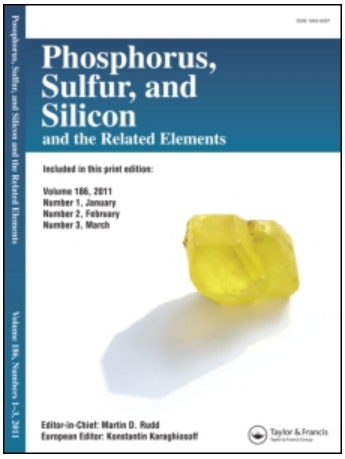

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Synthesis and Reactions of Some Novel Quinoxalines for Anticancer Evaluation

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Synthesis and Reactions of Some Novel Quinoxalines for Anticancer Evaluation

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*1,2-Dihydro-3-(2′-naphthyl)quinoxaline-2-one (**4**) was prepared from the reaction of methyl(2′-naphthyl)glyoxylate (**3**). Also, 2-chloro- and 2-hydrazinoquinoxaline derivatives **5** and **6** were prepared, which, upon reacting with different reagents, afforded the triazolo, tetrazolo, and amino quinoxaline derivatives. Compounds **5**, **8b**, **9**, **10b**, and **11b** were evaluated for their anticancer activity.*

Keywords Acetyl naphthalene; anticancer evaluation; hydrazinoquinoxaline; quinoxalinone

INTRODUCTION

A literature survey revealed that attention has been increasingly paid to the synthesis of heterocyclic quinoxaline derivatives, which exhibit various biological activities including anticancer,[1–6] antitubercular,[7–11] antibacterial,[12,13] anticonvulsant,[14] and adenosine receptor antagonistic properties.[15,16] As an extension, our efforts are directed toward the development of convenient synthetic approaches for the synthesis of new heterocyclic compounds with an expected broad spectrum of biological activity. In this article we report on the synthesis of new quinoxaline derivatives starting with 2-bromoacetylnaphthalene (**2**).[17]

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DISCUSSION

Synthesis of the new compounds was achieved by reaction of naphthalen-2-yl-oxo-acetic acid methyl ester (**3**)[18] with *O*-Phenylenediamine (OPDA) to afford 3-naphthalen-2-yl-1*H*-quinoxalin-2-one (**4**). The elemental and spectroscopic data are consistent with assigned structures. The IR spectral bands due to the C=O and the NH groups in compound **4** appeared in the region 1662 and 3447 cm^{-1}, respectively. The mass spectrum of compound **4** showed a molecular ion peak at m/z = 272, as a base peak, which is consistent with its molecular formula $C_{18}H_{12}N_2O$. The reaction of compound **4** with phosphorus oxychloride afforded the corresponding 2-chloro-3-naphthalen-2-yl-quinoxaline (**5**), which, upon treating with hydrazine hydrate, gave the corresponding 3-(naphthalen-2-yl-quinoxalin-2-yl)hydrazine (**6**). The structures of compounds **5** and **6** were confirmed with microanalyses and spectral data. The IR spectrum of the chloro derivative **5** revealed the disappearance of the carbonyl band at 1662 cm^{-1} and the presence of absorption bands at 1598 cm^{-1} (C=N) and 1077 cm^{-1}(strong, C-Cl-aryl). The mass spectrum of compound **5** showed the two isotopic molecular ion peaks ($C_{18}H_{11}ClN_2$) at m/z = 290, which is the base peak, and M^++2 at m/z = 292 (31.3%). The IR spectrum of compound **6** showed the absorption bands at 3420 cm^{-1} and 3290 cm^{-1} (NH-NH_2). The ^{1}H NMR spectrum of compound **6** (DMSO-d_6, δ) showed signals at 4.9 (s, 2H, NH_2, exchangeable with D_2O), 6.9–8.2 (m, 11H, Ar—H), and 9.8 (s, 1H, NH, exchangeable with D_2O). Compound **6** reacted with phenylisothiocyanate in dry benzene to give 2-(aminophenylthioxohydrazidyl)-3-(2′-naphthyl)quinoxaline (**7**). The IR spectrum of the latter compound showed the absorption bands at 3398, 3290, and 3057 cm^{-1}(3 NH) and an absorption band at 1260 cm^{-1} (C=S).

