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Intramolecular cyclisation of functionalised heteroaryllithiums. Synthesis of novel indolizinone-based compounds

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Dedicated to the memory of Professor Marcial Moreno Mañas

Abstract—The intramolecular cyclisation of heteroaryllithiums derived from *N*-heteroarylmethylpyrrole-2-carboxamides takes place smoothly at low temperature when *N*-methoxy-*N*-methyl and morpholine amides are used as internal electrophiles. Halogen–lithium exchange using *n*-BuLi is the method of choice to achieve metalation on the quinoline and pyridine derivatives, while directed lithiation (LDA) works better for furan. In the case of thiophene both methodologies can be applied. These metalation–cyclisation sequences provide a useful entry to several types of indolizidine based compounds (pyrrolo[1,2-*b*]acridinones, pyrrolo[1,2-*g*]quinolones, thieno and furo[3,2-*f*]indolizinones).

1. Introduction

The synthetic utility of lithium–halogen exchange reaction for the metalation of aromatic substrates, though mechanistically controversial,[1] is well established and has been subjected to several comprehensive reviews.[2] A particularly useful application[3,4] of this reaction has been the facile construction of benzo-fused carbocyclic[5] and heterocyclic[6] ring systems via intramolecular reaction of the so-generated aryllithium compounds with internal electrophiles, a metalation–cyclisation process pioneered by Parham.[7]

On the other hand, the ease with which halogenated heterocycles may be prepared regioselectively make the use of these compounds as substrates for permutational halogen–metal interconversions extremely attractive. Organolithium derivatives of all simple heterocycles at all possible positions have been made by this method.[2,8] Thus, heteroaryllithiums may be employed in Parham cyclisation for the synthesis of several types of heterocyclic systems.[9] For instance, Avendaño[10] used a tandem directed *ortho*-metalation/metal–halogen exchange reaction for the synthesis of 1,8-diazanthracene-9,10-diones. It was necessary to prepare the second heteroaryllithium, a 2-lithiopyridine intermediate, by halogen–metal exchange, since directed metalation was unsuccessful due to the presence of competitive *ortho*-metalation sites. Other 3-lithio- and 2-lithiopyridine derivatives have been used as intermediates in the Parham cyclisation for the synthesis of azatetralones[11] and dipyridocycloheptenones,[9] respectively. Maddaluno[12] has also used 2-lithiopyridine intermediates in the intramolecular carbolithiation of propargyl acetals that provided furo[3,2-*b*]pyridines. Pearson[13] has demonstrated that 3-lithiopyridines and 3-lithiofurans, generated by metal–halogen exchange with *t*-butyllithium, may be used for the synthesis of indanones derived from monic acid. Mesityllithium was found to be an excellent selective lithiating agent to prepare heteroaryllithium compounds having alkoxycarbonyl groups, whose intramolecular cyclisation led to an important precursor for the synthesis of camptothecin.[14] Selnick[15] developed a new route to thieno[2,3-*b*]thiophenes by a metal–halogen exchange initiated intramolecular acylation of 3-bromothiophenes with Weinreb amides as internal electrophiles. A recent enantioselective synthesis of polyhydroxylated piperidines used as a key step for the formation of heteroaryllithiums, derived from 5-bromo-oxazoles or thiazoles, which cyclised to give the corresponding oxazolo- and thiazolo[4,5-*c*]pyridones. [16]

In connection with our interest in Parham cyclistions, we have developed an anionic cyclisation approach towards the construction of the pyrrolo[1,2-*b*]isoquinolone core present in some natural products such as the lycorine class of *Amaryllidaceae* alkaloids[17] and the phenanthroindolizidine alkaloids.[18] Thus, we have shown[19] that *N*-(*o*-iodobenzyl)-pyrrole-2-carboxamides tolerate lithium–iodine exchange reaction conditions,[20] allowing the efficient synthesis of

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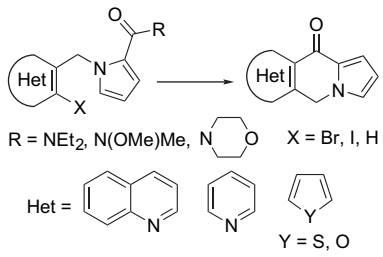


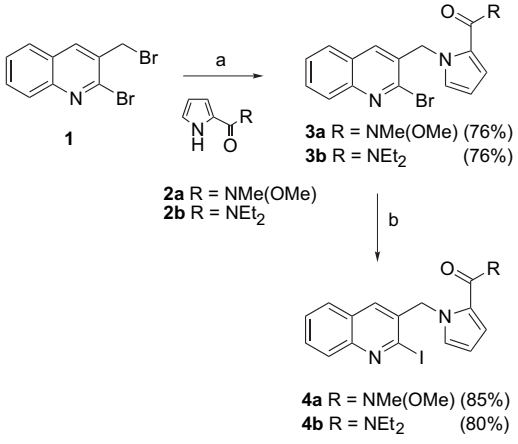
Figure 1.

the pyrrolo[1,2-*b*]isoquinoline nucleus. The *N*-methoxy-*N*-methyl and morpholine amides behave as excellent internal electrophiles, improving the results obtained with *N*,*N*-diethyl amides. This procedure has also been applied to the construction of fused seven and eight-membered rings, opening also new routes to other heterocyclic systems (pyrrolo[1,2-*a*]benzazepines and pyrrolo[1,2-*a*]benzazocines).

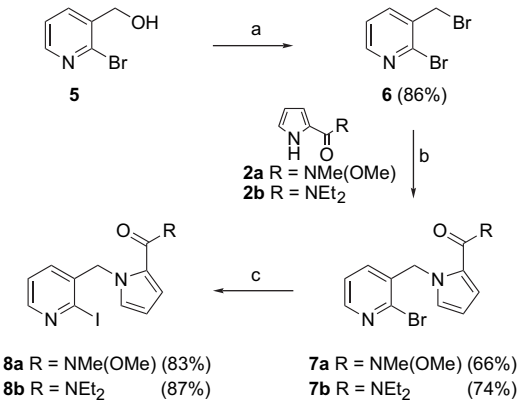
Therefore, we decided to expand this procedure by using heteroaryllithium compounds as intermediates in this aromatic metalation–cyclisation sequence and thus afford convenient access to fused indolizidinone systems.[21] For this purpose, we employed a series of *N*-(2-haloheteroarylmethyl)pyrrole-2-carboxamides as substrates for the Parham cyclisation. We chose both electron-deficient (pyridine, quinoline) and electron-rich (thiophene, furan) heteroaromatic ring systems that incorporated *N*,*N*-diethyl- and *N*-methoxy-*N*-methyl or morpholine amides as internal electrophiles (Fig. 1).

