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SYNTHESIS AND ALKYLATION OF SPIRO-2-OXAZOLINES CONTAINING FUSED 3,4-DIHYDROPYRAZIN-2(1*H*)-ONES[#]

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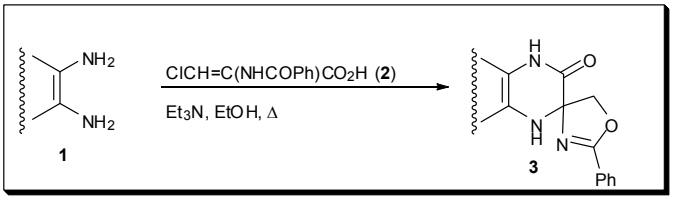
Abstract – Spiro-2-oxazolines containing 3,4-dihydroquinoxalin-2(1*H*)-one, 3,4-dihydrobenzoquinoxalin-2(1*H*)-one, 1,2-dihydropyrido[2,3-*b*]pyrazin-3(4*H*)-one or 5,6-dihydropteridin-7(8*H*)-one moiety were prepared by heating of aromatic or heteroaromatic diamines with 2-benzoylamino-3-chloropropenoic acid in the presence of triethylamine. Treatment of spiro-2-oxazolines with MeI or EtBr using Bu_4NHSO_4 and K_2CO_3 introduced the methyl or ethyl group on the lactam nitrogen atom.

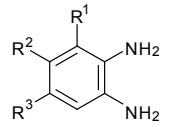
2-Oxazolines (4,5-dihydro-1,3-oxazoles) which contain spiro linkage at the carbon atom C4 with another heterocyclic system represent a less known group of organic compounds. Such spirooxazolines have been occasionally reported as intermediates, side products or unexpected products in various reactions. For example, 4,5-dihydro-1,3-oxazole-4-spiro-2'-thiiranes were described as intermediates in the synthesis of thietanes.[1] One spiro-2-oxazoline derivative containing penicillin system was identified as a by-product in the preparation of fluoromethyl substituted penicillin derivative.[2] Spiro-2-oxazolines with protected sugar moiety were prepared in some glycosidation reactions.[3] Compounds with spiro 2-oxazoline structural motif were also reported in the synthesis of parasitic insecticides.[4] Recently, several spiro-2-oxazolines were formed with a combinatorial approach to a structurally diverse library of polycyclic lactams.[5] During the investigations of the transformations of simple amino acid derivatives,[6] we designed a general method for the formation of spiro-2-oxazolines having 3,4-dihydroquinoxalin-2(1*H*)-one, 3,4-dihydrobenzoquinoxalin-2(1*H*)-one, 1,2-dihydropyrido[2,3-*b*]pyrazin-3(4*H*)-one or 5,6-dihydropteridin-7(8*H*)-one system.[6b] This paper deals with the spirocyclic products obtained in our investigations in more detail.

[#] Dedicated to Professor Miha Tišler on the occasion of his 85th birthday

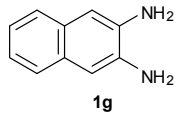
Treatment of aromatic and heteroaromatic diamines **1** with 2-benzoylamino-3-chloropropenoic acid (**2**)[7] in the presence of triethylamine in ethanol resulted in the formation of spiro-2-oxazolines **3** in 17–50% yields. Reactions with *o*-phenylenediamines **1a**–**f** produced 1'*H*,5*H*-spiro[oxazole-4,2'-quinoxalin]-3'(4'*H*)-ones **3a**–**f**. When naphthalene-2,3-diamine **1g** was applied, 1*H*,5'*H*-spiro[benzo-[g]quinoxaline-2,4'-oxazole]-3(4*H*)-one **3g** was formed. The use of pyridine-2,3-diamine **1h** gave 1'*H*,5*H*-spiro[oxazole-4,2'-pyrido[3,2-*b*]pyrazin]-3'(4'*H*)-one **3h**, while reaction with pyrimidine-2,3-diamine **1i** yielded 5*H*,5'*H*-spiro[oxazole-4,6'-pteridin]-7'(8'*H*)-one **3i** (Scheme 1).



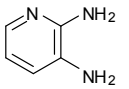
Diamines **1**:



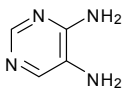
	R^1	R^2	R^3
1a	H	H	H
1b	NO_2	H	H
1c	H	NO_2	H
1d	H	Cl	H
1e	H	COPh	H
1f	H	Cl	Cl



1g

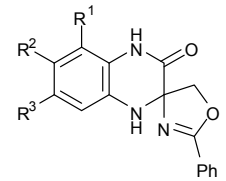


1h

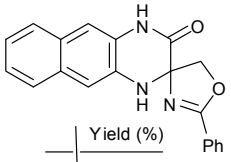


1i

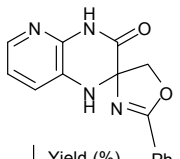
Spiro products **3**:



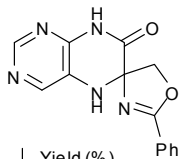
	R^1	R^2	R^3	Yield (%)
3a	H	H	H	23
3b	NO_2	H	H	17
3c	H	H	NO_2	46 (mixture of **3c**
3c'	H	NO_2	H	and **3c'**)
3d	H	Cl	H	20 (mixture of **3d**
3d'	H	H	Cl	and **3d'**)
3e	H	H	COPh	31 (mixture of **3e**
3e'	H	COPh	H	and **3e'**)
3f	H	Cl	Cl	34



