European Journal of Medicinal Chemistry 44 (2009) 1579–1591

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Synthesis and in vitro antitumor activity of new quinoxaline derivatives

Paola Corona*, Antonio Carta, Mario Loriga, Gabriella Vitale, Giuseppe Paglietti

Dipartimento Farmaco Chimico Tossicologico, Università degli Studi di Sassari, Via Muroni 23/A, 07100 Sassari, Italy

ARTICLE INFO

Article history:
Received 3 April 2008
Received in revised form 14 July 2008
Accepted 17 July 2008
Available online 26 July 2008

Keywords:
5,7-Diamino-3-phenyl-2-benzylamino, 2-phenoxy and 2-phenylthio substituted quinoxalines
Antitumor activity

ABSTRACT

A series of novel 5,7-diamino-3-phenyl-2-benzylamino, 2-phenoxy, and 2-thiophenyl substituted quinoxalines has been designed, synthesized and evaluated for their in vitro antitumor activity towards cell lines of nine different types of human cancers. Some of these compounds exhibited inhibitory effects on the growth of a wide range of cancer cell lines generally at 10^{-6} M, in some cases at 10^{-7} M and 10^{-8} M concentrations. Within this series the benzylamino quinoxaline derivatives **1b–7b** were the most active, whereas compound **2c** showed the highest MG_MD value (−5.66).

1. Introduction

Cancer is the second leading cause of death in industrialized countries. Although an upsurge in the search for new antitumor agents has recently been observed, the survival rate of patients still remains low. One of the reasons is the poor sensitivity of tumours to drugs. Therefore, major progress in chemotherapy would require new and useful antitumor agents to eradicate the entire range of cancer diseases in the world over. New compounds can be identified by a wide variety of approaches from empirical screening to rational design [1,2]. Many synthetic small molecules derived from different groups of heterocycles with influence on carcinogenesis have been reported and several of them are currently in clinical trials [3,4]. Quinoxalines have shown a broad spectrum of biological activities such as antibacterial [5], antiviral [6], herbicidal [7] and anti-inflammatory activity [8,9], hence they are an important class of nitrogen-containing heterocycles and useful intermediates in organic synthesis [10,11]. Recently some of this type of molecules have been reported as candidates for the treatment of cancer and disorders associated with angiogenesis functions [12–17].

Our continuous interest in the synthesis of new quinoxalines derivatives as potential antitumor agents [18–33] led to the discovery of the 5,7-diamino-3-phenyl-2-anilino substituted quinoxalines **1–7a** (Fig. 1), which exhibited potent activity against some cell lines of leukemia, CNS cancer, melanoma, renal cancer and ovarian cancer [33]. In this series compounds **2a** and **4a**, possessing the 3,5-dimethoxyanilino and 3,4,5-trimethoxyanilino, respectively, moiety at 2-position of the quinoxaline ring, were the most active as they showed growth inhibitory activity at nanomolar concentrations against both leukemia CCRF-CEM and ovarian cancer OVCAR-4 cell lines. In the light of these results and in order to further explore the structure–activity relationships for this class of compounds, in the present study we synthesized a new series of 5,7-diamino-3-phenylquinoxalin-2-yl substituted derivatives depicted in Fig. 2. The antitumor activity of all new compounds was preliminarily evaluated on three human tumor cell lines according to the protocols available at the National Cancer Institute (NCI, Bethesda, MD), and successively the active compounds were tested on the whole panel of 60 tumor cell lines.

2. Results and discussion

2.1. Chemistry

The synthetic routes to obtain the designed compounds **1b–7b**, **c** and **1d–5d** (Fig. 2) and their intermediates are described in Scheme 1. 5,7-Dinitro-3-phenyl-2-chloroquinoxaline (**8**), synthesized as previously reported by us [33], underwent nucleophilic attack by the corresponding benzylamines **9–13**, phenols **14**, **16–21**, thiophenols **23–26** and esters **15** [34], **22** [35], **45** [36,37] to give both the 5,7-dinitrosubstituted quinoxalines **27–44** and **46**. The desired 5,7-diamino-3-phenylquinoxalines **1b–3b**, **5b–7b**, **1c–5c**, **7c**, **1d–5d** were obtained by reduction with an excess of hydrazine hydrate in ethanol and in presence of 10% palladised charcoal or by catalytic hydrogenation with hydrogen and 10% palladised charcoal (**4b**, **6c**).

* Corresponding author. Tel.: +39 079228764; fax: +39 079228720.
E-mail address: pcorona@uniss.it (P. Corona).

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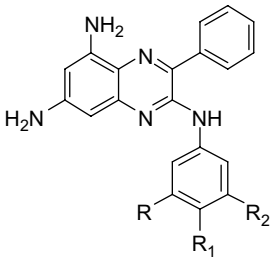
doi:10.1016/j.ejmech.2008.07.025

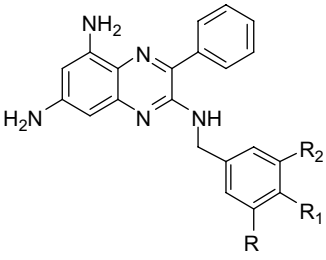


1a: R = R_2 = H; R_1 = OCH_3
2a: R = R_2 = OCH_3; R_1 = H
3a: R = R_1= OCH_3; R_2 = H
4a: R = R_1 = R_2 = OCH_3
5a: R= R_1 = Cl; R_2 = H
6a: R = R_2 = H; R_1 = F
7a: R = R_2 = H; R_1 = CO-Glu-Et

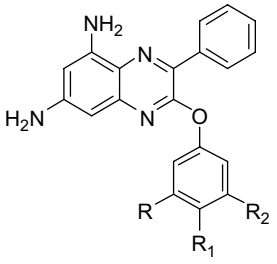
Fig. 1. Chemical structure of the series of quinoxalines previously described [33].

2.2. Biology

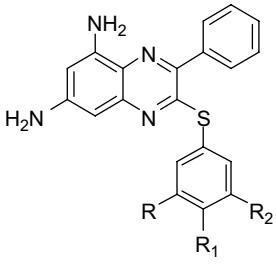
Evaluation of anti-cancer activity for the diamino-quinoxalines **1b**–**7b**, **c** and **1d**–**5d**, described in this paper, was performed at the National Cancer Institute (NCI), Bethesda, MD. First, all compounds were evaluated in the three-cell line panel consisting of NCI-H460 (Lung), MCF-7 (Breast), and SF-268 (CNS) cell lines. In the assay protocol, each cell line was inoculated and preincubated on a microtiter plate. Test agents were added in a single concentration (10^{-4} M) and the culture was incubated for 48 h. End-point determinations were made with alamar blue. Results for each compound were reported as the percent of growth of the treated cells compared to the untreated control cells (Table 1). For the NCI criteria, compounds which reduce the growth of anyone of the cancer cell lines to ca. 32% or less (negative numbers indicate cell kill) are identified as 'active' and subsequently are evaluated in a full panel of 60 cell lines over a 5-log dose range. The diamino-quinoxalines **1b**–**7b**, **1c**, **2c**, **5c**, **6c**, **1d**, **3d**, **4d** matched these criteria and were evaluated for their anti-cancer activity following the known in vitro disease-oriented antitumor screening program which is based upon the use of a multiple panel of 60 human tumor cell lines [38,39]. A 48 h drug exposure protocol was used and a sulforhodamine B (SRB) protein assay was employed to estimate cell viability or growth [40]. Moreover, based upon the data of anti-cancer activities of **7b**, two more compounds (**7c** and **5d**) with the same benzoyl glutamic moiety were included for evaluation against the full panel of 60 tumor cell lines. The anti-cancer activity of a tested compound is given by three parameters for each cell line: $\log_{10}$ GI_{50} value (GI_{50} = molar concentration of the compound that inhibits 50% net cell growth), $\log_{10}$ TGI value (TGI = molar concentration of the compound leading to total inhibition of net cell growth), and $\log_{10}$ LC_{50} value (LC_{50} = molar concentration of the compound leading to 50% net cell death). Furthermore, a mean graph midpoint (MG_MID) is calculated for each of the mentioned parameters, giving an averaged activity of each compound deduced from dose–response curves. For the calculation of the MG_MID, insensitive cell lines are included with the highest concentration tested [41–43]. Selectivity of the compound with respect to one or more cell lines of the screen is characterized by a high deviation (Δ) of the particular cell line parameter compared to the MG_MID value.



1b: R = R_2 = H; R_1 = OCH_3
2b: R = R_2 = OCH_3; R_1 = H
3b: R = R_1 = OCH_3; R_2 = H
4b: R = R_1 = R_2 = OCH_3
5b: R = R_1 = Cl; R_2 = H
6b: R = R_2 = H; R_1 = F
7b: R = R_2 = H; R_1 = CO-Glu-Et



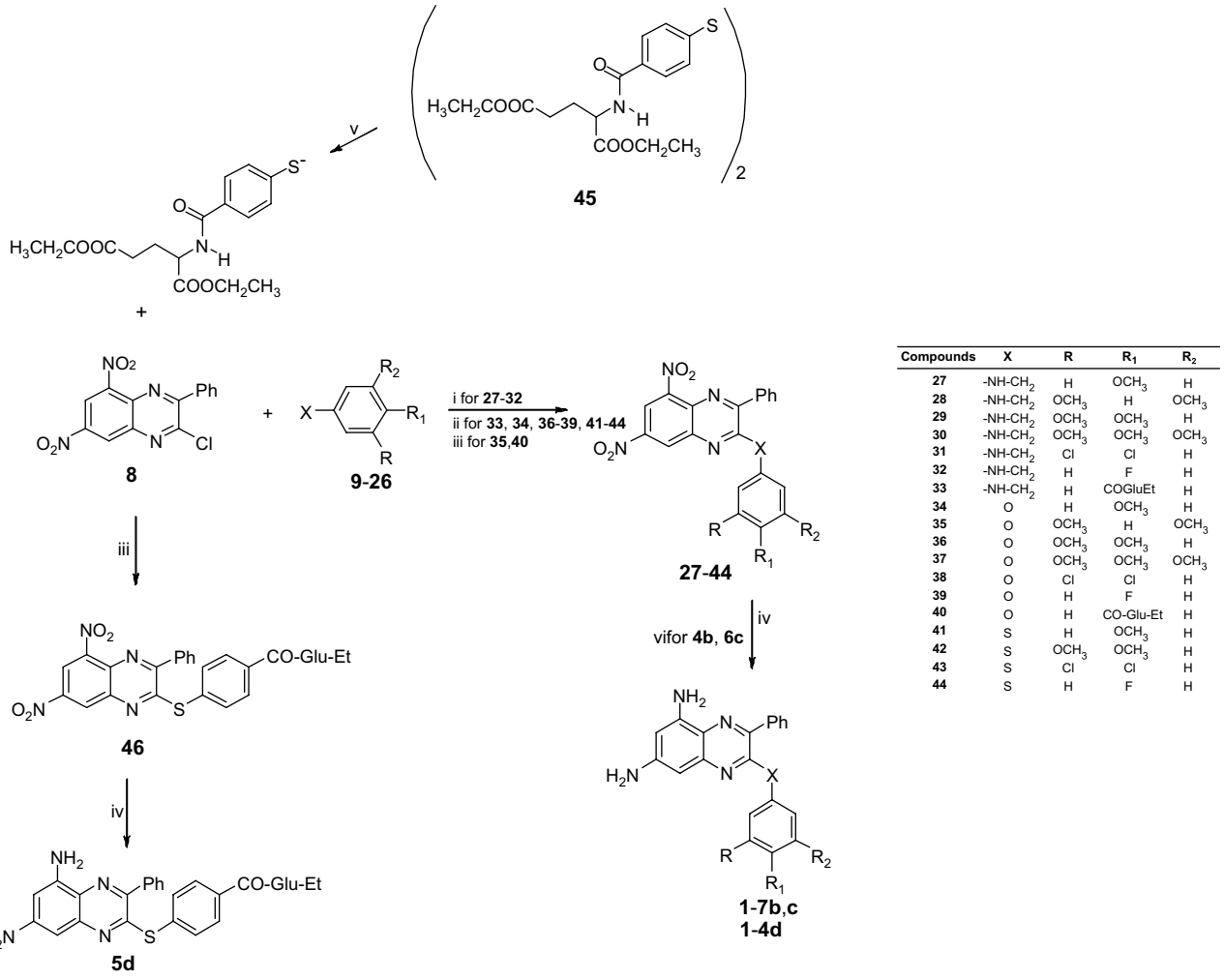
1c: R = R_2 = H; R_1 = OCH_3
2c: R = R_2 = OCH_3; R_1 = H
3c: R = R_1 = OCH_3; R_2 = H
4c: R = R_1 = R_2 = OCH_3
5c: R = R_1 = Cl; R_2 = H
6c: R = R_2 = H; R_1 = F
7c: R = R_2= H; R_1 = CO-Glu-Et



1d: R = R_2 = H; R_1 = OCH_3
2d: R = R_1 = OCH_3; R_2 = H
3d: R = R_1=Cl; R_2 = H
4d: R = R_2 = H; R_1=F
5d: R = R_2 = H; R_1 = CO-Glu-Et

Fig. 2. Designed compounds **1**–**7b**, **c** and **1**–**5d**.

The $\log_{10}$ GI_{50}, $\log_{10}$ TGI and $\log_{10}$ LC_{50} values provided by NCI for compounds **1b**–**7b**, **1c**, **2c**, **5c**–**7c**, **1d**, **3d**–**5d** are reported in Tables 2 and 3. From the analysis of the values of anti-cancer activity it is evident that most compounds were active against the 60 human tumor cell lines and showed inhibitory activities at sub-micromolar concentrations. The aminobenzyl quinoxalines **2b**–**6b** and the phenoxy derivative **2c** proved to be the most active within the series, showing both potent and broad spectrum of antitumor activity (MG_MID log GI_{50} values ranged from −5.01 to −5.66). Compounds **7b**, **1c**, **5c**–**7c**, **1d**, **3d**–**5d** exhibited a moderate to high selectivity towards one or more tumor cell lines. The 5,7-diamino-3-phenyl-2-[(3,5-dimethoxy)phenoxy]quinoxaline (**2c**) was the most active in the series showing high cytostatic activity on all 60 human tumor cell lines (MG_MID log GI_{50} value −5.66), remarkable anti-cancer activity has been observed against non-small cell lung cancer NCI-H522 (log GI_{50} value −6.05), CNS cancer SNB-75 (log GI_{50} value −6.90), melanoma MALME-3M (log GI_{50} −6.37), breast cancer MDA-MB-435 (log GI_{50} −6.41) and MDA-N (log GI_{50} −6.12). The 5,7-diamino-3-phenyl-2-[(3,5-dimethoxy-benzyl)amino]quinoxaline (**2b**) exhibited high sensitivity against ovarian cancer OVCAR-4 (log GI_{50} value −7.85). Introduction of one or more methoxy groups into the aminobenzyl or into the phenoxy groups induced a significant antiproliferative activity. In fact compounds **1b**, **2b**, **3b** and **4b** showed log MG_MID values of −4.87, −5.23, −5.01, −5.42, respectively, and compound **2c** was more potent than **1c** (log MG_MID values −5.66 and −4.51). Significantly, the 5,7-diamino-3-phenyl-2-[(3,4,5-trimethoxy-benzyl)amino]quinoxaline (**4b**) exhibited high sensitivity against several leukemia RPMI-8226, SR (log GI_{50} value −6.16, −6.05), colon cancer KM 12 (log GI_{50} value −6.32), CNS cancer SNB-75 (log GI_{50} value −6.09), melanoma SK-MEL-5 (log GI_{50} value −6.14) and breast cancer MDA-MB-435 (log GI_{50} value −6.64) cell lines. Compound **5b**, which bears two chlorine atoms at 3- and 4-position on the benzyl ring, showed good cytotoxic activities against all leukemia cell lines, especially on CCRF-CEM (log GI_{50} value −6.88)



Compounds	X	R	R_1	R_2
27	-NH-CH_2	H	OCH_3	H
28	-NH-CH_2	OCH_3	H	OCH_3
29	-NH-CH_2	OCH_3	OCH_3	H
30	-NH-CH_2	OCH_3	OCH_3	OCH_3
31	-NH-CH_2	Cl	Cl	H
32	-NH-CH_2	H	F	H
33	-NH-CH_2	H	COGluEt	H
34	O	H	OCH_3	H
35	O	OCH_3	H	OCH_3
36	O	OCH_3	OCH_3	H
37	O	OCH_3	OCH_3	OCH_3
38	O	Cl	Cl	H
39	O	H	F	H
40	O	H	CO-Glu-Et	H
41	S	H	OCH_3	H
42	S	OCH_3	OCH_3	H
43	S	Cl	Cl	H
44	S	H	F	H

Scheme 1. Synthesis of **1**–**7b**, **c** and **1**–**5d**. Reagents and conditions: (i) 1-propanol, reflux for 30 min to 168 h. (ii) DMF anhydrous, Cs_2CO_3, 70 °C for 30 min to 6 h. (iii) DMF anhydrous, N_2, Cs_2CO_3, room temperature for 1 h to 9 h and 45 min. (iv) NH_2–$NH_2 \cdot H_2O$, reflux for 10 min to 6 h. (v) Ethanol, N_2, $NaBH_4$, room temperature for 30 min. (vi) H_2, 10% Pd/C, EtOH.

and its counterpart derivative **5c**, which has one oxygen atom between the quinoxaline scaffold and the phenyl ring, displayed lower cytotoxicity against the same cell lines, accompanied with higher cytotoxicity against renal cancer A498 cell line (log GI_{50} value −6.35). Among all of these compounds **7b** and **5d** displayed a moderate to high selectivity towards leukemia cell lines (Δlog GI_{50} ranged from 1.38 to 3.12; Table 4), particularly remarkable is the considerable antiproliferative activity of **5d** against leukemia K-562 (log GI_{50} value less than −8.00).

