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A simple synthesis of 3,4-dihydrobenzo[*f*]quinoxalin-6(2*H*)-one derivatives substituted in the ring B

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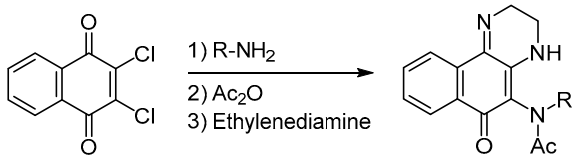


We followed a simple, inexpensive, and efficient route to synthesize a series of 3,4-dihydrobenzo[*f*]quinoxalin-6(2*H*)-one derivatives substituted in the ring B, with the expectation that this scaffold might exhibit antineoplastic activity. 5-Chlorobenzo[*f*]quinoxalin-6-yl-acetate and 4-benzylbenzo[*f*]quinoxalin-6(4*H*)-one were obtained for the first time.

Keywords: acetamide derivatives, 3,4-dihydrobenzo[*f*]quinoxalin-6(2*H*)-ones, 1,4-naphthoquinones, cyclization reaction, nucleophilic substitution.

Quinoxaline derivatives have been thoroughly explored as luminescent materials,[1,2] fluorescent probes[3] and have been examined for such biological effects as antitumor,[4] antiparasitic,[5–8] and antiHIV activity.[9] More specifically, 3,4-dihydrobenzo[*f*]quinoxalin-6(2*H*)-ones (Fig. 1) constitute a family of molecules that can be obtained from 1,4-naphthoquinone by several reactions. Considering the relative ease of synthesis of these compounds and their long history, one would expect the availability of extensive pharmacological data about them, but this is not the case.

3,4-Dihydrobenzo[*f*]quinoxalin-6(2*H*)-one may be viewed as an imino-cyclized derivative of naphthoquinone. Current data show that incorporation of an additional five- or six-membered heterocyclic ring fused to anthraquinone nucleus increases its cytotoxic activity and decreases the cardiotoxic side effects associated with the quinonoid system.[10–14] The incorporation of an additional heterocyclic ring strongly favors passive diffusion through biological membranes, overcoming multidrug resistance in experiments involving *in vivo* models. The examples of such compounds include anthraquinone derivatives, such as anthrapyrazoles and 1,3-diazabenzanthrones (Fig. 2).[15,16]

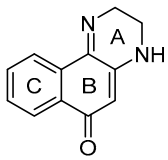


Figure 1. The structures of 3,4-dihydrobenzo[*f*]quinoxalin-6(2*H*)-one.

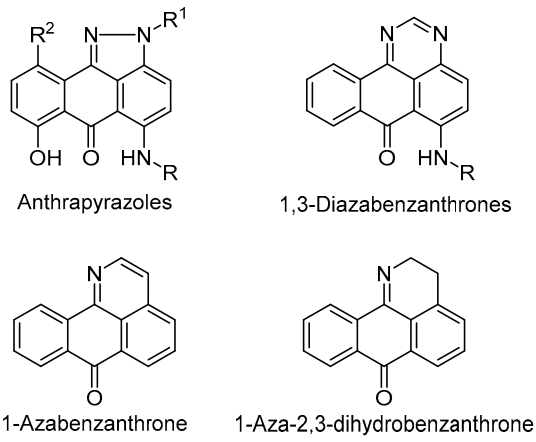


Figure 2. The structures of anthrapyrazoles, 1,3-diazabenzanthrones, 1-azabenzanthrone, and 1-aza-2,3-dihydrobenzanthrone.

The degree of unsaturation of the heterocyclic ring fused to the quinone in some cases determines the cytotoxic activity and selectivity of these compounds. For example, 1-aza-2,3-dihydrobenzanthrone derivatives are generally more active than their oxidized counterparts (1-aza-benzanthrones), showing an IC_{50} value close to 0.9 μM and a selectivity index of 33 against the human bladder carcinoma J82 cell line (Fig. 2).[11] Based on the above observations, the 3,4-dihydrobenzo[*f*]quinoxalin-6(2*H*)-one framework is an interesting starting point for the development of a new family of compounds with potential antineoplastic activity.

There are few literature precedents for the synthesis and cytotoxic activity characterization of 3,4-dihydrobenzo[*f*]-quinoxalin-6(2*H*)-ones. Two compounds with this structure were synthesized over thirty years ago,[17,18] and only the lapachol derivatives **1** and **2** are known to be active against the HL-60 promyelocytic leukemia cell line.[19] 6-(Hydroxy-imino)-2,3-dimethyl-2,3,4,6-tetrahydro-5*H*-benzo[*h*]chromen-5-one (**1**) has strong cytotoxic activity against HL-60 cells. Another derivative, 6-(3-methylbut-2-en-1-yl)-7a,8,9,10,11,11a-hexahydrobenzo[*a*]phenazin-5(7*H*)-one (**2**), shown in Figure 3, is the only documented naphthoquinone-derived heterocycle with two nitrogen atoms that has moderate activity against human cancer cell lines.[19]

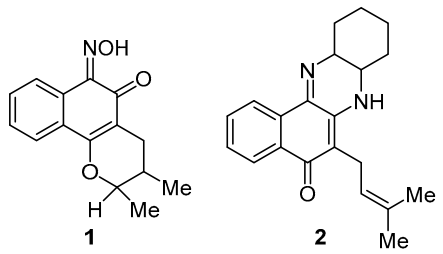


Figure 3. Cytotoxic naphthoquinone-derived heterocyclic compounds.