Recently, it has been reported that hydrazino quinoxalines can be considered as key starting materials for the synthesis of diverse nitrogen bridgehead compounds. Thus, the hydrazino quinoxaline **6** reacted with formic or acetic acids to give the symmetrical **4-**naphthalen-2-yl-[1,2,4]triazolo[4,3-*a*]quinoxaline (**8a**) and 1-methyl-4-naphthalen-2-yl-[1,2,4]triazolo[4,3-*a*]quinoxaline (**8b**), respectively. Moreover, when compound **6** was reacted with nitrous acid, it gave 4-naphthalen-2-yl-tetrazolo[4,5-*a*]quinoxaline (**9**). The elemental and spectroscopic data of compounds **8** and **9** are consistent with the assigned structures. Condensation of compound **6** with *p*-methoxybenzaldehyde and/or thiophene-2-carboxaldehyde took place by heating under reflux in ethanol in the presence of a few drops of acetic acid. The *N*-(4-methoxy-benzylidene)-*N*′-(3-naphthalen-2-yl-quinoxalin-2-yl) hydrazine (**10a**) and/or *N*-(3-naphthalen-2-yl-quinoxalin-2-yl)-*N*′- thiophen-2-ylmethylene-hydrazine (**10b**) were produced.

Compound (10) underwent cyclocondensation with thioglycolic acid in dry benzene[19] to obtain 2-(4-methoxy-phenyl)-3-(3-naphthalen-2-yl-quinoxalin-2-ylamino)thiazolidin-4-one (**11a**) and 3-(3-naphthalen-2-yl-quinoxalin-2-ylamino)-2-thiophen-2-yl-thiazoli-din-4-one (**11b**). The IR spectra of compound **10** displayed absorption bands near 3220 cm^{-1}(NH) and 1615 cm^{-1} (C=N), Spectra of **11a,b** displayed absorption bands near 3447 cm^{-1}(NH), 1613 cm^{-1} (C=N) and 1720 cm^{-1}(C=O). The ^{1}H NMR spectrum (DMSO-d_6, δ) of **10a** showed signals at 3.70 (s, 3H, OCH_3), 7.60-9.75 (m, 15H, Ar—H + N=CH), and 10.30 (s, 1H, NH, exchangeable with D_2O). The^{1}H NMR spectrum (DMSO-d_6, δ) of **11a**, as an example, showed signals at δ 3.25 ppm (d, 2H, thiazolidine-H), 3.40 (s, 1H, CH-N), 3.75 (s, 3H, OCH_3), 7.60–9.70 (m, 15H, Ar—H), and 10.25 (s, 1H, NH, exchangeable with D_2O).

On the other hand, the reaction of compound **5** with different amines, namely morpholine, phenylhydrazine, and/or *p*-toluidine, afforded the corresponding 2-morpholin-4-yl-3-naphthalen-2-yl-quinoxaline (**12a**), *N*-(3-naphthalen-2-yl-quinoxalin-2-yl)-*N′*-phenyl-hydrazine (**12b**), and/or (3-naphthalen-2-yl-quinoxalin-2-yl)-*p*-tolylamine (**12c**) in high yields. The elemental and spectroscopic data of compounds **12a–c** are consistent with the assigned structures (Scheme 1).