3. Conclusion

In summary, we have synthesized a series of 5,7-diamino-3-phenyl-2-benzylamino, 2-phenoxy and 2-phenylthio substituted quinoxalines. Some of these had excellent growth inhibition activity against most of the cancer cell lines tested. Among the examined series the 5,7-diamino-3-phenyl-2-benzylamino quinoxaline derivatives **1b**–**6b** exhibited better anti-cancer activity than the corresponding 5,7-diamino-3-phenyl-2-anylino **1a**–**7a** analogues previously described [33] (Table 5). Introduction of two or more methoxy groups on the phenyl side chain at 2-position of quinoxaline ring produces a favourable effect on the anti-cancer activity on the whole as well as the presence of fluorine and chlorine atoms. Compound **2c** shows the best antiproliferative profile of all the series reported (MG_MD value 5.66). It posses 3,5-dimethoxy phenyl moiety in analogy with **2a** (Fig. 1), which is the most active of the series described [33]. The results of this investigation prompt us to continue the development and testing of novel diamino quinoxaline derivatives and to carry out further studies to investigate SAR and their mechanisms of action.

4. Experimental

4.1. Chemistry

4.1.1. General remarks

Melting points were carried out with a Köfler hot stage or Digital Electrothermal melting point apparatus and are uncorrected. Infrared spectra were recorded as nujol mulls on NaCl plates with a Perkin–Elmer 781 IR spectrophotometer and are expressed in ν (cm^{-1}). UV spectra are qualitative and were recorded in nanometer (nm) for solutions in EtOH with a Perkin–Elmer Lambda 5 spectrophotometer. Nuclear magnetic resonance (^1H NMR) spectra were determined in $CDCl_3$, DMSO-d_6, $CDCl_3$/DMSO-d_6 (1:3 ratio) and were recorded with a Varian XL-200 (200 MHz) spectrometer. Chemical shifts (δ scale) are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) used as internal standard. Splitting patterns are designated, as follows: s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet; br s, broad singlet; dd, double doublet.

Table 1
Primary assay results for anti-cancer activity of diamino-quinoxalines **1–7b**, **c** and **1–5d**

Compound	R	R_1	R_2	Growth percentage at 10^{-4} M concentration cancer cell line		
				NCI-H460 (lung)	MCF-7 (breast)	SF-268 (CNS)
1b	H	OCH_3	H	0	0	0
2b	OCH_3	H	OCH_3	−1	−72	−28
3b	OCH_3	OCH_3	H	3	0	47
4b	OCH_3	OCH_3	OCH_3	7	0	15
5b	Cl	Cl	H	0	0	0
6b	H	F	H	1	1	1
7b	H	CO–Glu–Et	H	97	2	79
1c	H	OCH_3	H	−48	−89	−56
2c	OCH_3	H	OCH_3	2	0	1
3c	OCH_3	OCH_3	H	118	117	131
4c	OCH_3	OCH_3	OCH_3	N.t.[a]	N.t.[a]	N.t.[a]
5c	Cl	Cl	H	0	2	0
6c	H	F	H	0	2	6
7c	H	CO–Glu–Et	H	73	42	75
1d	H	OCH_3	H	0	8	7
2d	OCH_3	OCH_3	H	119	121	136
3d	Cl	Cl	H	0	12	11
4d	H	F	H	0	7	0
5d	H	CO–Glu–Et	H	97	65	42

[a] Not tested.

The assignment of exchangeable protons (O*H* and N*H*) was confirmed by the addition of D_2O. Ms spectra were performed on combined HP 5790-HP 5970 GC/MS apparatus or with a combined Liquid Chromatograph-Agilent 1100 series Mass Selective Detector (MSD). Analytical thin-layer chromatography (TLC) was performed on Merck silica gel F-254 plates. Pure compounds showed a single spot in TLC. For flash chromatography, Merck silica gel 60 was used with a particle size 0.040–0.063 mm (230–400 mesh ASTM). Elemental analysis was performed on a Perkin–Elmer 2400 instrument at Laboratorio di Microanalisi, Dipartimento di Chimica, Università di Sassari, Italy, and the results were within ±0.4% of theoretical values.

4.1.2. Intermediates

The intermediate chloroquinoxaline (**8**) has been prepared as described by us in a recent paper [33]. The esters *N*-[4(amino-methyl)benzoyl]glutamic acid diethyl ester [34] (**15**), *N*-[4-(hydroxy)benzoyl]glutamic acid diethyl ester (**22**) [35] and tetraethyl 4,4′-dithiobis(*N*-benzoyl-L-glutamate) (**45**) [36,37] are not commercially available and were obtained according to the procedure described in the cited literature.

*4.1.2.1. General procedure for preparation of 5,7-dinitro-3-phenyl-2-aminobenzyl substituted quinoxalines (**27–33**).* A solution of **8** (150 mg, 0.45 mmol) in 1-propanol (15 mL) was obtained by heating under reflux. Then to this solution an excess of either the required substituted benzylamines (**9–14**) or the ester (**15**) [34] was added. Heating was maintained for different times as reported below. After cooling, the formed coloured precipitates were filtered off to give the desired aminobenzyl quinoxalines.

*4.1.2.1.1. 5,7-Dinitro-3-phenyl-2-[(4-methoxy-benzyl)amino]quinoxaline (**27**).* This compound was obtained in 95% yield by the protocol described in the general procedure starting from **8** (150 mg, 0.45 mmol) and 4-methoxy-benzylamine (**9**) (185 mg, 1.35 mmol) for 1 h; m.p. 201–202 °C (from CH_3CN); TLC (petroleum ether/ethyl acetate 8:2): R_f 0.35; IR (nujol): ν 3380, 1610, 1530, 1345 cm^{-1}; UV (EtOH): λ_{max} 403, 287, 247, 210 nm; ^1H NMR ($CDCl_3$): δ 8.75 (1H, d, $J = 2.6$ Hz, H-6), 8.46 (1H, $J = 2.4$ Hz, H-8), 7.89–7.79 (2H, m, Ar), 7.61–7.52 (3H, m, Ar), 7.31 (2H, d, $J = 8.6$ Hz, Ar), 6.89 (2H, d, $J = 8.6$ Hz, Ar), 6.04 (1H, t, exc. with D_2O, NH), 4.73 (2H, d, CH_2), 3.80 (3H, s, CH_3). GC/MS: *m*/*z* 431 $[M]^+$. Anal. Calcd. for $C_{22}H_{17}N_5O_5$: C, 61.25; H, 3.97; N, 16.23; found C, 61.15; H, 3.84; N, 16.11.

*4.1.2.1.2. 5,7-Dinitro-3-phenyl-2-[(3,5-dimethoxy-benzyl)amino]-quinoxaline (**28**).* This compound was obtained in 95% yield by the protocol described in the general procedure starting from **8** (150 mg, 0.45 mmol) and 3,5-dimethoxy-benzylamine (**10**) (226 mg, 1.35 mmol) for 30 min; m.p. 178–179 °C (from C_2H_6O); TLC (petroleum ether/ethyl acetate 7:3): R_f 0.42; IR (nujol): ν 3440, 1610, 1535, 1345 cm^{-1}; UV (EtOH): λ_{max} 402, 285, 244 nm; ^1H NMR ($CDCl_3$): δ 8.74 (1H, d, $J = 2.6$ Hz, H-6), 8.46 (1H, d, $J = 2.6$ Hz, H-8), 7.90–7.80 (2H, m, Ar), 7.61–7.50 (3H, m, Ar), 6.49 (2H, d, $J = 2.2$ Hz, Ar), 6.39 (1H, t, Ar), 6.07 (1H, t, exc. with D_2O, NH), 4.74 (2H, d, CH_2), 3.78 (6H, s, $2 \times CH_3$). GC/MS: *m*/*z* 461 $[M]^+$. Anal. Calcd. for $C_{23}H_{19}N_5O_6$: C, 59.87; H, 4.15; N, 15.18; found C, 60.23; H, 4.15; N, 15.00.

*4.1.2.1.3. 5,7-Dinitro-3-phenyl-2-[(3,4-dimethoxy-benzyl)amino]-quinoxaline (**29**) [44].* This compound was obtained in 90% yield by the protocol described in the general procedure starting from **8** (150 mg, 0.45 mmol) and 3,4-dimethoxy-benzylamine (**11**) (226 mg, 1.35 mmol) for 30 min; m.p. 190–191 °C (from C_2H_6O); TLC (petroleum ether/ethyl acetate 8:2): R_f 0.39; IR (nujol): ν 3420, 1590, 1525, 1350 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.76 (1H, d, $J = 2.4$ Hz, Ar), 8.49 (1H, d, $J = 2.4$ Hz, Ar), 7.88–7.80 (2H, m, Ar) 7.60–7.52 (3H, m, Ar), 6.98–6.81 (3H, m, Ar), 6.02 (1H, t, exc. with D_2O, NH), 4.73 (2H, d, CH_2), 3.88 (6H, s, $2 \times CH_3$). ^{13}C NMR ($CDCl_3$): δ 43.2 (CH_2), 56 ($2 \times CH_3$), 109.3 (CH), 112.4 (CH), 115 (CH), 120 (CH), 126.2 (CH), 127.3 ($2 \times$ CH), 128.5 (CH), 129.3 ($2 \times$ CH), 130 (C), 133.5 (C), 135.2 (C), 138.1 (C), 141.3 (C), 143 (C), 147.6 (C), 148 (C), 149.6 (C), 154.5 (C). GC/MS: *m*/*z* 461 $[M]^+$. Anal. Calcd. for $C_{23}H_{19}N_5O_6$: C, 59.87; H, 4.15; N, 15.18; found C, 59.76; H, 4.04; N, 14.97.

*4.1.2.1.4. 5,7-Dinitro-3-phenyl-2-[(3,4,5-trimethoxy-benzyl)amino]quinoxaline (**30**).* This compound was obtained in 95% yield by the protocol described in the general procedure starting from **8** (150 mg, 0.45 mmol) and 3,4,5-trimethoxy-benzylamine (**12**) (266 mg, 1.35 mmol) for 1 h; m.p. 101–102 °C (from C_2H_6O); TLC (petroleum ether/ethyl acetate 6:4): R_f 0.35; IR (nujol): ν 3420, 1590, 1535, 1345 cm^{-1}; UV (EtOH): λ_{max} 400, 286, 245 nm; ^1H NMR ($CDCl_3$): δ 8.76 (1H, d, $J = 2.6$ Hz, H-6), 8.48 (1H, d, $J = 2.6$ Hz, H-8), 7.90–7.80 (2H, m, Ar), 7.65–7.55 (3H, m, Ar), 6.60 (2H, s, Ar), 6.04 (1H, t, exc. with D_2O, NH), 4.73 (2H, d, CH_2), 3.85 (6H, s, $2 \times CH_3$), 3.84 (3H, s, CH_3). GC/MS: *m*/*z* 491 $[M]^+$. Anal. Calcd. for $C_{24}H_{21}N_5O_7$: C, 58.65; H, 4.31; N, 14.25; found C, 58.58; H, 4.00; N, 14.01.

*4.1.2.1.5. 5,7-Dinitro-3-phenyl-2-[(3,4-dichloro-benzyl)amino]quinoxaline (**31**).* This compound was obtained in 86% yield by the protocol described in the general procedure starting from **8** (150 mg, 0.45 mmol) and 3,4-dichlorobenzylamine (**13**) (238 mg, 1.35 mmol) for 1 h and 50 min; m.p. 217–218 °C (from C_2H_6O); TLC (petroleum ether/ethyl acetate 8:2): R_f 0.53; IR (nujol): ν 3390, 1595, 1525, 1350 cm^{-1}; UV (EtOH): λ_{max} 400, 283, 242 nm; ^1H NMR ($CDCl_3$): δ 8.61 (1H, d, $J = 2.6$ Hz, H-6), 8.41 (1H, d, $J = 2.6$ Hz, H-8), 8.00 (1H, t, exc. with D_2O, NH), 7.87 (2H, dd, $J = 6.2$ Hz and $J = 2.4$ Hz, Ar), 7.66–7.54 (3H, m, Ar), 7.46–7.35 (3H, m, Ar), 4.71 (2H, d, CH_2). GC/MS: *m*/*z* 469 $[M]^+$. Anal. Calcd. for $C_{21}H_{13}Cl_2N_5O_4$: C, 59.63; H, 2.79; N, 14.89; found C, 59.40; H, 2.55; N, 14.75.

*4.1.2.1.6. 5,7-Dinitro-3-phenyl-2-[(4-fluoro-benzyl)amino]quinoxaline (**32**).* This compound was obtained in 89% yield by the protocol described in the general procedure starting from **8** (150 mg, 0.45 mmol) and 4-fluoro-benzylamine (**14**) (169 mg, 1.35 mmol) for 1 h and 30 min; m.p. 213–214 °C (from C_2H_6O); TLC (petroleum ether/ethyl acetate 7:3): R_f 0.53; IR (nujol): ν 3490, 1605, 1520, 1350 cm^{-1}; UV (EtOH): λ_{max} 415, 302, 260, 204 nm; ^1H NMR ($CDCl_3$/DMSO-d_6): δ 8.75 (1H, d, $J = 2.6$ Hz, H-6), 8.48 (1H, d, $J = 2.6$ Hz, H-8), 7.82 (2H, dd, $J = 6.2$ Hz and $J = 2.4$ Hz, Ar), 7.65–7.55 (3H, m, Ar), 7.42–7.32 (2H, m, Ar), 7.12–7.02 (2H, m, Ar), 6.08 (1H, t, exc. with D_2O, NH), 4.77 (2H, d, CH_2). GC/MS: *m*/*z* 419 $[M]^+$. Anal. Calcd. for $C_{21}H_{14}FN_5O_4$: C, 60.14; H, 3.36; N, 16.70; found C, 60.00; H, 3.13; N, 16.45.

Table 2
Inhibition of in vitro cancer lines by selected 5,7-diamino-3-phenyl-2-anylino-quinoxalines, **1**–**7b**, **1c**[a]

