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Design, synthesis and biological evaluation of (*E*)-2-(2-arylhydrazinyl)quinoxalines, a promising and potent new class of anticancer agents

Felipe A. R. Rodrigues [a], Igor da S. Bomfim [a], Bruno C. Cavalcanti [a], Claudia do Ó. Pessoa [a], James L. Wardell [b,c], Solange M. S. V. Wardell [d], Alessandra C. Pinheiro [b], Carlos Roland Kaiser [e], Thais C. M. Nogueira [b,e], John N. Low [c], Ligia R. Gomes [f], Marcus V. N. de Souza [b,*]

[a] *Laboratório de Oncologia Experimental, Universidade Federal do Ceará, Fortaleza, CE, Brazil*
[b] *FioCruz-Fundação Oswaldo Cruz, Instituto de Tecnologia em Fármacos-Far-Manguinhos, Rua Sizenando Nabuco, 100, Manguinhos, 21041-250 Rio de Janeiro, RJ, Brazil*
[c] *Department of Chemistry, University of Aberdeen, Old Aberdeen AB 24 3UE, Scotland, UK*
[d] *CHEMSOL, 1 Harcourt Road, Aberdeen AB15 5NY, Scotland, UK*
[e] *Programa de Pós-Graduação em Química, Instituto de Química, Universidade Federal do Rio de Janeiro, CP 68563, 21945-970 Rio de Janeiro, Brazil*
[f] *REQUIMTE, Departamento de Química e Bioquímica, Faculdade de Ciências da Universidade do Porto, Rua Campo Alegre, 687, P-4169-007, Porto P-4200-150, Portugal*

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ABSTRACT

A series of forty-seven quinoxaline derivatives, 2-(XYZC$_6$H$_2$CH=N–NH)-quinoxalines, **1**, have been synthesized and evaluated for their activity against four cancer cell lines: potent cytotoxicities were found (IC_{50} ranging from 0.316 to 15.749 μM). The structure–activity relationship (SAR) analysis indicated that the number, the positions and the type of substituents attached to the aromatic ring are critical for biological activity. The activities do not depend on the electronic effects of the substituents nor on the lypophilicities of the molecules. A common feature of active compounds is an *ortho*-hydroxy group in the phenyl ring. A potential role of these *ortho*-hydroxy derivatives is as *N*,*N*,*O*-tridentate ligands complexing with a vital metal, such as iron, and thereby preventing proliferation of cells. The most active compound was (**1**: X,Y = 2,3-(OH)$_2$, Z = H), which displayed a potent cytotoxicity comparable to that of the reference drug doxorubicin.

As indicated by the estimated costs of cancer in 2007 of $226.8 billion,[1] and by the 7.6 million cancer world-wide deaths (13% of all deaths) in 2008,[2] cancer is clearly a major concern. The need for effective treatment and new anticancer agents is of paramount importance.

We have previously reported on the biological activities of hydrazone derivatives of a number of different heteroaromatic compounds.[3–10] Now we wish to report the results of an evaluation of the anti-cancer activities of a series of hydrazone-quinoxaline derivatives, 2-XYZC$_6$H$_4$–CH=N–NH)-quinoxaline, **1**.

Quinoxaline compounds have a wide range of uses, mainly as biologically active compounds, but also as dyestuffs.[11–21] The biological uses of quinoxaline compounds include as antibacterial, antitubercular, antimicrobial, antifungal, antimalarial, anti-inflammatory, antileishmanial, and antitumor agents, as well as herbicides, insecticides[11–21] The biological activities of hydrazone derivatives of heteroaromatic compounds have also been well reported,[22–31] with anticancer activities being of significant interest.[24–31] Our report, however, is the first of the use of hydrazinyl-quinoxalines of the type, 2-(XYZC$_6$H$_3$–CH=N–NH)-quinoxaline, **1**, as anticancer agents. Compounds **1** were obtained by molecular hybridization, see Scheme 1.

The quinoxalinyl-hydrazones, 2-(XYZC$_6$H$_2$CH=N–NH)-quinoxalines, **1**, were synthesized from reactions of 2-hydrazinylquinoxaline, **3**, and arenecarbaldehydes, in 55–96% yields, as shown in Scheme 1. As can be seen from Table 1, compounds with a wide range of substituents were prepared and studied.

Characterization of the compounds **1** was generally achieved from NMR and IR spectral data. In the ^{1}H NMR spectra, the signal for the N=C*H* proton was in the region 7.98–8.54 ppm, while the N–H and N=C stretching vibrations in the IR spectra were at 3400–3491 and 1565–1612 cm^{-1}, respectively. The spectral data are included in the Supplementary section, along with melting points and yields of the derivatives.

