinoxalines **(IXa, b)**; cyclocondensation with thioglycolic acid of the Schiff bases **VIIIa, c, d** to the corresponding 3-(5, 6, 7, 8-tetrahydronaphthalen-2-yl)-2-[(2-aryl-4-oxo-thiazolidin-3-yl) amino]quinoxalines **(Xa-c)**; and the treatment of **(Xb)** with paraformaldehyde and diethyl amine to yield the corresponding Mannich base **(XI)**.

Table 1. Analytical data of the new synthesized compounds **(II-XI)***

Comp*	Melting point (°C)	Yield (%)	Mol formula/ (Mol wt)	C,H,N Analysis** calculated values C (%)	H (%)	N (%)
II	75	70	$C_{18}H_{15}ClN_2$ (294.77)	73.33 (73.00	5.13 4.80	9.50 9.00)
III	150	70	$C_{18}H_{18}N_4$ (290.35)	74.45 (74.23	6.24 6.00	19.29 19.15)
IV	215	70	$C_{22}H_{20}N_4O$ (356.41)	74.13 (73.83	5.65 5.20	15.72 15.51)
V	119	75	$C_{23}H_{22}N_4O_2$ (386.44)	71.48 (71.11	5.74 5.32	14.49 14.22)
VI	110	72	$C_{23}H_{22}N_4$ (354.44)	77.93 (77.81	6.25 6.00	15.80 15.60)
VIIa	210	70	$C_{22}H_{23}N_3O$ (345.42)	76.49 (76.11	6.71 6.50	12.16 12.00)
VIIb	230	75	$C_{23}H_{26}N_4$ (358.47)	77.05 (76.55	7.31 6.91	15.63 15.33)
VIIc	218	70	$C_{25}H_{23}N_3$ (365.45)	82.15 (81.82	6.34 6.00	11.49 11.14)
VIIIa	170	70	$C_{25}H_{22}N_4$ (378.46)	79.33 (79.00	5.86 5.42	14.80 14.40)
VIIIb	175	65	$C_{27}H_{27}N_5$ (421.53)	76.92 (76.50	6.45 6.23	16.61 16.42)
VIIIc	184	65	$C_{25}H_{21}N_5O_2$ (423.46)	70.90 (70.51	5.00 4.91	16.53 16.40)
VIIId	160	70	$C_{23}H_{20}N_4S$ (384.48)	71.84 (71.52	5.24 5.00	14.57 14.22)
VIIIe	190	75	$C_{27}H_{24}N_4$ (404.49)	80.16 (79.81	5.98 5.55	13.85 13.42)
IXa	240	74	$C_{29}H_{28}ClN_5O$ (498.00)	69.93 (69.46	5.66 5.23	14.06 14.31)
IXb	245	72	$C_{29}H_{25}ClN_4O$ (480.97)	72.41 (72.00	5.24 5.11	11.65 11.21)
Xa	155	65	$C_{27}H_{24}N_4OS$ (452.55)	71.65 (71.50	5.34 5.00	12.38 12.12)
Xb	172	65	$C_{27}H_{23}N_5O_3S$ (497.55)	65.17 (64.67	4.65 4.20	14.07 14.00)
Xc	150	65	$C_{25}H_{22}N_4OS_2$ (458.59)	65.47 (65.24	4.83 4.41	12.21 12.00)
XI	110	65	$C_{32}H_{34}N_6O_3S$ (582.70)	65.95 (65.45	5.88 5.41	14.42 14.00)

* refer to Fig. 1, 2 for chemical nomenclature of the compounds
** within paranthesis are the experimental values for C, H, N analysis

Table 2. IR, ^{1}H NMR and mass spectral data of the new synthesized compounds **(II-XI)***

