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The reactivity of Oxone towards 4,6-di(cycloamino)-1,3-phenylenediamines: synthesis of spirocyclic oxetane ring-fused imidazobenzimidazoles

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Dedicated to Professor Jan Bergman on the occasion of his 80th birthday

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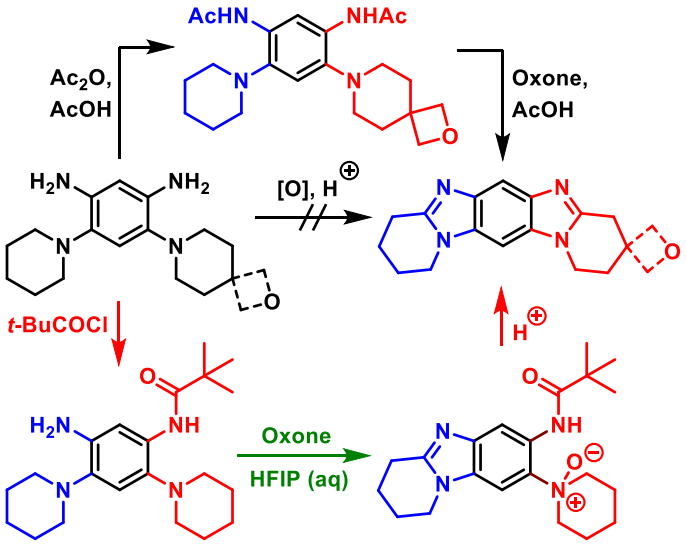
Abstract

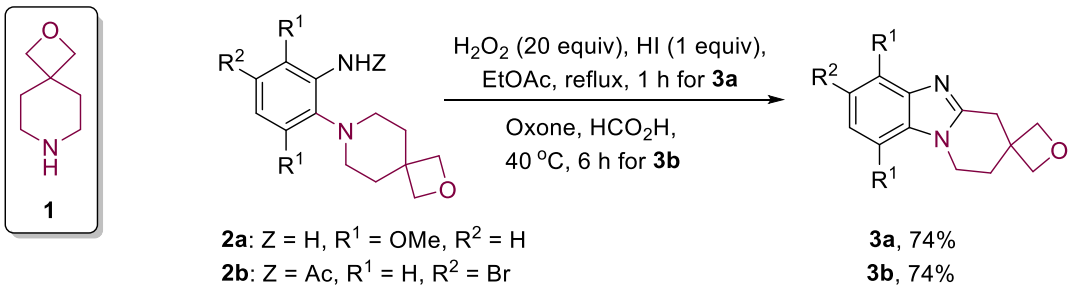
Spirocyclic oxetane ring-fused imidazo[4,5-*f*]benzimidazole and imidazo[5,4-*f*]benzimidazole are reported. Oxone-mediated ring-closures to give imidazobenzimidazoles require acid and the functionalization of the 4,6-di(cycloamino)-1,3-phenylenediamine to the anilides. This is in contrast to benzimidazole forming oxidative cyclizations, which use 2-(cycloamino)anilines and require no acid. New evidence for *N*-oxide and nitroso-intermediates in respective imidazobenzimidazole and benzimidazole forming reactions is provided.



Keywords: Anilide, oxidative cyclization, benzimidazole, heterocycle, HFIP

Introduction

Imidazobenzimidazoles exist in a [4,5-*f*] and [5,4-*f*] arrangement and are scaffolds at the core of antitumor agents.[1–5] A valuable strategy for the discovery of chemotherapeutics is the targeting of proteins over-expressed in solid tumors, such as NAD(P)H:quinone oxidoreductase 1 (NQO1, also known as DT-diaphorase).[6] For iminoquinone derivatives of imidazo[5,4-*f*]benzimidazoles, a hydrogen bonding acceptor improves binding at the NQO1 active site.[5] Oxetane is a robust hydrogen bonding alternative to carbonyl functionalities and a polar analogue of the *gem*-dimethyl group.[7,8] Spirocyclic oxetane **1** was fused onto benzimidazole via oxidative cyclizations of 2-(2-oxa-7-azaspiro[3.5]nonan-7-yl)aniline **2a** and acetamide analogue **2b** using H_2O_2 with HI and Oxone (potassium peroxymonosulfate) in formic acid to give **3a** and **3b** respectively (Scheme 1).[9,10] In this article, our synthetic targets are spirocyclic oxetane ring-fused isomers, imidazo[4,5-*f*]benzimidazole **4** and imidazo[5,4-*f*]benzimidazole **5** (Figure 1).



Scheme 1. Reported preparations of benzimidazoles with ring-fused spirocyclic oxetane [9,10]

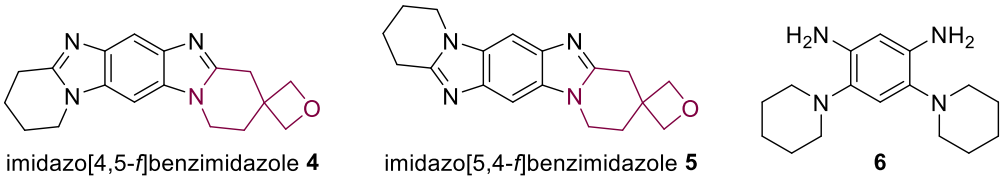
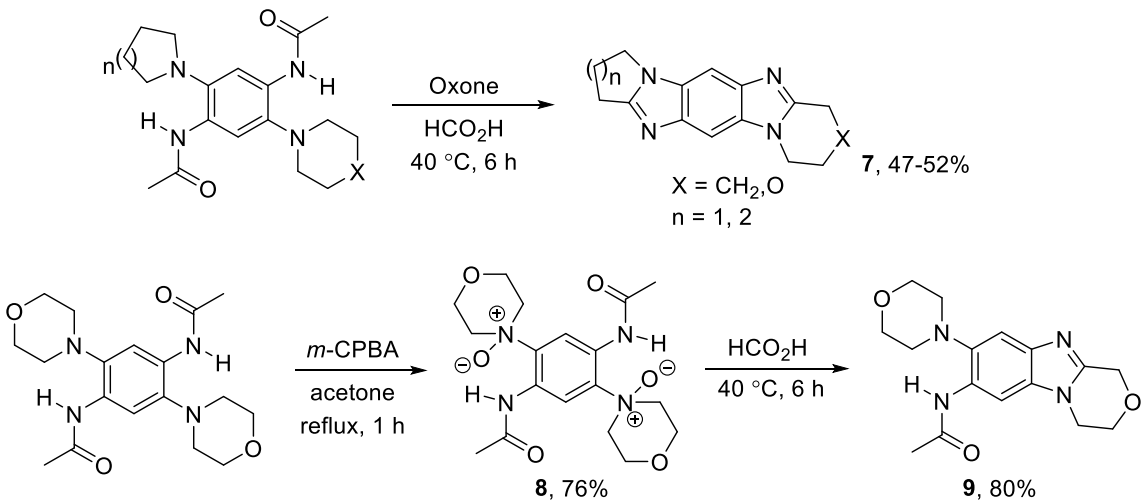