2. Results

Our first task was to extend the scope of our carbanionic heterocyclisation method to the synthesis of pyrrolo[1,2-*b*]acridones and pyrrolo[1,2-*g*]quinolones. Thus, we first prepared *N*-(2-bromoquinolylmethyl)pyrrole-2-carboxamides **3a**,**b** by N-alkylation of the corresponding pyrrole-2-carboxamide **2** with 2-bromo-3-bromomethylquinoline **1**[22] under standard conditions. These carboxamides were converted into the corresponding iodinated derivatives **4** by a bromine–iodine exchange reaction following Buchwald procedure (NaI, CuI, *N*,*N*′-dimethylethylene diamine)[23] (Scheme 1). The same sequence of reactions was applied to obtain the *N*-(2-halopyridylmethyl)pyrrole-2-carboxamides **7** and **8**, prepared from 2-bromo-3-hydroxymethylpyridine (**5**)[24] as described in Scheme 2.

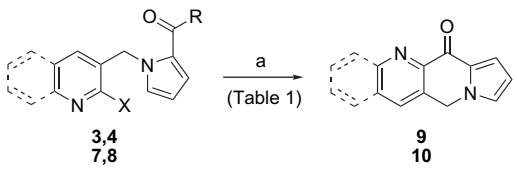


Scheme 1. Reagents: (a) KOH, DMSO, rt; (b) NaI, CuI (5% mol) $MeHN(CH_2)_2NHMe$, dioxane, reflux.



Scheme 2. Reagents: (a) PBr_3, CH_2Cl_2, rt; (b) KOH, DMSO, rt; (c) NaI, CuI (5% mol) $MeHN(CH_2)_2NHMe$, dioxane, reflux.

Next, we applied the metalation–cyclisation sequence to these amides. However, when the metalation of **3b** was performed with *t*-BuLi (2 equiv) under usual conditions (−78 °C, 3 h), a complex mixture of compounds was obtained. Only the corresponding dehalogenated amides were isolated in low yields (23–25%), both quenching at low temperature or allowing the mixture to warm up to room temperature before quenching. Although *t*-BuLi usually tends to undergo addition reaction with electron-deficient heterocycles, no addition product was detected. Therefore, *n*-BuLi was tested as metalating agent. Several experimental conditions were tried and we found that cyclisation of amides **3** and **4** took place smoothly when the heteroaryllithium was generated with *n*-BuLi (2.2 equiv) at low temperature for a shorter period of time (−90 °C, 5 min) and the reaction was quenched at low temperature (Scheme 3, Table 1, entries 1–4). No cyclisation products were isolated when heteroaryllithiums derived from **3** and **4** were allowed to reach room temperature. The effect of the halogen atom on the halogen–lithium exchange reaction was as expected, and better yields of the pyrrolo[1,2-*b*]acridone **9** were obtained with iodides **4** than with bromides **3**, particularly when *N*,*N*-diethylcarboxamides were used as internal electrophiles. This result suggested that in this case the extra stabilisation of the intermediate formed after cyclisation by formation of an internal chelate with Weinreb amides is needed to obtain good yields. In a similar fashion, the halogen–metal exchange reaction on amides **7** and **8** gave access to pyrrolo[1,2-*a*]quinolone **9** in moderate to good yields, obtaining the best results when X=I, and Weinreb amide was used as internal electrophile (Scheme 3, Table 1, entries 5–8).

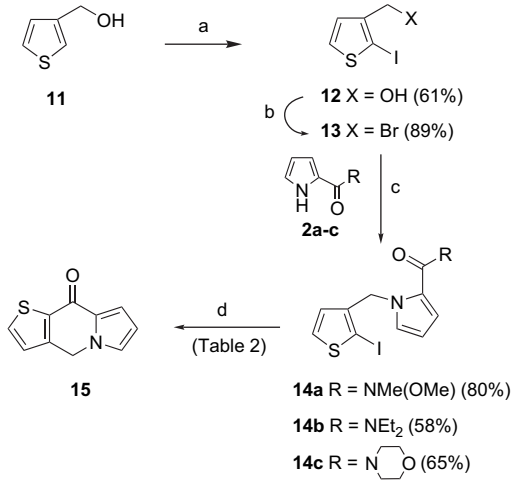


Scheme 3. Reagents: (a) *n*-BuLi (2 equiv), −90 °C, 5 min.

Table 1. Parham cyclisation of amides **3**–**4**, **7**–**8**

Entry	Substrates	X	R	Product	Yield (%)
1	**3a**	Br	NMe(OMe)	**9**	61
2	**3b**	Br	NEt_2	**9**	28
3	**4a**	I	NMe(OMe)	**9**	85
4	**4b**	I	NEt_2	**9**	83
5	**7a**	Br	NMe(OMe)	**10**	70
6	**7b**	Br	NEt_2	**10**	60
7	**8a**	I	NMe(OMe)	**10**	85
8	**8b**	I	NEt_2	**10**	80

We then began to test the feasibility of this Parham type cyclisation with electron-rich heterocycles. In view of the results obtained with quinoline and pyridine systems, and our previous results,[19] no attempts to perform bromine–lithium exchange were undertaken, and we decided to test this metalation–cyclisation sequence using also a morpholine amide as internal electrophile. Thus, the preparation of the *N*-thiophenylmethylpyrroles **14a**–**c** was achieved in three steps from 3-hydroxymethylthiophene (**11**), as depicted in Scheme 4.



Scheme 4. Reagents: (a) I_2, CF_3CO_2Ag, $CHCl_3$, 0 °C; (b) PBr_3, rt; (c) KOH, DMSO, rt; (d) *t*-BuLi (2.2 equiv), −78 °C (see Table 2).

