Synthesis Paper

Syntheses of Pyrazine-, Quinoxaline-, and Imidazole-Fused Pyrroline Nitroxides

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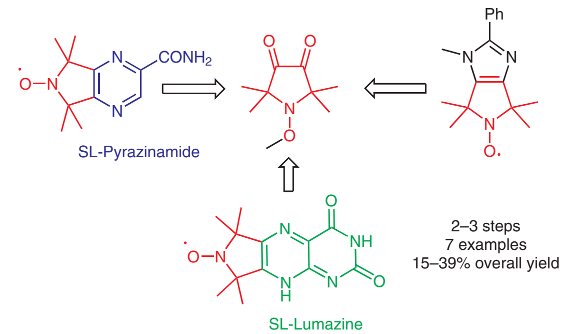
Dedicated to the memory of Prof. Kálmán Hideg



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Abstract A synthesis of a new diamagnetic synthon, 1-methoxy-2,2,5,5-tetramethylpyrrolidine-3,4-dione, was developed. Condensation of this compound with aliphatic or aromatic 1,2-diamines followed by deprotection yielded pyrroline nitroxide-fused pyrazines, pteridines, or quinoxalines, demonstrated on 7 examples in 15–39% overall yield over 2 or 3 steps. Reaction of the diamagnetic 1,2-diketone with an aldehyde and ammonium acetate produced a pyrrolo[3,4-*d*]imidazole scaffold in the Debus–Radziszewski reaction.

Key words free radicals, CH functionalization, oxidation, pyrazines, protecting groups

One of the main groups of long-lived stable radicals is the nitroxide (aminoxyl) radicals.[1] Extensive studies of stable nitroxide free radicals first appeared 60 years ago, and their application is rather diverse and extends beyond spin labeling.[2] They are used as co-oxidants in organic chemistry,[3] building blocks for magnetic materials,[4] superoxide dismutase mimics,[5] antiproliferative compounds,[6] mediators of polymerization,[7] redox active materials in batteries,[8] and magnetic resonance imaging (MRI)[9] as well as electron paramagnetic resonance imaging (EPRI)[10] contrast agents. These applications demand various scaffolds with diverse substitution patterns on pyrroline and piperidine nitroxides, including condensation with miscellaneous carbocycles and heterocycles. Synthesis of pyrroline nitroxide-fused carbocycles and heterocycles is one of the main activities of our laboratory, such as the synthesis of pyridazine-[11] and pyrimidine-fused[12] nitroxides (Figure 1). The latter was used in environmental studies investigating the distribution of sulfadiazine in a humic acid model system.[13]

Until now, we could not find a method for the synthesis of pyrazine (1,4-diazine)-fused pyrroline nitroxide. Pyrazines are important structural motifs of many biologically active molecules, such as riboflavin, and drugs such as pyrazinamide (antituberculotics) and varenicline (stop-smoking drug) (Figure 2).

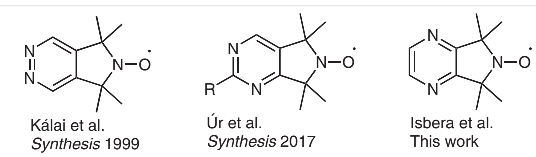

Figure 1 Pyrroline nitroxide fused diazines

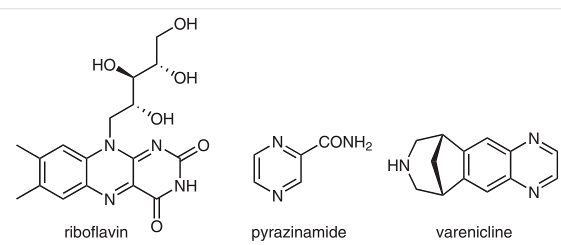

Figure 2 Pyrazine-ring-containing bioactive molecules and drugs

It was obvious that the condensation of 1,2-diamines with paramagnetic 1,2-diketones suggests a synthetic route to novel paramagnetic 1,4-diazines and quinoxalines.[14,15] Inspired by the work of Sandris and Ourisson,[16] we attempted the synthesis of 1-oxyl-2,2,5,5-tetramethylpyrrolidine-3,4-dione by SeO_2 oxidation of 1-oxyl-2,2,5,5-tetramethylpyrrolidine-3-one (**1**)[17] (Scheme 1); however, no reaction occurred, and only starting material was recovered.

Based on our previous findings regarding sluggish reactions, we proposed that the free radical moiety must be protected; however, neither the *N*–OAc protection[18] nor the hydroxylamine HCl salt form was sufficient for camouflaging

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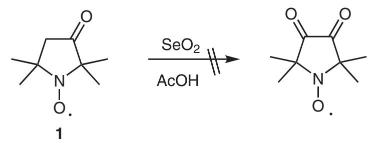
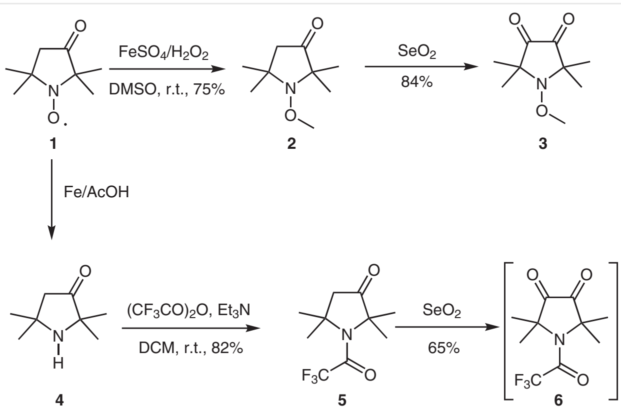


Scheme 1 Attempted synthesis of a paramagnetic diketone

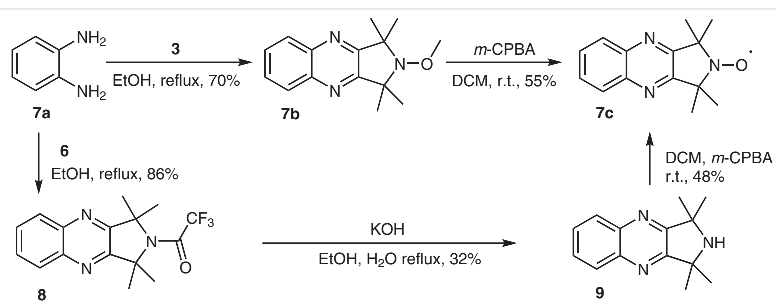
the nitroxide moiety in the oxidation reaction with SeO_2. For nitroxide protection, we used the *O*-methylation technique by a Fenton reaction in the presence of DMSO, which was worked out in Bottle's group.[19a] Treatment of compound **1** with a methyl radical generating system (Fe^{2+} and aq H_2O_2 mixture in DMSO) yielded compound **2**, which could be oxidized smoothly by refluxing with 1.5 equivalents of SeO_2 in AcOH to afford compound **3** in a 63% yield over two steps (Scheme 2). Deprotection of compound **3** with 3-chloroperbenzoic acid (*m*-CPBA)[19b] gave an unstable five-membered diketo nitroxide compound, which decomposed during purification.



Scheme 2 Synthesis of precursors of 1-oxyl-2,2,5,5-tetramethylpyrrolidine-3,4-dione

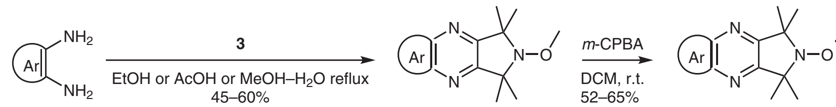
Alternatively, we returned to the Sandris and Ourisson method, but instead of an *N*-acetyl derivative, the NH functionality was protected with a readily hydrolyzable trifluoroacetyl group,[20] and thus, compound **4**[21] was treated with trifluoroacetic anhydride to give compound **5** in an 82% yield. Compound **5** could also be oxidized to diketo compound **6** in a 65% yield with SeO_2 in AcOH, but it was unstable and the crude product was used immediately in the next step. The diketo compounds **3** and **6** were condensed with 1,2-diaminobenzene (**7a**) to furnish pyrrolo[3,4-*b*]quinoxalines **7b** and **8**, respectively. Treatment of compound **7b** with *m*-CPBA in dichloromethane (DCM) yielded nitroxide **7c**. Compound **7c** was also available via hydrolysis of compound **8** with aqueous KOH in EtOH, which produced compound **9** with prolonged reaction time and in a low (32%) yield. Compound **9** was then oxidized with *m*-CPBA in DCM to furnish **7c** in a 13% yield over three steps (Scheme 3).