Cell lines	Respnse parameters: (A) log GI_{50}[b] [M], (B) log TGI[c] [M], (C) log LC_{50}[d] [M]																										
	1b			**2b**			**3b**			**4b**			**5b**			**6b**			**7b**			**1c**		
	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C
Leukemia																								
CCRF-CEM	−5.47	−4.19	>−4.00	−5.76	−5.25	>−4.00	−5.46	−4.15	>−4.00	–	–	–	−6.88	−5.74	−4.76	–	–	–	−4.64	>−4.00	>−4.00	−5.53	−4.90	>−4.00
HL-60(TB)	−4.87	−4.29	>−4.00	−5.42	>−4.00	>−4.00	−5.50	−4.09	>−4.00	−5.90	>−4.30	>−4.30	−5.74	−5.10	>−4.00	5.41	>−4.00	>−4.00	−5.64	−4.69	−4.17	−4.81	>−4.00	>−4.00
K-562	−4.60	−4.01	>−4.00	−5.44	−5.03	>−4.00	−5.22	>−4.00	>−4.00	−5.75	>−4.30	>−4.30	−5.51	−4.75	>−4.00	−5.36	>−4.00	>−4.00	−5.06	>−4.00	>−4.00	−4.58	>−4.00	>−4.00
RPMI-8226	−5.38	−4.80	>−4.00	−5.66	−5.21	>−4.00	−5.67	−5.14	>−4.00	−6.16	−5.52	>−4.30	−5.78	−5.43	−5.08	−5.60	−5.20	>−4.00	−4.55	>−4.00	>−4.00	−4.98	−4.15	>−4.00
SR	−5.39	>−4.00	>−4.00	−5.42	>−4.00	>−4.00	−5.48	−4.74	>−4.00	−6.05	>−4.30	>−4.30	−5.79	−5.22	>−4.00	−5.39	>−4.00	>−4.00	−6.30	−5.24	−4.03	−4.73	>−4.00	>−4.00
MOLT-4	–	–	–	−5.52	>−4.00	>−4.00	−5.46	>−4.00	>−4.00	−4.91	>−4.30	>−4.30	−5.68	>−4.00	>−4.00	>−4.00	>−4.00	>−4.00	−5.74	−5.01	−4.46	−5.27	−4.03	>−4.00
Non-small cell lung cancer																								
A549/ATCC	−4.67	−4.22	>−4.00	−4.48	>−4.00	>−4.00	−4.68	−4.30	>−4.00	−5.37	−4.48	>−4.30	−4.97	−4.56	−4.16	−4.75	−4.46	−4.16	>−4.00	>−4.00	>−4.00	−4.43	>−4.00	>−4.00
EKVX	−4.83	−4.55	−4.27	−5.55	−5.05	>−4.00	−5.23	−4.52	>−4.00	−5.71	−5.08	−4.56	−4.96	−4.41	>−4.00	−5.72	−5.39	−5.06	>−4.00	>−4.00	>−4.00	−4.61	−4.20	>−4.00
HOP-62	−4.76	−4.46	−4.16	−4.87	−4.50	−4.14	−4.74	−4.46	−4.19	−4.77	>−4.30	>−4.30	−4.80	−4.50	−4.19	−4.41	>−4.00	>−4.00	>−4.00	>−4.00	>−4.00	−4.71	−4.39	−4.06
HOP-92	−4.89	−4.43	>−4.00	−5.94	−5.48	−5.02	−4.87	−4.53	−4.18	−5.92	−5.51	>−4.30	–	–	–	−5.48	−5.16	>−4.00	−4.04	>−4.00	>−4.00	–	−5.09	−4.11
NCI-H226	−4.69	−4.15	>−4.00	–	–	–	−4.84	−4.51	−4.19	−5.00	−4.65	>−4.30	−4.65	−4.33	−4.02	−4.65	−4.32	>−4.00	>−4.00	>−4.00	>−4.00	–	–	–
NCI-H23	−4.77	−4.46	−4.15	−4.79	>−4.00	>−4.00	−4.77	−4.40	−4.04	−5.06	−4.77	−4.47	−4.85	−4.56	−4.26	−5.62	−5.34	−5.05	−4.34	>−4.00	>−4.00	−4.60	>−4.00	>−4.00
NCI-H322M	−4.64	−4.28	>−4.00	−4.35	>−4.00	>−4.00	−4.64	−4.32	−4.00	−5.52	−4.80	>−4.30	−4.87	−4.52	−4.16	−5.46	−4.94	−4.39	>−4.00	>−4.00	>−4.00	>−4.00	>−4.00	>−4.00
NCI-H460	−4.69	−4.32	>−4.00	−4.98	>−4.00	>−4.00	−4.62	−4.04	>−4.00	−5.82	>−4.30	>−4.30	−4.68	−4.33	>−4.00	−5.39	−4.59	>−4.00	−4.50	>−4.00	>−4.00	−4.51	>−4.00	>−4.00
NCI-H522	−5.00	−4.66	−4.32	−5.54	−4.64	>−4.00	−5.57	−5.20	−4.20	>−4.30	>−4.30	>−4.30	−5.69	−5.31	−4.65	>−4.00	>−4.00	>−4.00	−4.57	>−4.00	>−4.00	−4.50	>−4.00	>−4.00
Colon cancer																								
COLO 205	−4.81	−4.47	−4.13	−5.62	−5.22	>−4.00	−5.10	>−4.00	>−4.00	−5.42	>−4.30	>−4.30	−4.77	−4.47	−4.18	−5.60	−5.21	>−4.00	−4.71	>−4.00	>−4.00	>−4.00	>−4.00	>−4.00
HCC-2998	−4.66	−4.29	>−4.00	–	–	–	−4.64	−4.25	>−4.00	–	–	–	–	–	–	–	–	–	>−4.00	>−4.00	>−4.00	–	–	–
HCT-116	−4.84	−4.56	−4.28	−5.51	−4.95	−4.14	–	–	–	−5.01	−4.72	−4.43	−4.94	−4.62	−4.30	−4.89	>−4.00	>−4.00	−4.04	>−4.00	>−4.00	−4.54	−4.12	>−4.00
HCT-15	−4.80	−4.46	−4.12	−4.71	–	–	−4.52	>−4.00	>−4.00	−5.49	−4.86	>−4.30	−5.33	>−4.00	>−4.00	−5.48	−4.72	>−4.00	−4.32	>−4.00	>−4.00	−4.28	>−4.00	>−4.00
HT29	−4.61	−4.22	>−4.00	−5.09	−4.35	>−4.00	−5.73	−4.61	>−4.00	−5.06	−4.71	−4.36	–	–	–	−5.50	−4.90	>−4.00	>−4.00	>−4.00	>−4.00	−4.40	>−4.00	>−4.00
KM12	−4.88	−4.58	>−4.00	−5.37	−4.13	>−4.00	−4.88	−4.51	−4.14	−6.32	−4.99	>−4.30	−5.47	−4.67	>−4.00	−5.55	−5.13	>−4.00	>−4.00	>−4.00	>−4.00	−4.43	>−4.00	>−4.00
SW-620	−4.89	−4.52	−4.15	−5.35	>−4.00	>−4.00	−5.28	>−4.00	>−4.00	−5.81	−5.35	>−4.30	−5.49	−5.01	>−4.00	−5.66	−5.02	>−4.00	>−4.00	>−4.00	>−4.00	−4.05	>−4.00	>−4.00
CNS cancer																								
SF-268	−5.01	−4.66	−4.31	−5.27	>−4.00	>−4.00	−4.83	−4.22	>−4.00	−5.53	−4.85	−4.31	−4.70	−4.26	>−4.00	−5.55	−5.12	−4.39	>−4.00	>−4.00	>−4.00	−4.68	>−4.00	>−4.00
SF-295	−4.75	−4.49	−4.23	−4.85	−4.45	−4.06	−4.88	−4.55	−4.23	−5.78	−5.25	−4.43	−4.81	−4.43	−4.05	−5.46	−4.87	−4.19	>−4.00	>−4.00	>−4.00	−4.63	−4.28	>−4.00
SF-539	–	–	–	−5.28	−4.67	−4.11	−4.70	−4.34	>−4.00	−5.87	−5.10	−4.57	−5.34	−4.73	−4.08	−5.74	−5.45	−5.16	>−4.00	>−4.00	>−4.00	−4.63	−4.21	>−4.00
SNB-19	−4.38	>−4.00	>−4.00	−4.63	>−4.00	>−4.00	−4.59	>−4.00	>−4.00	−5.14	−4.68	>−4.30	−4.65	−4.29	>−4.00	−5.18	−4.70	−4.28	>−4.00	>−4.00	>−4.00	−4.19	>−4.00	>−4.00
SNB-75	–	−4.52	−4.14	–	–	–	−4.79	−4.40	−4.01	−6.09	−4.84	>−4.30	–	–	–	−5.67	−5.30	>−4.00	>−4.00	>−4.00	>−4.00	–	–	–
U251	−4.87	−4.58	−4.29	−5.29	>−4.00	>−4.00	−4.77	−4.41	−4.05	−5.76	−5.20	−4.52	−5.68	–	>−4.00	−5.80	−5.50	5.20	>−4.00	>−4.00	>−4.00	−4.58	>−4.00	>−4.00
Melanoma																								
LOX IMVI	−4.87	−4.56	−4.26	−5.35	−4.09	>−4.00	−5.51	−4.85	>−4.00	−5.50	−4.98	−4.58	−5.67	–	–	−5.82	−5.50	−5.18	>−4.00	>−4.00	>−4.00	−4.46	>−4.00	>−4.00
MALME-3M	−4.97	−4.65	−4.32	−5.31	−4.47	>−4.00	−5.25	−4.73	−4.32	–	–	–	−5.47	−4.86	−4.30	–	–	–	−4.69	−4.41	−4.13	−4.29	>−4.00	>−4.00
M14	−4.74	−4.49	−4.24	−5.00	−4.31	>−4.00	−5.37	−5.11	−4.47	−5.02	−4.74	−4.46	−4.80	−4.46	−4.12	−4.63	−4.25	>−4.00	−4.34	>−4.00	>−4.00	>−4.00	>−4.00	>−4.00
SK-MEL-2	−4.83	−4.54	−4.24	−5.11	−4.39	>−4.00	−5.06	−4.52	>−4.00	−4.79	>−4.30	>−4.30	−5.72	−5.37	−5.02	−5.28	>−4.00	>−4.00	−4.56	−4.11	>−4.00	−4.60	−4.06	>−4.00
SK-MEL-28	−4.76	−4.49	−4.22	−5.75	−5.06	>−4.00	−4.87	−4.52	−4.17	−5.07	−4.75	−4.44	−4.73	−4.38	−4.03	−5.72	−5.42	−5.13	−4.57	−4.25	>−4.00	−4.71	−4.31	>−4.00
SK-MEL-5	−4.75	−4.50	−4.25	−4.89	−4.38	>−4.00	−5.00	−4.56	−4.11	−6.14	−5.11	−4.53	−5.46	−4.97	−4.46	−5.73	−5.44	−5.16	−4.16	>−4.00	>−4.00	−4.35	>−4.00	>−4.00
UACC-257	−4.79	−4.52	−4.25	−4.59	>−4.00	>−4.00	−4.89	−4.57	−4.26	−5.46	−4.97	−4.56	−5.34	−4.80	−4.36	−5.69	−5.37	−5.05	−4.71	−4.43	−4.16	>−4.00	>−4.00	>−4.00
UACC-62	−4.83	−4.53	−4.23	−5.27	−4.51	>−4.00	−4.89	−4.58	−4.27	−5.09	−4.81	−4.53	−4.85	−4.51	−4.17	−4.81	−4.53	−4.25	>−4.00	>−4.00	>−4.00	−4.20	>−4.00	>−4.00
Ovarian cancer																								
IGROV1	−4.89	−4.57	−4.25	−5.06	−4.25	>−4.00	−4.94	−4.39	>−4.00	−5.04	>−4.30	>−4.30	−5.71	−5.23	−4.53	−5.51	>−4.00	>−4.00	>−4.00	>−4.00	>−4.00	−4.60	>−4.00	>−4.00
OVCAR-3	−5.65	−5.11	−4.41	−5.73	−5.34	>−4.00	−5.88	−5.48	−5.07	−5.94	−5.47	−4.74	−5.58	−5.16	−4.50	−5.62	−5.19	>−4.00	−4.31	>−4.00	>−4.00	−4.83	−4.14	>−4.00
OVCAR-4	−5.09	−4.67	−4.32	−7.85	−6.01	−5.49	−5.57	−5.13	−4.28	–	–	–	−4.93	>−4.00	>−4.00	−5.77	−5.09	−4.22	–	−4.10	>−4.00	−5.43	−4.61	>−4.00
OVCAR-5	−4.68	−4.34	>−4.00	−5.23	−4.53	>−4.00	−4.68	−4.38	−4.09	−4.67	>−4.30	>−4.30	−4.62	−4.39	−4.16	−5.58	−5.12	>−4.00	>−4.00	>−4.00	>−4.00	−4.02	>−4.00	>−4.00
OVCAR-8	−4.83	−4.40	>−4.00	−5.55	−5.09	>−4.00	−5.17	−4.47	>−4.00	−5.16	−4.83	−4.50	−5.47	−4.87	>−4.00	−5.58	−5.22	−4.66	>−4.00	>−4.00	>−4.00	−4.49	>−4.00	>−4.00
SK-OV-3	–	−4.24	>−4.00	−4.82	−4.27	>−4.00	−4.66	−4.33	>−4.00	−5.27	−4.86	−4.44	−4.73	−4.44	−4.16	−4.89	−4.58	−4.27	>−4.00	>−4.00	>−4.00	−4.59	−4.26	>−4.00

(*continued on next page*)

Table 2 (*continued*)

Cell lines	Respnse parameters: (A) log GI_{50}[b] [M], (B) log TGI[c] [M], (C) log LC_{50}[d] [M]																								
	1b			**2b**			**3b**			**4b**			**5b**			**6b**			**7b**			**1c**		
	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C
Renal cancer																								
786-0	−4.82	−4.38	>−4.00	−4.90	−4.35	>−4.00	−4.81	−4.46	−4.12	−4.81	>−4.30	>−4.30	−4.88	−4.52	−4.15	−4.63	−4.21	>−4.00	>−4.00	>−4.00	>−4.00	−4.61	>−4.00	>−4.00
A498	>−4.00	>−4.00	>−4.00	−4.04	>−4.00	>−4.00	–	–	–	−5.20	−4.83	−4.47	−4.76	−4.49	−4.22	−4.77	−4.51	−4.24	>−4.00	>−4.00	>−4.00	−4.31	>−4.00	>−4.00
ACHN	−4.83	−4.47	−4.12	−5.03	−4.32	>−4.00	−4.86	−4.48	−4.09	−5.27	−4.95	−4.63	–	–	–	−5.77	−5.51	−5.25	>−4.00	>−4.00	>−4.00	−4.44	>−4.00	>−4.00
CAKI-1	−4.79	−4.44	−4.10	−4.80	>−4.00	>−4.00	−4.95	−4.61	−4.27	−5.72	−5.06	−4.50	−4.88	−4.28	>−4.00	−4.82	−4.43	−4.05	>−4.00	>−4.00	>−4.00	−4.10	>−4.00	>−4.00
RXF393	−5.27	−4.74	−4.35	−5.22	−4.23	>−4.00	−4.72	>−4.00	>−4.00	−5.13	−4.70	>−4.30	−5.51	−4.77	>−4.00	−4.91	−4.57	−4.22	>−4.00	>−4.00	>−4.00	−4.70	−4.13	>−4.00
SN12C	−4.77	−4.46	−4.16	−4.94	>−4.00	>−4.00	–	–	–	−5.06	−4.78	−4.49	−5.22	−4.62	−4.06	−5.12	−4.63	−4.19	>−4.00	>−4.00	>−4.00	−4.30	>−4.00	>−4.00
TK-10	−4.55	−4.24	>−4.00	−4.61	−4.20	>−4.00	−4.78	−4.49	−4.19	−5.20	−4.75	>−4.30	−4.89	−4.52	−4.14	−5.23	−4.70	−4.27	>−4.00	>−4.00	>−4.00	−4.27	>−4.00	>−4.00
UO-31	−4.94	−4.54	−4.14	−5.39	>−4.00	>−4.00	−4.87	−4.34	>−4.00	−4.95	>−4.30	>−4.30	−5.38	>−4.00	>−4.00	−5.42	>−4.00	>−4.00	>−4.00	>−4.00	>−4.00	−4.55	>−4.00	>−4.00
Prostate cancer																								
PC-3	−4.99	−4.56	−4.14	−5.52	−4.84	>−4.00	−5.08	−4.56	−4.08	−5.66	>−4.30	>−4.30	−5.76	−5.29	−4.72	−5.46	−4.81	>−4.00	>−4.00	>−4.00	>−4.00	−4.82	>−4.00	>−4.00
DU-145	−4.66	−4.24	>−4.00	−4.53	>−4.00	>−4.00	−460	−4.06	>−4.00	−5.28	−4.70	>−4.30	−4.79	−4.48	−4.16	−5.82	−5.42	−5.01	>−4.00	>−4.00	>−4.00	−4.16	>−4.00	>−4.00
Brest cancer																								
MCF-7	−4.88	−4.58	−4.27	−5.08	>−4.00	>−4.00	−4.59	>−4.00	>−4.00	−5.81	>−4.30	>−4.30	−4.91	−4.27	>−4.00	−5.52	>−4.00	>−4.00	>−4.00	>−4.00	>−4.00	−4.32	>−4.00	>−4.00
NCI/ADR-RES	−4.64	−4.08	>−4.00	−5.26	−4.48	>−4.00	−4.75	−4.18	>−4.00	−4.99	−4.66	−4.33	−4.76	−4.34	>−4.00	−5.61	−5.24	−4.55	>−4.00	>−4.00	>−4.00	−4.22	>−4.00	>−4.00
MDA-MB-231/ ATCC	−5.54	−4.86	−4.19	−5.68	−5.22	>−4.00	−4.95	−4.53	−4.10	−5.14	−4.82	−4.50	−5.80	−5.35	>−4.00	−5.67	−5.29	−4.71	−4.58	>−4.00	>−4.00	−4.69	−4.19	>−4.00
HS 578T	−4.57	>−4.00	>−4.00	−5.07	>−4.00	>−4.00	−4.47	>−4.00	>−4.00	−5.52	−4.48	>−4.30	−5.23	−4.33	>−4.00	−5.31	>−4.00	>−4.00	>−4.00	>−4.00	>−4.00	−4.61	>−4.00	>−4.00
MDA-MB-435	−5.00	−4.66	−4.33	−5.67	−5.37	–	−5.71	−5.39	−5.07	−6.64	−6.04	−5.54	−5.56	−5.12	−4.28	−5.70	−5.43	−5.16	−4.18	>−4.00	>−4.00	−4.39	>−4.00	>−4.00
MDA-N	−4.85	−4.56	−4.27	−5.63	−5.28	>−4.00	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	−4.45	>−4.00	>−4.00
BT-549	−5.19	−4.51	>−4.00	−5.01	>−4.00	>−4.00	−4.87	−4.49	−4.10	−5.42	−4.95	−4.56	–	–	–	−5.77	−5.49	−5.20	>−4.00	>−4.00	>−4.00	−4.49	>−4.00	>−4.00
T-47D	−5.55	−4.96	−4.14	−5.78	−5.34	>−4.00	−5.35	>−4.00	>−4.00	–	–	–	−4.71	−4.26	>−4.00	–	–	–	–	–	–	−4.82	−4.01	>−4.00
MG_MID	−4.87	−4.45	−4.14	−5.23	−4.48	−4.05	−5.01	−4.44	−4.11	−5.42	−4.76	−4.41	−5.21	−4.65	−4.18	−5.34	−4.79	−4.34	−4.26	−4.07	−4.02	−4.51	−4.09	−4.00

– cell line not tested.