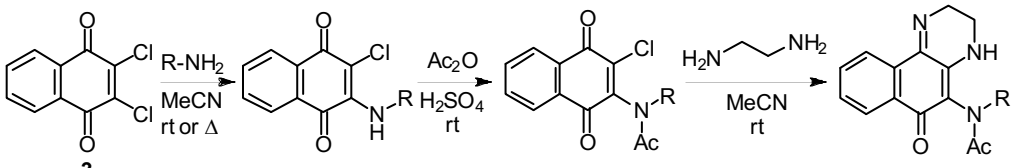
In order to carry out preliminary pharmacological studies on the 3,4-dihydrobenzo[*f*]quinoxalin-6(2*H*)-one system, we needed to obtain a series of compounds that could provide tentative structure–activity relationships and guide future synthetic efforts leading to active structures. In this context, and according to the evidence presented in the literature,[20–23] we followed a simple, inexpensive, and reasonably efficient synthetic route that allowed us to obtain 3,4-dihydrobenzo[*f*]quinoxalin-6(2*H*)-ones substituted in the ring B.[17,18] This approach involves the incorporation of different amines at C-2 position of 2,3-dichloronaphthoquinone (**3**) scaffold (Scheme 1). Subsequent transformations of these amino groups into acetamides enabled the subsequent addition of ethylenediamine to the C-3 atom, leading to intramolecular cyclization. With this methodology, we obtained a series of new substances, which we expect to be of pharmacological interest.

The synthesis of 3,4-dihydrobenzo[*f*]quinoxalin-6(2*H*)-one derivatives substituted in ring B starts with nucleophilic substitution reactions of compound **3** with different amines.[24] These reactions have been widely studied in various media, including water.[25,26] We were unable to reproduce the reported data for reactions in water, while the results for reactions in methanol and chloroform were unsatisfactory. In order to be able to use concentrated aqueous ammonia, we carried out the reaction in acetonitrile and obtained 2-amino-3-chloronaphthoquinones **4a**–**j** in good yields (Scheme 1).

The incorporation of a second amine at the C-3 atom was not possible, even by using an excess of nucleophile, due to the diminished reactivity of the system after the initial amination. To reverse this problem, the amino derivatives **4** after isolation and characterization were acetylated with acetic anhydride.[17,18] The reaction mixtures were kept at room temperature for 10 to 30 min to give the respective acetamides **5a**–**j** in good yields (Scheme 1). Finally, the treatment of compounds **5a**–**j** with ethylenediamine in acetonitrile afforded the acetyl derivatives **6a**–**j** in variable yields.

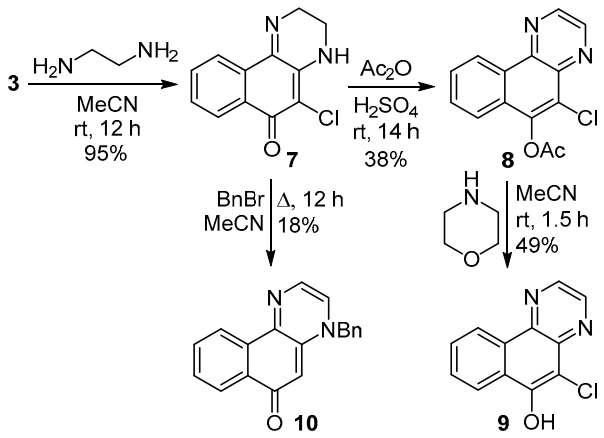
Considering these results, we synthesized 5-chloro-3,4-dihydrobenzo[*f*]quinoxalin-6(2*H*)-one (**7**) for the purpose of further modification by acetylation at the N-4 atom and incorporation of various amines at the C-5 atom. The synthesis of compound **7** was performed *via* nucleophilic substitution reaction of compound **3** with ethylenediamine (Scheme 2). We again tested different solvents and stoichiometric ratios of nucleophile and electrophile (N–E). The best conditions for this reaction were using dry acetonitrile as solvent and molar N–E ratio of 2:1, giving compound **7** in 95% yield. Acetylation at the N-4 atom was performed with acetic anhydride under the conditions

Scheme 1



R = H	**4a** 94%	**5a** 78%	**6a** 39%
R = Me	**4b** 90%	**5b** 79%	**6b** 60%
R = Et	**4c** 97%	**5c** 72%	**6c** 41%
R = *n*-Pr	**4d** 95%	**5d** 86%	**6d** 36%
R = *n*-Bu	**4e** 95%	**5e** 71%	**6e** 32%
R = *i*-Pr	**4f** 92%	**5f** 77%	**6f** 17%
R = Cy	**4g** 95%	**5g** 90%	**6g** 27%
R = Ph	**4h** 95%	**5h** 64%	**6h** 29%
R = Bn	**4i** 92%	**5i** 86%	**6i** 24%
R = CH_2CH_2Ph	**4j** 99%	**5j** 94%	**6j** 65%

Scheme 2



described in Scheme 2. However, this reaction led to a mixture of products where the major product was the completely aromatic derivative **8**, isolated in 38% yield. A similar transformation of compound **7** into benzoquinoxalin-6-ol **9** has been documented and is favored in acidic or basic medium.[23,27] It is likely that in our case electrophilic attack of the acetic anhydride on the carbonyl oxygen of compound **7** led to a fully conjugated system that underwent facile oxidation, presumably by O_2, as contact with air was not excluded in this case.

We tested the reactivity of compound **8** with various nucleophiles (morpholine, piperidine, butylamine, isopropylamine, homopiperazine, and tryptamine), considering that the aromatization of molecular structure and the presence of a heterocyclic ring might favor aromatic nucleophilic substitution at the C-5 atom. However, in all cases aminolysis of the ester occurred, affording 5-chlorobenzo-[*f*]quinoxalin-6-ol (**9**). Depending on the amine used, the yields went from 49 to 61% for secondary amines and up to 86% for the primary amines (Scheme 2).

