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Graphical Abstract

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Substrate scope in the direct imine acylation of *ortho*-subtituted benzoic acid derivatives: The total synthesis (±)-cavidine

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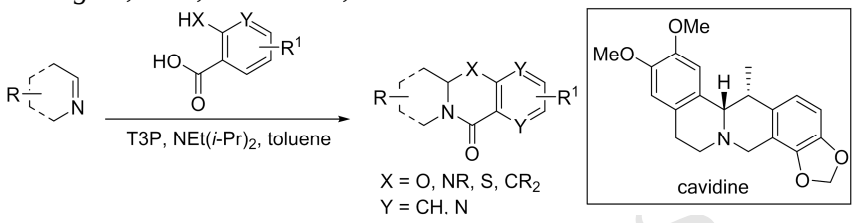
Christiana Kitsiou, William P. Unsworth, Graeme Coulthard and Richard J. K. Taylor*
University of York, Heslington, York, YO10 5DD, UK



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Substrate scope in the Direct Imine Acylation of *ortho*-substituted benzoic acid derivatives: The total synthesis (±)-cavidine

Christiana Kitsiou, William P. Unsworth, Graeme Coulthard and Richard J. K. Taylor*†

University of York, Heslington, York, YO10 5DD, UK

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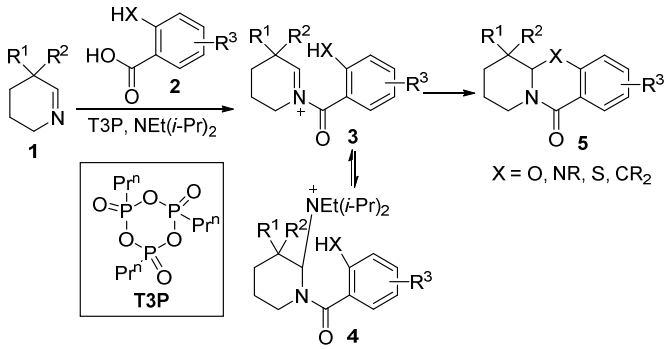
ABSTRACT

The direct imine acylation (DIA) and subsequent cyclisation of a range of imines with *ortho*-substituted benzoic acid derivatives is described. Variation in the coupling reagents, imine and benzoic acid were all examined. The DIA procedure was also applied in the total synthesis of (±)-cavidine.

1. Introduction

The controlled synthesis of diverse heterocycles is crucial in both the pharmaceutical and agrochemical industries.[1] Novel methods that expedite their synthesis are therefore of great importance, especially those which furnish a range of diverse scaffolds whose biological activity has not previously been well-examined. Such diversity-oriented-synthesis[2] has attracted widespread interest in recent years as a strategy to accelerate the discovery of new therapeutically important compounds.

In order for these methods to be widely adopted by the synthetic community, both in industry and in academia, various conditions must be satisfied: the new methods must be reliable, operationally simple, high yielding and crucially be capable of generating a broad range of structures without significant optimisation. Our research group recently reported one such method, based on the concept of 'Direct Imine Acylation' (DIA).[3] This methodology centres on a novel way to generate *N*-acyliminium ions and their subsequent reaction with tethered nucleophiles. The initial communication focused on the direct coupling of a range of imines (**1**) with *ortho*-substituted benzoic acids (**2**) using propylphosphonic acid anhydride (T3P)[4] and NEt(*i*-Pr)$_2$ (DIPEA) to activate the benzoic acid towards nucleophilic attack by the imine nitrogen to form the key *N*-acyliminium ion **3** (Scheme 1). An accompanying mechanistic study, in which the progress of the reaction was monitored *in situ* by IR spectroscopy using ReactIR™, shed further light on the process. It is proposed that the *N*-acyliminium **3** exists only briefly and is trapped by excess DIPEA in the reaction mixture, affording ammonium salt **4**. This process is reversible and so the extrusion of DIPEA results in the regeneration of the *N*-acyliminium ion **3**, which is subsequently trapped by the *ortho*-nucleophile in a one-pot process, driving the equilibrium towards the formation of the desired heterocyclic product **5**.



Scheme 1. Direct Imine Acylation

Diversity was initially examined both in terms of the imine **1** and the benzoic acid derivative **2**. Most notably, the methodology was shown to be compatible with phenols, anilines, thiols and carbon pro-nucleophiles as the *ortho*-substituent on the benzoic acid (**2**, X = O, NMe, S, CH(CO$_2$Me)$_2$). Furthermore, we more recently disclosed preliminary results which demonstrate that DIA is also compatible with aliphatic carboxylic acids.[5] Protected aliphatic alcohols, protected amines, thiols and a range of carbon pro-nucleophiles can also be tethered to the carboxylic acid and react with the *N*-acyliminium ion using broadly similar conditions to those described above, dramatically increasing the range of heterocyclic scaffolds accessible. DIA has also been used in target synthesis; the total synthesis of evodiamine **6**[3,6] was

completed in high yield (95%, see later) and DIA methodology was also used to construct the spirooxoquinolizidinone ring system of the proposed structures of the complex marine natural product 'upenamide **7** (Figure 1).[7]

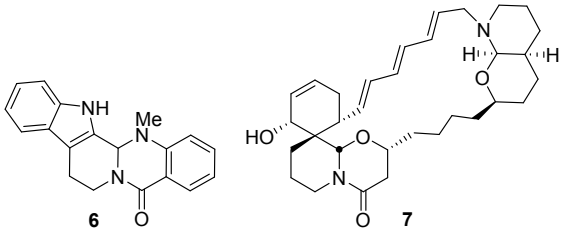


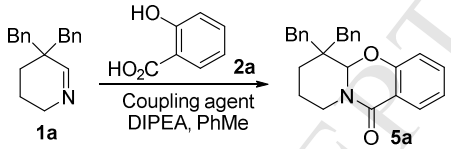
Figure 1 The structure of evodiamine **6** and one of the proposed structures of 'upenamide **7**.

Herein we report extended substrate scoping studies for DIA using benzoic acid derivatives. We also describe the application of DIA in the total synthesis the natural product (±)-cavidine.

2. Results and Discussion

In our initial communication, all of the DIA reactions reported were performed by simply mixing the imine, carboxylic acid, T3P and DIPEA in toluene and heating to 90 °C in most cases, or 120 °C if t.l.c. analysis indicated that the reaction was incomplete after 20 h. All of the reagents were used as supplied, without drying or purification, and it was not necessary to exclude air from the reaction. We have since discovered that both CDI and DCC may be used in place of T3P in the reaction of imine **1a** with salicylic acid **2a** (Table 1, entries 1–3). The same reaction was also tested using EDC as the coupling reagent but this failed, most likely because of the poor solubility of EDC in toluene. Thus, the highest yield was obtained using our original T3P conditions, but it is important to note that other coupling reagents can also be used, in cases where T3P is either unavailable or unsuitable.

Table 1. Alternative coupling reagents[a]



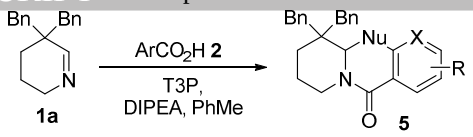
entry	coupling agent	yield[b]
1	T3P	83%
2	CDI	52%
3	DCC	77%
4	EDC	0%

[a] Unless stated, reactions were performed on a 0.1–0.3 mmol scale using imine **1a** (1 equiv.), salicylic acid **2a** (1.2 equiv.), coupling reagent (1.5 equiv.), DIPEA (1.85 equiv.) in PhMe at 90 ºC for 20 h.

[b] Isolated yields after purification by column chromatography.

The scope of the T3P-meditated DIA conditions described above (Table 1, entry 1) was first tested with regard to the acid coupling partner **2** (Table 2). Note that examples reported in our prior communication are indicated with an asterisk and that the majority of the new examples led to the formation of novel compounds.

Table 2. Benzoic acid scope in DIA with imine **1a**[a]



entry	acylating agent	product	yield[b]
1	**2a** R = H	**5a** R = H	83%*[c,d]
2	**2b** R = 3-NO_2	**5b** R = 3-NO_2	89%
3	**2c** R = 5-NO_2	**5c** R = 5-NO_2	91%*
4	**2c**	**5c**	90%*[e]
5	**2d** R = 5-Cl	**5d** R = 5-Cl	96%
6	**2e** R = 4-OMe	**5e** R = 4-OMe	82%[f]
7	**2f** R = 5-OMe	**5f** R = 5-OMe	60%
8	**2g** R = 6-OMe	**5g** R = 6-OMe	64%[f]
9	**2h** R = 4,6-OH	**5h** R = 4,6-OH	60%
10	**2i**	**5i**	95%*
11	**2j**	**5j**	92%*
12	**2k**	**5k**	97%*
13	**2l**	**5l**	63%
14	**2m**	**5m**	96%*[g]
15	**2n** R = Me	**5n** R = Me	97%*[c]
16	**2o** R = Ph	**5o** R = Ph	95%
17	**2p** E = CO_2Me	**5p** E = CO_2Me	84%*[c]

[a] Unless stated, reactions were performed on a 0.1–0.3 mmol scale using imine **1a** (1 equiv.), benzoic acid **2a-p** (1.2 equiv.), T3P (1.5 equiv.), DIPEA (1.85 equiv.) in PhMe at 90 ºC for 20 h.

