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Photochemical homologation for the preparation of aliphatic aldehydes in flow

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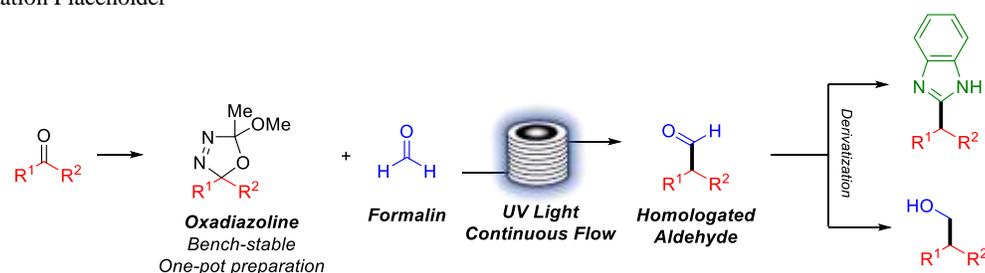
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Supporting Information Placeholder

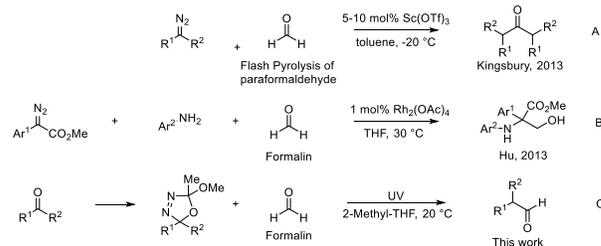


ABSTRACT: Cheap and readily available aqueous formaldehyde was used as a formylating reagent in a homologation reaction with non-stabilized diazo compounds, enabled by the UV photolysis of bench-stable oxadiazolines in a flow photoreactor. Various aliphatic aldehydes were synthesized along with the corresponding derivatized alcohols and benzimidazoles. No transition metal catalyst or additive was required to affect the reaction which proceeded at room temperature over 80 minutes.

Following the discovery of the Buchner-Curtius-Schlotterbeck reaction over a century ago,¹ the interactions between carbonyl compounds and diazo compounds have been extensively studied.^{2,3} These methods constitute a powerful synthetic tool for C-C bond formation, especially for the extension of carbon chains and for the construction and decoration of ketones.⁴⁻⁶ However, the controlled formation of aldehyde products using diazo chemistry is not a simple task; carbonyl groups and diazo compounds are highly reactive coupling partners. The reliable and safe generation of non-stabilised diazo compounds is currently an area of intense research⁷⁻¹⁰ and one our laboratory has been interested in due to the application of flow chemistry as an enabling technology¹¹⁻¹³ to overcome the safety issues traditionally associated with diazo compounds.¹⁴⁻¹⁶ Following the pioneering work from Warkentin and co-workers,^{17,18} we have recently published two reports on the use of oxadiazolines as bench stable, non-stabilised diazo compound precursors and their application in protodeboronative and oxidative C(sp²)-C(sp³) cross-coupling with boronic acids¹⁹ and aldehyde C-H functionalisation to afford unsymmetrical ketones.²⁰

During this work, two reports in the literature caught our attention (Scheme 1). Kingsbury and co-workers demonstrated a Lewis acid catalysed double homologation reaction by combining *ex-situ* prepared diazo compounds and the flash-pyrolyzed preparation of anhydrous formaldehyde (Scheme 1, A)²¹ and Hu *et. al* reported an interesting three-component coupling of aryldiazoacetate, aniline and aqueous formaldehyde (Scheme 1, B).²² Both of these reactions

passed through, but did not stop at, the aldehyde oxidation state on way to a final product, either the doubly homologated ketone or the α -aryl serine derivative. These examples encouraged us to control the homologation reaction and stop at the aldehyde product in as simple a manner as possible and without the use of a protecting group strategy. Herein, we report the controlled homologation of non-stabilised diazo compounds generated from bench stable precursors in flow to form aldehydes and their derivatives (Scheme 1, C).

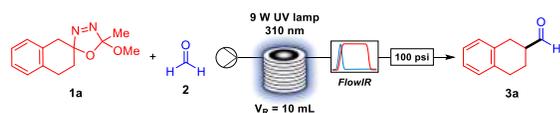


Scheme 1: Examples of homologation reactions involving diazo and carbonyl compounds

Our investigation began by combining 2-tetralone oxadiazoline **1a** with different sources of formaldehyde under UV irradiation (Table 1). Common formaldehyde surrogates trioxane and dioxolane both delivered only trace amount of desired aldehyde product **3a** despite

almost complete conversion of the oxadiazoline starting material (entry 1 and 2).²³ While we established our first success using a stock solution of monomeric formaldehyde created via thermolysis of paraformaldehyde,²⁴ resulting in a 55% yield of the desired aldehyde (entry 3), practical considerations of the procedure and the propensity of the stock solution to polymerize without warning on warming above -78 °C made this an unattractive approach. We then turned our attention to formalin, a 37% aqueous solution of formaldehyde, which pleasingly gave a modest yield (48%) of the target aldehyde (**3a**, entry 4).²⁵ Lowering the reaction temperature to 10 °C led to a diminished conversion and yield (entry 5) while a decrease in the reaction concentration does not result in an improved yield despite a higher conversion (entry 6). Elongating the residence time to 80 min improved both conversion (87%) as well as yield (60%) (entry 7). Formaldehyde ratio changes were ineffective (entry 8 and 9). Similarly, switching to tetrahydrofuran also marginally lowered the yield to 41%, while with dichloromethane this dropped to 12% (entry 10 and 11).

Table 1: Optimization of aldehyde formation



Entry ^a	Formaldehyde Source	Ox. /M	t _R /min	T /°C	Conv.	Yield
1	Dioxolane	0.1	40	20	99%	0%
2	Trioxane	0.1	40	20	96%	2%
3	Thermolysed Paraformaldehyde	0.1	40	20	67%	55%
4	37% aq	0.1	40	20	78%	48%
5	37% aq	0.1	40	10	72%	41%
6	37% aq	0.05	40	10	80%	39%
7	37% aq	0.1	80	20	87%	60%
						(50%) ^b
8 ^c	37% aq	0.1	80	20	86%	58%
9 ^d	37% aq	0.1	80	20	87%	56%
10 ^e	37% aq	0.1	80	20	78%	41%
11 ^f	37% aq	0.1	80	20	79%	12%

^a Reaction conditions: oxadiazoline (0.4 mmol), Formalin (0.3 mL, 37 wt%, 4.0 mmol), 2-methyltetrahydrofuran (4 mL). NMR yields calculated with 1,3,5-trimethoxybenzene as an internal standard. ^b Isolated yield. ^c 100 equiv. of formaldehyde was used. ^d 5.0 equiv. of formaldehyde was used. ^e Tetrahydrofuran was used instead of 2-methyltetrahydrofuran. ^f Dichloromethane was used instead of 2-methyltetrahydrofuran.

After multiple reaction optimisation attempts, we accepted the isolated yield of aldehyde of around 50%, albeit with a higher conversion of the oxadiazoline. On further examination of the crude sample mixture, along with the required aliphatic aldehyde we found significant amount of hydrated material was also present. At no time did we observe more than 10% of the doubly homologated ketone. We presume that formation of the hydrate, due to the presence of a large amount of water in the reaction media, acts as an *in-situ* protecting group and this, coupled with a very low concentration of diazo compound throughout the course of the reaction, disfavours double homologation. We further observed that over an extended period of time the corresponding carboxylic acid product

was formed, most likely as a result of an aerobic oxidative transformation, which is not uncommon for aldehydes of this type.

Also owing to volatility of some of the aldehydic products, we decided to directly reduce the crude mixture with sodium borohydride (NaBH₄), thereby converting the products into the corresponding alcohol (**4a**), resulting in an improved yield of 60% over two steps (Table 2, entry 1). We also saw this procedure as a way of storing these unstable aliphatic aldehydes through recycling *via* a secondary oxidation process back to aldehydes should this be necessary. To further exemplify the method and to better capture the unstable and sometimes volatile small molecule products the crude aldehydes were additionally subjected to oxidative condensation with *o*-phenylenediamine following a modified procedure originally reported by Jiao *et. al.*²⁶ This procedure gave 2-substituted benzimidazole (**5a**) from 1,2,3,4-tetrahydronaphthalene-2-carbaldehyde (**3a**) via in-situ generated aliphatic aldehyde in an overall 72% isolated yield (Table 2, entry 1).

With these various conditions in hand, we set about examining the scope of the reactions (Table 2). Tetrahydropyran substrate (**1b**) was able to produce the corresponding aldehyde (**3b**) in a 48% yield while providing 53% of alcohol (**4b**), and 76% benzimidazole (**5b**). Similarly, tetrahydrothiopyran (**1c**), tetrahydrothiophene (**1d**) and cyclohexyldioxolo (**1e**) derivatives all underwent these three individual transformations to give products (**3c-e**, **4c-e**, **5c-e**) in reasonable yields (entry 3, 4 and 5). As for nitrogen-based functional groups, Boc-protected amine (**1f**) and *N*-pyrimidinyl piperidine (**1g**) were also tolerated (entry 6 and 7). Bulky 2-adamantyl aldehyde (**3h**) was isolated in 68%, together with 75% of 2-adamantanemethanol (**4h**) and 79% of 2-adamantylbenzimidazole (**5h**). Lastly, cyclobutyl oxadiazoline (**1i**) did not give useful isolated yields owing to aldehyde and alcohol volatility (**3i** and **4i**), although the formation of 2-cyclobutylbenzimidazole was achieved in 59% yield (**5i**).

Except for methoxynaphthalene substrate (**3j**, entry 10), α -methyl aldehydes we obtained have displayed a tendency towards hydration or aerobic oxidation, thus result in low crude NMR yields and difficulty in isolation (**3k – 3p**), which is well-known for similar materials. The efficiency of the reaction was generally better represented by comparing the yield of alcohols and benzimidazoles. In some cases, such as 5-hydroxy-2-methylpentanal (**3k**), homologated product was identified as 81% of the hydrated form when only 4% of aldehyde was observed in NMR analysis, even though 66% of alcohol product (**4k**) was isolated over two steps. Pyridine (**1l**) and furan (**1m**) were all successfully homologated into corresponding products (**4l-m**, **5l-m**) respectively (entry 12 and 13). Alkyne and alkene substituted oxadiazolines (**1n**, **1o**) both gave reasonable isolated yields as aldehyde derivatives (**4n**, **5n-o**), with alkyne substrate produced lower yield arguably owing to larger steric hinderance (**5o**). Even though 2-cyclopropylpropanal (**3p**) and 2-cyclopropylpropan-1-ol (**4p**) were not able to give good isolated yields, the formation of 69% 2-(1-cyclopropylethyl)-benzimidazole (**5p**) proved the effectiveness of oxadiazoline as a successful diazo precursor for homologation. Many of these products can be thought of as branched, or iso, aldehydes which would be difficult to prepare through traditional methods such as hydroformylation, particularly in the presence of alkenes or alkynes.

The homologation reaction of oxadiazolines obtained from ketones has provided us with satisfying results towards α,α -disubstituted branched aliphatic aldehydes. However, similar oxadiazolines generated from aldehydes are difficult to obtain, which therefore obstructed the access towards linear aldehydes. To overcome this difficulty, we applied an alternative route to diazo compounds generated from hydrazones, prepared from the corresponding benzaldehydes according to our previously reported procedure.^{27,28} With the help of a glass static mixer chip, ethyl acetate

1 solution of diazo compound was combined with 37 wt% aqueous
2 formaldehyde solution in-line, and the resulting homologated alde-
3 hyde product was collected in the output stream and purified (Table
4 3, **7a-c**), or extracted and reduced directly to the corresponding al-
5 cohool in good yields (**8a-c**). No attempt was made to further

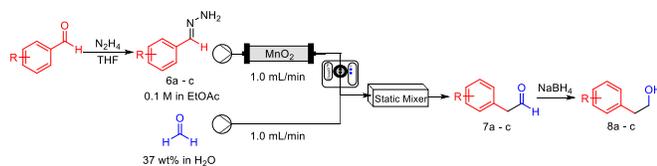
exemplify this procedure, although it should be noted that the
method does overcome classical issues associated with phenacetal-
dehyde preparation.

