A Chemo- and Regioselective Tandem [3 + 2]Heteroannulation Strategy for Carbazole Synthesis: Combining Two Mechanistically Distinct Bond-Forming Processes

Emma Campbell, § Andrea Taladriz-Sender, § Olivia I. Paisley, Alan R. Kennedy, Jacob T. Bush, and Glenn A. Burley*

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ABSTRACT: A modular approach to prepare tri- and tetracyclic carbazoles by a sequential [3 + 2] heteroannulation is described. First, optimization of Pd-catalyzed Buchwald–Hartwig amination followed by C/N-arylation in a one-pot process is established. Second, mechanistic analyses identified the origins of chemo- and regioselective sequential control of both bond-forming steps. Finally, the substrate scope is demonstrated by the preparation of a range of tri- and tetracyclic carbazoles, including expedient access to several natural products and anti-cancer agents.

INTRODUCTION

Carbazoles are ubiquitous N-heterocycles used throughout medicinal chemistry and material sciences.¹−³ From a pharmaceutical perspective, the carbazole core features extensively in drugs and natural products, many of which exhibit potent anti-proliferative activities (Figure 1a).⁴−⁹ The breadth of applications has inspired the development of numerous methodologies for their preparation.²,⁹,¹⁰ Pd-catalyzed processes in particular enable a [3 + 2]heteroannulation via Pd(0)-catalyzed Buchwald–Hartwig amination followed by Pd(II)-catalyzed C-arylation at a late stage in a synthetic workflow.¹²−²⁵ However, a generalized set of guidelines that control the chemoselectivity of each C−N/C−C bond-forming reaction, and the factors that influence Pd(0) versus Pd(II) catalysis in a one-pot process have not been established. Furthermore, a mechanistic understanding of any regiocontrol underpinning the second C−H activation step for the formation of tetracyclic carbazoles is unknown.

In this manuscript, we establish reaction guidelines to prepare tri- and tetracyclic carbazoles by controlling the chemo-selectivity of the first Pd(0)-catalyzed C−N bond-forming step and the regioselectivity of the second Pd(II)-catalyzed C/N-arylation (Figure 1b). Our rationale was to use α-chloroanilines (1) to define the A-ring of a carbazole core and heteroaryl bromides to form the C/D-rings of tricyclic and tetracyclic products. An initial version of this work was deposited in ChemRxiv on the 24th of November 2021.²⁶

RESULTS AND DISCUSSION

The motivation for this work was to develop a robust, one-pot synthetic framework that can access both tri- and tetracyclic carbazoles. The synthesis of tetracyclic carbazoles using a heteroaryl bromide substrate such as 3 has potentially two

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competing C–H activation sites. If the C-arylation proceeded via a Pd(II)-catalyzed intermediate, then we surmised that the more nucleophilic 5-position of an isoquinoline will result in preferential C–H bond activation at this site. However, the mechanistic determinants that control the regioselectivity of such Pd(II)-catalyzed C-arylation are not known with respect to a convergent [3 + 2]
heteroannulation approach.28

Our studies commenced with optimizing reaction conditions for the Pd(0)-catalyzed C–N bond-forming step using 4-methoxy-2-chloroaniline (1a) and 6-bromoisoquinoline (6a) as exemplar substrates (Scheme 1). An extensive screen (Table S1) identified DavePhos and K$_3$PO$_4$ as the optimal ligand/base pairing, which formed 7a in 87% yield. Using these conditions, secondary anilines 7b–e (56–91%) were obtained using chloroanilines (1b–e) bearing electron-rich and electron-withdrawing substituents when reacted with 6-bromoisoquinoline (6a). The conditions tolerated a range of heteroaryl bromides to form 7g–j, except for 2-bromoquinoline (6d). In this case, a mixture of secondary (7i, 27%) and tertiary anilines (8, 25%) was formed. Using 5-bromo-1,3-dihydroisobenzofuran (6e) formed 7 in 18% yield. This process was also compatible with 2-bromonaphthalene-1,4-dione (6f) producing 1,4-naphthoquinones (7k–p) in 59–82%. Whilst this reaction could conceivably proceed via Michael addition, the reaction afforded the secondary anilines 7k–p in 5–7% in the absence of a Pd catalyst.

With conditions for the Pd(0)-catalyzed C–N bond-forming step established, the optimization of the one-pot process was explored (Table S2). The optimal ligand/base pairing of HPCy$_3$BF$_4$ with K$_3$PO$_4$ was identified, which formed 9a from 1a and 6a in 82% yield (Scheme 2a). This highlights that the second C–H activation step is regioselective for the 7-position of 6a. To further understand how the nature of the chloroaniline and heteroaryl bromide substrates influenced the chemo- and regioselectivity of both bond-forming steps, a series of test reactions was undertaken. Exchanging 6-bromoisoquinoline (6a) for isoquinoline (10) formed dimethoxyphenazine (11) and the tertiary aniline (12) in 35 and 25% isolated yields, respectively (Scheme 2b). No dihydrophenazine was isolated from the reaction, which suggests that an in situ oxidation occurred.33 No reaction occurred when isoquinoline (10) was the coupling partner with 1-chloro-3-methoxybenzene (13, Scheme 2c). Only secondary aniline (15) was isolated when para-anisidine (14) was reacted with 6-bromoisoquinoline (6a, Scheme 2d). Taken collectively, these test reactions highlighted the following requirements for the preparation of the tetracyclic core: (i) aryl bromide is essential and prevents dimerization of the C-core: (i) aryl bromide is essential and prevents dimerization of the C-ring and render the tertiary aniline (13) from the reaction, which suggests that an oxidative addition of the C–Cl bond in 7a occurs first and proceeds via a Pd(0) species to form 18 (Scheme 2f). Pd(II)-catalyzed C-arylation forms the palladacycle (20), which could proceed through a concerted metalation–deprotonation pathway via the formation of 19a.12

This series of reactions has guided us to propose that oxidative addition of the C–Cl bond in 7a occurs first and proceeds via a Pd(0) species to form 18 (Scheme 2f). Pd(II)-catalyzed C-arylation forms the palladacycle (20), which could proceed through a concerted metalation–deprotonation pathway via the formation of 19a.12

![Scheme 1. Scope (Isolated Yields) of Buchwald–Hartwig Amination](image-url)
Scheme 2. Mechanistic Studies of the [3 + 2]Heteroannulation$^a$

(a) Optimized conditions for the one-pot [3+2]heteroannulation process.

(b) Influence of the heteroaryl bromide.