[b] Isolated yields after purification by column chromatography.

[c] Reaction performed in the absence of T3P gave 0% yield of product.

[d] Reaction performed in the absence of DIPEA gave 0% yield of product.

[e] Reaction performed on a 3 mmol scale under the standard conditions.

[f] Reaction performed at 120 ºC for 20 h.

[g] Reaction performed in the absence of T3P gave 20% yield of product.

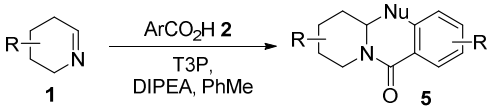
*entries highlighted with an asterisk were reported in the earlier communication (see reference 3).

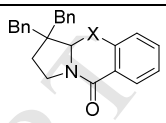
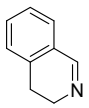
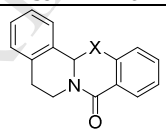
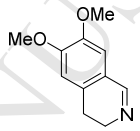
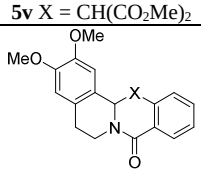
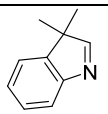
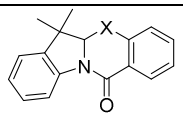
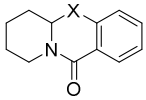
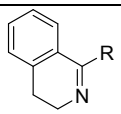
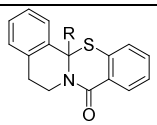
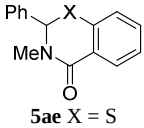
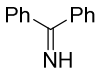
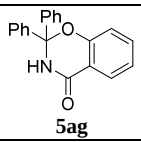
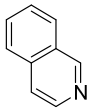
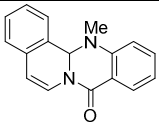
Imine **1a** was reacted with a wide range of salicylic acid derivatives **2a–2h**[3] using the standard DIA procedure, affording *N*,*O*-acetals **5a–5h** in good to excellent yields (Table 2, entries 1–9). All of these reactions were performed using the same conditions with the exceptions of entries 6 and 8; in both of these cases a higher reaction temperature (120 °C) was required in order to achieve full conversion into the respective products **5e** and **5g**. The initial *N*-acylation appears to be significantly slower in these two examples, which is unsurprising as the activated carboxylic acid is presumably less electrophilic than the other systems tested as a result of the presence and position of the electron-rich methoxy groups. Naphthalene and pyridine derivatives **2i–2l** are also well tolerated, affording products **5i–5l** again in good to excellent yields (entries 10–13). Clearly, *ortho*-hydroxy aromatics are excellent substrates, but the real strength of the DIA procedure is its versatility, which is demonstrated by the similarly efficient reactions of thiosalicylic acid **2m** and anthranilic acids **2n** and **2o** (entries 14–16). Perhaps most impressively, diester **2p** also takes part in DIA, demonstrating that C–C bond formation can also be achieved in very good yield (entry 17). Crucially, all of these examples were performed using the standard reaction conditions and are unoptimised, highlighting the operational simplicity of the process and its significant potential for the rapid synthesis of diverse compound libraries for biological screening.

The substrate scope with respect to the imine component was next examined (Table 3). The requisite imines **1a–1k** were either generated as described in our previous reports, were available commercially or were made via literature methods.[3,5,8,9] The basic procedure is clearly very broad in scope, with a range of imines compatible; DIA reactions using imines **1b–1e** and benzoic acids derivatives bearing *O*-, *S*-, *N*- and *C*-nucleophiles were tested, affording a diverse range of products in moderate to excellent yields (Table 3, entries 1–10). The yields for some of these reactions are lower than for those using imine **1a**, but it is important to recognise that all of these reactions are unoptimised and the only change made to the reaction conditions was to increase the temperature to 120 °C if t.l.c. analysis showed that the reaction was incomplete under the standard conditions (90 °C). We believe that the comparative stabilities of the products may partially explain this variability in yield. For example, the DIA of 3,4-dihydroisoquinoline **1c** and acid **2a** proceeded in high yield but the analogous reaction with the dimethoxy imine **1d** proceeded in lower yield (entries 4 and 7), which may be explained by the increased propensity for the product **5w** to ring-open (and thus regenerate the intermediate *N*-acyliminium ion) as a result of the two electron-donating groups. Greater reversibility in the cyclisation step would not only lead to an increased reaction time, but may also lead to hydrolysis of the product during aqueous work-up and during column chromatography. Nonetheless, significant quantities of material were isolated in all cases and indeed some of the yields (*e.g.* entries 2–5, 8) were excellent and comparable with those reported in Table 2.

The coupling of imine **1f** was examined next. This imine, which exists primarily in its trimeric form dodecahydro-4a,8a,12a-triazatriphenylene,[9] is known to oligomerise and so must be generated *in situ*. Nevertheless, it reacted with acids **2m** and **2n** under the standard DIA conditions to form products **5aa** and **5ab**, albeit in moderate yield (entries 11 and 12). Note that none of the imine systems **1a–1e** can tautomerise to enamines and it is significant that this comparatively unstable imine is also compatible with the standard DIA procedure.

Table 3. Imine scope in DIA with benzoic acid derivatives[a]



entry	imine	acid	product	yield[b]
1	 **1b**	**2a**	 **5q** X = O	48%[c]
2	**1b**	**2m**	**5r** X = S	99%
3	**1b**	**2n**	**5s** X = NMe	87%*
4	 **1c**	**2a**	 **5t** X = O	89%*[c]
5	**1c**	**2m**	**5u** X = S	97%[c]
6	**1c**	**2p**	**5v** X = $CH(CO_2Me)_2$	69%*[c]
7	 **1d**	**2a**	 **5w** X = O	48%
8	**1d**	**2n**	**5x** X = NMe	87%
9	 **1e**	**2m**	 **5y** X = S	53%
10	**1e**	**2n**	**5z** X = NMe	41%
11	 **1f**[d]	**2m**	 **5aa** X = S	31%
12	**1f**	**2n**	**5ab** X = NMe	40%*
13	 **1g** R = Me	**2m**	 **5ac** R = Me	80%[c]
14	**1h** R = Ph	**2m**	**5ad** R = Ph	0%
15	 **1i**	**2m**	 **5ae** X = S	99%*
16	**1i**	**2o**	**5af** X = NPh	68%
17	 **1j**	**2a**	 **5ag**	60%*[c]
18	 **1k**	**2n**	 **5ah**	94%*

[a] Unless stated, reactions were performed on a 0.1–0.3 mmol scale using imines **1b–1k** (1 equiv.), benzoic acid **2a–2p** (1.2 equiv.), T3P (1.5 equiv.), DIPEA (1.85 equiv.) in PhMe at 90 ºC for 20 h.

[b] Isolated yields after purification by column chromatography

[c] Reaction performed at 120 ºC for 20 h.

[d] Imine **1f** was generated by de-oligomerisation of dodecahydro-4a,8a,12a-triazatriphenylene *in situ*.

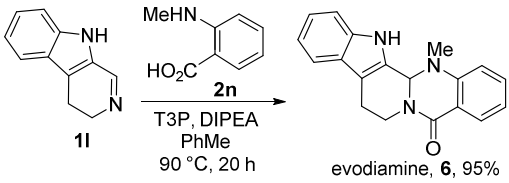
*entries highlighted with an asterisk were reported previously (see reference 3).

Ketimine **1g** (which also is able to tautomerise to an enamine) is compatible with DIA, reacting with thiosalicylic acid **2m**, generating product **5ac** in good yield (entry 13). However, the analogous reactions using benzoic acids substituted with *O*-, *N*- and *C*-nucleophiles (**2a**, **2n**, and **2p**, not shown in the table) did not furnish the expected products. Instead, *C*-acylation took place preferentially (presumably via the enamine tautomer of the imine), resulting in the predominant formation of *Z*-enaminones.[10] The analogous reaction with phenyl substituted ketimine **1h** (which cannot undergo such *C*-acylation) was also screened but this imine did not react at all with thiosalicylic acid **2m** (entry 14) or indeed with any of the benzoic acid derivatives **2a**, **2n** or **2p** (not shown in the table). This result is in line with previous studies which also found that ketimines fail to undergo DIA with carboxylic acids bearing *O*-, *N*- or *C*-nucleophiles and this is most likely because the increased steric hindrance around the imine inhibits the requisite *N*-acylation reaction. The contrasting reactivity of thiosalicylic acid **2m** has intriguing mechanistic implications and is consistent with our previous work. Of the two successful DIA-type reactions of ketimines that were reported previously,[7] both involved thiol-substituted carboxylic acids, indicating that an alternative mechanism most likely operates. Thus, it seems likely that in sulfur-containing systems the nucleophilic thiol moiety attacks the imine carbon first, before intramolecular *N*-acylation takes place.[7] Additional support for this mechanism is found in the fact that partial product formation (20 % yield) was observed in a related example even in the absence of T3P (Table 1, entry 14).