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Table 2: Scope and derivatisation on oxadiazolines and aqueous formaldehyde

Entry	Aldehyde 3a – h ^a	Alcohol 4a – h ^b	Benzimidazole 5a – h ^c	Entry	Aldehyde 3i – p ^a	Alcohol 4i – p ^b	Benzimidazole 5i – p ^c
1	 3a, 60% ^d (50%)	 4a, 60%	 5a, 72%	9	 3i, n.d. ^e	 4i, n.d. ^e	 5i, 59%
2	 3b, 48%	 4b, 53%	 5b, 76%	10	 3j, 57%	 4j, 75%	 5j, n.d. ^e
3	 3c, 56%	 4c, 72%	 5c, 55%	11	 3k, 85% ^f	 4k, 66%	 5k, n.d. ^e
4	 3d, 85% ^d (75%)	 4d, 89% ^d (77%)	 5d, 60%	12	 3l, 35% ^d	 4l, 50%	 5l, 48%
5	 3e, 65%	 4e, 75%	 5e, 80%	13	 3m, 25% ^d	 4m, 60%	 5m, 75%
6	 3f, 58% ^d (49%)	 4f, 53%	 5f, 49%	14	 3n, 58% ^d	 4n, 88% ^d (69%)	 5n, 73%
7	 3g, 55% ^d	 4g, 68% ^d	 5g, 72%	15	 3o, 18% ^d	 4o, n.d. ^e	 5o, 39%
8	 3h, 68%	 4h, 75%	 5h, 79%	16	 3p, 8% ^d	 4p, 58% ^d	 5p, 69%

^a Reaction conditions: oxadiazoline (1.0 equiv., 0.1 M), formaldehyde (10 equiv., 37 wt% in H₂O, 1.0 M) in 2-methyltetrahydrofuran. ^b Aldehyde reduced directly with NaBH₄ (10 equiv., 0.5 M) in ethanol. ^c Aldehyde reacted with *o*-phenylenediamine (1.5 equiv., 0.075 M) in toluene. ^d NMR yield, calculated using 1,3,5-trimethoxybenzene as an internal standard. ^e Not determined due to volatility or product contamination. ^f 81% of the product identified as the hydrated form.

Table 3: Homologation of aldehydes with aqueous formaldehyde via hydrazine

Entry	Aldehyde –7a – c	Alcohol 8a – c ^a
1	 7a, 53%	 8a, 57%
2	 7b, 58%	 8b, 66%
3	 7c, 57%	 8c, 66%

^a Aldehyde extracted with ethyl acetate then reduced directly with NaBH₄ (10 equiv., 0.5 M) in ethanol.

We present a mild, operationally straightforward procedure for the overall homologation of ketones and aryl aldehydes via non-stabilised diazo compounds in flow. The route complements other homologation methods whilst avoiding expensive and reactive transition metal catalysts and uses formalin as a cheap and readily available source of carbon.

EXPERIMENTAL SECTION

General Information

All batch reactions were performed under an atmosphere of nitrogen using oven-dried glassware unless otherwise stated. UV flow reactions were performed using a Vapourtec E-series and UV-150 system. Hydrazone flow reactions were performed using a Uniqsis FlowSyn platform. Reagents were purchased from Sigma-Aldrich, Alfa Aesar, Acros and Fluorochem and were used as supplied unless stated otherwise. 2-Methyltetrahydrofuran (2-MeTHF, anhydrous, inhibitor-free, ≥99.9%) and tetrahydrofuran (THF, anhydrous, inhibitor-free, ≥99.9%) were purchased from Sigma-Aldrich and used as supplied. Work-up solvents, were employed directly from commercial sources, i.e. Sigma-Aldrich unless stated otherwise. Petroleum ether refers to the fractions of petrol collected between 40–60 °C b.p.

Flash column chromatography was performed using a Biotage SPX system with single use disposable silica columns of the appropriate size (SiliaSep Flash Cartridges 4 or 12 g 40–60 μm ISO04/012). Analytical thin layer chromatography (TLC) was performed using silica gel 60 F254 pre-coated glass backed plates and visualized by ultraviolet radiation (254 nm) and appropriate dip (typically potassium permanganate or ninhydrin).

¹H NMR and ¹³C{¹H} NMR spectra were recorded on a 600 MHz Bruker DRX-600 Spectrometer. Chemical shifts (δ) are referenced to the residual solvent as CDCl₃ or DMSO-d₆ in the unit of parts per million (ppm). Signals are reported with the descriptions of their environments (e.g. ArH, NH, OH). Coupling constants *J* are quoted in the unit of hertz (Hz). Proton and carbon multiplicity is recorded as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) and broad (br), or combinations thereof. All compounds examined were dried in vacuo to remove residual solvents. Spectra are assigned as fully as possible, using ¹H-tCOSY, DEPT-135, HSQC and ¹H NOESY where appropriate to facilitate structural determination. Multiple signals arising from (pseudo)axial/equatorial positions are suffixed for example *H_a* and *H_a'*. ¹H

NMR signals are reported to two decimal places and ¹³C signals to one decimal place.

Infrared spectra were recorded neat on a Perkin-Elmer Spectrum One FTIR spectrometer with a universal ATR sampling accessory, selected peaks are reported.

Low resolution mass spectrometry was performed on a Advion Express CMS spectrometer. High resolution mass spectrometry (HRMS) was performed using positive or negative electrospray ionisation (ESI+) by the Mass Spectrometry Service for the Chemistry Department at the University of Cambridge.

Melting points were recorded on a Stanford Research Systems OptiMelt Automated Melting Point System.

The oxadiazolines (**1a – p**) were synthesised according to the precedent literature procedure without further modifications.¹⁹ The hydrazones (**6a – c**) were synthesised according to precedent procedure published by our group.²⁸

All compounds listed in the paper are >95% purity. Some products appear to be very hygroscopic therefore contain 0.2 – 0.5 mol equivalents of water (2 – 5 wt%) present in the ¹H NMR spectra as shown below. Volatile compounds are reported with minor solvents. Inseparable impurities are noted.

Synthesis of aliphatic aldehydes

General procedure A for the synthesis of aliphatic aldehydes

A solution of the appropriate oxadiazoline (1.0 equiv., 0.05 mmol/mL) and formaldehyde (10 equiv. aqueous solution, 37% w/w) in 2-MeTHF (0.5 mol/mL) was pumped (0.125 mL min⁻¹, *t_R* = 80 min) through a Vapourtec UV-150 photochemical reactor (10 mL, FEP tubing) while irradiate by a 310 nm UV lamp (output power: 9W) held at 20 °C. The reactor output was monitored using a Mettler Toledo FlowIR[®] instrument (SiComp head, bands of interest: C=O stretch signal at 1750–1700 cm⁻¹ for methyl acetate, generated by the decomposition of oxadiazoline). Once the FlowIR[®] detector showed the signal of the reaction slug, the output stream was collected in a sealed sample vial containing a biphasic solution of dichloromethane and brine with stirring to separate excess formaldehyde and other potential impurities. The collected material was rested, and the organic phase was separated and concentrated under reduced pressure. The remaining residue was purified *via* flash silica gel column chromatography with appropriate eluent combination to give the desired product.

1,2,3,4-Tetrahydronaphthalene-2-carbaldehyde (3a)

General Procedure A was followed using 5'-methoxy-5'-methyl-3,4-dihydro-1*H*,5'*H*-spiro(naphthalene-2,2'-[1,3,4]oxadiazole) (92 mg, 0.4 mmol, 1.0 eq.) and formaldehyde (0.3 mL, 37 wt% in H₂O, 4 mmol, 10 eq.). The crude mixture was purified *via* flash column chromatography (0 – 20% EtOAc in petroleum ether) to give the titled product as a transparent oil (32 mg, 50%). ¹H NMR (600 MHz, CDCl₃) δ 9.80 (d, *J* = 1.2 Hz, 1H, HCO), 7.13 (dt, *J* = 6.3, 3.5 Hz, 3H, H_{Ar}), 7.10 (q, *J* = 4.1, 3.5 Hz, 1H, H_{Ar}), 3.04 – 2.95 (m, 2H, ArCH₂CH₂), 2.94 – 2.82 (m, 2H, ArCH₂), 2.75 – 2.68 (m, 1H, HCOCH), 2.26 – 2.19 (m, 1H, ArCH_a), 1.84 – 1.75 (m, 1H, ArCH_a); ¹³C{¹H} NMR (151 MHz, CDCl₃) δ 203.9 (HCO), 136.1 (C_{Ar}), 134.4 (C_{Ar}), 129.4 (C_{Ar}H), 129.0 (C_{Ar}H), 126.2 (C_{Ar}H), 126.1 (C_{Ar}H), 47.0 (HCOCH), 28.6 (ArCH₂CH₂), 28.2 (ArCH₂CH), 23.1 (C_a). HRMS (ESI) calcd for C₁₁H₁₂ONa⁺ [M+Na]⁺ 183.0780, found 183.0775. IR ν max (film): 2904, 2851, 1723, 1702, 1432, 1110, 1042 cm⁻¹. The data presented are consistent with literature precedent.²⁹

Tetrahydro-2*H*-pyran-4-carbaldehyde (3b)

General Procedure A was followed using 3-methoxy-3-methyl-4,8-dioxo-1,2-diazaspiro[4.5]dec-1-ene (74 mg, 0.4 mmol, 1.0 eq.) and formaldehyde (0.3 mL, 37 wt% in H₂O, 4 mmol, 10 eq.). The crude mixture was purified *via* flash column chromatography (0 –

15% EtOAc in petroleum ether) to give the titled product as a volatile transparent oil (23 mg, 48%). ¹H NMR (600 MHz, CDCl₃) δ 9.68 (d, *J* = 1.0 Hz, 1H, HCO), 4.00 – 3.92 (m, 2H, OCH_a + OCH_b), 3.48 (ddd, *J* = 11.5, 10.7, 2.6 Hz, 2H, OCH_a' + OCH_b'), 2.55 – 2.36 (m, 1H, HCOCH), 1.89 – 1.83 (m, 2H, OCH_c + OCH_d), 1.70 (dtd, *J* = 13.7, 10.7, 4.2 Hz, 2H, OCH_c' + OCH_d')³⁰; ¹³C{¹H} NMR (151 MHz, CDCl₃) δ 203.0 (HCO), 66.8 (C_a + C_b), 46.9 (HCOCH), 25.8 (C_c + C_d). LRMS (ESI, *m/z*) 115.2 ([M+H]⁺, 100%). IR ν max (film): 2968, 1879, 1720, 1279, 1201, 1135, 1080, 924 cm⁻¹. The data presented are consistent with literature precedent.³⁰

Tetrahydro-2H-thiopyran-4-carbaldehyde (3c)

General Procedure A was followed using 3-methoxy-3-methyl-4-oxa-8-thia-1,2-diazaspiro[4.5]dec-1-ene (81 mg, 0.4 mmol, 1.0 eq.) and formaldehyde (0.3 mL, 37 wt% in H₂O, 4 mmol, 10 eq.). The crude mixture was purified *via* flash column chromatography (0 – 20% EtOAc in petroleum ether) to give the titled product as a volatile transparent oil (29 mg, 56%). ¹H NMR (600 MHz, CDCl₃) δ 9.59 (s, 1H, HCO), 2.67 (dt, *J* = 10.2, 3.6 Hz, 4H, SCH₂), 2.34 – 2.22 (m, 3H, HCOCH + CH_a + CH_b), 1.75 (dtd, *J* = 14.3, 10.2, 4.5 Hz, 2H, CH_a' + CH_b')³¹; ¹³C{¹H} NMR (151 MHz, CDCl₃) δ 203.3 (HCO), 49.3 (HCOCH), 27.6 (SCH₂), 27.2 (C_a + C_b); HRMS (ESI) calcd for C₆H₁₁OS⁺ [M+H]⁺: 131.0528, found 131.0531. IR ν max (film): 2918, 2849, 2369, 1724, 1239, 1130, 1088, 983 cm⁻¹. The data presented are consistent with literature precedent.³¹

Tetrahydrothiophene-3-carbaldehyde (3d)