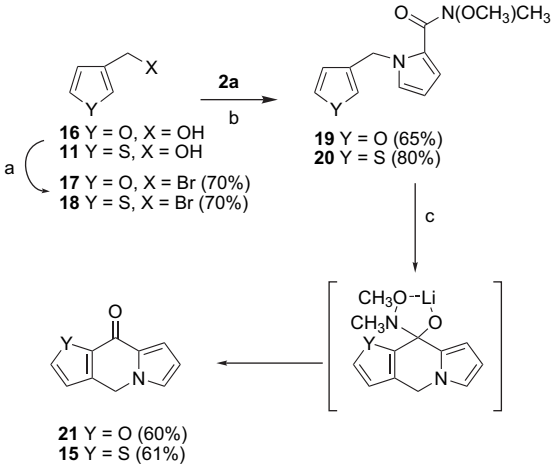
It was necessary to optimise the cyclisation conditions for this electron-rich heterocycle, and we finally chose two methods (A and B), using *t*-BuLi as metalating agent and quenching the reaction at low temperature, or allowing the reaction mixture to reach room temperature before quenching (Table 2). In this case, iodine–lithium exchange worked properly at −78 °C when Weinreb amide was used as internal electrophile (**14a**) and the reactions were quenched at low temperature. However, the use of *N*,*N*-diethyl amide **14b** only allowed the isolation of the thienoindolizidine **15** in modest yields (42%) under the same reaction conditions.[25] Besides, under method B conditions only dehalogenated amide was isolated (77% yield). This result is in agreement with our previously reported results[19] on the Parham cyclisation of *N*-arylmethylpyrrole-2-carboxamides with the *N*,*N*-diethylcarbamoyl group as internal electrophile. The iodine–lithium exchange on morpholine amide **14b** also took place efficiently, though it was necessary to use 3.5 equiv of the organolithium. The so-generated 2-lithiothiophene added smoothly to the amide. The intermediate was probably stabilised by chelate formation and only evolves to the ketone in aqueous media. Thus, the use of this type of amide also prevents elimination of the *N*,*N*-dialkyl group under basic conditions.

Table 2. Parham cyclisation of amides **14a**–**c**

Entry	Substrates	R	**15**, Yield (%)	
			Method A[a]	Method B[b]
1	**14a**	NMe(OMe)	71	49
2	**14b**	NEt_2	42	[c]
3	**14c**	Morpholine[d]	67	63

[a] *t*-BuLi (2.2 equiv), −78 °C, 3 h.
[b] *t*-BuLi (2.2 equiv), −78 °C, 3 h; →rt, 4 h.
[c] Dehalogenated amide was isolated (77%).
[d] *t*-BuLi (3.5 equiv) was used.

We then try to apply an analogous sequence to the construction of the furoindolizidine skeleton. However, since all attempts to prepare the 2-iodo-3-hydroxymethylfuran failed, we decided to generate the heteroaryllithium intermediates by hydrogen–lithium exchange. Therefore, we prepared the *N*-furylmethylpyrrole-2-carboxamide **19** from 3-furanmethanol **16** (Scheme 5). In this case, the intermediate 3-bromomethylfuran **17** was very unstable, so it was prepared and used in the alkylation step without prior purification. Although it is known that electron-rich five-membered aromatic heterocycles can be lithiated using alkyllithiums,[2b] in our case the use of *n*-BuLi or *t*-BuLi always resulted in addition to the amide carbonyl, so the corresponding ketones were the only reaction products.



Scheme 5. Reagents: (a) PBr_3, rt; (b) KOH, DMSO, rt; (c) LDA (2 equiv), −78 °C, 3 h.

However, LDA was capable of deprotonating **19** and the resulting 2-lithiofuran derivative gave the furo[3,2-*f*]indolizidone **21** in moderate yield (60%). In view of these results, the *ortho*-lithiation–cyclisation sequence was also applied to the non-halogenated *N*-thienylmethylpyrrole **20**, under the same reaction conditions, which provided the expected thienoindolizidone **15** in moderate yield (61%).

3. Conclusion

We have shown that the intramolecular cyclisation of heteroaryllithiums provides a useful entry to several types of

indolizidine based compounds starting from *N*-heteroarylmethylpyrrole-2-carboxamides. Halogen–lithium exchange reaction using *n*-BuLi (−90 °C, 5 min) is the method of choice to achieve metalation on the quinoline and pyridine derivatives, while directed lithiation (LDA, −78 °C) works better for furan. In the case of the thiophene both methodologies can be applied, but *t*-BuLi is needed to perform the iodine–lithium exchange. In all cases, cyclisation takes place smoothly when the reactions are quenched at low temperature. As expected, *N*-methoxy-*N*-methyl and morpholine amides behave as excellent internal electrophiles, improving the results obtained with *N*,*N*-diethyl amides. Therefore, these anionic heterocyclic annulation reactions represent a convenient approach to the preparation of pyrrolo[1,2-*b*]acridinones, pyrrolo[1,2-*g*]quinolones, as well as thieno and furo[3,2-*f*]indolizinones.

4. Experimental

4.1. General

Melting points were determined in unsealed capillary tubes and are uncorrected. IR spectra were obtained on KBr pellets (solids) or neat (oils). NMR spectra were recorded at 20–25 °C, running at 250 MHz for ^{1}H and 62.8 MHz for ^{13}C in $CDCl_3$ solutions. Assignment of individual ^{13}C resonances is supported by DEPT experiments. ^{1}H–{^{1}H} NOE experiments were carried out in the difference mode by irradiation of all the lines of a multiplet.[26] Mass spectra were recorded under electron impact at 70 eV. GC–MS analyses were performed using a TRB-1 column (methyl polysiloxane, 30 m×0.25 mm×0.25 μm). TLC was carried out with 0.2 mm thick silica gel plates. Visualisation was accomplished by UV light. Flash column chromatography[27] on silica gel was performed with Kieselgel 60 (230–400 mesh). All solvents used in reactions were anhydrous and purified according to standard procedures.[28] Organolithium reagents were titrated with diphenylacetic acid periodically prior to use. All air- or moisture-sensitive reactions were performed under argon; the glassware was dried (130 °C) and purged with argon.

4.2. Iodination of 11. Synthesis of 3-hydroxymethyl-2-iodothiophene (12)

A solution of I_2 (3.28 g, 12.9 mmol) in dry $CHCl_3$ (20 mL) was added over a suspension of CF_3COOAg (2.85 g, 12.9 mmol) and 3-hydroxymethylthiophene **11** (1.47 g, 12.9 mmol) in $CHCl_3$ (20 mL). The reaction mixture was stirred at 0 °C during 30 min, the resulting AgI precipitate was filtered through a Celite pad, and the resulting solution was washed with satd $Na_2S_2O_3$. The organic phase was dried (Na_2SO_4) and the solvent was evaporated. Flash column chromatography (silica gel, 30% hexane/AcOEt) afforded **12** as a colourless oil (1.88 g, 61%): IR (neat) 3333 cm^{-1}; ^{1}H NMR ($CDCl_3$) 3.66 (s, 1H), 4.48 (s, 2H), 6.92 (d, *J*=5.5 Hz, 1H), 7.40 (d, *J*=5.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) 61.6, 74.6, 127.7, 131.0, 145.1; MS (EI) *m*/*z* (rel intensity) 242 (M^++2, 4), 241 (M^++1, 6), 240 (M^+, 72), 223 (12), 113 (44), 112 (11), 111 (20), 96 (11), 85 (100), 84 (39), 83 (10), 82 (13), 81 (10), 69 (14), 58 (18), 57 (11). Anal. Calcd for C_5H_5IOS: C, 25.02; H, 2.10. Found: C, 25.22; H, 2.15.

