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Solid-phase parallel synthesis of trisubstituted dihydroimidazolyl dihydroquinoxalin-2(1*H*)-ones

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Abstract—An efficient approach for the solid-phase synthesis of dihydroimidazolyl dihydroquinoxalin-2(1*H*)-ones is described. Following reduction of a resin-bound amino acid amide, the primary amine of the resulting di-amine was selectively N-acylated with 4-fluoro-3-nitrobenzoic acid. Treatment with $POCl_3$ led to formation of a dihydroimidazolyl derivative via dehydrative cyclization. Following displacement of the aryl fluoro group with an α-amino acid methyl ester, the dihydroimidazolyl moiety was alkylated with an alkyl halide. Reduction of aromatic nitro group with concomitant intramolecular cyclization using tin(II) chloride dihydrate led to formation of the dihydroimidazolyl dihydroquinoxalin-2(1*H*)-one. The compound was characterized by LC–MS, and ^1H and ^{13}C NMR spectroscopy.

1. Introduction

The chemistry involved in the solid-phase synthesis of peptides and organic compounds has witnessed an exponential growth over the last decade.[1] Starting from the pioneering work of Merrifield,[2] where a tetrapeptide was synthesized on the solid-support, this technique has been accepted as a standard approach for synthesis of oligosaccharides,[3] nucleotides,[4] peptides,[5] and heterocycles.[1] Review articles have appeared describing various approaches for synthesis of a large number of heterocycles derived from amino acids and peptides that mimic the biological and pharmacological properties.[1] Dihydroquinoxalin-2(1*H*)-ones (benzopiperazinones) exhibit a range of biological properties including inhibition of aldose reductase,[6] acting as partial agonists of the α-aminobutyric acid (GABA)/benzodiazepine receptor complex,[7] and as angiotensin II receptor antagonists.[8] Dihydroimidazoles (imidazolines) are reported to exhibit diverse biological and pharmacological activities including acting as α-adrenergic inhibitors, vasodepressor agents, sympathomimetic agents, antihistaminic agents, antihypertensive agents,[9] anticancer agents,[10] and potent antihyperglycemic agents.[11] With the potent biological and pharmacological activities of two heterocycles described above in mind, the development of solid-phase strategies for the synthesis of substituted dihydroimidazolyl dihydroquinoxalin-2(1*H*)-ones was explored.

Keywords: dihydroimidazole; imidazoline; quinoxalinone; benzopiperazinone; combinatorial synthesis.

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2. Results and discussion

The synthetic strategy presented involves two steps: (i) the synthesis of dihydroimidazoles derived from resin-bound reduced amino acid amides using 4-fluoro-3-nitrobenzoic acid; and (ii) the synthesis of dihydroquinoxalin-2(1*H*)-one moiety using the bifunctional behavior of the fluoro-nitro phenyl groups.[12,13]

2.1. Trisubstituted dihydroimidazolyl dihydroquinoxalin-2(1*H*)-one

(i) A Boc-protected amino acid was coupled to *p*-methylbenzhydrylamine (MBHA) resin, followed by deprotection of the Boc group to generate compound **1** (Scheme 1). Reduction of **1** by treatment with BH_3–THF[14] generated resin-bound di-amine **2** having both a primary amine and a secondary amine. In order to synthesize the resin-bound dihydroimidazole, the primary amine of the di-amine **2** was selectively N-acylated with 4-fluoro-3-nitro-benzoic acid in the presence of 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) and *N*,*N*′-diisopropylethylamine (DIEA). The resulting resin-bound amide **3** was treated with $POCl_3$ to form the dihydroimidazole derivative **4** via intramolecular cyclization through the in situ imidoyl chloride intermediate.[15–17] Complete cyclization was observed by LC–MS and reverse-phase high-pressure liquid chromatography (RP-HPLC).