Figure 1. Target imidazobenzimidazoles and the investigated diamine

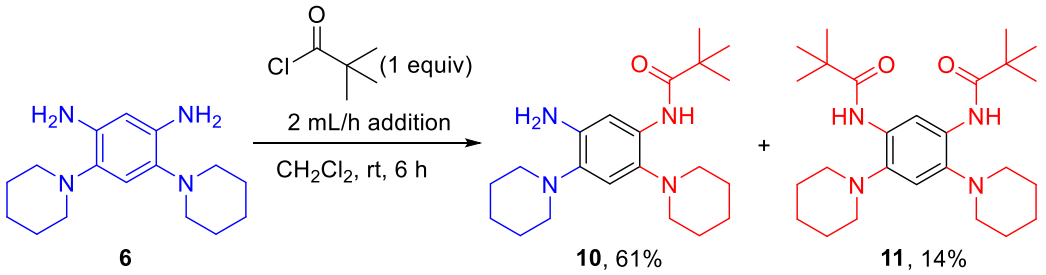
The fundamental advantage of using the Oxone protocol over earlier reported radical cyclization methods,[3] is the ability to synthesize imidazobenzimidazoles (e.g. **7**) containing two different fused rings (Scheme 2).[4] For cyclization, acid has to be present, and *m*-CPBA in acetone gave the diamine *N*-oxide **8**, as the sole product. Treatment of diamine-*N*-oxide **8** with formic acid in the absence of an external oxidant gave ring-fused benzimidazole **9**, and a mechanism for oxidative cyclization through the internal conjugated system of **8** was provided.[4] The use of Oxone for the preparation of these fanciful imidazobenzimidazole scaffolds is reminiscent of early work by Spiegel and Kaufmann, who utilized Caro's acid (peroxysulfuric acid) to cyclize 5-nitro-2-(piperidin-1-yl)aniline to give benzimidazole.[11] Our group has also shown that H_2O_2 can be utilized in the absence of acid for some cyclizations of 2-(cycloamino)anilines,[12] and with HX (X = Cl and Br) to give selectively halogenated ring-fused benzimidazoles,[13] and benzimidazolequinones.[14] In this article, we examine the reactivity of Oxone towards anilide derivatives of 4,6-di(piperidin-1-yl)-1,3-phenylenediamine (**6**) (Figure 1), as part of studies towards the preparation of spirocyclic oxetane ring-fused imidazobenzimidazoles **4** and **5**.



Scheme 2. Reported oxidative cyclizations and evidence of diamine *N*-oxide intermediate [4]

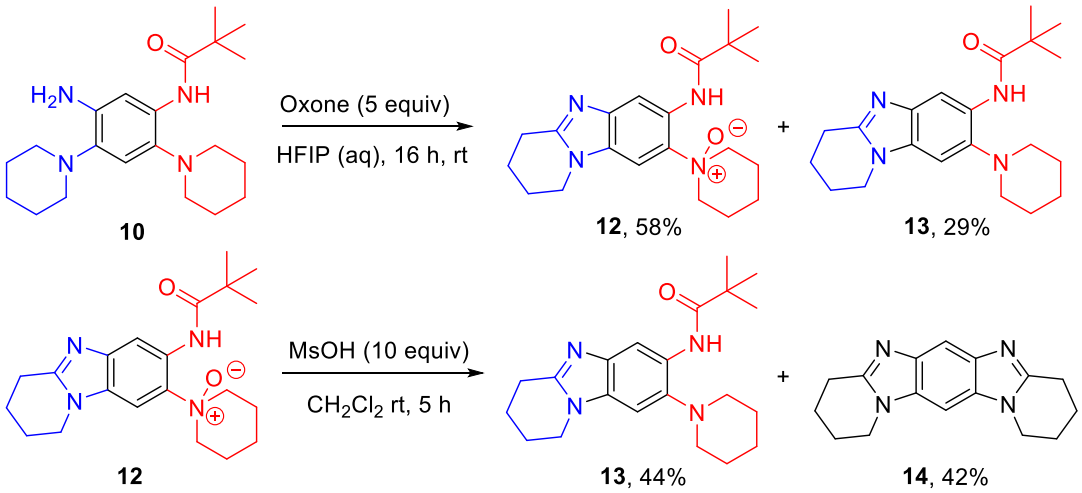
Results and Discussion

Treating diamine **6** with Oxone in acid did not give imidazo[4,5-*f*]benzimidazole, but led to intractable mixtures. This is in line with our findings in Scheme 2,[4] where decreasing the electron-density by acetylating at the primary amines of **6** was necessary. This led us to investigate the effect of Oxone on the mono-anilide derivative of **6**. Slow addition of sterically hindered pivaloyl chloride was necessary in order to minimize reaction at both amines of **6**, which gave the desired *N*-[5-amino-2,4-di(piperidin-1-yl)phenyl]-2,2-dimethylpropanamide (**10**) and *N*,*N*'-[4,6-di(piperidin-1-yl)-1,3-phenylene]bis(2,2-dimethylpropanamide) (**11**) in 61 and 14% yield respectively (Scheme 3).



Scheme 3. Functionalizing 4,6-di(piperidin-1-yl)-1,3-phenylenediamine (**6**) with pivaloyl chloride

Reaction of amine-anilide **10** with Oxone in a 10% aqueous solution of hexafluoroisopropanol (HFIP) gave the intriguing adduct **12** in 58% yield, resulting from cyclization and *N*-oxide formation at the amine and anilide parts respectively (Scheme 4). Mono-cyclized adduct **13** was also formed in 29% yield due to insufficient oxidation to **12**. The amide singlet is shifted to 14 ppm in the ^{1}H-NMR spectrum of **12**, consistent with strong hydrogen bonding to the *N*-oxide (amide-NH at ≈ 9.3 ppm in compounds **10** , **11** and **13**), a trait observed for related *N*-oxides, including diacetamide **8**.[4] The use of HFIP as reaction solvent enabled the solvation of hydrogen-bonding acceptors, including **10** and/or intermediates.[15] Treating **12** with methanesulfonic acid (MsOH) gave the imidazo[4,5-*f*]benzimidazole **14** in 42%,[3,16] and benzimidazole-anilide **13** in 44% yield, in which presumably the *N*-oxide part of **12** allowed intermolecular oxidative aromatization.[4]