Finally, in view of the expected nucleophilicity of the N-4 atom, the reactivity of compound **7** was tested with methyl iodide, allyl bromide, and benzyl bromide. Methyl iodide and allyl bromide in acetonitrile as solvent did not generate any nucleophilic substitution products. When allyl bromide was used, the respective *N*-allylated derivative was obtained in 38% yield. However, quite unexpectedly, the reaction with benzyl bromide led to substitution at the N-4 atom, albeit with the loss of halogen and formation of a double bond between C-2 and C-3 atoms, giving the quinoxalinone **10** in a poor yield (18%) (Scheme 2).

In summary, we have developed a simple and efficient methodology for the synthesis of 3,4-dihydrobenzo[*f*]-quinoxalin-6(2*H*)-one derivatives substituted in the ring B.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III 400 spectrometer (400 and 100 MHz, respectively), as well as on a Bruker Avance 200 spectrometer (200 and 50 MHz, respectively) in $CDCl_3$ or DMSO-d_6 solution and with TMS as internal standard. High-resolution mass spectra were recorded for MeOH solutions on a Bruker Microflex MALDI-TOF instrument in the positive ion detection mode. Melting points were determined on a Reichert Galen III hot plate with a DUAL JTEK Dig – Sense thermocouple thermometer, and are uncorrected. Analytical TLC was performed on Merck silica gel 60 F_{254} foil-backed plates. The solvents used as eluents are specified in each case. The chromatographic purification of all products was carried out on silica gel columns and the solvents used are specified in each case. Commercially available, laboratory grade reagents were used without further purification.

2-Amino-3-chloronaphthalene-1,4-dione (4a). Aqueous 25% ammonia solution (33 ml) was added to a suspension of compound **3** (5.0 g, 22.02 mmol) in acetonitrile (50 ml), and the reaction mixture was refluxed for 2.5 h. The mixture was then cooled and water (50 ml) was added. The precipitate that formed was filtered off and dried to afford product **4a**. Yield 4.30 g (94%), orange powder, mp 203–204°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 7.53 (2H, s, NH_2); 7.74 (1H, t, *J* = 7.5, H Ar); 7.82 (1H, t, *J* = 7.5, H Ar); 7.98 (2H, d, *J* = 7.7, H Ar). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 112.7; 126.8; 127.1; 130.0; 132.7; 132.9; 135.1; 145.2; 176.6; 179.3.

2-Chloro-3-(methylamino)naphthalene-1,4-dione (4b). Aqueous 40% methylamine solution (2.28 ml, 26.4 mmol) was added to a suspension of compound **3** (3.0 g, 13.21 mmol) in acetonitrile (40 ml). The reaction mixture was stirred at room temperature for 1.5 h, concentrated under reduced pressure, and water (100 ml) was added. The precipitate that formed was filtered off and dried to afford product **4b**. Yield 2.64 g (90%), red crystals, mp 167–168°C (mp 101°C[28]). ^{1}H NMR spectrum (200 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 3.44 (3H, s, CH_3); 6.08 (1H, s, NH); 7.55–7.80 (2H, m, H Ar); 8.03 (1H, dd, *J* = 7.5, *J* = 1.3, H Ar); 8.15 (1H, dd, *J* = 7.6, *J* = 1.2, H Ar). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 32.7; 110.5; 126.8; 126.9; 129.8; 132.5; 132.8; 135.0; 145.0; 176.9; 180.5.

2-Chloro-3-(ethylamino)naphthalene-1,4-dione (4c). 2.0 M Ethylamine solution in THF (18.3 ml, 36.4 mmol) was added to a suspension of compound **3** (3.0 g, 13.21 mmol) in acetonitrile (40 ml). The reaction mixture was stirred at room temperature for 2.5 h. The mixture was then concentrated under reduced pressure, and water (100 ml) was added. The precipitate that formed was filtered off and dried to afford product **4c**. Yield 3.01 g (97%), red crystals, mp 134–135°C. ^{1}H NMR spectrum (200 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.33 (3H, t, *J* = 7.2, CH_3); 3.90 (2H, q, *J* = 7.2, CH_2); 6.01 (1H, s, NH); 7.52–7.82 (2H, m, H Ar); 8.02 (1H, dd, *J* = 7.5, *J* = 1.4, H Ar), 8.14 (1H, dd, *J* = 7.6, *J* = 1.3, H Ar). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 16.4; 40.0; 110.2; 126.8; 126.9; 129.8; 132.4; 132.8; 135.0; 144.2; 176.9; 180.5.

2-Chloro-3-(phenylamino)naphthalene-1,4-dione (4h). Freshly distilled aniline (4.92 g, 4.8 ml, 52.84 mmol) was added to a suspension of compound **3** (3.0 g, 13.21 mmol) in acetonitrile (40 ml). The reaction mixture was refluxed for 8 h. The resulting mixture was concentrated under reduced pressure, and water (100 ml) was added. The

precipitate that formed was filtered off and dried to afford product **4h**. Yield 3.66 g (98%), purple crystals, mp 213–214°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 7.08–7.13 (3H, m, H Ar); 7.31 (2H, t, *J* = 7.8, H Ar); 7.81 (1H, t, *J* = 7.5, H Ar); 7.87 (1H, t, *J* = 7.4, H Ar); 8.04 (2H, d, *J* = 7.6, H Ar); 9.29 (1H, s, NH). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 115.1; 124.4; 125.8; 127.1; 127.3; 128.6; 130.0; 132.8; 133.1; 135.2; 137.6; 141.7; 177.6; 180.7.