General Procedure A was followed using 3-methoxy-3-methyl-4-oxa-7-thia-1,2-diazaspiro[4.4]non-1-ene (37 mg, 0.2 mmol, 1.0 eq.) and formaldehyde (0.16 mL, 37 wt% in H₂O, 2.0 mmol, 10 eq.). A NMR 85% yield was calculated using 1,3,5-trimethoxybenzene (11mg, 0.066 mmol, 0.33 eq.) as an internal standard. The crude mixture was purified *via* flash column chromatography (0 – 20% EtOAc in petroleum ether) to give the titled product as a colourless volatile oil (17 mg, 75%) with less than 10% of dichloromethane. ¹H NMR (600 MHz, CDCl₃) δ 9.63 (d, *J* = 1.3 Hz, 1H, HCO), 3.16 (dd, *J* = 10.9, 5.0 Hz, 1H, SCH_cCH), 3.09 – 3.04 (m, 1H, HCOCH), 2.98 (dd, *J* = 10.9, 7.0 Hz, 1H, SCH_cCH), 2.91 – 2.85 (m, 1H, SCH_bCH₂), 2.85 – 2.78 (m, 1H, SCH_bCH₂), 2.38 (td, *J* = 12.7, 5.9 Hz, 1H, CHCH_a), 2.12 (dq, *J* = 13.4, 6.9 Hz, 1H, CHCH_a')³²; ¹³C{¹H} NMR (151 MHz, CDCl₃) δ 201.3 (HCO), 55.1 (HCOCH), 31.1 (C_c), 30.9 (C_b), 30.5 (C_a). LRMS (ESI, *m/z*) 117.1 ([M+H]⁺, 100%). IR ν max (film): 2944, 1720, 1416, 1235, 1028, 956 cm⁻¹. The data presented are consistent with literature precedent.³²

1,4-Dioxaspiro[4.5]decane-8-carbaldehyde (3e)

General Procedure A was followed using 3-methoxy-3-methyl-4,9,12-trioxa-1,2-diazadispiro[4.2.4⁸.2⁵]tetradec-1-ene (102 mg, 0.4 mmol, 1.0 eq.) and formaldehyde (0.3 mL, 37 wt% in H₂O, 4 mmol, 10 eq.). The crude mixture was purified *via* flash column chromatography (0 – 20% EtOAc in petroleum ether) to give the titled product as a colourless volatile oil (44 mg, 65%). ¹H NMR (600 MHz, CDCl₃) δ 9.64 (d, *J* = 1.3 Hz, 1H, HCO), 3.94 (dd, *J* = 5.3, 3.4 Hz, 4H, OCH₂CH₂O), 2.25 (ttd, *J* = 9.7, 4.1, 1.4 Hz, 1H, HCOCH), 1.97 – 1.91 (m, 2H, CH_e + CH_d), 1.80 – 1.71 (m, 4H, CH_c' + CH_d' + CH_e + CH_f), 1.61 – 1.56 (m, 2H, CH_e + CH_f)³³; ¹³C{¹H} NMR (151 MHz, CDCl₃) δ 204.2 (HCO), 108.2 (OCO), 64.5 (C_a), 64.5 (C_b), 48.4 (HCOCH), 33.5 (C_c + C_d), 23.4 (C_e + C_f). LRMS (ESI, *m/z*) 171.4 ([M+H]⁺, 100%). IR ν max (film): 2949, 2881, 1722, 1447, 1362, 1239, 1142, 1104, 1033, 948, 881 cm⁻¹. The data presented are consistent with literature precedent.³³

tert-Butyl 4-formylpiperidine-1-carboxylate (3f)

General Procedure A was followed using *tert*-butyl 3-methoxy-3-methyl-4-oxa-1,2,8-triazaspiro[4.5]dec-1-ene-8-carboxylate (57 mg, 0.2 mmol, 1.0 eq.) and formaldehyde (0.16 mL, 37 wt% in H₂O, 2.0 mmol, 10 eq.). A NMR 58% yield was calculated using

1,3,5-trimethoxybenzene (11 mg, 0.066 mmol, 0.33 eq.) as an internal standard. The crude mixture was purified *via* flash column chromatography (0 – 20% EtOAc in petroleum ether) to give the titled product as a colourless oil (21 mg, 49%). ¹H NMR (600 MHz, CDCl₃) δ 9.65 (s, 1H, HCO), 3.97 (br s, 2H, NCH_c + NCH_d), 3.02 – 2.81 (m, 2H, NCH_c' + NCH_d'), 2.47 – 2.36 (m, 1H, HCOCH), 1.98 – 1.80 (m, 2H, CH_a + CH_b), 1.59 – 1.50 (m, 2H, CH_a' + CH_b')³⁴, 1.44 (s, 9H, C(CH₃)₃); ¹³C{¹H} NMR (151 MHz, CDCl₃) δ 203.1 (HCO), 154.8 (NCOO), 79.8 (C(CH₃)₃), 48.1 (HCOCH), 43.0 (br, C_c + C_d), 28.5 (C(CH₃)₃), 25.3 (C_a + C_b). LRMS (ESI, *m/z*) 214.3 ([M+H]⁺, 100%). IR ν max (film): 2927, 1726, 1688, 1418, 1365, 1273, 1232, 1168, 1128, 958, 864, 769 cm⁻¹. The data presented are consistent with literature precedent.³⁴

Adamantane-2-carbaldehyde (3h)

General Procedure A was followed using 5'-methoxy-5'-methyl-5'-H-spiro[adamantane-2,2'-[1,3,4]oxadiazole] (94 mg, 0.4 mmol, 1.0 eq.) and formaldehyde (0.3 mL, 37 wt% in H₂O, 4 mmol, 10 eq.). The crude mixture was purified *via* flash column chromatography (0 – 20% EtOAc in petroleum ether) to give the titled product as a white solid (45 mg, 68%). ¹H NMR (600 MHz, CDCl₃) δ 9.73 (s, 1H, HCO), 2.44 – 2.37 (m, 3H, HCOCH+HCOCHCH), 2.01 – 1.67 (m, 12H, CH_b + CH_c + CH_d); ¹³C{¹H} NMR (151 MHz, CDCl₃) δ 206.1 (HCO), 56.7 (HCOCH), 38.0 (C_b), 37.2 (C_a), 33.7 (C_b'), 28.3 (C_a), 28.0 (C_c), 27.6 (C_c')³⁵; HRMS (ESI) calcd for C₁₁H₁₇O⁺ [M+H]⁺: 165.1274, found 165.1271. IR ν max (film): 2936, 2896, 1752, 1463, 1190, 1076, 912 cm⁻¹. M.p.: 164 – 166 °C. The data presented are consistent with literature precedent.³⁵

4-(6-Methoxynaphthalen-2-yl)-2-methylbutanal (3j)

General Procedure A was followed using 2-methoxy-5-(2-(6-methoxynaphthalen-2-yl)ethyl)-2,5-dimethyl-2,5-dihydro-1,3,4-oxadiazole (126 mg, 0.4 mmol, 1.0 eq.) and formaldehyde (0.3 mL, 37 wt% in H₂O, 4 mmol, 10 eq.). The crude mixture was purified *via* flash column chromatography (0 – 20% EtOAc in petroleum ether) to give the titled product as a transparent oil (55 mg, 57%) together with 7% of oxidized carboxylic acid. ¹H NMR (600 MHz, CDCl₃) δ 9.65 (d, *J* = 1.8 Hz, 1H, HCO), 7.68 (dd, *J* = 8.5, 3.4 Hz, 2H, H_{Ar}), 7.55 (d, *J* = 1.8 Hz, 1H, H_{Ar}), 7.30 (dd, *J* = 8.4, 1.8 Hz, 1H, H_{Ar}), 7.16 – 7.10 (m, 2H, H_{Ar}), 3.92 (s, 3H, OCH₃), 2.88 – 2.75 (m, 2H, HCOCH + ArCH_a), 2.41 (qd, *J* = 6.9, 1.8 Hz, 1H, ArCH_a'), 2.19 – 2.10 (m, 1H, ArCH₂CH_b), 1.78 – 1.70 (m, 1H, ArCH₂CH_b')³⁶, 1.18 (d, *J* = 7.1 Hz, 3H, CHCH₃); ¹³C{¹H} NMR (151 MHz, CDCl₃) δ 205.0 (HCO), 157.4 (C_{Ar}), 136.6 (C_{Ar}'), 133.2 (C_{Ar}), 129.2 (C_{Ar}'), 129.0 (C_{Ar}H), 127.7 (C_{Ar}H), 127.1 (C_{Ar}H'), 126.5 (C_{Ar}H), 119.0 (C_{Ar}H'), 105.8 (C_{Ar}H), 55.3 (OCH₃), 45.6 (HCOCH), 33.0 (C_a), 32.1 (C_b), 13.4 (CHCH₃); HRMS (ESI) calcd for C₁₆H₁₉O₂⁺ [M+H]⁺: 243.1385, found 243.1386. IR ν max (film): 2933, 1721, 1634, 1606, 1483, 1390, 1264, 1229, 1031, 850 cm⁻¹.

Synthesis of alcohols

General Procedure B for the synthesis of alcohols

The reaction slug from **General Procedure A** was directly collected into a round bottom flask containing NaBH₄ (10 equiv.) in EtOH (0.5 mmol/mL) and stirred for a further hour. The resulting mixture was then quenched with ice water, extracted with ethyl acetate (2 × 20 mL) and washed with brine (2 × 20 mL). The organic phase was combined, dried over MgSO₄, filtered and concentrated under reduced pressure. The remaining residue was purified *via* flash column chromatography with appropriate eluents to give the desired alcohol.

(1,2,3,4-Tetrahydronaphthalen-2-yl)metanol (4a)

General Procedure B was followed using 5'-methoxy-5'-methyl-3,4-dihydro-1H,5'H-spiro[naphthalene-2,2'-[1,3,4]oxadiazole] (92 mg, 0.4 mmol, 1.0 eq.), formaldehyde (0.3 mL, 37 wt% in H₂O, 4 mmol, 10 eq.) and sodium borohydride (153 mg, 4.0 mmol, 10 eq.). The crude mixture was purified *via* flash

column chromatography (10 – 40% EtOAc in petroleum ether) to give the titled product as a transparent oil (39 mg, 60%). ¹H NMR (600 MHz, CDCl₃) δ 7.09 (app. p, *J* = 2.2 Hz, 4H, *H*_{Ar}), 3.69 – 3.59 (m, 2H, HOCH₂), 2.93 – 2.79 (m, 3H, ArCH₂CH + ArCH_a), 2.52 (dd, *J* = 16.3, 10.7 Hz, 1H, ArCH_a'), 2.06 – 1.95 (m, 2H, ArCH₂CH₂), 1.55 – 1.39 (m, 2H, HOCH₂CH + CH₂OH); ¹³C{¹H} NMR (151 MHz, CDCl₃) δ 136.8 (*C*_{Ar}), 136.0 (*C*_{Ar}'), 129.3 (*C*_{Ar}H), 128.9 (*C*_{Ar}H'), 125.7 (*C*_{Ar}H), 125.7 (*C*_{Ar}H'), 67.8 (HOCH₂), 37.1 (HOCH₂CH), 32.5 (ArCH₂), 28.8 (*C*_a), 26.0 (ArCH₂CH₂). HRMS (ESI) calcd for C₁₁H₁₄O₃Na⁺ [M+Na]⁺ 185.0937, found 185.0931. IR ν max (film): 3370, 2918, 1494, 1453, 1436, 1065, 1022, 900 cm⁻¹. The data presented are consistent with literature precedent.³⁶

(Tetrahydro-2*H*-pyran-4-yl)metanol (4b)

General Procedure B was followed using 3-methoxy-3-methyl-4,8-dioxo-1,2-diazaspiro[4.5]dec-1-ene (74 mg, 0.4 mmol, 1.0 eq.), formaldehyde (0.3 mL, 37 wt% in H₂O, 4 mmol, 10 eq.) and sodium borohydride (153 mg, 4.0 mmol, 10 eq.). The crude mixture was purified *via* flash column chromatography (10 – 40% EtOAc in petroleum ether) to give the titled product as a transparent oil (25 mg, 53%). ¹H NMR (600 MHz, CDCl₃) δ 3.99 (ddt, *J* = 11.5, 4.6, 1.1 Hz, 2H, OCH_a + OCH_b), 3.51 (d, *J* = 6.5 Hz, 2H, HOCH₂), 3.41 (td, *J* = 11.5, 2.1 Hz, 2H, OCH_a' + OCH_b'), 1.79 – 1.73 (m, 1H, HOCH₂CH), 1.68 – 1.64 (m, 2H, CH_c + CH_d), 1.38 – 1.32 (m, 2H, CH_c' + CH_d'); ¹³C{¹H} NMR (151 MHz, CDCl₃) δ 68.1 (HOCH₂), 67.8 (*C*_a + *C*_b), 37.7 (HOCH₂CH), 29.4 (*C*_c + *C*_d). LRMS (ESI, *m/z*) 115.3 ([M-H]⁻, 100%). IR ν max (film): 3368, 2918, 2847, 1652, 1443, 1235, 1140, 1031, 1012, 984, 849 cm⁻¹. The data presented are consistent with literature precedent.³⁰