Considering the instability of the diketo compound **6** and the fact that the deprotection of the sterically hindered trifluoroacetamido group required harsh basic conditions, which is not compatible with many functional groups and its troublesome application (reduction of nitroxide, trifloroacetylation, oxidation, condensation, hydrolysis of the trifluoroacetyl group, and restoring nitroxide function), in the following work, we used the *O*-methylation procedure, followed by oxidation, condensation, and mild deprotection with *m*-CPBA. Thus, we preferred compound **3** as the main building block instead of compound **6**. In analogous reactions, compound **3** was condensed with different aromatic and heteroaromatic 1,2-diamino compounds such as 2,3-diaminobenzamide (**10a**),[22] 1,2,4,5-tetraaminobenzene (**11a**), 4,5-diaminopyrimidine (**12a**), 5,6-diaminouracil (**13a**) in ethanol, glacial acetic acid, or aqueous methanol to give the pyrazine ring condensed polycyclic compounds **10b**, **11b**, **12b**, and **13b**, respectively. Deprotection of **10b** with *m*-CPBA gave the paramagnetic 5-carboxamidoquinoxaline **10c**, which can be regarded as a potential poly (ADP-ribose) polymerase (PARP) inhibitor,[23] and deprotection of compound **11b** offered the rigid biradical compound **11c** giving a quintet line in the EPR spectrum [see the Supporting Information (SI)]. Deprotection of compound **12b** furnished the paramagnetic pteridine **12c**, and deprotection of compound **13b** offered the paramagnetic pteridine-2,4(3*H*,8*H*)-dione **13c**, the spin-labeled (SL) lumazine (Table 1).

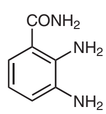
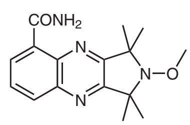
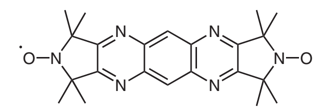
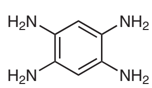
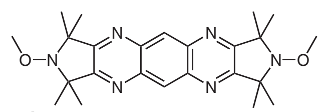
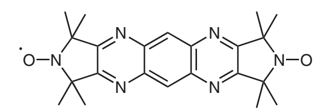
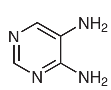
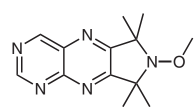
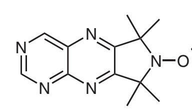
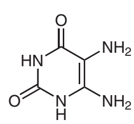
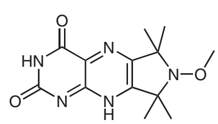
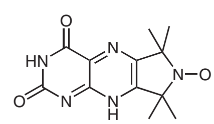


Scheme 3 Synthesis of diamagnetic and paramagnetic pyrrolo[3,4-*b*]qunoxaline scaffolds

Table 1 Synthesis of Pyrazine Condensed Paramagnetic Polycyclic Compounds



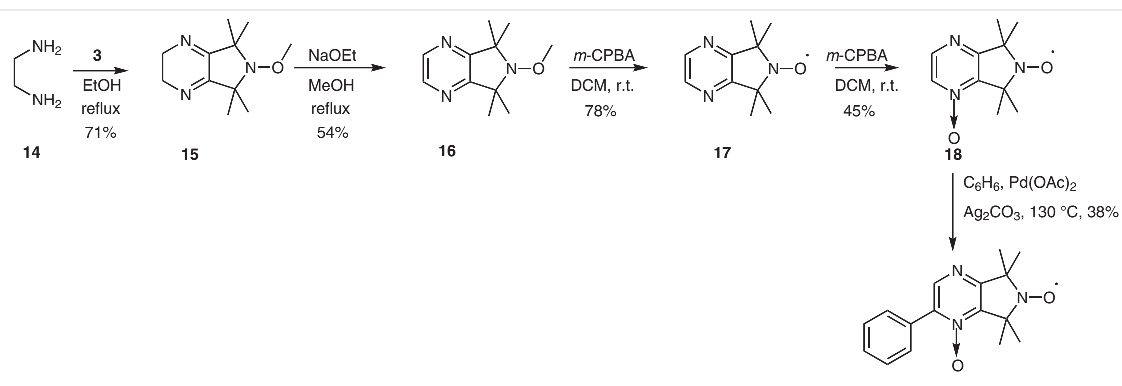
10–13a 10–13b 10–13c

Entry	1,2-Diamino compound	Diamagnetic product	Paramagnetic product
1	 **10a**	 **10b**	 **10c**
2	 **11a**	 **11b**	 **11c**
3	 **12a**	 **12b**[a]	 **12c**
4	 **13a**	 **13b**[b]	 **13c**

[a] Reflux in AcOH.
[b] Reflux in MeOH–H_2O.

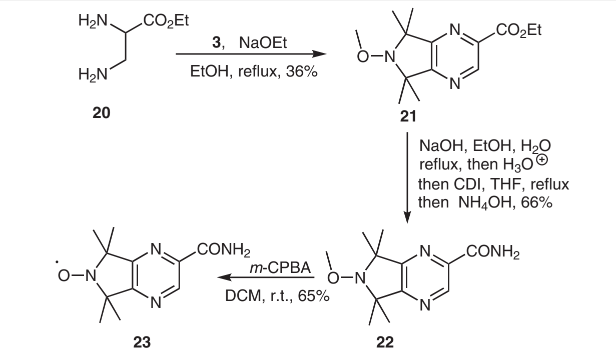
To construct the pyrrolo[3,4-*b*]pyrazine scaffold, compound **3** was condensed with 1,2-diaminoethane (**14**) yielding compound **15**. Aromatization of **15** by treatment with 2.0 equivalents of sodium ethoxide in methanol at reflux temperature[24] followed by standing overnight yielded the pyrazine-condensed precursor **16**, which was deprotected with *m*-CPBA to give compound **17** in a 30% yield over three steps. Upon prolonged reaction time and excess *m*-CPBA (5.0 equiv) the formation of *N*-oxide **18** was observed, which could be arylated at the C2-position by palladium catalysis[25] with benzene as a reaction solvent to give compound **19** in a 38% yield (Scheme 4).

To achieve the paramagnetic analogue of the antituberculotic drug pyrazinamide,[26] a condensation reaction of compound **3** was conducted with ethyl 2,3-diaminopropanoic acid HCl salt **20**[27] in EtOH with 4.0 equivalents of sodium

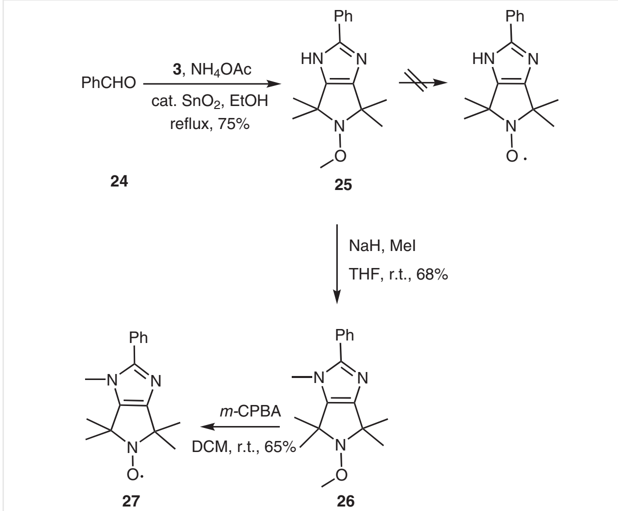


Scheme 4 Synthesis of diamagnetic and paramagnetic pyrrolo[3,4-*b*]pyrazine scaffolds and its CH functionalization

ethoxide to furnish compound **21**. Its hydrolysis with NaOH to the carboxylic acid and the treatment of the crude product with 1,1′-carbonyldimidazole (CDI) in THF followed by treatment with aqueous 25% ammonia gave amide **22**. Treatment of compound **22** with *m*-CPBA gave the spin labeled analogue **23** of pyrazinamide in an 11% overall yield over four steps (Scheme 5).