The crystal structures of (**1**: X = Y = Z = H) and the mono-halo-derivatives, (**1**: X = 2-, 3-, 4-Br, 2-, 3-, 4-Cl; Y = Z = H) have been reported.[32] As is discussed below, (**1**: X = Y = Z = H) and the mono-halo derivatives are all, at best, poorly active. Thus, the structure determination of a reasonably active compound was

* Corresponding author. Tel.: +55 2139772404; fax: +55 2125602518.
E-mail address: marcos_souza@far.fiocruz.br (M.V.N. de Souza).

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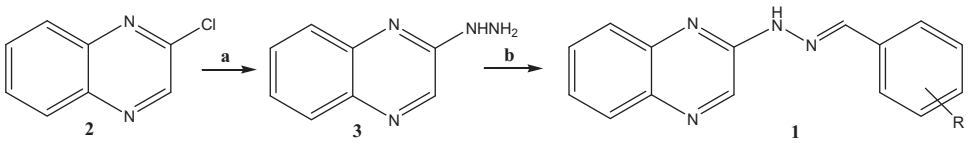


Scheme 1. Reagent and conditions (a) $N_2H_4{\cdot}H_2O$ (80%), EtOH, rt, 48 h, 85% (b) ArCHO, EtOH, rt 24 h, 55–96%.

Table 1
Parameters for hydrogen bond and intermolecular interactions (Å, o)

(a) Hydrogen bonds

D–H···A	D–H	H···A	D···A	D–H···A
O1–H1···N5	0.84	1.94	2.6826(13)	147
N3–HN3···N4^{i}	0.92(2)	2.54(2)	3.4323(17)	165.5(12)
O2–H2···O3	0.84	1.88	2.7137(15)	176
C5–H5···N1^{ii}	0.95	2.52	3.4585(18)	172
C15–H15···O1^{i}	0.95	2.50	3.1836(17)	129
C16–H16C···O2^{i}	0.98	2.51	3.3754(17)	148

Symmetry operation: *i* = −1+*x*,*y*,*z*; *ii* = 1+*x*,*y*,*z*.

(b) C–H···Cg[a]

C–H···Cg[a]	C···Cg	H_{perp}	γ	C–H···Cg	C···Cg
C18–H18B···Cg3^{i}	2.65	2.64	2.93	140	3.4534(13)

Symmetry operations: *i* = 1−*x*,1−*y*,1−*z*.

(c) Cg–Cg[a]

Cg(I)···Cg(J)[a]	Cg···Cg	α	β	γ	CgI_{perp}	CgJ_{perp}
Cg1···Cg1^{i}	4.1140(7)	0	36.68	33.68	3.2993(4)	3.2993(4)
Cg1···Cg1^{ii}	3.6103(7)	0	24.45	24.45	3.2864(4)	3.2864(4)

Symmetry operations: *i* = 2−*x*,2−*y*,−*z*; *ii* = 3−*x*,1−*y*,−*z*.

[a] Cg1 and Cg3 are the centroids of the rings defined by [N1,C2,C3,N4,C4A,C8A] and, [C10–C15], respectively.

considered to be a useful exercise as it would indicate any conformational differences between active and non-active compounds.

Suitable crystals of an acetone solvate of (**1**: X,Y = (2,4-$(OH)_2$, Z = H), an active compound, were grown from an acetone solution. The crystal structure of [(**1**: X,Y = (2,4-$(OH)_2$, Z = H)·Me_2CO] was determined from data collected at 100(1) K.[33–35] Atomic coordinates, bond lengths, angles and thermal parameters have been deposited at the Cambridge Crystallographic Data centre, deposition number 960209. The asymmetric unit of [(**1**: X,Y = (2,4-$(OH)_2$, Z = H)·Me_2CO] consists of a molecule each of (**1**: X = Y = Z = H) and Me_2CO. Figure 1 shows the atom arrangements and numbering scheme of the solvate.

The arrangement of the *ortho*-hydroxy group in (**1**: X,Y = (2,4-$(OH)_2$, Z = H) allows intramolecular hydrogen bonding to occur with the imino N atom, see Figure 1. The arrangements of the *ortho* halogen atoms in (**1**: X = 2-Br and Cl; Y = Z = H) are different as shown in Figure 2. Considerable steric hindrance would have resulted if the positions of the halo groups in (**1**: X = 2-Br and Cl; Y = Z = H) were the same as that of the 2-OH group in (**1**: X,Y = (2,4-$(OH)_2$, Z = H).