(ii) The resin-bound dihydroimidazole derivative **4** was treated with an α-amino acid methyl ester hydrochloride ($NH_2CH(R^2)CO_2CH_3 \cdot HCl$) in the presence of DIEA to yield an anilino compound of structure **5** via aryl fluoro

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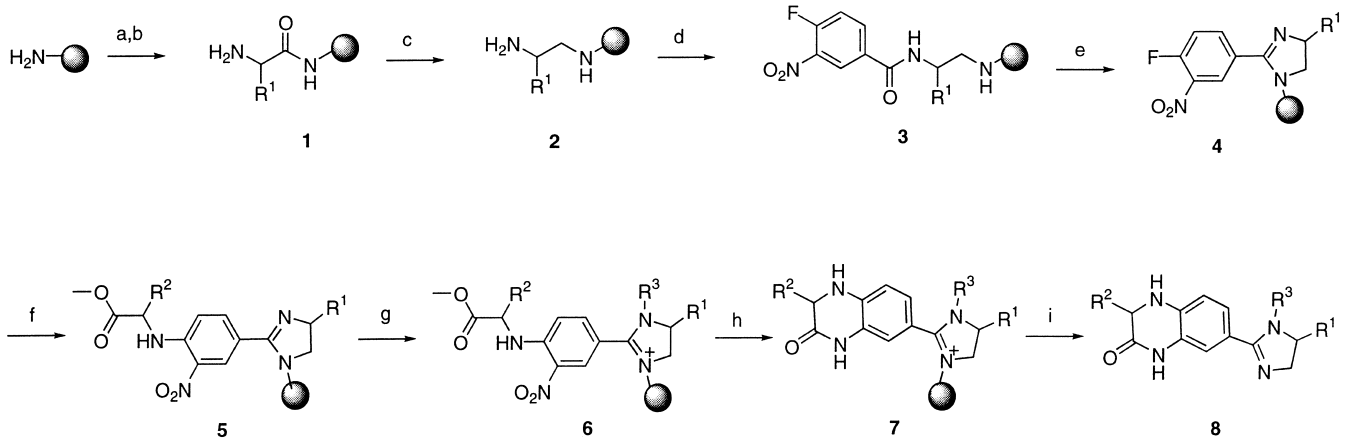


Scheme 1. (a) Boc–NHCH(R^1)CO_2H (6 equiv., 0.1 M, DMF), DIC (6 equiv.), HOBt (6 equiv.), 2 h, rt; (b) 55% TFA/45% DCM, 30 min, rt; (c) (i) BH_3–THF, 65°C, 72 h; (ii) Piperidine, 65°C, 20 h; (d) 4-fluoro-3-nitrobenzoic acid (3 equiv., 0.06 M, DMF), HBTU (3 equiv.), DIEA (6 equiv.), 3 h, rt; (e) $POCl_3$ (10 equiv., 0.09 M, anhydrous dioxane), 110°C, 2.5 h; (f) $NH_2CH(R^2)CO_2CH_3$·HCl (20 equiv., 0.2 M, DMF), DIEA (25 equiv.), 20 h, rt; (g) R^3X (X=I, Br) (20 equiv., 0.2 M, DMF), DIEA (10 equiv.), rt, 20 h; (h) $SnCl_2·2H_2O$ (20 equiv., 0.5 M, DMF), 15 h, rt; (i) HF, anisole, 0°C, 7 h.

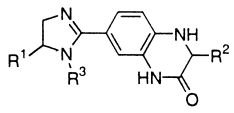
displacement. Subsequent treatment with an alkyl halide (R^3X, X=Br, I) in the presence of DIEA formed compound of structure **6**. The resulting resin-bound Compound **6** was treated with tin(II) chloride dihydrate ($SnCl_2·2H_2O$) yielding the dihydroimidazole derivative of dihydroquinoxalin-2(1*H*)-one **7** via reduction of aromatic nitro group with concomitant intramolecular cyclization. Morales et al. reported the intramolecular cyclization via reduction of aromatic nitro group using aqueous 2 M $SnCl_2$ (80°C, overnight) to generate substituted dihydroquinoxalin-2(1*H*)-ones on the solid-phase.[13] It is noteworthy to mention here that complete cyclization, as determined by LC–MS, was achieved at a much lower concentration of tin(II) chloride dihydrate (i.e. using 20 equiv., 0.5 M) in DMF and at lower temperature (i.e. 15 h at room temperature) in comparison to the Morales et al. conditions.[13] The compound was cleaved from the solid-support using anhydrous HF, followed by extraction with 95% acetic acid in water to yield dihydroimidazolyl dihydroquinoxalin-2(1*H*)-one **8**.