Scheme 4. Reactions of anilide derivatives of **6**

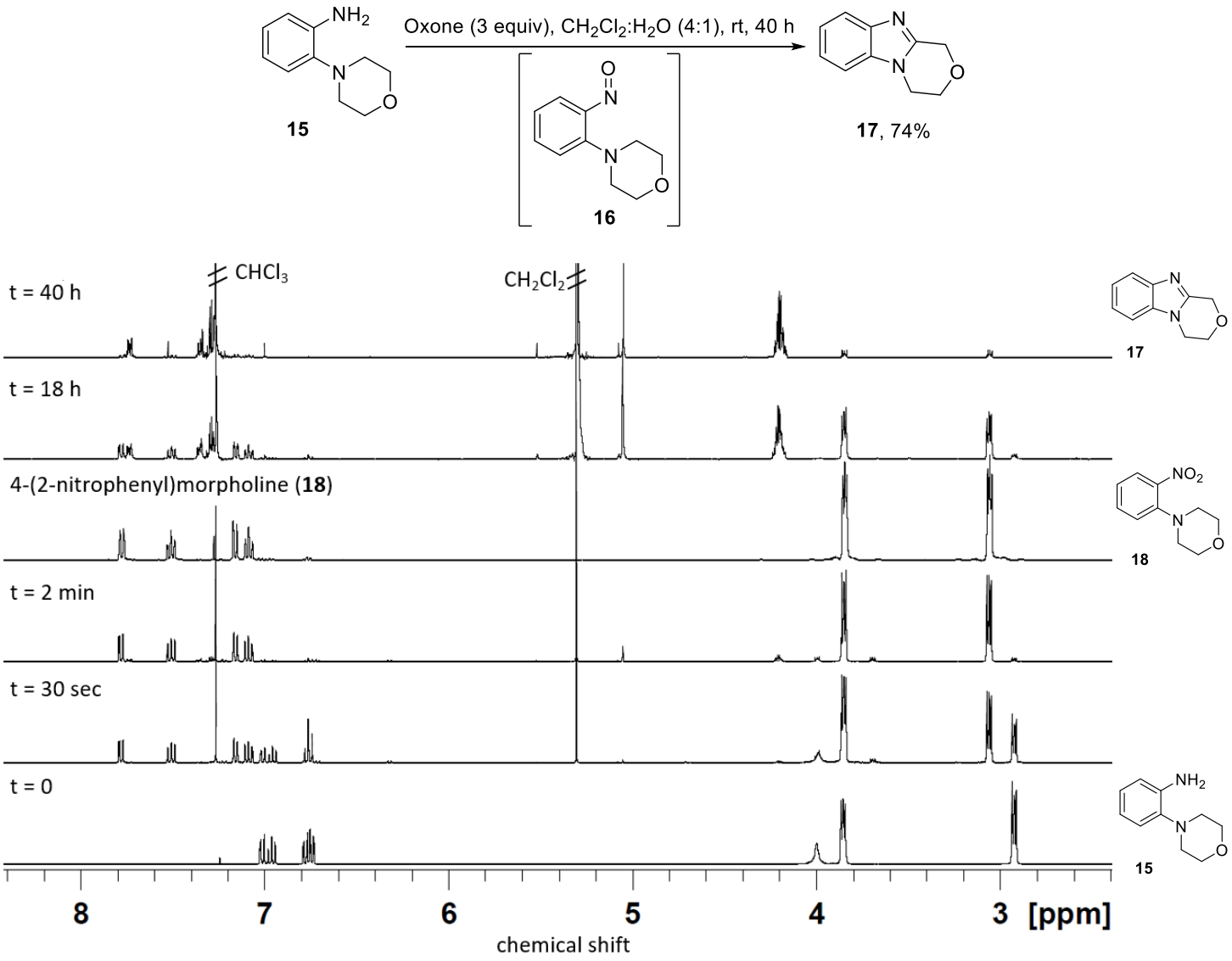
The formation of **12** highlights the difference in mechanism for oxidative cyclization of 2-(cycloamino)anilines and 2-(cycloamino)anilides (Scheme 4). Literature advocates a nitroso intermediate for the formation of benzimidazoles from 2-(cycloamino)anilines,[9,17-19] although the *o*-nitroso-*tert*-aniline has never been isolated. Most recently, we observed the 4-(2-nitrosophenyl)morpholine intermediate by GC-MS from the oxidative cyclization to the ring-fused benzimidazole, which under certain conditions underwent displacement of oxazine to give 1,4,6,9-tetramethoxyphenazine.[9] Evidence for the *o*-nitroso-*tert*-aniline intermediate **16** is now provided from the reaction of 2-(morpholin-4-yl)aniline (**15**) with Oxone in a CH_2Cl_2:H_2O mixture (Scheme 5). Quenching this reaction at short times of 30 s and 2 min gave mostly 4-(2-nitrophenyl)morpholine (**18**), which indicates formation of intermediate **16** and advantageous air-oxidation. After 18 and 40 h, it is apparent from the ^{1}H NMR spectra that the morpholine signals at 3.06 and 3.85 ppm for 4-(2-nitrophenyl)morpholine (**18**) have been replaced by those for benzimidazole **17** at 4.20 and 5.05 ppm.

The above mechanistic work clarified the requirement for diacetamides **21** and **24** for the respective formation of imidazobenzimidazoles **4** and **5**, negating direct oxidative cyclizations from phenylenediamines **20** and **23** (Scheme 6). Moreover treatment of diamines **20** and **23** with Oxone in HFIP under the conditions of Scheme 4 gave an intractable mixture. Syntheses began by nucleophilic aromatic substitution (S_NAr) onto 1,5-difluoro-2,4-dinitrobenzene and 1,4-difluoro-2,5-dinitrobenzene with bis(2-oxa-7-azaspiro[3.5]nonan-7-ium) ethanedioate (oxalate salt of **1**), followed by S_NAr with the stronger nucleophile, piperidine to give the respective unsymmetrically substituted dinitrobenzenes **19** and **22** in 79 and 85% yield. Hydrogenation to the phenylenediamines **20** and **23** occurred in 91 and 88% yield, and reaction with acetic anhydride gave the cyclization precursors **21** and **24** in 84 and 86% yield respectively. Oxidative cyclizations of **21** and **24** with Oxone (6 equiv) in acetic acid gave imidazo[4,5-*f*]benzimidazole **4** and imidazo[5,4-*f*] benzimidazole **5** in 55 and 49% yield respectively, representing cumulative yields of ≥70% for each ring closure.