Synthesis of compounds 4d–g,i,j (General method). The appropriate amine (39.6 mmol) was added to a suspension of starting compound **3** (3.0 g, 13.21 mmol) in acetonitrile (40 ml). The reaction mixture was stirred at room temperature for 1.5 h. The mixture was then concentrated under reduced pressure, and water (100 ml) was added. The precipitate that formed was filtered off and dried to afford the pure product.

2-Chloro-3-(propylamino)naphthalene-1,4-dione (4d). Yield 3.31 g (95%), red crystals, mp 119–120°C (mp 110–112°C[28]). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.01 (3H, t, *J* = 7.4, CH_3); 1.62–1.81 (2H, m, CH_2); 3.81 (2H, t, *J* = 7.0, CH_2); 6.09 (1H, s, NH); 7.61 (1H, t, *J* = 7.5, H Ar); 7.72 (1H, t, *J* = 7.5, H Ar); 8.03 (1H, d, *J* = 7.6, H Ar); 8.15 (1H, d, *J* = 7.6, H Ar). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 11.2; 24.4; 46.7; 126.9 (2C); 129.8; 132.5; 132.9; 135.0; 144.3; 176.9; 180.6.

3-(Butylamino)-2-chloronaphthalene-1,4-dione (4e). Yield 3.30 g (95%), red crystals, mp 113–114°C (mp 112°C,[28] 109°C[29]). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 0.97 (3H, t, *J* = 7.4, CH_3); 1.38–1.49 (2H, m, CH_2); 1.62–1.76 (2H, m, CH_2); 3.85 (2H, t, *J* = 6.7, CH_2); 6.06 (1H, s, NH); 7.62 (1H, t, *J* = 7.5, H Ar); 7.72 (1H, t, *J* = 7.5, H Ar); 8.03 (1H, d, *J* = 7.7, H Ar); 8.15 (1H, d, *J* = 7.7, H Ar). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 13.8; 19.9; 33.1; 44.8; 110.2; 126.8; 126.9; 129.8; 132.4; 132.9; 135.0; 144.3; 176.8; 180.6.

2-Chloro-3-(isopropylamino)naphthalene-1,4-dione (4f). Yield 3.04 g (92%), red crystals, mp 119–120°C (mp 117°C[28]). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.32 (6H, d, *J* = 6.4, $2CH_3$); 4.65–4.94 (1H, m, CH); 5.93 (1H, s, NH); 7.61 (1H, t, *J* = 7.5, H Ar); 7.71 (1H, t, *J* = 7.5, H Ar); 8.03 (1H, d, *J* = 7.6, H Ar); 8.14 (1H, d, *J* = 7.7, H Ar). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 24.4; 45.8; 110.0; 126.8; 129.7; 132.4; 132.8; 134.9; 143.4; 176.8; 180.5.

2-Chloro-3-(cyclohexylamino)naphthalene-1,4-dione (4g). Yield 3.74 g (98%), purple crystals, mp 116–117°C (mp 116°C[29]). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.14–1.50 (5H, m) and 1.62–1.71 (1H, m, $3CH_2$); 1.73–1.86 (2H, m, CH_2); 2.03–2.16 (2H, m, CH_2); 4.34–4.52 (1H, m, CH); 6.03 (1H, s, NH); 7.61 (1H, t, *J* = 7.6, H Ar); 7.71 (1H, t, *J* = 7.6, H Ar); 8.02 (1H, d, *J* = 7.7, H Ar); 8.14 (1H, d, *J* = 7.7, H Ar). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 24.6; 25.4; 34.7; 52.6; 110.0; 126.9; 129.9; 132.4; 133.0; 135.0; 143.4; 176.9; 180.7.

3-(Benzylamino)-2-chloronaphthalene-1,4-dione (4i). Yield 3.62 g (92%), red crystals, mp 111–112°C (mp 112°C[29]). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 5.05 (2H, d, *J* = 4.5, CH_2); 6.22 (1H, s, NH); 7.28–7.46 (5H, m, H Ar); 7.62 (1H, t, *J* = 7.5, H Ar); 7.72 (1H, t, *J* = 7.5, H Ar); 8.03 (1H, d, *J* = 7.6, H Ar); 8.15 (1H, d, *J* = 7.6, H Ar). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 48.9; 111.3; 126.9; 127.7; 128.1; 129.1; 129.8; 132.6; 132.6; 135.0; 138.0; 144.1; 176.9; 180.4.

2-Chloro-3-(phenethylamino)naphthalene-1,4-dione (4j). Yield 4.08 g (99%), red crystals, mp 112–113°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.89–2.95 (2H, m, CH_2); 3.86–4.06 (2H, m, CH_2); 7.12–7.35 (5H, m, H Ar); 7.48 (1H, s, NH); 7.74 (1H, t, *J* = 7.4, H Ar); 7.82 (1H, t, *J* = 7.5, H Ar); 7.92–8.01 (2H, m, H Ar). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 37.4; 46.1; 110.9; 126.9 (2C); 127.0; 128.9 (2C); 129.8; 132.5; 132.8; 135.0; 137.8; 144.2; 176.9; 180.5.

***N*-(3-Chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-acetamide (5a)**. A mixture of compound **4a** (1.0 g, 4.82 mmol) in acetic anhydride (1.62 g, 1.5 ml) was treated by dropwise addition of 98% sulfuric acid (0.92 g, 0.5 ml). The mixture was stirred for 15 min and water (20 ml) was added. The precipitate that formed was filtered off, dried, and purified by chromatography (hexane–EtOAc, 3:1) to afford product **5a**. Yield 0.94 g (78%), yellow powder, mp 209–210°C (mp 219–220°C[30]). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 2.30 (3H, s, $COCH_3$); 7.68 (1H, s, NH); 7.77 (2H, d, *J* = 7.3, H Ar); 8.11 (1H, d, *J* = 7.1, H Ar); 8.18 (1H, d, *J* = 7.1, H Ar). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 24.3; 127.2; 127.7; 130.4; 131.7; 133.7; 134.3; 135.0; 139.2; 166.7; 177.8; 180.0.