The *para*-hydroxy group in (**1**: X,Y = (2,4-$(OH)_2$, Z = H) is also involved in hydrogen bonding, in this case with the oxygen of the acetone solvent solvate within the asymmetric unit, see Figure 1. The arrangement about the C=N bond in (**1**: X,Y = (2,4-$(OH)_2$, Z = H) is (*E*), as was found in (**1**: X = Y = Z = H) and monohalo derivatives, (**1**: X = 2-, 3-, 4-Br and Cl; Y = Z = H).[32] All compounds **1**, so far studied, show only small deviations from planarity and it is clear that there are no significant differences in the molecular conformations adopted by non-active and active compounds in the solid state.

Electron delocalization in the —NH—N=CH— link between the quinoxaline and phenyl groups in (**1**: X,Y = (2,4-$(OH)_2$, Z = H) is indicated by the bond lengths: C2–N3 = 1.3665(17), N3–N5 = 1.3729(13), N5–C9 = 1.2895(17) and C9–C10 = 1.4496(16) Å, respectively. A similar finding was obtained for the other (*E*)-2-(2-arylhydrazinyl)quinoxalines recently reported.[32]

The presence of nitrogen and hydroxyl groups in (**1**: X,Y = (2,4-$(OH)_2$, Z = H) allows for various intra- and inter-molecular interactions, see Table 2 for details of the symmetry operations and the geometric parameters. A PLATON analysis[34e] indicated the presence of intermolecular N–H···N and C–H···O hydrogen bonds as well as π···π and C–H···π interactions, see Table 1. The importance of weaker intermolecular interactions, such as C–H···O hydrogen bonds, π···π and C–H···π interactions, in crystal structures have been well documented.[36] Additionally, a theoretical study of π···π interactions in the quinoxaline dimer has recently been published[37] and has provided a firm understanding of such interactions.

There are two major subsets of intermolecular interactions present in the crystal of [(**1**: X,Y = (2,4-$(OH)_2$, Z = H)·Me_2CO]. The first subset involves N–H···N and C–H···O hydrogen bonds, which generate columns of linked (**1**: X,Y = (2,4-$(OH)_2$, Z = H) and acetone molecules, see Figure 3a. Figure 3b shows the orientation of two of these columns through the crystallographic cell. The strongest interaction, the N3–HN3···N4 hydrogen bond, generates C(6) chains.[38] The N3–HN3···N4 hydrogen bond together with O2–H2···O3 and weaker C5–H5···N1, C15–H15···O1 and C16–H16C···O2 hydrogen bonds forms a series of rings, $R^2_2(8)R^2_2(16)R^3_3(15)$.[38] The second major subset is formed from alternating stronger and weaker π(pyridine)—π(pyridine) stacking interactions, see Figure 3c. Table 2 contains details of the interactions. There is an additional, but less important, intermolecular

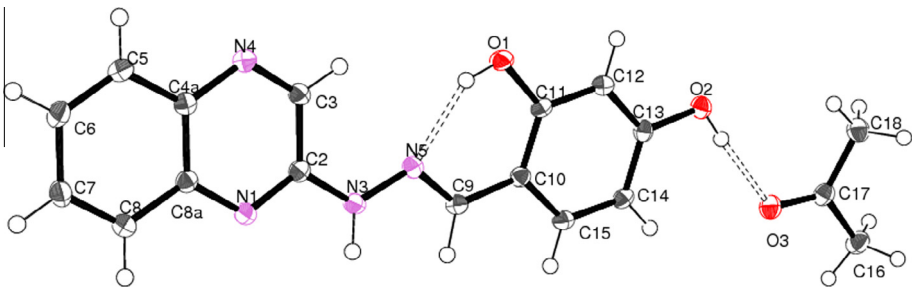


Figure 1. Atom arrangements and numbering scheme for [(**1**: X,Y = (2,4-$(OH)_2$, Z = H)·Me_2CO]. Probability ellipsoids are drawn at the 50% level. Hydrogen atoms are drawn as spheres of arbitrary radius. Hydrogen bonds are drawn as dashed lines.

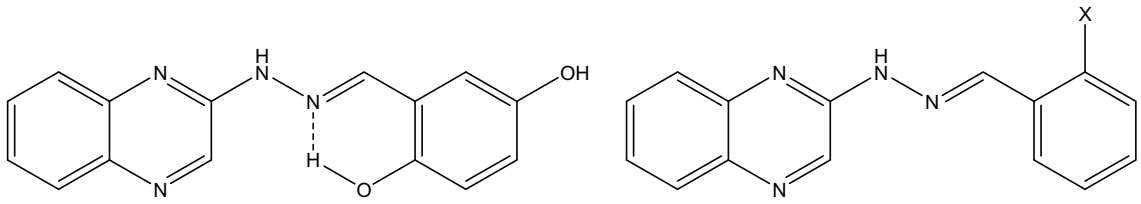


Figure 2. Different positions of the *ortho* substituents in (**1**: X,Y = (2,4-$(OH)_2$, Z = H) and (**1**: X = 2-Cl or 2-Br,Y = Z = H).