Conclusions

This article demonstrates the necessity for converting 4,6-di(cycloamino)-1,3-phenylenediamines to dianilide/diacetamide prior to imidazobenzimidazole formation. New evidence is presented for nitroso and *N*-oxide intermediates in the respective oxidative cyclizations of 2-(cycloamino)anilines and 2-(cycloamino)anilides. Oxetane is incorporated into ring-fused imidazobenzimidazoles for the first time, with

Oxone in acetic acid allowing the formation of both [4,5-*f*] and [5,4-*f*] isomers. Future work should complete overall oxidation of the aromatic part of **4** and **5** to give the (imino)quinone NQO1 substrates.

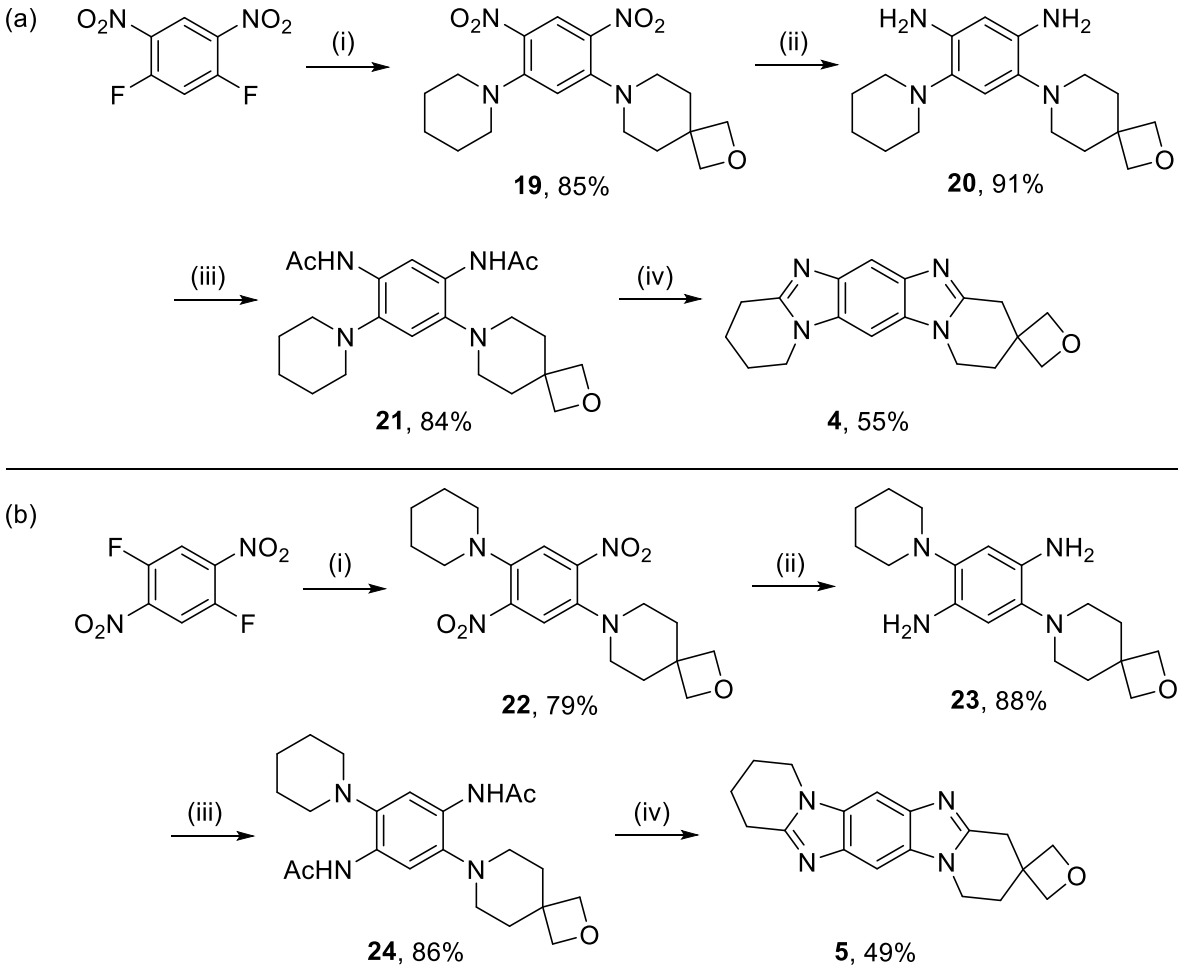


Scheme 5. ^{1}H NMR reaction monitoring, providing evidence for the *o*-nitroso-*tert*-aniline intermediate **16**

Experimental Section

Materials. Pd-C (Sigma Aldrich, 5% wt. loading), EtOAc (VWR, 99.9%), pet. ether (Fisher Scientific, 40-60°C, Extra Pure, SLR), pivaloyl chloride (Sigma Aldrich, 99%), Oxone (Sigma Aldrich, $KHSO_5$•$0.5KHSO_4$•$0.5K_2SO_4$), HFIP (Fluorochem, 99%), $NaHCO_3$ (Fisher Scientific, ≥99.7%), 1,5-difluoro-2,4-dinitrobenzene (Sigma Aldrich, 97%), MeCN (Fisher Scientific, HPLC grade), piperidine (ACROS Organics™, 99%), AcOH (Fisher Scientific, glacial), Ac_2O (ACROS Organics™, 99+%), MsOH (Fluorochem, >98%), Na_2CO_3 (Fisher Scientific, 99.5%), D_2O (Fluorochem, >99.9%), and $MgSO_4$ (Fisher Scientific, Extra Pure, SLR, Dried) were used as received. CH_2Cl_2 (Fisher Scientific, 99.8%) was distilled over CaH_2 (ACROS Organics™, ca. 93%, extra pure, 0-2 mm grain size) prior to use. 1,1'-(4,6-Dinitro-1,3-phenylene)dipiperidine was prepared (1.198 g, 92%) by modifying the

reported procedure,[2] by reacting piperidine (2.50 mL, 29.00 mmol) and $NaHCO_3$ (1.600 g, 19.50 mmol) with 1,5-difluoro-2,4-dinitrobenzene (0.800 g, 3.90 mmol) in THF (30 mL) at room temperature for 1 h. The synthesis of 4-(2-nitrophenyl)morpholine (**18**) (1.042 g, 83%) was achieved by S_NAr of morpholine (1.56 ml, 18.09 mmol, Alfa Aesar, 99%) onto 1-fluoro-2-nitrobenzene (0.850 g, 6.03 mmol, Fluorochem, 99%) in the absence of solvent at 110 °C for 1 h. 2-(Morpholin-4-yl)aniline (**15**)[13] was obtained in 91% yield, through reduction of **18** with iron powder, according to our previously reported method.[9,10,12,14] The Aldabbagh group has previously described the synthesis of bis(2-oxa-7-azaspiro[3.5]nonan-7-ium) ethanedioate (oxalate salt of **1**),[10] and 1,4-difluoro-2,5-dinitrobenzene.[4] All reactions (apart from those using aqueous solutions) were carried out under an inert nitrogen atmosphere. Thin Layer Chromatography (TLC) was carried out on TLC silica gel 60 F_{254} plates, and preparative TLC was done on TLC Silica Gel 60 F_{254} glass plates. Flash column chromatography was carried out on silica gel (Apollo Scientific 60/40−63 µm).