Synthesis of compounds 5b–j (General method). A suspension of the appropriate 2-amino-3-chloro-1,4-naphthoquinone **4** (6.0 mmol) in acetic anhydride (21.60 g, 20 ml, 0.211 mol) was treated by dropwise addition of 98% sulfuric acid (0.92 g, 0.5 ml). The reaction mixture was stirred at room temperature for 10–30 min. After the reaction was complete, the mixture was concentrated under reduced pressure. The residue was purified by chromatography (CH_2Cl_2 and hexane–EtOAc, 1:1) to afford the pure product.

***N*-(3-Chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-*N*-methylacetamide (5b)**. Yield 1.25 g (79%), yellow powder, mp 123–124°C. ^{1}H NMR spectrum (200 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.99 (3H, s, $COCH_3$); 3.20 (3H, s, CH_3); 7.76–7.91 (2H, m, H Ar); 8.10–8.30 (2H, m, H Ar). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 22.0; 34.5; 127.6; 131.4; 134.8; 135.0; 143.1; 146.4; 177.9; 179.2; 187.3.

***N*-(3-Chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-*N*-ethylacetamide (5c)**. Yield 1.19 g (72%), yellow powder, mp 94–95°C. ^{1}H NMR spectrum (200 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.16 (3H, t, *J* = 7.2, CH_3); 1.94 (3H, s, $COCH_3$); 3.61–3.82 (2H, m, CH_2); 7.71–7.90 (2H, m, H Ar); 8.09–8.27 (2H, m, H Ar). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 13.4; 22.4; 43.0; 127.6; 130.9; 131.3; 134.7; 135.0; 143.7; 145.5; 169.0; 177.8; 179.7.

***N*-(3-Chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-*N*-propylacetamide (5d)**. Yield 1.50 g (86%), yellow-brown oil. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 0.71–0.92 (3H, m, CH_3); 1.34–1.61 (2H, m,

CH_2); 1.85 (3H, s, $COCH_3$); 3.40–3.55 (2H, m, CH_2); 7.89–7.97 (2H, m, H Ar); 8.03–8.16 (2H, m, H Ar). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 11.4; 21.6; 22.3; 49.7; 127.6; 130.9; 131.3; 134.7; 134.9; 143.6; 145.7; 169.1; 177.8; 179.8.

***N*-Butyl-*N*-(3-chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)acetamide (5e)**. Yield 1.30 g (71%), yellow-brown oil. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 0.83 (3H, t, *J* = 7.2, CH_3); 1.14–1.32 (2H, m, CH_2); 1.35–1.56 (2H, m, CH_2); 1.85 (3H, s, $COCH_3$); 3.43–3.60 (2H, m, CH_2); 7.87–7.98 (2H, m, H Ar); 8.02–8.18 (2H, m, H Ar). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 13.8; 20.3; 22.4; 30.4; 47.9; 127.7 130.9; 131.4; 134.8; 135.0; 143.7; 145.8; 169.1; 177.9; 179.8.

***N*-(3-Chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-*N*-isopropylacetamide (5f)**. Yield 1.34 g (77%), yellow powder, mp 75–76°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.18 (3H, d, *J* = 6.6, CH_3); 1.23 (3H, d, *J* = 6.6, CH_3); 1.81 (3H, s, $COCH_3$); 4.16–4.36 (1H, m, CH); 7.86–8.03 (2H, m, H Ar); 8.03–8.24 (2H, m, H Ar). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 20.8; 20.9; 23.2; 51.5; 127.8; 130.9; 131.4; 134.8; 135.1; 145.2; 145.7; 168.8; 177.9; 180.7.

***N*-(3-Chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-*N*-cyclohexylacetamide (5g)**. Yield 1.79 g (90%), yellow powder, mp 135–136°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 1.20–1.43 (5H, m) and 1.51–1.63 (1H, m, $3CH_2$); 1.66–1.77 (2H, m, CH_2); 1.87 (3H, s, $COCH_3$); 1.90–2.08 (2H, m, CH_2); 4.18–4.37 (1H, m, CH); 7.79–7.91 (2H, m, H Ar); 8.12–8.30 (2H, m, H Ar). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 22.9; 25.4; 25.9; 31.0; 31.1; 58.8; 127.6; 127.7; 130.9; 131.3; 134.7; 135.0; 145.1; 145.9; 168.5; 177.8; 180.7.

***N*-(3-Chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-*N*-phenylacetamide (5h)**. Yield 1.24 g (64%), orange powder, mp 136–137°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 2.08 (3H, s, $COCH_3$); 7.17–7.61 (5H, m, H Ar); 7.85–7.99 (2H, m, H Ar); 8.03–8.16 (2H, m, H Ar). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 22.2; 127.5; 127.6; 128.4; 128.7; 129.7; 131.3; 131.4; 134.5; 134.7; 140.2; 143.3; 146.1; 170.9; 178.1; 179.1.

***N*-Benzyl-*N*-(3-chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)acetamide (5i)**. Yield 1.76 g (86%), yellow powder, mp 115–116°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.92 (3H, s, $COCH_3$); 4.65 (1H, d, *J* = 14.4) and 4.77 (1H, d, *J* = 14.4, CH_2); 7.10–7.42 (5H, m, H Ar); 7.86–7.97 (2H, m, H Ar); 7.99–8.16 (2H, m, H Ar). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 22.5; 50.5; 127.5; 128.0; 128.4; 129.5; 130.7; 131.1; 134.7; 134.9; 135.5; 144.1; 144.9; 169.2; 177.6; 179.4.