Table 2
Growth inhibition (%)[a] for three tumors cells line by the MTT Assay and calculated Log*P* values

Compound	SF-295 (sd)%	OVCAR-8 (sd)%	HCT-116 (sd)%	Log*P*[b]
(**1**: X = Y = Z = H)	−3.37(12.09)	34.46(1.61)	−18.44(4.62)	3.15
(**1**: X = 2-F, Y = Z = H)	12.76(5.35)	0.00(0.00)	7.01(5.99)	3.27
(**1**: X = 3-F, Y = Z = H)	8.36(2.34)	5.59(5.08)	10.80(0.76)	3.29
(**1**: X = 2-Cl, Y = Z = H)	31.86(0.17)	9.09(0.00)	12.07(7.66)	3.78
(**1**: X = 3-Cl, Y = Z = H)	33.23(1.79)	0.00(0.00)	0.00(0.00)	3.80
(**1**: X = 4-Cl, Y = Z = H)	44.48(4.24)	41.72(7.14)	−10.20(1.66)	3.83
(**1**: X ,Y = 2,3-Cl, Z = H)	84.33(3.66)	100.17(1.73)	97.53(1.61)	4.41
(**1**: X ,Y = 2,6-Cl, Z = H)	52.04(1.60)	53.55(2.81)	71.19(1.84)	4.41
(**1**: X ,Y = 2,4-Cl, Z = H)	28.48(3.35)	4.90(7.17)	16.48(0.09)	4.44
(**1**: X ,Y = 3,4-Cl, Z = H)	37.83(2.91)	0.00(0.00)	0.50(2.27)	4.44
(**1**: X = 2-Br, Y = Z = H)	35.24(3.56)	18.01(5.44)	23.64(5.86)	3.91
(**1**: X = 3-Br, Y = Z = H)	14.18(9.76)	0.00(0.00)	0.00(0.00)	3.94
(**1**: X = 4-Br, Y = Z = H)	33.47(2.76)	18.18(5.56)	23.20(5.08)	3.96
(**1**: X = 2-NO_2, Y = Z = H)	21.90(2.55)	21.81(4.29)	23.02(5.57)	3.06
(**1**: X = 3-NO_2, Y = Z = H)	23.45(9.25)	16.94(5.82)	−20.99(6.04)	3.09
(**1**: X = 4-NO_2, Y = Z = H)	26.97(19.00)	40.58(14.93)	−18.64(3.98)	3.11
(**1**: X = 2-Me, Y = Z = H)	46.35(1.86)	17.82(7.58)	28.69(3.83)	3.55
(**1**: X = 3-Me, Y = Z = H)	39.84(5.06)	39.87(0.65)	33.40(1.47)	3.58
(**1**: X = 4-Me, Y = Z = H)	18.05(9.78)	28.96(9.57)	−19.55(10.74)	3.60
(**1**: X = 3-CN, Y = Z = H)	44.55(2.20)	11.48(3.41)	30.72(1.15)	2.88
(**1**: X = 4-CN, Y = Z = H)	16.03(6.70)	50.85(2.77)	−31.58(2.35)	2.91
(**1**: X = 2-OH, Y = Z = H)	61.48(0.89)	95.38(0.63)	77.00(0.55)	3.09
(**1**: X = 3-OH, Y = Z = H)	27.52(2.55)	51.48(7.43)	29.56(1.33)	2.65
(**1**: X = 4-OH, Y = Z = H)	39.43(7.05)	67.29(16.01)	20.24(1.18)	2.67
(**1**: X ,Y = 2,3-$(OH)_2$, Z = H)	81.17(3.46)	97.90(0.99)	83.95(0.19)	2.39
(**1**: X ,Y = 2,4-$(OH)_2$, Z = H)	85.27(0.68)	84.19(0.13)	85.09).96)	2.59
(**1**: X ,Y = 2,5-$(OH)_2$, Z = H)	50.69(6.10)	60.49(2.47)	89.23(0.66)	2.59
(**1**: X ,Y = 3,4-$(OH)_2$, Z = H)	47.60(1.95)	46.32(1.64)	69.36(2.11)	2.18
(**1**: X = Y = Z = 3,4,5-$(OH)_3$	37.75(3.46)	12.76(7.91)	14.88(7.47)	1.89
(**1**: X = 2-OMe, Y = Z = H)	21.78(5.69)	20.99(6.89)	4.45(0.63)	3.16
(**1**: X=3-OMe, Y = Z = H)	35.84(7.76)	41.56(3.95)	−14.48(2.90)	3.18
(**1**: X = 4-OMe, Y = Z = H)	0.52(3.53)	14.42(11.20)	-43.61(7.96)	3.21
(**1**: X ,Y = 2,3-$(OMe)_2$, Z = H)	22.16(2.13)	0.00(0.00)	0.00(0.00)	2.97
(**1**: X ,Y = 2,4-$(OMe)_2$, Z = H)	46.89(0.42)	7.19(2.91)	12.76(0.48)	3.19
(**1**: X ,Y = 2,5-$(OMe)_2$, Z = H)	44.65(7.52)	18.53(20.03)	0.00(0.00)	3.19
(**1**: X ,Y = 2,6-$(OMe)_2$, Z = H)	44.73(8.03)	25.09(9.52)	19.36(0.38)	3.17
(**1**: X ,Y = 3,4-$(OMe)_2$, Z = H)	16.53(2.96)	17.64(0.51)	22.32(4.03)	2.80
(**1**: X = Y = Z = 3,4,5-$(OMe)_3$)	60.12(9.32)	38.81(1.89)	20.69(4.98)	2.78
(**1**: X = 3-OEt, Y = Z = H)	7.19(10.55)	41.17(0.36)	1.29(1.96)	3.56
(**1**: X = 4-OEt, Y = Z = H)	12.30(10.67)	50.28(1.07)	−17.56(24.69)	3.58
(**1**: X = 2-OH, Y = 4-Me, Z = H)	59.88(4.57)	31.49(1.51)	17.37(7.38)	3.52
(**1**: X = 2-OH, Y = 5-Me, Z = H)	38.40(0.51)	25.44(2.10)	13.67(6.15)	3.52
(**1**: X = 2-OH, Y = 4-OMe, Z = H)	66.37(6.49)	80.93(0,90)	83.13(2.21)	3.12
(**1**: X = 2-OH, Y = 5-NO_2, Z=H)	78.51(0.10)	95.63(1.24)	92.11(1,51)	3.03
(**1**: X = = 3-NO_2, Y = 4-Cl, Z = H)	36.75(2.44)	9.00(0.12)	20.56(2.84)	3.72
(**1**:X = 3-Cl, Y = 4-OH, Z = H)	46.65(5.84)	28.81(7.71)	16.22(8.44)	3.54
(**1**: X = 2-Cl, Y = 3-OH, Z = 4-OMe)	32.43(2.03)	13.81(3.46)	24.51(7.85)	3.32