Eighty individual control compounds were prepared using 30 amino acids at the first position (R^1) of diversity, 20 α-amino acid methyl esters at the second position (R^2) of diversity, and 30 alkyl halides at the third position (R^3) of diversity. Serine and threonine analogs at the first position of diversity (R^1) yielded undesirable byproducts most likely during $POCl_3$ treatment. Amino acids having either an extra amine functionality (e.g. arginine) or generating an extra amine functionality after reduction (e.g. glutamine) were not included at the first position (R^1) of diversity due to formation of undesirable byproducts during N-acylation and/or $POCl_3$ treatment. Cysteine and histidine ester analogs at the second position (R^2) of diversity gave undesirable impurities during alkylation. Ethyl bromide, α-bromoxylenes (*o*, *m*, and *p*), 2-(bromomethyl)naphthalene, and geranyl bromide yielded primarily starting materials following alkylation of the dihydroimidazolyl moiety at the third position (R^3) of diversity. In all other cases, negligible amounts of starting materials were observed during $POCl_3$ mediated cyclization, alkylation using alkyl halides, and $SnCl_2·2H_2O$ mediated cyclization.

Nineteen randomly chosen individual control compounds are presented here (Table 1). These compounds were derived from 5 amino acids (L-Val, L-phenylglycine, *O*-ethyl-L-tyrosine, L-cyclohexylglycine, and L-Ala) at the first position (R^1) of diversity, 8 α-amino acid methyl esters (L-Ala, L-Leu, L-Met, L-cyclohexylalanine, L-Val, L-Ser, L-phenylglycine, and L-Tyr) at the second (R^2) position of diversity, and 8 alkyl halides (benzyl bromide, 2-bromobenzyl bromide, 1-bromomethyl-2-[(phenylsulfonyl)-methyl]benzene, 3-methoxybenzyl bromide, 3-chlorobenzyl bromide, iodomethane, allyl bromide, and 3,4-difluorobenzyl bromide) at the third (R^3) position of diversity. The final products were obtained in moderate yield (>60%) based on the theoretical loading of the resin (1.15 mequiv./g) and in high purity (see Table 1). The reaction stoichiometry of 10 equiv. excess of $POCl_3$ (with respect to resin substitution) in anhydrous dioxane (110°C, 2.5 h) was found to yield compound **4** in high purity. The final products **8** were purified by RP-HPLC and subsequently characterized by ^1H and ^{13}C NMR spectroscopy. Negligible amounts of racemization (<1%) were observed by ^1H NMR during BH_3–THF reduction[14] and cyclization to form dihydroimidazoles (for R^1) in conformity with our earlier observation.[16,17] Similarly compounds were ~95% enantiomerically pure by ^1H NMR during fluoro displacement by an α-amino acid methyl ester[13] and alkylation with an alkyl halide.

A broad singlet at δ ~10.78 ppm (d_6-DMSO) in the ^1H NMR spectra was found for **4e** (following cleavage) (**e**, R^1=–CH_3) corresponding to the protonated dihydroimidazole.[17] This confirmed our earlier observation that either a broad singlet or two singlets with separation of ~0.2 ppm at δ 9.9–10.5 ppm in the ^1H NMR spectra were observed for protonated dihydroimidazoles.[16,17] Two signals also appeared in the ^1H NMR spectra for **8** at δ ~10.6 and ~10.2 ppm corresponded to an anilide proton (–NH–CO–)[13] and a dihydroimidazolyl –NH– proton,[16,17] respectively. This indicated that alkylation occurred at the dihydroimidazolyl moiety, confirming structures **6**–**8**. This is in conformity with the earlier observation that alkylation is most likely prevented at the secondary aniline nitrogen due to the

Table 1. MW and RP-HPLC purity found for trisubstituted dihydroimidazolyl dihydroquinoxalin-2(1*H*)-ones **8**