(c) Aniline is essential for C-N and C-C bond formation.

(d) Aryl chloride essential for C-arylation.

(e) Availability of aniline lone pair influences regiochemistry of C-H activation.

(f) Proposed mechanism of regioselectivity of C-arylation.

$^a$Reaction conditions: Pd(OAc)$_2$ (5 mol%), HPCy$_3$BF$_4$ (10 mol%), K$_3$PO$_4$ (3 equiv), 1,4-dioxane; (i) 30 min, 120 °C MW; (ii) 8 h, 160 °C MW; wrt = with respect to.

Alternatively, since the efficiency of the reaction is higher with the lone pair of aniline (18) donating into the ring, a Friedel–Crafts-like electrophilic aromatic substitution mechanism proceeding via imine (19b) followed by tautomerization might also be possible to form 20. Finally, reductive elimination of 20 produces the C-arylated product (9a).
established, the substrate scope of the process was investigated (Scheme 3).

The reaction conditions formed 7H-pyrido[3,4-c]carbazole analogues (9a−c). The presence of a nitro group resulted in only trace amounts of 9d formed, with the secondary aniline (7e) isolated in 79% yield. The reaction conditions also tolerated heteroatom changes and saturation in the D-ring of the heteroaryl bromide (9e−j). The [3 + 2]heteroannulation strategy was also compatible with the formation of carbazole-1,4-quinones (21a−f). Access to N-arylated products is also possible, forming a mixture of fused imidazoles (9k−l) via an N-arylation step, alongside tertiary anilines (22−23). Steric bulk ortho to the aniline substrate is also tolerated, forming 9m in 62%. However, when 3-methyl-2-chloroaniline is used as a substrate, a mixture of regioisomers was formed as an inseparable mixture (see Supporting Information).

The modularity of this strategy is also exemplified by the preparation of natural products glycozoline (9n), harmane (9o), and murrayafoline A (9p). In addition, preparation of 9q demonstrates that the reaction conditions tolerate functional groups bearing potential Pd-chelating sites and bulky substituents ortho to the corresponding aryl bromide.

Our [3 + 2]heteroannulation strategy was extended to the targeted synthesis of biologically active tetracyclic carbazoles.
Carbazole-1,4-quinones (e.g., 21a–f) have established anti-cancer activity via topo-isomerase inhibition or by the production of reactive oxygen species. We used 21b as a key intermediate for the targeted synthesis of a deaza analogue of the natural product 9-methoxyellipticine (Scheme 4a), producing 26 in three steps and in an overall yield of 20%.44

Further exemplification of our strategy was demonstrated by the preparation of alkylated 7H-pyrido[4,3-c]carbazoles (e.g., 9a–e), which have well-established anti-cancer activity. Previous preparative methods of this series of compounds have involved a six-step linear synthesis affording compound 9e in 28% overall yield. Our two-step convergent strategy accessed the 7H-pyrido[4,3-c]carbazole core 9e in a single step (83%), followed by alkylation (30–32) to produce mono-N-alkylated examples (27–28) and the potent anti-cancer agent ditercalinium dichloride (29, Scheme 4b).48

**CONCLUSIONS**

In summary, we have established a mechanistic framework for the preparation of fused tetracyclic carbazoles. The key to the modularity of this [3 + 2]heteroannulation approach is knowledge of the molecular hallmarks that underpin both the chemo- and regioselectivity of the process. The strategy is amenable for the diversification of tri- and tetracyclic carbazoles and is a scalable method for target-focused synthesis of tetracyclic carbazoles. We envisage that this convergent approach could find application in medicinal chemistry for structure–activity profiling and in broader synthetic applications that require step-efficient access to carbazole scaffolds.

**EXPERIMENTAL SECTION**

**General Information.** All reagents and solvents were obtained from commercial suppliers and were used without further purification unless otherwise stated. Purification was carried out according to standard laboratory methods. Starting materials were purchased from commercial suppliers and used without further purification unless otherwise stated. Dry solvents for reactions were purchased from Sigma-Aldrich and stored under nitrogen. Dichloromethane, chloroform, methanol, ethyl acetate, and petroleum ether (40−60 °C) for purification purposes were used as obtained from suppliers, without further purification. Reactions were carried out using conventional glassware for the preparation of starting materials. Microwave reactions were carried out in capped 2−5 mL microwave vials purchased from Biotage. Microwave reactions were carried out at elevated temperatures using a Biotage Initiator+ equipped with a Robot Eight microwave system. Thin-layer chromatography was carried out using Merck silica plates coated with a fluorescent indicator UV254, and they were analyzed under both 254 and 375 nm UV light or developed using potassium permanganate solution. Normal phase flash chromatography was carried out using 60 Å, 40−63 μm silica gel from Fluorochem.

**Preparative Methods of this Series of Compounds.** The preparation of starting materials has involved a six-step linear synthesis affording compound 9e in 28% overall yield. Our two-step convergent strategy accessed the 7H-pyrido[4,3-c]carbazole core 9e in a single step (83%), followed by alkylation (30–32) to produce mono-N-alkylated examples (27–28) and the potent anti-cancer agent ditercalinium dichloride (29), Scheme 4b.

**Analytical Methods.** Analytical reversed-phase HPLC purifications were carried out on a Shimadzu Prominence instrument equipped with a PDA detector. Analytical reversed-phase HPLC purifications were carried out on a Shimadzu Prominence instrument equipped with a PDA detector scanning from 190 to 600 nm using a Shimadzu Hypersil GOLD column 100 × 4.6 mm, with a particle size of 5 μm. The Fourier transform infrared (FTIR) spectra were obtained on a Shimadzu IR Affinity-1 instrument. Only major absorbance bands are reported. The 1H NMR, 13C NMR, and 19F NMR spectra were obtained on a Bruker AV 400 at 400, 101, and 376 MHz, respectively. Chemical shifts are reported in parts per million (ppm) and coupling constants are reported in hertz with DMSO-d6 referenced to 2.50 (1H) and 39.52 ppm (13C) and MeOD-d4 referenced to 3.31 (1H) and 49.0 ppm (13C). Assignment of 13C NMR signals is based on HSQC and HMBC experiments. The COSY and NOESY spectra were used to assign unequivocally atom connectivities. The high-resolution mass spectra were recorded on a Bruker microTOF II mass spectrometer at the SIRCAMs facility at the University of Edinburgh or on an LTQ Orbitrap XL at the EPSRC National Facility in Swansea.
The reaction was carried out according to the general procedure using 6-bromoquinoline (104 mg, 0.50 mmol, 1.0 equiv) and 4-nitro-2-chloroaniline (87 mg, 0.60 mmol, 1.2 equiv) as starting materials. The crude residue was purified by silica gel column chromatography, petroleum ether (40–60 °C):EtOAc (6:4), to obtain compound 7f in 74% yield (101 mg, yellow solid).