A significant advantage to DIA is its ability to generate acyclic *N*-acyliminium ions, which are far less stable than their cyclic analogues, particularly with respect to hydrolysis.[11] This means that *N*-acyliminium ion precursors are difficult to prepare and handle, but DIA technology overcomes this by forming the unstable *N*-acyliminium ions *in situ*, and trapping them in one pot. This is exemplified by the formation of DIA products **5ae–5ag** in good to excellent yields from commercially available acylic imines **1i** and **1j** (entries 15–17). Note also that imine **1j** is a ketimine; *N*-substituted ketimines has so far proven to be incompatible with DIA but pleasingly this substituted ketimine furnished *N,O*-acetal **5ag** in good yield under standard DIA conditions at 120 °C (entry 17).

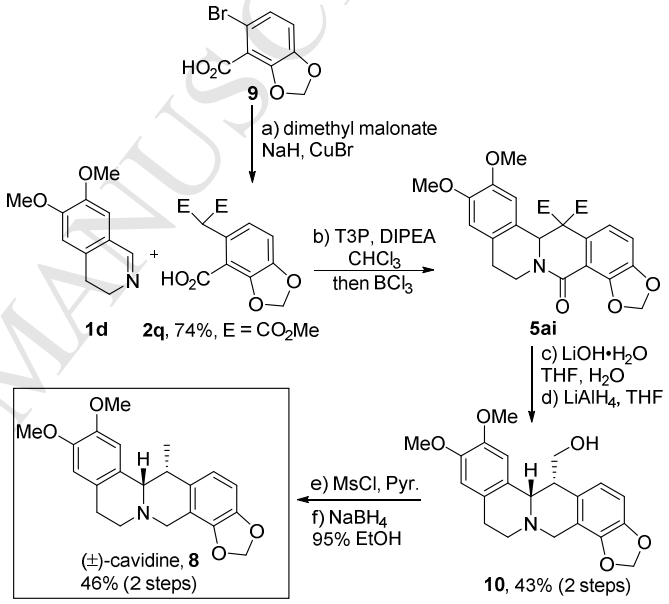
The high yielding DIA reaction of isoquinoline **1k** with anthranilic acid **2n** is significant given that it proceeded despite the loss of aromaticity (entry 18). Unfortunately, this dearomatising DIA reaction appears not to be general; the analogous reactions of isoquinoline **1k** with acids **2a**, **2m**, and **2p** under identical conditions all failed to furnish any product. Other aromatic heterocycles containing C=N bonds (quinolone, pyridine, DMAP, pyrimidine, pyrazine, oxazole, thiazole, *N*-Boc imidazole and 1,3,5-triazine) were also examined under DIA conditions at 120 °C with anthranilic acid **2n** but no products were isolated in any case. Note that similar dearomatising reactions of isoquinolines have been reported,[12] and that the degree of aromaticity in the precursor is likely to crucial in the outcome of these reactions.

Finally, the formation of the natural product evodiamine **6** from dihydrocarboline **1l** and anthranilic acid **2n** is a particularly noteworthy example (Scheme 2). Evodiamine is a key component in various weight-loss supplements and also is known to inhibit DNA topoisomerase I.[13] Its synthesis in 95% yield from two easily available coupling partners highlights well the potential of DIA in target synthesis.



Scheme 2 The total synthesis of evodiamine **6**

Additional biologically important targets are also being pursued, *e.g.* cavidine **8**, a member of a large family of alkaloids known as protoberberines[14] with extremely broad biological activity.[15] Cavidine was first isolated from a *Corydalis* plant in 1964 by Taguchi[16] and its structure was later assigned by Manske.[17] Its synthesis has been completed previously,[18] but nonetheless, we considered that DIA methodology would expedite an efficient convergent synthesis (Scheme 3).



Scheme 3 The total synthesis of (±)-cavidine **8**

To begin, commercially available bromide **9** was converted into the novel dimethyl malonate derivative **2q** via a known method based on the Hurtley reaction.[19] Acid **2q** was then reacted with imine **1d** using our standard DIA coupling conditions. We were pleased that the DIA was successful on this more complex system, furnishing lactam **5ai** in moderate yield (39%). Previous studies in our group have shown that, in some cases, the addition of Lewis acids to the crude reaction mixture following *N*-acylation can lead to improved yields,[5] and therefore additional optimisation reactions were performed. The most common additive used in the DIA reactions reported to date is $BF_3 \cdot OEt_2$, but on this system it did not improve the isolated yield of product **5ai** (36%). However, by switching the additive to BCl_3 (2 equivalents) allowed product **5ai** to be obtained in 69% yield at RT in chloroform.[20] Importantly, the work-up for this reaction was straightforward and this result is easily reproducible. It is also noteworthy that no competing demethylation products were observed.

The synthesis was then completed using an approach based on that in Cushman's route.[18c] Ester hydrolysis and decarboxylation using LiOH in aqueous THF followed by reduction with $LiAlH_4$, afforded alcohol **10** as a single diastereoisomer following column

chromatography. Mesylation, followed by deoxygenation with $NaBH_4$ in refluxing ethanol[21] then completed the synthesis, affording (±)-cavidine **8**, the spectral data of which were in full accord with those previously reported (Scheme 3).[14j-k, 18c]

Conclusion

A detailed substrate scoping study of the DIA reactions of a range of imines and *ortho*-substituted benzoic acids has been completed. The reaction has been shown to be very broad in scope, proceeds under operationally simple conditions and generally affords the desired product in good to excellent yield without optimisation of the reaction conditions. This should result in DIA being used for the construction of diverse compound libraries for biological evaluation. The total synthesis of (±)-cavidine was also completed; in this instance the DIA was low yielding under the standard conditions, but could be improved significantly by using a Lewis acid additive. The fact that the coupling reagents (T3P and DIPEA) are compatible with Lewis acid additives is significant as this allows such one-pot optimisation processes to be performed easily. The success of this example also augurs well for the similar optimisation of other DIA reactions (especially the lower yielding cases) further expanding its wide scope. This in turn is expected to lead to DIA being widely used in the synthesis of other biologically important natural product/drug targets.

3. Experimental section

Except where stated, all reagents were purchased from commercial sources and used without further purification. Anhydrous dichloromethane and toluene were obtained from an Innovative Technology Pure Solv solvent purification system. Anhydrous THF was obtained by distillation over sodium benzophenone ketyl immediately before use. Flash column chromatography was carried out using slurry packed silica gel (SiO_2), 35–70 μm, 60 Å, under light positive pressure eluting with the specified solvent system. Thin layer chromatography (TLC) was carried out on Merck silica gel $60F_{254}$ pre-coated aluminium foil sheets and were visualised using UV light (254 nm) and stained with either basic aqueous potassium permanganate or ethanolic p- anisaldehyde as appropriate. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Jeol ECX-400 NMR or Jeol ECS400 spectrometer operating 400 MHz and 100 MHz, respectively, or on a Bruker DRX500 spectrometer, operating at 500 MHz and 125 MHz, respectively. All spectra was acquired at 295 K. Chemical shifts (δ) are quoted in parts per million (ppm). The multiplicity abbreviations used are: s, singlet; d, doublet; t, triplet; q, quartet; multiplet; br, broad or combinations of these. Signal assignment was achieved by analysis of DEPT, COSY, NOESY, HMBC and HSQC experiments where required. The residual solvent peaks, δ_H 7.26 and δ_C 77.0 for $CDCl_3$ were used as references. Infrared spectra (IR) were recorded on a ThermoNicolet IR-100 spectrometer with NaCl plates as a thin film dispersed from either CH_2Cl_2 or $CDCl_3$. High Resolution Mass Spectra (HRMS) were obtained by University of York Mass spectrometer Service, using ionisation (ESI) on a Bruker Daltonics, MicrOTOF spectrometer. Melting points were measured on a Gallenkamp melting point apparatus and are uncorrected. Compounds **1i-k**, **2a-o** were all purchased from Sigma-Aldrich and used as supplied. Compounds **1a**[3], **1b**[3], **1c**,[8a] **1d**,[8b] **1e**,[8c] **1f**,[9] **1g**,[8d] **1h**,[8e] **1l**,[8f] **2p**,[3,22] **5a**,[3] **5c**,[3] **5d**,[3] **5i–k**,[3] **5m**,[3] **5n**,[3] **5p**,[3] **5s**,[3] **5t**,[3] **5v**,[3] **5ab**,[3] **5ae**,[3] **5ag**,[3] **5ah**,[3] **6**[3] were prepared using literature procedures.

3.1 General procedure for the DIA reaction

To a solution of imine (1 mmol) and acid (1.2 mmol) in dry toluene (10 mL) was added sequentially DIPEA (1.85 mmol) and then T3P (1.5 mmol, 50% in THF). The resulting solution was heated at 90 °C or 120 °C in a sealable tube for the specified time, before cooling to RT and pouring into sat. aq. $NaHCO_3$ (20 mL). The aqueous layer was extracted with DCM (3 × 30 mL), concentrated *in vacuo* and purified by column chromatography.

