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Unusual reactivity of 2-amino-1*H*-indole-3-carboxylate esters

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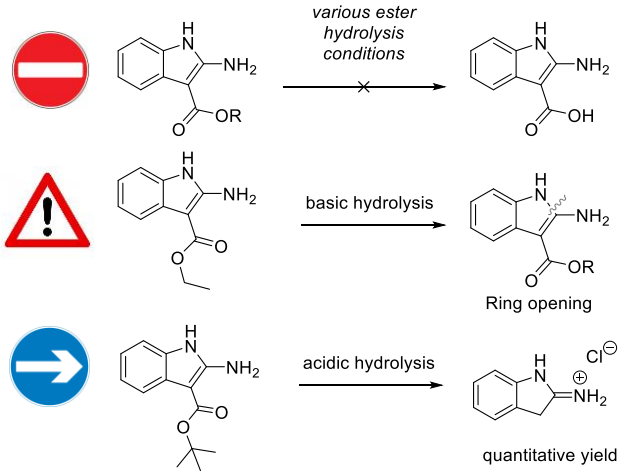
Abstract

We report the outcome of the attempted synthesis of amino-1*H*-indole-3-carboxylic acid from the corresponding ethyl and *tert*-butyl esters. Subjection of the *tert*-butyl ester to acidic conditions led to quantitative conversion to indolin-2-imine hydrochloride and the ethyl ester to basic conditions led to a ring-opened product, showing that the carboxylic acid is not easily-accessible *via* the corresponding esters. During the synthesis of the esters, the novel compound 2-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-1-yl)phenol was isolated and was shown to be chiral due to atropisomerism.



Keywords: Amino-1*H*-indole-3-carboxylate esters, 2-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-1-yl)phenol, atropisomerism, unusual reactivity

Introduction

The 2-aminoindole-3-carboxamide motif has increasingly appeared in drug discovery as a privileged heterocyclic scaffold. Examples include antitumor agent **1**, antibacterial agent **2** and gut-selective NaPib inhibitor **3 (Figure 1)**.[1-3]

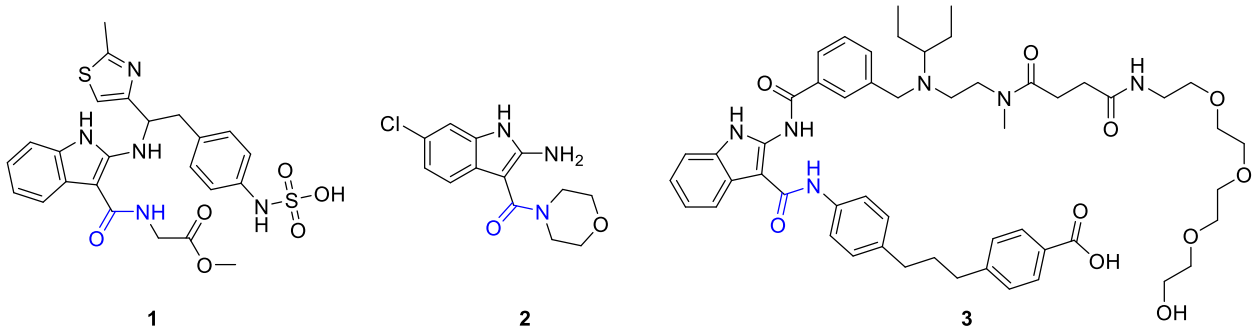
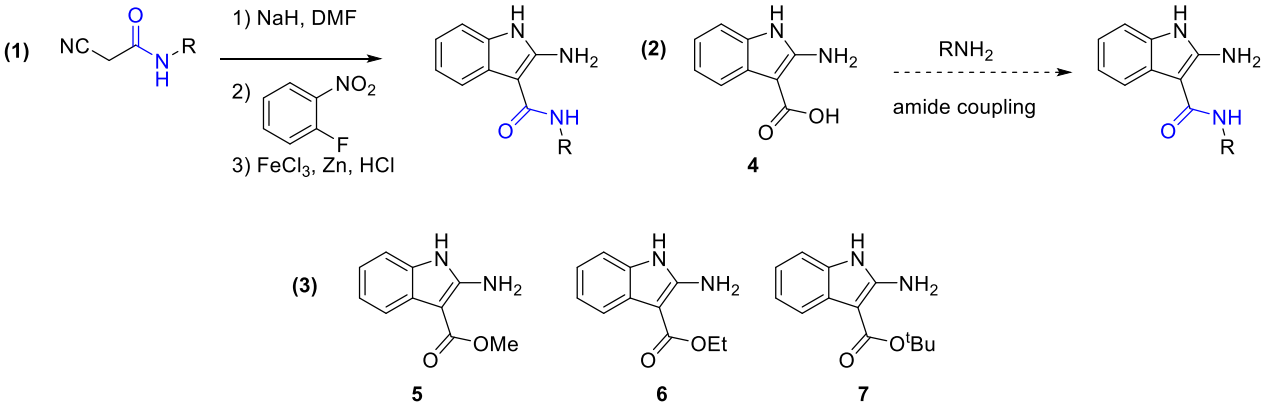