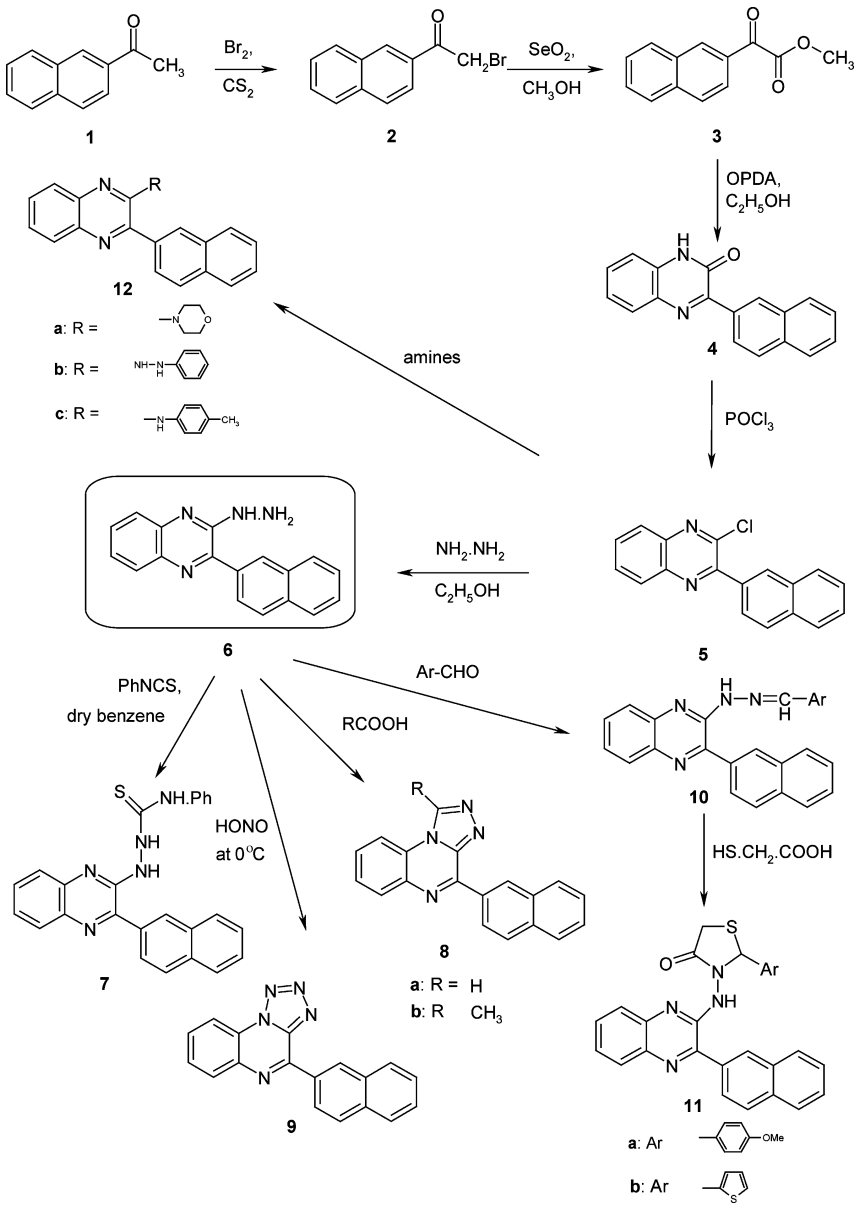
In conclusion, quinoxaline derivatives were synthesized for their anticancer activity. Some of the new synthesized derivatives, **9** and **10b**, exhibited activities against liver carcinoma.

ANTICANCER EVALUATION

Five selected new compounds, **5**, **8b**, **9**, **10b**, and **11b**, were tested for cytotoxic activity against the $HEPG_2$ (liver carcinoma cell line) and H460 (lung carcinoma cell line).

MATERIALS AND METHODS

- Tumor: human tumor cell
- $HEPG_2$ (liver carcinoma cell line)
- H460 (lung carcinoma cell line)
- All tested new compounds were dissolved in DMSO in different concentrations (1, 2.5, 5, and 10 μg/mL).
- Preliminary experiments were made using the human tumor cell line to identify the cytotoxicity of the selected compounds according to Skehan and Storeng.[20]



SCHEME 1

Measurement of Potential Cytotoxicity by Sulforhodamine B: (SRB) Assay

- Cells were plated in 96 multiwell plates (10^4 cells/well) for 24 h before treatment with the compounds to allow attachment of cells to the walls of the plate.
- Different concentrations of the compounds (1, 2.5, 5, and 10 μg/mL) were added to the cell monolayer.
- Triplicate wells were prepared for each individual dose.
- Monolayer cells were incubated with the compounds for 48 h at 37°C and in an atmosphere of 5% CO_2.
- After 48 h, cells were fixed, washed, and stained with Sulforhoolamine B (SRB) stain.
- Excess stain was washed with acetic acid, and the attached stain was recovered with tris ethyl enediamine tetraacetate (EDTA) buffer.
- Color intensity was measured in an enzyme linked immuno sorbent assay (ELISA) Reader.
- The relation between surviving fraction and drug concentrations was plotted to obtain the survival curve of each tumor cell line of the specified compound.[20]