Compound	IR: (KBr, cm^{-1}), ^{1}H NMR (270 MHz, δ ppm), MS
II	IR: 1085 cm^{-1} (C-Cl aryl); 1533 cm^{-1} (C=N) MS: two isotopic molecular ion peaks $C_{18}H_{15}ClN_2$ at m/z 294.2 (100%) and M^+ +2 at m/z 296.2 (32.5%)
III	IR: 3288 cm^{-1}, 3172 cm^{-1} (NH-NH_2); 2929 cm^{-1} (CH-alicyclic ring); 1557 cm^{-1} (C=N) ^{1}H NMR ($CDCl_3$, δ ppm): signals at 1.85, 2.80 (m, m, 4H, 4H of tetralin), 4.90 (s, 2H, of NH_2), 6.90-8.2 (m, 7H, aromatic protons), 9.8 (s, 1H, of NH)
IV	IR: 1704 cm^{-1} (C=O); 1627 cm^{-1} (C=N) MS: molecular ion peak $C_{22}H_{20}N_4O$ at m/z 356 (2.0%)
V	IR: 1700 cm^{-1} (C=O), 1620 cm^{-1} (C=N) MS: molecular ion peak, base peak $C_{23}H_{22}N_4O_2$ at m/z 386 (100%)
VI	IR: 1620 cm^{-1} (C=N); 1372 cm^{-1} (CH_3) MS: molecular ion peak $C_{23}H_{22}N_4$ at m/z 354 (97.2%)
VIIa	IR: 2938 cm^{-1} (CH-alicyclic); 1660 cm^{-1} (C=N) ^{1}H NMR ($CDCl_3$, δ ppm): 1.80 and 2.80 (m, m, 4H, 4H of tetralin), 3.3 (m, m, 4H, CH_2-N-CH_2), 3.6 (m, m, 4H), CH_2-O-CH_2), 6.90-8.0 (m, 7H, aromatic protons) MS: molecular ion peak
VIIb	IR: 2928 cm^{-1} (CH-alicyclic); 1655 cm^{-1} (C=N) MS: molecular ion peak $C_{23}H_{26}N_4$ at m/z 358 (20%)
VIIc	MS: molecular ion peak, base peak $C_{18}H_{18}N_3$ at m/z 276 (100%)
VIIIa	IR: 3400 cm^{-1} (NH); 1600 cm^{-1} (C=N) MS: molecular ion peak $C_{25}H_{22}N_4$ at m/z 378 (17%)
VIIIb	IR: 3417 cm^{-1} (NH); 1596 cm^{-1} (C=N)
VIIIc	IR: 3441 cm^{-1} (NH); 1596 cm^{-1} (C=N); 1508 cm^{-1}, 1328 cm^{-1} (NO_2)
VIIId	MS: molecular ion peak $C_{23}H_{20}N_5S$ at m/z 384 (3%)
VIIIe	IR: 3456 cm^{-1} (NH); 1540 cm^{-1} (C=N) MS: molecular ion peak $C_{24}H_{24}N_4$ at m/z 404 (4.0%)
IXa	IR: 2432 cm^{-1} (NH_2); 2928 cm^{-1} (CH-alicyclic rings); 1660 cm^{-1} (C=O); 1550 cm^{-1} (C=N); 691 cm^{-1} (C-Cl) MS: isotopic molecular ion peaks $C_{29}H_{28}ClN_5O$ at m/z 498 (1.0%) and at m/z 500 (0.3%), base peak at m/z 87 (100%)
IXb	IR: 3330 cm^{-1} (NH); 3024 cm^{-1} (CH-aromatic); 2982 cm^{-1} (CH-alicyclic); 1671 cm^{-1} (C=O); 1593 cm^{-1} (C=N); 696 cm^{-1} (C-Cl) MS: isotopic molecular ion peaks $C_{29}H_{25}ClN_4O$ at m/z 481 and 483 (3% and 1%, respectively), base peak at m/z 118 (100%)
Xa	IR: 3400 cm^{-1} (NH); 1690 cm^{-1} (C=O); 1594 cm^{-1} (C=N)
Xb	IR: 3400 cm^{-1} (NH); 1690 cm^{-1} (C=O); 1590 cm^{-1} (C=N); 1523 cm^{-1}, 1346 cm^{-1} (NO_2)

(...Continued next page)

(...Table 2 continued)