[a] Data obtained from the NCI's in vitro disease-oriented human tumor cells screen (see Refs. [38–43]).

[b] The log of the molar concentration that inhibits 50% net cell growth.

[c] The log of the molar concentration giving total growth inhibition.

[d] The log of the molar concentration leading to 50% net cell death.

Table 3
Inhibition of in vitro cancer lines by selected 5,7-diamino-3-phenyl-2-anylino-quinoxalines, **2–7c**, **1d**, **3d**, **4d**, **5d**[a]

Cell lines	Response parameters: (A) log GI_{50}[b] [M], (B) log TGI[c] [M], (C) log LC_{50}[d] [M]																										
	2c			**5c**			**6c**			**7c**			**1d**			**3d**			**4d**			**5d**		
	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C
Leukemia																								
CCRF-CEM	−5.71	−5.06	−4.10	−5.53	>−4.00	>−4.00	–	–	–	−4.91	>−4.00	>−4.00	−5.64	−5.08	>−4.00	−5.60	>−4.00	>−4.00	–	–	–	−5.38	>−4.00	>−4.00
HL-60(TB)	−5.51	−4.59	>−4.00	−5.29	>−4.00	>−4.00	−4.73	−4.19	>−4.00	−4.50	−4.02	>−4.00	−5.37	>−4.00	>−4.00	−5.10	>−4.00	>−4.00	−4.41	>−4.00	>−4.00	−6.53	>−4.00	>−4.00
K-562	−5.42	−4.49	>−4.00	−5.45	>−4.00	>−4.00	−4.96	>−4.00	>−4.00	–	–	–	−5.01	>−4.00	>−4.00	−4.80	>−4.00	>−4.00	−4.40	−4.41	>−4.00	<−8.00	−4.61	>−4.00
RPMI-8226	−5.54	−5.07	−4.34	−5.46	>−4.00	>−4.00	−4.91	−4.33	>−4.00	>−4.00	>−4.00	>−4.00	−5.40	−4.07	>−4.00	−5.42	−4.50	>−4.00	−4.55	−4.09	>−4.00	−6.47	>−4.00	>−4.00
SR	−5.73	−4.54	>−4.00	−4.47	−4.62	>−4.00	−5.09	>−4.00	>−4.00	–	–	–	–	–	–	−5.33	−4.45	>−4.00	−4.45	>−4.00	>−4.00	−5.11	−4.09	>−4.00
MOLT-4	–	–	–	−5.20	>−4.00	>−4.00	−5.18	>−4.00	>−4.00	−4.41	>−4.00	>−4.00	−5.38	>−4.00	>−4.00	−5.39	>−4.00	>−4.00	>−4.00	>−4.00	>−4.00	–	>−4.00	>−4.00
Non-small cell lung cancer																								
A549/ATCC	−5.54	−4.88	−4.44	−4.74	−4.36	>−4.00	−4.62	−4.33	−4.05	>−4.00	>−4.00	>−4.00	−4.37	>−4.00	>−4.00	−4.87	−4.28	>−4.00	−4.87	−4.51	−4.15	−4.69	>−4.00	>−4.00
EKVX	−5.42	−4.71	−4.31	−5.67	−5.08	−4.38	−4.83	−4.47	−4.11	−4.21	>−4.00	>−4.00	–	–	–	–	–	–	−4.69	−4.38	−4.08	−4.73	−4.22	>−4.00
HOP-62	−5.67	−4.89	−4.45	−4.77	−4.42	−4.07	−4.67	−4.31	>−4.00	−4.44	−4.06	>−4.00	>−4.00	>−4.00	>−4.00	−4.91	−4.11	>−4.00	−4.78	−4.46	−4.15	−4.81	−4.07	>−4.00
HOP-92	−5.87	−5.05	−4.20	–	–	–	−4.91	−4.53	−4.14	−4.52	>−4.00	>−4.00	–	–	–	–	–	–	−4.64	−4.26	>−4.00	−5.42	−4.63	−4.09
NCI-H226	−5.18	−4.37	>−4.00	−4.82	−4.31	>−4.00	−4.69	−4.31	>−4.00	−5.53	−4.60	>−4.00	–	–	>−4.00	>−4.00	−5.04	>−4.00	−4.72	−4.33	>−4.00	−4.75	−4.36	>−4.00
NCI-H23	−5.77	−4.90	−4.45	−4.81	−4.40	>−4.00	−4.68	−4.40	−4.11	−4.81	−4.52	−4.22	>−4.00	>−4.00	>−4.00	−4.90	−4.46	−4.02	−4.72	−4.40	−4.09	−4.93	−4.47	−4.02
NCI-H322M	−5.65	−4.82	−4.22	−4.67	−4.23	>−4.00	−4.77	−4.43	−4.09	−4.17	>−4.00	>−4.00	−4.45	>−4.00	>−4.00	−5.15	−4.45	>−4.00	−4.69	−4.42	−4.15	−4.46	>−4.00	>−4.00
NCI-H460	−5.53	−4.90	−4.45	−4.74	−4.15	>−4.00	−4.40	>−4.00	>−4.00	−4.02	>−4.00	>−4.00	−4.70	>−4.00	>−4.00	−4.98	−4.47	>−4.00	−4.66	−4.18	>−4.00	−4.56	>−4.00	>−4.00
NCI-H522	−6.05	−5.37	−4.67	−5.08	−4.47	>−4.00	−4.19	>−4.00	>−4.00	−4.56	>−4.00	>−4.00	−5.49	>−4.00	>−4.00	−5.12	−4.47	>−4.00	>−4.00	>−4.00	>−4.00	−4.67	>−4.00	>−4.00
Colon cancer																								
COLO 205	−4.97	−4.65	−4.33	−4.69	−4.17	>−4.00	−4.70	−4.44	−4.18	−4.52	>−4.00	>−4.00	−4.71	>−4.00	>−4.00	−4.97	−4.47	>−4.00	−4.66	−4.32	>−4.00	−4.55	>−4.00	>−4.00
HCC-2998	−5.60	−4.86	−4.39	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	−5.33	−4.77	−4.15
HCT-116	−5.63	−5.00	−4.50	−4.80	−4.32	>−4.00	−4.83	−4.09	>−4.00	−4.82	−4.54	−4.27	−4.83	>−4.00	>−4.00	−5.03	−4.32	>−4.00	−4.83	−4.55	−4.26	−4.67	>−4.00	>−4.00
HCT-15	−5.69	−4.91	−4.37	−4.70	>−4.00	>−4.00	−4.44	>−4.00	>−4.00	−4.46	>−4.00	>−4.00	–	–	–	–	–	–	−4.87	−4.56	−4.25	−4.87	−4.37	>−4.00
HT29	−5.36	−4.75	−4.37	–	–	–	−4.64	−4.29	>−4.00	–	–	–	–	–	–	–	–	–	−4.75	−4.34	>−4.00	−5.02	>−4.00	>−4.00
KM12	−5.99	−5.22	−4.58	−5.20	−4.40	>−4.00	−4.84	−4.39	>−4.00	−4.56	>−4.00	>−4.00	−4.55	>−4.00	>−4.00	−4.95	>−4.00	>−4.00	−4.68	−4.31	>−4.00	−4.62	>−4.00	>−4.00
SW-620	−5.65	−4.99	−4.50	−5.01	−4.52	−4.04	−4.71	−4.30	>−4.00	−4.53	>−4.00	>−4.00	−4.58	>−4.00	>−4.00	−4.68	−4.08	>−4.00	−4.64	−4.30	>−4.00	−4.93	>−4.00	>−4.00
CNS cancer																								
SF-268	−5.76	−5.15	−4.57	−4.77	−4.28	>−4.00	−4.86	−4.32	>−4.00	−4.39	>−4.00	>−4.00	>−4.00	>−4.00	>−4.00	−4.86	−4.29	>−4.00	−4.75	−4.41	−4.07	−4.79	−4.35	>−4.00
SF-295	−5.66	−5.07	−4.40	−4.86	−4.51	−4.16	−4.69	−4.41	−4.14	−4.39	>−4.00	>−4.00	>−4.00	>−4.00	>−4.00	−4.75	−4.22	>−4.00	−4.86	−4.52	−4.19	−4.60	>−4.00	>−4.00
SF-539	–	–	–	−4.87	−4.53	−4.19	−4.74	−4.45	−4.15	−4.47	>−4.00	>−4.00	−5.00	>−4.00	>−4.00	−4.84	−4.38	>−4.00	−4.67	−4.40	−4.12	–	–	–
SNB-19	−5.60	−4.90	−4.45	−4.68	−4.28	>−4.00	−4.76	−4.47	−4.18	−4.50	>−4.00	>−4.00	>−4.00	>−4.00	>−4.00	−4.77	−4.24	>−4.00	−4.70	−4.38	−4.06	−4.25	>−4.00	>−4.00
SNB-75	−6.90	−5.57	−4.92	–	–	–	−4.63	−4.31	>−4.00	–	–	–	–	–	–	–	–	–	−4.68	−4.32	>−4.00	−4.49	−4.20	>−4.00
U251	−5.58	−4.97	−4.48	−4.92	−4.50	−4.08	−4.63	−4.10	>−4.00	>−4.00	>−4.00	>−4.00	>−4.00	>−4.00	>−4.00	−4.99	>−4.00	>−4.00	−4.79	−4.50	−4.21	−4.84	>−4.00	>−4.00
Melanoma																								
LOX IMVI	−5.53	−4.89	−4.44	−4.79	−4.47	−4.14	−4.36	>−4.00	>−4.00	−4.92	−4.58	−4.24	−4.29	>−4.00	>−4.00	−5.13	−4.61	−4.14	−4.64	−4.39	−4.13	−5.52	−5.07	>−4.00
MALME-3M	−6.37	−5.29	−4.52	−4.80	−4.43	−4.05	–	–	–	−4.73	−4.45	−4.18	−4.48	−4.02	>−4.00	−4.71	−4.30	>−4.00	–	–	–	−4.71	−4.43	−4.15
M14	−5.80	−5.11	−4.54	−4.85	−4.15	>−4.00	−4.77	−4.35	>−4.00	−4.40	>−4.00	>−4.00	>−4.00	>−4.00	>−4.00	−4.49	>−4.00	>−4.00	−4.80	−4.51	−4.23	−4.48	>−4.00	>−4.00
SK-MEL-2	−5.64	−4.99	−4.42	−5.25	−4.63	−4.05	−4.37	>−4.00	>−4.00	−4.39	>−4.00	>−4.00	–	>−4.00	>−4.00	−5.21	−4.51	>−4.00	−4.42	>−4.00	>−4.00	−4.72	−4.20	>−4.00
SK-MEL-28	−5.50	−4.81	−4.41	−4.67	−4.19	>−4.00	−4.71	−4.33	>−4.00	−4.84	−4.52	−4.19	−4.61	>−4.00	>−4.00	−4.86	−4.24	>−4.00	−4.63	−4.27	>−4.00	−5.17	−4.47	>−4.00
SK-MEL-5	−5.72	−5.19	−4.61	−5.01	−4.54	−4.08	−4.91	−4.50	−4.08	−4.74	−4.27	>−4.00	−4.62	>−4.00	>−4.00	−4.67	−4.02	>−4.00	−4.81	−4.48	−4.15	−4.90	−4.49	−4.07
UACC-257	−5.66	−4.91	−4.43	−4.55	−4.06	>−4.00	−4.63	−4.37	−4.11	−4.57	−4.26	>−4.00	−4.36	>−4.00	>−4.00	−4.75	−4.23	>−4.00	−4.78	−4.50	−4.22	−4.76	−4.39	−4.02
UACC-62	−5.39	−4.74	−4.32	−4.79	−4.32	>−4.00	−4.80	−4.48	−4.16	−4.79	−4.51	−4.23	−4.42	>−4.00	>−4.00	−5.17	−4.37	>−4.00	−4.78	−4.50	−4.22	−4.75	−4.41	−4.06
Ovarian cancer																								
IGROV1	−5.58	−4.91	−4.42	−4.94	−4.49	−4.04	−4.55	>−4.00	>−4.00	−4.74	−4.10	>−4.00	–	>−4.00	>−4.00	−5.53	−4.56	>−4.00	−4.60	>−4.00	>−4.00	−5.32	>−4.00	>−4.00
OVCAR-3	−5.65	−5.06	−4.26	−4.97	−4.57	−4.18	−4.81	−4.38	>−4.00	−4.79	−4.39	>−4.00	–	>−4.00	>−4.00	−4.93	−4.33	>−4.00	−4.79	−4.47	−4.16	−4.91	−4.42	>−4.00
OVCAR-4	−5.54	−4.79	−4.23	−4.48	>−4.00	>−4.00	−5.08	−4.45	>−4.00	−4.45	>−4.00	>−4.00	–	>−4.00	>−4.00	−4.70	>−4.00	>−4.00	−4.64	−4.25	>−4.00	−4.78	−4.27	>−4.00
OVCAR-5	−5.49	−4.79	−4.39	−4.60	−4.23	>−4.00	−4.69	−4.32	>−4.00	−4.10	>−4.00	>−4.00	>−4.00	>−4.00	>−4.00	−4.41	−4.23	−4.04	−4.72	−4.34	>−4.00	−4.22	>−4.00	>−4.00
OVCAR-8	−5.54	−4.79	−4.30	−4.55	−4.05	>−4.00	−4.65	−4.32	−4.00	−4.42	>−4.00	>−4.00	>−4.00	>−4.00	>−4.00	−4.61	>−4.00	>−4.00	−4.78	−4.46	−4.14	−4.92	−4.40	>−4.00
SK-OV-3	−5.46	−4.79	−4.16	−4.62	−4.18	>−4.00	−4.68	−4.38	−4.08	−4.55	−4.01	>−4.00	−4.48	>−4.00	>−4.00	−4.83	−4.40	>−4.00	−4.80	−4.50	−4.20	−4.75	−4.35	>−4.00

(*continued on next page*)

Table 3 (*continued*)

Cell lines	Response parameters: (A) log GI_{50}[b] [M], (B) log TGI[c] [M], (C) log LC_{50}[d] [M]																										
	2c			**5c**			**6c**			**7c**			**1d**			**3d**			**4d**			**5d**					
	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C			
Renal cancer																											
786-0	−5.66	−4.94	−4.47	−4.71	−4.39	−4.06	−4.80	−4.44	−4.08	−4.05	>−4.00	>−4.00	−4.28	>−4.00	>−4.00	−4.66	−4.04	>−4.00	–	−4.64	−4.31	−4.21	>−4.00	>−4.00			
A498	−5.71	−4.84	>−4.00	−6.35	−4.91	−4.36	−4.66	−4.40	−4.15	–	–	–	>−4.00	>−4.00	>−4.00	−4.66	−4.03	>−4.00	−4.56	−4.34	−4.11	–	–	–			
ACHN	−5.37	−4.75	−4.29	–	–	–	−4.66	−4.07	>−4.00	−4.55	>−4.00	>−4.00	–	–	–	–	–	–	−4.85	−4.56	−4.27	−4.84	−4.08	>−4.00			
CAKI-1	−5.38	−4.62	>−4.00	−4.84	−4.44	−4.05	−4.71	−4.43	−4.15	−4.31	>−4.00	>−4.00	−5.01	>−4.00	>−4.00	−4.85	−4.39	>−4.00	−4.74	−4.44	−4.13	−4.72	−5.52	−4.71			
RXF393	−5.99	−5.36	−4.69	−4.60	−4.07	>−4.00	−4.68	−4.33	>−4.00	−4.36	>−4.00	>−4.00	>−4.00	>−4.00	>−4.00	−4.85	−4.25	>−4.00	−4.88	−4.53	−4.19	−5.52	−4.71	−4.02			
SN12C	−5.36	−4.65	−4.06	−4.84	−4.50	−4.17	−4.71	−4.28	>−4.00	–	–	–	>−4.00	>−4.00	>−4.00	−4.63	>−4.00	>−4.00	−4.75	−4.45	−4.15	−4.75	−4.35	>−4.00			
TK-10	−5.76	−5.07	−4.53	−4.75	−4.42	−4.09	−4.69	−4.33	>−4.00	>−4.00	>−4.00	>−4.00	−4.51	>−4.00	>−4.00	−4.84	−4.50	−4.16	−4.76	−4.37	>−4.00	−4.51	>−4.00	>−4.00			
UO-31	−5.46	−4.82	−4.34	−4.88	−4.22	>−4.00	−4.53	>−4.00	>−4.00	−4.31	>−4.00	>−4.00	>−4.00	>−4.00	>−4.00	−4.85	−4.12	>−4.00	−4.49	>−4.00	>−4.00	−4.64	>−4.00	>−4.00			
Prostate cancer																											
PC-3	−5.41	−4.76	−4.19	−4.81	>−4.00	>−4.00	−5.14	−4.33	>−4.00	−4.13	>−4.00	>−4.00	−5.19	>−4.00	>−4.00	−5.24	−4.44	>−4.00	−4.53	>−4.00	>−4.00	−4.77	>−4.00	>−4.00			
DU-145	−5.34	−4.60	−4.01	−5.00	−4.57	−4.13	−4.76	−4.43	−4.10	−4.21	>−4.00	>−4.00	−4.84	>−4.00	>−4.00	−4.95	−4.60	−4.25	−4.70	−4.42	−4.15	−4.42	>−4.00	>−4.00			
Brest cancer																											
MCF-7	−5.77	−5.34	−4.84	−4.85	−4.15	>−4.00	−4.69	>−4.00	>−4.00	−4.27	>−4.00	>−4.00	−4.78	>−4.00	>−4.00	−5.28	−4.42	>−4.00	−4.70	−4.20	>−4.00	−5.24	>−4.00	>−4.00			
NCI/ADR-RES	−5.95	−5.41	−4.74	−4.93	−4.44	>−4.00	−4.74	−4.44	−4.15	−4.56	>−4.00	>−4.00	>−4.00	>−4.00	>−4.00	−4.72	−4.22	>−4.00	−4.78	−4.46	−4.14	−4.67	>−4.00	>−4.00			
MDA-MB-231/ATCC	−5.40	−4.66	−4.06	−4.99	−4.58	−4.18	−5.41	−4.54	>−4.00	−4.95	−4.49	−4.03	>−4.00	>−4.00	>−4.00	−4.78	−4.27	>−4.00	−4.76	−4.42	−4.08	−5.10	−4.45	>−4.00			
HS 578T	−5.88	−5.38	−4.59	−4.97	−4.47	>−4.00	−4.70	−4.27	>−4.00	−4.36	>−4.00	>−4.00	>−4.00	>−4.00	>−4.00	−4.52	>−4.00	>−4.00	−4.57	−4.21	>−4.00	−4.86	−4.12	>−4.00			
MDA-MB-435	−6.41	−5.74	−5.30	−5.30	−4.68	−4.03	−4.80	−4.49	−4.17	−4.52	>−4.00	>−4.00	>−4.00	>−4.00	>−4.00	−4.74	−4.22	>−4.00	−4.79	−4.48	−4.18	−4.95	−4.47	>−4.00			
MDA-N	−6.12	−5.65	−5.27	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–			
BT-549	−5.83	−5.16	−4.42	–	–	–	−4.82	−4.46	−4.09	−4.47	>−4.00	>−4.00	–	–	–	–	–	–	−4.66	−4.36	−4.05	−5.20	−4.28	>−4.00			
T-47D	−5.63	−5.04	−4.29	−4.61	−4.10	>−4.00	–	–	–	–	–	–	>−4.00	>−4.00	>−4.00	−4.88	>−4.00	>−4.00	–	–	–	−4.54	>−4.00	>−4.00			
MG_MID	−5.66	−4.96	−4.40	−4.93	−4.34	−4.05	−4.74	−4.29	−4.04	−4.48	−4.11	−4.03	−4.48	−4.02	−4.00	−4.93	−4.27	−4.01	−4.67	−4.33	−4.09	−4.88	−4.21	−4.01			