HNMR ((CD3)2SO, 400 MHz): δ 9.06 (s, 1H, H'), 8.51 (s, 1H, NH), 8.31 (d, 1H, J = 5.8 Hz, H'), 7.98 (d, 1H, J = 8.9 Hz, H'), 7.58 (d, 1H, J = 5.8 Hz, H'), 7.57 (dd, 1H, J = 9.0, 6.0 Hz, H'), 7.47 (dd, 1H, J = 8.9, 2.2 Hz, H'), 7.33–7.27 (m, 2H, H), 6.95 (dd, 1H, J = 8.8, 3.0 Hz, H'). 13C{1H} NMR ((CD3)2SO, 101 MHz): δ 161.2 (d, J = 244.7 Hz, C'), 151.3 (C'), 144.7 (C'), 143.2 (C'), 143.2 (C'), 140.2 (d, J = 10.8 Hz, C'), 136.9 (C'), 131.5 (d, J = 10.0 Hz, C'), 129.0 (C'), 124.0 (C'), 120.8 (C'), 120.5 (d, J = 3.3 Hz, C'), 119.2 (C'), 110.5 (d, J = 20.9 Hz, C'), 108.5 (d, J = 26.0 Hz, C'), 107.7 (C'). 19F NMR ((CD3)2SO, 376 MHz): δ = −113.1.

IR νmax (cm⁻¹): 3221 (N–H stretch), 1584 (C≡N bend), 1508 (N–O stretch), 1474 (C≡C stretch), 1333 (N–O stretch), 821 (C–Cl stretch).

HRMS (ESI) m/z: [M + H]+ calcd for C14H12N2ClF, 300.0534; found, 300.0538.

N-(2-Chloro-5-fluorophenyl)isoquinolin-6-amine (7f). The reaction was carried out according to the general procedure using 6-bromoquinoline (104 mg, 0.50 mmol, 1.0 equiv) and 2-chloro-5-fluoroaniline (87 mg, 0.60 mmol, 1.2 equiv) as starting materials. The crude residue was purified by silica gel column chromatography, petroleum ether (40–60 °C):EtOAc (6:4), to obtain compound 7f in 74% yield (101 mg, yellow solid).

HNMR ((CD3)2SO, 400 MHz): δ 9.06 (s, 1H, H'), 8.51 (s, 1H, NH), 8.31 (d, 1H, J = 5.8 Hz, H'), 7.98 (d, 1H, J = 8.9 Hz, H'), 7.58 (d, 1H, J = 5.8 Hz, H'), 7.57 (dd, 1H, J = 9.0, 6.0 Hz, H'), 7.47 (dd, 1H, J = 8.9, 2.2 Hz, H'), 7.33–7.27 (m, 2H, H), 6.95 (dd, 1H, J = 8.8, 3.0 Hz, H'). 13C{1H} NMR ((CD3)2SO, 101 MHz): δ 161.2 (d, J = 244.7 Hz, C'), 151.3 (C'), 144.7 (C'), 143.2 (C'), 143.2 (C'), 140.2 (d, J = 10.8 Hz, C'), 136.9 (C'), 131.5 (d, J = 10.0 Hz, C'), 129.0 (C'), 124.0 (C'), 120.8 (C'), 120.5 (d, J = 3.3 Hz, C'), 119.2 (C'), 110.5 (d, J = 20.9 Hz, C'), 108.5 (d, J = 26.0 Hz, C'), 107.7 (C'). 19F NMR ((CD3)2SO, 376 MHz): δ = −113.1.

IR νmax (cm⁻¹): 3221 (N–H stretch), 1584 (C≡N bend), 1508 (N–O stretch), 1474 (C≡C stretch), 1333 (N–O stretch), 821 (C–Cl stretch).

HRMS (ESI) m/z: [M + H]+ calcd for C14H12N2ClF, 300.0534; found, 300.0538.
The reaction was carried out according to the general procedure using 5-bromo-1,3-dihydrobenzo[2,1,3]oxa[5-amine (7)]. The reaction was carried out according to the general procedure using 5-bromo-1,3-dihydrobenzo[2,1,3]oxa[5-amine (7)]. The reaction was carried out according to the general procedure using 5-bromo-1,3-dihydrobenzo[2,1,3]oxa[5-amine (7)].
2-((2-Chlorophenyl)amino)naphthalene-1,4-dione (7m). The reaction was carried out according to the general procedure using 2-bromo-1,4-naphthoquinone (119 mg, 0.50 mmol, 1.0 equiv) and 2-chloroaniline (77 mg, 0.60 mmol, 1.2 equiv) as starting materials. The crude residue was purified by silica gel column chromatography, petroleum ether (40–60 °C): EtOAc (9:1) to obtain compound 7m in 64% yield (90 mg, brown solid).

1H NMR ((CD$_3$)$_2$SO, 400 MHz): δ 9.08 (s, 1H, NH), 8.10–8.06 (m, 1H, H$_7$), 7.98–7.94 (m, 1H, H$_9$), 7.91–7.85 (m, 1H, H$_5$), 7.85–7.79 (m, 1H, H$_7$), 7.68 (dd, 1H, J = 9.0, 5.7 Hz, H$_8$), 7.43 (dd, 1H, J = 9.5, 3.0 Hz, H$_6$), 7.26 (ddd, 1H, J = 8.8, 8.1, 3.0 Hz, H$_5$), 5.60 (s, 1H, H$_H$).

IR (cm$^{-1}$): 3310 (N–H stretch), 2858 (C–H stretch), 1675 (C=C stretch), 1675 (C=C stretch), 1599 (C=C stretch), 1541 (C=C stretch), 722 (C=Cl stretch).

HRMS (ESI) m/z: [M + H]$^+$ for C$_{18}$H$_{14}$O$_5$NClF$_3$, 302.0379; found, 302.0380.