RESULTS

The tested compounds **9** and **10b** showed cytotoxic activities against the $HEPG_2$ at the chosen drug concentrations 9.80 μg/ml and 9.97μg/ml, respectively (chart I). However, the other compounds had no cytotoxic activity against the $HEPG_2$.

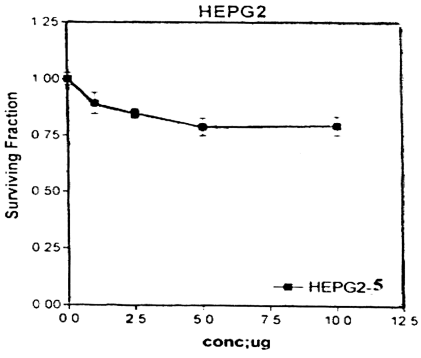
On the other hand, all tested compounds exhibited no cytotoxic activity against the H460 at the chosen drug concentrations (chart II).

EXPERIMENTAL

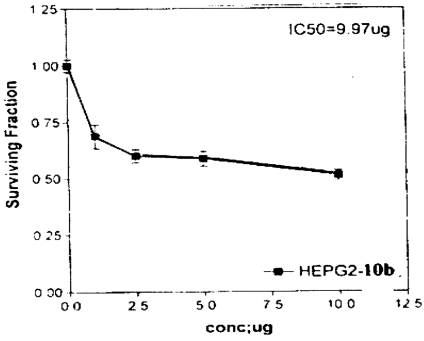
All melting points are uncorrected and were measured using an Electrothermal IA 9100 apparatus. Analytical data were performed by a Vario El Mentar apparatus, organic microanalysis section, at the National Research Centre, Cairo, Egypt. Their results were found to be in agreement with the calculated values ($\pm$ 0.5). The IR spectra (KBr) were recorded on a Perkin-Elmer 1650 spectrophotometer. ^{1}H NMR spectra were determined on a Jeol 300 MHz in DMSO-d_6, and chemical shifts were expressed in δ value relative to TMS as the internal reference. Mass spectra were run at 70 eV on EI + Q1 MSLMR UPLR.

Naphthalen-2-yl-oxo-Acetic Acid Methyl Ester (3)

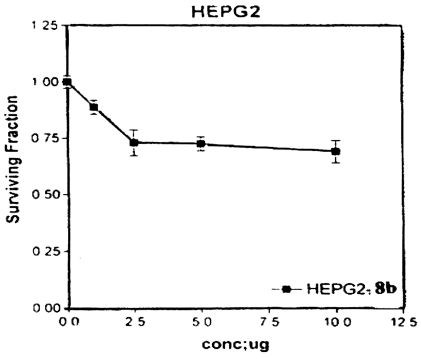
To a solution of 2-bromoacetylnaphthalene (**2**, 12.5 gm, 50 mmol) in absolute methanol was added SeO_2 (5.5 g, 50 mmol). The solution was