	Yield (%)
3g	28



	Yield (%)
3h	50



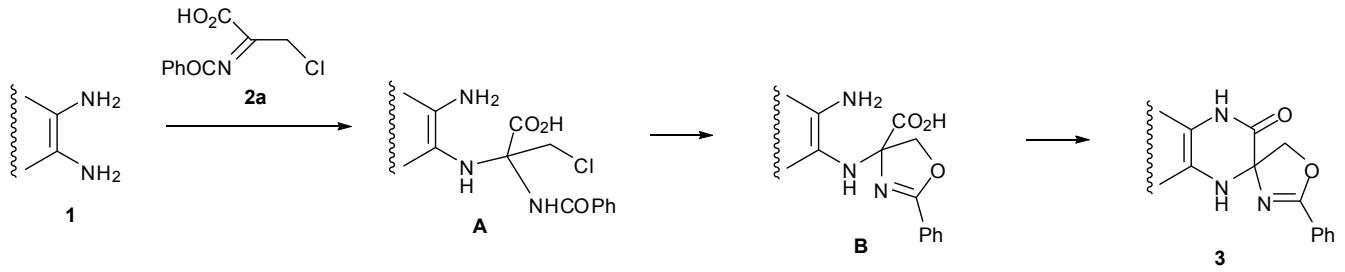
	Yield (%)
3i	37

Scheme 1

Diamines with symmetrical structure (**1a**, **1f**, and **1g**) afforded one product (**3a**, **3f**, and **3g**) in their reactions. One product was also obtained in reactions with unsymmetrical diamines **1b**, **1h** and **1i**. In the case of unsymmetrical *o*-phenylenediamines **1c**–**e**, mixtures of the corresponding isomers (**3c/c'**, **3d/d'**, and **3e/e'**) were isolated with the spiro compounds **3c**, **3d** or **3e** as the major and **3c'**, **3d'** or **3e'** as the minor isomers. The ratios between the major and minor isomer in the crude product mixtures, established on the basis of ^{1}H NMR spectra of the isolated products, were 6:1 for **3c**/**c'**, 2:1 for **3d**/**d',** and 13:1 for **3e**/**e'** pair. Our attempts to completely separate the spirooxazoline isomers by crystallization or chromatographic techniques failed although crystallization increased the amount of the major component in these pairs giving ratios of 7:1 (**3c**/**c'**), 3:1 (**3d**/**d'**), and 33:1 (**3e**/**e'**), respectively.

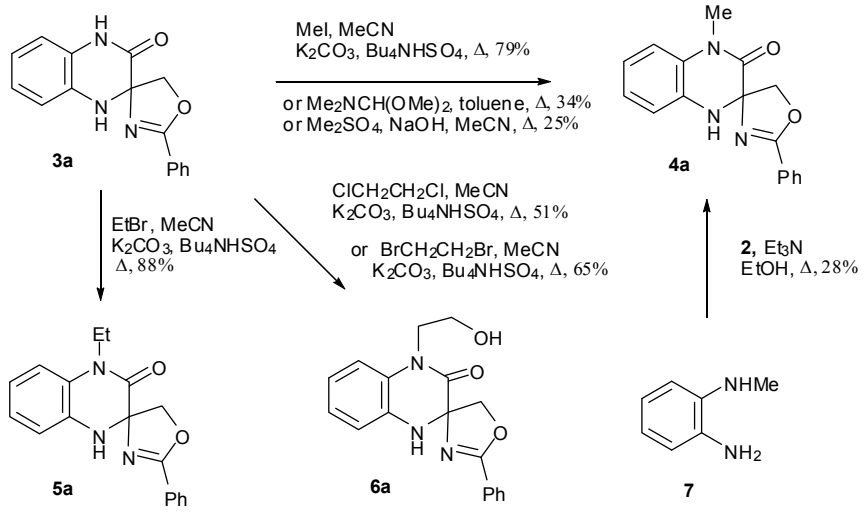
The structural assignments of compounds **3a**–**f** were mainly carried out by ^{1}H, ^{13}C, and 2D NMR spectroscopy. ^{1}H NMR spectra of these spiro compounds exhibited two doublets at 4.24–4.36 and 5.11–5.22 ppm for CH_2 protons of the oxazoline ring with coupling constants of 9.0–9.8 Hz. Their ^{13}C NMR spectra showed the spiro carbon atoms at 84–85 ppm. Structures of the spiro products obtained in reactions with unsymmetrical diamines were determined on the basis of HMBC correlations between NH protons in the dihydropyrazinone system and carbon atoms in the adjacent fused ring.

Structure and ratio of products obtained in reactions with unsymmetrical diamines indicate that the more basic amino group predominantly reacts with the α-carbon atom of the starting acid **2** and the less basic amino group with the carboxylic group. This transformation probably starts with an attack of the amino group to the acid tautomeric imine form **2a** giving intermediate **A** which then cyclises into the oxazoline intermediate **B** followed by the formation of the pyrazinone system (Scheme 2). Such reaction sequence is supported by a conversion of the acid **2** into benzamide via **2a**,[7] an easy approach to oxazolines by cyclization of β-haloamides,[8] and generally known unsuitableness of the preparation of amides by treatment of carboxylic acids with amines.



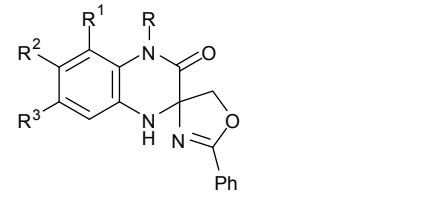
Scheme 2

In order to get insight into the reactivity of these spiro products, we began with alkylation reactions of **3**. Heating of **3a** with *N,N*-dimethylformamide dimethyl acetale in toluene introduced one methyl group on the lactam nitrogen atom in the pyrazinone part giving **4a** in 34% yield. Low yield of **4a** was also obtained with dimethyl sulphate and NaOH in acetonitrile (25%). On the other hand, better results were obtained by treatment with methyl iodide, using Bu_4NHSO_4 as a catalyst and an excess of K_2CO_3 at 80 ^{o}C, giving **4a** in 79% yield. An alternative approach to the synthesis of **4a**, heating of *N*-methyl substituted diamine **7** with **2** under standard conditions for the formation of the spirooxazolines **1**–**3**, afforded **4a** in 28% yield. Taking into account these results, **5a** was prepared from **3a** with ethyl bromide in the presence of Bu_4NHSO_4 and K_2CO_3 in 88% yield. Applying 1,2-dibromoethane or 1,2-dichloroethane as the alkylation reagent, 2-hydroxyethyl derivative **6a** was synthesized in 65 and 51% yield, respectively (Scheme 3).

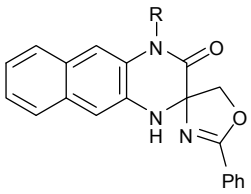


Scheme 3

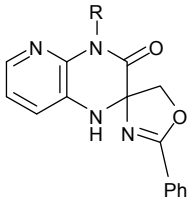
With these results in hand, using the same alkylation procedure with methyl iodide or ethyl bromide, we prepared other *N*-alkyl derivatives of spirooxazolines in 19-84% yields. Methylation of mixtures of **3c**/**c'** and **3d**/**d'** afforded mixtures of the corresponding methyl derivatives **4c**/**c'** and **4d**/**d'**. Ethylation of **3d**/**d'** gave a mixture of the corresponding ethyl derivatives **5d**/**d'**. On the other hand, ethylation of **3c**/**c'** afforded only one isomer, compound **5c** (Figure 1).