4.3. Synthesis of bromides. General procedure

PBr_3 (0.19 mL, 2 mmol) was added over a solution of alcohols **5**, **12**, **16** or **11** (1 mmol) in dry CH_2Cl_2 (10 mL), and the reaction mixture was stirred at rt for 16 h. Solvent was evaporated and the resulting oil was treated with satd $NaHCO_3$. The resulting aqueous phase was extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo, yielding bromides **6**, **13**, **17** or **18**.

4.3.1. 2-Bromo-3-bromomethylpyridine (6).[29] According to the general procedure, **5** (2 g, 10 mmol) was treated with PBr_3 (1.9 mL, 20 mmol). After work-up, flash column chromatography (silica gel, 20% hexane/AcOEt) afforded **6** as a colourless oil (2.3 g, 86%): ^{1}H NMR ($CDCl_3$) 4.41 (s, 2H), 7.12 (dd, *J*=7.5, 4.8 Hz), 7.62 (dd, *J*=7.5, 1.8 Hz, 1H), 8.13 (dd, *J*=4.8, 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) 31.2, 122.4, 134.3, 138.9, 144.1, 149.8.

4.3.2. 3-Bromomethyl-2-iodothiophene (13). According to the general procedure, **12** (457 mg, 1.9 mmol) was treated with PBr_3 (0.3 mL, 3.8 mmol). After work-up, flash column chromatography (silica gel, 20% hexane/AcOEt) afforded **13** as a colourless oil (507 mg, 89%): IR (neat) 2923, 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$) 4.45 (s, 2H), 6.99 (d, *J*=5.5 Hz, 1H), 7.44 (d, *J*=5.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) 28.9, 78.3, 128.3, 131.6, 142.0; MS (EI) *m*/*z* (rel intensity) 305 (M^++2, 1), 304 (M^++1, 8), 303 (M^+, 1), 223 (100), 96 (38), 70 (22), 69 (19). Anal. Calcd for C_5H_4BrIS: C, 19.82; H, 1.33. Found: C, 19.14; H, 1.53.

4.3.3. 3-Bromomethylfurane (17).[30] According to the general procedure, **16** (0.2 mL, 2.3 mmol) was treated with PBr_3 (0.4 mL, 4.6 mmol). After work-up, flash column chromatography (silica gel, 20% hexane/AcOEt) afforded **17** as a colourless oil (261 mg, 70%): ^{1}H NMR ($CDCl_3$) 4.38 (s, 2H), 6.45 (s, 1H), 7.40 (s, 1H), 7.48 (s, 1H); ^{13}C NMR ($CDCl_3$) 23.5, 110.7, 118.6, 140.7, 143.6.

4.3.4. 3-Bromomethylthiophene (18).[31] According to the general procedure, **11** (0.2 mL, 2.3 mmol) was treated with PBr_3 (0.4 mL, 4.6 mmol). After work-up, flash column chromatography (silica gel, 20% hexane/AcOEt) afforded **18** as a colourless oil (283 mg, 70%): ^{1}H NMR ($CDCl_3$) 4.52 (s, 2H), 6.95 (s, 2H), 7.22 (s, 1H); ^{13}C NMR ($CDCl_3$) 33.9, 119.8, 125.7, 129.1, 135.6.

4.4. Alkylation reactions. General procedure

Pyrrole-2-carboxamide **2a**, **2b** or **2c**[19] (1 mmol) was added over a suspension of powdered KOH (224 mg, 4 mmol) in DMSO (5 mL). The mixture was stirred at rt for 2 h, bromide **1**, **6**, **13**, **17** or **18** (2 mmol) was added, and the reaction mixture was stirred for 3 h. H_2O (10 mL) was added and the resulting aqueous phase was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were washed with brine (3×10 mL), dried (Na_2SO_4) and concentrated in vacuo. Flash column chromatography (silica gel) afforded the corresponding carboxamides **3a**,**b**, **7a**,**b**, **14a**–**c**, **19** or **20**.

4.4.1. 1-(2-Bromoquinolin-3-ylmethyl)pyrrole-2-carboxylic acid methoxy methyl amide (3a). According to the

general procedure, *N*-methoxy-*N*-methylpyrrole-2-carboxamide **2a** (308 mg, 2 mmol) was treated with KOH (448 mg, 8 mmol) in DMSO (10 mL), and bromide **1** (1.2 g, 4 mmol). After work-up, flash column chromatography (silica gel, 30% hexane/AcOEt) afforded **3a** as a white solid, that was crystallised from Et_2O (585 mg, 76%): mp (Et_2O) 136–138 °C; IR (KBr) 1613 cm^{-1}; ^1H NMR ($CDCl_3$) 3.24 (s, 3H), 3.66 (s, 3H), 5.72 (s, 2H), 6.30 (dd, *J*=3.7, 2.6 Hz, 1H), 6.91 (dd, *J*=2.6, 1.8 Hz, 1H), 7.10 (dd, *J*=3.7, 1.8 Hz, 1H), 7.14 (s, 1H), 7.44–7.51 (m, 1H), 7.59–7.69 (m, 2H), 7.99 (d, *J*=8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) 33.4, 52.1, 61.0, 108.8, 117.6, 123.0, 127.1, 127.4, 127.5, 127.8, 128.2, 130.0, 133.4, 134.9, 141.3, 147.4, 161.7; MS (EI) *m/z* (rel intensity) 375 (M^++2, 3), 373 (M^+, 6), 316 (20), 315 (97), 314 (21), 313 (100), 264 (28), 223 (16), 222 (82), 221 (14), 220 (88), 209 (12), 208 (13), 207 (63), 206 (17), 205 (17), 178 (11), 176 (30), 141 (20), 140 (33), 103 (21). Anal. Calcd for $C_{17}H_{16}BrN_3O_2$: C, 54.56; H, 4.31; N, 11.23. Found: C, 54.88; H, 4.42; N, 11.19.