Scheme 5 Synthesis of paramagnetic pyrazinamide



Scheme 6 Synthesis of diamagnetic and paramagnetic 1-methyl-2-phenyl-4,6-dihydropyrrolo[3,4-*d*]imidazole scaffold

In order to extend the scope of utilization of compound **3**, we tested it in a multicomponent Debus–Radziszewski imidazole formation[28] with modification of the Fallah and Mokhtary[29] method utilizing tin oxide nanoparticles as catalysts. Therefore, compound **3**, benzaldehyde (**24**), and ammonium acetate in the presence of SnO_2 nanoparticles were heated at reflux temperature for 3 hours in EtOH. After the isolation of compound **25** in a 75% yield, we attempted the deprotection to nitroxide with *m*-CPBA, but the formation of (4,4,6,6-tetramethyl-2-phenyl-4,6-dihydropyrrolo[3,4-*d*]imidazol-5-yl)oxidanyl was not observed. Considering, that Chalmers et al. reported a similar deprotection on N-substituted imidazole containing scaffolds,[30] we decided on the protection of the imidazole NH by alkylation. Therefore, treatment of **25** with MeI in THF in the presence of NaH furnished compound **26**, which can be deprotected to afford 1-methylimidazole-fused pyrroline nitroxide **27** in 44% yield in two steps (Scheme 6).

In conclusion, we have developed access to 1-methoxy-2,2,5,5-tetramethylpyrrolidine-3,4-dione nitroxide precursor **3**, which could be condensed with 1,2-diamines to give various quinoxalines, pyrazines, and pteridines fused with the pyrroline nitroxide precursor. The nitroxide functionality was restored by treatment of the NOMe moiety with *m*-CPBA. Compound **3** also was used in 1-substituted imidazole-fused pyrroline nitroxide synthesis, as the *m*-CPBA deprotection cannot be conducted seemingly in the presence of the imidazole NH functional group.

We hope that compound **3**, as a universal building block, can be used for the synthesis of further pyrroline nitroxide-fused structures. The evaluation of further possibilities as well as biological study of newly synthesized pyrazine derivatives are in progress in our laboratory.

Melting points were determined with a Boetius micro-melting point apparatus and are uncorrected. Elemental analyses (C, H, N, and S) were performed with a Fisons EA 1110 CHNS elemental analyzer. Mass spectra were recorded on a ThermoQuest automass Multi spectrometer. NMR spectra were recorded on a Bruker Avance III Ascend 500 spectrometer; chemical shifts are referenced to TMS. The paramagnetic compounds were reduced to *N*-hydroxylamines with five equivalents of hydrazobenzene (DPPH)/radicals in situ in the NMR tube. Measurements were performed at a probe temperature 298 K in $CDCl_3$ or DMSO-d_6 or CD_3OD solution. ESR spectra were recorded on Miniscope MS 200 in $CHCl_3$ solution. All monoradicals gave a triplet line at a_N = 14.5 G, biradical **11c** gave a quintet line at a_N = 7.3 G. IR spectra were recorded with a Bruker Alpha FT-IR instrument with ATR support (ZnSe plate). Flash column chromatography was performed on Merck Kieselgel 60 (0.040–0.063 mm). Compounds **1**,[17] **4**,[21] **10a**,[22] and **20**[27] were prepared as described previously. Compounds **7a**, **10a–13a**, **14**, **24** and other reagents were purchased from Merck, Alfa Aesar, and TCI.

1-Methoxy-2,2,5,5-tetramethylpyrrolidin-3-one (2)

To a stirred solution of **1** (1.56 g, 10.0 mmol) and $FeSO_4{\cdot}7H_2O$ (6.9 g, 25.0 mmol) in DMSO (30 mL) at 0 °C was added 30% aq H_2O_2 (5 mL) dropwise over 2 h. The reaction was monitored by TLC. Upon consumption of the starting material, distilled H_2O (50 mL) was added and the aqueous solution was extracted with Et_2O (3 × 30 mL). The combined organic phases were dried ($MgSO_4$), filtered, and evaporated, and the crude product was purified by flash column chromatography (hexane–EtOAc, 2:1) to give **2** as a colorless oil; yield: 1.28 g (75%); R_f = 0.58 (hexane–EtOAc 2:1).

IR (neat): 2972, 2940, 1751 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.72 (s, 3 H, OCH_3), 2.34 (s, 2 H, CH_2), 1.29 (s, 6 H, 2 × CH_3), 1.26 (s, 6 H, 2 × CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 216.3 (C=O), 67.2 (C), 65.2 (CH_2), 61.2 (OCH_3), 49.76 (C), 31.59 (2 × CH_3), 22.65 (2 × CH_3).

MS (EI): m/z (%) = 171 (3, [M]$^+$), 156 (25), 70 (48), 42 (100).

Anal. Calcd for $C_9H_{17}NO_2$: C, 63.13; H, 10.01; N, 8.18. Found: C, 63.06; H, 9.81; N, 8.02.

2,2,5,5-Tetramethyl-1-trifluoroacetylpyrrolidin-3-one (5)

To a stirred solution of a mixture of **4** (1.2 g, 8.5 mmol) and Et_3N (1.01g, 10.0 mmol) in DCM (20 mL) was added $(CF_3CO)_2O$ (2.1 g, 10.0 mmol) in DCM (5 mL) dropwise at 0 °C and the mixture was stirred at r.t. for 1 h. The mixture was washed with distilled H_2O (20 mL) and the organic phase was separated. It was then dried ($MgSO_4$), filtered, evaporated, and the crude product was purified by flash column chromatography (hexane–Et_2O, 2:1) to give **5** as a yellow oil; yield: 1.64 g (82%); R_f = 0.51 (hexane–Et_2O 2:1).

IR (neat): 2977, 2942, 1762, 1666 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 2.68 (s, 2 H, CH_2), 1.64 (s, 6 H, 2 × CH_3), 1.58 (s, 6 H, 2 × CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 211.4 (C=O), 157.0 (C=O, q, $^2J_{C,F}$ = 38.3 Hz), 115.8 (CF_3, q, $^1J_{C,F}$ = 285.1 Hz), 99.9 (CH_2), 61.94 (C), 50.76 (C), 27.54 (2 × CH_3), 24.96 (2 × CH_3).

MS (EI): *m*/*z* (%) = 237 (41, $[M]^+$), 222 (48), 154 (50), 69 (91), 42 (100).

Anal. Calcd for $C_{10}H_{14}F_3NO_2$: C, 50.63; H, 5.95; N, 5.90. Found: C, 50.49; H, 5.85; N, 5.78.

Oxidation of Compounds 2 and 5 with SeO_2; General Procedure

To a solution of compound **2** or **5** (7.0 mmol) in glacial AcOH (10 mL) was added SeO_2 (1.16 g, 10.5 mmol) and the mixture was refluxed for 1 h. After cooling, the mixture was diluted with distilled H_2O (10 mL), and filtered through a Celite pad. The pad was then washed with EtOAc (10 mL). The filtrate was basified using solid $NaHCO_3$, and extracted with EtOAc (2 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated to give **3** (from **2**) as a brown oil; yield: 1.08 g (84%). The oil solidified upon standing in a refrigerator.

Compound **6** (from **5**) was obtained as a yellow oil; yield: 1.15 g (65%); R_f = 0.56 (hexane–EtOAc 2:1).