*6,6-Dibenzyl-4-nitro-6,7,8,9-tetrahydro-5aH,11H-pyrido[2,1-b][1,3]benzoxazin-11-one (**5b**).* Synthesised using the general DIA procedure from imine **1a** (56.1 mg, 0.213 mmol), acid **2b** (46.9 mg, 0.256 mmol), DIPEA (68.6 μL, 0.394 mmol) and T3P (204 mg, 0.320 mmol) in toluene (1.5 mL) at 90 °C for 20 h. Purification by column chromatography (5:1 petrol:ethyl acetate) afforded **5b** as a colourless oil (81.1 mg, 89%); R_f 0.43 (5:1 petrol:ethyl acetate); ν_{max} (thin film)/cm^{-1} 1647, 1589, 1506, 1449, 1311, 1275; δ_H (400 MHz, $CDCl_3$) 8.24 (1H, dd, *J* = 7.7, 1.7 Hz), 8.19 (1H, dd, *J* = 8.2, 1.7 Hz), 7.34–7.13 (11H, m, H-9), 5.31 (1H, s), 4.75–4.68 (1H, m), 3.35 (1H, d, *J* = 13.4 Hz), 3.17 (1H, d, *J* = 13.4 Hz), 2.85 (1H, d, *J* = 13.4 Hz), 2.53–2.42 (2H, m), 2.18–2.05 (1H, m), 1.68–1.59 (2H, m), 1.50–1.40 (1H, m); δ_C (100 MHz, $CDCl_3$) 159.4, 150.2, 137.0, 136.4, 136.1, 133.7, 131.2, 131.0, 130.2, 128.2, 126.6, 121.0, 118.2, 90.6, 43.2, 42.2, 40.9, 35.6, 27.6, 19.6; HRMS (ESI$^+$): Found: 429.1827; $C_{26}H_{25}N_2O_4$ (MH$^+$) Requires: 429.1809 (−4.3 ppm error).

*6,6-Dibenzyl-2-chloro-6,7,8,9-tetrahydro-5aH,11H-pyrido[2,1-b][1,3]benzoxazin-11-one (**5d**).* Synthesised using the general DIA procedure from imine **1a** (66.9 mg, 0.254 mmol), acid **2d** (52.6 mg, 0.305 mmol), DIPEA (81.9 μL, 0.470 mmol) and T3P (242 mg, 0.381 mmol) in toluene (1.5 mL) at 90 °C for 20 h. Purification by column chromatography (5:1 petrol:ethyl acetate) afforded **5d** as a white solid (46.7 mg, 96%); m.p. 198–201 °C; R_f 0.29 (5:1 petrol:ethyl acetate); ν_{max} (thin film)/cm^{-1} 1668, 1608, 1475, 1441, 1325, 1283, 704; δ_H (400 MHz, $CDCl_3$) 7.90 (1H, d, *J* = 2.7 Hz), 7.42 (1H, dd, *J* = 8.8, 2.7 Hz), 7.34–7.20 (9H, m), 7.11–7.09 (1H, m), 7.05 (1H, d, *J* = 8.8 Hz), 5.09 (1H, s), 4.68–4.62 (1H, m), 3.21–3.16 (2H, m), 2.86 (1H, d, *J* = 13.5 Hz), 2.49–2.40 (2H, m), 2.18–2.04 (1H, m), 1.65–1.56 (2H, m), 1.42–1.31 (1H, m); δ_C (100 MHz, $CDCl_3$) 161.4, 154.5, 137.0, 136.3, 134.2, 131.0, 131.0, 128.1, 128.1, 127.7, 127.3, 126.6, 126.6, 117.3, 117.2, 89.5, 42.5, 42.0, 41.4, 35.8, 27.6, 19.5; HRMS (ESI$^+$): Found: 418.1585; $C_{26}H_{25}{}^{35}ClNO_2$ (MH$^+$) Requires: 418.1568 (−3.9 ppm error).

*6,6-Dibenzyl-3-methoxy-6,7,8,9-tetrahydro-5aH,11H-pyrido[2,1-b][1,3] benzoxazin-11-one (**5e**).* Synthesised using the general DIA procedure from imine **1a** (31.2 mg, 0.118 mmol), acid **2e** (23.9 mg, 0.142 mmol), DIPEA (38.0 μL, 0.219 mmol) and T3P (113 mg, 0.178 mmol) in toluene (1.5 mL) at 120 °C for 20 h. Purification by column chromatography (3:1 → 1:1 petrol:ethyl acetate → pure ethyl acetate) afforded **5e** as a white solid (40.0 mg, 82%); m.p. 158–162 °C; R_f 0.7 (ethyl acetate); ν_{max} (thin film)/cm^{-1} 1635, 1593, 1562, 1473, 1423, 1381, 1352, 1257, 1181; δ_H (400 MHz, $CDCl_3$) 7.85 (1H, d, *J* = 8.6 Hz), 7.34–7.19 (8H, m), 7.13–7.09 (2H, m), 6.63–6.56 (2H, m), 5.06 (1H, s), 4.67–4.60 (1H, m), 3.90 (3H, s) 3.24–3.19 (2H, m), 2.89 (1H, d, *J* = 13.7 Hz), 2.45–2.37 (2H, m), 2.16–2.03 (1H, m), 1.63–1.54 (2H, m), 1.42–1.28 (1H, m); δ_C (100 MHz, $CDCl_3$) 164.8, 163.0, 157.8, 137.5, 136.6, 131.2, 131.2, 129.7, 128.2, 128.2, 126.6, 126.5, 109.5, 109.0, 100.2, 89.5, 55.8, 42.5, 41.8, 41.5, 35.9, 27.8, 19.8; HRMS (ESI$^+$): Found: 414.2076; $C_{27}H_{28}NO_3$ (MH$^+$) Requires: 414.2064 (−0.6 ppm error).

*6,6-Dibenzyl-2-methoxy-6,7,8,9-tetrahydro-5aH,11H-pyrido[2,1-b][1,3] benzoxazin-11-one (**5f**).* Synthesised using the general DIA procedure from imine **1a** (37.0 mg, 0.141 mmol), acid **2f** (28.4 mg, 0.169 mmol), DIPEA (45.5 μL, 0.261 mmol)

and T3P (135 mg, 0.212 mmol) in toluene (1.4 mL) at 90 °C for 20 h. Purification by column chromatography (4:1 petrol:ethyl acetate) afforded **5f** as a colourless solid (35.0 mg, 60%); m.p. 108–109 °C; R_f 0.7 (ethyl acetate); ν_{max} (thin film)/cm^{-1} 1641, 1471, 1447, 1431, 1413, 1375, 1309, 1264, 1193, 692; δ_H (400 MHz, $CDCl_3$) 7.41 (1H, d, *J* = 2.6 Hz), 7.33–7.16 (8H, m), 7.11–7.02 (4H, m), 5.01 (1H, s), 4.67–4.60 (1H, m), 3.81 (3H, s) 3.22–3.18 (2H, m), 2.92 (1H, d, *J* = 13.9 Hz), 2.48–2.40 (2H, m), 2.17–2.05 (1H, m), 1.66–1.55 (2H, m), 1.38–1.28 (1H, m); δ_C (100 MHz, $CDCl_3$) 163.1, 154.6, 150.2, 137.3, 136.5, 131.1, 131.0, 128.1, 126.4, 126.4, 122.4, 116.9, 116.5, 109.9, 89.1, 55.9, 42.2, 41.9, 41.5, 35.9, 27.6, 19.5; HRMS (ESI$^+$): Found: 414.2074; $C_{27}H_{28}NO_3$ (MH^+) Requires: 414.2064 (−2.8 ppm error).

*6,6-Dibenzyl-1-methoxy-6,7,8,9-tetrahydro-5aH,11H-pyrido[2,1-b][1,3] benzoxazin-11-one (**5g**).* Synthesised using the general DIA procedure from imine **1a** (50.1 mg, 0.190 mmol), acid **2g** (38.3 mg, 0.228 mmol), DIPEA (61.3 µL, 0.352 mmol) and T3P (182 mg, 0.286 mmol) in toluene (1.5 mL) at 120 °C for 20 h. Purification by column chromatography (3:1 → 1:1 petrol:ethyl acetate → pure ethyl acetate) afforded **5g** as a white solid (51.0 mg, 64%); m.p. 186–187 °C; R_f 0.29 (1:1 ethyl acetate); ν_{max} (thin film)/cm^{-1} 1641, 1581, 1560, 1457, 1432, 1248, 1090; δ_H (400 MHz, $CDCl_3$) 7.37 (1H, dd, *J* = 8.3, 8.3 Hz), 7.03-7.14 (8H, m), 7.10–7.05 (2H, m), 6.72 (1H, d, *J* = 8.3 Hz), 6.60 (1H, d, *J* = 8.3 Hz), 4.95 (1H, s), 4.67–4.60 (1H, m), 3.91 (3H, s) 3.23 (1H, d, *J* = 13.8 Hz), 3.19 (1H, d, *J* = 13.4 Hz), 2.90 (1H, d, *J* = 13.8 Hz), 2.47–2.37 (2H, m), 2.17–2.04 (1H, m), 1.65–1.53 (2H, m), 1.35–1.24 (1H, m); δ_C (100 MHz, $CDCl_3$) 162.1, 160.7, 158.3, 137.5, 136.6, 134.3, 131.1, 128.1, 126.4, 126.3, 108.4, 109.5, 105.4, 88.4, 56.3, 42.0, 41.5, 41.4, 36.0, 27.5, 19.6; HRMS (ESI$^+$): Found: 414.2075; $C_{27}H_{28}NO_3$ (MH^+) Requires: 414.2064 (−2.8 ppm error).