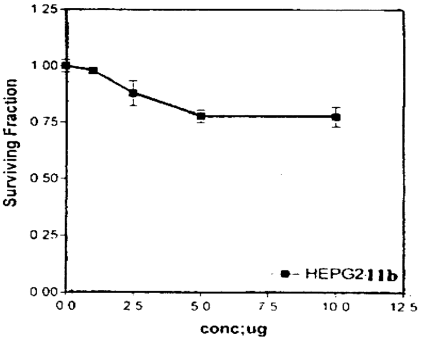
Compound **5**



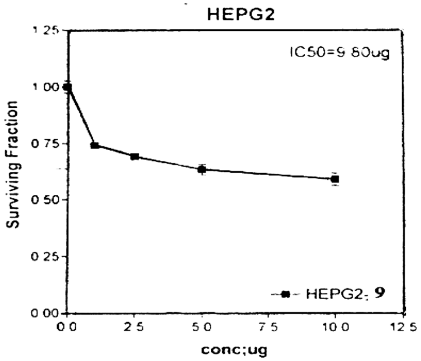
Compound **10b**



Compound **8b**

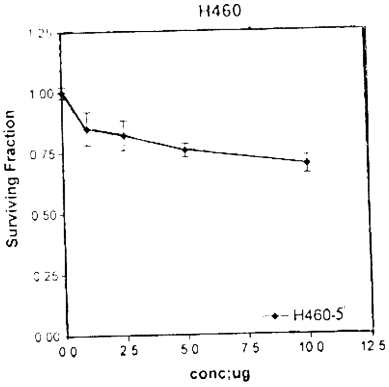


Compound **11b**

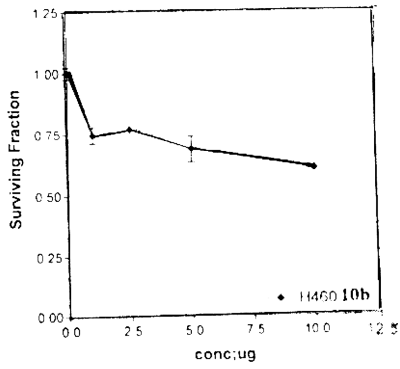


Compound **9**

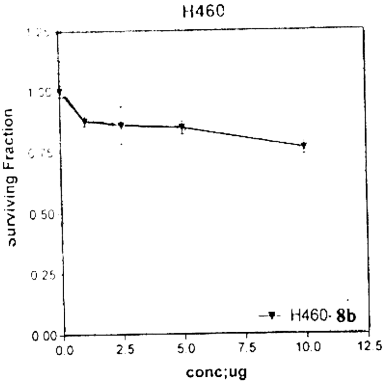
Chart I



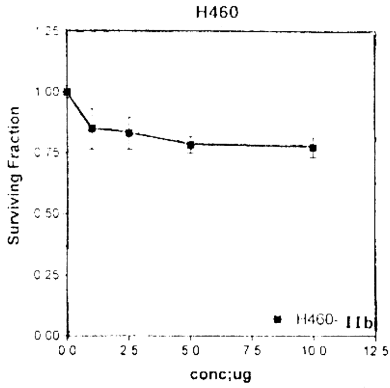
Compound **5**



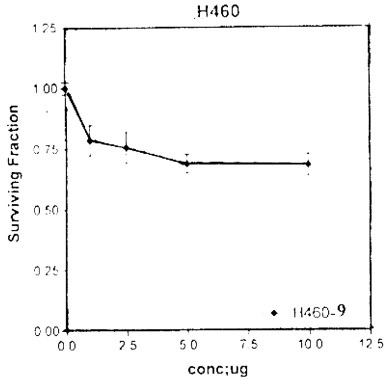
Compound **10b**



Compound **8b**



Compound **11b**



Compound **9**

Chart II

refluxed with stirring for 48 h. Se was removed by filtration, and the filtrate was evaporated leaving the oily glyoxylate **3** in a 90% yield; IR spectrum (KBr, cm^{-1}): 1740 (CO), 1683 (CO). MS, m/z (%): 214 (M^+, 4.45), 155 (100).

3-Naphthalen-2-yl-1*H*-quinoxalin-2-one (4)

To a solution of OPDA (1.11 g, 10 mmol) in ethanol (20 mL) was added compound **3** (2.11 g, 10 mmol), and the reaction mixture was refluxed on a steam bath for 1 h. The formed precipitate was filtered off and recrystallized from methanol to give compound **4** in an 80% yield; m.p. 230°C. IR spectrum (KBr, cm^{-1}): 3447 (NH), 1662 (CO), 1598 (C=N). MS, m/z (%): 272 (M^+, 100). Analysis for $C_{18}H_{12}N_2O$ (272.31): required C, 79.40; H, 4.44; N, 10.29; found C, 79.20; H, 4.32; N, 10.00.