Entry	R^1	R^2	R^3	MW (calcd)	MW (found)	Yield[a] (%)	Purity[b] (%)
8a	$-CH(CH_3)_2$	$-CH_3$	$-CH_2C_6H_5$	362.5	363.2 ($M+H^+$)	62	78
8b	$-C_6H_5$	$-CH_3$	$-CH_2C_6H_5$	396.5	397.3 ($M+H^+$)	65	81
8c	$-CH_2C_6H_4(4\text{-}OC_2H_5)$	$-CH_3$	$-CH_2C_6H_5$	454.6	455.3 ($M+H^+$)	70	77
8d	$-C_6H_{11}$	$-CH_3$	$-CH_2C_6H_5$	402.5	403.3 ($M+H^+$)	66	78
8e	$-CH_3$	$-CH_3$	$-CH_2C_6H_5$	334.5	335.3 ($M+H^+$)	72	77
8f	$-CH_3$	$-CH_2CH(CH_3)_2$	$-CH_2C_6H_5$	376.5	377.2 ($M+H^+$)	65	75
8g	$-CH_3$	$-(CH_2)_2SCH_3$	$-CH_2C_6H_5$	394.5	395.2 ($M+H^+$)	68	74
8h	$-CH_3$	$-CH_2C_6H_{11}$	$-CH_2C_6H_5$	416.6	417.3 ($M+H^+$)	63	75
8i	$-CH_3$	$-CH(CH_3)_2$	$-CH_2C_6H_5$	362.5	363.2 ($M+H^+$)	60	80
8j	$-CH_3$	$-CH_2OH$	$-CH_2C_6H_5$	350.4	351.3 ($M+H^+$)	66	78
8k	$-CH_3$	$-C_6H_5$	$-CH_2C_6H_5$	396.5	397.2 ($M+H^+$)	73	78
8l	$-CH_3$	$-CH_2C_6H_4(4\text{-}OH)$	$-CH_2C_6H_5$	426.5	427.2 ($M+H^+$)	72	60
8m	$-CH_3$	$-CH_3$	$-CH_2C_6H_4(2\text{–}Br)$	413.3	415.1 ($M+H^+$)	68	79
8n	$-CH_3$	$-CH_3$	$-CH_2C_6H_4(2\text{-}CH_2SO_2C_6H_5)$	488.6	489.2 ($M+H^+$)	65	76
8o	$-CH_3$	$-CH_3$	$-CH_2C_6H_4(3\text{-}OCH_3)$	364.4	365.3 ($M+H^+$)	62	78
8p	$-CH_3$	$-CH_3$	$-CH_2C_6H_4(3\text{-Cl})$	368.9	369.3 ($M+H^+$)	64	78
8q	$-CH_3$	$-CH_3$	$-CH_3$	258.3	259.2 ($M+H^+$)	66	80
8r	$-CH_3$	$-CH_3$	$-CH_2CHCH_2$	284.3	285.2 ($M+H^+$)	68	81
8s	$-CH_3$	$-CH_3$	$-CH_2C_6H_3(3,4\text{-}F_2)$	370.4	371.2 ($M+H^+$)	65	82

[a] The yields (by weight) obtained were 60–75% with respect to the initial loading of the resin (1.15 mequiv./g).
[b] Purity was determined from the relative peak areas (%) of HPLC chromatograms run with a gradient of 5–95% acetonitrile in water (0.05% TFA) for 30 min at λ=214 nm.

electron-withdrawing character of the *o*-nitro group on the phenyl ring.[12]

3. Conclusion

A novel and efficient approach for the synthesis of trisubstituted dihydroimidazolyl dihydroquinoxalin-2(1*H*)-ones has been described. Substituted dihydroimidazoles were prepared from the resin-bound reduced amino acid amides via cyclization of the in situ formed imidoyl chloride intermediate. New conditions (lower concentration of $SnCl_2{\cdot}2H_2O$ and at lower temperature) for reduction of the aromatic nitro group with concomitant intramolecular cyclization to form the dihydroquinoxalin-2(1*H*)-ones were reported. These approaches can be extended to prepare combinatorial libraries using the 'libraries from libraries' approach.[18]

4. Experimental

Boc-amino acids, α-amino acid methyl ester hydrochlorides, HBTU, and *N*-hydroxybenzotriazole (HOBt) were purchased from Calbiochem–Novabiochem Corp. (San Diego, CA), and Bachem Bioscience, Inc. (Philadelphia, PA). MBHA resin (1% divinylbenzene, 100–200 mesh, 1.15 mequiv./g substitution) and *N*,*N*′-diisopropylcarbodiimide (DIC) were purchased from Chem Impex, Int. (Wood Dale, IL). HF was purchased from Air Products (San Marcos, CA). Alkyl halides, anhydrous solvents, and all other reagents were purchased from Aldrich Chemical Co. (Milwaukee, WI). All amino acids and α-amino acid methyl esters used had the L-configurations.