***N*-(3-Chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-*N*-phenethylacetamide (5j)**. Yield 1.99 g (94%), yellow powder, mp 128–129°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 1.89 (3H, s, $COCH_3$); 2.63–3.00 (2H, m, CH_2); 3.53–3.88 (2H, m, CH_2); 7.03–7.32 (5H, m, H Ar); 7.88–8.02 (2H, m, H Ar); 8.04–8.21 (2H, m, H Ar). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 22.5; 34.5; 49.0; 126.5; 127.5; 127.6; 128.5; 128.7; 130.9; 131.3; 134.7; 134.9; 138.5; 143.1; 145.6; 169.4; 177.7; 179.7.

Synthesis of *N*-(6-oxo-2,3,4,6-tetrahydrobenzo[*f*]-quinoxalin-5-yl)acetamides 6a–j (General method). Ethylenediamine (210 mg, 233 μl, 3.5 mmol) was added to a suspension of the appropriate 2-acetamido-3-chloro-1,4-naphthoquinone **5a–j** (3.5 mmol) in acetonitrile (30 ml). The reaction mixture was stirred at room temperature and monitored by TLC (EtOAc). Once the reaction was complete, the mixture was concentrated under reduced pressure. The obtained residue was purified by chromatography (EtOAc) to give the pure product.

***N*-(6-Oxo-2,3,4,6-tetrahydrobenzo[*f*]quinoxalin-5-yl)-acetamide (6a)**. Yield 350 mg (39%), reddish-orange powder, mp 178–179°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.01 (3H, s, CH_3); 3.20–3.30 (2H, m, CH_2); 4.04 (2H, t, *J* = 6.4, CH_2); 7.33 (1H, s, NH); 7.54–7.65 (2H, m, H Ar); 7.88–7.97 (1H, m, H Ar); 8.04–8.14 (1H, m, H Ar); 8.82 (1H, s, NH). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 24.3; 37.0; 48.2; 112.2; 123.9; 125.8; 130.3; 131.0; 132.1; 133.4; 134.5; 153.7; 169.6; 178.3. Found, *m*/*z*: 256.1103 $[M+H]^+$. $C_{14}H_{13}N_3O_2$. Calculated, *m*/*z*: 256.1086.

***N*-Methyl-*N*-(6-oxo-2,3,4,6-tetrahydrobenzo[*f*]quinoxalin-5-yl)acetamide (6b)**. Yield 564 mg (60%), orange powder, mp 165–166°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.89 (3H, s, $COCH_3$); 3.05 (3H, s, CH_3); 3.39–3.56 (2H, m, CH_2); 4.18 (2H, t, *J* = 6.5, CH_2); 7.50–7.60 (2H, m, H Ar); 7.95 (1H, s, NH); 8.08–8.13 (1H, m, H Ar); 8.13–8.19 (1H, m, H Ar). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 21.4; 34.0; 36.5; 48.4; 115.9; 123.8; 126.0; 131.2; 131.5; 131.9; 132.9; 140.3; 153.9; 173.3; 178.0. Found, *m*/*z*: 270.1240 $[M+H]^+$. $C_{15}H_{15}N_3O_2$. Calculated, *m*/*z*: 270.1243.

***N*-Ethyl-*N*-(6-oxo-2,3,4,6-tetrahydrobenzo[*f*]quinoxalin-5-yl)acetamide (6c)**. Yield 407 mg (41%), orange powder, mp 179–180°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.11 (3H, t, *J* = 7.2, CH_3); 1.89 (3H, s, $COCH_3$); 3.31–3.56 (2H, m, CH_2); 3.70–3.93 (2H, m, CH_2); 4.05–4.31 (2H, m, CH_2); 7.41 (1H, s, NH); 7.53–7.65 (2H, m, H Ar); 8.10–8.17 (1H, m, H Ar); 8.17–8.25 (1H, m, H Ar). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 13.0; 22.0; 36.7; 41.6; 48.5; 114.6; 123.9; 126.3; 131.4; 131.5; 132.0; 132.9; 140.7; 154.0; 172.9; 178.7. Found, *m*/*z*: 284.1409 $[M+H]^+$. $C_{16}H_{17}N_3O_2$. Calculated, *m*/*z*: 284.1399.

***N*-(6-Oxo-2,3,4,6-tetrahydrobenzo[*f*]quinoxalin-5-yl)-*N*-propylacetamide (6d)**. Yield 378 mg (36%), yellow powder, mp 164–165°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 0.86 (3H, t, *J* = 7.4, CH_3); 1.40–1.67 (2H, m, CH_2); 1.89 (3H, s, $COCH_3$); 3.08–3.28 (1H, m) and 3.61–3.86 (1H, m, CH_2); 3.37–3.57 (2H, m, CH_2); 4.04–4.33 (2H, m, CH_2); 7.47–7.63 (3H, m, NH, H Ar); 8.09–8.16 (1H, m, H Ar); 8.16–8.24 (1H, m, H Ar). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 11.7; 21.3; 21.9; 36.7; 48.5; 48.8; 114.9; 123.9; 126.2; 131.4; 131.5; 132.0; 132.8; 140.5; 154.0; 172.9; 178.7. Found, *m*/*z*: 298.1564 $[M+H]^+$. $C_{17}H_{19}N_3O_2$. Calculated, *m*/*z*: 298.1556.