[a] Mean of three determinations.
[b] Calculated using Ref. 39.

interaction, of the type C–H···π, which produces dimeric units of [(**1**: X,Y = (2,4-$(OH)_2$, Z = H)·Me_2CO]: this is not drawn. Overall a three-dimensional array is produced from the combination of all the molecular interactions.

All compounds **1** were initially tested in vitro against three cancer cells, SF-295 (glioblastoma), OVCAR-8 (human ovary) and HCT-116 (colon) at a concentration of 5 μg/mL using the MTT assay. The results are shown in Table 2 along with calculated lypophilicities.[39]

Compounds showing good activity in this initial evaluation were (**1**: X,Y = 2,3-Cl_2, Z = H), (**1**: X = 2-OH, Y = Z = H), (**1**: X,Y = 2,3-$(OH)_2$, Z = H), (**1**: X,Y = 2,4-$(OH)_2$, Z = H), (**1**: X = 2-OH, Y = 4-OMe, Z = H) and (**1**: X = 2-OH, Y = 5-NO_2, Z = H). It is striking that all but one of these compounds, (**1**: X,Y = 2,3-Cl_2, Z = H), contained a 2-hydroxy group, with a range of other substituents, both electron releasing and withdrawing, also present. The compounds with 2-hydroxy substituents have low log*P* values, but so do other