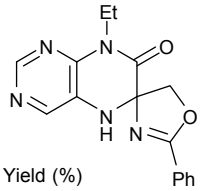
	R	R^1	R^2	R^3	Yield (%)
4c	Me	H	H	NO_2	84 (mixture of **4c**
4c'	Me	H	NO_2	H	and **4c'**)
4d	Me	H	Cl	H	69 (mixture of **4d**
4d'	Me	H	H	Cl	and **4d'**)
4f	Me	H	Cl	Cl	72
5c	Et	H	H	NO_2	60
5d	Et	H	Cl	H	28 (mixture of **5d**
5d'	Et	H	H	Cl	and **5d'**)
5f	Et	H	Cl	Cl	81



	R	Yield (%)
4g	Me	57
5g	Et	69



	R	Yield (%)
4h	Me	71
5h	Et	66



	Yield (%)
5i	19

Figure 1

In summary, we described the synthesis of several spiro-2-oxazolines and their alkylation. This work represents a novel contribution to the synthesis of heterocyclic spiro compounds[9] as well as a new confirmation of a great diversity of the use of various dehydroamino acid derivatives in heterocyclic synthesis.

EXPERIMENTAL

Melting points were determined on a Kofler micro hot stage. NMR spectra were recorded on a Bruker AVANCE DPX-300 spectrometer (300 MHz for ^{1}H and 75.5 MHz for ^{13}C) in DMSO-d_6 with TMS as an internal standard. MS spectra were obtained on a VG-Analytical AutoSpec Q instrument. Elemental analyses were performed on a Perkin-Elmer CHN Analyzer 2400. TLC was carried out on Fluka silica gel TLC-cards. Radial chromatography was performed on Merck Kieselgel PF_{254} silica gel. Compound **2** was prepared as described in the literature.[7] All other compounds were used without purification as obtained from commercial sources.

5'-Nitro-2-phenyl-1'*H*,5*H*-spiro[oxazole-4,2'-quinoxalin]-3'(4'*H*)-one (3b). *Typical Procedure A*: To a mixture of 3-nitrobenzen-1,2-diamine (**1b**) **(**153 mg, 1 mmol), 2-benzoylamino-3-chloropropenoic acid (**2**) **(**226 mg, 1 mmol) and EtOH (4 mL), Et_3N (160 mg, 1.6 mmol) was added. The reaction mixture was heated under reflux for 6.5 h. Upon cooling to rt, the precipitate was filtered off and washed with EtOH to give **3b** (54 mg, 17%). mp 222–224 °C (MeOH). ^{1}H NMR δ: 4.36 (d, 1H, J = 9.8 Hz, CH_2), 5.18 (d, 1H, J = 9.8 Hz, CH_2), 7.10 (deg. dd, 1H, J = 7.9, 7.9 Hz, H7'), 7.17 (dd, 1H, J = 1.5, 7.9 Hz, H8'), 7.44–7.51 (m, 2H, Ph), 7.55–7.62 (m, 2H, 1H of Ph, H6'), 7.84–7.89 (m, 3H, 2H of Ph, NH), 10.43 (s, 1H, NHCO). ^{13}C NMR δ: 72.6, 83.9, 115.0, 119.7, 120.6, 122.9, 126.2, 128.3, 128.8, 132.5, 134.6, 135.0, 163.9, 164.2. MS (EI, *m/z*, %): 324 (M^+, 35). *Anal.* Calcd for $C_{16}H_{12}N_4O_4$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.19; H, 3.69; N, 17.09.

7'-Nitro-2-phenyl-1'*H*,5*H*-spiro[oxazole-4,2'-quinoxalin]-3'(4'*H*)-one (3c) and 6'-Nitro-2-phenyl-1'*H*,5*H*-spiro[oxazole-4,2'-quinoxalin]-3'(4'*H*)-one (3c'). Following the typical procedure A, treatment of diamine **1c** (153 mg, 1.0 mmol), with acid **2** (226 mg, 1.0 mmol) and Et_3N (160 mg, 1.6 mmol) in EtOH (4 mL) gave a mixture of **3c** (major isomer) and **3c'** (minor isomer) (149 mg, 46%) in a ratio of 6:1; crystallization from EtOH gave a ratio of 7:1. ^{1}H NMR δ (**3c**): 4.32 (d, 1H, J = 9.6 Hz, CH_2), 5.16 (d, 1H, J = 9.6 Hz, CH_2), 7.06 (d, 1H, J = 8.7 Hz, H5'), 7.44–7.51 (m, 2H, Ph), 7.56–7.62 (m, 2H, 1H of Ph, H8'), 7.71 (dd, 1H, J = 2.6, 8.7 Hz, H6'), 7.79 (s, 1H, NH), 7.84–7.89 (m, 2H, Ph), 11.42 (s, 1H, NHCO). ^{1}H NMR δ (**3c'**): 4.37 (d, 1H, J = 9.6 Hz, CH_2), 5.15 (d, 1H, J = 9.6 Hz, CH_2), 6.86 (d, 1H, J = 9.0 Hz, H8'), 7.44–7.51 (m, 2H, Ph), 7.56–7.62 (m, 1H, Ph), 7.77 (d, 1H, J = 2.3 Hz, H5'), 7.83–7.89 (m, 3H, H7', 2H of Ph), 8.38 (s, 1H, NH), 11.20 (s, 1H, NHCO). ^{13}C NMR δ (**3c**): 72.9, 84.2, 108.4, 114.8, 115.1, 126.2, 128.2, 128.8, 131.7, 132.4, 142.6, 163.8, 164.5. MS (FAB, *m/z*, %) (**3c/c'**): 325 (MH^+, 61). *Anal.* Calcd for $C_{16}H_{12}N_4O_4$ (**3c/c'**): C, 59.26; H, 3.73; N, 17.28. Found: C, 59.18; H, 3.51; N, 17.54.

6'-Chloro-2-phenyl-1'*H*,5*H*-spiro[oxazole-4,2'-quinoxalin]-3'(4'*H*)-one (3d) and 7'-Chloro-2-phenyl-1'*H*,5*H*-spiro[oxazole-4,2'-quinoxalin]-3'(4'*H*)-one (3d'). Following the typical procedure A, treatment of diamine **1d** (71 mg, 0.5 mmol) with acid **2** (113 mg, 0.5 mmol) and Et_3N (80 mg, 0.8 mmol)

in EtOH (2 mL) gave a mixture of **3d** (major isomer) and **3d'** (minor isomer) (31 mg, 20%) in a ratio of 2:1; crystallization from EtOH gave a ratio of 3:1. ^{1}H NMR δ (**3d**): 4.25 (d, 1H, *J* = 9.0 Hz, CH_2), 5.10 (d, 1H, *J* = 9.0 Hz, CH_2), 6.74 (d, 1H, *J* = 9.4 Hz, H8'), 6.88–6.92 (m, 2H, H5', H7'), 7.33 (s, 1H, NH), 7.43–7.51 (m, 2H, Ph), 7.56–7.62 (m, 1H, Ph), 7.82–7.88 (m, 2H, Ph), 10.88 (s, 1H, NHCO). ^{1}H NMR δ (**3d'**): 4.26 (d, 1H, *J* = 9.4 Hz, CH_2), 5.11 (d, 1H, *J* = 9.4 Hz, CH_2), 6.73–6.80 (m, 2H, H6', H8'), 6,86 (d, 1H, *J* = 8.3 Hz, H5'), 7.40 (s, 1H, NH), 7.43–7.51 (m, 2H, Ph), 7.56–7.62 (m, 1H, Ph), 7.82–7.88 (m, 2H, Ph), 10.88 (s, 1H, NHCO). MS (FAB, *m/z*, %) (**3d/d'**): 314 (MH^+, 100). *Anal.* Calcd for $C_{16}H_{12}ClN_3O_2$ (**3d/d'**): C, 61.25; H, 3.86; N, 13.39. Found: C, 61.29; H, 3.61; N, 13.62.