Analytical RP-HPLC was carried out on a Beckman System Gold Instrument (Fullerton, CA). Purification of the samples was carried out using a Vydac 218TP54 C18 column (0.46×25 cm^2). All HPLC experiments were performed using gradient elution: solvent A (H_2O with 0.05% TFA) and solvent B (CH_3CN with 0.05% TFA). Flow rates were 1.0 and 6.0 mL/min for analytical and preparative chromatograms, respectively, at λ=214 nm. LC–MS (ESI and APCI) were recorded on a Finnigan Mat LCQ mass spectrometer (ThermoQuest Corporation, CA) at 214 nm using a Betasil C18, 3 μm, 100A, 3×50 mm^2 column.

4.1. Typical procedure for the synthesis of trisubstituted dihydroimidazolyl dihydroquinoxalin-2(1*H*)-one (Scheme 1)

100 mg of MBHA resin (0.115 mequiv.) was sealed inside a polypropylene mesh packet.[19] Polypropylene bottles were used for all the reactions. The resin was washed with dichloromethane (DCM), followed by neutralization with 5% DIEA in DCM and washing with DCM. (a) Coupling of an amino acid to MBHA resin. A Boc-amino acid (6 equiv., 0.1 M) in DMF was coupled to MBHA resin using DIC and HOBt (6 equiv. each) for 2 h at room temperature, followed by washes with DMF (three times) and DCM (three times). Deprotection of the Boc group was carried out using 55% trifluoroacetic acid (TFA) in DCM for 30 min, followed by washes with DCM (two times), IPA (two times), and DCM (two times). (b) Exhaustive reduction of the resin-bound amino acid amide with BH_3–THF. Exhaustive reduction of the resin-bound amino acid amide was carried out in 50 mL glass conical tubes under nitrogen. To each tube was added boric acid (12 equiv.), followed by trimethyl borate (12 equiv.). Borane–THF complex (1 M, 40 equiv.) was added slowly. Following cessation of hydrogen evolution, the resin packet (0.115 mequiv. resin, 100 mg of starting resin) was added and the capped tubes

were heated at 65°C for 72 h, followed by decantation of the reaction solution and quenching with MeOH.[14] Following four washes with MeOH, the resin was treated with piperidine at 65°C for 20 h to disproportionate the borane complexes.[14] Following decantation of the resulting solution of piperidine–borane complex, the resin was washed with DMF (four times), DCM (four times) and MeOH (two times) and air dried. (c) Selective N-acylation at the primary amine of the di-amine using 4-fluoro-3-nitrobenzoic acid. The resin-bound di-amine was treated with 4-fluoro-3-nitrobenzoic acid (3 equiv., 0.06 M) in DMF in the presence of HBTU (3 equiv.) and DIEA (6 equiv.) for 3 h at room temperature. The resin was washed with DMF (four times), DCM (two times), IPA (two times), and DCM (three times). A negative ninhydrin test established the completeness of the coupling reactions.[20] (d) Cyclization using $POCl_3$. Dehydrative cyclization of the resin-bound amide using $POCl_3$ was carried out in 50 mL conical tubes under nitrogen. To each tube, the resin packet (0.115 mequiv.) and $POCl_3$ (10 equiv., 0.09 M) in anhydrous dioxane was added. The capped tubes were heated at 110°C for 2.5 h, followed by washes with dioxane, DMF and MeOH (five times each), IPA (two times), and DCM (three times). (e) α-Amino acid methyl ester coupling. The resin-bound dihydroimidazole **4** was treated with an α-amino acid methyl ester hydrochloride (20 equiv., 0.2 M) in DMF in the presence of DIEA (25 equiv.) for 20 h at room temperature, followed by washes with DMF (four times), DCM (two times), IPA (two times), and DCM (three times). (f) Alkylation using an alkyl halide. Alkylation was performed using an alkyl halide (20 equiv., 0.2 M in DMF) in the presence of DIEA (10 equiv.) for 20 h at room temperature, followed by washes with DMF (four times), IPA (two times), and DCM (three times). (g) Reduction of nitro group. Reduction of aromatic nitro group with concomitant intramolecular cyclization was carried out using tin(II) chloride dihydrate (20 equiv., 0.5 M) in DMF for 15 h at room temperature. The resin was washed with DMF (eight times), MeOH (two times), and DCM (three times).

All resin-bound compounds were cleaved from the solid-support using anhydrous HF in the presence of anisole for 7 h at 0°C,[21] followed by extraction with 95% acetic acid in water and lyophilized.