*6,6-Dibenzyl-1,3-dihydroxy-6,7,8,9-tetrahydro-5aH,11H-pyrido[2,1 b][1,3] benzoxazin-11-one (**5h**).* Synthesised using the general DIA procedure from imine **1a** (41.3 mg, 0.157 mmol), acid **2h** (35.7 mg, 0.188 mmol), DIPEA (50.9 µL, 0.290 mmol) and T3P (151 mg, 0.235 mmol) in toluene (1.5 mL) at 90 °C for 20 h. Purification by column chromatography (3:1 → 2:1 petrol:ethyl acetate) afforded **5h** as a white solid (39.0 mg, 60%); m.p. 135–136 °C; R_f 0.57 (1:1 petrol:ethyl acetate); ν_{max} (thin film)/cm^{-1} 3269, 1619, 1589, 1491, 1471, 1441, 1293, 1257, 1137; δ_H (400 MHz, $CDCl_3$) 12.10 (1H, br s), 7.35–7.20 (8H, m), 7.10–7.06 (2H, m), 6.09 (1H, d, *J* = 2.0 Hz), 6.01 (1H, d, *J* = 2.0 Hz), 5.48 (1H, br s), 4.96 (1H, s), 4.55–4.47 (1H, m), 3.18 (1H, d, *J* = 13.7 Hz), 3.17 (1H, d, *J* = 13.4 Hz), 2.90 (1H, d, *J* = 13.7 Hz), 2.46–2.37 (2H, m), 2.15–2.05 (1H, m), 1.67–1.55 (2H, m), 1.37–1.22 (1H, m); δ_C (100 MHz, $CDCl_3$) 167.0, 162.8, 162.8, 157.5, 137.0, 136.3, 131.0, 128.2, 128.2, 126.6, 126.5, 97.2, 95.2, 93.8, 88.9, 42.1, 41.4, 41.1, 35.7, 27.4, 19.4; HRMS (ESI$^+$): Found: 416.1847; $C_{26}H_{26}NO_4$ (MH^+) Requires: 416.1856 (2.3 ppm error).

*6,6-Dibenzyl-6,7,8,9-tetrahydro-5aH,11H-dipyrido[2,1-b:2',3'-e][1,3]oxazin-11-one (**5l**).* Synthesised using the general DIA procedure from imine **1a** (43.0 mg, 0.163 mmol), acid **2l** (27.2 mg, 0.196 mmol), DIPEA (52.6 µL, 0.302 mmol) and T3P (156 mg, 0.245 mmol) in toluene (1.5 mL) at 90 °C for 20 h. Purification by column chromatography (3:1 → petrol:ethyl acetate → pure ethyl acetate → ethyl acetate, 10% MeOH) afforded **5l** as an orange oil (39.1 mg, 63%); R_f 0.23 (ethyl acetate); ν_{max} (thin film)/cm^{-1} 1654, 1450, 1415, 1382, 1314, 1228, 718; δ_H (400 MHz, $CDCl_3$) 8.47–8.43 (1H, m), 7.49–7.40 (2H, m), 7.34–7.19 (8H, m) 7.12–7.06 (2H, m), 5.19 (1H, s), 4.80–4.73 (1H, m), 3.25–3.17 (2H, m), 2.86 (1H, d, *J* = 13.7 Hz), 2.55–2.42 (2H, m), 2.17–2.04 (1H, m), 1.64–1.56 (2H, m), 1.42–1.32 (1H, m); δ_C (100 MHz, $CDCl_3$) 161.3, 153.6, 144.5, 136.9, 136.3, 133.7, 131.1, 131.1, 128.4, 128.3, 128.3, 126.8, 126.7, 124.3, 89.9, 42.7, 42.5, 41.5, 35.9, 27.8, 19.6; HRMS (ESI$^+$): Found: 385.1906; $C_{25}H_{25}N_2O_2$ (MH^+) Requires: 385.1911 (−1.1 ppm error).

*6,6-Dibenzyl-5-phenyl-5,5a,6,7,8,9-hexahydro-11H-pyrido[2,1-b]quinazolin-11-one (**5o**).* Synthesised using the general DIA procedure from imine **1a** (38.0 mg, 0.144 mmol), acid **2o** (36.9 mg, 0.173 mmol), DIPEA (46.4 µL, 0.266 mmol) and T3P (137 mg, 0.216 mmol) in toluene (1.4 mL) at 90 °C for 20 h. Purification by column chromatography (2:1 petrol:ethyl acetate) afforded **5o** as a white solid (63.0 mg, 95%). R_f 0.59 (ethyl acetate); m.p. 177–178 °C; ν_{max} (thin film)/cm^{-1} 1625, 1579, 1469, 1451, 1431, 1410, 1362, 1280, 1198, 739, 693; δ_H (400 MHz, $CDCl_3$) 8.05 (1H, dd, *J* = 7.7, 1.5 Hz), 7.62–7.57 (2H, m), 7.52–7.46 (2H, m), 7.40–7.20 (5H, m), 7.13–6.92 (7H, m), 6.35 (2H, d, *J* = 7.3 Hz), 5.21 (1H, s), 4.94 (1H, ddd, *J* = 12.7, 2.1, 2.1 Hz), 3.27 (1H, d, *J* = 13.9 Hz), 3.02 (1H, d, *J* = 13.2 Hz), 2.58 (1H, d, *J* = 13.2 Hz), 2.52 (1H, ddd, *J* = 12.7, 12.7, 3.0 Hz), 2.52 (1H, d, *J* = 13.9 Hz) 2.15–2.04 (1H, m), 1.62–1.55 (1H, m), 1.51–1.44 (1H, m), 1.19–1.09 (1H, m); δ_C (100 MHz, $CDCl_3$) 162.4, 151.2, 147.8, 137.5, 137.3, 133.2, 131.4, 131.1, 130.1, 128.9, 128.4, 128.1, 127.9, 127.0, 126.4, 126.1, 121.8, 119.8, 119.7, 81.4, 47.9, 45.1, 38.5, 36.6, 30.9, 21.4; HRMS (ESI$^+$): Found: 459.2436; $C_{32}H_{31}N_2O$ (MH^+) Requires: 459.2431 (−1.2 ppm error).

*3,3-Dibenzyl-1,2,3,3a-tetrahydro-9H-pyrrolo[2,1-b][1,3]benzoxazin-9-one (**5q**).* Synthesised using general the DIA procedure from imine **1b** (33.2 mg, 0.133 mmol), acid **2a** (22.1 mg, 0.160 mmol), DIPEA (42.9 µL, 0.246 mmol) and T3P (127 mg, 0.200 mmol) in toluene (1.5 mL) at 120 °C for 20 h. Purification by column chromatography (3:1 petrol:ethyl acetate) afforded **5q** as a yellow oil (23.7 mg, 48%). R_f 0.27 (2:1 petrol:ethyl acetate); ν_{max} (thin film)/cm^{-1} 2980, 1647, 1587, 1446, 1412, 1329, 1195, 1083, 1059, 693; δ_H (400 MHz, $CDCl_3$) 7.85 (1H, dd, *J* = 7.7, 1.7 Hz), 7.40 (1H, ddd, *J* = 8.2, 7.4, 1.7 Hz), 7.28–7.13 (8H, m), 7.07–7.00 (4H, m), 5.21 (1H, s), 3.49–3.37 (2H, m), 2.95 (1H, d, *J* = 14.1), 2.96 (1H, d, *J* = 13.8 Hz), 2.89 (1H, d, *J* = 14.1 Hz), 2.73 (1H, d, *J* = 13.8 Hz), 1.81 (1H, ddd, *J* = 13.3, 6.7, 1.4 Hz), 1.62–1.56 (1H, m); δ_C (100 MHz, $CDCl_3$) 161.3, 157.2, 137.4, 136.4, 134.0, 131.0, 130.9, 128.4, 128.4, 127.9, 126.8, 126.8, 122.7, 119.3, 116.7, 90.5, 48.0, 40.8, 40.2, 37.9, 26.4; HRMS (ESI$^+$): Found: 370.1792; $C_{25}H_{24}NO_2$ (MH^+) Requires: 370.1802 (2.7 ppm error).