Both crude diketo compounds **3** and **6** were used immediately in the next step. Purification of the crude products were attempted by flash chromatography (hexane–EtOAc 2:1) for analysis only, however, compound **6** proved to be unstable.

1-Methoxy-2,2,5,5-tetramethylpyrrolidin-3,4-dione (3)

Yellow crystals; mp 41–42 °C; R_f = 0.51 (hexane–EtOAc 2:1); visualized by I_2 vapor.

IR (neat): 2986, 2940, 1754 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 3.76 (s, 3 H, OCH_3), 1.39 (s, 12 H, 4 × CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 202.6 (2 × C=O), 67.3 (2 C), 65.7 (OCH_3), 25.3 (2 × CH_3), 19.7 (2 × CH_3).

MS (EI): *m*/*z* (%) = 186 (33, $[M + H]^+$), 185 (7), 144 (23), 98 (100), 88 (60), 43 (27).

Anal. Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.48; H, 8.11; N, 7.36.

Preparation of Compounds 7b, 8, 10b, and 11b; General Procedure

To a solution of compound **3** or **6** (5.0 mmol) in anhyd EtOH (20 mL) was added compound **7a**, or **10a**, or **11a** (the latter was previously released from its 2 HCl salt with 2.0 equiv of NaOEt) (5.0 mmol) and the mixture was refluxed for 3 h and allowed to stay in air overnight. The solvent was evaporated and the residue was purified by flash column chromatography (hexane–Et_2O 2:1 or hexane–EtOAc 2:1, or $CHCl_3$–Et_2O) to give compounds **7b** or **8** or **10b** or **11b**.

2-Methoxy-1,1,3,3-tetramethyl-2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinoxaline (7b)

Yield: 900 mg (70%): white powder; mp 131–134 °C; R_f = 0.63 (hexane–Et_2O 2:1).

IR (neat): 3087, 3045, 2976, 1668 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.13 (dd, ^1J = 7.0 Hz, ^2J = 7.0 Hz, 2 H, ArH), 7.73 (dd, ^1J = 7.0 Hz, ^2J = 7.0 Hz, 2 H, ArH), 3.88 (s, 3 H, OCH_3), 1.62 (s, 12 H, 4 × CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.2 (2 C), 142.9 (2 C), 129.1 (2 × CH), 128.9 (2 × CH), 65.8 (2 C), 65.7 (OCH_3), 27.2 (2 × CH_3), 23.2 (2 × CH_3).

MS (EI): *m*/*z* (%) = 257 (31, $[M]^+$), 242 (100), 196 (38), 42 (31).

Anal. Calcd for $C_{15}H_{19}N_3O$: C, 70.01; H, 7.44; N, 16.33. Found: C, 70.12; H, 7.58; N, 16.37.

2,2,2-Trifluoro-1-(1,1,3,3-tetramethyl-1*H*-pyrrolo[3,4-*b*]quinoxalin-2(3*H*)-yl)ethanone (8)

Yield: 1.38 g (86%); white powder; mp 166–168 °C; R_f = 0.60 (hexane–Et_2O 2:1).

IR (neat): 3027, 3011, 1658, 1501 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.17 (dd, ^1J = 7 Hz, ^2J = 7 Hz, 2 H, ArH), 7.82 (dd, ^1J = 7 Hz, ^2J = 7 Hz, 2 H, ArH), 1.97 (s, 12 H, 4 × CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.4 (2 C), 157.1 (C=O, q, *J* = 38 Hz), 143.4 (2 C), 129.9 (2 × CH), 129.3 (2 × CH), 119.4 (CF_3, q, 285.2 Hz), 67.6 (2 C), 27.7 (4 × CH_3).

MS (EI): *m*/*z* (%) = 323 (7, $[M]^+$), 308 (100), 195 (70), 69 (26).

Anal. Calcd for $C_{16}H_{16}F_3N_3O$: C, 59.44; H, 4.99; N, 13.00. Found: C, 59.42; H, 4.82; N, 12.86.

2-Methoxy-1,1,3,3-tetramethyl-2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinoxalin-5-carboxamide (10b)

Yield: 414 mg (46%); white powder; mp 225–228 °C; R_f = 0.42 ($CHCl_3$–Et_2O 2:1).

IR (neat): 3332, 3148, 2978, 2936 1681, 1576 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 9.24 (s, 1 H, NH), 8.49 (d, *J* = 7 Hz, 1 H), 8.29 (d, *J* = 8.5 Hz, 1 H, ArH), 7.95 (s, 1 H, NH), 7.93 (t, *J* = 8.5 Hz, 1 H, ArH), 3.82 (s, 3 H, OCH_3), 1.55 (s, 12 H, 4 × CH_3).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 166.4 (C=O), 160.2 (C), 159.5 (C), 142.8 (C), 139.8 (C), 132.9 (C), 132.3 (CH), 131.6 (CH), 129.6 (CH), 66.0 (2 C), 65.9 (OCH_3), 28.0 (2 × CH_3), 24.0 (2 × CH_3).

MS (EI): *m*/*z* (%) = 300 (18, $[M]^+$), 285 (100), 268 (10), 42 (13).

Anal. Calcd for $C_{16}H_{20}N_4O_2$: C, 63.98; H, 6.71; N, 18.65. Found: C, 63.85; H, 6.68; N, 18.58.

2,8-Dimethoxy-1,1,3,3,7,7,9,9-octamethyl-1,2,3,7,8,9-hexahydropyrrolo[3,4-*b*]pyrrolo[3′,4′:5,6]pyrazino[2,3-g]quinoxaline (11b)

Yield: 588 mg (45%); beige powder; mp 246–250 °C; R_f = 0.51 (hexane–EtOAc 2:1).

IR (neat): 2977, 2918, 1636 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.86 (s, 2 H, ArH), 3.91 (s, 6 H, 2 × OCH_3), 1.68 (s, 24 H, 8 × CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.3 (4 C), 141.3 (4 C), 128.5 (2 × CH), 66.0 (4 C), 65.8 (2 × OCH_3), 27.8 (4 × CH_3), 22.6 (4 × CH_3).

MS (EI): *m*/*z* (%) = 436 (21, $[M]^+$), 421 (100), 375 (20), 329 (10), 43 (2).

Anal. Calcd for $C_{24}H_{32}N_6O_2$: C, 66.03; H, 7.39; N, 19.25. Found: C, 66.06; H, 7.26; N, 19.18.

7-Methoxy-6,6,8,8-tetramethyl-7,8-dihydro-6*H*-pyrrolo[3,4-g]pteridine (12b)

To a solution of compound **3** (555 mg, 3.0 mmol) in glacial AcOH (10 mL) was added compound **12a** (330 mg, 3.0 mmol) and the mixture was refluxed for 3 h. After cooling, the solvent was evaporated, and the residue was treated with distilled H_2O (20 mL) and sat. aq K_2CO_3 (20 mL). The mixture was extracted with $CHCl_3$ (3 × 30 mL), the combined organic phases were dried ($MgSO_4$), filtered, and evaporated. The residue was purified by flash column chromatography (hexane–EtOAc, 1:1) to give compound **12b** as a beige powder; yield: 385 mg (50%); mp 115–117 °C; R_f = 0.57 ($CHCl_3$–Et_2O 2:1).

IR (neat): 3068, 2980, 1616, 1573 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.67 (s, 1 H, ArH), 9.51 (s, 1 H, ArH), 3.86 (s, 3 H, OCH_3), 1.63 (s, 12 H, 4 × CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.2 (CH), 163.9 (CH), 162.4 (C), 158.0 (C), 154.6 (C), 134.6 (C), 66.4 (C), 66.0 (C), 65.8 (OCH_3), 28.13 (2 × CH_3), 23.02 (2 × CH_3).

MS (EI): *m*/*z* (%) = 259 (14, $[M]^+$), 244 (100), 213 (33), 198 (22), 42 (8).