General Experimental Procedure A for Microwave-Assisted One-Pot Buchwald–Hartwig Amination/Direct Arylation. Aryl bromide (0.50 mmol, 1 equiv), chloroaniline (0.60 mmol, 1.2 equiv), Pd(OAc)$_2$ (5 mol %), DPEPhos (10 mol %), and K$_2$PO$_4$ (1.50 mmol, 3 equiv) were added to a microwave vial (2–5 mL), 1,4-Dioxide (5.0 mL, 0.1 M) was added and the vial was capped, evacuated and purged with argon three times, and heated at 120 °C for 30 min followed by 160 °C for 8 h under microwave irradiation in a Biotage microwave. The reaction was allowed to cool to rt, diluted with DCM (50 mL), and the solid was filtered under vacuum. The solvent was removed in vacuo, and the crude sample was dry-loaded onto silica gel without work up. The crude compound was purified by silica column chromatography.

General Experimental Procedure B for Microwave-Assisted One-Pot Buchwald–Hartwig Amination/Direct Arylation. Aryl bromide (0.50 mmol, 1 equiv), chloroaniline (0.60 mmol, 1.2 equiv), Pd(OAc)$_2$ (5 mol %), P(C$_2$H$_5$)$_3$B, HBF$_4$ (10 mol %), and K$_2$PO$_4$ (1.50 mmol, 3 equiv) were added to a microwave vial (2–5 mL), 1,4-Dioxide (5.0 mL, 0.1 M) was added, the vial was capped, evacuated and purged with argon three times, and heated at 120 °C for 30 min followed by 160 °C for 8 h under microwave irradiation in a Biotage microwave. The reaction was allowed to cool to rt and diluted with DCM (50 mL). The solvent was removed in vacuo, and the crude sample dry-loaded onto silica gel without work up. The crude compound was purified by silica column chromatography.

10-Methoxy-7H-pyrido[3,4-c]carbazole (9a). The reaction was carried out according to the general procedure B using 6-bromoisouquinoline (104 mg, 0.50 mmol, 1.0 equiv) and 2-chloro-4-methoxyaniline (95 mg, 0.60 mmol, 1.2 equiv) as starting materials. The crude residue was purified by silica gel column chromatography, petroleum ether (40–60 °C): EtOAc (1:1), to obtain compound 9a in 82% yield (102 mg, brown solid).

1H NMR ((CD$_3$)$_2$SO, 400 MHz): δ 11.94 (s, 1H, −NH), 9.30 (s, 1H, H$_7$), 8.63 (dd, 1H, J = 5.8 Hz, H$_9$), 8.58 (d, 1H, J = 5.8 Hz, H$_5$), 8.05–7.99 (m, 2H, H$^{11,11}$), 7.85 (dd, 1H, J = 8.8 Hz, H$_8$), 7.60 (dd, 1H, J = 8.8 Hz, H$_7$), 7.13 (dd, 1H, J = 8.8, 2.4 Hz, H$_6$), 3.96 (s, 3H, −OCH$_3$).

IR (cm$^{-1}$): 2830 (C–H stretch), 1616 (C=C stretch), 1458 (C=C stretch), 1229 (C=C stretch), 1031 (C=C stretch).

HRMS (ESI) m/z: [M + H]$^+$ for C$_{21}$H$_{17}$ON$_2$, 249.1022; found, 249.1021.

2-(Chloro-5-fluoroaminophenyl)naphthalene-1,4-dione (7p). The reaction was carried out according to the general procedure using 2-bromo-1,4-naphthoquinone (119 mg, 0.50 mmol, 1.0 equiv) and 2-chloro-5-fluoroaniline (87 mg, 0.60 mmol, 1.2 equiv) as starting materials. The crude residue was purified by silica gel column chromatography, petroleum ether (40–60 °C): EtOAc (1:1) to obtain compound 7p in 54% yield (63 mg, brown solid).

1H NMR ((CD$_3$)$_2$SO, 400 MHz): δ 11.97 (s, 1H, −NH), 9.31 (s, 1H, H$_7$), 8.63 (d, 1H, J = 5.7 Hz, H$_5$), 8.58 (d, 1H, J = 5.7 Hz, H$_5$), 8.41
75% yield (93 mg, yellow solid).

The crude residue was purified by silica gel column chromatography, petroleum ether (40–60 °C): EtOAc (1:1), to obtain compound 9g in 65% yield (80 mg, off-white solid).

1H NMR ((CD3)2SO, 400 MHz): δ 11.77 (s, 1H, −NH), 9.17 (d, 1H, J = 8.3 Hz, H7), 8.82 (dd, 1H, J = 4.2, 1.4 Hz, H3'), 8.02 (dd, 1H, J = 2.3 Hz, H9'), 7.99–7.92 (m, 2H, H2', H8'), 7.67 (dd, 1H, J = 8.3, 4.2 Hz, H5'), 7.58 (d, 1H, J = 8.8 Hz, H7'), 7.11 (dd, 1H, J = 8.8, 2.3 Hz, H3), 3.95 (s, 3H, −OCH3). 13C{1H} NMR ((CD3)2SO, 101 MHz): δ 153.8 (C16), 146.1 (C14), 144.2 (C12), 137.4 (C7), 133.9 (C9), 130.8 (C8), 127.4 (C10), 124.4 (C11a), 121.3 (C5), 116.9 (C3), 114.2 (C11b), 113.3 (C10a), 112.6 (C10b), 103.9 (C6), 55.8 (−OCH3).

IR νmax (cm⁻¹): 3146 (N–H stretch), 2997 (C–H stretch), 1571 (C=N stretch), 1534 (C=C stretch), 1493 (C=C stretch), 1227 (C=C stretch), 1035 (C–O stretch).

HRMS (ESI) m/z: [M + H]+ calc'd for C14H10N2O2, 249.1022; found, 249.1026.

10-Methoxy-7H-pyrind[2,3-c]carbazole (9h). The reaction was carried out according to the general procedure B using 8-bromoisouquinoline (104 mg, 0.50 mmol, 1.0 equiv) and 2-chloro-4-methoxylaniline (95 mg, 0.60 mmol, 1.2 equiv) as starting materials. The crude residue was purified by silica gel column chromatography, petroleum ether (40–60 °C): EtOAc (1:1), to obtain compound 9h in 90% yield (111 mg, gray solid).