– cell line not tested.

[a] Data obtained from the NCI's in vitro disease-oriented human tumor cells screen (see Refs. [38–43]).

[b] The log of the molar concentration that inhibits 50% net cell growth.

[c] The log of the molar concentration giving total growth inhibition.

[d] The log of the molar concentration leading to 50% net cell death.

Table 4
The in vitro selectivity towards leukemia cell lines for compounds **7b** and **5d**

Compound	Leukemia cell lines	log GI_{50}[a] [M]	Selectivity towards leukemia cell lines (Δ) for log GI_{50}[b]	Mean value for all tested cell lines (MG_MID)[c] for log GI_{50} [M]
7b	SR	−6.30	2.04	−4.26
	HL-60(TB)	−5.64	1.38	
	MOLT-4	−5.74	1.48	
5d	HL-60(TB)	−6.53	1.65	−4.88
	K-562	<−8.00	3.12	
	RPMI-8226	−6.47	1.59	

[a] The log of the molar concentration that inhibits 50% net cell growth, data obtained from the NCI's in vitro disease-oriented human tumor cells screen (see Refs. [19–21]).

[b] The reported data represent the logarithmic difference between the parameter values referred to the leukemia cell line and the same mean graph midpoint, Δ is considered low <1, moderate >1 and >3, high if >3.

[c] MG_MID = mean graph midpoint = arithmetical mean value for all tested cancer cell lines.

4.1.2.1.7. N-*[4-[(5,7-Dinitro-3-phenylquinoxalin-2-ylamino)methyl]benzoyl]glutamic acid diethyl ester (**33**) [44].* This compound was obtained in 29% yield by the protocol described in the general procedure starting from **8** (150 mg, 0.45 mmol) and *N*-[4(aminomethyl)benzoyl]glutamic acid diethyl ester (**15**) [34] (454 mg, 1.35 mmol) for 168 h; m.p. 301–303 °C (from C_3H_8O); TLC (petroleum ether/ethyl acetate 4:6): R_f 0.30; IR (nujol): ν 3370, 3320, 1720, 1645, 1620, 1525, 1410, 1350 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.73 (1H, d, $J = 2.4$ Hz, H-6), 8.48 (1H, d, $J = 2.2$ Hz, H-8), 7.90–7.79 (4H, m, Ar), 7.60 (3H, d, $J = 7.8$ Hz, Ar), 7.45 (2H, d, $J = 8.2$ Hz, Ar), 7.09 (1H, d, $J = 7.4$ Hz, exc. with D_2O, CONH), 6.17 (1H, t, exc. with D_2O, $NHCH_2$), 4.86 (2H, d, $J = 5.6$ Hz, $NHCH_2$), 4.86–4.70 (1H, m, CH), 4.23 (2H, q, $J = 7.2$ Hz, CH_2), 4.11 (2H, q, $J = 7.2$ Hz, CH_2), 2.60–2.02 (4H, m, CH_2CH_2), 1.30 (3H, t, $J = 7.2$ Hz, CH_3), 1.23 (3H, t, $J = 7.2$ Hz, CH_3). ^{13}C NMR ($CDCl_3$): δ 14 (2 × CH_3), 26.3 (CH_2), 30.3 (CH_2), 43.3 (CH_2), 52.8 (CH), 61.2 (2 × CH_2), 116 (CH), 126.3 (CH), 126.9 (2 × CH), 127.3 (2 × CH), 127.6 (2 × CH), 128.6 (CH), 129.1 (2 × CH), 130 (C), 132.3 (C), 135.4 (C), 138.3 (C), 141.5 (C), 143 (C), 143.4 (C), 147 (C), 154.3 (C), 167.3 (C), 171.3 (C), 173 (C). GC/MS: *m/z* 630 $[M]^+$. Anal. Calcd. for $C_{31}H_{30}N_6O_9$: C, 59.04; H, 4.80; N, 13.33; found C, 59.10; H, 4.72; N, 13.20.

Table 5
Antitumor activity (log GI_{50} (MG_MID)) comparison between compounds **1**–**7b**, **5** and **1**–**5d** and the corresponding 2-anylino derivatives **1**–**7a** previously reported [33]

	MG_MID log GI_{50}		MG_MID log GI_{50}
Series 2-benzylamino		*Series 2-anylino*	
1b	−4.87	**1a** [33]	−4.73
2b	−5.23	**2a** [33]	−5.04
3b	−5.01	**3a** [33]	−4.72
4b	−5.42	**4a** [33]	−4.90
5b	−5.21	**5a** [33]	−5.08
6b	−5.34	**6a** [33]	−4.82
7b	−4.26	**7a** [33]	−4.87
Series 2-phenoxy			
1c	−4.51	**1a** [33]	−4.73
2c	−5.66	**2a** [33]	−5.04
3c	–	**3a** [33]	−4.72
4c	No tested	**4a** [33]	−4.90
5c	−4.93	**5a** [33]	−5.08
6c	−4.74	**6a** [33]	−4.82
7c	−4.48	**7a** [33]	−4.87
Series 2-thiophenyl			
1d	−4.48	**1a** [33]	−4.73
2d	–	**3a** [33]	−4.72
3d	−4.93	**5a** [33]	−5.08
4d	−4.67	**6a** [33]	−4.82
5d	−4.88	**7a** [33]	−4.87

– no evaluated in the full panel of 60 cell lines.

*4.1.2.2. General procedure for preparation of 5,7-dinitro-3-phenyl-2-phenoxy substituted quinoxalines (**34**–**40**) and 5,7-dinitro-3-phenyl-2-thiophenol substituted quinoxalines (**41**–**44**).* A mixture of equimolar amounts (150 mg, 0.45 mmol) of **8** and the corresponding phenols (**16**–**22**) or thiophenols (**23**–**26**) (0.45 mmol) in anhydrous DMF (5 mL) in the presence of one mole equivalent of Cs_2CO_3 was stirred at 70 °C or at room temperature (**35**, **40**) for the time reported below. Then, water was added to give solids which were filtered off or solutions which were extracted several times with $CHCl_3$. The crude products were purified by flash chromatography using a mixture of petroleum ether/ethyl acetate as eluent in different ratios or by recrystallization as reported below.

*4.1.2.2.1. 5,7-Dinitro-3-phenyl-2-[(4-methoxy)phenoxy]quinoxaline (**34**).* This compound was obtained in 97% yield by the protocol described in the general procedure starting from **8** (150 mg, 0.45 mmol), 4-methoxyphenol (**16**) (56 mg, 0.45 mmol) and Cs_2CO_3 (147 mg, 0.45 mmol) at 70 °C for 2 h; m.p. 201–202 °C (from CH_3CN); TLC (petroleum ether/ethyl acetate 8:2): R_f 0.5; IR (nujol): ν 1600, 1535, 1345 cm^{-1}; UV (EtOH): λ_{max} 345, 206 nm; ^1H NMR ($CDCl_3$): δ 8.78 (1H, d, $J = 2$ Hz, H-6), 8.71 (1H, d, $J = 2$ Hz, H-8), 8.50–8.38 (2H, m, Ar), 7.68–7.50 (3H, m, Ar), 7.20 (2H, d, $J = 9$ Hz, Ar), 7.02 (2H, d, $J = 9$ Hz, Ar), 3.66 (3H, s, CH_3). GC/MS: *m/z* 418 $[M]^+$. Anal. Calcd. for $C_{21}H_{14}N_4O_6$: C, 60.29; H, 3.37; N, 13.39; found C, 60.18; H, 3.29; N, 13.20.

*4.1.2.2.2. 5,7-Dinitro-3-phenyl-2-[(3,5-dimethoxy)phenoxy]quinoxaline (**35**).* This compound was obtained in 88% yield by the protocol described in the general procedure starting from **8** (150 mg, 0.45 mmol), 3,5-dimethoxyphenol (**17**) (69 mg, 0.45 mmol) and Cs_2CO_3 (147 mg, 0.45 mmol) under a N_2 atmosphere at room temperature for 6 h and 30 min; the compound was purified by silica gel column chromatography eluting with a 8:2 mixture of petroleum ether/ethyl acetate; m.p. 169–171 °C (from CH_3CN); TLC (petroleum ether/ethyl acetate 8:2): R_f 0.43; IR (nujol): ν 1625, 1535, 1345 cm^{-1}; UV (EtOH): λ_{max} 364, 203 nm; ^1H NMR ($CDCl_3$): δ 8.84 (1H, d, $J = 2.8$ Hz, H-6), 8.74 (1H, d, $J = 2.8$ Hz, H-8), 8.48–8.36 (2H, m, Ar), 7.65–7.53 (3H, m, Ar), 6.50–6.40 (3H, m, Ar), 3.83 (6H, s, 2 × CH_3). GC/MS: *m/z* 448 $[M]^+$. Anal. Calcd. for $C_{22}H_{16}N_4O_7$: C, 58.93; H, 3.60; N, 12.50; found C, 58.75; H, 3.49; N, 12.33.

*4.1.2.2.3. 5,7-Dinitro-3-phenyl-2-[(3,4-dimethoxy)phenoxy]quinoxaline (**36**) [44].* This compound was obtained in 61% yield by the protocol described in the general procedure starting from **8** (150 mg, 0.45 mmol), 3,4-dimethoxyphenol (**18**) (69 mg, 0.45 mmol) and Cs_2CO_3 (147 mg, 0.45 mmol) at 70 °C for 4 h and 40 min; m.p. 192–194 °C (from CH_3CN); TLC (petroleum ether/ethyl acetate 7:3): R_f 0.41; IR (nujol): ν 1600, 1510, 1340 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.80 (1H, d, $J = 2.4$ Hz, H-6), 8.73 (1H, d, $J = 2.4$ Hz, H-8), 7.45–7.40 (2H, m, Ar), 7.64–7.56 (3H, m, Ar), 6.99 (1H, d, $J = 8.8$ Hz, Ar), 6.86 (1H, d, $J = 2.6$ Hz, Ar), 6.83–6.77 (1H, m, Ar), 3.96 (3H, s, CH_3), 3.90 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$): δ 56 (2 × CH_3), 108.3 (CH), 115.8 (CH), 116.2 (CH), 118 (CH), 127.3 (2 × CH), 128.2 (CH), 128.6 (CH), 129.1 (2 × CH), 131.6 (C), 132 (C), 139.5 (C), 142.5 (C), 144 (C), 145.8 (C), 148.4 (C), 150 (C), 150.6 (C), 175 (C). GC/MS: *m/z* 448 $[M]^+$. Anal. Calcd. for $C_{22}H_{16}N_4O_7$: C, 58.93; H, 3.60; N, 12.50; found C, 58.76; H, 3.58; N, 12.30.

*4.1.2.2.4. 5,7-Dinitro-3-phenyl-2-[(3,4,5-trimethoxy)phenoxy]quinoxaline (**37**).* This compound was obtained in 93% yield by the protocol described in the general procedure starting from **8** (150 mg, 0.45 mmol), 3,4,5-trimethoxyphenol (**19**) (83 mg, 0.45 mmol) and Cs_2CO_3 (147 mg, 0.45 mmol) at 70 °C for 1 h and 40 min; the compound was purified by silica gel column chromatography eluting with a 9:1 mixture of petroleum ether/ethyl acetate; m.p. 230–231 °C (from CH_3CN); TLC (petroleum ether/ethyl

acetate 8:2): R_f 0.33; IR (nujol): ν 1625, 1535, 1345 cm^{-1}; UV (EtOH): λ_{max} 364, 203 nm; ^1H NMR ($CDCl_3$): δ 8.84 (1H, d, $J = 2.4$ Hz, H-6), 8.72 (1H, d, $J = 2.4$ Hz, H-8), 8.42 (2H, dd, $J = 1.4$ and $J = 7$ Hz, Ar), 7.68–7.57 (3H, m, Ar), 6.50 (2H, m, Ar), 3.93 (3H, s, CH_3), 3.87 (6H, s, $2 \times CH_3$). GC/MS: m/z 478 $[M]^+$. Anal. Calcd. for $C_{23}H_{18}N_4O_8$: C, 57.74; H, 3.79; N, 11.71; found C, 57.86; H, 3.66; N; 11.60.

*4.1.2.2.5. 5,7-Dinitro-3-phenyl-2-[(3,4-dichloro)phenoxy]quinoxaline (**38**).* This compound was obtained in 98% yield by the protocol described in the general procedure starting from **8** (150 mg, 0.45 mmol), 3,4-dichlorophenol (**20**) (73 mg, 0.45 mmol) and Cs_2CO_3 (147 mg, 0.45 mmol) at 70 °C for 1 h; m.p. 196–198 °C (from CH_4O); TLC (petroleum ether/ethyl acetate 8:2): R_f 0.63; IR (nujol): ν 1625, 1535, 1345 cm^{-1}; UV (EtOH): λ_{max} 364, 203 nm; ^1H NMR ($CDCl_3$/DMSO-d_6): δ 9.02 (1H, d, $J = 2.2$ Hz, H-6), 8.74 (1H, d, $J = 2.4$ Hz, H-8), 8.27 (2H, dd, $J = 2.0$ and $J = 6.6$ Hz, Ar), 7.84 (1H, d, $J = 2.6$ Hz, Ar), 7.78 (1H, d, $J = 8.8$ Hz, Ar), 7.69–7.58 (3H, m, Ar), 7.48 (1H, dd, $J = 8.8$ Hz and $J = 2.8$ Hz, Ar). GC/MS: m/z 456 $[M]^+$. Anal. Calcd. for $C_{20}H_{10}Cl_2N_4O_5$: C, 52.54; H, 2.20; N, 12.25; found C, 52.33; H, 2.13; N, 12.23.

*4.1.2.2.6. 5,7-Dinitro-3-phenyl-2-[(4-fluoro)phenoxy]quinoxaline (**39**).* This compound was obtained in 88% yield by the protocol described in the general procedure starting from **8** (150 mg, 0.45 mmol), 4-fluorophenol (**21**) (50 mg, 0.45 mmol) and Cs_2CO_3 (147 mg, 0.45 mmol) at 70 °C for 2 h; m.p. 248–249 °C (from CH_3CN); TLC (cyclohexane/ethyl acetate 9:1): R_f 0.35; IR (nujol): ν 1580, 1530, 1350 cm^{-1}; UV (EtOH): λ_{max} 308, 236, 226, 203 nm; ^1H NMR ($CDCl_3$/DMSO-d_6): δ 8.81 (1H, d, $J = 2.2$ Hz, H-6), 8.74 (1H, d, $J = 2.4$ Hz, H-8), 8.50–8.30 (2H, m, Ar), 7.71–7.50 (3H, m, Ar), 7.41–7.13 (4H, m, Ar). GC/MS: m/z 406 $[M]^+$. Anal. Calcd. for $C_{20}H_{11}FN_4O_5$: C, 59.12; H, 2.73; N, 13.79; found C, 59.01; H, 2.50; N, 13.58.