Anal. Calcd for $C_{13}H_{17}N_5O$: C, 60.21; H, 6.61; N, 27.01. Found: C, 60.15; H, 6.42; N, 26.91.

7-Methoxy-6,6,8,8-tetramethyl-6,7,8,9-tetrahydro-2*H*-pyrrolo-[3,4-g]pteridine-2,4(3*H*)-dione (13b)

To a suspension of compound **13a** sulfate (476 mg, 2.0 mmol) in distilled H_2O (25 mL) was added powdered $NaHCO_3$ (336 mg, 4.0 mmol) and the mixture was stirred at r.t. for 15 min. Then a solution of compound **3** (370 mg, 2.0 mmol) in MeOH (20 mL) was added to the mixture. The resulting mixture was refluxed for 3 h. After cooling, the mixture was filtered on a sintered glass funnel to remove inorganic salts. The solvents were evaporated, and the residue was partitioned between distilled H_2O (15 mL), MeOH (5 mL), and $CHCl_3$ (20 mL). The organic phase was separated, dried ($MgSO_4$), filtered, and evaporated. The residue was purified by flash column chromatography ($CHCl_3$–Et_2O 2:1) to give compound **13b** as an orange powder; yield: 350 mg (60%); mp 163–166 °C; R_f = 0.33 ($CHCl_3$–MeOH 24:1).

IR (neat): 3187, 3072, 2983, 1691, 1575, 1527 cm^{-1}.

^1H NMR (500 MHz, CD_3OD): δ = 3.82 (s, 3 H, OCH_3), 1.52 (s, 12 H, 4 × CH_3).

^{13}C NMR (125 MHz, CD_3OD): δ = 164.1 (C=O), 162.0 (C=O), 154.9 (C), 150.2 (C), 150.0 (C), 126.3 (C), 65.9 (C), 65.6 (C), 64.7 (OCH_3), 27.0 (2 × CH_3), 22.2 (2 × CH_3).

MS (EI): *m*/*z* (%) = 291 (14, $[M]^+$), 276 (100), 245 (25), 230 (23), 42 (23).

Anal. Calcd for $C_{13}H_{17}N_5O_3$: C, 53.60; H, 5.88; N, 24.04. Found: C, 53.59; H, 5.65; N, 23.96.

1,1,3,3-Tetramethyl-2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinoxaline (9)

To a solution of compound **8** (646 mg, 2.0 mmol) in EtOH (20 mL) was added a solution of KOH (5.6 g, 0.1 mol) in H_2O (20 mL) and the mixture was heated at reflux temperature until consumption of the starting material (~24 h), as monitored by TLC. After cooling, the EtOH was evaporated, and the mixture was acidified (pH 2) with aq 30% H_2SO_4, followed by extraction with DCM (10 mL). The organic phase was separated, and discarded, and the aqueous phase was basified with aq 25% NH_4OH to pH 10. The aqueous phase was extracted with $CHCl_3$ (2 × 30 mL). The combined organic phases were dried ($MgSO_4$), filtered, and evaporated. The crude was purified by flash column chromatography (hexane–Et_2O 1:1, then $CHCl_3$–Et_2O 2:1) to give compound **9** as a white powder; yield: 145 mg (32%); mp 121–124 °C; R_f = 0.65 ($CHCl_3$–MeOH 9:1).

IR (neat): 3321, 3066, 2973, 2926, 1573, 1503 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.14 (d, *J* = 9 Hz, 2 H, ArH), 7.75 (d, *J* = 9 Hz, 2 H, ArH), 1.63 (s, 12 H, 4 × CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.9 (2 C), 142.3 (2 C), 129.1 (2 × CH), 128.9 (2 × CH), 59.85 (2 C), 30.3 (4 × CH_3) .

MS (EI): *m*/*z* (%) = 227 (16 $[M]^+$), 212 (100), 197 (28), 42 (72).

Anal. Calcd for $C_{14}H_{17}N_3$: C, 73.98; H, 7.54; N, 18.49. Found: C, 73.81; H, 7.66; N, 18.32.

(1,1,3,3-Tetramethyl-2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinoxaline-2-yl)oxidanyl (7c)

To a stirred solution of compound **9** (113 mg, 0.5 mmol) in anhyd DCM (5 mL) was added 3-chloroperbenzoic acid (~60%, 172 mg, 0.6 mmol) in 2–3 portions at 0 °C over 10 min. The solution turned yellow-orange, and the stirring was continued for an additional 30 min at r.t. Then, the solution was washed with 10% aq Na_2CO_3 (2 × 10 mL), and the organic phase was separated, dried ($MgSO_4$), filtered, and evaporated. The residue was subjected to flash column chromatography (hexane–Et_2O 2:1) to afford compound **7c** as a yellow powder; yield: 58 mg (48%); mp 168–170 °C; R_f = 0.41 (hexane–Et_2O, 2:1).

IR (neat): 3064, 2976, 2930, 1639, 1619, 1501 cm^{-1}.

^1H NMR [500 MHz, DMSO-d_6 + $(PhNH)_2$]: δ = 8.12 (dd, ^1J = 7 Hz, ^2J = 7 Hz, 2 H, ArH), 7.80 (dd, ^1J = 7 Hz, ^2J = 7 Hz, 2 H, ArH), 1.47 (s, 12 H, 4 × CH_3).

^{13}C NMR [125 MHz, $CDCl_3$ + $(PhNH)_2$]: δ = 160.9 (2 C), 142.6 (2 C), 129.3 (2 × CH), 129.2 (2 × CH), 65.2 (2 C), 25.30 (4 × CH_3) .

MS (EI): *m*/*z* (%) = 242 (100, $[M]^+$), 211 (32), 197 (71), 42 (47).

Anal. Calcd for $C_{14}H_{16}N_3O$: C, 69.34; H, 6.66; N, 17.34. Found: C, 69.34; H, 6.58; N, 17.17.

Preparation of 7c, 10c, 11c, 12c, 13c, 17, 23, and 27 by Deprotection of Methoxyamines; General Procedure

Methoxyamine **7b** or **10b** or **11b** or **12b** or **13b** or **16** or **22** or **26** (2.0 mmol) was stirred in DCM (20 mL) at r.t. Solid 3-chloroperbenzoic acid (~60%, 1.43 g, 5.0 mmol and 2.86 g 10.0 mmol for **11b**) was added portionwise over a period of 10 min. The reaction was monitored by TLC and upon the consumption of the starting material (10–30 min), DCM (10 mL) was added. The organic layer was washed with aq 10% Na_2CO_3 (2 × 15 mL) and then H_2O (10 mL). The organic phase was separated, dried ($MgSO_4$), filtered and evaporated, and the residue was purified flash column chromatography.

(1,1,3,3-Tetramethyl-2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinoxaline-2-yl)oxidanyl (7c)

Yield: 266 mg (55%); yellow solid; mp 169–171 °C; R_f = 0.41 (hexane–Et_2O 2:1).

Spectroscopic data were the same as that of compound **7c** obtained by the oxidation of compound **9** (see above).

Anal. Calcd for $C_{14}H_{16}N_3O$: C, 69.34; H, 6.66; N, 17.34. Found: C, 69.30; H, 6.60; N, 17.29.

(1,1,3,3-Tetramethyl-2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinoxaline-5-carboxamide-2-yl)oxidanyl (10c)

Purified by flash column chromatography (hexane–EtOAc 2:1) to obtain an orange powder; yield: 348 mg (61%); mp 249–252 °C; R_f = 0.30 ($CHCl_3$–Et_2O 2:1).

IR (neat): 3357, 3180, 2984, 1672, 1575 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.42 (s, 1 H, NH_2), 8.56 (dd, *J* = 7.5 Hz, 1 H, ArH), 8.29 (dd, J = 8 Hz, 1 H, ArH), 8.01 (m, 2 H, ArH and NH_2), 1.48 (s, 12 H, 4 × CH_3).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 166.4 (C=O), 161.0 (C), 160.3 (C), 142.7 (C), 139.3 (C), 133.0 (C), 132.3 (CH), 131.2 (CH), 129.3 (CH), 65.3 (2 C), 25.2 (2 × CH_3), 25.1 (2 × CH_3).