(Tetrahydro-2*H*-thiopyran-4-yl)metanol (4c)

General Procedure B was followed using 3-methoxy-3-methyl-4-oxa-8-thia-1,2-diazaspiro[4.5]dec-1-ene (81 mg, 0.4 mmol, 1.0 eq.), formaldehyde (0.3 mL, 37 wt% in H₂O, 4 mmol, 10 eq.) and sodium borohydride (153 mg, 4.0 mmol, 10 eq.). The crude mixture was purified *via* flash column chromatography (10 – 40% EtOAc in petroleum ether) to give the titled product as a transparent oil (38 mg, 72%). ¹H NMR (600 MHz, CDCl₃) δ 3.47 (d, *J* = 6.4 Hz, 2H, HOCH₂), 2.70 (ddd, *J* = 14.3, 11.9, 2.6 Hz, 2H, SCH_a + SCH_b), 2.64 – 2.58 (m, 2H, SCH_a' + SCH_b'), 2.07 (dd, *J* = 13.5, 3.5 Hz, 2H, CH_c + CH_d), 1.59 (br s, 1H, OH), 1.57 – 1.48 (m, 1H, HOCH₂CH), 1.39 (dtd, *J* = 13.1, 11.8, 3.5 Hz, 1H, CH_c' + CH_d'); ¹³C{¹H} NMR (151 MHz, CDCl₃) δ 68.4 (HOCH₂), 40.2 (HOCH₂CH), 30.8 (*C*_a + *C*_b), 28.3 (*C*_c + *C*_d). HRMS (ESI) calcd for C₆H₁₃O³²S⁺ [M+H]⁺ 133.0682, found 133.0681. IR ν max (film): 3584, 2924, 1454, 1422, 1273, 1036 cm⁻¹. The data presented are consistent with literature precedent.³⁷

(Tetrahydrothiophen-3-yl)methanol (4d)

General Procedure B was followed using 3-methoxy-3-methyl-4-oxa-7-thia-1,2-diazaspiro[4.4]non-1-ene (37 mg, 0.2 mmol, 1.0 eq.), formaldehyde (0.16 mL, 37 wt% in H₂O, 2.0 mmol, 10 eq.) and sodium borohydride (76 mg, 2.0 mmol, 10 eq.). A NMR 89% yield was calculated using 1,3,5-trimethoxybenzene (11 mg, 0.066 mmol, 0.33 eq.) as an internal standard. The crude mixture was purified *via* flash column chromatography (0 – 40% EtOAc in petroleum ether) to give the titled product as a colourless oil (18 mg, 77%) with less than 5% of ethyl acetate. ¹H NMR (600 MHz, CDCl₃) δ 3.64 (dt, *J* = 6.8, 3.5 Hz, 2H, HOCH₂), 2.94 (dd, *J* = 10.6, 6.8 Hz, 1H, SCH₂CH), 2.87 (ddd, *J* = 7.2, 5.9, 1.6 Hz, 2H, SCH_bCH₂ + SCH_b'CH₂), 2.65 (dd, *J* = 10.6, 7.2 Hz, 1H, SCH_c'CH), 2.44 (dpd, *J* = 8.3, 6.8, 5.5 Hz, 1H, HOCH₂CH), 2.12 (dq, *J* = 11.9, 5.7 Hz, 1H, CHCH_a), 1.85 – 1.71 (m, 2H, OH + CHCH_a'); ¹³C{¹H} NMR (151 MHz, CDCl₃) δ 64.8 (HOCH₂), 46.7 (HOCH₂CH), 33.8 (*C*_c), 33.4 (*C*_d), 30.9 (*C*_a). LRMS (ESI, *m/z*) 117.3 ([M-H]⁻, 100%). IR ν max (film): 3336, 2928, 2860, 2355, 1438, 1264, 1210, 1079, 1049, 1028, 967, 945, 885, 684 cm⁻¹. The data presented are consistent with literature precedent.³⁸

(1,4-Dioxaspiro[4.5]decan-8-yl)metanol (4e)

General Procedure B was followed using 3-methoxy-3-methyl-4,9,12-trioxo-1,2-diazaspiro[4.2.4^{8,25}]tetradec-1-ene (102 mg, 0.4 mmol, 1.0 eq.), formaldehyde (0.3 mL, 37 wt% in H₂O, 4 mmol, 10 eq.) and sodium borohydride (152 mg, 4.0 mmol, 10 eq.). The crude mixture was purified *via* flash column chromatography (10 – 40% EtOAc in petroleum ether) to give the titled product as a transparent oil (52 mg, 75%). ¹H NMR (600 MHz, CDCl₃) δ 4.09 – 3.78 (m, 4H, OCH₂CH₂O), 3.46 (d, *J* = 6.5 Hz, 2H, HOCH₂), 1.86 (br s, 1H, HO), 1.78 – 1.73 (m, 4H, CH_c + CH_d), 1.52 (td, *J* = 13.5, 12.8, 4.6 Hz, 3H, HOCH₂CH + OCCH_a + OCCH_b), 1.26 (dtd, *J* = 13.5, 12.8, 11.7, 4.0 Hz, 2H, OCCH_a' + OCCH_b'); ¹³C{¹H} NMR (151 MHz, CDCl₃) δ 109.1 (OCO), 67.8 (HOCH₂), 64.2 (OCH₂CH₂O), 39.2 (HOCH₂CH), 34.2 (*C*_a + *C*_b), 26.7 (*C*_c + *C*_d). HRMS (ESI) calcd for C₉H₁₆O₃Na⁺ [M+Na]⁺ 195.0992, found 195.0987. IR ν max (film): 3460, 2928, 2863, 1106, 1032, 928, 890 cm⁻¹. The data presented are consistent with literature precedent.³⁹

tert-Butyl 4-(hydroxymethyl)piperidine-1-carboxylate (4f)

General Procedure B was followed using *tert*-butyl 3-methoxy-3-methyl-4-oxa-1,2,8-triazaspiro[4.5]dec-1-ene-8-carboxylate (57 mg, 0.2 mmol, 1.0 eq.), formaldehyde (0.16 mL, 37 wt% in H₂O, 2.0 mmol, 10 eq.) and sodium borohydride (76 mg, 2.0 mmol, 10 eq.). The crude mixture was purified *via* flash column chromatography (10 – 50% EtOAc in petroleum ether) to give the titled product as a colourless oil (23 mg, 53%). ¹H NMR (600 MHz, CDCl₃) δ 4.12 (br s, 2H, NCH_c + NCH_d), 3.56 – 3.44 (m, 2H, HOCH₂CH), 2.69 (br s, 2H, NCH_c' + NCH_d'), 1.75 – 1.68 (m, 2H, CH_a + NCH_b), 1.66 – 1.59 (m, 1H, HOCH₂CH), 1.45 (s, 9H, C(CH₃)₃), 1.20 – 1.05 (m, 2H, CH_a' + CH_b'); ¹³C{¹H} NMR (151 MHz, CDCl₃) δ 155.0 (NCOO), 79.5 (C(CH₃)₃), 67.8 (HOCH₂), 43.8 (br, *C*_c + *C*_d), 39.0 (HOCH₂CH), 28.7 (br, *C*_a + *C*_b), 28.6 (C(CH₃)₃). HRMS (ESI) calcd for C₁₁H₂₂O₃N⁺ [M+H]⁺ 216.1594, found 216.1591. IR ν max (film): 3455, 2974, 2924, 2857, 2355, 1693, 1669, 1424, 1366, 1313, 1274, 1247, 1168, 1087, 1039, 962, 864, 769 cm⁻¹. The data presented are consistent with literature precedent.⁴⁰

(Adamantan-2-yl)metanol (4h)

General Procedure B was followed using 5'-methoxy-5'-methyl-5'*H*-spiro[adamantane-2,2'-[1,3,4]oxadiazole] (94 mg, 0.4 mmol, 1.0 eq.), formaldehyde (0.3 mL, 37 wt% in H₂O, 4 mmol, 10 eq.) and sodium borohydride (153 mg, 2.0 mmol, 10 eq.). The crude mixture was purified *via* flash column chromatography (10 – 40% EtOAc in petroleum ether) to give the titled product as a transparent oil (50 mg, 75%). ¹H NMR (600 MHz, CDCl₃) δ 3.74 (d, *J* = 7.1 Hz, 2H, HOCH₂), 1.94 – 1.90 (m, 1H, HOCH₂CH), 1.89 – 1.84 (m, 4H, CH_b), 1.83 – 1.79 (m, 3H, CH_b' + CH_a), 1.79 – 1.77 (m, 1H, CH_a'), 1.75 – 1.72 (m, 2H, CH_b'), 1.57 (br s, 1H, CH_c), 1.55 (br s, 3H, CH_c' + CH_d), 1.25 (br s, 1H, HO); ¹³C{¹H} NMR (151 MHz, CDCl₃) δ 65.3 (HOCH₂), 47.3 (HOCH₂CH), 39.1 (*C*_b), 38.2 (*C*_d), 31.9 (*C*_b'), 29.2 (*C*_a), 28.4 (*C*_c), 27.9 (*C*_c'). HRMS (ESI) calcd for C₁₁H₁₈O₃Na⁺ [M+Na]⁺ 189.1250, found 189.1247. IR ν max (film): 3260, 2861, 2849, 1466, 1452, 1066, 1033, 1007, 971 cm⁻¹. The data presented are consistent with literature precedent.⁴¹

4-(6-Methoxynaphthalen-2-yl)-2-methylbutan-1-ol (4j)

General Procedure B was followed using 2-methoxy-5-(2-(6-methoxynaphthalen-2-yl)ethyl)-2,5-dimethyl-2,5-dihydro-1,3,4-oxadiazole (98 mg, 0.4 mmol, 1.0 eq.), formaldehyde (0.3 mL, 37 wt% in H₂O, 4 mmol, 10 eq.) and sodium borohydride (153 mg, 2.0 mmol, 10 eq.). The crude mixture was purified *via* flash column chromatography (10 – 40% EtOAc in petroleum ether) to give the titled product as a yellow oil (73 mg, 75%). ¹H NMR (600 MHz, CDCl₃) δ 7.66 (d, *J* = 8.4 Hz, 2H, *H*_{Ar}), 7.55 (s, 1H, *H*_{Ar}'), 7.33 (dd, *J* = 8.3, 1.8 Hz, 1H, *H*_{Ar}'), 7.14 – 7.09 (m, 2H, *H*_{Ar}'), 3.91 (s, 3H, OCH₃), 3.56 (br s, 1H, HOCH_c), 3.54 – 3.51 (m, 1H, HOCH_c'), 2.89 – 2.79 (m, 1H, ArCH_a), 2.78 – 2.68 (m, 1H, ArCH_a'), 1.91 – 1.80 (m, 1H, CH_b), 1.76 – 1.66 (m, 1H, CH_b'), 1.61 – 1.50 (m, 2H,

HOCH₂CH + OH), 1.02 (d, *J* = 6.7 Hz, 3H, CHCH₃); ¹³C{¹H} NMR (151 MHz, CDCl₃) δ 157.3 (C_{Ar}), 137.9 (C_{Ar}), 133.1 (C_{Ar}), 129.2 (C_{Ar}), 129.0 (C_{Ar}H), 127.9 (C_{Ar}H), 126.9 (C_{Ar}H), 126.3 (C_{Ar}H), 118.6 (C_{Ar}H), 105.6 (C_{Ar}H), 68.2 (C_c), 55.3 (OCH₃), 35.3 (C_a), 34.9 (C_b), 33.2 (HOCH₂CH), 16.5 (CHCH₃). HRMS (ESI) calcd for C₁₆H₂₀O₂⁺ [M+H]⁺ 244.1467, found 244.1463. IR ν max (film): 3342, 2961, 2926, 2850, 1634, 1604, 1484, 1462, 1391, 1263, 1228 cm⁻¹.