*3,3-Dibenzyl-1,2,3,3a-tetrahydro-9H-pyrrolo[2,1-b][1,3]benzothiazin-9-one (**5r**).* Synthesised using general the DIA procedure from imine **1b** (49.5 mg, 0.199 mmol), acid **2m** (36.7 mg, 0.238 mmol), DIPEA (64.0 µL, 0.367 mmol) and T3P (189 mg, 0.298 mmol) in toluene (1.5 mL) at 90 °C for 20 h. Purification by column chromatography (5:1 petrol:ethyl acetate) afforded **5r** as a white solid (66.4 mg, 87%). R_f 0.80 (3:1 petrol:ethyl acetate); ν_{max} (thin film)/cm^{-1} 2874, 1620, 1567, 1424, 1387, 732, 694; δ_H (400 MHz, $CDCl_3$) 8.00 (1H, d, *J* = 7.7 Hz), 7.32–7.25 (5H, m), 7.20–7.13 (7H, m), 6.98 (1H, d, *J* = 8.0 Hz), 4.91 (1H, s), 3.77–3.72 (1H, m), 3.67–3.60 (1H, m), 3.10 (1H, d, *J* = 13.6 Hz), 2.83 (1H, d, *J* = 14.0 Hz), 2.78 (1H, d, *J* = 14.0 Hz), 2.77 (1H, d, *J* = 13.6 Hz), 1.78 (1H, ddd, *J* = 12.3, 5.8, 0.9 Hz), 1.51–1.42 (1H, m); δ_C (100 MHz, $CDCl_3$) 163.4, 137.1, 135.8, 134.8, 131.8, 130.9, 130.6, 129.9, 129.8, 128.4, 127.7, 126.9, 126.8, 126.0, 65.8, 49.8, 44.1, 41.1, 39.4, 27.1; HRMS (ESI$^+$): Found: 386.1574; $C_{25}H_{24}NOS$ (MH^+) Requires: 386.1573 (−0.2 ppm error).

*13a-Methyl-5, 13a-dihydro-6H, 8H-isoquinolino[1,2-b][1,3]benzothiazin-8-one (**5u**).* Synthesised using the general DIA procedure from imine **1c** (37.7 mg, 0.287 mmol), acid **2m** (53.2 mg, 0.345 mmol), DIPEA (92.6 μL, 0.532 mmol) and T3P (274 mg, 0.431 mmol) in toluene (1.5 mL) at 120 °C for 20 h. Purification by column chromatography (4:1 petrol:ethyl acetate) afforded **5u** as a white solid (74.4 mg, 97%). R_f 0.80 (2:1 petrol:ethyl acetate); ν_{max} (thin film)/cm^{-1} 1664, 1656, 1618, 1579, 1434, 1358, 1290, 1216, 1126, 731; δ_H (400 MHz, $CDCl_3$) 8.19 (1H, ddd, *J* = 7.7, 1.5, 0.6 Hz), 7.44–7.24 (7H, m), 6.24 (1H, s), 4.83–4.79 (1H, m), 3.24–3.11 (2H, m), 3.00–2.93 (1H, m); δ_C (100 MHz, $CDCl_3$) 164.9, 137.8, 136.4, 131.8, 131.2, 130.8, 129.1, 128.9, 128.6, 127.7, 127.3, 127.0, 126.3, 60.7, 40.7, 29.6; HRMS (ESI$^+$): Found: 268.0611; $C_{16}H_{13}NNaOS$ (MNa$^+$) Requires: 290.0610 (−0.2 ppm error).

*2,3-Dimethoxy-5,13a-dihydro-6H,8H-isoquinolino[1,2-b][1,3]benzoxazin-8-one (**5w**).* Synthesised using the general DIA procedure from imine **1d** (66.6 mg, 0.348 mmol), acid **2a** (57.7 mg, 0.418 mmol), DIPEA (112 μL, 0.644 mmol) and T3P (332 mg, 0.522 mmol) in toluene (1.5 mL) at 90 °C for 20 h. Purification by column chromatography (1:1 petrol:ethyl acetate) afforded **5w** as a white solid (51.6 mg, 48%); R_f 0.33 (ethyl acetate); ν_{max} (thin film)/cm^{-1} 1641, 1587, 1494, 1446, 1394, 1247, 1209, 1095; δ_H (400 MHz, $CDCl_3$) 8.03 (1H, dd, *J* = 7.8, 1.7 Hz), 7.48 (1H, ddd, *J* = 8.2, 7.3, 1.7 Hz), 7.16 (1H, ddd, *J* = 7.8, 7.3, 0.5 Hz), 7.08 (1H, dd, *J* = 8.2, 0.5 Hz), 7.03 (1H, s), 6.71 (1H, s), 6.23 (1H, s) 4.58 (1H, ddd, *J* = 12.8, 4.8, 3.5 Hz), 3.95 (3H, s), 3.92 (3H, s), 3.33 (1H, ddd, *J* = 12.8, 11.3, 3.5 Hz), 3.05 (1H, ddd, *J* = 15.6, 11.3, 4.8 Hz), 2.77 (1H, ddd, *J* = 15.6, 3.5, 3.5 Hz); δ_C (100 MHz, $CDCl_3$) 163.1, 157.6, 150.0, 148.4, 134.2, 129.1, 128.7, 122.8, 122.4, 118.8, 116.6, 111.0, 110.6, 84.2, 56.2, 56.1, 38.4, 28.1; HRMS (ESI$^+$): Found: 334.1058; $C_{18}H_{17}NNaO_4$ (MNa$^+$) Requires: 334.1050 (−2.6 ppm error).

*2,3-Dimethoxy-13-methyl-5,6,13,13a-tetrahydro-8H-isoquinolino[1,2-b]quinazolin-8-one (**5x**).* Synthesised using the general DIA procedure from imine **1d** (76.9 mg, 0.402 mmol), acid **2n** (73.0 mg, 0.483 mmol), DIPEA (130 μL, 0.744 mmol) and T3P (384 mg, 0.603 mmol) in toluene (1.5 mL) at 90 °C for 20 h. Purification by column chromatography (1:1 petrol:ethyl acetate) afforded **5x** as a colourless oil (114 mg, 87%); R_f 0.54 (ethyl acetate); ν_{max} (thin film)/cm^{-1} 1625, 1583, 1492, 1446, 1401, 1342, 1318, 1241, 1215, 1094, 1001, 746; δ_H (400 MHz, $CDCl_3$) 8.07–8.04 (1H, m), 7.47–7.42 (1H, m), 7.13–7.09 (2H, m), 6.87 (1H, s), 6.67 (1H, s), 5.66 (1H, m), 4.64 (1H, ddd, *J* = 12.8, 5.0, 2.7 Hz), 3.89 (3H, s), 3.88 (3H, s), 3.20–3.13 (1H, m), 2.95–2.87 (1H, m), 2.78–2.71 (1H, m), 2.47 (3H, s); δ_C (100 MHz, $CDCl_3$) 164.6, 151.2, 149.1, 148.3, 133.0, 129.7, 128.9, 123.7, 122.9, 122.8, 121.0, 111.0, 110.8, 71.3, 56.2, 56.0, 39.1, 36.0, 28.3; HRMS (ESI$^+$): Found: 347.1361; $C_{19}H_{21}N_2NaO_3$ (MNa$^+$) Requires: 347.1366 (1.6 ppm error).

*6,6-Dimethyl-5a,6-dihydro-12H-indolo[2,1-b][1,3]benzothiazin-12-one (**5y**).* Synthesised using the general DIA procedure from imine **1e** (38.8 mg, 0.267 mmol), acid **2m** (49.4 mg, 0.321 mmol), DIPEA (86.1 μL, 0.494 mmol) and T3P (255 mg, 0.401 mmol) in toluene (1.5 mL) at 90 °C for 20 h. Purification by column chromatography (19:1 petrol:ethyl acetate) afforded **5y** as a colourless oil (39.7 mg, 53%); R_f 0.76 (1:1 petrol:ethyl acetate); ν_{max} (thin film)/cm^{-1} 2918, 1625, 1572, 1457, 1369, 1310, 1269, 1143, 1078, 739; δ_H (400 MHz, $CDCl_3$) 8.35 (1H, ddd, *J* = 8.1, 1.0, 0.6 Hz), 8.22 (1H, ddd, *J* = 7.8, 1.5, 0.5 Hz), 7.44–7.28 (4H, m), 7.21 (1H, ddd, *J* = 7.5, 1.4, 0.6 Hz), 7.14 (1H, ddd, 7.4, 7.4, 1.1 Hz), 5.43 (1H, s, H-1), 1.53 (3H, s), 1.45 (3H, s); δ_C (100 MHz, $CDCl_3$) 162.1, 140.2, 138.5, 135.1, 132.1, 130.4, 130.4, 128.3, 127.8, 126.4, 124.6, 121.8, 116.3, 73.4, 44.2, 27.6, 26.4; HRMS (ESI$^+$): Found: 282.0958; $C_{17}H_{16}NOS$ (MH$^+$) Requires: 282.0947 (−3.8 ppm error).