***N*-Butyl-*N*-(6-oxo-2,3,4,6-tetrahydrobenzo[*f*]quinoxalin-5-yl)acetamide (6e)**. Yield 345 mg (32%), orange powder, mp 155–156°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 0.87 (3H, t, *J* = 7.3, CH_3); 1.16–1.36 (2H,

m, CH_2); 1.38–1.65 (2H, m, CH_2); 1.89 (3H, s, $COCH_3$); 3.24 (1H, ddd, J = 13.1, J = 11.2, J = 5.0) and 3.74 (1H, ddd, J = 13.1, J = 11.0, J = 5.6, CH_2); 3.38–3.57 (2H, m, CH_2); 4.06–4.31 (2H, m, CH_2); 7.31 (1H, s, NH); 7.54–7.62 (2H, m, H Ar); 8.10–8.16 (1H, m, H Ar); 8.16–8.22 (1H, m, H Ar). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 14.0; 20.6; 21.9; 29.9; 36.7; 46.9; 48.5; 115.1; 123.8; 126.3; 131.4; 131.5; 132.0; 132.9; 140.4; 154.0; 173.0; 178.7. Found, *m*/*z*: 312.1652 $[M+H]^+$. $C_{18}H_{21}N_3O_2$. Calculated, *m*/*z*: 312.1712.

***N*-Isopropyl-*N*-(6-xo-2,3,4,6-tetrahydrobenzo[*f*]-quinoxalin-5-yl)acetamide (6f)**. Yield 177 mg (17%), orange powder, mp 166–167°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.01 (6H, d, J = 6.6, $2CH_3$); 1.70 (3H, s, $COCH_3$); 3.19–3.31 (2H, m, CH_2); 3.89–4.03 (1H, m) and 4.08–4.21 (1H, m, CH_2); 4.51–4.64 (1H, m, CH); 7.56–7.70 (2H, m, H Ar); 7.92–8.00 (1H, m, H Ar); 8.04 (1H, s, NH); 8.07–8.16 (1H, m, H Ar). ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ, ppm: 19.7; 20.9; 22.0; 35.8 (2C); 47.8; 111.1; 123.3; 125.4; 131.0; 131.2; 131.5; 132.5; 142.4; 153.0; 170.5; 178.0. Found, *m*/*z*: 298.1547 $[M+H]^+$. $C_{17}H_{19}N_3O_2$. Calculated, *m*/*z*: 298.1556.

***N*-Cyclohexyl-*N*-(6-oxo-2,3,4,6-tetrahydrobenzo[*f*]-quinoxalin-5-yl)acetamide (6g)**. Yield 320 mg (34%), orange powder, mp 131–132°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.11–1.39 (5H, m, CH_2); 1.45–1.59 (1H, m, CH_2); 1.63–1.76 (2H, m, CH_2); 1.79–1.88 (3H, m, CH_2); 1.91–2.02 (1H, m, CH_2); 2.03–2.15 (1H, m, CH_2); 3.32–3.43 (1H, m, CH_2); 3.44–3.56 (1H, m, CH_2); 3.99–4.12 (1H, m) and 4.14–4.26 (1H, m, CH_2); 4.27–4.41 (1H, m, CH); 7.48–7.60 (2H, m, H Ar); 8.03 (1H, s, NH); 8.06–8.21 (2H, m, H Ar). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 22.5; 25.5; 26.0; 26.2, 29.7, 31.2, 36.4; 48.4; 56.6; 112.4; 123.6; 126.1; 131.2; 131.5; 131.7; 132.8; 142.4; 153.9; 172.4; 179.1. Found, *m*/*z*: 338.1881 $[M+H]^+$. $C_{20}H_{23}N_3O_2$. Calculated, *m*/*z*: 338.1869.

***N*-(6-Oxo-2,3,4,6-tetrahydrobenzo[*f*]quinoxalin-5-yl)-*N*-phenylacetamide (6h)**. Yield 337 mg (29%), orange powder, mp 153–154°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 2.03 (3H, s, $COCH_3$); 3.16–3.47 (2H, m, CH_2); 3.89–4.25 (2H, m, CH_2); 7.12–7.36 (3H, m, H Ar and NH); 7.41–7.64 (4H, m, H Ar); 7.96–8.39 (2H, m, H Ar). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 22.6; 36.5; 48.3; 116.0; 123.7; 126.1; 128.9; 131.2; 131.4; 131.9; 132.9; 140.8; 153.8; 173.0; 178.4. Found, *m*/*z*: 332.1401 $[M+H]^+$. $C_{20}H_{17}N_3O_2$. Calculated, *m*/*z*: 332.1399.

***N*-Benzyl-*N*-(6-oxo-2,3,4,6-tetrahydrobenzo[*f*]quinoxalin-5-yl)acetamide (6i)**. Yield 292 mg (24%), orange powder, mp 146–147°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.80 (3H, s, $COCH_3$); 2.92–3.12 (1H, m) and 3.12–3.27 (1H, m, CH_2); 3.70–3.89 (1H, m) and 3.97–4.13 (1H, m, CH_2); 4.53 (1H, d, J = 13.8) and 4.64 (1H, d, J = 13.8, CH_2); 7.00–7.34 (5H, m, H Ar); 7.50–7.69 (2H, m, H Ar); 7.85–7.96 (2H, m, H Ar); 8.01 (1H, s, NH). ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ, ppm: 21.5; 35.6; 47.5; 49.2; 112.9; 123.3; 125.2; 127.0; 127.5; 129.3; 130.9; 131.0; 131.5; 132.4; 136.8; 140.6; 152.8; 171.2; 176.9. Found, *m*/*z*: 346.1532 $[M+H]^+$. $C_{21}H_{19}N_3O_2$. Calculated, *m*/*z*: 346.1556.