1H NMR ((CD3)2SO, 400 MHz): δ 12.30 (s, 1H, −NH), 9.36 (s, 1H, H7), 8.62 (d, 1H, J = 5.7 Hz, H3), 8.38 (d, 1H, J = 8.5 Hz, H5), 8.32 (d, 1H, J = 5.7 Hz, H7), 7.81 (d, 1H, J = 2.3 Hz, H9), 7.75 (d, 1H, J = 8.5 Hz, H5), 7.60 (d, 1H, J = 8.8 Hz, H7), 7.13 (dd, 1H, J = 8.8, 2.3 Hz, H3), 3.89 (s, 3H,−OCH3). 13C{1H} NMR ((CD3)2SO, 101 MHz): δ 153.7 (C12), 152.0 (C14), 142.8 (C13), 134.1 (C11a), 133.7 (C10a), 126.6 (C10b), 124.1 (C11a), 123.0 (C6a), 121.2 (C5), 120.5 (C3), 117.4 (C1), 115.7 (C10a), 114.9 (C10b), 112.5 (C6), 102.3 (C10), 55.6 (−OCH3).

IR νmax (cm⁻¹): 3149 (N–H stretch), 1619 (C=N stretch), 1480 (C=C stretch), 1439 (C=C stretch), 1215 (C–O stretch), 1027 (C–O stretch).

HRMS (ESI) m/z: [M + H]+ calc'd for C14H10N2O2, 249.1022; found, 249.1026.

8-Methoxy-11H-pyrind[4,3-c]carbazole (9i). The reaction was carried out according to the general procedure B using 8-bromoisouquinoline (104 mg, 0.50 mmol, 1.0 equiv) and 2-chloro-4-methoxylaniline (95 mg, 0.60 mmol, 1.2 equiv) as starting materials. The crude residue was purified by silica gel column chromatography, hexane:EtOAc (3:7), to obtain compound 9h in 94% yield (104 mg, gray solid).

1H NMR ((CD3)2SO, 400 MHz): δ 12.39 (s, 1H, −NH), 9.86 (s, 1H, H7), 8.55 (d, 1H, J = 5.6 Hz, H5), 8.48 (d, 1H, J = 8.5 Hz, H9), 7.91 (d, 1H, J = 5.6 Hz, H7), 7.79 (d, 1H, J = 2.5 Hz, H3), 7.61 (d, 1H, J = 8.5 Hz, H5), 7.59 (d, 1H, J = 8.8 Hz, H7), 7.10 (dd, 1H, J = 8.2, 2.5 Hz, C5), 3.89 (s, 3H,−OCH3). 13C{1H} NMR ((CD3)2SO, 101 MHz): δ 153.8 (C12), 146.4 (C14), 142.6 (C13), 134.7 (C11a), 134.4 (C11b), 133.7 (C10a), 124.6 (C10b), 123.2 (C6a), 121.1 (C5), 118.8 (C3), 116.8 (C10), 116.6 (C1), 114.9 (C10a), 112.3 (C6), 102.2 (C10), 55.6 (−OCH3).

IR νmax (cm⁻¹): 3074 (N–H stretch), 2962 (C–H stretch), 1627 (C=N stretch), 1474 (C=C stretch), 1437 (C=C stretch), 1217 (C–O stretch), 1027 (C–O stretch).

HRMS (ESI) m/z: [M + H]+ calc'd for C14H10N2O2, 249.1022; found, 249.1032.

9-Methoxy-3,6-dihydro-1H-furo[3,4-c]carbazole (9j). The reaction was carried out according to the general procedure A using 8-bromo-1,3-dihydroisobenzofuran (99 mg, 0.50 mmol, 1.0 equiv) and 2-chloro-4-methoxylaniline (95 mg, 0.60 mmol, 1.2 equiv) as starting materials. The crude residue was purified by reverse-phase semi-preparative HPLC over a 5–95% gradient B (solvant A: 0.1% TFA in water, solvent B: 0.1% TFA in acetonitrile) to obtain compound 9j in 10% yield (35 mg, white solid).

1H NMR ((CD3)2SO, 400 MHz): δ 11.15 (s, 1H, −NH), 7.41 (d, 1H, J = 8.8 Hz, H5), 7.38 (d, 1H, J = 8.3 Hz, H3), 7.30 (d, 1H, J = 2.6 Hz, H2'), 7.29 (d, 1H, J = 8.3 Hz, H7), 7.06 (dd, 1H, J = 8.8, 2.6 Hz),
5.52 (t, 2H, J = 2.2 Hz, 2 × H²), 5.14 (t, 2H, J = 2.2 Hz, 2 × H²), 3.84 (s, 3H, −OCH₃). ¹³C(NMR (CD₃)₂SO, 101 MHz): δ 153.1 (C⁴), 140.0 (C⁵), 134.8 (C⁶), 131.5 (C⁷), 128.2 (C⁸), 121.6 (C⁹), 116.0 (C¹⁰), 114.6 (C¹¹), 111.6 (C¹²), 110.0 (C¹³), 104.2 (C¹⁴), 72.8 (C¹⁵), 72.4 (C¹⁶), 55.7 (−OCH₃).

IR (cm⁻¹): 3246 (N−H stretch), 2867 (C−H stretch), 1478 (C=O stretch), 1439 (C=C stretch), 1214 (C−O stretch), 1014 (C−O stretch).

HRMS (ESI) m/z: [M + H⁺]⁺ calculated for C₂₄H₳₂O₪N₂, 520.0975; found, 520.0982.

8-Methyl-7H-pyrido[3,4-c]carbazole (9m).

The reaction was carried out according to the general procedure B using 6-bromoisonicotline (104 mg, 0.50 mmol, 1.0 equiv) and 2-chloro-6-methylamine (85 mg, 0.60 mmol, 1.2 equiv) as starting materials. The crude residue was purified by silica gel column chromatography, DCM:MeOH (10% to 20% MeOH), to obtain compound 9n in 62% yield (72 mg, white solid).

¹H NMR ((CD₃)₂SO, 400 MHz): δ 12.01 (s, 1H, −NH), 9.32 (s, 1H, H¹), 8.63 (d, 1H, J = 5.8 Hz, H²), 8.56 (d, 1H, J = 5.7 Hz, H³), 8.42 (d, 1H, J = 7.2, 1H, H⁴), 8.06 (d, 1H, J = 8.9 Hz, H⁵), 7.91 (d, 1H, J = 8.9 Hz, H⁶), 7.31−7.24 (m, 2H, H⁷), 6.25 (s, 3H, −CH₃). ¹³C(NMR (CD₃)₂SO, 101 MHz): δ 152.2 (C¹), 144.1 (C²), 139.6 (C³), 138.1 (C⁴), 132.0 (C⁵), 125.9 (C⁶), 125.2 (C⁷), 123.9 (C⁸), 122.4 (C⁹), 121.1 (C¹⁰), 132.3 (C¹¹), 119.1 (C¹²), 116.3 (C¹³), 114.9 (C¹⁴), 112.8 (C¹⁵), 17.5 (−CH₃).