2-Chloro-3-naphthalen-2-yl-quinoxaline (5)

A mixture of compound **4** (1.4 g, 5 mmol) in phosphorous oxychloride (4 mL) was heated in a sand bath over 90–130°C for 1 h. The solution was cooled, cautiously poured onto ice water, and then was made slightly basic with 30% NaOH solution. If salts separated at this point, they were filtered off, and the desired compound was extracted with chloroform. The dried magnesium sulfate extracts were concentrated, and the brown residues were filtered off and recrystallized from methanol to give the desired compound **5** in a 70% yield; m.p. 155°C. IR spectrum (KBr, cm^{-1}): 1598 (C=N), 1077 (C-Cl, aryl). MS, m/z (%):292 (M^+, Cl^{37}, 31.3), 290 (M^+, Cl^{35}, 100). Analysis for $C_{18}H_{11}ClN_2$ (290.75): required C, 74.35; H, 3.81; N, 9.63; found C, 74.05; H, 3.52; N, 9.41.

3-(Naphthalen-2-yl-quinoxalin-2-yl)hydrazine (6)

To a solution of compound**5** (1.5 g, 5 mmol) in absolute ethanol (50 mL) was added hydrazine hydrate (98%) in about a five-fold excess (1.3 g, 25 mmol), and the reaction mixture was refluxed for 3 h. Upon cooling, a yellow precipitate formed, which was filtered off and recrystallized from acetic acid to give compound **6** in a 75% yield; m.p. 198°C. IR spectrum (KBr, cm^{-1}): 3420, 3290 (NH_2, NH), 3096 (CH, Ar), 1598 (C=N); ^1H NMR spectrum (DMSO-d_6, δ): 4.9 (s, 2 H, NH_2, D_2O exchangeable), 6.9–8.2 (m, 11 H, Ar—H), 9.8 (s, 1 H, NH, D_2O exchangeable); MS, m/z (%): 269 (M^+—NH_3, 100). Analysis for $C_{18}H_{14}N_4$ (286.34): required C, 75.50; H, 4.93; N, 19.57; found C, 75.22; H, 4.69; N, 19.33.

2-(Aminophenylthioxohydrazidyl)-3-(2′-naphthyl)quinoxaline (7)

A mixture of **6** (2.8 g, 10 mmol), phenyl isothiocyanate (1.7 g, 13 mmol), and triethylamine (3 drops) in dry benzene (50 mL) was refluxed for 6 h. The solid that separated upon concentration and cooling was filtered off and recrystallized from dioxane to give compound **7** in an 80% yield; m.p. 280°C. IR spectrum (KBr, cm^{-1}): 3398, 3290, 3057 (3 NH), 1260 (C=S). MS, m/z (%): 328 (M^+—C_6H_7N, 100), 135 (50). Analysis for $C_{25}H_{19}N_5S$ (421.53): required C, 71.24; H, 4.54; N, 16.61; S, 7.61; found C, 71.00; H, 4.41; N, 16.46; S, 7.32.

Synthesis of 8a and 8b: General Procedure

A solution of compound **6** (2.8 g, 10 mmol) in formic acid or acetic acid (25 mL) was allowed to stand at 25°C for 24 h and then was refluxed for 4 h. The reaction mixture was cooled and poured onto crushed ice. The separated solids were filtered off, washed with cold water, and recrystallized from dioxane to give compounds **8a** and **8b**, respectively.

4-Naphthalen-2-yl-[1,2,4]triazolo[4,3-*a*]quinoxaline (8a)

Yield 70%; m.p. 230°C. IR spectrum (KBr, cm^{-1}): 3054 (CH, Ar), 1537 (C=N); ^{1}H NMR spectrum (DMSO-d_6, δ): 7.5–9.5 (m, 12 H, Ar—H); MS, m/z (%): 296 (M^+, 45), 269 (100). Analysis for $C_{19}H_{12}N_4$ (296.33): required C, 77.01; H, 4.07; N, 18.90; found C, 77.00; H, 4.01; N, 18.62.