*5,6,6-Trimethyl-5a,6-dihydroindolo[2,1-b]quinazolin-12(5H)-one (**5z**).* Synthesised using the general DIA procedure from imine **1e** (31.8 mg, 0.219 mmol), acid **2n** (39.7 mg, 0.263 mmol), DIPEA (70.6 μL, 0.405 mmol) and T3P (210 mg, 0.329 mmol) in toluene (1.5 mL) at 90 °C for 20 h. Purification by column chromatography (19:1 petrol:ethyl acetate) afforded **5z** as a colourless oil (25.0 mg, 41%); R_f 0.64 (5:2 petrol:ethyl acetate); ν_{max} (thin film)/cm^{-1} 2924, 1636, 15577, 1461, 1435, 1409, 1390, 741; δ_H (400 MHz, $CDCl_3$) 8.35 (1H, dd, *J* = 8.0, 1.1 Hz), 8.10 (1H, dd, *J* = 7.8, 1.7 Hz), 7.45 (1H, ddd, *J* = 8.4, 7.3, 1.7 Hz), 7.31–7.27 (1H, m), 7.21 (1H, dd, *J* = 7.5, 1.4 Hz), 7.13 (1H, ddd, 7.5, 7.5, 1.1 Hz), 6.96 (1H, ddd, *J* = 7.8, 7.3, 0.8 Hz), 6.88 (1H, d, *J* = 8.4 Hz), 4.98 (1H, s), 3.02 (3H, s), 1.70 (3H, s), 1.34 (3H, s); δ_C (100 MHz, $CDCl_3$) 160.9, 149.5, 139.0, 138.8, 134.0, 128.6, 128.2, 124.5, 121.6, 119.3, 116.8, 116.8, 112.4, 85.2, 46.0, 34.8, 26.0, 23.3; HRMS (ESI$^+$): Found: 279.1492; $C_{18}H_{19}N_2O$ (MH$^+$) Requires: 279.1492 (−0.1 ppm error).

*6,7,8,9-Tetrahydro-5a*H*,11*H*-pyrido[2,1-*b*][1,3]benzothiazin-11-one (**5aa**).*[23] Synthesised using the general DIA procedure from imine **1f** (47.3 mg, 0.190 mmol), acid **2m** (105 mg, 0.683 mmol), DIPEA (184 μL, 0.510 mmol) and T3P (544 mg, 0.854 mmol) in toluene (2 mL) at 90 °C for 20 h. Purification by column chromatography (5:0.5:0.5 petrol:ethyl acetate:CH_2Cl_2) afforded **5aa** as a white solid (39.0 mg, 31%). R_f 0.76 (ethyl acetate); m.p. 52–54 °C (literature 53.5–54.5 °C); [23] ν_{max} (thin film)/cm−1 3062, 2939, 2858, 1635, 1440, 1275, 1204, 920, 742; δ_H (400 MHz, $CDCl_3$) 8.16 (1H, dd, *J* = 7.7, 1.2 Hz), 7.35 (1H, ddd, *J* = 7.7, 7.7, 1.2 Hz), 7.23 (1H, ddd, *J* = 7.7, 7.7, 1.2 Hz), 7.18 (1H, dd, *J* = 7.7, 1.2 Hz), 4.83 (1H, dd, *J* = 10.8, 3.8 Hz), 4.50–4.59 (1H, m), 2.98 (1H, ddd, *J* = 13.5, 11.8, 4.0 Hz), 2.10–2.01 (1H, m), 2.01–1.88 (2H, m), 1.87–1.75 (1H), 1.74–1.49 (2H, m); δ_C (100 MHz, CDCl3); 164.7, 134.8, 131.9, 130.6, 127.7, 126.4, 125.8, 59.0, 44.5, 31.9, 23.7, 23.1; HRMS (ESI$^+$): Found: 220.0792; $C_{12}H_{14}NOS$ (MH$^+$) Requires: 220.0791 (−0.8 ppm error).[23]

5,*13a-Dihydro-6H,8H-isoquinolino[1,2-b][1,3]benzothiazin-8-one (**5ac**).* Synthesised using the general DIA procedure from imine **1g** (40.0 mg, 0.275 mmol), acid **2m** (51.0 mg, 0.330 mmol), DIPEA (88.7 μL, 0.510 mmol) and T3P (263 mg, 0.413 mmol) in toluene (1.5 mL) at 120 °C for 20 h. Purification by column chromatography (5:1 petrol:ethyl acetate) afforded **5ac** as an orange oil (58.5 mg, 80%); R_f 0.34 (5:1 petrol:ethyl acetate); ν_{max} (thin film)/cm^{-1} 2879, 1657, 1618, 1609, 1564, 1422, 1366, 1332, 1275, 1231, 732; δ_H (400 MHz, $CDCl_3$) 8.15 (1H, ddd, *J* = 7.8, 1.5, 0.5 Hz), 7.42 (1H, dd, *J* = 7.8, 1.6 Hz), 7.35 (1H, ddd, *J* = 7.7, 7.7, 1.6 Hz), 7.30–7.15 (5H, m), 5.04 (1H, ddd, 12.6, 9.7, 1.9 Hz), 3.03 (1H, ddd, *J* = 15.4, 12.6, 9.7 Hz), 2.93 (1H, ddd, *J* = 12.6, 12.6, 2.8 Hz), 2.86 (1H, ddd, *J* = 15.4, 2.8, 1.9 Hz), 1.91 (3H, s); δ_C (100 MHz, $CDCl_3$) 163.6, 135.8, 135.4, 134.8, 132.1, 130.9, 129.4, 128.2, 128.1, 127.3, 127.1, 126.2, 126.1, 65.9, 37.3, 29.7, 28.5; HRMS (ESI$^+$): Found: 304.0766; $C_{17}H_{15}NNaOS$ (MNa$^+$) Requires: 304.0767 (0.3 ppm error).

*3-Methyl-1,2-diphenyl-2,3-dihydroquinazolin-4(1H)-one (**5af**).* Synthesised using the general DIA procedure from imine **1i** (24.6 μL, 0.200 mmol), acid **2o** (51.2 mg, 0.240 mmol), DIPEA (64.5 μL, 0.370 mmol) and T3P (191 mg, 0.300 mmol) in toluene (2.0 mL) at 90 °C for 20 h. Purification by column chromatography (4:1 petrol:ethyl acetate) afforded **5af** as a white solid (43.0 mg, 68%). m.p. 220–223 °C; R_f 0.57 (ethyl acetate); ν_{max} (thin film)/cm^{-1} 1625, 1581, 1471, 1373, 1279, 1238,

1207; δ_H (400 MHz, $CDCl_3$) 8.02 (1H, dd, *J* = 7.9, 1.2 Hz), 7.37–7.24 (8H, m), 7.19–7.13 (3H, m), 6.96 (1H, ddd, *J* = 7.9, 7.9, 1.1 Hz), 6.85 (1H, dd, *J* = 8.2, 1.1 Hz), 5.96 (1H, s), 3.18 (3H, s); δ_C (100 MHz, $CDCl_3$) 162.8, 146.1, 143.9, 139.3, 133.0, 129.8, 128.9, 128.8, 128.6, 126.5, 124.8, 123.3, 121.3, 120.5, 118.8, 80.0, 34.3; HRMS (ESI^+): Found: 315.1493; $C_{21}H_{19}N_2O$ (MH^+) Requires: 315.1492 (−0.5 ppm error).

*5-(1,3-Dimethoxy-1,3-dioxopropan-2-yl)-1,3-benzodioxole-4-carboxylic acid (**2q**)*. Sodium hydride (60 % in mineral oil, 419 mg, 10.5 mmol) was added portionwise to a rapidly stirred cold suspension (0 °C) of 5-bromobenzo[1,3]dioxole-4-carboxylic acid **9** (1.00 g, 4.37 mmol), cuprous bromide (62.6 mg, 0.437 mmol) and dimethyl malonate (17.3 mL). After the addition of the sodium hydride had been completed, the mixture was stirred for 10 min at r.t and then for 20 h at 70 °C. The suspension, which had turned to a solid mass, was dissolved in water (30 mL), washed with ether (3 × 80 mL) and then acidified with 10% HCl. The acidic aqueous layer, was extracted with ethyl acetate (3 × 100 mL), and the organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (5:1 → pure ethyl acetate) afforded **2q** as a colourless solid (1.01 g, 74%); R_f 0.1 (1:1 petrol:ethyl acetate); m.p. 88–93 °C; ν_{max} (thin film)/cm^{-1} 2912, 2877, 1704, 1688, 1456, 1431, 1216, 1137, 1039, 1012; δ_H (400 MHz, $CDCl_3$) 6.95 (1H, d, J = 8.2 Hz), 6.88 (1H, d, J = 8.2 Hz), 6.11 (2H, s), 5.53 (1H, s), 3.76 (6H, s); δ_C (100 MHz, $CDCl_3$) 169.2, 149.7, 148.5, 127.1, 123.9, 111.9, 107.3, 102.5, 100.0, 54.2, 53.0; HRMS (ESI+): Found: 319.0424; $C_{13}H_{12}NaO_8$ (MNa^+) Requires: 319.0424 (0.2 ppm error).