HRMS (ESI) m/z: [M + H⁺]⁺ calculated for C₁₃H₁₄N₂, 233.1073; found, 233.1070.

Glycozoline (9n).

Preparation 1. The reaction was carried out according to the general procedure A using 4-bromotoluene (85 mg, 0.50 mmol, 1.0 equiv) and 4-chloro-2-methylaniline (95 mg, 0.60 mmol, 1.2 equiv) as starting materials. The crude residue was purified by silica gel column chromatography, petroleum ether (40−60 °C): EtOAc (100:6), to obtain compound 9n in 36% yield (38 mg, brown crystalline solid).

Preparation 2. The reaction was carried out according to the general procedure A using 4-bromotoluene (85 mg, 0.50 mmol, 1.0 equiv) and 2-chloro-4-methylaniline (95 mg, 0.60 mmol, 1.2 equiv) as starting materials with the addition of PhOCH₃ (15.3 mg, 0.15 mmol, 0.3 equiv). The crude residue was purified by silica gel column chromatography, petroleum ether (40−60 °C): EtOAc (100:6), to obtain compound 9n in 64% yield (66 mg, brown crystalline solid).

¹H NMR ((CD₃)₂SO, 400 MHz): δ 10.85 (s, 1H, −NH), 7.87 (d, 1H, J = 10.3 Hz, H¹), 7.61 (d, 1H, J = 2.5 Hz, H²), 7.34 (d, 1H, J = 8.8 Hz, H³), 7.32 (d, 1H, J = 8.3 Hz, H⁴), 7.16 (d, 1H, J = 8.3, 1.0 Hz, H⁵), 6.98 (d, 1H, J = 8.8, 2.5 Hz, H⁶), 3.83 (s, 3H, −OCH₃), 2.45 (s, 3H, −CH₃). ¹³C(NMR (CD₃)₂SO, 101 MHz): δ 152.8 (C¹), 138.6 (C²), 134.8 (C³), 126.7 (C⁴), 126.5 (C⁵), 125.8 (C⁶), 119.9 (C⁷), 114.5 (C⁸), 111.5 (C⁹), 110.6 (C¹⁰), 102.8 (C¹¹), 55.5 (−OCH₃), 21.0 (−CH₃).

IR (cm⁻¹): 3401 (N−H stretch), 3003 (C−H stretch), 2835 (C−H stretch), 1474 (C=C stretch), 1458 (C=C stretch), 1212 (C−O stretch), 1037 (C−O stretch).

HRMS (ESI) m/z: [M + H⁺]⁺ calculated for C₁₅H₁₄N₄O₂, 212.1070; found, 212.1079.

Harmane (9o).

The reaction was carried out according to the general procedure A using 3-bromo-7-methylpyridine (86 mg, 0.50 mmol, 1.0 equiv) and 2-chloroaniline (77 mg, 0.60 mmol, 1.2 equiv) as starting materials. The crude residue was purified by silica gel column chromatography, EtOAc (100%), to obtain compound 9o in 45% yield (40 mg, pale yellow solid).

¹H NMR ((CD₃)₂SO, 400 MHz): δ 11.53 (s, 1H, NH), 8.20 (d, 1H, J = 5.3 Hz, H¹), 8.18 (d, 1H, J = 8.0 Hz, H²), 7.92 (d, 1H, J = 5.3 Hz, H³), 7.61−7.57 (m, 1H, H⁴), 7.52 (d, 1H, J = 8.3, 7.0, 1.2 Hz, H⁵), 7.22 (d, 1H, J = 8.0, 7.0, 1.2 Hz, H⁶), 2.76 (s, 3H, −CH₃). ¹³C(NMR (CD₃)₂SO, 101 MHz): δ 142.1 (C¹), 140.3 (C²), 137.5 (C³), 134.4 (C⁴), 127.7 (C⁵), 126.8 (C⁶), 121.7 (C⁷), 121.0 (C⁸), 119.1 (C⁹), 112.6 (C¹⁰), 111.9 (C¹¹), 20.4 (−CH₃).

IR (cm⁻¹): 3062 (N−H stretch), 2954 (C−H stretch), 1627 (C=N stretch), 1571 (C=C stretch), 1506 (C=C stretch).

HRMS (ESI) m/z: [M + H⁺]⁺ calculated for C₁₆H₁₈N₂, 283.0917; found, 283.0927.

Murrayafoline A (9p).

The reaction was carried out according to the general procedure A using 2-bromo-5-methylisoulole (101 mg, 0.50 mmol, 1.0 equiv) and 2-chloroisoulole (77 mg, 0.60 mmol, 1.2 equiv) as starting materials with the addition of PhOCH₃ (15.3 mg, 0.15 mmol, 0.3 equiv). The crude residue was purified by silica gel column chromatography, hexane:EtOAc (7:3), to obtain compound 9p in 43% yield (45 mg, brown crystalline solid).
and 2-chloro-4-(2-(dimethylamino)ethoxy)aniline (128 mg, 0.60 mmol, 1.0 equiv) and 2-bromonaphthalene-1,4-dione (119 mg, 0.50 mmol, 1.0 equiv) in 68% yield (94 mg, red solid).

1H NMR ((CD$_3$)$_2$SO, 400 MHz): δ 11.04 (s, 1H, –NH), 7.67 (d, 1H, J = 2.4 Hz, H$^7$), 7.46 (d, 1H, J = 8.7 Hz, H$^6$), 7.12 (dd, 1H, J = 8.7, 2.4 Hz, H$^5$), 7.06 (d, 1H, J = 7.2 Hz, H$^4$), 6.82 (d, 1H, J = 7.2 Hz, H$^3$), 4.40 (t, 2H, J = 5.1 Hz, H$^2$), 3.44 (t, 2H, J = 5.1 Hz, H$^1$), 2.82 (s, 3H, –N(CH$_3$)$_2$), 2.50 (s, 3H, C$_6$H$_3$–CH$_3$). 13C{1H} NMR ((CD$_3$)$_2$SO, 101 MHz): δ 151.1 (C$^1$), 139.8 (C$^2$), 135.2 (C$^3$), 129.6 (C$^4$), 125.8 (C$^5$), 120.3 (C$^6$), 119.6 (C$^7$), 117.5 (C$^8$), 114.1 (C$^{11}$), 111.4 (C$^{12}$), 107.0 (C$^{13}$), 63.7 (C$^4$), 56.0 (C$^3$), 41.2 ((–N(CH$_3$)$_2$), 20.2 (C$_6$H$_3$–CH$_3$), 16.7 (C$_6$H$_3$–CH$_3$).