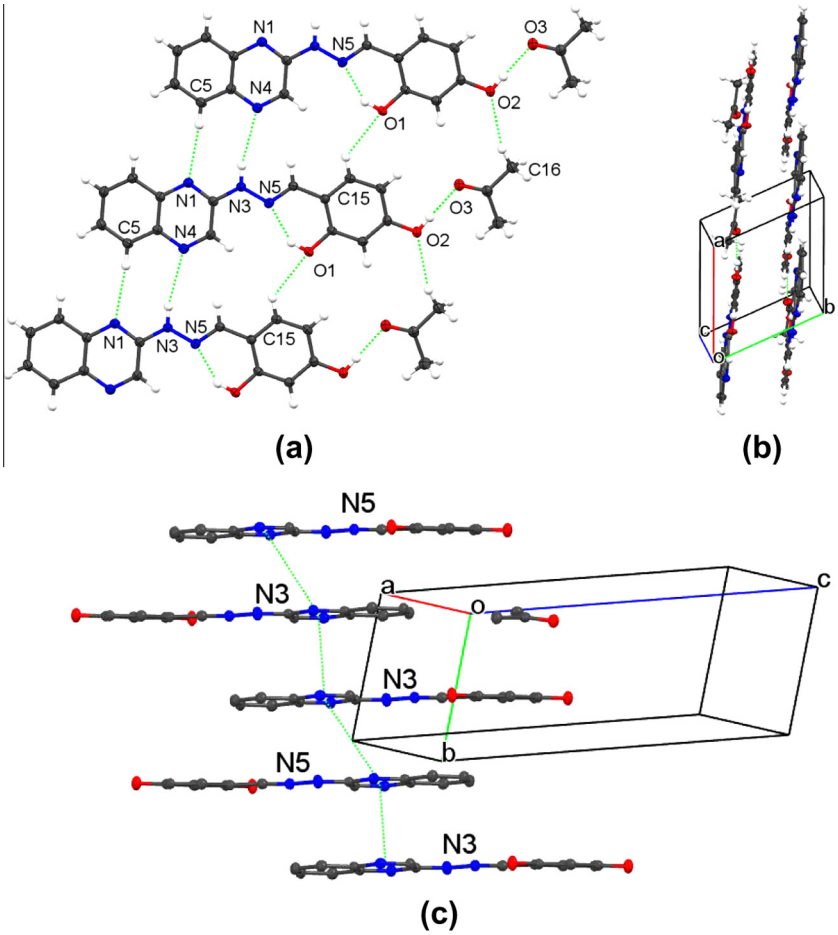


Figure 3. (a) Columns of molecules generated from N3–HN3···N4, O2–H2···O3, C5–H5···N1, C15–H15···O1 and C16–H16C···O2 hydrogen bonds, (b) A view of two of the columns passing through the cell, (c) a π---π stack of molecules. See Table 2 for symmetry operations and geometric parameters.

compounds, which are poorly active at best, such as methoxy substituted derivatives and (**1**: X = 3-OH, Y = Z = H), (**1**: X = 4-OH, Y = Z = H), (**1**: X,Y = 3,4-$(OH)_2$, Z = H) and (**1**: X = Y = Z = 3,4,5-$(OH)_3$). Hence a low lypophilicity is not a requirement for activity.

The majority of the active compounds from the first phase were selected for further evaluation against the four human cancer cell lines: OVCAR-8 (human ovary), SF-295 (glioblastoma), HCT-116 (colon) and HL-60 (leukemia), using the MTT assay. The concentrations that induce 50% inhibition of cell growth (IC_{50}) in μg/mL are reported in Table 3.

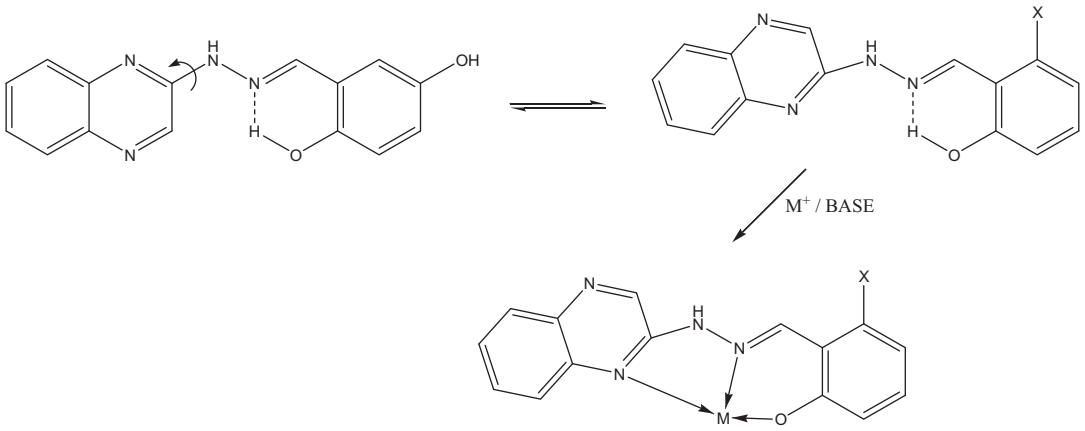
Compound (**1**: X,Y = 2,3-$(OH)_2$, Z = H) exhibited the best results against all four cancer lines in the second phase of the study. Other active compounds in the second phase were (**1**: X = 2-OH, Y = Z = H) and (**1**: X = 2-OH, Y = 5-NO_2, Z = H).