MS (EI): *m*/*z* (%) = 285 (100, [M]$^+$), 255 (12), 238 (48), 42 (20).

Anal. Calcd for $C_{15}H_{17}N_4O_2$: C, 63.14; H, 6.01; N, 19.64. Found: C, 63.24; H, 5.88; N, 19.55.

(1,1,3,3,7,7,9,9-Octamethyl-7,9-dihydropyrrolo[3,4-*b*]pyrrolo-[3′,4′:5,6]pyrazino[2,3-*g*]quinoxaline-2,8-diyl)dioxidanyl (11c)

Purified by flash column chromatography (hexane–EtOAc 2:1) to afford a brown powder; yield: 422 mg (52%); mp 235–238 °C; R_f = 0.44 ($CHCl_3$–Et_2O 2:1).

IR (neat): 2990, 2933, 1548 cm^{-1}.

^{1}H NMR and ^{13}C NMR spectra cannot be recorded because of precipitation of compound **11c** in DMSO-d_6 in the presence of 10.0 equiv of $(PhNH)_2$. For an EPR spectrum, see SI.

MS (EI): *m*/*z* (%) = 406 (100, [M]$^+$), 391 (63), 361 (48), 346 (43), 331 (27), 158 (29).

Anal. Calcd for $C_{22}H_{26}N_6O_2$: C, 65.01; H, 6.45; N, 20.68. Found: C, 65.04; H, 6.35; N, 20.76.

(6,6,8,8-Tetramethyl-6*H*-pyrrolo[3,4-*g*]pteridin-7-yl)oxidanyl (12c)

Purified by flash column chromatography (hexane–EtOAc 2:1) to afford a bordeaux colored powder; yield: 317 mg (65%); mp 202–205 °C; R_f = 0.41($CHCl_3$–Et_2O 2:1).

IR (neat): 3063, 3023, 2979, 2931, 1615, 1572, 1556 cm^{-1}.

^{1}H NMR [500 MHz, $CDCl_3$ + $(PhNH)_2$]: δ = 9.74 (s, 1 H, ArH), 9.60 (s, 1 H, ArH), 1.71 (s, 6 H, 2 × CH_3), 1.67 (s, 6 H, 2 × CH_3).

^{13}C NMR [125 MHz, $CDCl_3$ + $(PhNH)_2$]: δ = 169.2 (CH), 163.9 (CH), 162.3 (C), 158.0 (C), 154.7 (C), 134.70 (C), 66.5 (C), 66.1 (C), 24.9 (2 × CH_3), 24.8 (2 × CH_3).

MS (EI): *m*/*z* (%) = 244 (77, [M]$^+$), 214 (28), 213 (33), 199 (100), 184 (38).

Anal. Calcd for $C_{12}H_{14}N_5O$: C, 59.00; H, 5.78; N, 28.67. Found: C, 58.80; H, 5.63; N, 28.51.

(6,6,8,8-Tetramethyl-6,7,8,9-tetrahydro-2*H*-pyrrolo[3,4-*g*]pteridine-2,4(3*H*)-dione-7-yl)oxidanyl (13c)

Purified by flash column chromatography ($CHCl_3$–Et_2O 2:1) to afford an orange powder; yield: 342 mg (62%); mp 250–252 °C (MeOH–Et_2O); R_f = 0.30 ($CHCl_3$–MeOH 24:1).

IR (neat): 3509, 3181, 3044, 2979, 1730, 1702, 1673, 1537 cm^{-1}.

^{1}H NMR [500 MHz, DMSO-d_6 + $(PhNH)_2$]: δ = 1.37 (s, 12 H, 4 × CH_3).

^{13}C NMR [125 MHz, DMSO-d_6 + $(PhNH)_2$]: δ = 163.4 (C=O), 161.4 (C=O), 154.6 (C), 150.5 (C), 150.4 (C), 127.1 (C), 66.5 (C), 65.0 (C), 25.3 (2 × CH_3), 25.0 (2 × CH_3).

MS (EI): *m*/*z* (%) = 276 (65, [M]$^+$), 246 (100), 231 (89), 42 (76).

Anal. Calcd for $C_{12}H_{14}N_5O_3$: C, 52.17; H, 5.11; N, 25.35. Found: C, 52.02; H, 5.07; N, 25.20.

(5,5,7,7-Tetramethyl-5*H*-pyrrolo[3,4-*b*]pyrazin-6-yl)oxidanyl (17)

Yield: 300 mg (78%); yellow powder; mp 118–121 °C; R_f = 0.43 (hexane–EtOAc 2:1).

IR (neat): 2973, 2929, 1541 cm^{-1}.

^{1}H NMR [500 MHz, DMSO-d_6 + $(PhNH)_2$]: δ = 8.47 (s, 2 H, ArH), 1.36 (s, 12 H, 4 × CH_3).

^{13}C NMR [125 MHz, DMSO-d_6 + $(PhNH)_2$]: δ = 159.0 (2 C), 144.2 (2 × CH), 65.3 (2 C), 25.30 (4 C).

MS (EI): *m*/*z* (%) = 192 ([M]$^+$, 50) 162 (41), 147 (100), 132 (30), 42 (37).

Anal. Calcd for $C_{10}H_{14}N_3O$: C, 62.48; H, 7.34; N, 21.86. Found: C, 62.37; H, 7.70; N, 21.78.

(5,5,7,7-Tetramethyl-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyrazine-2-carboxamide-6-yl)oxidanyl (23)

Purified by flash column chromatography ($CHCl_3$–Et_2O 2:1) to afford a yellow powder; yield: 90 mg (65%); mp 220–223 °C; R_f = 0.51 ($CHCl_3$–MeOH 24:1).

IR (neat): 3475, 3268, 2981, 1692, 1572 cm^{-1}.

^{1}H NMR [500 MHz, DMSO-d_6 + $(PhNH)_2$]: δ = 9.08 (s, 1 H, ArH), 1.41 (s, 6 H, 2 × CH_3), 1.39 (s, 6 H, 2 × CH_3).

^{13}C NMR [125 MHz, DMSO-d_6 + $(PhNH)_2$]: δ = 165.6 (C=O), 161.9 (C), 157.7 (C), 145.0 (C), 143.1 (CH), 65.5 (C), 65.2 (C), 25.18 (4 × CH_3).

MS (EI): *m*/*z* (%) = 235 (57, [M]$^+$), 205 (34), 190 (44), 42 (100).

Anal. Calcd for $C_{11}H_{15}N_4O_2$: C, 56.16; H, 6.43; N, 23.81. Found: C, 56.24; H, 6.18; N, 23.76.

(1,4,4,6,6-Pentamethyl-2-phenyl-4,6-dihydropyrrolo[3,4-*d*]imidazol-5-yl)oxidanyl (27)

Purified by flash column chromatography (hexane–EtOAc 2:1) to afford yellow crystals; yield: 350 mg (65%); mp 133–135 °C; R_f = 0.47 ($CHCl_3$–Et_2O 2:1).

IR (neat): 2973, 2927, 1577 cm^{-1}.

^{1}H NMR [500 MHz, $CDCl_3$ + $(PhNH)_2$]: δ = 7.69 (d, *J* = 7.5 Hz, 2 H, ArH), 7.47–7.44 (m, 1 H, ArH), [2 aromatic H overlapped with $(PhNH)_2$ signals], 3.69 (s, 3 H, NCH_3), 1.59 (s, 6 H, 2 × CH_3), 1.58 (s, 6 H, 2 × CH_3).

^{13}C NMR [125 MHz, $CDCl_3$ + $(PhNH)_2$]: δ = 150.2 (C), 148.9 (C), 145.8 (C), 134.8 (C), 130.7 (CH), 129.0 (2 × CH), 128.5 (2 × CH), 64.7 (C), 64.1 (C), 32.4 (NCH_3), 25.4 (2 × CH_3), 25.2 (2 × CH_3).