Figure 1. Examples of the 2-aminoindole-3-carboxamide scaffold.

During continued efforts at developing new therapies at our Medicines Discovery Institute, this scaffold appeared in a promising hit compound. Several reported methods exist for the synthesis of 2-aminoindole-3-carboxamides, with the most high-throughput being a two-step, one-pot protocol consisting of an SNAr reaction followed by a zinc and iron-mediated reductive cyclisation **(Scheme 1.1)**.[4] Despite being an attractive method of preparing analogues, the necessity of pre-forming the amide bond and the use of harsh conditions and metals in the final step of the synthesis limit its convenience as a route in medicinal chemistry.

Arrays are often employed in modern drug discovery projects as a way of rapidly understanding Structure Activity Relationships of new series, with amide bond forming reactions often used due to commercial availability of starting materials and the robust and reproducible nature of amide coupling reactions. Although discussed as a possible route, there is no report on the direct amide bond formation from 2-amino-1*H*-indole-3-carboxylic acid to form 2-aminoindole-3-carboxamides **(Scheme 1.2)**. This is despite the fact that the key carboxylic acid (**4**) has a CAS registry number, and that the corresponding esters have been published **(5**-**7**, **Scheme 1.3)**.[5,6] Esters **5**-**7** have been synthesised in moderate yields using 1,4-dihydropyridine in the presence of Pd/C in refluxing ethanol from the 2-nitrophenylcyano esters.[5] Esters **5** and **6** have also been prepared in better yields by a copper-catalysed route from the *N*-(2-halophenyl)-2,2,2-trifluoroacetamides and alkyl cyanoacetates.[6] In both instances, their hydrolysis is not discussed.

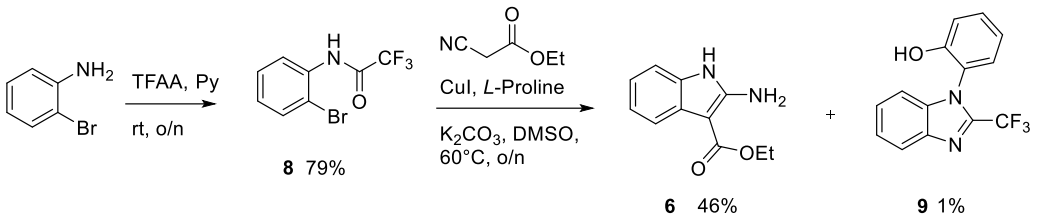


Scheme 1. Established one-pot synthesis, direct route and reported esters.

Herein, we report our efforts in the synthesis of 2-amino-1*H*-indole-3-carboxylic acid **4** for use in amide couplings, and include the synthesis of two unexpected products from the corresponding esters.

Results and Discussion

N-(2-Bromophenyl)-2,2,2-trifluoroacetamide **8** was prepared by a reported procedure and subjected to the copper-catalysed protocol.[6] The required ester, ethyl 2-amino-1*H*-indole-3-carboxylate **6**, was successfully isolated in a 46% yield **(Scheme 2)**.