4.4.2. 1-(2-Bromoquinolin-3-ylmethyl)pyrrole-2-carboxylic acid diethyl amide (3b). According to the general procedure, *N*,*N*-diethylpyrrole-2-carboxamide **2b** (336 mg, 2 mmol) was treated with KOH (448 mg, 8 mmol) in DMSO (10 mL), and bromide **1** (1.2 g, 4 mmol). After work-up, flash column chromatography (silica gel, 30% hexane/AcOEt) afforded **3b** as a white solid, that was crystallised from Et_2O (585 mg, 76%): mp (Et_2O) 136–138 °C; IR (KBr) 1615 cm^{-1}; ^1H NMR ($CDCl_3$) 1.02 (t, *J*=6.7 Hz, 6H), 3.38 (q, *J*=6.7 Hz, 4H), 5.48 (s, 2H, CH_2), 6.16 (dd, *J*=3.8, 2.8 Hz, 1H), 6.42 (d, *J*=2.8, 1.6 Hz, 1H), 6.82 (br s, 1H), 7.43–7.48 (m, 2H), 7.60–7.65 (m, 2H), 7.95 (d, *J*=8.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) 13.4, 40.9, 51.0, 107.6, 111.6, 125.4, 125.8, 127.1, 127.2, 127.5, 128.1, 130.2, 132.5, 136.4, 141.8, 147.4, 163.1; MS (EI) *m/z* (rel intensity) 387 (M^++2, 47), 385 (M^+, 46), 316 (8), 315 (42), 314 (17), 313 (42), 312 (10), 307 (18), 306 (79), 305 (7), 286 (17), 285 (17), 235 (10), 234 (22), 233 (72), 223 (14), 222 (97), 221 (16), 220 (100), 207 (75), 206 (30), 205 (46), 141 (40), 140 (66), 115 (7), 114 (15), 113 (10), 103 (14), 100 (16), 72 (20). Anal. Calcd for $C_{19}H_{20}BrN_3O$: C, 59.08; H, 5.22; N, 10.88. Found: C, 59.18; H, 5.53; N, 10.56.

4.4.3. 1-(2-Bromopyridin-3-ylmethyl)pyrrole-2-carboxylic acid methoxy methyl amide (7a). According to the general procedure, *N*-methoxy-*N*-methylpyrrole-2-carboxamide **2a** (481 mg, 3.12 mmol) was treated with KOH (701 mg, 12.5 mmol) in DMSO (10 mL), and bromide **6** (1.6 g, 6.25 mmol). After work-up, flash column chromatography (silica gel, 30% hexane/AcOEt) afforded **7a** as an oil (668 mg, 66%): IR (neat) 1624 cm^{-1}; ^1H NMR ($CDCl_3$) 3.25 (s, 3H), 3.66 (s, 3H), 5.56 (s, 2H), 6.25 (dd, *J*=4.0, 2.6 Hz, 1H), 6.78 (dd, *J*=7.5, 1.6 Hz, 1H), 6.84 (dd, *J*=2.6, 1.8 Hz, 1H), 7.04 (dd, *J*=4.0, 2.0 Hz, 1H), 7.13 (dd, *J*=7.5, 4.8 Hz, 1H), 8.22 (dd, *J*=4.8, 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) 33.0, 51.4, 60.6, 108.4, 116.7, 122.5, 122.7, 127.5, 135.4, 135.9, 140.6, 147.9, 161.2; MS (EI) *m/z* (rel intensity) 325 (M^++2, 3), 323 (M^+, 4), 266 (13), 265 (100), 264 (13), 263 (100), 184 (15), 170 (50), 156 (19), 155 (21). Anal. Calcd for $C_{13}H_{14}BrN_3O_2$: C, 48.16; H, 4.35; N, 12.96. Found: C, 48.24; H, 4.53; N, 12.85.

4.4.4. 1-(2-Bromopyridin-3-ylmethyl)pyrrole-2-carboxylic acid diethyl amide (7b). According to the general procedure, *N*,*N*-diethylpyrrole-2-carboxamide **2b** (762 mg, 4.49 mmol) was treated with KOH (1.03 g, 18.3 mmol) in DMSO (10 mL), and bromide **6** (2.3 g, 9.2 mmol). After work-up, flash column chromatography (silica gel, 30% hexane/AcOEt) afforded **7b** as an oil (2.28 mg, 74%): IR (neat) 1616 cm^{-1}; ^1H NMR ($CDCl_3$) 1.10 (t, *J*=6.7 Hz, 6H), 3.23 (q, *J*=6.7 Hz, 4H), 5.33 (s, 2H), 6.14 (dd, *J*=4.0, 2.6 Hz, 1H), 6.38 (dd, *J*=4.0, 2.0 Hz, 1H), 6.84 (dd, *J*=2.6, 1.8 Hz, 1H), 7.04 (dd, *J*=7.5, 1.6 Hz, 1H), 7.13 (dd, *J*=7.5, 4.8 Hz, 1H), 8.19 (dd, *J*=4.8, 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) 13.4, 41.3, 50.6, 107.7, 111.4, 122.9, 125.1, 126.0, 135.7, 137.0, 141.5, 148.5, 163.0; MS (EI) *m/z* (rel intensity) 337 (M^++2, 43), 335 (M^+, 44), 266 (14), 265 (99), 264 (18), 263 (100). Anal. Calcd for $C_{15}H_{18}BrN_3O$: C, 53.58; H, 5.39; N, 12.49. Found: C, 53.46; H, 5.30; N, 12.53.

4.4.5. 1-(2-Iodothiophen-3-ylmethyl)pyrrole-2-carboxylic acid methoxy methyl amide (14a). According to the general procedure, *N*-methoxy-*N*-methylpyrrole-2-carboxamide **2a** (154 mg, 1 mmol) was treated with KOH (224 mg, 4 mmol) in DMSO (5 mL), and bromide **13** (610 mg, 2 mmol). After work-up, flash column chromatography (silica gel, 20% hexane/AcOEt) afforded **14a** as a white solid, that was crystallised from Et_2O (301 mg, 80%): mp (Et_2O) 91–92 °C; IR (KBr) 1620 cm^{-1}; ^1H NMR ($CDCl_3$) 3.32 (s, 3H), 3.63 (s, 3H), 5.43 (s, 2H), 6.15 (dd, *J*=4.0, 2.6 Hz, 1H), 6.60 (d, *J*=5.5 Hz, 1H), 6.85 (dd, *J*=2.6, 1.8 Hz, 1H), 6.92 (dd, *J*=4.0, 1.6 Hz, 1H), 7.34 (d, *J*=5.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) 33.6, 49.0, 60.8, 74.6, 107.9, 116.4, 122.8, 127.0, 127.8, 130.9, 143.1, 162.1; MS (EI) *m/z* (rel intensity) 376 (M^+, 1), 316 (23), 249 (21), 223 (31), 191 (6), 190 (14), 189 (100), 188 (6), 161 (6), 160 (9), 96 (14), 70 (6). Anal. Calcd for $C_{12}H_{13}IN_2O_2S$: C, 38.31; H, 3.48; N, 7.45. Found: C, 38.26; H, 3.45; N, 7.32.