MS (EI): *m*/*z* (%) = 270 (2, [M]$^+$), 240 (100), 225 (89), 211 (20), 77 (15), 43 (16).

Anal. Calcd for $C_{16}H_{20}N_3O$: C, 71.08; H, 7.46; N, 15.54. Found: C, 71.02; H, 7.35; N, 15.67.

6-Methoxy-5,5,7,7-tetramethyl-3,5,6,7-tetrahydro-2*H*-pyrrolo-[3,4-*b*]pyrazine (15)

A solution of compound **3** (740 mg, 4.0 mmol) and 1,2-diaminoethane (240 mg, 4.0 mmol) in anhyd EtOH (20 mL) was refluxed for 1 h under N_2 and then left to stand overnight. The solvent was evaporated, and the residue was purified by flash column chromatography (hexane–EtOAc 2:1) to afford a colorless oil; yield: 593 mg (71%); R_f = 0.33 ($CHCl_3$–Et_2O 2:1).

IR (neat): 2978, 2940, 2900, 1641 cm^{-1}.

^{1}H NMR [500 MHz, $CDCl_3$ + $(PhNH)_2$]: δ = 3.73 (s, 3 H, OCH_3), 3.54 (s, 4 H, 2 × CH_2), 1.34 (s, 12 H, 4 × CH_3).

^{13}C NMR [125 MHz, $CDCl_3$ + $(PhNH)_2$]: δ = 166.1 (2 C), 65.6 (OCH_3), 64.3 (2 C), 44.9 (2 × CH_2), 27.0 (2 × CH_3), 21.0 (2 × CH_3).

MS (EI): *m*/*z* (%) = 209 (31, [M]$^+$), 194 (100), 162 (62), 42 (34).

Anal. Calcd for $C_{11}H_{19}N_3O$: C, 63.13; H, 9.15; N, 20.08. Found: C, 63.05; H, 9.10; N, 20.03.

6-Methoxy-5,5,7,7-tetramethyl-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyrazine (16)

To a stirred solution of compound **15** (418 mg, 2.0 mmol) in anhyd MeOH (10 mL) was added a solution of NaOEt [freshly prepared from Na (92 mg, 4.0 mmol) and anhyd EtOH (20 mL)] and then, the resulting mixture was refluxed for 4 h under N_2. After cooling, the solvents were evaporated, and the residue was partitioned between sat. aq NH_4Cl (20 mL) and $CHCl_3$ (50 mL). The organic phase was separated, dried ($MgSO_4$), filtered, and evaporated. The residue was purified by flash column chromatography (hexane–Et_2O 2:1) to give compound **16** as a colorless oil; yield: 223 mg (54%); R_f = 0.56 (hexane–EtOAc 2:1).

IR (neat): 3049, 2980, 2934, 1545 cm^{-1}.

^{1}H NMR [500 MHz, $CDCl_3$ + $(PhNH)_2$]: δ = 8.38 (s, 2 H, ArH), 3.82 (s, 3 H, OCH_3), 1.51 (s, 12 H, 4 × CH_3).

^{13}C NMR [125 MHz, $CDCl_3$ + $(PhNH)_2$]: δ = 158.8 (2 C), 143.7 (2 × CH), 65.8 (OCH_3), 65.6 (2 C), 28.2 (2 × CH_3), 23.5 (2 × CH_3).

MS (EI): *m*/*z* (%) = 207 (15, [M]$^+$), 192 (100), 160 (23), 146 (46), 42 (42).

Anal. Calcd for $C_{11}H_{17}N_3O$: C, 63.74; H, 8.27; N, 20.27. Found: C, 63.65; H, 8.18; N, 20.10.

(1-Oxyl-5,5,7,7-tetramethyl-5*H*-pyrrolo[3,4-*b*]pyrazin-6-yl)oxidanyl (18)

To a stirred solution of compound **17** (768 mg, 4.0 mmol) in DCM (40 mL) was added solid 3-chloroperbenzoic acid (~60%, 5.73 g, 20.0 mmol) over a period of 1 h. The reaction was monitored by TLC, and upon the consumption of the starting material (24 h), the precipitated 3-chlorobenzoic acid was filtered out on a sintered glass funnel. DCM (40 mL) was added and the organic layer was washed with aq 10% Na_2CO_3 (2 × 20 mL) followed by H_2O (20 mL). The organic phase was separated, dried ($MgSO_4$), filtered, and evaporated. The residue was purified flash column chromatography (hexane–EtOAc 2:1 then $CHCl_3$–Et_2O 4:1); yield: 374 mg (45%); yellow powder; mp 103–106 °C; R_f = 0.33 ($CHCl_3$–Et_2O 2:1).

IR (neat): 3086, 2979, 2968, 1691, 1588 cm^{-1}.

^{1}H NMR [500 MHz, $CDCl_3$ + $(PhNH)_2$]: δ = 8.36 (d, *J* = 4.5 Hz, 1 H, ArH), 8.18 (d, *J* = 4.5 Hz, 1 H, ArH), 1.83 (s, 6 H, 2 × CH_3), 1.67 (s, 6 H, 2 × CH_3).

^{13}C NMR [125 MHz, $CDCl_3$ + $(PhNH)_2$]: δ = 147.0 (C), 143.1 (C), 134.5 (CH), 134.1 (CH), 69.0 (C), 68.1 (C), 24.1 (2 × CH_3), 21.3 (2 × CH_3).

MS (EI): *m*/*z* (%) = 208 (16, [M]$^+$), 178 (64), 161 (100), 42 (33).

Anal. Calcd for $C_{10}H_{14}N_3O_2$: C, 57.68; H, 6.78; N, 20.18. Found: C, 57.84; H, 6.61; N, 20.06.

(1-Oxyl-2-phenyl-5,5,7,7-tetramethyl-5*H*-pyrrolo[3,4-*b*]pyrazin-6-yl)oxidanyl (19)

A degassed mixture of $Pd(OAc)_2$ (22.0 mg, 0.1 mmol), Ag_2CO_3 (605 mg, 2.2 mmol), and compound **18** (208 mg, 1.0 mmol) in benzene (5 mL) in a screw-capped vial was stirred at 130 °C for 16 h in an oil bath. After cooling, the mixture was filtered through a plug of Celite, and then washed with EtOAc (40 mL). The solvents were evaporated and the residue was purified by flash column chromatography (hexane–EtOAc 2:1) to give compound **19** as yellow crystals; yield: 108 mg (38%); mp 121–124 °C; R_f = 0.33 (hexane–EtOAc 2:1).

IR (neat): 3060, 2978, 2932, 1585 cm^{-1}.

^{1}H NMR [500 MHz, $CDCl_3$ + $(PhNH)_2$]: δ = 8.55 (s, 1 H, ArH), 7.87 (d, *J* = 9.5 Hz, 2 H, ArH), [3 aromatic H overlapped with $(PhNH)_2$ signals], 1.78 (s, 6 H, 2 × CH_3), 1.63 (s, 6 H, 2 × CH_3).

^{13}C NMR [125 MHz, $CDCl_3$ + $(PhNH)_2$]: δ = 161.4 (C), 147.0 (CH), 144.3 (C), 144.1 (C), 130.1 (CH), 129.5 (2 × CH), 129.3 (C), 128.6 (2 × CH), 67.1 (C), 66.6 (C), 24.8 (2 × CH_3), 22.0 (2 × CH_3).

MS (EI): *m*/*z* (%) = 284 (14, [M]$^+$), 254 (52), 239 (100), 195 (75), 77 (57), 42 (85).

Anal. Calcd for $C_{16}H_{18}N_3O_2$: C, 67.58; H, 6.38; N, 14.08. Found: C, 67.38; H, 6.43; N, 14.08.