IR $v_{max}$ (cm$^{-1}$): 3857 (N–H stretch), 2925 (C–H stretch), 1523 (C=C stretch), 1465 (C=C stretch), 1057 (C=C stretch). HRMS (ESI) m/z: [M + H]$^+$ calc'd for C$_{19}$H$_{16}$N$_2$O$_2$, 313.1220; found, 313.1221.

5H-Benzob[c]carbazole-6,11-dione (21a). The reaction was carried out according to the general procedure A using 2-bromonaphthalene-1,4-dione (119 mg, 0.50 mmol, 1.0 equiv) and 5-chloro-2-methoxyaniline (95 mg, 0.60 mmol, 1.2 equiv) as starting materials. The crude residue was purified by silica gel column chromatography, petroleum ether (40–60 °C):EtOAc:NEt$_3$ (100:2:4), to obtain compound 21a in 35% yield (54 mg, orange solid).

1H NMR ((CD$_3$)$_2$SO, 400 MHz): δ 13.44 (s, 1H, –NH), 8.49–8.45 (m, 1H, H$^7$), 8.16–8.08 (m, 2H, H$^{10}$), 7.91–7.81 (m, 2H, H$^8$), 7.70–7.61 (m, 2H, H$^5$). 13C{1H} NMR ((CD$_3$)$_2$SO, 101 MHz): δ 180.3 (C$^1$), 177.5 (C$^2$), 139.5 (C$^3$), 139.0 (C$^4$), 134.5 (C$^5$), 133.8 (C$^6$), 133.5 (C$^7$), 132.3 (C$^8$), 126.2 (C$^{11}$), 126.2 (C$^{12}$), 124.7 (q, J = 3.4 Hz, C$^9$), 119.6 (q, J = 4.3 Hz, C$^1$), 117.6 (C$^{11}$), 111.5 (C$^{12}$). 19F NMR ((CD$_3$)$_2$SO, 376 MHz): δ −59.7.

IR $v_{max}$ (cm$^{-1}$): 3234 (N–H stretch), 1655 (C=O stretch), 1631 (C=O stretch), 1586 (C=C stretch), 1541 (C=C stretch). HRMS (ESI) m/z: [M + H]$^+$ calc'd for C$_{19}$H$_{15}$F$_3$NO$_3$, 368.0580; found, 368.0585.

2-Methyl-5H-benzo[b]carbazole-6,11-dione (21b). The reaction was carried out according to the general procedure A using 2-bromonaphthalene-1,4-dione (119 mg, 0.50 mmol, 1.0 equiv) and 5-fluoro-2-chloroaniline (87 mg, 0.60 mmol, 1.2 equiv) as starting materials. The crude residue was purified by silica gel column chromatography, petroleum ether (40–60 °C):EtOAc:NtB (10:1:1), to obtain compound 21b in 68% yield (94 mg, red solid).

1H NMR ((CD$_3$)$_2$SO, 400 MHz): δ 12.89 (s, 1H, –NH), 8.11–8.03 (m, 3H, H$^7$–H$^{10}$), 7.87–7.76 (m, 2H, H$^8$), 7.00 (dd, 1H, J = 8.8, 2.0 Hz, H$^9$), 6.98 (d, 1H, J = 2.0 Hz, H$^9$), 3.85 (s, 3H, –OCH$_3$). 13C{1H} NMR ((CD$_3$)$_2$SO, 101 MHz): δ 180.5 (C$^1$), 176.8 (C$^2$), 159.4 (C$^3$), 139.8 (C$^4$), 136.4 (C$^5$), 134.0 (C$^6$), 133.9 (C$^7$), 133.2 (C$^8$), 127.2 (C$^{11}$), 126.0 (C$^{12}$), 125.9 (C$^{13}$), 123.2 (C$^{14}$), 118.0 (C$^{11}$), 117.9 (C$^{12}$), 95.1 (C$^9$), 55.4 (–OCH$_3$).

IR $v_{max}$ (cm$^{-1}$): 3189 (N–H stretch), 2927 (C–H stretch), 1664 (C=O stretch), 1629 (C=O stretch), 1532 (C=C stretch). HRMS (ESI) m/z: [M + H]$^+$ calc'd for C$_{19}$H$_{15}$F$_3$NO$_3$, 378.0812; found, 378.0809.

2-Methyl-5H-benzo[b]carbazole-6,11-dione (21c). The reaction was carried out according to the general procedure A using 2-bromonaphthalene-1,4-dione (119 mg, 0.50 mmol, 1.0 equiv) and 5-fluoro-2-chloroaniline (87 mg, 0.60 mmol, 1.2 equiv) as starting materials. The crude residue was purified by silica gel column chromatography, petroleum ether (40–60 °C):EtOAc:NtB (100:2:4), to obtain compound 21c in 58% yield (76 mg, orange solid).

1H NMR ((CD$_3$)$_2$SO, 400 MHz): δ 13.12 (s, 1H, –NH), 8.19 (dd, 1H, J = 8.8, 5.5 Hz, H$^9$), 8.11–8.05 (m, 2H, H$^{10}$), 7.87 (m, 2H, H$^8$), 7.50 (d, 1H, J = 5.5 Hz, H$^7$), 7.31 (d, 1H, J = 5.5 Hz, H$^6$), 7.09 (dd, 1H, J = 8.8, 2.0 Hz, H$^5$), 6.82 (d, 1H, J = 1.1 Hz, H$^2$), 3.96 (s, 3H, –OCH$_3$), 2.46 (s, 3H, –CH$_3$). 13C NMR (CD$_3$COCD$_3$, 101 MHz): δ 180.2 (C$^1$), 177.2 (C$^2$), 157.0 (C$^3$), 137.0 (C$^4$), 134.2 (C$^{10}$), 133.4 (C$^5$), 133.1 (C$^6$), 132.7 (C$^7$), 126.0 (C$^{11}$), 124.8 (C$^{12}$), 118.4 (C$^8$), 117.0 (C$^{13}$), 115.0 (C$^9$), 102.1 (C$^{14}$), 55.4 (–OCH$_3$).
2-Methody-5-(4-methoxybenzyl)-5H-benzo[b]carbazole-6,11-dione (24). 2-Methody-5H-benzo[b]carbazole-6,11-dione (21b) (74 mg, 0.27 mmol, 1.0 equiv) was stirred in anhydrous DMF (8 mL) and cooled to 0 °C in an ice bath. NaN₃ (16 mg, 0.06 mmol, 2.4 equiv) was added and stirred for 1 h. Next, benzyl bromide (0.078 mL, 0.66 mmol, 2.4 equiv) was added and the reaction was stirred for 2 h at rt. The reaction mixture was diluted with EtOAc, washed with water and a saturated ammonium chloride aqueous solution. The product was extracted three times with EtOAc. The combined organic phases were dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude was purified by silica gel column chromatography (methanol ether (40–60 °C):EtOAc (10:1)) to afford the desired compound 24 in 83% yield (81 mg, orange solid).