4.4.6. 1-(2-Iodothiophen-3-ylmethyl)pyrrole-2-carboxylic acid diethyl amide (14b). According to the general procedure, *N*,*N*-diethylpyrrole-2-carboxamide **2b** (225 mg, 1.3 mmol) was treated with KOH (304 mg, 5.4 mmol) in DMSO (5 mL), and bromide **13** (821 mg, 2.7 mmol). After work-up, flash column chromatography (silica gel, 30% hexane/AcOEt) afforded **14b** as an oil (305 mg, 58%): IR (KBr) 1609 cm^{-1}; ^1H NMR ($CDCl_3$) 1.14 (t, *J*=7.1 Hz, 6H), 3.45 (q, *J*=7.1 Hz, 4H), 5.22 (s, 2H), 6.09 (d, *J*=2.8 Hz, 1H), 6.34 (dd, *J*=2.8, 1.6 Hz, 1H), 6.63 (d, *J*=5.5 Hz, 1H), 6.81 (d, *J*=1.6 Hz, 1H), 7.33 (d, *J*=5.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) 13.5, 40.9, 48.3, 75.0, 107.0, 111.1, 124.8, 125.8, 128.0, 130.9, 143.0, 163.5; MS (EI) *m/z* (rel intensity) 388 (M^+, 5), 262 (19), 261 (100), 223 (41), 190 (16), 189 (52), 188 (18), 168 (92), 162 (13), 160 (14), 100 (11), 97 (16), 96 (24), 94 (10), 72 (33), 70 (15), 56 (11). Anal. Calcd for $C_{14}H_{17}IN_2OS$: C, 43.31; H, 4.41; N, 7.21. Found: C, 43.22; H, 4.31; N, 7.35.

4.4.7. 1-(2-Iodothiophen-3-ylmethyl)pyrrole-2-carboxylic acid morpholino amide (14c). According to the general procedure, 2-morpholinocarbonylpyrrole **2c** (163 mg, 0.91 mmol) was treated with KOH (203 mg, 3.62 mmol) in DMSO (5 mL), and bromide **13** (548 mg, 1.81 mmol). After work-up, flash column chromatography (silica gel, 20% hexane/AcOEt) afforded **14c** as an oil (237 mg,

65%): IR (KBr) 1609 cm^{-1}; ^1H NMR ($CDCl_3$) 3.51–3.56 (m, 4H), 3.63–3.67 (m, 4H), 5.21 (s, 2H), 6.08 (dd, *J*=4.0, 2.8 Hz, 1H), 6.27 (dd, *J*=4.0, 1.6 Hz, 1H), 6.60 (d, *J*=5.6 Hz, 1H), 6.83 (dd, *J*=2.8, 1.6 Hz, 1H), 7.32 (d, *J*=5.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) 45.3, 48.2, 66.7, 75.1, 107.2, 112.8, 124.3, 125.5, 128.0, 131.0, 142.8, 162.7; MS (EI) *m/z* (rel intensity) 486 (M^+, 3), 360 (23), 359 (100), 307 (17), 273 (6), 267 (9), 266 (55), 114 (7), 70 (8). Anal. Calcd for $C_{14}H_{15}IN_2O_2S$: C, 41.80; H, 3.76; N, 6.96. Found: C, 41.84; H, 3.63; N, 6.61.

4.4.8. 1-(Furan-3-ylmethyl)pyrrole-2-carboxylic acid methoxy methyl amide (19). According to the general procedure, *N*-methoxy-*N*-methylpyrrole-2-carboxamide **2a** (382 mg, 2.3 mmol) was treated with KOH (520 mg, 9.3 mmol) in DMSO (5 mL), and bromide **17** (747 mg, 4.6 mmol). After work-up, flash column chromatography (silica gel, 20% hexane/AcOEt) afforded **19** as an oil (369 mg, 65%): IR (KBr) 1624 cm^{-1}; ^1H NMR ($CDCl_3$) 3.30 (s, 3H), 3.59 (s, 3H), 5.35 (s, 2H), 6.13 (dd, *J*=4.0, 2.6 Hz, 1H), 6.29 (s, 1H), 6.32 (dd, *J*=2.6, 1.8 Hz, 1H), 6.89 (dd, *J*=4.0, 1.8 Hz, 1H), 7.32–7.34 (m, 2H); ^{13}C NMR ($CDCl_3$) 33.8, 43.5, 60.9, 107.7, 110.1, 116.6, 122.7, 122.8, 126.9, 140.2, 143.2, 162.5; MS (EI) *m/z* (rel intensity) 235 (M^++1, 1), 234 (M^+, 8), 175 (11), 174 (94), 146 (22), 81 (100). Anal. Calcd for $C_{12}H_{14}N_2O_3$: C, 61.52; H, 6.02; N, 11.96. Found: C, 61.84; H, 6.13; N, 12.04.

4.4.9. 1-(Thiophen-3-ylmethyl)pyrrole-2-carboxylic acid methoxy methyl amide (20). According to the general procedure, *N*-methoxy-*N*-methylpyrrole-2-carboxamide **2a** (154 mg, 1 mmol) was treated with KOH (224 mg, 4 mmol) in DMSO (5 mL), and bromide **18** (354 mg, 2 mmol). After work-up, flash column chromatography (silica gel, 20% hexane/AcOEt) afforded **20** as an oil (200 mg, 80%): IR (KBr) 1620 cm^{-1}; ^1H NMR ($CDCl_3$) 3.27 (s, 3H), 3.55 (s, 3H), 5.51 (s, 2H), 6.15 (dd, *J*=4.0, 2.6 Hz, 1H), 6.85–6.93 (m, 3H), 7.01 (dd, *J*=2.6, 1.8 Hz, 1H), 7.21 (dd, *J*=4.0, 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) 33.6, 47.2, 60.5, 107.9, 116.2, 121.7, 122.6, 125.6, 126.6, 126.8, 139.4, 162.1; MS (EI) *m/z* (rel intensity) 250 (M^+, 3), 191 (9), 190 (64), 97 (100). Anal. Calcd for $C_{12}H_{14}N_2O_2S$: C, 57.58; H, 5.64; N, 11.19. Found: C, 57.33; H, 5.55; N, 11.09.