Scheme 2. Synthesis of ethyl 2-amino-1*H*-indole-3-carboxylate.

An intriguing side-product that was not mentioned in the original reported synthesis and worthy of discussion (**9**), was also isolated in low amounts. ^{1}H and DEPT ^{13}C NMR spectroscopic analysis of the side-product pointed at 8 distinct aromatic C–H chemical environments and the distinctive quartet of the trifluoromethyl group being present. Despite also ionising cleanly to give a mass of 279.1 in +ive mode, we were at a loss to identify the dimer side-product. A single crystal grown by vapour diffusion and analysed by X-ray definitively assigned the structure as 2-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-1-yl)phenol **(Figure 2)**.

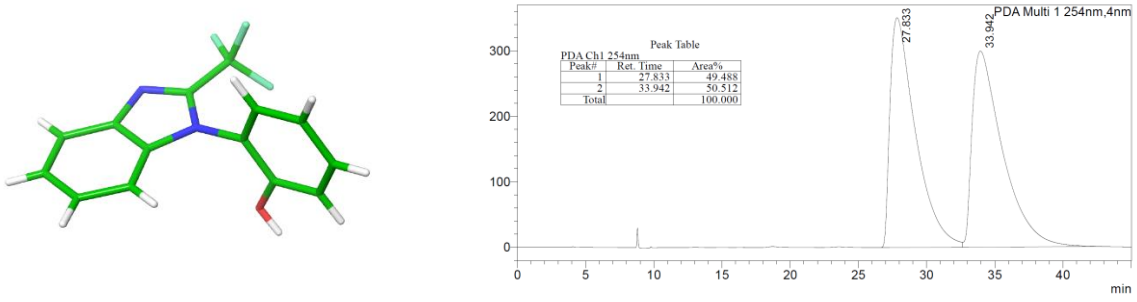


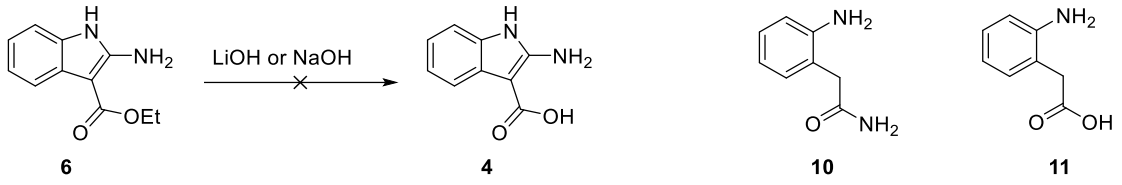
Figure 2. X-ray crystal structure and chiral HPLC analysis of **9**.

Such ortho-substituted trifluoromethyl biaryl compounds have gained considerable interest of late as they can display the property of atropisomerism.[7] Indeed, the analogous compound to **9**, with replacement of the alcohol by a carboxylic acid, is a promising chiral derivatising agent.[8] Since such compounds with a 2-hydroxy substitution pattern have not been reported in the literature, we set about confirming whether **9** was indeed chiral.

Two test reactions were run without the presence of ethyl cyanoacetate, one with *L*-proline and the other with *D*-proline to probe whether this was an enantioselective process. Both reactions again produced **9**, this time as the major component by UPLC analysis of the crude reaction mixtures. Isolated yields were poor (~1%), which may reflect on work-up and purification methods rather than reaction conditions, however, enough material was recovered from both reactions. The purified product **9** from both reactions were analysed by chiral HPLC analysis using a CHIRACEL OD-H column. Both showed clear separation of the enantiomers (**Figure 2**), confirming that **9** is chiral from atropisomerism. The equal relative integrations of the peaks indicate that either the reactions produced a racemic mixture, or that epimerisation occured during isolation or HPLC analysis. The reaction requires considerable optimisation, however it is expected to be of interest to the synthetic community due to the considerable potential applications of this type of compound.