7'-Benzoyl-2-phenyl-1'*H*,5*H*-spiro[oxazole-4,2'-quinoxalin]-3'(4'*H*)-one (3e) and 6'-Benzoyl-2-phenyl-1'*H*,5*H*-spiro[oxazole-4,2'-quinoxalin]-3'(4'*H*)-one (3e'). Following the typical procedure A, treatment of diamine **1e** (212 mg, 1.0 mmol) with acid **2** (226 mg, 1.0 mmol) and Et_3N (160 mg, 1.6 mmol) in EtOH (4 mL) gave a mixture of **3e** (major isomer) and **3e'** (minor isomer) (118 mg, 31%) in a ratio of 13:1; crystallization from EtOH gave a ratio of 33:1. ^{1}H NMR δ (**3e**): 4.27 (d, 1H, *J* = 9.4 Hz, CH_2), 5.15 (d, 1H, *J* = 9.6 Hz, CH_2), 7.02 (d, 1H, *J* = 7.9, H5'), 7.18–7.24 (m, 2H, H6', H8'), 7.43–7.72 (m, 9H, 8H of Ph, NH), 7.83–7.89 (m, 2H, Ph), 11.18 (s, 1H, NHCO). ^{1}H NMR δ (**3e'**): 6.85 (d, 1H, *J* = 8.3, H8'), 7.35 (dd, 1H, *J* = 1.9, 8.3 Hz, H7'), 7.97 (s, 1H, NH), 10.96 (s, 1H, NHCO). ^{13}C NMR δ (**3e**): 72.9, 84.6, 114.5, 115.2, 121.9, 126.5, 128.2, 128.3, 128.7, 129.1, 129.9, 131.5, 131.9, 132.0, 132.3, 137.9, 163.5, 164.6, 194.7. MS (EI, *m/z*, %) (**3e/e'**): 383 (M^+, 15). *Anal.* Calcd for $C_{23}H_{17}N_3O_3$ (**3e/e'**): C, 72.05; H, 4.47; N, 10.96. Found: C, 71.94; H, 4.37; N, 10.81.

6',7'-Dichloro-2-phenyl-1'*H*,5*H*-spiro[oxazole-4,2'-quinoxalin]-3'(4'*H*)-one (3f). Following the typical procedure A, treatment of diamine **1f** (89 mg, 0.5 mmol) with acid **2** (113 mg, 0.5 mmol) and Et_3N (80 mg, 0.8 mmol) in EtOH (2 mL) gave **3f** (60 mg, 34%). mp 252–254 °C (EtOH). ^{1}H NMR δ: 4.28 (d, 1H, *J* = 9.4 Hz, CH_2), 5.11 (d, 1H, *J* = 9.4 Hz, CH_2), 6.90 (s, 1H, H8'), 7.03 (s, 1H, H5'), 7.44–7.62 (m, 4H, 3H of Ph, NH), 7.82–7.88 (m, 2H, Ph), 11.00 (s, 1H, NHCO). MS (EI, *m/z*, %): 347 (M^+, 38). *Anal.* Calcd for $C_{16}H_{11}Cl_2N_3O_2$: C, 55.19; H, 3.18; N, 12.07. Found: C, 54.87; H, 3.25; N, 11.80.

2'-Phenyl-1*H*,5'*H*-spiro[benzo[g]quinoxaline-2,4'-oxazole]-3(4*H*)-one (3g). Following the typical procedure A, treatment of diamine **1g** (158 mg, 1.0 mmol) with acid **2** (226 mg, 1.0 mmol) and Et_3N (160 mg, 1.6 mmol) in EtOH (4 mL), gave **3g** (91 mg, 28%). mp 284–285 °C (DMF–EtOH). ^{1}H NMR δ: 4.34 (d, 1H, *J* = 9.4 Hz, CH_2), 5.16 (d, 1H, *J* = 9.4 Hz, CH_2), 7.10 (s, 1H, H10), 7.20–7.31 (m, 3H, H5, H7, H8), 7.42–7.51 (m, 3H, 2 H of Ph, NH), 7.54–7.61 (m, 1H, Ph), 7.61–7.71 (m, 2H, H6, H9), 7.82–7.87 (m, 2H, Ph), 11.11 (s, 1H, NHCO). MS (EI, *m/z*, %): 329 (M^+, 73). *Anal.* Calcd for $C_{20}H_{15}N_3O_2$: C, 72.94; H, 4.59; N, 12.76. Found: C, 72.91; H, 4.73; N, 12.93.

2-Phenyl-1'*H*,5*H*-spiro[oxazole-4,2'-pyrido[3,2-*b*]pyrazin]-3'(4'*H*)-one (3h). Following the typical procedure A, treatment of diamine **1h** (55 mg, 0.5 mmol) with acid **2** (113 mg, 0.5 mmol) and Et_3N (80 mg, 0.8 mmol) in EtOH (2 mL) gave **3h** (70 mg, 50%). mp 265–266 °C (DMF–MeOH). ^{1}H NMR δ: 4.29 (d, 1H, *J* = 9.4 Hz, CH_2), 5.13 (d, 1H, *J* = 9.4 Hz, CH_2), 6.91 (dd, 1H, *J* = 4.9, 7.9 Hz, H7'), 7.09 (dd, 1H, *J* = 1.5, 7.9 Hz, H8'), 7.38 (s, 1H, NH), 7.43–7.50 (m, 2H, Ph), 7.55–7.61 (m, 1H, Ph), 7.74 (dd, 1H, *J* = 1.5, 4.9 Hz, H6'), 7.83–7.88 (m, 2H, Ph), 11.24 (s, 1H, NHCO). ^{13}C NMR δ: 72.8, 84.7, 118.9, 120.1, 126.5, 128.0, 128.2, 128.7, 132.3, 137.4, 140.0, 163.5, 165.2. MS (EI, *m/z*, %): 280 (M^+, 56). *Anal.* Calcd for $C_{15}H_{12}N_4O_2$: C, 64.28; H, 4.32; N, 19.99. Found: C, 63.92; H, 4.02; N, 20.04.