2-Methylpentane-1,5-diol (4k)

General Procedure B was followed using 3-(5-methoxy-2,5-dimethyl-2,5-dihydro-1,3,4-oxadiazol-2-yl)propan-1-ol (37 mg, 0.2 mmol, 1.0 eq.), formaldehyde (0.16 mL, 37 wt% in H₂O, 2.0 mmol, 10 eq.) and sodium borohydride (76 mg, 2.0 mmol, 10 eq.). The crude mixture was purified *via* flash column chromatography (2% MeOH in dichloromethane) to give the titled product as a colourless oil (16 mg, 66%). ¹H NMR (600 MHz, CDCl₃) δ 3.60 (t, *J* = 6.1 Hz, 2H, HOCH₂CH₂), 3.48 – 3.36 (m, 2H, HOCH₂CH), 3.16 (br s, 2H, OH), 1.66 – 1.56 (m, 2H, HOCH₂CH₂), 1.54 – 1.45 (m, 2H, CH₂CH₂CHCH₃), 1.16 – 1.06 (m, 1H, CHCH₃), 0.88 (d, *J* = 6.7 Hz, 3H, CH₃); ¹³C{¹H} NMR (151 MHz, CDCl₃) δ 67.8 (HOCH₂CH₂), 62.8 (HOCH₂CH), 35.4 (HOCH₂CH₂), 29.7 (CH₂CH₂CHCH₃), 29.1 (CHCH₃), 16.7 (CH₃). HRMS (ESI) calcd for C₆H₁₅O₂⁺ [M+H]⁺ 119.1067, found 119.1066. IR ν max (film): 3291, 2932, 2869, 1652, 1455, 1418, 1377, 1104, 1038, 940, 897, 731 cm⁻¹. The data presented are consistent with literature precedent.⁴²

2-Methyl-3-(pyridin-4-yl)propan-1-ol (4l)

General Procedure B was followed using 2-methoxy-2,5-dimethyl-5-(pyridin-4-ylmethyl)-2,5-dihydro-1,3,4-oxadiazole (88 mg, 0.4 mmol, 1.0 eq.), formaldehyde (0.3 mL, 37 wt% in H₂O, 4 mmol, 10 eq.) and sodium borohydride (153 mg, 2.0 mmol, 10 eq.). The crude mixture was purified *via* flash column chromatography (30 – 70% EtOAc in petroleum ether) to give the titled product as a transparent oil (30 mg, 50%). ¹H NMR (600 MHz, CDCl₃) δ 8.51 (br s, 2H, H_{Ar}), 7.12 (d, *J* = 4.9 Hz, 2H, H_{Ar}), 3.51 (dd, *J* = 5.9, 1.0 Hz, 2H, HOCH₂), 2.81 (dd, *J* = 13.4, 6.0 Hz, 1H, CH_a), 2.40 (dd, *J* = 13.4, 8.4 Hz, 1H, CH_a'), 2.03 – 1.93 (m, 1H, HOCH₂CH), 1.75 (br s, 1H, OH), 0.91 (d, *J* = 6.8 Hz, 3H, CHCH₃); ¹³C{¹H} NMR (151 MHz, CDCl₃) δ 150.2 (C_{Pyridine}), 149.6 (C_{Pyridine}H), 124.8 (C_{Pyridine}H), 67.2 (HOCH₂), 39.0 (C_a), 37.2 (HOCH₂CH), 16.4 (CHCH₃). HRMS (ESI) calcd for C₉H₁₄NO⁺ [M+H]⁺ 152.1071, found 152.1075. IR ν max (film): 3353, 2924, 2348, 2185, 1605, 1043 cm⁻¹. The data presented are consistent with literature precedent.⁴³

3-(Furan-2-yl)-2-methylpropan-1-ol (4m)

General Procedure B was followed using 2-(furan-2-ylmethyl)-5-methoxy-2,5-dimethyl-2,5-dihydro-1,3,4-oxadiazole (84 mg, 0.4 mmol, 1.0 eq.), formaldehyde (0.3 mL, 37 wt% in H₂O, 4 mmol, 10 eq.) and sodium borohydride (152 mg, 4.0 mmol, 10 eq.). The crude mixture was purified *via* flash column chromatography (10 – 40% EtOAc in petroleum ether) to give the titled product as a transparent oil (34 mg, 60%). ¹H NMR (600 MHz, CDCl₃) δ 7.31 (dd, *J* = 1.9, 0.9 Hz, 1H, H_{Furan}), 6.29 (dd, *J* = 3.2, 1.9 Hz, 1H, H_{Furan}), 6.02 (dd, *J* = 3.2, 0.9 Hz, 1H, H_{Furan}), 3.50 (d, *J* = 6.0 Hz, 2H, HOCH₂), 2.73 (dd, *J* = 14.9, 6.4 Hz, 1H, CH_a), 2.54 (dd, *J* = 14.9, 7.4 Hz, 1H, CH_a'), 2.03 (dq, *J* = 13.2, 6.4 Hz, 1H, HOCH₂CH), 1.46 (br s, 1H, OH), 0.94 (d, *J* = 6.8 Hz, 3H, CHCH₃); ¹³C{¹H} NMR (151 MHz, CDCl₃) δ 154.7 (C_{Furan}), 141.2 (C_{Furan}H), 110.3 (C_{Furan}H), 106.3 (C_{Furan}H), 67.6 (HOCH₂), 35.4 (C_a), 31.5 (HOCH₂CH), 16.5 (CHCH₃). HRMS (ESI) calcd for C₈H₁₁O₂ [M-H]⁻ 139.0754, found 139.0753. IR ν max (film): 3342, 2919, 1595, 1507, 1460, 1381, 1146, 1033, 927 cm⁻¹. The data presented are consistent with literature precedent.⁴⁴

2-Methylhex-5-en-1-ol (4n)

General Procedure B was followed using 2-(but-3-en-1-yl)-5-methoxy-2,5-dimethyl-2,5-dihydro-1,3,4-oxadiazole (37 mg, 0.2 mmol, 1.0 eq.), formaldehyde (0.16 mL, 37 wt% in H₂O, 2.0 mmol, 10 eq.) and sodium borohydride (76 mg, 2.0 mmol, 10 eq.). A NMR 88% yield was calculated using 1,3,5-trimethoxybenzene (11mg, 0.066 mmol, 0.33 eq.) as an internal standard. The crude mixture was purified *via* flash column chromatography (0 – 40% EtOAc in petroleum ether) to give the titled product as a colourless oil (16 mg, 69%). ¹H NMR (600 MHz, CDCl₃) δ 5.81 (ddt, *J* = 17.0, 10.2, 6.6 Hz, 1H, CH₂=CH), 5.02 (dd, *J* = 17.0, 1.9 Hz, 1H, H_b), 4.95 (dd, *J* = 10.2, 1.9 Hz, 1H, H_a), 3.48 (dd, *J* = 45.3, 10.5, 6.1 Hz, 2H, CHCH₂OH), 2.18 – 2.09 (m, 1H, CH₂=CHCH_c), 2.09 – 1.99 (m, 1H, CH₂=CHCH_c'), 1.70 – 1.60 (m, 1H, CH₂CH_aCHCH₃), 1.58 – 1.47 (m, 1H, CH₂CH_a'CHCH₃), 1.33 (br s, 1H, OH), 1.28 – 1.16 (m, 1H, CHCH₃), 0.93 (d, *J* = 6.7 Hz, 3H, CH₃); ¹³C{¹H} NMR (151 MHz, CDCl₃) δ 139.0 (CH₂=CH), 114.6 (CH₂=CH), 68.3 (CHCH₂OH), 35.4 (C_c), 32.4 (C_a), 31.3 (CHCH₃), 16.6 (CH₃). LRMS (ESI, m/z) 113.5 ([M+H]⁺, 100%). IR ν max (film): 3436, 2969, 2355, 2316, 1448, 1329, 1046 cm⁻¹. The data presented are consistent with literature precedent.⁴⁵

Synthesis of benzimidazoles

General Procedure C for the synthesis of benzimidazoles

The procedure was a modification of the literature procedure from Jiao *et al.*²⁵

The reaction slug from **General Procedure A** was collected into a round bottom flask containing a biphasic solution of brine and toluene with stirring. Upon resting, the toluene phase was syringed out and injected into another open round bottom flask charged with freshly activated 4 Å molecular sieves. The mixture was stirred for another 1 minute before *o*-phenylenediamine (1.5 equiv.) was added. The reaction mixture was then bubbled with one O₂ balloon and stirred at room temperature (30 °C) for 12 h. Molecular sieves was filtered over filter paper and the filtrate was concentrated under vacuum before purified *via* flash chromatography with appropriate eluent combinations to afford the final benzimidazole derivatives.

2-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-benzimidazole (5a)

General Procedure C was followed using 5'-methoxy-5'-methyl-3,4-dihydro-1H,5'H-spiro[naphthalene-2,2'-[1,3,4]oxadiazole] (46 mg, 0.2 mmol, 1.0 eq.), formaldehyde (0.15 mL, 37 wt% in H₂O, 2 mmol, 10 eq.) and *o*-phenylenediamine (32 mg, 0.3 mmol, 1.5 eq.). The crude mixture was purified *via* flash column chromatography (10 – 40% EtOAc in petroleum ether) to give the titled product as a white solid (36 mg, 72%). ¹H NMR (600 MHz, CDCl₃) δ 9.06 (br s, 1H, NH), 7.76 (br s, 1H, H_{Ar}), 7.40 (br s, 1H, H_{Ar}), 7.24 (d, *J* = 5.5 Hz, 2H, H_{Ar}), 7.29 – 7.13 (m, 4H, H_{Ar}), 3.41 (tdd, *J* = 10.3, 5.5, 3.1 Hz, 1H, CCH), 3.35 – 3.20 (m, 2H, ArCH₂CH), 2.97 (qp, *J* = 10.3, 5.5 Hz, 2H, ArCH₂CH₂), 2.48 – 2.37 (m, 1H, CHCH_a'), 2.14 (dtd, *J* = 13.0, 10.3, 6.2 Hz, 1H, CHCH_c'); ¹³C{¹H} NMR (151 MHz, Methanol-*d*₄) δ 159.8 (C_{Ar}), 136.8 (C_{Ar}), 136.1 (C_{Ar}), 130.0 (C_{Ar}H), 129.9 (C_{Ar}H), 127.1 (C_{Ar}H), 126.9 (C_{Ar}H), 123.3 (C_{Ar}H), 115.4 (br, C_{Ar}H), 36.7 (CCH), 35.4 (ArC-H₂CH), 30.0 (ArCH₂CH₂), 29.6 (C_a). One aromatic carbon is not seen in the ¹³C{¹H} NMR spectrum due to peak broadening. HRMS (ESI) calcd for C₁₇H₁₇N₂⁺ [M+H]⁺: 249.1387, found 249.1392. IR ν max (film): 2921, 1423, 1275, 1009, 993, 932, 743 cm⁻¹. M.p.: 239 – 241 °C.

2-(Tetrahydro-2H-pyran-4-yl)-1H-benzimidazole (5b)

General Procedure C was followed using 3-methoxy-3-methyl-4,8-dioxo-1,2-diazaspiro[4.5]dec-1-ene (37 mg, 0.2 mmol, 1.0 eq.), formaldehyde (0.15 mL, 37 wt% in H₂O, 2 mmol, 10 eq.) and *o*-phenylenediamine (32 mg, 0.3 mmol, 1.5 eq.). The crude mixture was purified *via* flash column chromatography (10 – 40% EtOAc in petroleum ether) to give the titled product as a transparent oil (31 mg, 76%). ¹H NMR (600 MHz, Methanol-*d*₄) δ 7.51 (dd, *J* = 6.1,

3.2 Hz, 2H, H_{Ar}), 7.19 (dd, $J = 6.1, 3.2$ Hz, 2H, H_{Ar}), 4.06 (dt, $J = 11.5, 3.3$ Hz, 2H, $OCH_c + OCH_d$), 3.65 – 3.53 (m, 2H, $OCH_c' + OCH_d'$), 3.24 – 3.15 (m, 1H, CCH), 2.04 – 1.92 (m, 4H, $CH_a + OCH_b$); $^{13}C\{^1H\}$ NMR (151 MHz, Methanol- d_4) δ 159.0 (C_{Ar}), 123.3 (C_{ArH}), 115.2 (br, C_{ArH}), 68.6 ($C_c + C_d$), 36.8 (CCH), 32.4 ($C_a + C_b$). One aromatic carbon is not seen in the $^{13}C\{^1H\}$ NMR spectrum due to peak broadening. HRMS (ESI) calcd for $C_{12}H_{15}N_2O^+ [M+H]^+$: 203.1181, found 203.1184. IR ν max (film): 2958, 2922, 2852, 1457, 1427, 1128, 739 cm^{-1} . M.p.: 225 – 227 °C.