Scheme 6. Synthesis of (a) imidazo[4,5-*f*]benzimidazole **4** and (b) imidazo[5,4-*f*]benzimidazole **5**: (i) **1** oxalate salt, $NaHCO_3$, MeCN (aq), rt, 16 h; piperidine, rt, 1 h; (ii) H_2 (balloon), Pd-C, EtOAc, rt, 18 h; (iii) Ac_2O (10 equiv), AcOH, 80 °C, 30 min; (iv) Oxone (6 equiv), AcOH, 40 °C, 7 h.

Instruments. Melting points were measured on a Stuart Scientific melting point apparatus SMP1. IR spectra were recorded using a PerkinElmer Spec 1 with ATR attached. NMR spectra were recorded using a Bruker Avance II 400 MHz spectrometer. Chemical shifts are in ppm, relative to Me_4Si. ^1H NMR NH amide and amine assignments were verified by D_2O exchange experiments. ^{13}C NMR spectra are at 100 MHz with complete proton decoupling and assignments supported by Distortionless Enhancement by Polarization Transfer (DEPT).

NMR assignments for synthetic targets **4** and **5** used data of reported spirocyclic oxetane ring-fused compounds.[9,10] HRMS spectra of compounds **4**, **5**, **19**, **21**, **22** and **24** were obtained at the National University of Ireland Galway, using an ESI time-of-flight mass spectrometer (TOFMS) on a Waters LCT Mass Spectrometry instrument. HRMS spectra of all other compounds were obtained at the National Mass Spectrometry Facility at Swansea University using a Waters Xevo G2-S mass spectrometer with an Atmospheric Solids Analysis Probe (ASAP) or Thermo Scientific LTQ Orbitrap XL instrument with Nanospray Ionization (NSI). The precision of all accurate mass measurements was better than 5 ppm.

Synthesis of 4,6-di(piperidin-1-yl)benzene-1,3-diamine (6). 1,1'-(4,6-Dinitro-1,3-phenylene)dipiperidine (0.750 g, 2.25 mmol), and Pd-C (75 mg) in EtOAc (50 mL) were stirred under H_2 at room temperature for 24 h. The mixture was filtered through Celite and evaporated to dryness. The residue was purified by column chromatography using gradient elution of pet. ether and EtOAc to give the title compound (0.512 g, 83%) as a brown solid; R_f 0.32 (2:1 pet. ether:EtOAc); mp 172-174 °C; ν_{max} (neat, cm^{-1}) 3378, 3264, 2946, 2923, 2844, 2799, 2742, 1626, 1518, 1466, 1441, 1382, 1339, 1296, 1273, 1257, 1242, 1214, 1201, 1149, 1129, 1111, 1037, 1029; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.69 (s, 1H), 6.11 (s, 1H), 4.00-3.31 (br.s, 4H, NH_2), 2.85-2.55 (br.s, 8H), 1.64-1.55 (m, 8H), 1.54-1.36 (br.s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.6, 132.5 (both C), 112.6, 102.1 (both CH), 53.6, 27.1, 24.4 (all CH_2); HRMS (ASAP) *m/z* $[M+H]^+$ found 275.2234, $C_{16}H_{27}N_4$ requires 275.2236.

Anilide formation. Pivaloyl chloride (45 µL, 0.37 mmol) in CH_2Cl_2 (8 mL) was added via syringe pump at a rate of 2 mL/h to diamine **6** (0.103 g, 0.37 mmol) in CH_2Cl_2 (8 mL). The mixture was stirred for a further 2 h at room temperature. H_2O (20 mL) was added, and the mixture was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were dried ($MgSO_4$), evaporated and purified by column chromatography using gradient elution of pet. ether and EtOAc.

***N*-[5-Amino-2,4-di(piperidin-1-yl)phenyl]-2,2-dimethylpropanamide (10).** (81 mg, 61%); pale brown solid; R_f 0.44 (7:3 pet. ether:EtOAc); mp 149-151 °C; ν_{max} (neat, cm^{-1}) 3423, 3333, 2931, 2851, 2801, 2739, 2360, 1669 (C=O), 1618, 1593, 1519, 1480, 1435, 1377, 1364, 1321, 1272, 1235, 1206, 1193, 1150, 1121, 1110, 1063, 1035, 1029; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.13 (s, 1H, NH), 7.92 (s, 1H), 6.85 (s, 1H), 4.05-3.82 (br.s, 2H, NH_2), 2.90-2.62 (m, 8H), 1.75-1.64 (m, 8H), 1.63-1.47 (br.s, 4H), 1.31 (s, 9H, Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.2 (C=O), 138.9, 135.7, 133.8, 130.5 (all C), 112.4, 105.5 (both CH), 54.3, 53.0 (both CH_2), 40.0 (C), 27.8 (Me), 27.3, 26.9, 24.4, 24.1 (all CH_2); HRMS (ASAP) *m/z* $[M+H]^+$ found 359.2809, $C_{21}H_{35}N_4O$ requires 359.2811.

***N,N'*-[4,6-Di(piperidin-1-yl)-1,3-phenylene]bis(2,2-dimethylpropanamide) (11).** (22 mg, 14%); brown solid; R_f 0.37 (pet. ether:EtOAc); mp 236-237 °C; ν_{max} (neat, cm^{-1}) 3344, 2949, 2930, 2917, 2849, 1682 (C=O), 1596, 1519, 1480, 1448, 1428, 1393, 1377, 1362, 1356, 1340, 1309, 1269, 1219, 1190, 1162, 1150, 1103, 1063, 1027; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.36 (s, 1H), 8.77 (s, 1H, NH), 6.95 (s, 1H), 2.74 (t, *J* 5.2 Hz, 8H), 1.75-1.68 (m, 8H), 1.62-1.55 (m, 4H), 1.30 (s, 18H, Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.6 (C=O), 138.0, 130.8 (both C), 112.4, 110.7 (both CH), 53.9 (CH_2), 39.9 (C), 27.8 (Me), 27.1, 24.1 (CH_2); HRMS (ASAP) *m/z* $[M+H]^+$ found 443.3384, $C_{26}H_{43}N_4O_2$ requires 443.3386.