In looking for factors why the 2-hydroxy-substituted compounds are active, the possibility of coordination with vital metal centres cannot be ignored. There are various reports in the literature of (pyridin-2-yl)NHN = CH–C_6H_4OH-2 and related compounds acting as tridentate, *N*,*N*,*O*-ligands to metal centres. Indeed, crystal structures of complexes with VO(IV),[40] VO(V),[41] MoO_2(VI),[42]

Table 3
Cytotoxic activity of selected compounds [IC_{50} (μM)] on tumor cell lines[a]

Compound	HCT-116	OVCAR-8	HL-60	SF-295
(**1**: X ,Y = 2,3-Cl_2, Z = H)	7.006	6.189	10.776	6.205
	4.795–10.234	5.054–7.579	9.455–12.284	4.486–8.585
(**1**: X = 2-OH, Y = Z = H)	4.941	3.472	0.819	2.308
	3.169–7.702	1.654–3.035	0.745–0.900	1.700–3.133
(**1**: X ,Y = 2,3-$(OH)_2$, Z = H)	1.758	1.065	0.316	1.264
	1.549–1.994	0.909–1.248	0.245–0.407	0.931–1.715
(**1**: X = 2-OH, Y = 4-OMe, Z = H)	14.233	7.550	4.193	15.749
	13.255–15.287	6.513–8.756	1.816–9.673	7.659–32.391
(**1**: X = 2-OH, Y = 5-NO_2, Z = H)	4.323	2.839	1.746	2.108
	3.961–4.717	2.291–3.518	1.403–2.174	1.629–2.728
Doxorubicin	0.230	0.488	0.037	0.423
	(0.165–0.313)	(0.313–0.561)	0.018–0.037	0.350–0.460

[a] Data are presented as IC_{50} values and 95% confidence intervals obtained by nonlinear regression for all cell lines colon (HCT-116), ovarium (OVCAR-8), (leukemia (HL-60), glioblastoma (SF-295), from three independent experiments. Doxorubicin (Dox) was used as positive control. Experiments were performed in triplicate. IC_{50} = concentrations that induce 50% inhibition of cell growth in μM.



Scheme 2. Required conformation for action as a *N,N,O* tridentate ligand.

Ru(III),[43] Fe(III),[44] Cu(II),[45–49] Zn(II),[50] Mn,[51–53] mixed Mn-lanthanide,[53] and tin(IV)[54] have all been reported to contain these *N,N,O*-ligands. While the emphasis of many of these reports were on non-biological aspects, some did highlight biological activities, OK the anticancer activity,[49] the antimicrobial activity[46] and interactions with DNA[44] of Cu(II) complexes were all mentioned. While most of these complexes involve pyridin-2-yl species, the Russian work[47] shows that quinolin-2-yl derivatives also form these complexes. Whilst quinoxaline is considerably less basic than either pyridine or quinoline, as shown by the pK_a values,[55] complexes of quinoxalines with transition metals have been known for many years, see Refs. 56–58. The report by Lakshmi et al. on the antimicrobial activities of oxovanadium(IV) complexes of 3-hydroxy-2-(2-hydroxypheny-lCH═N—NH)-quinoxaline (or its carbonyl tautomer) and related ligands is particular pertinent to our work.[59] Lakshmi et al.'s compounds were characterized spectroscopically and by elemental analyses, however no crystal structure was determined and so the precise binding mode of the ligand to the metal centre remains unknown. A theoretical treatment of the bonding between quinoxaline and copper ions was very recently reported[37] and provides a good basis for the interactions of metals generally with quinoxaline ligands.

Of all the metals mentioned above, iron is particularly relevant. Iron is very important in DNA synthesis, adenosine triphosphate production and cell replication. Studies have demonstrated that cancer cells are susceptible to iron complexing ligands.[60] Acylhydrazones have shown potential as iron chelators.[61] Chelation therapy has demonstrated that effective iron regulation is antitumor[62] in humans by depriving cancer cells of iron, an essential ingredient for proliferation.