	^{1}H-NMR ($CDCl_3$, δ ppm): 1.80 (m, 4H of tetralin overlapped with a singlet of 1H of CH-N of thiazolidinone ring), 2.8 (m, 4H of tetralin), 3.4 (s, 2H of thiazolidinone), at 7.2-8.5 (m, 11H, aromatic protons) MS: molecular ion peaks $C_{27}H_{23}N_5O_3S$ at m/z 497 (6%), base peak at m/z 95 (100%)
Xc	^{1}H-NMR ($CDCl_3$, δ ppm): 1.80 (m, 4H of tetralin overlapped with a singlet of 1H of CH-N of thiazolidinone ring), 2.8 (m, 4H of tetralin), 3.2 (s, 2H of thiazolidinone), at 7.0-8.4 (m, 10H, aromatic protons)
XI	^{1}H-NMR ($CDCl_3$, δ ppm): 1.1, 1.3 (t, t, 3H, 3H of $2CH_3$ of 2 ethyl groups), 1.7 (m, 4H of tetralin overlapped with a singlet of amino methyl group and 1H of CH-N of thiazolidinone ring), 2.7 (broad s, 4H of tetralin overlapped with 9, 4H of $2CH_2$ of 2 ethyl groups), 3.2 (s, 1H, CH-S of thiazolidinone), at 6.8-8.7 (m, 11H, aromatic protons) MS: molecular ion peak $C_{23}H_{17}N_2O_2S$ at m/z 583 (1%), base peak $C_{14}H_{17}N_2O_2S$ at m/z 277 (100%)

* refer to Fig. 1, 2 for chemical nomenclature of the compounds

Results and Discussion

The conversion of quinoxalone derivative, the already known compound 3-(5,6,7,8-tetrahydronaphthalen-2y-l)-2-(1H)-quinoxalone, the compound **I** into the derivative compounds **II-VIIa, b, c** are schematically shown in Fig. 1.

Treatment of the quinoxalone derivative **I** with phosphorous oxychloride yielded the corresponding 2-chloro derivative, namely, 3-(5,6,7,8-tetrahydronaphthalen-2-yl)-2-chloro-quinoxaline **(II)**, which upon treatment with hydrazine hydrate gave the corresponding 2-hydrazino-quinoxaline derivative **(III)**. Further treatment of the compound **III** with ethyl acetoacetate, diethyl malonate and/or acetyl acetone, according to the reported methods (Nabih *et al.,* 1986), yielded 3-(5,6,7,8-tetrahydronaphthalen-2-yl)-2-(3-methyl-5-oxopyrazolin-1-yl) quinoxaline **(IV)**, 3-(5,6,7,8-tetrahydronaphthalen-2-yl)-2-(3-ethoxy-5-oxopyrazolin-1-yl)quinoxaline **(V)** and 3-(5,6,7,8-tetrahydronaphthalen-2-yl)-2-(3,5-dimethylpyrazol-1-yl) quinoxaline **(VI)**, respectively (Fig. 1).

The compound **(II)** was also allowed to react with morpholine, N-methylpiprazine, and/or *p*-toluidine to obtain the corresponding 2-morpholono-2-(N-methylpiprazino) and/or 2-(*p*-toluidino)-3-(5,6,7,8-tetrahydronaphthalen-2-yl) quinoxalines **(VIIa-c)**, respectively in 70-75% yield (Fig.1).

In addition, it was of interest to synthesize a new series of hydrazino-quinoxaline-Schiff bases which may be useful as key intermediates (Popp, 1969; 1964; 1962) to obtain different types of heterocycles of biological importance. So, reaction of the 2-hydrazino-quinoxaline derivative **VIII** with different aromatic aldehydes gave the corresponding Schiff bases, namely, 3-(5,6,7,8-tetrahydronaphthalen-2-yl)-2-arylidinehydrazino-quinoxalines **(VIIIa-e)**, respectively (Fig. 2).

Cyclocondensation of the Schiff bases **VIIIb** and/or **VIIIe** with chloroacetyl chloride afforded the corresponding 3-(5,6,7,8-tetrahydronaphthalen-2-yl)-2-[(3-chloro-4-aryl-2-oxo-azetidin-1-yl)amino]quinoxalines **(IXa, b)**, respectively (Fig. 2).

The wide range of biological activities of thiazolidinones led us to synthesize some new thiazolidinones incorporated to tetralylquinoxalines through cyclocondensation of the Schiff bases **(VIIIa, c, d)** with thioglycolic acid according to a reported method (Ebeid *et al*., 1996) to give 3-(5,6,7,8-tetrahydronaphthalen-2-yl)-2-[(2-aryl-4-oxo-thiazolidin-3-yl)amino] quinoxalines **(Xa-c)**, respectively.

Treatment of 3-(5,6,7,8-tetrahydronaphthalen-2-yl)-2-[(*p*-nitrophenyl)-4-oxo-thiazolidin-3-yl)amino]quinoxalines **Xb** with paraformaldehyde and diethylamine gave the corresponding Mannich base **(XI)** (Fig. 2).

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