*Dimethyl 8,9-dimethoxy-14-oxo-11,12-dihydro-6aH-[1,3]dioxolo[4,5-h]isoquino [2,1-b] isoquinoline-6,6(14H)-dicarboxylate (**5ai**)*. To a solution of imine **1d** (484 mg, 2.53 mmol), and acid **2q** (900 mg, 3.04 mmol) in chloroform (25 mL) was added sequentially DIPEA (0.815 mL, 4.68 mmol) and T3P (2.42 g, 3.80 mmol, 50% solution in THF). The resulting solution was stirred for 20 min at r.t. before BCl_3 (5.10 mL, 5.10 mmol, 1.0 M solution in DCM) was added. The resulting solution was stirred at r.t. for 20 h before it was poured into sat. aq. $NaHCO_3$ (100 mL). The aqueous layer was extracted with DCM (3 × 100 mL), dried over $MgSO_4$, concentrated *in vacuo* and purified by column chromatography (1:1 → 1:2 petrol:ethyl acetate) to afford **5ai** as a yellow solid (819 mg, 69%); R_f 0.5 (ethyl acetate); m.p. 152–156 °C; ν_{max} (thin film)/cm^{-1} 2908, 1707, 1626, 1588, 1494, 1440, 1412, 1103, 1029, 718; δ_H (400 MHz, $CDCl_3$) 6.91 (1H, d, *J* = 8.1 Hz), 6.81 (1H, s), 6.69 (1H, s), 6.54 (1H, d, *J* = 8.1 Hz), 6.22 (1H, d, *J* = 1.3 Hz), 6.10 (1H, d, 1.3 Hz), 5.58 (1H, s), 4.85–4.78 (1H, m), 3.88 (3H, s), 3.87 (3H, s), 3.80 (3H, s), 3.51 (3H, s), 2.92–2.87 (2H, m), 2.67–2.64 (1H, m); δ_C (100 MHz, $CDCl_3$) 170.1, 167.0, 162.0, 149.0, 148.3, 148.2, 147.1, 131.6, 130.3, 123.1, 120.1, 112.2, 111.1, 110.9, 110.7, 102.7, 65.9, 61.2, 55.9, 55.7, 53.0, 52.9, 39.3, 28.9; HRMS (ESI^+): Found: 470.1454; $C_{24}H_{24}NO_9$ (MH^+) Requires: 470.1446 (−1.7 ppm error).

*(±)-cis-2,3-Dimethoxy-8-oxo-9,10-(methylenedioxy)13-(hydroxymethyl) tetrahydro protoberberine (**10**)*. To a round bottom flask containing diester **5ai** (106.5 mg, 0.227 mmol) in THF (0.7 mL), lithium hydroxide monohydrade (28.6 mg, 0.681 mmol) in water (0.7 mL) was added at r.t. The reaction mixture was stirred for 16 h at 90 °C. The solution was diluted with water (10 mL), washed with DCM (10 mL) and then acidified with 10% aq. HCl. The acidic aqueous layer was then extracted with ethyl acetate (3 × 20 mL), and the organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was then added to a solution of $LiAlH_4$ (30.7 mg, 0.808 mmol) in THF (10 mL) and heated at 70 °C for 2 h, before it was cooled to 0 °C and quenched by the sequential addition of water (0.031 mL), 15 % aq. NaOH (0.031 mL) and water (0.092 mL). The resulting solids were removed by filtration and washed with EtOAc. The solids were then collected and refluxed in EtOAc for 2 h and filtered a second time. The combined filtrates were dried with $MgSO_4$ and evaporated. Purification by column chromatography (1:1 petrol: ethyl acetate→ EtOAc) afforded **10** as a yellow solid; (35.7 mg, 43 %); R_f 0.6 (ethyl acetate); mp: 145–147 °C (literature 193–195 °C);[18c] ν_{max} (thin film)/cm^{-1} 3261, 2924, 1609, 1516, 1462, 1360, 1257, 1232, 11209, 1138, 1044; δ_H (400 MHz, $CDCl_3$) 6.78 (2H, s), 6.64 (1H, br s), 6.61 (1H, br s), 6.01 (1H, d, *J* = 1.5 Hz), 5.95 (1H, d, *J* = 1.5 Hz), 4.14 (1H, d, *J* = 15.2 Hz), 4.00 (1H, br s), 3.88 (3H, s), 3.66 (3H, s), 3.75 (1H, dd, *J* = 10.4, 2.0 Hz), 3.58–3.54 (1H, m), 3.53 (1H, d, *J* = 15.2 Hz), 3.19–3.15 (3H, m), 2.68–2.56 (2H, m); δ_C (100 MHz, $CDCl_3$) 147.8, 147.8, 145.5, 143.1, 131.0, 127.9, 126.3, 120.9, 117.2, 111.5, 108.4, 107.4, 101.2, 66.0, 63.4, 56.1, 55.9, 53.0, 51.2, 43.9, 29.0; HRMS (ESI^+): Found: 370.1632; $C_{21}H_{24}NO_5$ (MH^+) Requires: 370.1649 (4.4 ppm error); Obtained data in accord with those reported in the literature.[18c]

(±)-cis-2,3-Dimethoxy-8-oxo-9,10-(methylenedioxy)13-(methanesulfoxymethyl) tetrahydro protoberberine. Methanesulfonyl chloride (23.8 µL, 0.308 mmol) was added to a solution of alcohol **10** (35.5 mg, 0.096) in pyridine (1 mL). The reaction mixture was stirred at r.t. for 1.5 h and then quenched with water (10 mL). The mixture was extracted with Et_2O (3 × 20 mL). The organic extract was dried and evaporated. Purification by column chromatography (2:1 → 1:1 hexene:ethyl acetate → EtOAc) afforded the *title compound* as a yellow oil (25.5 mg, 68 %); R_f 0.9 (ethyl acetate); ν_{max} (thin film)/cm^{-1} 2936, 1517, 1462, 1353, 1334, 1172, 1142, 1041, 955, 730; δ_H (400 MHz, $CDCl_3$) 6.84 (1H, d, *J* = 8.0 Hz), 6.75 (1H, s), 6.73 (1H, d, *J* = 8.0 Hz), 6.61 (1H, s), 6.00 (1H, d, *J* = 1.4 Hz), 5.97 (1H, d, *J* = 1.4 Hz), 4.22–4.08 (3H, m), 3.92–3.86 (2H, m), 3.90 (3H, s), 3.88 (3H, s), 3.56–3.52 (2H, m), 3.11–3.00 (2H, m), 2.63–2.55 (1H, m), 2.62 (3H, s); δ_C (100 MHz, $CDCl_3$) 147.8, 147.4, 145.3, 142.9, 132.9, 128.1, 126.3, 1261, 123.1, 111.4, 108.5, 106.7, 101.4, 72.4, 61.5, 56.2, 56.0, 53.2, 51.2, 43.7, 36.8, 29.2; HRMS (ESI^+): Found: 448.1427; $C_{22}H_{26}NO_7S$ (MH^+) Requires: 448.1424 (–1.3 ppm error);

(±)-Cavidine (**8**) To a solution of (±)-*cis*-2,3-dimethoxy-8-oxo-9,10-(methylenedioxy)13-(methanesulfoxymethyl) tetrahydro protoberberine (22.4 mg, 0.058 mmol) in 95% EtOH (3.5 mL) was added $NaBH_4$ (32.8 mg, 0.867 mmol). The resulting mixture was heated at reflux (80 °C) for 2 h and then poured into H_2O (15 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The organic extracts were dried ($MgSO_4$) and evaporated to yield the crude product. Purification by column chromatography (5:1 hexane:ethyl acetate) afforded cavidine **8** as a white solid (13.6 mg, 67 %); R_f 0.4 (1:1 hexane:ethyl acetate); mp: 180–184 °C (literature 188–189 °C) ν_{max} (thin film)/cm^{-1} 2909, 2757, 1514, 1457, 1333, 1356, 1254, 1228, 1042, 729; δ_H (400 MHz, $CDCl_3$) 6.72 (1H, d, *J* = 8.0 Hz), 6.68 (1H, s), 6.67 (1H, d, *J* = 8.0 Hz), 6.61 (1H, s), 5.97 (1H, d, *J* = 1.5 Hz), 5.93 (1H, d, *J* = 1.5 Hz), 4.09 (1H, d, *J* = 15.3 Hz), 3.88 (3H, s), 3.88 (3H, s), 3.73 (1H, br. s), 3.50 (1H, d, *J* = 15.3 Hz), 3.28–3.22 (1H, m), 3.16–3.07 (2H, m), 2.63–2.57 (2H, m), 0.94 (3H, d, *J* = 6.9 Hz); δ_C (100 MHz, $CDCl_3$) 147.6, 147.1, 144.6, 143.0, 135.9, 128.3, 128.3, 121.2, 116.8, 111.1, 108.5, 106.7, 101.0, 63.1, 56.1, 55.8, 53.3, 51.2, 38.5, 29.3, 18.4; HRMS (ESI^+): Found: 354.1683; $C_{21}H_{24}NO_4$ (MH^+) Requires: 354.1700 (4.3 ppm error); Obtained data in accord with those reported in the literature.[14j-k, 18c]

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