The reaction mixture was stirred at 80 °C for 3 h. Next, the reaction was quenched with water and extracted with CHCl₃. The combined organic phases were washed with water and dried over Na₂SO₄. The filtrate was concentrated in vacuo and purified by silica gel flash column chromatography (methanol ether (40–60 °C):EtOAc (10:1)) to afford the desired compound 25 in 88% yield (111 mg, yellow solid).

HRMS (ESI +ve mode): m/z = 259.0342 (25) [M + H⁺] calc for C₂₀H₁₅N₂O₃: 259.0339.

2-Methody-6,11-dimethyl-5H-benzo[b]carbazole (26). The N-debenzylation protocol was based on a literature procedure.⁵-⁶ Benzyl-2-methody-6,11-dimethyl-5H-benzo[b]carbazole (25) (10 mg, 0.027 mmol, 1 equiv) was dissolved in DMSO (0.5 mL) and added to a flame-dried vial. While stirring the solution at room temperature, KO'Bu (21 mg, 0.19 mmol, 7 equiv) in THF (0.5 mL) was added. An oxygen balloon was then bubbled into the solution for 30 min. After stirring at room temperature for 5 h, the reaction was quenched with a saturated ammonium chloride aqueous solution. The product was extracted three times with EtOAc. The combined organic phases were dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude was purified by silica gel column chromatography using hexane:EtOAc (7:3) to afford the desired compound 26 in 61% yield (4.5 mg, yellow solid). Characterization of 26 is in agreement with that previously described in the literature.⁶

HRMS (ESI +ve mode): m/z = 271.1761 (26) [M + H⁺] calc for C₁₉H₁₇NO₂: 271.1769.
The precipitate was washed with cold Et2O and then recrystallized from precipitate, and the reaction was heated to 120 °C for a further 24 h. The reaction was cooled, and the precipitate was isolated by filtration. The precipitate was washed with cold Et2O and then recrystallized from hot EtOH five times to isolate 29 in 33% yield (52 mg, yellow solid).

¹H NMR ((CD₃)₂SO, 400 MHz): δ 12.69 (s, 2H, NH), 11.63 (s, 2H, NH), 10.51 (s (br), 2H, H°), 9.00–8.78 (s (br), 2H, H°), 8.77–8.67 (d, 2H, J = 5.8 Hz, H°), 8.49 (d, 2H, J = 8.8 Hz, H°), 8.45–8.29 (s (br), 2H, H°), 8.25 (d, 2H, J = 8.9 Hz, H°), 7.75 (d, 2H, J = 8.9 Hz, H°), 7.31 (dd, 2H, J = 9.0, 2.2 Hz, H°), 5.71–5.26 (m, 4H, H°), 4.03, 4.00–3.77 (m, 4H, H°), 3.73–3.50 (m, 4H, 4 × H°); 3.11–2.91 (m, 4H, 4 × H°); 2.06–1.51 (m, 8H, 4 × H° and 4 × H°); 1.48–1.29 (m, 2H, H°). C¹¹(C) NMR ((CD₃)₂SO, 101 MHz): δ 154.7 (C°), 143.7 (C°), 139.4 (C°), 134.4 (C°), 133.6 (C°), 132.6 (C°), 126.4 (C°), 124.8 (C°), 124.3 (C°), 123.6 (C₁₁), 121.3 (C₁₁'), 116.3 (C°), 114.1 (C₁₁), 113.4 (C°), 105.7 (C°), 56.4 (O–CH₃), 55.3 (C°), 54.3 (C°), 52.6 (2 × C°), 37.3 (2 × C°), 25.8 (2 × C°)...

IR νmax (cm⁻¹): 3342 (N–H stretch), 2927 (C–H stretch), 1616 (C=C stretch), 1472 (C=C stretch), 1402 (C=C stretch), 1214 (C=O stretch), 1031 (C=O stretch).

HRMS (ESI) m/z: [M⁺] calc'd for C₉₈H₇₈O₄N₉₂, 539.1992; found, 539.1991.

ASSOCIATED CONTENT

Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c02943.

Experimental procedures, characterization data, the ¹H and ¹³C NMR spectra for new compounds, DFT calculations, and crystallographic data (PDF)

Accession Codes
CCDC 2102053 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Author
Glenn A. Burley — Department of Pure Applied Chemistry, University of Strathclyde, Glasgow G1 1XL, U.K.; orcid.org/0000-0002-4896-113X; Email: glenn.burley@strath.ac.uk

Authors
Emma Campbell — Department of Pure Applied Chemistry, University of Strathclyde, Glasgow G1 1XL, U.K.
Andrea Taladriz-Sender — Department of Pure Applied Chemistry, University of Strathclyde, Glasgow G1 1XL, U.K.; orcid.org/0000-0002-8274-4761
Olivia I. Paisley — Department of Pure Applied Chemistry, University of Strathclyde, Glasgow G1 1XL, U.K.
Alan R. Kennedy — Department of Pure Applied Chemistry, University of Strathclyde, Glasgow G1 1XL, U.K.; orcid.org/0000-0003-3652-6015

Jacob T. Bush — GlaxoSmithKline, Medicines Research Centre, Hertfordshire SG1 2NY, U.K.; orcid.org/0000-0001-7165-0092

Complete contact information is available at: https://pubs.acs.org/doi/10.1021/acs.joc.1c02943

Author Contributions
E.C. and A.T.S. contributed equally. Conceptualization was done by G.A.B., E.C., A.T.S. and O.I.P.; methodology was performed by E.C., O.I.P., A.T.S, and J.B.; validation was done by E.C. and A.T.S.; formal analysis was done by E.C. and A.T.S.; and manuscript preparation was done by E.C., A.T.S., and G.A.B.

Notes
The authors declare no competing financial interest. All data underpinning this publication are openly available from the University of Strathclyde KnowledgeBase at https://doi.org/10.15129/f45b6f45-b8f7-435a-b5a3-097e3f7397c.

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