Reaction of amine-anilide 10 with Oxone (in the absence of acid). Oxone (0.277 g, 0.90 mmol) was added to amine-anilide **10** (65 mg, 0.18 mmol) in HFIP (3.6 mL, 10% aq.) and stirred at room temperature for 16 h. H_2O (10 mL) was added, and the mixture extracted with CH_2Cl_2 (2 x 10 mL). The organic extracts were dried ($MgSO_4$), evaporated and purified by column chromatography using gradient elution of CH_2Cl_2 and MeOH.

2,2-Dimethyl-*N*-[8-(1-oxidopiperidin-1-yl)-1,2,3,4-tetrahydropyrido[1,2-*a*]benzimidazol-7-yl]propenamide (12). (39 mg, 58%); pale brown solid; R_f 0.26 (9:1 CH_2Cl_2:MeOH); mp (decomp. >161 °C); ν_{max} (neat, cm^{-1}) 2952, 2927, 2866, 1652 (C=O), 1594, 1497, 1474, 1430, 1417, 1366, 1327, 1273, 1199, 1148, 1011; ^{1}H NMR (400

MHz, $CDCl_3$) δ: 13.99 (s, 1H, NH), 8.84 (s, 1H), 7.29 (s, 1H), 4.05 (t, *J* 6.0 Hz, 2H), 3.84 (d, *J* 10.7 Hz, 2H), 3.59-3.47 (m, 2H), 3.08 (t, *J* 6.3 Hz, 2H), 2.80-2.70 (m, 2H), 2.17-2.11 (m, 2H), 2.05-2.01 (m, 2H), 1.89 (d, *J* 13.0 Hz, 1H), 1.75 (d, *J* 13.6 Hz, 2H), 1.48-1.37 (m, 1H), 1.35 (s, 9H, Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.9 (C=O), 154.1, 142.7, 137.6, 130.6, 129.1 (all C), 114.0, 98.2 (both CH), 66.5, 42.5 (both CH_2), 40.0 (C), 27.8 (Me), 25.5, 22.5, 21.9, 20.9, 20.5 (all CH_2); HRMS (ASAP) *m/z* $[M+H]^+$ found 371.2447, $C_{21}H_{31}N_4O_2$ requires 371.2447, *m/z* 372 (25%), 371 (M+1, 100%), 356 (16%), 355 (M-16, 73%), 354 (26%), 353 (M-18, 97%), 269 (M-102, 28%).

2,2-Dimethyl-*N*-[8-(piperidin-1-yl)-1,2,3,4-tetrahydropyrido[1,2-*a*]benzimidazol-7-yl]propenamide (13). (19 mg, 29%); brown solid; R_f 0.44 (9:1 CH_2Cl_2:MeOH); mp 171-173 °C; ν_{max} (neat, cm^{-1}) 3340, 2935, 2863, 2809, 1667 (C=O), 1589, 1511, 1473, 1440, 1418, 1365, 1322, 1268, 1242, 1194, 1146, 1136, 1064, 1034; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.25 (s, 1H, NH), 8.74 (s, 1H), 7.08 (s, 1H), 4.03 (t, *J* 6.1 Hz, 2H), 3.05 (t, *J* 6.4 Hz, 2H), 2.96-2.67 (br.s, 4H), 2.16-2.06 (m, 2H), 2.05-1.95 (m, 2H), 1.84-1.54 (m, 6H), 1.36 (s, 9H, Me); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 176.0 (C=O), 151.7, 139.7, 139.1, 130.2, 129.8 (all C), 109.0, 101.0 (both CH), 54.7, 42.4 (both CH_2), 40.1 (C), 27.9 (Me), 27.2, 25.3, 24.1, 22.7, 20.7 (all CH_2); HRMS (ASAP) *m/z* $[M+H]^+$ found 355.2495, $C_{21}H_{31}N_4O$ requires 355.2498.

Ring-closure with acid. MsOH (0.05 mL, 0.77 mmol) was added to a solution of *N*-oxide **12** (28 mg, 0.08 mmol) in CH_2Cl_2 (0.8 mL) and stirred at room temperature for 5 h. Na_2CO_3 (satd., 2 mL) was added, and the mixture extracted with CH_2Cl_2 (3 x 2 mL). The organic extracts were dried ($MgSO_4$), evaporated and purified by preparative TLC.

2,2-Dimethyl-*N*-[8-(piperidin-1-yl)-1,2,3,4-tetrahydropyrido[1,2-*a*]benzimidazol-7-yl]propenamide (13). (12 mg, 44%); R_f 0.44 (9:1 CH_2Cl_2:MeOH); spectral data and melting point consistent with the above.

1,2,3,4,8,9,10,11-Octahydropyrido[1,2-*a*]pyrido[1',2':1,2]imidazo[4,5-*f*]benzimidazole (14).[3,16] (8 mg, 42%); off-white solid; R_f 0.20 (9:1 CH_2Cl_2:MeOH); mp (decomp. >261 °C; lit. m.p.[3] decomp. 266-270 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.95 (d, *J* 0.8 Hz, 1H), 7.04 (d, *J* 0.8 Hz, 1H), 4.09 (t, *J* 6.1 Hz, 4H), 3.11 (t, *J* 6.4 Hz, 4H), 2.20-2.13 (m, 4H), 2.07-2.00 (m, 4H).

Reaction of aniline 15 with Oxone. Aniline **15** (0.356 g, 2.00 mmol) and Oxone (1.846 g, 6.01 mmol) in CH_2Cl_2 (4 mL) and H_2O (1 mL) were rapidly stirred at rt. Aliquots (0.2 mL) were taken at the times shown in Scheme 4, quenched with water (0.5 mL), and extracted with $CDCl_3$ (0.5 mL) for ^{1}H NMR analysis. After 2 min, nitrobenzene **18** was the apparent major product; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.78 (dd, *J* 8.1 Hz, 1.6 Hz, 1H), 7.53-7.48 (m, 1H), 7.16 (dd, *J* 8.3, 1.2 Hz, 1H), 7.11-7.06 (m, 1H), 3.85 (t, *J* 4.6 Hz, 4H), 3.06 (t, *J* 4.6 Hz, 4H). The reaction under the same conditions was stirred for 40 h. H_2O (5 mL) was added, and the mixture extracted with CH_2Cl_2 (2 x 6 mL). The organic extracts were dried ($MgSO_4$), evaporated and purified by column chromatography using gradient elution of pet. ether and EtOAc to give 3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]benzimidazole (**17**) (0.259 g, 74%) as a pale brown solid; R_f 0.21 (EtOAc); mp 123-125 °C (lit m.p.[17] 129-130 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.76-7.72 (m, 1H), 7.37-7.32 (m, 1H), 7.31-7.27 (m, 2H), 5.05 (s, 2H), 4.24-4.16 (m, 4H). Spectral data and melting point were consistent with reported.[20]