2-(Tetrahydro-2H-thiopyran-4-yl)-1H-benzimidazole (5c)

General Procedure C was followed using 3-methoxy-3-methyl-4-oxa-8-thia-1,2-diazaspiro[4.5]dec-1-ene (40 mg, 0.2 mmol, 1.0 eq.), formaldehyde (0.16 mL, 37 wt% in H_2O , 2.0 mmol, 10 eq.) and *o*-phenylenediamine (32 mg, 0.3 mmol, 1.5 eq.). The crude mixture was purified *via* flash column chromatography (10 – 40% EtOAc in petroleum ether) to give the titled product as a white solid (24 mg, 55%). 1H NMR (600 MHz, Methanol- d_4) δ 7.51 (br s, 2H, H_{Ar}), 7.20 (dd, $J = 6.1, 3.1$ Hz, 2H, H_{Ar}), 4.59 (s, 1H, NH), 3.00 (ddd, $J = 12.0, 8.7, 3.3$ Hz, 1H, CCH), 2.92 – 2.85 (m, 2H, $SCH_c + SCH_d$), 2.73 (d, $J = 14.0$ Hz, 2H, $SCH_c' + SCH_b'$), 2.37 (dd, $J = 13.6, 3.1$ Hz, 2H, $CH_a + CH_b$), 2.06 (qd, $J = 12.5, 3.2$ Hz, 2H, $CH_a + CH_b$); $^{13}C\{^1H\}$ NMR (151 MHz, Methanol- d_4) δ 159.7 (C_{Ar}), 123.3 (br, C_{ArH}), 39.5 (CCH), 33.8 ($C_a + C_b$), 29.2 ($C_c + C_d$). Two aromatic carbons are not seen in the $^{13}C\{^1H\}$ NMR spectrum due to peak broadening. HRMS (ESI) calcd for $C_{12}H_{15}N_2S^+ [M+H]^+$: 219.0956, found 219.0955. IR ν max (film): 3394, 2924, 1709, 1432, 1274, 1047, 951, 744 cm^{-1} . M.p.: 220 – 222 °C.

2-(Tetrahydrothiophen-3-yl)-1H-benzimidazole (5d)

General Procedure C was followed using 3-methoxy-3-methyl-4-oxa-7-thia-1,2-diazaspiro[4.4]non-1-ene (38 mg, 0.2 mmol, 1.0 eq.), formaldehyde (0.15 mL, 37 wt% in H_2O , 2 mmol, 10 eq.) and *o*-phenylenediamine (32 mg, 0.3 mmol, 1.5 eq.). The crude mixture was purified *via* flash column chromatography (10 – 40% EtOAc in petroleum ether) to give the titled product as a white solid (29 mg, 72%). 1H NMR (600 MHz, Methanol- d_4) δ 7.55 – 7.38 (m, 2H, H_{Ar}), 7.21 – 7.13 (m, 2H, H_{Ar}), 3.60 (ddd, $J = 15.8, 9.7, 6.3$ Hz, 1H, CCH), 3.23 (dd, $J = 10.4, 6.9$ Hz, 1H, CCHCH $_a$), 3.14 (dd, $J = 10.4, 9.3$ Hz, 1H, CCHCH $_a'$), 2.98 (dd, $J = 8.4, 5.0$ Hz, 2H, SCH_2CH_2), 2.52 (dt, $J = 10.4, 5.1$ Hz, 1H, CCHCH $_b$), 2.36 – 2.26 (m, 1H, CCHCH $_b'$); $^{13}C\{^1H\}$ NMR (151 MHz, Methanol- d_4) δ 156.4 (C_{Ar}), 123.4 (C_{ArH}), 115.4 (br, C_{ArH}), 45.0 (CCH), 37.0 (C_b), 36.0 (C_a), 31.2 (SCH_2CH_2). One aromatic carbon is not seen in the $^{13}C\{^1H\}$ NMR spectrum due to peak broadening. HRMS (ESI) calcd for $C_{11}H_{13}N_2S^+ [M+H]^+$: 205.0805, found 205.0799. IR ν max (film): 2923, 2356, 2348, 2158, 2034, 1420, 740 cm^{-1} . M.p.: 242 – 244 °C.

2-(1,4-Dioxaspiro[4.5]decan-8-yl)-1H-benzimidazole (5e)

General Procedure C was followed using 3-methoxy-3-methyl-4,9,12-trioxa-1,2-diazaspiro[4.2.4 8 .2 5]tetradec-1-ene (51 mg, 0.2 mmol, 1.0 eq.), formaldehyde (0.15 mL, 37 wt% in H_2O , 2 mmol, 10 eq.) and *o*-phenylenediamine (32 mg, 0.3 mmol, 1.5 eq.). The crude mixture was purified *via* flash column chromatography (10 – 40% EtOAc in petroleum ether) to give the titled product as a white solid (41 mg, 80%). 1H NMR (600 MHz, $CDCl_3$) δ 7.57 – 7.51 (m, 2H, H_{Ar}), 7.20 (dd, $J = 6.1, 3.1$ Hz, 2H, H_{Ar}), 4.01 – 3.90 (m, 4H, OCH_2CH_2O), 3.02 (tt, $J = 11.8, 3.7$ Hz, 1H, CCH), 2.21 – 2.13 (m, 2H, $CHCH_a + CHCH_b$), 2.07 – 1.97 (m, 2H, $CHCH_a' + CHCH_b'$), 1.90 – 1.83 (m, 2H, $CCH_c + CCH_d$), 1.68 (td, $J = 13.2, 4.3$ Hz, 2H, $CCH_c' + CCH_d'$); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 157.9 (C_{Ar}), 122.4 (C_{ArH}), 114.8 (br, C_{ArH}), 108.1 (OCO), 64.5 (C_e), 64.4 (C_f), 37.3 (CCH), 34.4 ($C_c + C_d$), 29.2 ($C_a + C_b$). One aromatic carbon is not seen in the $^{13}C\{^1H\}$ NMR spectrum due to peak broadening. HRMS (ESI) calcd for $C_{15}H_{19}N_2O_2^+ [M+H]^+$: 259.1457, found 259.1447. IR ν max (film): 2988, 2945, 1678, 1588, 1402, 1344, 1249, 1219, 1089, 1013, 967, 838, 735 cm^{-1} . M.p.: 230 – 232 °C.

tert-Butyl 4-(1H-benzimidazol-2-yl)piperidine-1-carboxylate (5f)

General Procedure C was followed using *tert*-butyl 3-methoxy-3-methyl-4-oxa-1,2,8-triazaspiro[4.5]dec-1-ene-8-carboxylate (57 mg, 0.2 mmol, 1.0 eq.), formaldehyde (0.16 mL, 37 wt% in H_2O , 2.0 mmol, 10 eq.) and *o*-phenylenediamine (32 mg, 0.3 mmol, 1.5 eq.). The crude mixture was purified *via* flash column chromatography (10 – 40% EtOAc in petroleum ether) to give the titled product as a white solid (30 mg, 49%). 1H NMR (600 MHz, $CDCl_3$) δ 10.02 (br s, 1H, NH), 7.71 (br s, 1H, H_{Ar}), 7.41 (br s, 1H, H_{Ar}), 7.22 (dd, $J = 6.0, 3.1$ Hz, 2H, H_{Ar}), 4.23 (br s, 2H, $NCH_c + NCH_d$), 3.10 (tt, $J = 11.8, 3.8$ Hz, 1H, CCH), 2.89 (br s, 2H, $NCH_c' + NCH_d'$), 2.13 – 2.04 (m, 2H, $CH_a + CH_b$), 1.85 (qd, $J = 12.2, 4.3$ Hz, 2H, $CH_a' + CH_b'$), 1.47 (s, 9H, $C(CH_3)_3$); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 157.0 (C_{Ar}), 154.9 ($NCOOC(CH_3)_3$), 143.2 (br, C_{Ar}), 122.5 (br, C_{ArH}), 119.1 (br, C_{ArH}), 110.7 (br, C_{ArH}), 80.0 ($C(CH_3)_3$), 44.1 (br, $C_c + C_d$), 37.1 (CCH), 30.9 (br, $C_a + C_b$), 28.6 ($C(CH_3)_3$). HRMS (ESI) calcd for $C_{17}H_{24}O_2N_3^+ [M+H]^+$: 302.1869, found 302.1869. IR ν max (film): 2976, 1692, 1536, 1425, 1366, 1272, 1231, 1166, 1123, 980, 861, 768, 742 cm^{-1} . M.p.: 226 – 228 °C.

2-[1-(Pyrimidin-2-yl)piperidin-4-yl]-1H-benzimidazole (5g)

General Procedure C was followed using 3-methoxy-3-methyl-8-(pyrimidin-2-yl)-4-oxa-1,2,8-triazaspiro[4.5]dec-1-ene (55 mg, 0.2 mmol, 1.0 eq.), formaldehyde (0.16 mL, 37 wt% in H_2O , 2.0 mmol, 10 eq.) and *o*-phenylenediamine (32 mg, 0.3 mmol, 1.5 eq.). The crude mixture was purified *via* flash column chromatography (10 – 40% EtOAc in petroleum ether) to give the titled product as a white solid (40 mg, 72%). 1H NMR (600 MHz, $CDCl_3$) δ 9.75 (br s, 1H, NH), 8.30 (d, $J = 4.6$ Hz, 2H, $H_{Pyrimidine}$), 7.54 (br s, 2H, H_{Ar}), 7.22 (dd, $J = 5.9, 3.1$ Hz, 2H, H_{Ar}), 6.47 (t, $J = 4.6$ Hz, 1H, $H_{Pyrimidine}$), 4.86 (d, $J = 13.5$ Hz, 2H, $NCH_c + NCH_d$), 3.22 (tt, $J = 11.8, 3.7$ Hz, 1H, CCH), 3.10 – 2.99 (m, 2H, $NCH_c' + NCH_d'$), 2.19 (d, $J = 11.3$ Hz, 2H, $CH_a + CH_b$), 1.92 (qd, $J = 12.4, 3.9$ Hz, 2H, $CH_a' + CH_b'$); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 161.7 ($C_{Pyrimidine}$), 157.9 ($C_{PyrimidineH}$), 157.2 (C_{Ar}), 122.6 (br, C_{ArH}), 110.0 ($C_{PyrimidineH}$), 43.9 ($C_c + C_d$), 37.3 (CCH), 30.7 ($C_a + C_b$). Two aromatic carbons are not seen in the $^{13}C\{^1H\}$ NMR spectrum due to peak broadening. HRMS (ESI) calcd for $C_{16}H_{18}N_5^+ [M+H]^+$: 280.1557, found 280.1546. IR ν max (film): 2936, 2346, 1982, 1584, 1541, 1518, 1481, 1456, 1426, 1358, 1304, 1272, 1233, 1105, 1050, 977, 798, 741 cm^{-1} . M.p.: 222 – 224 °C.

2-(Adamantan-2-yl)-1H-benzimidazole (5h)

General Procedure C was followed using 5'-methoxy-5'-methyl-5'*H*-spiro[adamantane-2,2'-[1,3,4]oxadiazole] (47 mg, 0.2 mmol, 1.0 eq.), formaldehyde (0.15 mL, 37 wt% in H_2O , 2 mmol, 10 eq.) and *o*-phenylenediamine (32 mg, 0.3 mmol, 1.5 eq.). The crude mixture was purified *via* flash column chromatography (10 – 40% EtOAc in petroleum ether) to give the titled product as a dark yellow solid (40 mg, 79%). 1H NMR (600 MHz, $CDCl_3$) δ 7.57 (br s, 2H, H_{Ar}), 7.21 (dd, $J = 6.0, 3.1$ Hz, 2H, H_{Ar}), 3.27 (s, 1H, CCH), 2.66 – 2.59 (m, 2H, CH_a), 2.08 – 1.94 (m, 7H, $CH_c + C_b$), 1.87 – 1.86 (m, 1H, CH_c'), 1.83 (br s, 2H, C_d), 1.77 – 1.70 (m, 2H, C_b); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 157.2 (C_{Ar}), 122.3 (C_{ArH}), 44.6 (CCH), 38.4 (C_b), 37.6 (C_d), 33.1 (C_b'), 31.0 (C_a), 27.8 (C_c), 27.7 (C_c'). Two aromatic carbons are not seen in the $^{13}C\{^1H\}$ NMR spectrum due to peak broadening. HRMS (ESI) calcd for $C_{17}H_{21}N_2^+ [M+H]^+$: 253.1705, found 253.1700. IR ν max (film): 2922, 1422, 1275, 1009, 993, 743 cm^{-1} . M.p.: 244 – 246 °C.