4.5. Iodination of 3a,b and 7a,b. General procedure

A solution of **3a**,**b** or **7a**,**b** (1 mmol) in dry dioxane (5 mL) was added via cannula over a suspension of NaI (300 mg, 2 mmol), CuI (5% mol) and *N*,*N*′-dimethylethylene diamine (10% mol) in dioxane (10 mL). The mixture was refluxed for 16 h. H_2O (10 mL) was added and the resulting aqueous phase was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were washed with brine (3×10 mL), dried (Na_2SO_4) and concentrated in vacuo. Flash column chromatography (silica gel) afforded the corresponding iodides **4a**,**b** and **8a**,**b**.

4.5.1. 1-(2-Iodoquinolin-3-ylmethyl)pyrrole-2-carboxylic acid methoxy methyl amide (4a). According to the general procedure, **3a** (374 mg, 1 mmol) was treated with NaI (300 mg, 2 mmol), CuI (5% mol) and *N*,*N*′-dimethylethylene diamine (10% mol). After work-up, flash column chromatography (silica gel, 30% hexane/AcOEt) afforded **4a** as an oil (358 mg, 85%): IR (KBr) 1617 cm^{-1}; ^1H NMR ($CDCl_3$) 3.19 (s, 3H), 3.62 (s, 3H), 5.67 (s, 2H), 6.27 (dd, *J*=3.7, 2.6 Hz, 1H), 6.88 (dd, *J*=2.6, 1.8 Hz, 1H), 7.07 (dd, *J*=3.7, 1.8 Hz, 1H)*, 7.08 (s, 1H)* 7.42–7.44 (m, 1H), 7.53–7.60 (m, 2H), 7.95 (d, *J*=8.5 Hz, 1H) (*Partially overlapped signals); ^{13}C NMR ($CDCl_3$) 33.5, 56.1, 61.0, 108.9, 117.2, 127.2, 127.4, 127.4, 127.5, 127.8, 128.5, 129.9.0, 130.1, 133.3, 135.7, 148.6, 168.7; MS (EI) *m/z* (rel intensity) 421 (M^+, 7), 361 (100), 315 (6), 268 (48), 234 (61), 205 (27), 141 (44). Anal. Calcd for $C_{17}H_{16}IN_3O_2$: C, 48.47; H, 3.82; N, 9.97. Found: C, 48.23; H, 3.59; N, 9.92.

4.5.2. 1-(2-Iodoquinolin-3-ylmethyl)pyrrole-2-carboxylic acid diethyl amide (4b). According to the general procedure, **3b** (386 mg, 1 mmol) was treated with NaI (300 mg, 2 mmol), CuI (5% mol) and *N*,*N*′-dimethylethylene diamine (10% mol). After work-up, flash column chromatography (silica gel, 30% hexane/AcOEt) afforded **4b** as an oil (347 mg, 80%): IR (KBr) 1619 cm^{-1}; ^1H NMR ($CDCl_3$) 1.08 (t, *J*=6.7 Hz, 6H), 3.44 (q, *J*=6.7 Hz, 4H), 5.46 (s, 2H), 6.21 (dd, *J*=3.6, 2.8 Hz, 1H), 6.42 (dd, *J*=3.6, 1.8 Hz, 1H), 6.82 (br s, 1H), 7.33 (s, 1H), 7.50–7.53 (m, 1H), 7.63–7.69 (m, 2H), 8.02 (d, *J*=8.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) 13.3, 41.2, 54.8, 107.6, 111.5, 122.4, 125.8, 127.0, 127.1, 127.4, 128.1, 129.9, 132.5, 134.5, 134.9, 148.4, 163.0; MS (EI) *m/z* (rel intensity) 434 (M^++1, 13), 433 (M^+, 41), 306 (100), 268 (33), 234 (45), 207 (44), 205 (42), 141 (44), 140 (44), 100 (49). Anal. Calcd for $C_{19}H_{20}IN_3O$: C, 52.67; H, 4.65; N, 9.69. Found: C, 52.48; H, 4.57; N, 9.72.

4.5.3. 1-(2-Iodopyridin-3-ylmethyl)pyrrole-2-carboxylic acid methoxy methyl amide (8a). According to the general procedure, **7a** (324 mg, 1 mmol) was treated with NaI (300 mg, 2 mmol), CuI (5% mol) and *N*,*N*′-dimethylethylene diamine (10% mol). After work-up, flash column chromatography (silica gel, 30% hexane/AcOEt) afforded **8a** as an oil (310 mg, 83%): IR (KBr) 1622 cm^{-1}; ^1H NMR ($CDCl_3$) 3.23 (s, 3H), 3.66 (s, 3H), 5.44 (s, 2H), 6.23 (dd, *J*=4.0, 2.6 Hz, 1H), 6.60 (dd, *J*=7.5, 1.6 Hz, 1H), 6.80 (dd, *J*=2.6, 1.8 Hz, 1H), 7.02 (dd, *J*=4.0, 2.0 Hz, 1H), 7.08 (dd, *J*=7.5, 4.8 Hz, 1H), 8.17 (dd, *J*=4.8, 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) 33.4, 51.8, 61.0, 108.8, 117.0, 123.1, 127.7, 127.8, 135.9, 136.3, 141.0, 148.4, 161.7. Anal. Calcd for $C_{13}H_{14}IN_3O_2$: C, 42.06; H, 3.80; N, 11.32. Found: C, 42.35; H, 3.88; N, 11.47.

4.5.4. 1-(2-Iodopyridin-3-ylmethyl)pyrrole-2-carboxylic acid diethyl amide (8b). According to the general procedure, **7b** (335 mg, 1 mmol) was treated with NaI (300 mg, 2 mmol), CuI (5% mol) and *N*,*N*′-dimethylethylene diamine (10% mol). After work-up, flash column chromatography (silica gel, 30% hexane/AcOEt) afforded **8b** as an oil (346 mg, 87%): IR (KBr) 1621 cm^{-1}; ^1H NMR ($CDCl_3$) 1.05 (t, *J*=6.7 Hz, 6H), 3.37 (q, *J*=6.7 Hz, 4H), 5.20 (s, 2H), 6.10 (dd, *J*=4.0, 2.6 Hz, 1H), 6.34 (dd, *J*=4.0, 2.0 Hz, 1H), 6.69 (dd, *J*=2.6, 1.8 Hz, 1H), 6.80 (dd, *J*=7.5, 1.6 Hz, 1H), 7.06 (dd, *J*=7.5, 4.8 Hz, 1H), 8.11 (dd, *J*=4.8, 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) 13.4, 41.3, 50.6, 107.7, 111.4, 122.9, 125.1, 126.0, 135.7, 137.0, 141.5, 148.5, 163.0 (CO). Anal. Calcd for $C_{15}H_{18}IN_3O$: C, 47.01; H, 4.73; N, 10.96. Found: C, 47.11; H, 4.66; N, 10.89.