*4.1.2.2.7. N-[4-(5,7-Dinitro-3-phenylquinoxalin-2-yloxy)benzoyl] glutamic acid diethyl ester (**40**) [44].* This compound was obtained in 50% yield by the protocol described in the general procedure starting from **8** (150 mg, 0.45 mmol), *N*-[4-(hydroxy)benzoyl]glutamic acid diethyl ester (**22**) [35] (145 mg, 0.45 mmol) and Cs_2CO_3 (147 mg, 0.45 mmol) under a N_2 atmosphere at room temperature for 9 h and 45 min; m.p. 227–228 °C (from C_2H_6O); TLC (petroleum ether/ethyl acetate 6:4): R_f 0.41; IR (nujol): ν 3320, 1745, 1640, 1600, 1540, 1350 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.81–8.75 (2H, m, H-6, 8), 8.42 (2H, dd, $J = 6$ Hz and $J = 2.4$ Hz, Ar), 8.02 (2H, d, $J = 8.8$ Hz, Ar), 7.66–7.55 (3H, m, Ar), 7.35 (2H, d, $J = 8.8$ Hz, Ar), 7.23 (1H, d, $J = 7.4$ Hz, exc. with H_2O, CONH), 4.90–4.78 (1H, m, CH), 4.28 (2H, q, $J = 7.2$ Hz, CH_2), 4.15 (2H, q, $J = 7.2$ Hz, CH_2), 2.60–2.10 (4H, m, CH_2CH_2), 1.30 (3H, t, $J = 7.2$ Hz, CH_3), 1.22 (3H, t, $J = 7.2$ Hz, CH_3). ^{13}C NMR ($CDCl_3$): δ 14 ($2 \times CH_3$), 26.3 (CH_2), 30.4 (CH_2), 52.5 (CH), 61.2 ($2 \times CH_2$), 118 (CH), 121.3 ($2 \times$ CH), 127.4 ($2 \times$ CH), 128.2 (CH), 128.4 ($2 \times$ CH), 128.7 (CH), 129.1 ($2 \times$ CH), 130.1 (C), 131.5 (C), 132 (C), 139.5 (C), 142.5 (C), 144 (C), 151 (C), 158.3 (C), 167.5 (C), 171.4 (C), 173 (C), 176 (C). GC/MS: m/z 617 $[M]^+$. Anal. Calcd. for $C_{30}H_{27}N_5O_{10}$: C, 58.35; H, 4.41; N, 11.34; found C, 58.66; H, 4.47; N, 11.13.

*4.1.2.2.8. 5,7-Dinitro-3-phenyl-2-[(4-methoxy)phenylthio]quinoxaline (**41**).* This compound was obtained in 96% yield by the protocol described in the general procedure starting from **8** (150 mg, 0.45 mmol), 4-methoxythiophenol (**23**) (63 mg, 0.45 mmol) and Cs_2CO_3 (147 mg, 0.45 mmol) at 70 °C for 2 h; m.p. 192–193 °C (from CH_3CN); TLC (petroleum ether/ethyl acetate 8:2): R_f 0.53; IR (nujol): ν 1625, 1535, 1345 cm^{-1}; UV (EtOH): λ_{max} 366, 203 nm; ^1H NMR ($CDCl_3$): δ 8.71 (1H, d, $J = 2.2$ Hz, H-6), 8.69 (1H, d, $J = 2.4$ Hz, H-8), 8.10–8.00 (2H, m, Ar), 7.70–7.55 (3H, m, Ar), 7.46 (2H, d, $J = 8.8$ Hz, Ar), 7.03 (2H, d, $J = 8.8$ Hz, Ar), 3.91 (3H, s, CH_3). GC/MS: m/z 434 $[M]^+$. Anal. Calcd. for $C_{21}H_{14}N_4O_5S$: C, 58.06; H, 3.25; N, 12.90; found C, 57.98; H, 3.15; N, 12.70.

*4.1.2.2.9. 5,7-Dinitro-3-phenyl-2-[(3,4-dimethoxy)phenylthio]quinoxaline (**42**) [44].* This compound was obtained in 81% yield by the protocol described in the general procedure starting from **8** (150 mg, 0.45 mmol), 3,4-dimethoxythiophenol (**24**) (77 mg, 0.45 mmol) and Cs_2CO_3 (147 mg, 0.45 mmol) at 70 °C for 30 min; m.p. 196–198 °C (from CH_3CN); TLC (petroleum ether/ethyl acetate 7:3): R_f 0.47; IR (nujol): ν 1580, 1530, 1350 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.78–8.70 (2H, m, H-6, 8), 8.09–8.00 (2H, m, Ar), 7.68–7.55 (3H, m, Ar), 7.16 (1H, dd, $J = 1.4$ Hz and $J = 8.4$ Hz, Ar), 7.01 (1H, d, $J = 1.8$ Hz, Ar), 7.00 (1H, d, $J = 9.8$ Hz, Ar), 3.99 (3H, s, CH_3), 3.89 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$): δ 56 ($2 \times CH_3$), 111.5 (CH), 115 (CH), 118.2 (CH), 120 (CH), 127.2 ($2 \times$ CH), 128.6 (CH), 129.1 ($2 \times$ CH), 129.5 (CH), 129.8 (CH), 133 (C), 137 (CH), 139.1 (C), 141.5 (C), 148.1 (C), 150 (C), 150.2 (C), 152 (C), 155 (C). GC/MS: m/z 464 $[M]^+$. Anal. Calcd. for $C_{22}H_{16}N_4O_6S$: C, 56.89; H, 3.47; N, 12.06; found C, 56.59; H, 3.97; N, 11.76.

*4.1.2.2.10. 5,7-Dinitro-3-phenyl-2-[(3,4-dichloro)phenylthio]quinoxaline (**43**).* This compound was obtained in 81% yield by the protocol described in the general procedure starting from **8** (150 mg, 0.45 mmol), 3,4-dichlorothiophenol (**25**) (81 mg, 0.45 mmol) and Cs_2CO_3 (147 mg, 0.45 mmol) at 70 °C for 45 min; the compound was purified by silica gel column chromatography eluting with a 95:5 and 1:1 mixture of petroleum ether/ethyl acetate; m.p. 195–197 °C (from CH_3CN); TLC (petroleum ether/ethyl acetate 8:2): R_f 0.63; IR (nujol): ν 1570, 1530, 1350 cm^{-1}; UV (EtOH): λ_{max} 366, 203 nm; ^1H NMR ($CDCl_3$/DMSO-d_6): δ 8.79 (1H, d, $J = 2.4$ Hz, H-6), 8.75 (1H, d, $J = 2.4$ Hz, H-8), 8.08–7.95 (2H, m, Ar), 7.71 (1H, d, $J = 2$ Hz, Ar), 7.70–7.58 (4H, m, Ar), 7.46 (1H, dd, $J = 8.4$ Hz and $J = 2.2$ Hz, Ar). GC/MS: m/z 471 $[M]^+$. Anal. Calcd. for $C_{20}H_{10}Cl_2N_4O_4S$: C, 50.75; H, 2.13; N, 11.84; found C, 50.30; H, 2.00; N, 11.70.

*4.1.2.2.11. 5,7-Dinitro-3-phenyl-2-[(4-fluoro)phenylthio]quinoxaline (**44**).* This compound was obtained in 68% yield by the protocol described in the general procedure starting from **8** (150 mg, 0.45 mmol), 4-fluorothiophenol (**26**) (58 mg, 0.45 mmol) and Cs_2CO_3 (147 mg, 0.45 mmol) at 70 °C for 30 min; m.p. 162–164 °C (from CH_3CN); TLC (petroleum ether/ethyl acetate 8:2): R_f 0.35; IR (nujol): ν 1580, 1530, 1360 cm^{-1}; UV (EtOH): λ_{max} 389, 298, 237, 205 nm; ^1H NMR ($CDCl_3$): δ 8.71 (2H, s, Ar), 8.10–7.99 (2H, m, Ar), 7.70–7.50 (5H, m, Ar), 7.30–7.18 (2H, m, Ar). GC/MS: m/z 422 $[M]^+$. Anal. Calcd. for $C_{20}H_{11}FN_4O_4S$: C, 56.87; H, 2.62; N, 13.26; found C, 56.60; H, 2.43; N, 13.00.

*4.1.2.3. N-[4(5,7-Dinitro-3-phenylquinoxalin-2-ylthio)-benzoyl]glutamic acid diethyl ester (**46**).* Compound **45** (304 mg, 0.45 mmol), prepared as previously reported in the literature [36,37] was reduced in absolute EtOH (5 mL) with $NaBH_4$ (33 mg, 0.9 mmol) at room temperature. When the reduction was completed (30 min), 5,7-dinitro-3-phenyl-2-chloroquinoxaline (**8**) [33] (298 mg, 0.9 mmol) in 3 mL was added. The mixture was stirred under a N_2 atmosphere at room temperature for 1 h. After removal of the solvent *in vacuo*, the residue was suspended in water (22 mL) and the solid residue was collected by filtration and purified by flash chromatography over silica gel eluting with a 7:3 mixture of petroleum ether/ethyl acetate (31% yield); m.p. 160–161 °C (from C_3H_8O); TLC (petroleum ether/ethyl acetate 1:1): R_f 0.40; IR (nujol): ν 3300, 1720, 1640, 1530, 1350 cm^{-1}; UV (EtOH): λ_{max} 388, 222, 201 nm; ^1H NMR ($CDCl_3$): δ 8.73 (2H, s, H-6, 8), 8.10–8.00 (2H, m, Ar), 7.97 (2H, d, $J = 8.2$ Hz, Ar), 7.66 (2H, d, $J = 8.2$ Hz, Ar), 7.65–7.58 (3H, m, Ar), 4.82–4.79 (1H, m, OCH–CH_2), 4.28 (2H, q, CH_2CH_3), 4.15 (2H, q, CH_2CH_3), 2.70–2.10 (4H, m, CH_2CH_2), 1.30 (3H, t, CH_2CH_3), 1.25 (3H, t, CH_2CH_3). ^{13}C NMR ($CDCl_3$): δ 14.2 ($2 \times CH_3$), 26.4 (CH_2), 30.3 (CH_2), 52.5 (CH), 61.1 ($2 \times CH_2$), 121 (CH), 127.3 ($2 \times$ CH), 127.6 ($2 \times$ CH), 128.5 (CH), 129.8 (CH), 129.4 ($2 \times$ CH), 129.1 ($2 \times$ CH), 131 (C), 133 (C), 135 (C), 137 (C), 139.2 (C), 141.6 (C), 148 (C), 150.2 (C), 152 (C), 167.5 (C), 171.5 (C), 173.2 (C). GC/MS: m/z 633 $[M]^+$. Anal. Calcd. for $C_{30}H_{27}N_5O_9S$: C, 56.87; H, 4.30; N, 11.05; found C, 56.51; H, 4.08; N, 10.88.

*4.1.2.4. General procedure for preparation of 5,7-diamino-quinoxalines **1–3b**, **5–7b**, **1–5c**, **7c** and **1–5d**.* A mixture of **27–29**, **31–38**, **40–44** and **46** (0.28–0.82 mmol) and an excess of hydrazine hydrate

(2.40–12.3 mmol) in ethanol (12–181 mL) in the presence of 10% palladised charcoal was refluxed for the time reported below. The desired compounds were obtained by filtration of the palladised charcoal and evaporation *in vacuo* of the solvent. The crude solids were purified either by recrystallization or by flash chromatography over silica gel as reported below.

*4.1.2.4.1. 5,7-Diamino-3-phenyl-2-[(4-methoxy-benzyl)amino]quinoxaline (**1b**).* This compound was obtained in 97% yield by the protocol described in the general procedure starting from **27** (340 mg, 0.8 mmol), hydrazine hydrate (320 mg, 6.4 mmol) and palladised charcoal (34 mg) in ethanol (181 mL) after 1 h and 35 min under reflux; m.p. 74–77 °C (from $CH_4O + H_2O$); TLC (petroleum ether/ethyl acetate 4:6): R_f 0.40; IR (nujol): ν 3420, 3350, 1630 cm^{-1}; UV (EtOH): λ_{max} 359, 332, 285 nm; ^1H NMR ($CDCl_3$): δ 7.69 (2H, dd, $J = 8$ Hz and $J = 1.8$ Hz, Ar), 7.51–7.40 (3H, m, Ar), 7.28 (2H, d, $J = 8.4$ Hz, Ar), 6.85 (2H, d, $J = 8.6$ Hz, Ar), 6.33 (1H, d, $J = 2.2$ Hz, H-8), 6.10 (1H, d, $J = 2.2$ Hz, H-6), 5.24 (2H, t, exc. with D_2O, NH–CH_2), 4.66 (2H, d, NH–CH_2), 3.78 (3H, s, OCH_3). GC/MS: *m/z* 371 $[M]^+$. Anal. Calcd. for $C_{22}H_{21}N_5O$: C, 71.14; H, 5.70; N, 18.85; found C, 71.00; H, 5.22; N, 18.60.

*4.1.2.4.2. 5,7-Diamino-3-phenyl-2-[(3,5-dimethoxy-benzyl)amino]quinoxaline (**2b**).* This compound was obtained in 77% yield by the protocol described in the general procedure starting from **28** (150 mg, 0.32 mmol), hydrazine hydrate (130 mg, 2.6 mmol) and palladised charcoal (15 mg) in ethanol (70 mL) after 2 h under reflux; m.p. 161–163 °C (from $CH_4O + H_2O$); TLC (petroleum ether/ethyl acetate 6:4): R_f 0.31; IR (nujol): ν 3440, 3340, 1610 cm^{-1}; UV (EtOH): λ_{max} 382, 296, 270, 226, 204 nm; ^1H NMR ($CDCl_3$): δ 7.71 (2H, dd, $J = 7.8$ Hz and $J = 1.8$ Hz, Ar), 7.56–7.42 (3H, m, Ar), 6.51 (2H, d, $J = 2.2$ Hz, Ar), 6.37–6.30 (2H, m, Ar), 6.10 (1H, d, $J = 2.4$ Hz, H-8), 5.30 (1H, t, exc. with D_2O, NH), 4.68 (2H, d, CH_2), 3.76 (6H, s, $2 \times OCH_3$). GC/MS: *m/z* 401 $[M]^+$. Anal. Calcd. for $C_{23}H_{23}N_5O_2$: C, 68.81; H, 5.77; N, 17.44; found C, 68.74; H, 5.53; N, 17.24.

*4.1.2.4.3. 5,7-Diamino-3-phenyl-2-[(3,4-dimethoxy-benzyl)amino]quinoxaline (**3b**) [44].* This compound was obtained in 61% yield by the protocol described in the general procedure starting from **29** (150 mg, 0.32 mmol), hydrazine hydrate (240 mg, 4.8 mmol) and palladised charcoal (15 mg) in ethanol (21 mL) after 30 min under reflux; m.p. 105–108 °C (from C_2H_6O); TLC (petroleum ether/ethyl acetate 3:7): R_f 0.36; IR (nujol): ν 3420, 3340, 1610 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.71 (2H, dd, $J = 8.0$ Hz and $J = 2$ Hz, Ar), 7.53–7.41 (3H, m, Ar), 6.92 (1H, d, $J = 3$ Hz, Ar), 6.90 (1H, dd, $J = 8.0$ Hz and $J = 2.0$ Hz, Ar), 6.80 (1H, d, $J = 8$ Hz, Ar), 6.33 (1H, d, $J = 2.4$ Hz, H-8), 6.08 (1H, d, $J = 2.4$ Hz, H-6), 5.26 (1H, t, exc. with D_2O, NH), 4.73 (2H, br s, exc. with D_2O, NH_2), 4.66 (2H, d, CH_2), 3.88 (2H, br s, exc. with D_2O, NH_2), 3.86 (3H, s, OCH_3), 3.85 (3H, s, OCH_3). ^{13}C NMR ($CDCl_3$): δ 43.3 (CH_2), 56.0 ($2 \times CH_3$), 98 (CH), 109.1 (CH), 112.1 (CH), 118 (C), 120.1 (CH), 125.0 (CH), 127.4 ($2 \times$ CH), 128.6 (CH), 129.0 ($2 \times$ CH), 131 (C), 133.3 (C), 135.0 (C), 141 (C), 142.5 (C), 145 (C), 147.6 (C), 149.3 (C), 149.7 (C). GC/MS: *m/z* 401 $[M]^+$. Anal. Calcd. for $C_{23}H_{23}N_5O_2$: C, 68.81; H, 5.77; N, 17.44; found C, 68.72; H, 5.54; N, 17.15.