2-Phenyl-5*H*,5'*H*-spiro[oxazole-4,6'-pteridin]-7'(8'*H*)-one (3i). Following the typical procedure A, treatment of diamine **1i** (55 mg, 0.5 mmol) with acid **2** (113 mg, 0.5 mmol) and Et_3N (80 mg, 0.8 mmol) in EtOH (2 mL) gave **3i** (52 mg, 37%). mp 246–248 °C (EtOH). ^{1}H NMR δ: 4.33 (d, 1H, *J* = 9.6 Hz, CH_2), 5.14 (d, 1H, *J* = 9.6 Hz, CH_2), 7.44–7.51 (m, 2H, Ph), 7.56–7.65 (m, 2H, 1H of Ph, NH), 7.84–7.89 (m, 2H, Ph), 8.08 (s, 1H, H4'), 8.36 (s, 1H, H2'), 11.74 (s, 1H, NHCO). MS (EI, *m/z*, %): 281 (M^+, 46). *Anal.* Calcd for $C_{14}H_{11}N_5O_2$: C 59.78; H, 3.94; N, 24.90. Found: C, 59.49; H, 3.72; N, 25.01.

4'-Methyl-2-phenyl-1'*H*,5*H*-spiro[oxazole-4,2'-quinoxalin]-3'(4'*H*)-one (4a). *From **3a** using methyl iodide. Typical Procedure B*: To a mixture of spiro compound **3a** (140 mg, 0.5 mmol) and MeCN (5 mL), K_2CO_3 (690 mg, 5 mmol), Bu_4NHSO_4 (34 mg, 0.1 mmol), and MeI (0.13 mL, 2.1 mmol) were added. The reaction mixture was stirred at 80 °C for 6 h. Upon cooling to rt, the solid was filtered off and washed with MeCN (2 x 3 mL). The collected filtrate was evaporated under reduced pressure, the solid residue was suspended in MeOH (1 mL), filtered off and washed with MeOH to give **4a** (116 mg, 79%). mp 210-215 °C (MeOH). ^{1}H NMR δ: 3.37 (s, 3H, Me), 4.27 (d, 1H, *J* = 9.2 Hz, CH_2), 5.17 (d, 1H, *J* = 9.2 Hz, CH_2), 6.81 (dd, 1H, *J* = 1.5, 7.9 Hz, H8'), 6.86 (ddd, 1H, *J* = 1.5, 7.5, 7.9 Hz, H6'), 6.96 (ddd, 1H, *J* = 1.5, 7.5, 7.9 Hz, H7'), 7.09–7.14 (m, 1H, H5'), 7.25 (s, 1H, NH), 7.41–7.48 (m, 2H, Ph), 7.53–7.60 (m, 1H, Ph), 7.80–7.86 (m, 2H, Ph). ^{13}C NMR δ: 29.2, 73.4, 85.0, 114.2, 114.7, 119.0, 123.4, 126.6, 127.8, 128.2, 128.7, 132.2, 133.2, 163.5, 164.0. MS (EI, *m/z*, %): 293 (M^+, 78). *Anal.* Calcd for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.33. Found: C, 69.60; H, 5.17; N, 14.40.

*From **3a** using dimethyl sulphate*: To a mixture of spiro compound **3a** (98 mg, 0.35 mmol), Me_2SO_4 (65 mg, 0.5 mmol), and MeCN (2 mL), 33% NaOH was added until pH exceeded 8. The reaction mixture was then heated under reflux for 1.5 h. Upon cooling to rt, diluted H_2SO_4 (1:4) was added until pH = 6.5. Extraction with AcOEt (2 x 5 mL) gave the crude solid, which was suspended in MeOH (1 mL). The precipitated solid was filtered off and washed with MeOH to give **4a** (26 mg, 25%).

*From **3a** using N,N-dimethylformamide dimethyl acetal*. A mixture of spiro compound **3a** (140 mg, 0.5 mmol), *N*,*N*-dimethylformamide dimethyl acetal (179 mg, 1.5 mmol), and toluene (2 mL) was heated

under reflux for 8.5 h. The volatile compounds were then removed under reduced pressure and the solid residue was suspended in MeOH (1 mL), filtered off, washed with MeOH and crystallized from EtOH to give **4a** (50 mg, 34%).

*From N-methylbenzene-1,2-diamine and **2***: To a mixture of *N*-methylbenzene-1,2-diamine (**7**) (249 mg, 2 mmol) and acid **2** (451 mg, 2 mmol) in EtOH (8 mL), Et_3N (320 mg, 3.2 mmol) was added. The reaction mixture was then heated under reflux for 7 h. The volatile compounds were removed under reduced pressure, the residue was suspended in EtOH (2 mL), filtered off and washed with EtOH to give **4a** (166 mg, 28%).

4'-Methyl-7'-nitro-2-phenyl-1'*H*,5*H*-spiro[oxazole-4,2'-quinoxalin]-3'(4'*H*)-one (4c) and 4'-Methyl-6'-nitro-2-phenyl-1'*H*,5*H*-spiro[oxazole-4,2'-quinoxalin]-3'(4'*H*)-one (4c'). Following the typical procedure B, treatment of a mixture of spiro compounds **3c** and **3c'** (ratio 6:1) (113 mg, 0.35 mmol) with K_2CO_3 (483 mg, 3.4 mmol), Bu_4NHSO_4 (24 mg, 0.07 mmol) and MeI (0.09 mL, 1.4 mmol) in MeCN (4 mL) gave a mixture of **4c** (major isomer) and **4c'** (minor isomer) (99 mg, 84%); crystallization from DMF–MeOH gave a ratio of 14:1. ^{1}H NMR δ (**4c**): 3.46 (s, 3H, Me), 4.33 (d, 1H, J = 9.8 Hz, CH_2), 5.21 (d, 1H, J = 9.8 Hz, CH_2), 7.35 (d, 1H, J = 8.9 Hz, H5'), 7.43–7.50 (m, 2H, Ph), 7.55–7.62 (m, 1H, Ph), 7.63 (d, 1H, J = 2.6 Hz, H8'), 7.78 (dd, 1H, J = 2.6, 8.9 Hz, H6'), 7.81–7.86 (m, 2H, Ph), 7.79 (s, 1H, NH). ^{1}H NMR δ (**4c'**): 3.48 (s, 3H, Me), 4.38 (d, 1H, J = 9.4 Hz, CH_2), 5.20 (d, 1H, J = 9.4 Hz, CH_2), 6.92 (d, 1H, J = 9.0 Hz, H8'), 8.49 (s, 1H, NH). MS (EI, *m/z*, %) (**4c/c'**): 338 (M^+, 91). *Anal.* Calcd for $C_{17}H_{14}N_4O_4$ (**4c/c'**): C, 60.35; H, 4.17; N, 16.56. Found: C, 60.31; H, 4.06; N, 16.36.