Ethyl 6-Methoxy-5,5,7,7-tetramethyl-6,7-dihydro-5*H*-pyrrolo-[3,4-*b*]pyrazine-2-carboxylate (21)

To a stirred suspension of compound **20** HCl salt (1.03 g, 5.0 mmol) in EtOH (30 mL) was added freshly prepared NaOEt [from Na (230 mg, 10.0 mmol) and anhyd EtOH (20 mL)]. The precipitated NaCl was filtered out, and to the filtrate compound **3** (925 mg, 5.0 mmol) was added in one portion, followed by heating at reflux temperature for 1 h under N_2. A second portion of NaOEt (prepared from Na (230 mg, 10.0 mmol) and anhyd EtOH (20 mL)] was added, and the reaction mixture was refluxed for 4 h under N_2. After standing overnight at r.t. in air, solvents were evaporated, and the residue was partitioned between sat. aq NH_4Cl (20 mL) and $CHCl_3$ (50 mL). The organic phase was separated, dried ($MgSO_4$), filtered, and evaporated. The residue was purified by flash column chromatography (hexane–EtOAc, 2:1) to give compound **21** as a yellow oil; yield: 502 mg (36%); R_f = 0.55 (hexane–EtOAc 2:1).

IR (neat): 2979, 2936, 1720, 1573, 1559 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.09 (s, 1 H, ArH), 4.52 (q, *J* = 7.5 Hz, 2 H, OCH_2CH_3), 3.81 (s, 3 H, OCH_3), 1.55 (s, 12 H, 4 × CH_3), 1.46 (t, *J* = 7.5 Hz, 3 H, OCH_2CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.4 (C=O), 162.3 (C), 158.9 (C), 145.4 (CH), 143.0 (C), 66.0 (2 C), 65.7 (OCH_3), 62.0 (OCH_2), 28.0 (2 × CH_3), 22.9 (2 × CH_3), 14.3 (CH_3).

MS (EI): *m*/*z* (%) = 279 (12, [M]$^+$), 264 (100), 218 (6).

Anal. Calcd for $C_{14}H_{21}N_3O_3$: C, 60.20; H, 7.58; N, 15.04. Found: C, 60.26; H, 7.49; N, 14.96.

6-Methoxy-5,5,7,7-tetramethyl-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyrazine-2-carboxamide (22)

To a solution of compound **21** (558 mg, 2.0 mmol) in EtOH (20 mL) was added aq 10% NaOH (2 mL) and the mixture was heated for 1 h. After standing overnight at r.t., the EtOH was evaporated off. The residue was diluted with H_2O (10 mL) and the mixture was acidified with aq 5% H_2SO_4 (pH 2). The aqueous phase was extracted with $CHCl_3$ (2 × 30 mL), dried ($MgSO_4$), filtered, and evaporated. The crude product was dissolved in anhyd THF (25 mL), and carbonyl diimidazole (CDI, 405 mg, 2.5 mmol) was added to the resulting solution. The mixture was heated for 15 min, and then, 25% aq NH_4OH solution (5 mL) was added, followed by an additional 10 min of heating. After cooling, the mixture was extracted with $CHCl_3$ (2 × 30 mL). The combined organic phases were dried ($MgSO_4$), filtered, and evaporated. The residue was purified by flash column chromatography (hexane–EtOAc, 2:1) to give compound **22** as a beige solid; yield: 247 mg (66%); mp 158–160 °C; R_f = 0.36 ($CHCl_3$–Et_2O 2:1).

IR (neat): 3440, 3197, 2977, 2948, 1685, 1575 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.03 (s, 1 H, NH_2), 8.18 (s, 1 H, NH_2), 7.84 (s, 1 H, ArH), 3.77 (s, 3 H, OCH_3), 1.45 (s, 12 H, 4 × CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.4 (C=O), 160.9 (C), 156.8 (C), 145.3 (CH), 143.4 (C), 66.1 (C), 65.8 (C), 65.7 (OCH_3), 27.7 (2 × CH_3), 23.3 (2 × CH_3).

MS (EI): *m*/*z* (%) = 250 (14, $[M]^+$), 235 (100), 189 (20), 42 (43).

Anal. Calcd for $C_{12}H_{18}N_4O_2$: C, 57.58; H, 7.25; N, 22.38. Found: C, 57.57; H, 7.20; N, 22.28.

5-Methoxy-2-phenyl-4,4,6,6-tetramethyl-1,4,5,6-tetrahydropyrrolo[3,4-*d*]imidazole (25)

To a stirred solution of compound **3** (740 mg, 4.0 mmol) in anhyd EtOH (20 mL) were added NH_4OAc (616 mg, 8.0 mmol), SnO_2 nanoparticles (151 mg, 1.0 mmol), and benzaldehyde (**24**; 424 mg, 4.0 mmol). The resulting mixture was refluxed for 3 h, and after cooling, the mixture was filtered through plug of Celite, followed by evaporation of the filtrate. The residue was partitioned between DCM (50 mL) and distilled H_2O (30 mL). The organic phase was separated, dried ($MgSO_4$), filtered, and evaporated. The residue was purified by flash column chromatography (hexane–EtOAc 2:1) to give compound **25** as a white powder; yield: 813 mg (75%); mp 250–253 °C; R_f = 0.42 (hexane–EtOAc 2:1).

IR (neat): 3065, 3032, 2971, 1600 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 7 Hz, 2 H, ArH), 7.35–7.29 (m, 3 H, ArH), 3.75 (s, 3 H, OCH_3), 1.39 (s, 12 H, 4 × CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 148.7 (C), 140.0 (C), 130.2 (C), 128.8 (2 × CH), 128.6 (CH), 125.3 (2 × CH), 65.6 (OCH_3), 64.2 (2 C), 30.92 (4 × CH_3).

MS (EI): *m*/*z* (%) = 271 (8, $[M]^+$), 256 (42), 227 (43), 43 (100).

Anal. Calcd for $C_{16}H_{21}N_3O$: C, 70.82; H, 7.80; N, 15.49. Found: C, 70.75; H, 7.72; N, 15.64.

5-Methoxy-1,4,4,6,6-pentamethyl-2-phenyl-1,4,5,6-tetrahydropyrrolo[3,4-*d*]imidazole (26)

To a stirred suspension of NaH (48 mg, 2.0 mmol) in anhyd THF (10 mL) was added a solution of compound **25** (542 mg, 2.0 mmol) in THF (20 mL) dropwise at 0 °C under N_2. After 30 min, MeI (426 mg, 3.0 mmol) was added dropwise at 0 °C. After stirring the mixture for 3 h at r.t., the solvent was evaporated, and the residue was partitioned between EtOAc (40 mL) and distilled H_2O (20 mL). The organic phase was separated, dried ($MgSO_4$), filtered, and evaporated. The residue was purified by flash column chromatography (hexane–EtOAc 2:1) to give compound **26** as a white solid; yield: 387 mg (68%); mp 71–73 °C; R_f = 0.57 ($CHCl_3$–Et_2O 2:1).

IR (neat): 3060, 2971, 1691, 1580 cm^{-1}.

^{1}H NMR [500 MHz, $CDCl_3$ + $(PhNH)_2$]: δ = 7.62 (d, *J* = 8.5 Hz, 2 H, ArH), 7.47–7.38 (m, 3 H, ArH), 3.82 (s, 3 H, OCH_3), 3.66 (s, 3 H, NCH_3), 1.53 (s, 12 H, 4 × CH_3).

^{13}C NMR [125 MHz, $CDCl_3$ + $(PhNH)_2$]: δ = 150.0 (C), 145.7(C), 134.6 (C), 130.8 (C), 128.9 (2 × CH), 128.4 (CH), 128.3 (2 × CH), 65.8 (OCH_3), 64.3 (C), 63.8 (C), 32.2 (NCH_3), 28.5 (2 × CH_3), 23.5 (2 × CH_3).

MS (EI): *m*/*z* (%) = 285 (32, $[M]^+$), 270 (54), 238 (100), 43 (28).

Anal. Calcd for $C_{17}H_{23}N_3O$: C, 71.55; H, 8.12; N, 14.72. Found: C, 71.42; H, 8.06; N, 14.58.

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Supporting Information

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