Procedure for the synthesis of nitrobenzenes 19 and 22. Oxalate salt of **1** (0.540 g, 1.57 mmol), $NaHCO_3$ (1.020 g, 12.48 mmol) and 1,5-difluoro-2,4-dinitrobenzene or 1,4-difluoro-2,5-dinitrobenzene (0.636 g, 3.12 mmol) in MeCN (40 ml) and H_2O (4 ml) were stirred at room temperature for 16 h. Piperidine (3.00 ml, 30.42 mmol) was added to the mixture and stirred for a further 1 h. The mixture was evaporated, EtOAc (50 mL) added, washed with brine (3 x 50 mL), dried ($MgSO_4$), and evaporated to dryness. The residue was purified by column chromatography using gradient elution of pet. ether and EtOAc.

1-(2,4-Dinitro-5-piperidin-1-ylphenyl)-2-oxa-7-azaspiro[3.5]nonane (19). (0.993 g, 85%); yellow solid; R_f 0.32 (1:1 pet. Ether:EtOAc); mp 156-157 °C; ν_{max} (neat, cm^{-1}) 2941, 2855, 1600, 1555, 1489 (NO_2), 1441, 1326 (NO_2), 1299, 1254; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.66 (s, 1H), 6.25 (s, 1H), 4.48 (s, 4H, OCH_2), 3.12 (t, *J* 5.3 Hz, 4H), 3.04 (t, *J* 5.5 Hz, 4H), 2.06 (t, *J* 5.5 Hz, 4H), 1.76-1.69 (m, 4H), 1.69-1.62 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.8, 131.1, 130.6 (all C), 130.0, 107.4 (both CH), 81.4 (OCH_2), 52.3, 48.6 (both CH_2), 38.5 (C), 34.4, 25.5, 23.9 (all CH_2); HRMS (ESI) *m/z* $[M+H]^+$ found 377.1813, $C_{18}H_{25}N_4O_5$ requires 377.1825.

1-(2,5-Dinitro-4-piperidin-1-ylphenyl)-2-oxa-7-azaspiro[3.5]nonane (22). (0.926 g, 79%); red-brown solid; R_f 0.49 (4:1 pet. Ether:EtOAc); mp 148-149 °C; ν_{max} (neat, cm^{-1}) 2929, 2859, 2810, 1533, 1495 (NO_2), 1466, 1445, 1410, 1385, 1346 (NO_2), 1324 (NO_2), 1272, 1236, 1225, 1209, 1131, 1042; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.45 (s, 1H), 7.41 (s, 1H), 4.45 (s, 4H, OCH_2), 2.95 (t, *J* 5.3 Hz, 4H), 2.87 (t, *J* 5.5 Hz, 4H), 1.99 (t, *J* 5.5 Hz, 4H), 1.71-1.65 (m, 4H), 1.60-1.53 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 146.8, 144.9, 141.8, 139.5 (all C), 119.3, 118.1 (both CH), 81.6 (OCH_2), 53.1, 49.8 (both CH_2), 38.2 (C), 34.9, 25.9, 23.8 (all CH_2); HRMS (ESI) *m/z* $[M+H]^+$ found 377.1818, $C_{18}H_{25}N_4O_5$ requires 377.1825.

Procedure for the synthesis of diamines 20 and 23. Dinitrobenzene **19** or **22** (0.500 g, 1.33 mmol), and Pd-C (50 mg) in EtOAc (50 mL) were stirred under H_2 (balloon) at room temperature for 16 h. The mixture was filtered through Celite and evaporated to dryness.

4-(2-Oxa-7-azaspiro[3.5]nonan-7-yl)-6-(piperidin-1-yl)benzene-1,3-diamine (20). (0.381 g, 91%); brown solid; mp 187-188 °C; ν_{max} (neat, cm^{-1}) 3372, 3264, 2951, 2920, 2848, 2740, 1626, 1519, 1468, 1442, 1380, 1296, 1278, 1257, 1246, 1215, 1149, 1132, 1113, 1036, 1026; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.60 (s, 1H), 6.07 (s, 1H), 4.40 (s, 4H, OCH_2), 3.78-3.64 (br.s, 4H, NH_2), 2.81-2.41 (br.s, 8H), 2.02-1.79 (br.s, 4H), 1.64-1.53 (m, 4H), 1.52-1.36 (br.s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.9, 138.5, 132.5, 131.2 (all C), 112.4, 102.1 (both CH), 82.1 (OCH_2), 53.6, 49.6 (both CH_2), 38.5 (C), 36.1, 27.1, 24.4 (all CH_2); HRMS (NSI) *m/z* $[M+H]^+$ found 317.2342, $C_{18}H_{29}N_4O_1$ requires 317.2336.

2-(2-Oxa-7-azaspiro[3.5]nonan-7-yl)-5-(piperidin-1-yl)benzene-1,4-diamine (23). (0.369 g, 88%); grey solid; mp 197-199 °C; ν_{max} (neat, cm^{-1}) 3386, 3302, 3273, 3162, 2924, 2855, 2800, 2739, 1585, 1511, 1462, 1450, 1432, 1342, 1301, 1246, 1200, 1111, 1033; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.40 (s, 1H), 6.35 (s, 1H), 4.40 (s, 4H, OCH_2), 3.64-3.40 (br.s, 4H, NH_2), 2.78-2.54 (m, 8H), 1.96-1.84 (br.s, 4H), 1.65-1.56 (m, 4H), 1.53-1.40 (br.s, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 137.7, 136.1, 133.5, 133.3 (all C), 108.1, 107.8 (both CH), 82.0 (OCH_2), 53.0, 49.0 (both CH_2), 38.5 (C), 35.9, 26.9, 24.4 (all CH_2); HRMS (NSI) *m/z* $[M+H]^+$ found 317.2339, $C_{18}H_{29}N_4O_1$ requires 317.2336.

Procedure for the synthesis of diacetamides 21 and 24. Diamine **20** or **23** (0.354 g, 1.12 mmol) in Ac_2O (1.06 mL, 11.20 mmol) and AcOH (30 mL) was stirred at 80 °C for 30 min. The mixture was evaporated, $NaHCO_3$ (5%, 100 mL) added and stirred for 1 h. The precipitate was collected, washed with water, dried, and recrystallized from EtOAc.