6'-Chloro-4'-methyl-2-phenyl-1'*H*,5*H*-spiro[oxazole-4,2'-quinoxalin]-3'(4'*H*)-one (4d) and 7'-Chloro-4'-methyl-2-phenyl-1'*H*,5*H*-spiro[oxazole-4,2'-quinoxalin]-3'(4'*H*)-one (4d'). *Typical Procedure C*: To a mixture of spiro compounds **3d** and **3d'** (ratio 2:1) (110 mg, 0.35 mmol) in MeCN (4 mL), K_2CO_3 (483 mg, 3.4 mmol), Bu_4NHSO_4 (24 mg, 0.07 mmol), and MeI (0.09 mL, 1.4 mmol) were added. The reaction mixture was then stirred at 80 °C for 7 h. Upon cooling to rt, the solid was filtered off, washed with MeCN (2 x 3 mL) and suspended in water (2 mL). The insoluble residue was filtered off and washed with water to give pure **4d** (35 mg, 30%). mp 245-248 °C (EtOH–MeOH). The collected filtrate obtained by first filtration was evaporated under reduced pressure, the residue was suspended in MeOH (1 mL), filtered off and washed with MeOH to give a mixture of **4d** (minor isomer) and **4d'** (major isomer) (45 mg, 39%); crystallization from MeOH–EtOH gave a mixture of **4d/4d'** in a ratio of 1:5. ^{1}H NMR δ (**4d**): 3.37 (s, 3H, Me), 4.28 (d, 1H, J = 9.4 Hz, CH_2), 5.17 (d, 1H, J = 9.4 Hz, CH_2), 6.80 (d, 1H, J = 8.7 Hz, H8'), 7.00 (dd, 1H, J = 2.3, 8.7 Hz, H7'), 7.19 (d, 1H, J = 2.3 Hz, H5'), 7.41–7.49 (m, 3H, 2 H of Ph, NH), 7.54–7.61 (m, 1H, Ph), 7.80–7.86 (m, 2H, Ph). ^{1}H NMR δ (**4d'**): 3.36 (s, 3H, Me), 4.28 (d, 1H, J = 9.4 Hz, CH_2), 5.18 (d, 1H, J = 9.4 Hz, CH_2), 6.80 (d, 1H, J = 2.3 Hz, H8'), 6.89 (dd, 1H, J = 2.3, 8.7 Hz,

H6'), 7.13 (d, 1H, *J* = 8.7 Hz, H5'), 7.42–7.49 (m, 2H, Ph), 7.51 (s, 1H, NH), 7.55–7.61 (m, 1H, Ph), 7.80–7.86 (m, 2H, Ph). MS (FAB, *m/z*, %) (**4d**): 328 (MH^+, 8). *Anal.* Calcd for $C_{17}H_{14}ClN_3O_2$ (**4d**): C, 62.30; H, 4.31; N, 12.82. Found: C, 61.94; H, 4.17; N, 12.50.

6',7'-Dichloro-4'-methyl-2-phenyl-1'*H*,5*H*-spiro[oxazole-4,2'-quinoxalin]-3'(4'*H*)-one (4f). Following the typical procedure C, treatment of spiro compound **3f** (122 mg, 0.35 mmol) with K_2CO_3 (966 mg, 7 mmol), Bu_4NHSO_4 (48 mg, 0.14 mmol) and MeI (0.18 mL, 2.9 mmol) in MeCN (6 mL) gave **4f** (91 mg, 72%). mp 238–243 °C (DMF–MeOH). ^{1}H NMR δ: 3.38 (s, 3H, Me), 4.30 (d, 1H, *J* = 9.8 Hz, CH_2), 5.17 (d, 1H, *J* = 9.8 Hz, CH_2), 6.95 (s, 1H, H8'), 7.37 (s, 1H, H5'), 7.43–7.50 (m, 2H, Ph), 7.55–7.62 (m, 1H, Ph), 7.63 (s, 1H, NH), 7.81–7.86 (m, 2H, Ph). MS (EI, *m/z*, %): 361 (M^+, 68). *Anal.* Calcd for $C_{17}H_{13}Cl_2N_3O_2$: C, 56.37; H, 3.62; N, 11.60. Found: C, 56.17; H, 3.58; N, 11.43.

4-Methyl-2'-phenyl-1*H*,5'*H*-spiro[benzo[g]quinoxaline-2,4'-oxazole]-3(4*H*)-one (4g). Following the typical procedure C, treatment of spiro compound **3g** (115 mg, 0.35 mmol) with K_2CO_3 (966 mg, 7 mmol), Bu_4NHSO_4 (48 mg, 0.14 mmol) and MeI (0.18 mL, 2.9 mmol) in MeCN (6 mL) gave **4g** (68 mg, 57%). mp 248–252 °C dec. (DMF–MeOH). ^{1}H NMR δ: 3.51 (s, 3H, Me), 4.36 (d, 1H, *J* = 9.4 Hz, CH_2), 5.21 (d, 1H, *J* = 9.4 Hz, CH_2), 7.15 (s, 1H, H10), 7.25–7.37 (m, 2H, H7, H8), 7.41–7.47 (m, 2H, Ph), 7.53–7.69 (m, 4H, 1H of Ph, H6, H9, NH), 7.79–7.85 (m, 3H, 2H of Ph, H5). MS (EI, *m/z*, %): 343 (M^+, 83). *Anal.* Calcd for $C_{21}H_{17}N_3O_2$: C, 73.45; H, 4.99; N, 12.24. Found: C, 73.29; H, 5.29; N, 12.27.