1-Methyl-4-naphthalen-2-yl-[1,2,4]triazolo[4,3-*a*]quinoxaline (8b)

Yield 70%; m.p. 250°C. IR spectrum (KBr, cm^{-1}): 3049 (CH, Ar), 1599 (C=N); ^{1}H NMR spectrum (DMSO-d_6, δ): 3.0 (s, 3H, CH_3), 7.5–9.3 (m, 11 H, Ar—H); MS, m/z (%): 310 (M^+, 50), 269 (100). Analysis for $C_{20}H_{14}N_4$ (310.36): required C, 77.40; H, 4.54; N, 18.05; found C, 77.23; H, 4.32; N, 18.00.

4-Naphthalen-2-yl- tetrazolo[4,5-*a*]quinoxaline (9)

A solution of compound **6** (2.8 g, 10 mmol) in cold concentrated hydrochloric acid (30%, 5 mL) was treated gradually with a concentrated solution of sodium nitrite (1 g in 15 mL of water) at 0–5°C with stirring. The reaction mixture was set aside at r.t. for 1 h. The precipitated product was filtered, washed with cold water and recrystallized from dioxane

to give compound **9** in 72% yield; m.p. 220°C. IR spectrum (KBr, cm^{-1}): 3056 (CH, Ar), 1533 (C=N); MS, m/z (%): 297 (M^+, 11), 269 (100). Analysis for $C_{18}H_{11}N_5$ (297.32): required C, 72.71; H, 3.72; N, 23.55; found C, 72.41; H, 3.42; N, 23.22.

Synthesis of 10a and 10b: General Procedure

A mixture of **6** (2.8 g, 10 mmol); the appropriate aldehyde, namely *p*-methoxy-benzaldehyde and/or thiophene-2-carboxaldehyde; and acetic acid (3 drops) in absolute ethanol (25 mL) was refluxed for 10 h. The solvent was evaporated, and the formed precipitate was filtered off and recrystallized from the proper solvent to give compounds **10a** and **10b**.

N-(4-Methoxy-benzylidene)-*N′*-(3-naphthalen-2-yl-quinoxalin-2-yl)hydrazine (10a)

From: ethanol, yield 75%; m.p. 220°C. IR spectrum (KBr, cm^{-1}): 3220 (NH), 3056 (CH, Ar), 1615 (C=N); ^{1}H NMR spectrum (DMSO-d_6, δ): 3.7 (s, 3H, OCH_3), 7.60–9.75 (m, 15 H, Ar—H + N=CH), 10.3 (s, 1H, NH, D_2O exchangeable); MS, m/z (%): 296 (M^+—C_7H_8O, 25), 272 (100). Analysis for $C_{26}H_{20}N_4O$ (404.48): required C, 77.20; H, 4.98; N, 13.85; found C, 77.00; H, 4.63; N, 13.51.

N-(3-Naphthalen-2-yl-quinoxalin-2-yl)-*N′*-thiophen-2-ylmethylenehydrazine (10b)

From: dioxane, yield 65%; m.p. 240°C. IR spectrum (KBr, cm^{-1}): 3220 (NH), 3052 (CH, Ar), 1617 (C=N); ^{1}H NMR spectrum (DMSO-d_6, δ): 7.30–10.35 (m, 14 H, Ar—H + N=CH), 12.75 (s, 1H, NH, D_2O exchangeable); MS, m/z (%): 296 (M^+—C_4H_4S, 80), 269 (100). Analysis for $C_{23}H_{16}N_4S$ (380.48): required C, 72.61; H, 4.23; N, 14.72; S, 8.42; found C, 72.33; H, 4.00; N, 14.42; S, 8.00.

Synthesis of 11a and 11b: General Procedure

To a solution of compounds **10a,b** (5 mmol) in dry benzene (30 mL) was added thioglycolic acid (0.5 mL, 5 mmol) in dry benzene (5 mL), and the reaction mixture was refluxed for 10 h. The residue obtained after evaporation was recrystallized from the proper solvent to give the desired compounds **11a** and **11b**.