*4.1.2.4.4. 5,7-Diamino-3-phenyl-2-[(3,4-dichloro-benzyl)amino]quinoxaline (**5b**).* This compound was obtained in 38% yield by the protocol described in the general procedure starting from **31** (300 mg, 0.64 mmol), hydrazine hydrate (480 mg, 9.6 mmol) and palladised charcoal (30 mg) in ethanol (32 mL) after 10 min under reflux; m.p. 81–84 °C (from $CH_4O + H_2O$); TLC (petroleum ether/ethyl acetate 5:5): R_f 0.36; IR (nujol): ν 3440, 3340, 1610 cm^{-1}; UV (EtOH): λ_{max} 382, 296, 270, 226, 204 nm; ^1H NMR ($CDCl_3$): δ 7.70 (2H, dd, $J = 8.0$ Hz and $J = 1.6$ Hz, Ar), 7.60–7.42 (3H, m, Ar), 7.40–7.10 (3H, m, Ar), 6.28 (1H, d, $J = 2.4$ Hz, H-8), 6.08 (1H, d, $J = 2.2$ Hz, H-6), 5.28 (1H, t, exc. with D_2O, NH), 4.67 (2H, d, CH_2), 3.90–3.80 (2H, br s, exc. with D_2O, NH_2). LC/MS: *m/z* 410 $[M + H]$. Anal. Calcd. for $C_{21}H_{17}Cl_2N_5$: C, 61.47; H, 4.18; N, 17.07; found C, 61.32; H, 4.01; N, 16.90.

*4.1.2.4.5. 5,7-Diamino-3-phenyl-2-[(4-fluoro-benzyl)amino]quinoxaline (**6b**).* This compound was obtained in 22% yield by the protocol described in the general procedure starting from **32** (200 mg, 0.48 mmol), hydrazine hydrate (360 mg, 7.2 mmol) and palladised charcoal (20 mg) in ethanol (25 mL) after 10 min under reflux; m.p. 82–85 °C (from $CH_4O + H_2O$); TLC (petroleum ether/ethyl acetate 6:4): R_f 0.42; IR (nujol): ν 3440, 3340, 1610 cm^{-1}; UV (EtOH): λ_{max} 382, 296, 270, 226, 204 nm; ^1H NMR ($CDCl_3$): δ 7.69 (2H, dd, $J = 7.8$ Hz and $J = 1.6$ Hz, Ar), 7.58–7.40 (3H, m, Ar), 7.48–7.22 (2H, m, Ar), 7.18–6.90 (2H, t, Ar), 6.31 (1H, d, $J = 2.2$ Hz, H-8), 6.08 (1H, d, $J = 2.2$ Hz, H-6), 5.30 (1H, t, exc. with D_2O, NH–CH_2), 4.69 (2H, d, CH_2). LC/MS: *m/z* 360 $[M + H]$. Anal. Calcd. for $C_{21}H_{18}FN_5$: C, 70.18; H, 5.05; N, 19.49; found C, 70.00; H, 4.96; N, 19.39.

4.1.2.4.6. N-*[4-[(5,7-Diamino-3-phenylquinoxalin-2-ylamino)methyl]benzoyl]glutamic acid diethyl ester (**7b**) [44].* This compound was obtained in 78% yield by the protocol described in the general procedure starting from **33** (150 mg, 0.24 mmol), hydrazine hydrate (180 mg, 3.6 mmol) and palladised charcoal (15 mg) in ethanol (16 mL) after 10 min under reflux; m.p. 72–75 °C (from $C_3H_8O + H_2O$); TLC (petroleum ether/ethyl acetate 3:7): R_f 0.36; IR (nujol): ν 3460, 3340, 1735, 1640, 1600 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.81 (2H, d, $J = 8$ Hz, Ar), 7.71 (2H, dd, $J = 8.2$ Hz and $J = 2$ Hz, Ar), 7.48–7.41 (3H, m, Ar), 7.42 (2H, d, $J = 8.4$ Hz, Ar), 7.01 (1H, d, $J = 7.2$ Hz, exc. with D_2O, CONH), 6.28 (1H, d, $J = 2.2$ Hz, H-8), 6.08 (1H, d, $J = 2.2$ Hz, H-6), 5.36 (1H, t, exc. with D_2O, NH), 4.82–4.64 (1H, m, CH), 4.78 (2H, d, CH_2), 4.23 (2H, q, CH_2), 4.10 (2H, q, CH_2), 3.88 (2H, br s, exc. with D_2O, NH_2), 2.61–2.41 (4H, m, CH_2CH_2), 1.30 (3H, t, $J = 7.2$ Hz, CH_3), 1.21 (3H, t, $J = 7.2$ Hz, CH_3). ^{13}C NMR ($CDCl_3$): δ 14.0 ($2 \times CH_3$), 26.3 (CH_2), 30.3 (CH_2), 43.1 (CH_2), 52.1 (CH), 61.2 ($2 \times CH_2$), 98 (CH), 117 (C), 125.3 (CH), 127.0 ($2 \times$ CH), 127.2 ($2 \times$ CH), 127.4 ($2 \times$ CH), 128.5 (CH), 129.1 ($2 \times$ CH), 130 (C), 132.2 (C), 135.3 (C), 141 (C), 142.5 (C), 143.3 (C), 145 (C), 149.6 (C), 167.5 (C), 171.5 (C), 173.1 (C). GC/MS: *m/z* 570 $[M]^+$. Anal. Calcd. for $C_{31}H_{34}N_6O_5$: C, 65.25; H, 6.01; N, 14.73; found: C, 65.03; H, 45.95; N, 14.54.

*4.1.2.4.7. 5,7-Diamino-3-phenyl-2-[(4-methoxy)phenoxy]quinoxaline (**1c**).* This compound was obtained in 92% yield by the protocol described in the general procedure starting from **34** (290 mg, 0.69 mmol), hydrazine hydrate (311 mg, 6.2 mmol) and palladised charcoal (29 mg) in ethanol (160 mL) after 5 h and 15 min under reflux; m.p. 189–191 °C (from $CH_4O + H_2O$); TLC (petroleum ether/ethyl acetate 1:1): R_f 0.35; IR (nujol): ν 3440, 3340, 1610 cm^{-1}; UV (EtOH): λ_{max} 382, 296, 270, 226, 204 nm; ^1H NMR ($CDCl_3$): δ 8.15 (2H, dd, $J = 7.8$ Hz and $J = 1.6$ Hz, Ar), 7.55–7.39 (3H, m, Ar), 7.13 (2H, d, $J = 9$ Hz, Ar), 6.93 (2H, d, $J = 9$ Hz, Ar), 6.26 (1H, d, $J = 2.2$ Hz, H-8), 6.06 (1H, d, $J = 2.2$ Hz, H-6), 5.38 (2H, br s, exc. with D_2O, NH_2), 4.90 (2H, br s, exc. with D_2O, NH_2), 3.83 (3H, s, OCH_3). LC/MS: *m/z* 359 $[M + H]$. Anal. Calcd. for $C_{21}H_{18}N_4O_2$: C, 70.38; H, 5.06; N, 15.63; found C, 70.01; H, 4.96; N, 15.23.

*4.1.2.4.8. 5,7-Diamino-3-phenyl-2-[(3,5-dimethoxy)phenoxy]quinoxaline (**2c**).* This compound was obtained in 71% yield by the protocol described in the general procedure starting from **35** (360 mg, 0.8 mmol), hydrazine hydrate (320 mg, 6.4 mmol) and palladised charcoal (36 mg) in ethanol (181 mL) after 1 h; m.p. 159–160 °C (from $CH_4O + H_2O$); TLC (petroleum ether/ethyl acetate 4:6): R_f 0.49; IR (nujol): ν 3420, 3320, 1610, 1220 cm^{-1}; UV (EtOH): λ_{max} 379, 295, 270, 226, 204 nm; ^1H NMR ($CDCl_3$): δ 8.15 (2H, dd, $J = 6.4$ Hz and $J = 1.2$ Hz, Ar), 7.57–7.42 (3H, m, Ar), 6.41 (2H, d, $J = 2.2$ Hz, Ar), 6.35 (1H, d, $J = 2.2$ Hz, Ar), 6.31 (1H, d, $J = 2.2$ Hz, H-6), 6.24 (1H, d, $J = 2.2$ Hz, H-8), 5.38 (2H, br s, exc. with D_2O, NH_2), 4.90 (2H, br s, exc. with D_2O, NH_2), 3.78 (6H, s, $2 \times OCH_3$). LC/MS: *m/z* 389 $[M + H]$. Anal. Calcd. for $C_{22}H_{20}N_4O_3$: C, 68.03; H, 5.19; N, 14.42; found C, 67.98; H, 5.00; N, 14.22.

*4.1.2.4.9. 5,7-Diamino-3-phenyl-2-[(3,4-dimethoxy)phenoxy]quinoxaline (**3c**) [44].* This compound was obtained in 69% yield by the protocol described in the general procedure starting from **36** (300 mg, 0.7 mmol), hydrazine hydrate (526 mg, 10.5 mmol) and palladised charcoal (30 mg) in ethanol (25 mL) after 20 min; m.p.

195–198 °C (from $CH_4O + H_2O$); TLC (petroleum ether/ethyl acetate 4:6): R_f 0.31; IR (nujol): ν 3440, 3380, 1610 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.19 (2H, dd, $J = 8.2$ Hz and $J = 1.8$ Hz, Ar), 7.57–7.40 (3H, m, Ar), 6.90 (1H, d, $J = 9.4$ Hz, Ar), 6.83–6.75 (2H, m, Ar), 6.25 (1H, d, $J = 2.2$ Hz, H-8), 6.21 (1H, d, $J = 2.2$ Hz, H-6), 4.91 (2H, br s, exc. with D_2O, NH_2), 3.94 (3H, s, OCH_3), 3.86 (3H, s, OCH_3). ^{13}C NMR ($CDCl_3$): δ 56.3 (CH_3), 101 (CH), 108.4 (CH), 115.9 (CH), 116.2 (CH), 120 (C), 126.9 (CH), 127.4 (2 × CH), 128.7 (2 × CH), 129.2 (2 × CH), 130 (C), 131.6 (C), 142 (C), 143.6 (C), 145.7 (C), 147 (C), 148.3 (C), 150.8 (C), 170 (C). LC/MS: m/z 389 [M + H]. Anal. Calcd. for $C_{22}H_{20}N_4O_3$: C, 68.03; H, 5.19; N, 14.42; found C, 67.98; H, 5.00; N, 14.22.

*4.1.2.4.10. 5,7-Diamino-3-phenyl-2-[(3,4,5-trimethoxy)phenoxy]quinoxaline (**4c**).* This compound was obtained in 65% yield by the protocol described in the general procedure starting from **37** (350 mg, 0.7 mmol), hydrazine hydrate (526 mg, 10.5 mmol) and palladised charcoal (35 mg) in ethanol (26 mL) after 10 min; m.p. 203–205 °C (from CH_4O); TLC (petroleum ether/ethyl acetate 4:6): R_f 0.35; IR (nujol): ν 3420, 3320, 1610, 1220 cm^{-1}; UV (EtOH): λ_{max} 379, 295, 269, 223, 204 nm; ^1H NMR ($CDCl_3$): δ 8.17 (2H, dd, $J = 8.4$ Hz and $J = 2$ Hz, Ar), 7.57–7.40 (3H, m, Ar), 6.49 (2H, s, Ar), 6.29 (1H, d, $J = 2.4$ Hz, H-8), 6.24 (1H, d, $J = 2.4$ Hz, H-6), 4.93 (2H, br s, exc. with D_2O, NH_2), 3.98 (2H, br s, exc. with D_2O, NH_2), 3.87 (3H, s, OCH_3), 3.83 (6H, s, 2 × OCH_3). GC/MS: m/z 418 $[M]^+$. Anal. Calcd. for $C_{23}H_{22}N_4O_4$: C, 66.02; H, 5.30; N, 13.39; found C, 65.97; H, 5.35; N, 13.15.

*4.1.2.4.11. 5,7-Diamino-3-phenyl-2-[(3,4-dichloro)phenoxy]quinoxaline (**5c**).* This compound was obtained in 86% yield by the protocol described in the general procedure starting from **38** (150 mg, 0.33 mmol), hydrazine hydrate (248 mg, 4.95 mmol) and palladised charcoal (15 mg) in ethanol (12 mL) after 10 min; m.p. 178–180 °C (from $CH_4O + H_2O$); TLC (petroleum ether/ethyl acetate 5:5): R_f 0.57; IR (nujol): ν 3420, 3320, 1610 cm^{-1}; UV (EtOH): λ_{max} 379, 293, 268, 223, 206 nm; ^1H NMR ($CDCl_3$): δ 8.11 (2H, dd, $J = 1.8$ Hz and $J = 7.8$ Hz, Ar), 7.58–7.42 (4H, m, Ar), 7.39 (1H, d, $J = 2.4$ Hz, Ar), 7.11 (1H, dd, $J = 2.8$ Hz and $J = 8.8$ Hz, Ar), 6.24 (2H, s, Ar), 4.93 (2H, br s, exc. with D_2O, NH_2), 4.00 (2H, br s, exc. with D_2O, NH_2). LC/MS: m/z 397 [M + H]. Anal. Calcd. for $C_{20}H_{14}Cl_2N_4O$: C, 60.47; H, 3.55; N, 14.10; found C, 60.20; H, 3.86; N, 13.86.

*4.1.2.4.12. N-[4-(5,7-Diamino-3-phenylquinoxalin-2-yloxy)benzoyl]glutamic acid diethyl ester (**7c**) [44].* This compound was obtained in 74% yield by the protocol described in the general procedure starting from **40** (300 mg, 0.48 mmol), hydrazine hydrate (360 mg, 7.2 mmol) and palladised charcoal (30 mg) in ethanol (32 mL) after 30 min; m.p. 178–181 °C (from CH_4O); TLC (petroleum ether/ethyl acetate 4:6): R_f 0.30; IR (nujol): ν 3420, 3320, 1740, 1635, 1600 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.14 (2H, dd, $J = 8.2$ Hz and $J = 2.6$ Hz, Ar), 7.89 (2H, d, $J = 8.8$ Hz, Ar), 7.59–7.40 (3H, m, Ar), 7.30 (2H, d, $J = 8.8$ Hz, Ar), 7.09 (1, d, $J = 7.4$ Hz, exc. with H_2O, CONH), 6.26–6.20 (2H, m, H-8, 6), 4.94 (2H, br s, exc. with H_2O, NH_2), 4.84–4.68 (1H, m, CH), 4.25 (2H, q, $J = 7.2$ Hz, CH_2), 4.13 (2H, q, $J = 7.2$ Hz, CH_2), 3.99 (2H, br s, exc. with H_2O, NH_2), 2.64–2.00 (4H, m, CH_2CH_2), 1.32 (3H, t, $J = 7.2$ Hz, CH_3), 1.25 (3H, t, $J = 7.2$ Hz, CH_3). ^{13}C NMR ($CDCl_3$): δ 14.0 (2 × CH_3), 26.3 (CH_2), 30.5 (CH_2), 52.7 (CH), 61.3 (2 × CH_2), 102 (CH), 120 (C), 121.6 (2 × CH), 126.3 (CH), 127.5 (2 × CH), 128.5 (2 × CH), 128.7 (CH), 129.2 (2 × CH), 130 (C), 130.4 (C), 131.6 (C), 143 (C), 143.6 (C), 147 (C), 158.3 (C), 167.5 (C), 171 (C), 171.5 (C), 173.0 (C). GC/MS: m/z 557 $[M]^+$. Anal. Calcd. for $C_{30}H_{31}N_5O_6$: C, 64.62; H, 5.60; N, 12.56; found C, 64.41; H, 5.35; N, 12.43.

*4.1.2.4.13. 5,7-Diamino-3-phenyl-2-[(4-methoxy)phenylthio]quinoxaline (**1d**).* This compound was obtained in 54% yield by the protocol described in the general procedure starting from **41** (150 mg, 0.34 mmol), hydrazine hydrate (135 mg, 2.7 mmol) and palladised charcoal (15 mg) in ethanol (50 mL) after 8 h and 30 min; m.p. 162–163 °C (from $CH_4O + H_2O$); TLC (petroleum ether/ethyl acetate 7:3): R_f 0.41; IR (nujol): ν 3480, 3300, 1600 cm^{-1}; UV (EtOH): λ_{max} 284, 257, 229, 202 nm; ^1H NMR ($CDCl_3$): δ 8.45 (2H, br s, exc. with D_2O, NH_2), 8.05 (1H, s, H-8), 7.98 (1H, s, H-6), 7.95–7.85 (2H, m, Ar), 7.68–7.55 (3H, m, Ar), 7.46 (2H, dd, $J = 2.8$ Hz, Ar), 7.00 (2H, d, $J = 8.8$ Hz, Ar), 5.62 (2H, br s, exc. with D_2O, NH_2), 3.90 (3H, s, OCH_3). LC/MS: m/z 375 [M + H]. Anal. Calcd. for $C_{21}H_{18}N_4OS$: C, 67.36; H, 4.85; N, 14.96; found C, 67.25; H, 4.66; N, 14.78.