***N*-(6-oxo-2,3,4,6-tetrahydrobenzo[*f*]quinoxalin-5-yl)-*N*-phenethylacetamide (6j)**. Yield 820 mg (65%), yellow powder, mp 181–182°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.96 (3H, s, $COCH_3$); 2.75–2.93 (1H, m) and 3.10–3.25 (1H, m, CH_2); 3.28–3.42 (2H, m, CH_2); 3.68–3.83 (1H, m) and 3.85–4.02 (1H, m, CH_2); 4.11–4.28 (2H, m, CH_2); 6.93 (1H, s, NH); 7.15–7.32 (5H, m, H Ar); 7.62–7.71 (2H, m, H Ar); 8.17–8.28 (2H, m, H Ar). ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ, ppm: 21.9; 34.0; 36.8; 48.4; 49.0; 115.3; 123.8; 126.2; 126.4; 128.6; 128.8; 131.3; 131.4; 132.0; 132.9; 139.7; 140.3; 153.8; 173.3; 178.7. Found, *m*/*z*: 360.1707 $[M+H]^+$. $C_{22}H_{21}N_3O_2$. Calculated, *m*/*z*: 360.1712.

Synthesis of 5-chloro-3,4-dihydrobenzo[*f*]quinoxalin-6(2*H*)-one (7). Ethylenediamine (0.53 g, 0.6 ml, 8.80 mmol) was added to a suspension of compound **3** (1.0 g, 4.40 mmol) in dry acetonitrile (25 ml). The mixture was stirred at room temperature for 12 h. The resulting solution was concentrated under reduced pressure, and MeOH (5.0 ml) was added. The precipitate formed was filtered off and dried to afford compound **7**. Yield 0.98 g (95%), orange needles, mp 145–146°C (mp 135–138°C[20]). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 3.48 (2H, td, J = 6.4, J = 2.6, CH_2); 4.19 (2H, t, J = 6.4, CH_2); 5.62 (1H, s, NH); 7.52–7.63 (2H, m, H Ar); 8.09–8.23 (2H, m, H Ar). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 37.4; 48.6; 109.2; 124.0; 126.3; 131.2; 131.4; 132.0; 132.3; 139.6; 152.3; 176.5.

5-Chlorobenzo[*f*]quinoxalin-6-yl acetate (8). A solution of 5-chloro-3,4-dihydrobenzo[*f*]quinoxalin-6(2*H*)-one (**7**) (2.00 g, 8.60 mmol) in acetic anhydride (42 ml, 0.444 mol) was treated by the addition of 98% sulfuric acid (10 ml). The reaction mixture was stirred at room temperature for 14 h. The mixture was then diluted with water (200 ml), neutralized with K_2CO_3, and extracted with CH_2Cl_2. The organic extracts were combined and dried over anhydrous $MgSO_4$. The solvent was evaporated and the products were purified by chromatography (CH_2Cl_2–acetone, 9:1) to afford product **8**. Yield 0.892 g (38%), pale-white powder, mp 218–219°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 2.58 (3H, s, $COCH_3$); 7.75–7.87 (2H, m, H Ar); 7.88–8.02 (1H, m, H Ar); 8.94 (1H, s, H Ar); 9.00 (1H, s, H Ar); 9.14–9.27 (1H, m, H Ar). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 20.7; 121.8; 122.4; 125.2; 128.2; 128.7; 130.2 (2C); 139.6; 141.0; 143.7; 144.8; 146.1; 167.7. Found, *m*/*z*: 272.0601 $[M]^+$. $C_{14}H_9ClN_2O_2$. Calculated, *m*/*z*: 272.0353.

5-Chlorobenzo[*f*]quinoxalin-6-ol (9). Morpholine (0.12 g, 0.12 ml, 1.37 mmol) was added to a solution of compound **8** (200 mg, 0.733 mmol) in acetonitrile (20 ml). The reaction mixture was stirred at room temperature for 1.5 h. The mixture was then concentrated under reduced pressure, and MeOH (3.0 ml) was added. The precipitate that formed was filtered off and dried to afford product **9**. Yield 100 mg (49%), orange solid, mp 148–149°C (mp 216°C[27]). ^{1}H NMR spectrum (200 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 7.85–7.90 (2H, m, H Ar); 8.37–8.42 (1H, m, H Ar); 8.91 (1H, d, J = 2.1, H Ar); 9.00 (1H, d, J = 2.1, H Ar); 9.10–9.13 (1H, m, H Ar); 11.03 (1H, br. s, OH). Found, *m*/*z*:

231.0530 $[M+H]^+$. $C_{12}H_7ClN_2O_2$. Calculated, *m*/*z*: 231.0325.

4-Benzylbenzo[*f*]quinoxalin-6(4*H*)-one (10). Benzyl bromide (1.45 g, 1.01 ml, 8.52 mmol) was added to a solution of compound **7** (0.50 g, 2.13 mmol) in acetonitrile (30 ml). The reaction mixture was stirred and refluxed for 12 h, then concentrated under reduced pressure and purified by chromatography (EtOAc–MeOH, 10:1) to afford product **10**. Yield 0.11 g (18%), red solid, mp 139–140°C. ^{1}H NMR spectrum (200 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 5.50 (2H, s, CH_2); 5.96 (1H, s, H Ar); 7.24–7.45 (5H, m, H Ar); 7.72–7.83 (2H, m, H Ar); 7.96 (1H, d, *J* = 4.1, H Ar); 8.15–8.27 (2H, m, H Ar); 8.71–8.87 (1H, m, H Ar). ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ, ppm: 56.8; 96.1; 124.3; 124.6; 126.4; 127.1; 128.1; 129.0; 130.0; 130.6; 131.2; 131.6; 133.5; 134.0; 138.8; 144.3; 177.3. Found, *m*/*z*: 286.9630 $[M]^+$. $C_{19}H_{14}N_2O$. Calculated, *m*/*z*: 286.9116.

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