4.1.1. 2-(4-Fluoro-3-nitrophenyl)-4-methyl-4,5-dihydro-1*H*-imidazole (4a). ^{1}H NMR (500 MHz, d_6-DMSO): δ 1.36–1.37 (d, *J*=5.1 Hz, 3H), 3.59–3.63 (m, 1H), 4.13–4.17 (m, 1H), 4.50–4.52 (m, 1H), 7.93 (m, 1H), 8.30–8.32 (m, 1H), 8.78–8.80 (m, 1H), 10.78 (br s, 2H).

4.1.2. Methyl *N*-[4-(4-isopropyl-4,5-dihydro-1*H*-imidazol-2-yl)-2-nitrophenyl]alaninate (5a). ^{1}H NMR (500 MHz, d_6-DMSO): δ 0.92–0.95 (t, *J*=6.8 Hz, 3H), 1.36–1.66 (m, 7H), 3.61–3.64 (m, 1H), 3.79 (s, 2H), 4.04–4.07 (m, 1H), 4.32–4.36 (m, 1H), 4.82–4.83 (m, 1H), 7.29–7.30 (d, *J*=8.8 Hz, 1H), 7.99–8.00 (d, *J*=8.1 Hz, 1H), 8.77–8.79 (d, *J*=7.1 Hz, 1H), 8.87 (s, 1H), 10.41 (s, 2H).

4.1.3. Methyl *N*-[4-(1-benzyl-5-isopropyl-4,5-dihydro-1*H*-imidazol-2-yl)-2-nitrophenyl]alaninate (6a). ^{1}H NMR (500 MHz, d_6-DMSO): δ 0.86 (t, *J*=7.1 Hz, 3H), 1.22–1.34 (m, 2H), 1.49–1.50 (d, *J*=6.7 Hz, 3H), 1.64–1.74 (m, 2H), 3.66–3.72 (m, 4H), 4.05–4.10 (m, 2H), 4.65–4.68 (d, *J*=16.0 Hz, 1H), 4.76–4.82 (m, 1H), 7.22–7.24 (d, *J*=9.0 Hz, 1H), 7.31–7.38 (m, 5H), 7.77–7.79 (d, *J*=8.7 Hz, 1H), 8.51 (s, 1H), 8.65–8.66 (d, *J*=7.1 Hz, 1H), 10.61 (s, 1H).

4.1.4. 7-(1-Benzyl-5-isopropyl-4,5-dihydro-1*H*-imidazol-2-yl)-3-methyl-3,4-dihydroquinoxalin-2(1*H*)-one (8a). ^{1}H NMR (500 MHz, d_6-DMSO): δ 0.86 (t, *J*=7.4 Hz, 3H), 1.22–1.30 (m, 6H), 1.62–1.70 (m, 2H), 3.61–3.63 (dd, *J*=7.2, 10.8 Hz, 1H), 3.98–4.06 (m, 3H), 4.60–4.63 (d, *J*=16.2 Hz, 1H), 4.82–4.85 (d, *J*=16.1 Hz, 1H), 6.77–6.79 (d, *J*=8.5 Hz, 1H), 7.00–7.01 (d, *J*=1.5 Hz, 1H), 7.07 (s, 1H), 7.13–7.15 (m, 2H), 7.27–7.28 (d, *J*=7.3 Hz, 1H), 7.34–7.41 (m, 2H), 10.27 (s, 1H), 10.57 (s, 1H); ^{13}C NMR (125 MHz, d_6-DMSO): δ 13.6, 16.6, 18.3, 33.2, 41.4, 42.5, 47.1, 48.3, 50.3, 60.5, 109.7, 112.6, 114.5, 124.4, 125.8, 127.5, 128.1, 128.9, 134.5, 139.2, 166.1, 167.3.

4.1.5. 7-(1-Benzyl-5-methyl-4,5-dihydro-1*H*-imidazol-2-yl)-3-methyl-3,4-dihydroquinoxalin-2(1*H*)-one (8e). ^{1}H NMR (500 MHz, d_6-DMSO): δ 1.30 (t, *J*=7.4 Hz, 6H), 3.46–3.50 (dd, *J*=8.3, 11.3 Hz, 1H), 4.00–4.06 (m, 2H), 4.13–4.16 (m, 1H), 4.61–4.64 (d, *J*=16.2 Hz, 1H), 4.80–4.83 (d, *J*=16.2 Hz, 1H), 6.77–6.79 (d, *J*=8.5 Hz, 1H), 7.01 (d, *J*=1.7 Hz, 1H), 7.05 (s, 1H), 7.12–7.14 (dd, *J*=1.6, 7.8 Hz, 1H), 7.29–7.30 (d, *J*=7.3 Hz, 2H), 7.33–7.36 (m, 1H), 7.38–7.41 (m, 2H), 10.23 (s, 1H), 10.59 (s, 1H).