*4.1.2.4.14. 5,7-Diamino-3-phenyl-2-[(3,4-dimethoxy)phenylthio]quinoxaline (**2d**) [44].* This compound was obtained in 33% yield by the protocol described in the general procedure starting from **42** (210 mg, 0.45 mmol), hydrazine hydrate (338 mg, 6.7 mmol) and palladised charcoal (21 mg) in ethanol (50 mL) 30 min; m.p. 192–195 °C (from CH_3CN); TLC (petroleum ether/ethyl acetate 6:4): R_f 0.43; IR (nujol): ν 3400, 3380, 1580 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.98 (2H, s, exc. with D_2O, NH_2), 8.49 (2H, br s, exc. with D_2O, NH_2), 8.00–7.88 (4H, m, Ar), 7.58–7.44 (3H, m, Ar), 7.18 (1H, dd, $J = 8.4$ Hz and $J = 2$ Hz, Ar), 7.03 (1H, d, $J = 1.8$ Hz, Ar), 6.98 (1H, d, $J = 9.8$ Hz, Ar), 3.96 (3H, s, CH_3), 3.87 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$): δ 56.0 (2 × CH_3), 103 (CH), 111.6 (CH), 115.0 (CH), 118.2 (CH), 126 (C), 127.3 (2 × CH), 128.4 (CH), 128.7 (CH), 129.2 (2 × CH), 129.9 (CH), 133.0 (C), 139 (C), 142.7 (C), 143 (C), 144 (C), 147 (C), 150.1 (C), 155.3 (C). GC/MS: m/z 404 $[M]^+$. Anal. Calcd. for $C_{22}H_{20}N_4O_2S$: C, 65.33; H, 4.98; N, 13.85; found C, 65.23; H, 4.76; N, 13.64.

*4.1.2.4.15. 5,7-Diamino-3-phenyl-2-[(3,4-dichloro)phenylthio]quinoxaline (**3d**).* This compound was obtained in 61% yield by the protocol described in the general procedure starting from **43** (150 mg, 0.32 mmol), hydrazine hydrate (240 mg, 4.8 mmol) and palladised charcoal (15 mg) in ethanol (40 mL) after 30 min; m.p. 178–180 °C (from $CH_4O + H_2O$); TLC (petroleum ether/ethyl acetate 7:3): R_f 0.38; IR (nujol): ν 3500, 3300, 1600 cm^{-1}; UV (EtOH): λ_{max} 286, 252, 204 nm; ^1H NMR ($CDCl_3$/DMSO-d_6): δ 9.03 (2H, br s, exc. with D_2O, NH_2), 8.52 (2H, br s, exc. with D_2O, NH_2), 7.96 (2H, s, Ar), 7.95–7.81 (2H, m, Ar), 7.68 (1H, d, $J = 2$ Hz, Ar), 7.69–7.50 (3H, m, Ar), 7.58 (1H, d, $J = 8.6$ Hz, Ar), 7.42 (1H, dd, $J = 8.8$ Hz and $J = 1.8$ Hz, Ar). LC/MS: m/z 413 [M + H]. Anal. Calcd. for $C_{20}H_{14}Cl_2N_4S$: C, 58.12; H, 3.41; N, 13.56; found C, 58.02; H, 3.23; N, 13.35.

*4.1.2.4.16. 5,7-Diamino-3-phenyl-2-[(4-fluoro)phenylthio]quinoxaline (**4d**).* This compound was obtained in 54% yield by the protocol described in the general procedure starting from **44** (150 mg, 0.35 mmol), hydrazine hydrate (260 mg, 5.2 mmol) and palladised charcoal (15 mg) in ethanol (85 mL) after 3 h; m.p. 163–165 °C (from $CH_4O + H_2O$); TLC (petroleum ether/ethyl acetate 7:3): R_f 0.45; IR (nujol): ν 3410, 3300, 1590 cm^{-1}; UV (EtOH): λ_{max} 370, 279, 246, 203 nm; ^1H NMR ($CDCl_3$): δ 8.10–8.00 (2H, m, Ar), 8.00–7.84 (2H, m, Ar), 7.71–7.50 (5H, m, Ar), 7.28–7.11 (2H, m, Ar), 4.80 (2H, br s, exc. with D_2O, NH_2). LC/MS: m/z 363 [M + H]. Anal. Calcd. for $C_{20}H_{15}FN_4S$: C, 66.28; H, 4.17; N, 15.46; found C, 66.04; H, 4.00; N, 15.37.

*4.1.2.4.17. N-[4(5,7-Diamino-3-phenylquinoxalin-2-ylthio)-benzoyl]glutamic acid diethyl ester (**5d**) [44].* This compound was obtained in 56% yield by the protocol described in the general procedure starting from **46** (180 mg, 0.28 mmol), hydrazine hydrate (210 mg, 4.2 mmol) and palladised charcoal (18 mg) in ethanol (20 mL) after 45 min; m.p. 103–105 °C (from $CH_4O + H_2O$); TLC (petroleum ether/ethyl acetate 1:1): R_f 0.51; IR (nujol): ν 3400, 3300, 1720, 1630 cm^{-1}; UV (EtOH): λ_{max} 288, 224, 203 nm; ^1H NMR ($CDCl_3$): δ 8.50 (2H, br s, exc. with D_2O, NH_2), 8.08–7.98 (2H, m, Ar), 7.92 (2H, $J = 8.4$ Hz, Ar), 7.91–7.85 (2H, m, Ar), 7.65 (2H, d, $J = 8.4$ Hz, Ar), 7.64–7.58 (3H, m, Ar), 7.24 (1H, d, exc. with D_2O, CONH), 5.94 (2H, br s, exc. with D_2O, NH_2), 4.81–4.91 (1H, m, CH), 4.27 (2H, q, CH_2CH_3), 4.14 (2H, q, CH_2CH_3), 2.61–2.10 (4H, m, CH_2CH_2), 1.33 (3H, t, CH_2CH_3), 1.25 (3H, t, CH_2CH_3). ^{13}C NMR ($CDCl_3$): δ 14.0 (2 × CH_3), 26.6 (CH_2), 30.4 (CH_2), 52.7 (CH), 61.2 (2 × CH_2), 104 (CH), 125 (C), 127.5 (2 × CH_2), 127.8 (2 × CH), 128.2 (CH), 128.7 (CH), 129.1 (2 × CH), 129.7 (2 × CH), 131 (C), 134 (C), 135 (C), 138 (C), 142.7 (C), 143 (C), 145 (C), 146 (C), 167.5 (C), 171.2 (C), 173.1 (C). LC/MS: m/z 574 [M + H]. Anal. Calcd. for $C_{30}H_{31}N_5O_5S$: C, 62.81; H, 5.45; N, 12.21; found C, 62.52; H, 5.23; N, 12.00.

*4.1.2.5. 5,7-Diamino-3-phenyl-2-[(3,4,5-trimethoxy-benzyl)amino]quinoxaline (**4b**).* Compound **30** (300 mg, 0.61 mmol) was dissolved in 100 mL of ethanol followed by the addition of 30 mg of 10% palladised charcoal. This mixture was hydrogenated at 3 atm for 1 h and 30 min. After filtering and washing the catalyst thoroughly with ethanol, the filtrate was concentrated *in vacuo*. The crude residue was then purified by flash chromatography over silica gel eluting with 3:7 petroleum ether/ethyl acetate (65% yield); m.p. 61–63 °C (from $CH_4O + H_2O$); TLC (petroleum ether/ethyl acetate 4:6): R_f 0.46; IR (nujol): ν 3420, 3300, 1600 cm^{-1}; UV (EtOH): λ_{max} 287, 223, 203 nm; ^1H NMR ($CDCl_3$): δ 7.71 (2H, dd, $J = 8$ Hz and $J = 4.2$ Hz, Ar), 7.58 (3H, m, Ar), 6.60 (2H, s, Ar), 6.32 (1H, d, $J = 2.4$ Hz, H-8), 6.08 (1H, d, $J = 2.4$ Hz, H-6), 5.28 (1H, t, exc. with D_2O, NH), 4.67 (2H, d, CH_2), 3.82 (9H, s, $3 \times OCH_3$). LC/MS: *m/z* 432 [M + H]. Anal. Calcd. for $C_{24}H_{25}N_5O_3$: C, 66.81; H, 5.84; N, 16.23; found C, 66.70; H, 5.76; N, 16.03.

*4.1.2.6. 5,7-Diamino-3-phenyl-2-[(4-fluoro)phenoxy]quinoxaline (**6c**).* Compound **39** (200 mg, 0.49 mmol) was dissolved in 100 mL of ethanol followed by the addition of 20 mg of 10% palladised charcoal. This mixture was hydrogenated at 3 atm for 1 h and 30 min. After filtering and washing the catalyst thoroughly with ethanol, the filtrate was concentrated *in vacuo*. Then the crude residue was purified by flash chromatography over silica gel eluting 1:1 petroleum ether/ethyl acetate (59% yield); m.p. 141–144 °C (from $CH_4O + H_2O$); TLC (petroleum ether/ethyl acetate 1:1): R_f 0.36; IR (nujol): ν 3420, 3300, 1600 cm^{-1}; UV (EtOH): λ_{max} 287, 223, 203 nm; ^1H NMR ($CDCl_3$): δ 8.17 (2H, dd, $J = 8.2$ Hz and $J = 2.4$ Hz, Ar), 7.58–7.38 (3H, m, Ar), 7.23–7.00 (4H, m, Ar), 6.22 (2H, s, H-6, 8), 4.91 (2H, br s, exc. with D_2O, NH_2), 3.94 (2H, br s, exc. with D_2O, NH_2). LC/MS: *m/z* 347 [M + H]. Anal. Calcd. for $C_{20}H_{15}FN_4O$: C, 69.35; H, 4.37; N, 16.18; found C, 69.25; H, 4.20; N, 16.02.

Acknowledgments

The authors are grateful to the staff of the Department of Health and Human Services, National Cancer Institute, Bethesda, MD, USA, for the anti-cancer screening.

References

[1] G. Schawartsmann, M.J. Ratain, G.M. Cragg, J.E. Wong, N. Saijo, D.R. Parkinson, Y. Fujiwara, R. Pazdur, D.J. Newman, R. Dagher, L. DiLeone, J. Clin. Oncol. 20 (2002) 47–59.
[2] W.J. Slichenmyer, E.K. Rowinsky, R.C. Donehower, S.H. Kaufmann, J. Natl. Cancer Inst. 85 (1993) 271–278.
[3] S. Eckhardt, Curr. Med. Chem. Anticancer Agents 2 (2002) 419–439.
[4] <http://dtp.nci.nih.gov>.
[5] A. Kato, T. Sugiyama, S. Tanaka, Jpn. Kokai Tokkyo Koho JP 84,473, 2007.
[6] F. Rong, S. Chow, S. Yan, G. Larson, Z. Hong, J. Wu, Bioorg. Med. Chem. Lett. 17 (2007) 1663–1666.
[7] B. Li, H. Wu, D. Cui, D. Xiang, L. Bai, H. Yang, PCT Int. Appl. WO 125,337, 2006.
[8] P. Gaillard, A. Quattropiani, V. Pmell, T. Rueckle, J. Klicic, D. Church, PTC Int. Appl. WO 23,186, 2007.
[9] A. Burguete, E. Pontiki, D. Hadjipavlou-Litina, R. Villar, E. Vicente, B. Solano, S. Ancizu, S. Perez-Silanes, I. Aldana, A. Monge, Bioorg. Med. Chem. Lett. 17 (2007) 6439–6443.
[10] G.W.H. Cheeseman, E.S.G. Werstiuk, Adv. Heterocycl. Chem. 22 (1978) 367–431.
[11] N. Sato, in: A.R. Katritzky, C.W. Rees, E.F.V. Scriven (Eds.), Comprehensive Heterocyclic Chemistry II, vol. 6, Pergamon, Oxford, 1996, p. 233.
[12] S. Hazeldine, L. Polin, J. Kushner, J. Paluch, K. White, M. Edelstein, E. Palomino, T.H. Corbett, J.P. Horwitz, J. Med. Chem. 44 (2001) 1758–1776.
[13] S.T. Hazeldine, L. Polin, J. Kushner, K. White, N.M. Bouregeois, B. Crantz, E. Palomino, T.H. Corbett, J.P. Horwitz, J. Med. Chem. 45 (2002) 3130–3137.
[14] J.P. Horwitz, S.T. Hazeldine, T.H. Corbett, L. Polin, WO Patent 03/011832, 2003.
[15] S.T. Hazeldine, L. Polin, J. Kushner, K. White, T.H. Corbett, J. Biehl, J.P. Horwitz, Bioorg. Med. Chem. 13 (2005) 1069–1081.
[16] N. Neamati, U.S. Pat. Appl. Publ. US 235,034, 2006.
[17] Y. Hu, F. Jiang, B. Yang, Q. He, Faming Zhuanli Shenqing Gongkai Shuomingshu CN 1,951,923 Appl. 10,154,536, November 7, 2006.
[18] M. Loriga, M. Fiore, P. Sanna, G. Paglietti, Farmaco 50 (1995) 289–301.
[19] M. Loriga, M. Fiore, P. Sanna, G. Paglietti, Farmaco 51 (1996) 559–568.
[20] M. Loriga, S. Piras, P. Sanna, G. Paglietti, Farmaco 52 (1997) 157–166.
[21] M. Loriga, P. Moro, P. Sanna, G. Paglietti, Farmaco 52 (1997) 531–537.
[22] M. Loriga, G. Vitale, G. Paglietti, Farmaco 53 (1998) 139–149.
[23] G. Vitale, P. Corona, M. Loriga, G. Paglietti, Farmaco 50 (1998) 150–159.
[24] P. Corona, G. Vitale, M. Loriga, G. Paglietti, M.P. Costi, Farmaco 53 (1998) 480–493.
[25] G. Vitale, P. Corona, M. Loriga, G. Paglietti, Farmaco 53 (1998) 594–691.
[26] P. Corona, G. Vitale, M. Loriga, G. Paglietti, Farmaco 55 (2000) 77–86.
[27] S. Piras, M. Loriga, G. Paglietti, Farmaco 57 (2002) 1–8.
[28] M. Loriga, S. Piras, G. Paglietti, M.P. Costi, A. Venturelli, Farmaco 58 (2003) 51–61.
[29] S. Alleca, P. Corona, M. Loriga, G. Paglietti, R. Loddo, V. Mascia, B. Busonera, P. La Colla, Farmaco 58 (2003) 639–650.
[30] S. Piras, M. Loriga, G. Paglietti, Farmaco 59 (2004) 185–194.
[31] P. Corona, G. Vitale, M. Loriga, G. Paglietti, P. La Colla, G. Collu, G. Sanna, R. Loddo, Eur. J. Med. Chem. 41 (2006) 1102–1107.
[32] S. Piras, M. Loriga, A. Carta, G. Paglietti, M.P. Costi, S. Ferrari, J. Heterocycl. Chem. 43 (2006) 541–548.
[33] P. Corona, M. Loriga, M.P. Costi, S. Ferrari, G. Paglietti, Eur. J. Med. Chem. 43 (2008) 189–203.
[34] A. Gangjee, R. Devraj, J.J. McGuire, R.L. Kisliuk, J. Med. Chem. 38 (1995) 3798–3805.
[35] E.I. Fairburn, B.J. Magerlein, L. Stubberfield, E. Stapert, D.I. Weisblat, J. Am. Chem. Soc. 76 (1954) 676–679.
[36] E. Campaigne, W.W. Meyer, J. Org. Chem. 27 (1962) 2835–2841.
[37] Y.H. Kim, Y. Gaumont, R.L. Kisliuk, H.G. Mautner, J. Med. Chem. 18 (1975) 776–780.
[38] M.R. Grever, S.A. Schepartz, B.A. Chabner, Semin. Oncol. 19 (1992) 622–638.
[39] M.R. Boyd, K.D. Paul, Drug Dev. Res. 34 (1995) 91–109.
[40] P. Skehan, R. Storeng, D. Scudiero, J. Natl. Cancer Inst. 82 (1990) 1107–1112.
[41] M.R. Boyd, Am. Assoc. Cancer Res. 30 (1989) 652–655.
[42] A. Monks, D. Scudiero, P. Skehan, R. Shoemaker, K. Poull, D. Vistica, C. Hose, J. Langley, P. Cronise, A. Vaigro-Wolff, M. Gray-Goodrich, H. Cambell, M. Boyd, J. Natl. Cancer Inst. 83 (1991) 757–766.
[43] J.N. Weinstein, T.G. Myers, P.M. O'Connor, S.H. Friend, A.J. Fornance Jr., K.W. Kohn, T. Fojo, S.E. Bates, L.V. Rubinstein, N.L. Anderson, J.K. Buolamwini, W.W. van Osdol, A.P. Monks, D.A. Scudiero, E.A. Sausiville, D.W. Zaharevitz, B. Bunow, V.N. Viswanadhan, G.S. Johnson, R.E. Wittes, K.D. Paull, Science 275 (1997) 343–349.
[44] A. Cavazzuti, G. Paglietti, W.N. Hunter, F. Gamarro, S. Piras, M. Loriga, S. Alleca, P. Corona, K. McLuskey, L. Tulloch, F. Ghibellini, S. Ferrari, M.P. Costi, PNAS 105 (2008) 1448–1453.