2-(4-Methoxy-phenyl)-3-(3-naphthalen-2-yl-quinoxalin-2-ylamino)thiazolidin-4-one (11a)

From: ethanol, yield 73%; m.p. 225°C. IR spectrum (KBr, cm^{-1}): 3447 (NH), 1720 (CO), 1613 (C=N); ^1H NMR spectrum (DMSO-d_6, δ): 3.25 (d, 2H, thiazolidine protons), 3.40 (s, 1H, CH-N), 3.75 (s, 3H, OCH_3), 7.60–9.70 (m, 15 H, Ar—H), 10.25 (s, 1H, NH, D_2O exchangeable); MS, m/z (%): 269 (M^+—$C_{10}H_{11}NO_2S$, 100). Analysis for $C_{28}H_{22}N_4O_2S$ (478.58): required C, 70.27; H, 4.63; N, 11.70; S, 6.70; found C, 70.00; H, 4.31; N, 11.50; S, 6.49.

3-(3-Naphthalen-2-yl-quinoxalin-2-ylamino)-2-thiophen-2-yl-thiazolidin-4-one (11b)

From: dioxane, yield 70%; m.p. 245°C. IR spectrum (KBr, cm^{-1}): 3446 (NH), 1720 (CO), 1613 (C=N); ^1H NMR spectrum (DMSO-d_6, δ): 3.30 (d, 2H, thiazolidine protons), 3.35(s, 1H, CH-N), 7.65–9.70 (m, 14 H, Ar—H), 10.25 (s, 1H, NH, D_2O exchangeable); MS, m/z (%): 269 (M^+ —$C_7H_7NOS_2$, 100). Analysis for $C_{25}H_{18}N_4OS_2$ (454.58): required C, 66.05; H, 3.99; N, 12.32; S, 14.10; found C, 66.00; H, 3.70; N, 11.99; S, 13.99.

Synthesis of 12a–c: General Procedure

Compound**5** (1.5 g, 5 mmol) was fused with different aromatic amines, namely morpholine, phenyl hydrazine, and *p*-toluidine, at 150°C for 3 h. The obtained solid was recrystallized from the proper solvent to give desired compounds **12a–c**.

2-Morpholin-4-yl-3-naphthalen-2-yl-quinoxaline (12a)

From: benzene/ethanol, yield 75%; m.p. 130°C. IR spectrum (KBr, cm^{-1}): 3056 (CH, aromatic), 1598 (C=N); ^1H NMR spectrum (DMSO-d_6, δ): 3.30 (m, 4H, $N(CH_2)_2$), 3.60 (m, 4H, $O(CH_2)_2$), 7.30–9.10 (m, 11 H, Ar—H); MS, m/z (%): 341 (M^+, 100). Analysis for $C_{22}H_{19}N_3O$ (341.41): required C, 77.40; H, 5.60; N, 12.30; found C, 77.39; H, 5.42; N, 12.18.

N-(3-Naphthalen-2-yl-quinoxalin-2-yl)-*N′*-phenylhydrazine (12b)

From: dioxane, yield 72%; m.p. 220°C. IR spectrum (KBr, cm^{-1}): 3422 (2NH), 1590 (C=N); ^1H NMR spectrum (DMSO-d_6, δ): 7.10–9.30 (m, 16 H, Ar—H), 8.9 (s, 1H, NH, D_2O exchangeable), 9.7 (s, 1H, NH, D_2O

exchangeable); MS, m/z (%): 272 ($M^+ + H_2 - C_6H_6N$, 100). Analysis for $C_{24}H_{18}N_4$ (362.43): required C, 79.52; H, 5.00; N, 15.45; found C, 79.32; H, 4.88; N, 15.44.

(3-Naphthalen-2-yl-quinoxalin-2-yl)-*p*-tolylamine (12c)

From: benzene/methanol, yield 70%; m.p. 210°C. IR spectrum (KBr, cm^{-1}): 3398(NH), 1590 (C=N); ^1H NMR spectrum (DMSO-d_6, δ): 2.3 (s, 3H, CH_3), 7. 0–8.5 (m, 15H, Ar—H), 9.0 (s, 1H, NH, D_2O exchangeable); MS, m/z (%): 269 ($M^+ - C_7H_8$, 100). Analysis for $C_{25}H_{19}N_3$ (361.45): required C, 83.08; H, 5.30; N, 11.62; found C, 83.06; H, 5.00; N, 11.33.

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