4'-Methyl-2-phenyl-1'*H*,5*H*-spiro[oxazole-4,2'-pyrido[3,2-*b*]pyrazin]-3'(4'*H*)-one (4h). Following the typical procedure B, treatment of spiro compound **3h** (98 mg, 0.35 mmol) with K_2CO_3 (966 mg, 7 mmol), Bu_4NHSO_4 (48 mg, 0.14 mmol) and MeI (0.18 mL, 2.9 mmol) in MeCN (6 mL) gave **4h** (73 mg, 71%). mp 225–228 °C (MeOH). ^{1}H NMR δ: 3.44 (s, 3H, Me), 4.31 (d, 1H, *J* = 9.4 Hz, CH_2), 5.19 (d, 1H, *J* = 9.4 Hz, CH_2), 7.00 (dd, 1H, *J* = 4.9, 7.9 Hz, H7'), 7.14 (dd, 1H, *J* = 1.5, 7.9 Hz, H8'), 7.43–7.52 (m, 3H, 2H of Ph, NH), 7.55–7.61 (m, 1H, Ph), 7.82–7.89 (m, 3H, H6', 2H of Ph). MS (EI, *m/z*, %): 294 (M^+, 100). *Anal.* Calcd for $C_{16}H_{14}N_4O_2$: C, 65.30; H, 4.79; N, 19.04. Found: C, 65.24; H, 4.88; N, 18.95.

4'-Ethyl-7'-nitro-2-phenyl-1'*H*,5*H*-spiro[oxazole-4,2'-quinoxalin]-3'(4'*H*)-one (5c). Following the typical procedure B, treatment of a mixture of spiro compounds **3c** and **3c'** (ratio 6:1) (113 mg, 0.35 mmol) with, K_2CO_3 (725 mg, 5.25 mmol), Bu_4NHSO_4 (36 mg, 0.11 mmol) and EtBr (0.16 mL, 2.1 mmol) in MeCN (4 mL) for 3h gave only isomer **5c** (73 mg, 60%). mp 226–231 °C (EtOH). ^{1}H NMR δ: 1.18 (t, 3H, *J* = 7.0 Hz, CH_2CH_3), 4.03–4.16 (m, 2H, CH_2CH_3), 4.33 (d, 1H, *J* = 9.8 Hz, CH_2), 5.22 (d, 1H, *J* = 9.8 Hz, CH_2), 7.38–7.50 (m, 3H, 2H of Ph, H5'), 7.55–7.62 (m, 1H, Ph), 7.65 (d, 1H, *J* = 2.6 Hz, H8'), 7.76 (dd, 1H, *J* = 2.6, 9.1 Hz, H6'), 7.81–7.87 (m, 2H, Ph), 7.89 (s, 1H, NH). MS (EI, *m/z*, %): 352 (M^+, 73). *Anal.* Calcd for $C_{18}H_{16}N_4O_4$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.21; H, 4.94; N, 15.89.

6'-Chloro-4'-ethyl-2-phenyl-1'*H*,5*H*-spiro[oxazole-4,2'-quinoxalin]-3'(4'*H*)-one (5d) and 7'-Chloro-4'-ethyl-2-phenyl-1'*H*,5*H*-spiro[oxazole-4,2'-quinoxalin]-3'(4'*H*)-one (5d'). Following the typical procedure B, treatment of a mixture of spiro compounds **3d/d'** (ratio 2:1) (110 mg, 0.35 mmol) with, K_2CO_3 (725 mg, 5.25 mmol), Bu_4NHSO_4 (36 mg, 0.11 mmol) and EtBr (0.16 mL, 2.1 mmol) in MeCN (4 mL) for 3h gave a crude mixture of **5d/d'**; crystallization from EtOH gave a mixture of **5d** (major isomer) and **5d'** (minor isomer) (34 mg, 28%) in a ratio of 3:1. ^{1}H NMR δ (**5d**): 1.13 (t, 3H, *J* = 7.0 Hz, CH_2CH_3), 4.01 (q, 2H, *J* = 7.0 Hz, CH_2CH_3), 4.27 (d, 1H, *J* = 9.4 Hz, CH_2), 5.18 (d, 1H, *J* = 9.4 Hz, CH_2), 6.81 (d, 1H, *J* = 8.3 Hz, H8'), 6.99 (dd, 1H, *J* = 2.3, 8.3 Hz, H7'), 7.22 (d, 1H, *J* = 2.3 Hz, H5'), 7.41 (s, 1H, NH), 7.42 –7.49 (m, 2H, Ph), 7.54–7.61 (m, 1H, Ph), 7.80–7.86 (m, 2H, Ph). ^{1}H NMR δ (**5d'**): 1.13 (t, 3H, *J* = 7 Hz, CH_2CH_3), 4.0 (q, 2H, *J* = 7.0 Hz, CH_2CH_3), 4.27 (d, 1H, *J* = 9.4 Hz, CH_2), 5.18 (d, 1H, *J* = 9.4 Hz, CH_2), 6.81 (d, 1H, *J* = 2.3 Hz, H8'), 6.88 (dd, 1H, *J* = 2.3, 8.7 Hz, H6'), 7.17 (d, 1H, *J* = 8.7 Hz, H5'), 7.42–7.49 (m, 3H, 2H of Ph, NH), 7.54–7.61 (m, 1H, Ph), 7.80–7.86 (m, 2H, Ph). MS (EI, *m/z*, %) (**5d/d'**): 341 (M^+, 66). *Anal.* Calcd for $C_{18}H_{16}ClN_3O_2$ (**5d/d'**): C, 63.25; H, 4.72; N, 12.29. Found: C, 62.87; H, 4.69; N, 12.14.

6',7'-Dichloro-4'-ethyl-2-phenyl-1'*H*,5*H*-spiro[oxazole-4,2'-quinoxalin]-3'(4'*H*)-one (5f). Following the typical procedure B, treatment of spiro compound **3f** (122 mg, 0.35 mmol) with K_2CO_3 (7.25 mg, 5.25 mmol), Bu_4NHSO_4 (36 mg, 0.11 mmol) and EtBr (0.16 mL, 2.1 mmol) in MeCN (4 mL) for 2h gave **5f** (107 mg, 81%). mp 215–216 °C (EtOH). ^{1}H NMR δ: 1.13 (t, 3H, *J* = 7.1 Hz, CH_2CH_3), 4.02 (q, 2H, *J* = 7.1 Hz, CH_2CH_3), 4.29 (d, 1H, *J* = 9.6 Hz, CH_2), 5.18 (d, 1H, *J* = 9.6 Hz, CH_2), 6.97 (s, 1H, H8'), 7.41 (s, 1H, H5'), 7.43–7.50 (m, 2H, Ph), 7.55–7.63 (m, 2H, NH, 1H of Ph), 7.81–7.86 (m, 2H, Ph). MS (EI, *m/z*, %): 375 (M^+, 73). *Anal.* Calcd for $C_{18}H_{15}Cl_2N_3O_2$: C, 57.46; H, 4.02; N, 11.17. Found: C, 57.50; H, 4.19; N, 10.86.