2-Cyclobutyl-1H-benzimidazole (5i)

General Procedure C was followed using 7-methoxy-7-methyl-8-oxa-5,6-diazaspiro[3.4]oct-5-ene (31 mg, 0.2 mmol, 1.0 eq.), formaldehyde (0.16 mL, 37 wt% in H_2O , 2.0 mmol, 10 eq.) and *o*-phenylenediamine (32 mg, 0.3 mmol, 1.5 eq.). The crude mixture was purified *via* flash column chromatography (10 – 40% EtOAc

in petroleum ether) to give the titled product as a white solid (20 mg, 59%). ¹H NMR (600 MHz, CDCl₃) δ 7.56 (dd, *J* = 6.0, 3.2 Hz, 2H, *H*_{Ar}), 7.21 (dd, *J* = 6.0, 3.1 Hz, 2H, *H*_{Ar}), 3.80 (p, *J* = 8.7 Hz, 1H, CCH), 2.58 – 2.47 (m, 2H, *CH*_a + *CH*_b), 2.47 – 2.38 (m, 2H, *CH*_a' + *CH*_b'), 2.14 – 2.01 (m, 1H, *CH*_c), 1.99 – 1.91 (m, 1H, *CH*_c'); ¹³C{¹H} NMR (151 MHz, CDCl₃) δ 158.1 (*C*_{Ar}), 138.6 (br, *C*_{Ar}), 122.3 (*C*_{Ar}H), 114.8 (br, *C*_{Ar}H), 34.3 (CCH), 28.2 (*C*_a + *C*_b), 18.8 (*C*_c). HRMS (ESI) calcd for C₁₁H₁₃N₂⁺ [*M*+*H*]⁺ 173.1073, found 173.1069. IR ν max (film): 2942, 1537, 1455, 1419, 1328, 1272, 982, 740 cm⁻¹. M.p.: 186 – 188 °C. The data presented are consistent with literature precedent.⁴⁶

2-[1-(Pyridin-4-yl)propan-2-yl]-1*H*-benzimidazole (5l)

General Procedure C was followed using 2-methoxy-2,5-dimethyl-5-(pyridin-4-ylmethyl)-2,5-dihydro-1,3,4-oxadiazole (44 mg, 0.2 mmol, 1.0 eq.), formaldehyde (0.16 mL, 37 wt% in H₂O, 2.0 mmol, 10 eq.) and *o*-phenylenediamine (32 mg, 0.3 mmol, 1.5 eq.). The crude mixture was purified via flash column chromatography (10 – 100% EtOAc in petroleum ether) to give the titled product as a yellow solid (23 mg, 48%). ¹H NMR (600 MHz, CDCl₃) δ 10.14 (br s, 1H, *NH*), 8.40 – 8.36 (m, 2H, *H*_{Pyridine}), 7.73 (br s, 1H, *H*_{Ar}), 7.34 (br s, 1H, *H*_{Ar}), 7.23 (s, 2H, *H*_{Ar}), 7.00 – 6.98 (m, 2H, *H*_{Pyridine}), 3.35 (p, *J* = 7.0 Hz, 1H, CCH), 3.28 (dd, *J* = 13.4, 7.5 Hz, 1H, *CHCH*_a'), 3.00 (dd, *J* = 13.4, 6.8 Hz, 1H, *CHCH*_a'), 1.47 (d, *J* = 6.9 Hz, 3H, *CH*₃); ¹³C{¹H} NMR (151 MHz, CDCl₃) δ 157.3 (*C*_{Ar}), 149.5 (*C*_{Pyridine}H), 148.8 (*C*_{Pyridine}), 143.1 (br, *C*_{Ar}), 124.5 (*C*_{Pyridine}H), 122.3 (br, *C*_{Ar}H), 110.5 (br, *C*_{Ar}H), 41.8 (*C*_a), 35.9 (CCH), 19.4 (*CH*₃). HRMS (ESI) calcd for C₁₅H₁₆N₃⁺ [*M*+*H*]⁺ 238.1344, found 238.1344. IR ν max (film): 3051, 2969, 1603, 1559, 1535, 1484, 1454, 1419, 1328, 1272, 1219, 1110, 1070, 1043, 993, 907, 843, 795, 768, 747 cm⁻¹. M.p.: 188 – 190 °C.

2-[1-(Furan-2-yl)propan-2-yl]-1*H*-benzimidazole (5m)

General Procedure C was followed using 2-(furan-2-ylmethyl)-5-methoxy-2,5-dimethyl-2,5-dihydro-1,3,4-oxadiazole (42 mg, 0.2 mmol, 1.0 eq.), formaldehyde (0.15 mL, 37 wt% in H₂O, 2 mmol, 10 eq.) and *o*-phenylenediamine (32 mg, 0.3 mmol, 1.5 eq.). The crude mixture was purified via flash column chromatography (10 – 40% EtOAc in petroleum ether) to give the titled product as a white solid (34 mg, 75%). ¹H NMR (600 MHz, CDCl₃) δ 7.53 (dd, *J* = 6.1, 3.2 Hz, 2H, *H*_{Ar}), 7.30 – 7.27 (m, 1H, *H*_{Furan}), 7.23 – 7.18 (m, 2H, *H*_{Ar}), 6.24 (dd, *J* = 3.2, 1.9 Hz, 1H, *H*_{Furan}), 5.96 (d, *J* = 3.2 Hz, 1H, *H*_{Furan}), 3.51 (h, *J* = 7.1 Hz, 1H, CCH), 3.24 (dd, *J* = 15.0, 7.2 Hz, 1H, *CHCH*_a'), 3.06 (dd, *J* = 15.0, 7.2 Hz, 1H, *CHCH*_a'), 1.48 (d, *J* = 7.0 Hz, 3H, *CHCH*₃); ¹³C{¹H} NMR (151 MHz, CDCl₃) δ 158.1 (*C*_{Furan}), 153.3 (*C*_{Ar}), 141.5 (*C*_{Furan}H), 122.4 (*C*_{Ar}H), 115.1 (br, *C*_{Ar}H), 110.5 (*C*_{Furan}H), 107.1 (*C*_{Furan}H), 34.6 (*C*_a), 34.1 (CCH), 19.3 (*CH*₃). One aromatic carbon is not seen in the ¹³C{¹H} NMR spectrum. HRMS (ESI⁺): *m/z* calcd for C₁₄H₁₅N₂O⁺ [*M*+*H*]⁺: 227.1177, found 227.1184. IR ν max (film): 2921, 1423, 1275, 1009, 993, 932, 743 cm⁻¹. M.p.: 180 – 182 °C.

2-(Hex-5-en-2-yl)-1*H*-benzimidazole (5n)

General Procedure C was followed using 2-(but-3-en-1-yl)-5-methoxy-2,5-dimethyl-2,5-dihydro-1,3,4-oxadiazole (37 mg, 0.2 mmol, 1.0 eq.), formaldehyde (0.16 mL, 37 wt% in H₂O, 2.0 mmol, 10 eq.) and *o*-phenylenediamine (32 mg, 0.3 mmol, 1.5 eq.). The crude mixture was purified via flash column chromatography (10 – 40% EtOAc in petroleum ether) to give the titled product as a white solid (29 mg, 73%). ¹H NMR (600 MHz, CDCl₃) δ 10.18 (br s, 1H, *NH*), 7.55 (br s, 2H, *H*_{Ar}), 7.21 (dd, *J* = 6.0, 3.1 Hz, 2H, *H*_{Ar}), 5.75 (ddt, *J* = 17.0, 10.2, 6.6 Hz, 1H, *CH*₂=*CH*), 4.97 (dd, *J* = 17.0, 1.8 Hz, 1H, *H*_a), 4.93 (dd, *J* = 10.2, 1.8 Hz, 1H, *H*_b), 3.14 (h, *J* = 7.0 Hz, 1H, CCH), 2.14 – 2.05 (m, 2H, *CH*₂=*CHCH*₂), 2.04 – 1.97 (m, 1H, CCHCH_c'), 1.85 – 1.77 (m, 1H, CCHCH_c'), 1.45 (d, *J* = 7.1 Hz, 3H, *CH*₃); ¹³C{¹H} NMR (151 MHz, CDCl₃) δ 159.3 (*C*_{Ar}), 137.9 (*CH*₂=*CH*), 122.3 (*C*_{Ar}H), 115.3 (*CH*₂=*CH*), 35.6 (*C*_c), 34.2 (CCH), 31.6 (*CH*₂=*CHCH*₂), 19.8 (*CH*₃). Two aromatic carbons are not

seen in the ¹³C{¹H} NMR spectrum. HRMS (ESI) calcd for C₁₃H₁₇N₂⁺ [*M*+*H*]⁺ 201.1386, found 201.1379. IR ν max (film): 3074, 2968, 2932, 2736, 1818, 1640, 1538, 1454, 1426, 1330, 1272, 989, 906, 745, 729 cm⁻¹. M.p.: 182 – 185 °C.

2-(4,4-Dimethylhept-6-yn-2-yl)-1*H*-benzimidazole (5o)

General Procedure C was followed using 2-(2,2-dimethylpent-4-yn-1-yl)-5-methoxy-2,5-dimethyl-2,5-dihydro-1,3,4-oxadiazole (45 mg, 0.2 mmol, 1.0 eq.), formaldehyde (0.16 mL, 37 wt% in H₂O, 2.0 mmol, 10 eq.) and *o*-phenylenediamine (32 mg, 0.3 mmol, 1.5 eq.). The crude mixture was purified via flash column chromatography (10 – 40% EtOAc in petroleum ether) to give the titled product as a white solid (19 mg, 39%). ¹H NMR (600 MHz, CDCl₃) δ 9.68 (br s, 1H, *NH*), 7.71 (br s, 1H, *H*_{Ar}), 7.38 (br s, 1H, *H*_{Ar}), 7.21 (dd, *J* = 6.2, 2.9 Hz, 2H, *H*_{Ar}), 3.29 – 3.21 (m, 1H, CCHCH₃), 2.12 (dd, *J* = 14.4, 8.9 Hz, 1H, *CHCCH*_b'), 2.07 (dd, *J* = 16.2, 3.2 Hz, 1H, *CHCCH*_a'), 2.02 – 1.93 (m, 2H, *CHCCH*₂ + *CHCCH*_a'), 1.72 (dd, *J* = 14.4, 4.0 Hz, 1H, *CHCCH*_b'), 1.44 (d, *J* = 7.1 Hz, 3H, *CHCH*₃), 0.92 (d, *J* = 17.9 Hz, 6H, *C(CH*₃)₂); ¹³C{¹H} NMR (151 MHz, CDCl₃) δ 159.7 (*C*_{Ar}), 122.3 (br, *C*_{Ar}H), 110.7 (br, *C*_{Ar}H), 82.6 (*CHCCH*₂), 70.5 (*CHCCH*₂), 47.1 (*C*_b), 34.0 (*C(CH*₃)₂), 31.9 (*C*_a), 31.2 (CCHCH₃), 27.3 (*C(CH*₃)₂), 27.1 (*C(CH*₃)₂), 23.3 (CCHCH₃). One aromatic carbon is not seen in the ¹³C{¹H} NMR spectrum. HRMS (ESI) calcd for C₁₆H₂₁N₂⁺ [*M*+*H*]⁺ 241.1699, found 241.1690. IR ν max (film): 3311, 2965, 2752, 2367, 1538, 1453, 1424, 1335, 1269, 994, 746 cm⁻¹. M.p.: 191 – 192 °C.