***N,N'*-[4-(2-Oxa-7-azaspiro[3.5]nonan-7-yl)-6-piperidin-1-yl-1,3-phenylene]diacetamide (21).** (0.375 g, 84%); white solid; mp 226-228 °C; ν_{max} (neat, cm^{-1}) 3291, 2935, 2856, 2797, 2735, 1728, 1672 (C=O), 1659, 1589, 1524, 1491, 1420, 1378, 1368, 1289, 1276, 1256, 1232, 1218, 1196, 1158, 1136, 1122, 1112, 1066, 1032; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.98 (s, 1H), 8.19 (s, 1H, NH), 8.07 (s, 1H, NH), 6.76 (s, 1H), 4.43 (s, 4H, OCH_2), 2.71-2.58 (m, 8H), 2.13-2.06 (m, 6H, Me), 2.00-1.90 (br.s, 4H), 1.68-1.60 (m, 4H), 1.55-1.46 (br.s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.5 (C=O), 138.6, 137.4, 130.3, 129.8 (all C), 112.0 (2 x CH), 81.7 (OCH_2), 53.8, 49.9 (both CH_2), 38.3 (C), 35.8, 26.9 (both CH_2), 24.8 (Me), 24.0 (CH_2); HRMS (ESI) *m/z* $[M-H]^-$ found 399.2397, $C_{22}H_{31}N_4O_3$ requires 399.2396.

***N,N'*-[2-(2-Oxa-7-azaspiro[3.5]nonan-7-yl)-5-(piperidin-1-yl)-1,4-phenylene]diacetamide (24).** (0.386 g, 86%); pale brown solid; mp 221-222 °C; ν_{max} (neat, cm^{-1}) 3362, 3286, 2941, 2869, 2808, 1672 (C=O), 1527, 1477, 1417, 1367, 1296, 1239, 1220, 1195, 1108, 1062; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.44 (s, 1H, NH), 8.33 (s, 1H, NH), 8.16 (s, 1H), 8.11 (s, 1H), 4.42 (s, 4H, OCH_2), 2.71 (t, *J* 5.1 Hz, 4H), 2.66 (t, *J* 5.1 Hz, 4H), 2.11 (s, 3H, Me), 2.10 (s, 3H, Me), 2.01-1.87 (br.s, 4H), 1.68-1.59 (m, 4H), 1.57-1.46 (br.s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.0, 167.9 (both C=O), 139.3, 137.7, 129.4, 129.3 (all C), 112.0, 111.6 (both CH), 81.7 (OCH_2), 53.7, 49.9 (both CH_2), 38.3 (C), 35.9, 27.0 (both CH_2), 24.9 (Me), 24.0 (CH_2); HRMS (ESI) *m/z* $[M+H]^+$ found 401.2536, $C_{22}H_{33}N_4O_3$ requires 401.2553.

Procedure for the synthesis of imidazobenzimidazoles 4 and 5. Diacetamide **21** or **24** (50 mg, 0.13 mmol) and Oxone (0.250 g, 0.81 mmol) in AcOH (5 mL) were stirred at 40 °C for 7 h. The mixture was evaporated, H_2O (10 mL) added, neutralized with solid Na_2CO_3, and extracted with CH_2Cl_2 (3 x 5 mL). The organic extracts were dried ($MgSO_4$), evaporated and recrystallized from EtOAc.

6,7,11,12,13,14-Hexahydro-1*H*-2-oxa-7-azaspiro[3.5]nonan[1,2-*a*]pyrido[1',2':1,2]imidazo[4,5-*f*]benzimidazole (4). (22 mg, 55%); brown solid; mp (decomp. >279 °C); ν_{max} (neat, cm^{-1}) 3386, 2946, 2892, 1661, 1526, 1484, 1432, 1420, 1369, 1312, 1254, 1196, 1159, 1136, 1098; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.90 (d, *J* 0.9 Hz, 1H, 16-H), 6.99 (d, *J* 0.9 Hz, 1H, 9-H), 4.54 (s, 4H, 3,5-CH_2), 4.08 (t, *J* 6.3 Hz, 2H, 7-CH_2), 4.03 (t, *J* 6.1 Hz, 2H, 11-CH_2), 3.34 (s, 2H, 1-CH_2), 3.05 (t, *J* 6.4 Hz, 2H), 2.43 (t, *J* 6.3 Hz, 2H), 2.14-2.06 (m, 2H), 2.01-1.94 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.1, 149.5, 140.1, 140.0, 132.2, 131.6 (all C), 107.6 (16-CH), 87.3 (9-CH), 80.7 (3,5-CH_2), 42.6, 38.9 (7,11-CH_2), 38.0 (C), 35.0 (1-CH_2), 30.8, 25.7, 22.7, 20.8 (all CH_2); HRMS (ESI) *m/z* $[M+H]^+$ found 309.1720, $C_{18}H_{21}N_4O$ requires 309.1715.

6,7,11,12,13,14-Hexahydro-1*H*-2-oxa-7-azaspiro[3.5]nonan[1,2-*a*]pyrido[1',2':1,2]imidazo[5,4-*f*]benzimidazole (5). (20 mg, 49%); orange solid; mp (decomp. >297 °C); ν_{max} (neat, cm^{-1}) 2926, 2856, 1533, 1488, 1449, 1418, 1362, 1279, 1240, 1192, 1166, 1135, 1093; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.53 (d, *J* 0.8 Hz, 1H), 7.52 (d, *J* 0.8 Hz, 1H), 4.64 (ABq, *J* 6.2 Hz, 4H, 3,5-CH_2), 4.21 (t, *J* 6.3 Hz, 2H, 7-CH_2), 4.16 (t, *J* 6.1 Hz, 2H, 14-CH_2), 3.44 (s, 2H, 1-CH_2), 3.14 (t, *J* 6.4 Hz, 2H), 2.52 (t, *J* 6.3 Hz, 2H), 2.24-2.17 (m, 2H), 2.10-2.04 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), 152.6, 150.0, 139.90, 139.85, 132.5, 132.0 (all C), 97.2, 97.0 (both CH), 80.8 (3,5-CH_2), 42.6, 38.9 (7,14-CH_2), 38.0 (C), 35.2 (1-CH_2), 30.8, 25.7, 22.7, 20.8 (all CH_2); HRMS (ESI) *m/z* $[M+H]^+$ found 309.1721, $C_{18}H_{21}N_4O$ requires 309.1715.

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Supplementary Material

^{1}H and ^{13}C NMR spectra of novel compounds **4**-**6**, **10**-**13**, and **19**-**24**, and ^{1}H NMR spectra of known compounds **14**, **17** and **18** can be found in the Supplementary Material file. For spirocyclic oxetane ring-fused compounds **4** and **5** atom numbering is included, which is derived from the systematic compound names.

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