4.6. Metalation–cyclisation reactions

Only experimental procedures of the best yielding method for the synthesis of **9**, **10**, **15** and **21** are given.

4.6.1. Synthesis of 11*H*-pyrrolo[1,2-*b*]acridin-4-one (9). To a solution of iodinated pyrrole-2-carboxamide **4a** (421 mg, 1 mmol) in dry THF (15 mL), *n*-BuLi (1.4 mL of a 1.6 M solution in hexanes, 2.2 mmol) was added at −90 °C, and the resulting mixture was stirred at this temperature for 5 min. The reaction was quenched by the addition of satd NH_4Cl (10 mL). Et_2O (15 mL) was added, the organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Flash column chromatography (silica gel, 50% hexane/AcOEt) afforded pyrrolo[1,2-*b*]acridinone **9** (199 mg, 85%): IR (KBr) 1650 cm^{-1}; ^1H NMR ($CDCl_3$) 5.62 (s, 2H), 6.50 (dd, *J*=4.0, 2.4 Hz, 1H), 7.15 (br s, 1H), 7.38 (dd, *J*=4.0, 1.2 Hz, 1H), 7.62–7.68 (m, 1H), 7.76–7.82 (m, 1H), 7.85 (d, *J*=8.3 Hz, 1H), 8.20 (s, 1H), 8.43 (d, *J*=8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) 46.7, 112.6, 115.9, 126.3, 126.9, 127.3, 128.3, 129.7, 130.5, 131.3, 131.8, 133.9, 146.4, 148.8, 173.1. MS (EI) *m*/*z* (rel intensity) 235 (M^++1, 21), 433 (M^+, 100), 233 (29), 206 (44), 205 (81), 166 (10), 151 (9), 140 (18), 114 (10), 103 (13). Anal. Calcd for $C_{15}H_{10}N_2O$: C, 76.91; H, 4.30; N, 11.96. Found: C, 76.49; H, 4.27; N, 11.94.

4.6.2. Synthesis of 5*H*-pyrrolo[1,2-*g*]quinolin-10-one (10). According to the procedure described for the synthesis of **9**, pyrrole-2-carboxamide **8a** (371 mg, 1 mmol) was treated with *n*-BuLi (1.4 mL of a 1.6 M solution in hexanes, 2.2 mmol) at −90 °C for 5 min. After work-up, flash column chromatography (silica gel, 50% hexane/AcOEt) afforded pyrrolo[1,2-*g*]quinolone **10** (156 mg, 85%): IR (KBr) 1640 cm^{-1}; ^1H NMR ($CDCl_3$) 5.39 (s, 2H), 6.37 (dd, *J*=4.0, 2.4 Hz, 1H), 7.05 (br s, 1H), 7.18 (dd, *J*=4.0, 1.2 Hz, 1H), 7.40 (dd, 7.0, 4.0 Hz, 1H), 7.70 (dd, *J*=7.0, 1.6 Hz, 1H), 8.72 (dd, *J*=4.0, 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) 46.9, 112.6, 115.7, 127.3, 128.1, 130.3, 131.7, 133.6, 146.2, 148.0, 173.1. Anal. Calcd for $C_{11}H_8N_2O$: C, 71.73; H, 4.37; N, 15.21. Found: C, 71.56; H, 4.25; N, 15.04.

4.6.3. Synthesis of 5*H*-thieno[3,2-*f*]indolizin-9-one (15).[25] To a solution of iodinated pyrrole-2-carboxamide **14a** (199 mg, 0.53 mmol) in dry THF (15 mL), *t*-BuLi (0.73 mL of a 1.6 M solution in pentane, 1.17 mmol) was added at −78 °C, and the resulting mixture was stirred at this temperature for 3 h. The reaction was quenched by the addition of satd NH_4Cl (10 mL). After standard work-up, flash column chromatography (silica gel, 30% hexane/AcOEt) afforded thieno[3,2-*f*]indolizinone **15**, that was crystallised from ethanol (71 mg, 71%): mp (EtOH) 160–163 °C (lit.[6] 168–170 °C); IR (KBr) 1632 cm^{-1}; ^1H NMR ($CDCl_3$) 5.33 (s, 2H), 6.39–6.40 (m, 1H), 7.05−7.11 (m, 3H), 7.67 (d, *J*=5.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) 46.3, 111.5, 112.5, 125.2, 125.8, 129.6, 133.4, 136.1, 141.8, 170.4. MS (EI) *m*/*z* (rel intensity) 191 (M^++2, 5), 190 (M^++1, 13), 189 (M^+, 100), 160 (33), 134 (5), 83 (5).

4.6.4. Synthesis of 5*H*-furo[3,2-*f*]indolizin-9-one (21). To a solution of pyrrole-2-carboxamide **19** (199 mg, 0.53 mmol) in dry THF (15 mL), LDA (10 mL of a 0.28 M solution in THF, 2.8 mmol) was added at −78 °C, and the resulting mixture was stirred at this temperature for 3 h. The reaction was quenched by the addition of satd NH_4Cl (10 mL). After standard work-up, flash column chromatography (silica gel, 50% hexane/AcOEt) afforded furo[3,2-*f*]indolizinone **21** (146 mg, 60%): IR (KBr) 1654 cm^{-1}; ^1H NMR ($CDCl_3$) 5.27 (s, 2H), 6.37 (dd, *J*=4.3, 2.6 Hz, 1H), 6.56 (d, *J*=1.8 Hz, 1H), 7.07 (dd, *J*=2.6, 1.6 Hz, 1H), 7.11 (dd, *J*=4.2, 1.6 Hz, 1H), 7.68 (d, *J*=1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) 44.3, 109.5, 111.4, 112.8, 126.0, 129.4, 131.0, 146.2, 147.5, 165.6. MS (EI) *m*/*z* (rel intensity) 174 (M^++1, 14), 173 (M^+, 100), 172 (21), 145 (16), 144 (10), 117 (46), 116 (15), 90 (31). Anal. Calcd for $C_{10}H_7N_2O$: C, 69.36; H, 4.07; N, 8.09. Found: C, 69.28; H, 4.10; N, 8.10.

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