2-(1-Cyclopropylethyl)-1*H*-benzimidazole (5p)

General Procedure C was followed using 2-cyclopropyl-5-methoxy-2,5-dimethyl-2,5-dihydro-1,3,4-oxadiazole (34 mg, 0.2 mmol, 1.0 eq.), formaldehyde (0.16 mL, 37 wt% in H₂O, 2.0 mmol, 10 eq.) and *o*-phenylenediamine (32 mg, 0.3 mmol, 1.5 eq.). The crude mixture was purified via flash column chromatography (10 – 40% EtOAc in petroleum ether) to give the titled product as a white solid (26 mg, 69%). ¹H NMR (600 MHz, CDCl₃) δ 9.49 (br s, 1H, *NH*), 7.73 (br s, 1H, *H*_{Ar}), 7.41 (br s, 1H, *H*_{Ar}), 7.22 (dd, *J* = 6.1, 3.1 Hz, 2H, *H*_{Ar}), 2.36 (dq, *J* = 9.6, 7.0 Hz, 1H, CCH), 1.56 (d, *J* = 7.0 Hz, 3H, *CH*₃), 1.10 (dddd, *J* = 13.0, 9.6, 8.0, 4.9 Hz, 1H, *CHCHCH*₂), 0.71 – 0.63 (m, 2H, *CH*_a + *CH*_a'), 0.44 – 0.38 (m, 1H, *CH*_b), 0.36 – 0.30 (m, 1H, *CH*_b'); ¹³C{¹H} NMR (151 MHz, CDCl₃) δ 158.7 (*C*_{Ar}), 143.4 (br, *C*_{Ar}), 133.5 (br, *C*_{Ar}), 122.3 (*C*_{Ar}H), 119.4 (br, *C*_{Ar}H), 110.4 (br, *C*_{Ar}H), 39.5 (CCH), 19.0 (*CH*₃), 16.6 (CCHCH), 4.8 (*C*_a), 4.4 (*C*_b); HRMS (ESI) calcd for C₁₂H₁₅N₂⁺ [*M*+*H*]⁺ 187.1230, found 187.1221. IR ν max (film): 2969, 2317, 2135, 1456, 1414, 1274, 1076, 744 cm⁻¹. M.p.: 187 – 189 °C.

Synthesis of aldehydes from aryl hydrazones

General Procedure D for the synthesis of aldehydes from aryl hydrazones

Conditioning phase: A solution of triethylamine in MeOH (5 mL, 20% v/v) was passed through the column reactor (Omnifit[®] column, 6.6 mm i.d. × 50 mm length), packed with activated MnO₂ (1.0 g), at a flow rate of 1.0 mL/min for 5 min (phase 1) and the reactor output was monitored using a Flow-IR[®] device. The flow was switched to EtOAc for 10 min (phase 2). The column was then ready for the generation of the diazo compound.

Generation phase: A solution of hydrazone (2 mmol, 0.1 M) in EtOAc (20 mL) was passed through a conditioned column reactor (Omnifit[®] column, 6.6 mm i.d. × 50 mm length) (phase 3) at a flow rate of 1.0 mL/min. When the Mettler Toledo FlowIR[®] instrument (SiComp head) showed that the intensity of the diazo peak (region 2060 – 2080 cm⁻¹) was stable, 4 mL of the stream of diazo was combined with 4 mL of aqueous formaldehyde (37 wt%, 1.0 mL/min) in a UQ5102 Uniqsis Glass Static Mixer at room temperature. The output stream was extracted with extra EtOAc (20 mL × 2) and washed with water (20 mL). The combined organic phase was dried over MgSO₄, concentrated under vacuum and purified

over silica gel using appropriate eluent combinations to yield the desired aldehyde.

2-(4-Chlorophenyl)acetaldehyde (7a)

General Procedure D was followed using (4-chlorobenzylidene)hydrazine (0.1 M in EtOAc, 1.0 mL/min) and formaldehyde (37 wt% in H₂O, 1.0 mL/min). The crude mixture was purified via flash column chromatography (0 – 20% EtOAc in petroleum ether) to give the titled product as a colorless liquid (33 mg, 53%). ¹H NMR (600 MHz, CDCl₃) δ 9.74 (t, *J* = 2.1 Hz, 1H, HCO), 7.34 (d, *J* = 8.4 Hz, 2H, H_{Ar}), 7.15 (d, *J* = 8.3 Hz, 2H, H_{Ar}), 3.68 (d, *J* = 2.1 Hz, 2H, CH₂); ¹³C{¹H} NMR (151 MHz, CDCl₃) δ 198.8 (HCO), 133.6 (C_{Ar}), 131.1 (C_{Ar}H), 130.4 (C_{Ar}), 129.3 (C_{Ar}H), 49.9 (CH₂). LRMS (ESI, m/z) 155.3 ([³⁵M+H]⁺, 100%); The data presented are consistent with literature precedent.⁴⁷

2-(3-Bromophenyl)acetaldehyde (7b)

General Procedure D was followed using (3-bromobenzylidene)hydrazine (0.1 M in EtOAc, 1.0 mL/min) and formaldehyde (37 wt% in H₂O, 1.0 mL/min). The crude mixture was purified via flash column chromatography (0 – 20% EtOAc in petroleum ether) to give the titled product as a colorless liquid (46 mg, 58%). ¹H NMR (600 MHz, CDCl₃) δ 9.75 (t, *J* = 2.1 Hz, 1H, HCO), 7.45 (d, *J* = 8.0 Hz, 1H, H_{Ar}), 7.39 (t, *J* = 1.8 Hz, 1H, H_{Ar}), 7.24 (t, *J* = 7.9 Hz, 1H, H_{Ar}), 7.15 (d, *J* = 7.6 Hz, 1H, H_{Ar}), 3.68 (d, *J* = 2.2 Hz, 2H, CH₂); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 198.5 (HCO), 134.2 (C_{Ar}), 132.8 (C_{Ar}H), 130.8 (C_{Ar}H), 130.6 (C_{Ar}H), 128.4 (C_{Ar}H), 123.1 (C_{Ar}), 50.1 (CH₂). LRMS (ESI, m/z) 199.1 ([⁷⁹M+H]⁺, 100%). IR ν max (film): 2827, 1723, 1568, 1474, 1427, 1072, 782, 692 cm⁻¹. The data presented are consistent with literature precedent.⁴⁶

2-(*o*-Tolyl)acetaldehyde (7c)

General Procedure D was followed using (2-methylbenzylidene)hydrazine (0.1 M in EtOAc, 1.0 mL/min) and formaldehyde (37 wt% in H₂O, 1.0 mL/min). The crude mixture was purified via flash column chromatography (0 – 20% EtOAc in petroleum ether) to give the titled product as a colorless liquid (31 mg, 57%). ¹H NMR (400 MHz, CDCl₃) δ 9.71 (t, *J* = 2.3 Hz, 1H, HCO), 7.24 – 7.20 (m, 3H, H_{Ar}), 7.19 – 7.15 (m, 1H, H_{Ar}), 3.71 (d, *J* = 2.3 Hz, 2H, CH₂), 2.28 (s, 3H, CH₃); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 199.4 (HCO), 143.3 (C_{Ar}), 137.3 (C_{Ar}), 130.8 (C_{Ar}H), 130.7 (C_{Ar}H), 127.9 (C_{Ar}H), 126.6 (C_{Ar}H), 48.9 (CH₂), 19.9 (CH₃). LRMS (ESI, m/z) 135.3 ([M+H]⁺, 100%). IR ν max (film): 2827, 1723, 1568, 1474, 1427, 1072, 782, 692 cm⁻¹. The data presented are consistent with literature precedent.⁴⁸

Synthesis of alcohols from aryl hydrazones

General Procedure E for the synthesis of alcohols from aryl hydrazones

The reaction slug from **General Procedure D** was extracted with extra EtOAc (20 mL × 2) and washed with water (20 mL). The combined organic phase was concentrated and re-dissolved in EtOH (8 mL). NaBH₄ (10 equiv.) was added portionwise and the reaction mixture was stirred for a further hour. The resulting mixture was then quenched with ice water, extracted with ethyl acetate (2 × 20 mL) and washed with brine (2 × 20 mL). The organic phase was combined, dried over MgSO₄, filtered and concentrated under reduced pressure. The remaining residue was purified *via* flash column chromatography with appropriate eluents to give the desired alcohol.

2-(4-Chlorophenyl)ethan-1-ol (8a)

General Procedure E was followed using (4-chlorobenzylidene)hydrazine (0.1 M in EtOAc, 1.0 mL/min), formaldehyde (37 wt% in H₂O, 1.0 mL/min) and NaBH₄ (152 mg, 10.0 equiv.). The crude mixture was purified via flash column chromatography (0 – 20% EtOAc in petroleum ether) to give the titled product as a

colorless liquid (36 mg, 57%). ¹H NMR (600 MHz, CDCl₃) δ 7.28 (d, *J* = 8.4 Hz, 1H, H_{Ar}), 7.17 (d, *J* = 8.4 Hz, 1H, H_{Ar}), 3.85 (t, *J* = 6.6 Hz, 1H, HOCH₂), 2.84 (t, *J* = 6.5 Hz, 1H, ArCH₂), 1.39 (br s, 1H, HO); ¹³C{¹H} NMR (151 MHz, CDCl₃) δ 137.2 (C_{Ar}), 132.5 (C_{Ar}), 130.5 (C_{Ar}H), 128.8 (C_{Ar}H), 63.6 (HOCH₂), 38.6 (ArCH₂). LRMS (ESI, m/z) 157.1 ([³⁵M+H]⁺, 100%). IR ν max (film): 3335, 2932, 1492, 1406, 1090, 1046, 1015, 810 cm⁻¹. The data presented are consistent with literature precedent.⁴⁹

2-(3-Bromophenyl)ethan-1-ol (8b)

General Procedure E was followed using (3-bromobenzylidene)hydrazine (0.1 M in EtOAc, 1.0 mL/min), formaldehyde (37 wt% in H₂O, 1.0 mL/min) and NaBH₄ (152 mg, 10.0 equiv.). The crude mixture was purified via flash column chromatography (0 – 20% EtOAc in petroleum ether) to give the titled product as a colorless liquid (53 mg, 66%). ¹H NMR (400 MHz, CDCl₃) δ 7.47 – 7.29 (m, 2H, H_{Ar}), 7.22 – 7.06 (m, 2H, H_{Ar}), 3.85 (t, *J* = 6.5 Hz, 2H, HOCH₂), 2.83 (t, *J* = 6.5 Hz, 2H, ArCH₂), 1.56 (s, 1H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 141.1 (C_{Ar}), 132.2 (C_{Ar}H), 130.2 (C_{Ar}H), 129.7 (C_{Ar}H), 127.8 (C_{Ar}H), 122.7 (C_{Ar}), 63.4 (HOCH₂), 38.9 (ArCH₂). LRMS (ESI, m/z) 201.0 ([⁷⁹M+H]⁺, 100%). IR ν max (film): 3333, 2945, 1595, 1567, 1473, 1425, 1200, 1071, 1044, 997, 853, 806, 777, 692, 570 cm⁻¹. The data presented are consistent with literature precedent.⁵⁰

2-(*o*-Tolyl)ethan-1-ol (8c)

General Procedure E was followed using (2-methylbenzylidene)hydrazine (0.1 M in EtOAc, 1.0 mL/min), formaldehyde (37 wt% in H₂O, 1.0 mL/min) and NaBH₄ (152 mg, 10.0 equiv.). The crude mixture was purified via flash column chromatography (0 – 20% EtOAc in petroleum ether) to give the titled product as a colorless liquid (36 mg, 66%). ¹H NMR (400 MHz, CDCl₃) δ 7.21 – 7.02 (m, 4H, H_{Ar}), 3.84 (t, *J* = 6.9 Hz, 2H, HOCH₂), 2.90 (t, *J* = 6.9 Hz, 2H, ArCH₂), 2.35 (s, 3H, CH₃); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 136.7 (C_{Ar}), 136.6 (C_{Ar}), 130.6 (C_{Ar}H), 129.8 (C_{Ar}H), 126.7 (C_{Ar}H), 126.2 (C_{Ar}H), 62.8 (HOCH₂), 36.5 (ArCH₂), 19.6 (CH₃). LRMS (ESI, m/z) 137.3 ([M+H]⁺, 100%). IR ν max (film): 3328, 3017, 2944, 2874, 1604, 1492, 1455, 1379, 1167, 1112, 1040, 938, 853, 741, 612 cm⁻¹. The data presented are consistent with literature precedent.⁵¹

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Details of NMR spectra (PDF)

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Notes

D.C.B. is an employee and stockholder of Pfizer Inc.

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