4.1.6. 7-(1-Benzyl-5-methyl-4,5-dihydro-1*H*-imidazol-2-yl)-3-isopropyl-3,4-dihydroquinoxalin-2(1*H*)-one (8i). ^{1}H NMR (500 MHz, d_6-DMSO): δ 0.82–0.83 (d, *J*=6.7 Hz, 3H), 0.94–0.95 (d, *J*=6.9 Hz, 3H), 1.30–1.31 (d, *J*=6.2 Hz, 3H), 2.06–2.10 (m, 1H), 3.45–3.49 (dd, *J*=8.3, 11.4 Hz, 2H), 3.84–3.85 (m, 1H), 4.03 (t, *J*=10.9 Hz, 1H), 4.14–4.17 (m, 1H), 4.60–4.64 (d, *J*=16.4 Hz, 1H), 4.81–4.84 (d, *J*=16.3 Hz, 1H), 6.83–6.84 (d, *J*=8.4 Hz, 1H), 6.97 (d, *J*=1.6 Hz, 1H), 7.07–7.10 (m, 2H), 7.28–7.30 (d, *J*=7.2 Hz, 2H), 7.33–7.40 (m, 2H), 10.15 (s, 1H), 10.64 (s, 1H).

4.1.7. 7-(1-Benzyl-5-methyl-4,5-dihydro-1*H*-imidazol-2-yl)-3-(4-hydroxybenzyl)-3,4-dihydroquinoxalin-2(1*H*)-one (8l). ^{1}H NMR (500 MHz, d_6-DMSO): δ 1.28–1.29 (d, *J*=6.3 Hz, 3H), 2.79–2.87 (m, 2H), 3.43–3.47 (m, 1H), 4.01 (t, *J*=10.9 Hz, 1H), 4.13–4.15 (m, 1H), 4.23 (t, *J*=5.6 Hz, 1H), 4.58–4.61 (d, *J*=16.2 Hz, 1H), 4.75–4.78 (d, *J*=16.2 Hz, 1H), 6.57–6.59 (m, 2H), 6.73–6.75 (d, *J*=8.2 Hz, 1H), 6.87–6.88 (d, *J*=1.6 Hz, 1H), 6.92–6.94 (d, *J*=8.1 Hz, 1H), 7.01 (s, 1H), 7.06–7.08 (m, 1H), 7.28–7.29 (d, *J*=7.1 Hz, 1H), 7.33–7.36 (m, 2H), 7.38–7.41 (m, 3H), 9.16 (s, 1H), 10.14 (s, 1H), 10.57 (s, 1H); ^{13}C NMR (125 MHz, d_6-DMSO): δ 18.2, 37.9, 48.2, 49.1, 56.4, 57.2, 112.3, 114.1, 114.9, 124.3, 124.8, 126.4, 127.4, 128.0, 128.8, 130.7, 134.6, 138.7, 155.9, 165.8, 165.9.

4.1.8. 7-[1-(3-Methoxybenzyl-5-methyl-4,5-dihydro-1*H*-imidazol-2-yl]-3-methyl-3,4-dihydroquinoxalin-2(1*H*)-one (8o). ^{1}H NMR (500 MHz, d_6-DMSO): δ 1.28–1.32 (dd, *J*=6.2, 12.9 Hz, 6H), 3.46–3.50 (dd, *J*=8.6, 11.0 Hz, 1H), 3.74–3.76 (m, 3H), 4.00–4.06 (m, 2H), 4.15–4.19 (m, 1H), 4.57–4.60 (d, *J*=16.4 Hz, 1H), 4.76–4.79 (d, *J*=16.2 Hz, 1H), 6.77–6.85 (m, 3H), 6.90–6.91 (m, 1H), 7.00 (d,

J=1.6 Hz, 1H), 7.06 (s, 1H), 7.12–7.14 (dd, J=1.7, 7.9 Hz, 1H), 7.31 (t, J=7.9 Hz, 1H), 10.23 (s, 1H), 10.60 (s, 1H).

5. Supporting information available

LC–MS and ^{1}H and ^{13}C NMR spectra of selected compounds are available.

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