4-Ethyl-2'-phenyl-1*H*,5'*H*-spiro[benzo[g]quinoxaline-2,4'-oxazole]-3(4*H*)-one (5g). Following the typical procedure B, treatment of spiro compound **3g** (115 mg, 0.35 mmol) with K_2CO_3 (725 mg, 5.25 mmol), Bu_4NHSO_4 (36 mg, 0.11 mmol) and EtBr (0.16 mL, 2.1 mmol) in MeCN (4 mL) for 7.5h gave **5g** (after double crystallization: 86 mg, 69%). mp 247–249 °C (EtOH). ^{1}H NMR δ: 1.24 (br t, 3H, *J* = 7.0 Hz, CH_2CH_3), 4.14 (br q, 2H, *J* = 7.0 Hz, CH_2CH_3), 4.35 (d, 1H, *J* = 9.2 Hz, CH_2), 5.22 (d, 1H, *J* = 9.2 Hz, CH_2), 7.15 (s, 1H, H10), 7.23–7.86 (m, 11H, NH, H5, H6, H7, H8, H9, 5H of Ph). MS (EI, *m/z*, %): 357 (M^+, 100). *Anal.* Calcd for $C_{22}H_{19}N_3O_2$: C, 73.93; H, 5.36; N, 11.76. Found: C, 74.11; H, 5.61; N, 11.84.

4'-Ethyl-2-phenyl-1'*H*,5*H*-spiro[oxazole-4,2'-pyrido[3,2-*b*]pyrazin]-3'(4'*H*)-one (5h). Following the typical procedure B, treatment of spiro compound **3h** (98 mg, 0.35 mmol) with K_2CO_3 (725 mg, 5.25 mmol), Bu_4NHSO_4 (36 mg, 0.11 mmol) and EtBr (0.16 mL, 2.1 mmol) in MeCN (4 mL) for 7h gave **5h** (71 mg, 66%). mp 201–203 °C (EtOH). ^{1}H NMR δ: 1.15 (t, 3H, *J* = 7.0 Hz, CH_2CH_3), 4.02–4.30 (m, 2H,

CH$_2$CH$_3$), 4.30 (d, 1H, *J* = 9.4 Hz, CH$_2$), 5.19 (d, 1H, *J* = 9.4 Hz, CH$_2$), 7.00 (dd, 1H, *J* = 4.9, 7.9 Hz, H7'), 7.14 (dd, 1H, *J* = 1.5, 7.9 Hz, H8'), 7.43–7.50 (m, 3H, 2H of Ph, NH), 7.55–7.61 (m, 1H, Ph), 7.82–7.89 (m, 3H, 2H of Ph, H6'). MS (EI, *m/z*, %): 308 (M$^+$, 100). *Anal.* Calcd for $C_{17}H_{16}N_4O_2$: C, 66.22; H, 5.23; N, 18.17. Found: C, 66.08; H, 5.38; N, 18.06.

4'-Ethyl-2-phenyl-5*H*,5'*H*-spiro[oxazole-4,6'-pteridin]-7'(8'*H*)-one (5i). Following the typical procedure B, treatment of spiro compound **3i** (98 mg, 0.35 mmol) with K_2CO_3 (7.25 mg, 5.25 mmol), Bu_4NHSO_4 (36 mg, 0.11 mmol) and EtBr (0.16 mL, 2.1 mmol) in MeCN (4 mL) for 5 h afforded **5i** (after crystallization from EtOH: 20 mg, 19%). mp 189–194 °C. ^{1}H NMR δ: 1.17 (t, 3H, *J* = 7.2 Hz, CH$_2$*CH*$_3$), 4.01–4.07 (m, 2H, *CH*$_2$CH$_3$), 4.36 (d, 1H, *J* = 9.6 Hz, CH$_2$), 5.21 (d, 1H, *J* = 9.6 Hz, CH$_2$), 7.44–7.50 (m, 2H, Ph), 7.57–7.63 (m, 1H, Ph), 7.76 (s, 1H, NH), 7.83–7.88 (m, 2H, Ph), 8.14 (s, 1H, H4'), 8.50 (s, 1H, H2'). MS (EI, *m/z*, %): 309 (M$^+$, 59). *Anal.* Calcd for $C_{16}H_{15}N_5O_2$: C 62.13; H, 4.89; N, 22.64. Found: C, 61.83; H, 5.21; N, 22.83.

4'-(2-Hydroxyethyl)-2-phenyl-1'*H*,5*H*-spiro[oxazole-4,2'-quinoxalin]-3'(4'*H*)-one (6a). *From **3a** and 1,2-dibromoethane*: To a mixture of spiro compound **3a** (140 mg, 0.5 mmol) and MeCN (10 mL), K_2CO_3 (1.38 g, 10 mmol), Bu_4NHSO_4 (68 mg, 0.2 mmol), and 1,2-dibromoethane (0.86 mL, 10 mmol) were added. The reaction mixture was then stirred at 80 °C for 10.5 h. Upon cooling to rt, the solid was filtered off and washed with MeCN (2 x 4 mL). The collected filtrate was evaporated under reduced pressure and the oily residue was purified by radial chromatography ($CHCl_3$, MeOH 50:1) to give **6a** (105 mg, 65%).

*From **3a** and 1,2-dichloroethane*: To a mixture of **3a** (98 mg, 0.35 mmol) and MeCN (5 mL), K_2CO_3 (966 mg, 7 mmol), Bu_4NHSO_4 (48 mg, 0.14 mmol) and 1,2-dichloroethane (0.55 mL, 10 mmol) were added. The reaction mixture was then stirred at 80 °C for 9 h. Upon cooling to rt, the solid was filtered off and washed with MeCN (2 x 2 mL). The collected filtrate was evaporated under reduced pressure and the oily residue was purified by radial chromatography ($CHCl_3$, MeOH 50:1) to give **6a** (58 mg, 51%). mp 227–230 °C (EtOH). ^{1}H NMR δ: 3.50–3.61 (m, 2H, *CH*$_2$OH), 4.04 (br t, 2H, *J* = 6.8 Hz, *CH*$_2$CH$_2$OH), 4.26 (d, 1H, *J* = 9.0 Hz, CH$_2$), 4.88 (t, 1H, *J* = 5.5 Hz, CH$_2$*OH*, 5.17 (d, 1H, *J* = 9.0 Hz, CH$_2$), 6.78–6.97 (m, 3H, H6', H7', H8'), 7.19–7.24 (m, 2H, H5', NH), 7.42–7.48 (m, 2H, Ph), 7.54–7.60 (m, 1H, Ph), 7.80–7.85 (m, 2H, Ph). MS (EI, *m/z*, %): 323 (M$^+$, 83). *Anal.* Calcd for $C_{18}H_{17}N_3O_3$: C, 66.86; H, 5.30; N, 13.00. Found: C, 66.56; H, 5.61; N, 12.77.

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