The conformation determined for crystalline [(**1**: X,Y = 2,3-$(OH)_2$, Z = H). Me_2CO], is not the required one for complexation, but a simple rotation about the quinoxaline–N bond will provide the desired form, see Scheme 2. Findings gathered from the structures of complexes of related *N,N,O*-ligands indicate that tautomeric changes within the ligand can occur on complexation.

Specific mechanisms could be envisaged for (**1**: X,Y = 2,3-$(OH)_2$, Z = H), a catechol derivative. Catechol derivatives are well known to form *O,O*-chelates and to be involved in radical formation on oxidation. However as other di-hydroxy derivatives, (**1**: X,Y = 3,4-$(OH)_2$, Z = H) and **(1**: X = Y = Z = 3,4,5-$(OH)_3$), were not particularly active, such mechanisms appear less likely.

Comparison of the activities of **1** and the bioisosteric series, 4-(aryl-CH═N—NH)-7-chloro-quinoline, **4**[63–65] is of interest. As shown by the comparison of activities in Scheme 3, the quinoxaline compounds are more active than the corresponding 7-chloroquinoline derivatives.

In this work, we report the cytotoxicity activity of a series of quinoxaline derivatives, which have been evaluated against four cancer cell lines. The SAR of these compounds indicated that the positions and the type of substituents in the phenyl ring are critical for the biological activity. The compound (**1**: X = Y = 2,3-$(OH)_2$, Z = H) displayed a potent cytotoxicity activity compared to the reference drug doxorubicin.

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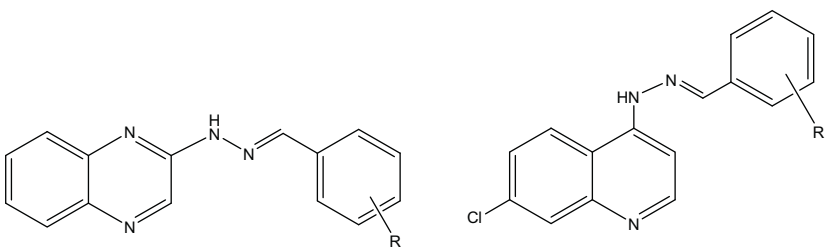

1: X,Y = 2,3-OH, Z = H; IC_{50} = 0.314 μM

1: X,Y = 2,3-Cl, Z = H; IC_{50} = 6.999 μM

1: X = OH, Y,Z = H; IC_{50} = 0.757 μM

4: X,Y = 2,3-OH, Z = H; IC_{50} = 4.080 μM

4: X,Y = 2,3-Cl, Z = H; Inactive

4: X = OH; Y,Z = H; IC_{50} = > 16.793 μM

Scheme 3. Comparison of anti-cancer activities of two series of hydrazones.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2013.12.074.

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33. Data for compound [(**1**: X, Y = (2,4-(OH)$_2$, Z = H).Me$_2$CO] were obtained at 100(1) K with Mo-K radiation by means of the Rigaku Saturn724+ (2 × 2 bin mode). Data collection, data reduction and unit cell refinement were carried out under the control of the program CrystalClear-SM Expert 2.0 r7 [34a]. All sets of data were collected at the NCS EPSRC Crystallographic Service, based at the University of Southampton. Correction for absorption was achieved by a semi-empirical method based upon the variation of equivalent reflections [34a]. The programs ORTEP-3 for Windows [34b] and MERCURY [34c] were used in the preparation of the Figures. SHELXL97 [34d] and PLATON [34e] were used in the calculation of molecular geometry. The structures were solved by direct methods using SHELXS-97 [34d] and fully refined by means of the program SHELXL-97 [34d]. Difference map peaks provided the position for the hydrogen atoms attached to the atom N3 for which the coordinates, along with isotropic displacement parameters, were fully refined. All other hydrogen atoms were placed in calculated positions.
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35. Crystal data collected at 100(2)K, colourless crystal: 0.19 × 0.04 × 0.01 mm. Formula: $C_{18}H_{18}N_4O_3$; M = 338.36; triclinic, P-1; a = 6.8085(5) Å, α = 80.338(5)°, b = 7.1011(5) Å, β = 81.011(5)°, c = 18.5922(13) Å, γ = 65.055(4)°, Z = 2, V = 799.80(10) Å^3, 3654 [$R_{(int)}$ = 0.0440], 3046 observed reflections [$i > 2\ \sigma\ (I)$]: parameters refined 3654; number of restraints 0; R(F) 0.038 [$i > 2\ \sigma\ (I)$], Largest diff. peak 0.31 Å_1. Atomic coordinates, bond lengths, angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre, deposition number 960209.
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