With the key ester in hand, basic hydrolysis using separately NaOH and LiOH was attempted. In both reactions, no progress was observed under conditions that would typically hydrolyse most esters (room temperature, excess of base). Although formally drawn as an ester, its doubly-vinylogous amidic nature and related reduced electrophilicity may explain this lack of reactivity. Upon sustained heating, the ester was slowly consumed but no evidence of the carboxylic acid was present in UPLC analyses of the crude reaction mixture. A new, highly polar species appeared (Rt = 0.38 min, m/z: 152.0 in +ive mode). Aqueous work-up was avoided, the mixture purified by reverse-phase chromatography and the material analysed by ^{1}H NMR spectroscopy.

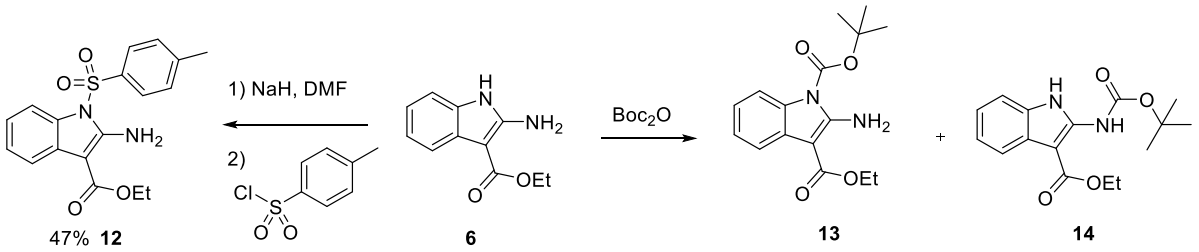
Two chemical species were present, with the major species possessing a distinctive 2H singlet at 1.89 ppm. This, along with the observed mass, indicated the aminoindole ring had opened in some way under the reaction conditions. **10** and **11** are possible degradation products, however, comparison with in-house generated ^{1}H NMR data ruled out **11**. Regardless of the exact identity, it was clear that typical basic hydrolysis conditions did not result in formation of the desired carboxylic acid **(Scheme 3)**.



6 **4** **10** **11**

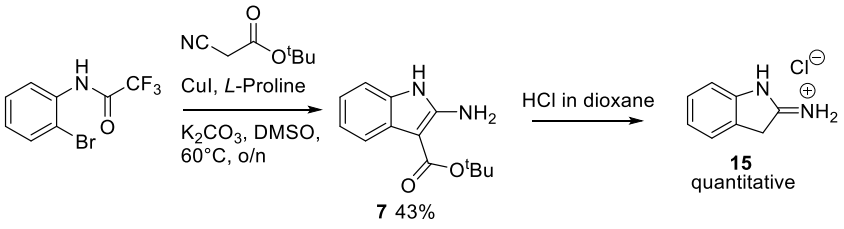
Scheme 3. Attempted basic hydrolysis of **3**.

Reasoning that the electron-donating character of the nitrogen atoms was the reason for **6**'s resistance to hydrolysis under basic conditions, we hypothesised that temporary protection of these nitrogens with a tosyl or Boc group would aid the ester hydrolysis. Reaction of **6** with tosyl chloride, although incomplete, led to the formation of only **12**, reacting solely on the indole nitrogen **(Scheme 4)**. Reaction of **6** with Boc anhydride, however, gave a mixture of two products resulting from reaction at both nucleophilic nitrogen sites **(13**, **14**, **Scheme 4)**. The crude products from these two reactions were subjected to typical basic reaction conditions for ester hydrolysis, however, no evidence of ester hydrolysis was observed by UPLC analysis, only removal of the protecting group to reform **6**.



Scheme 4. Nitrogen group protection.

To circumvent this synthetic hurdle, we chose to move our attention towards the analogous *tert*-butyl ester, which should be hydrolysable under acidic conditions. The *tert*-butyl ester **7** was synthesised as reported by Yang *et al*. in a similar yield to the ethyl ester **(Scheme 5)**.[6] The ester was dissolved in 4M HCl in dioxane. UPLC analysis indicated little conversion at room temperature, therefore the reaction mixture was gently heated to 50°C. UPLC analysis indicated complete consumption of starting material, however, there was no evidence of the desired carboxylic acid. No material was isolated following aqueous work-up.



Scheme 5. Synthesis and attempted acidic hydrolysis of **7**, forming **15.**

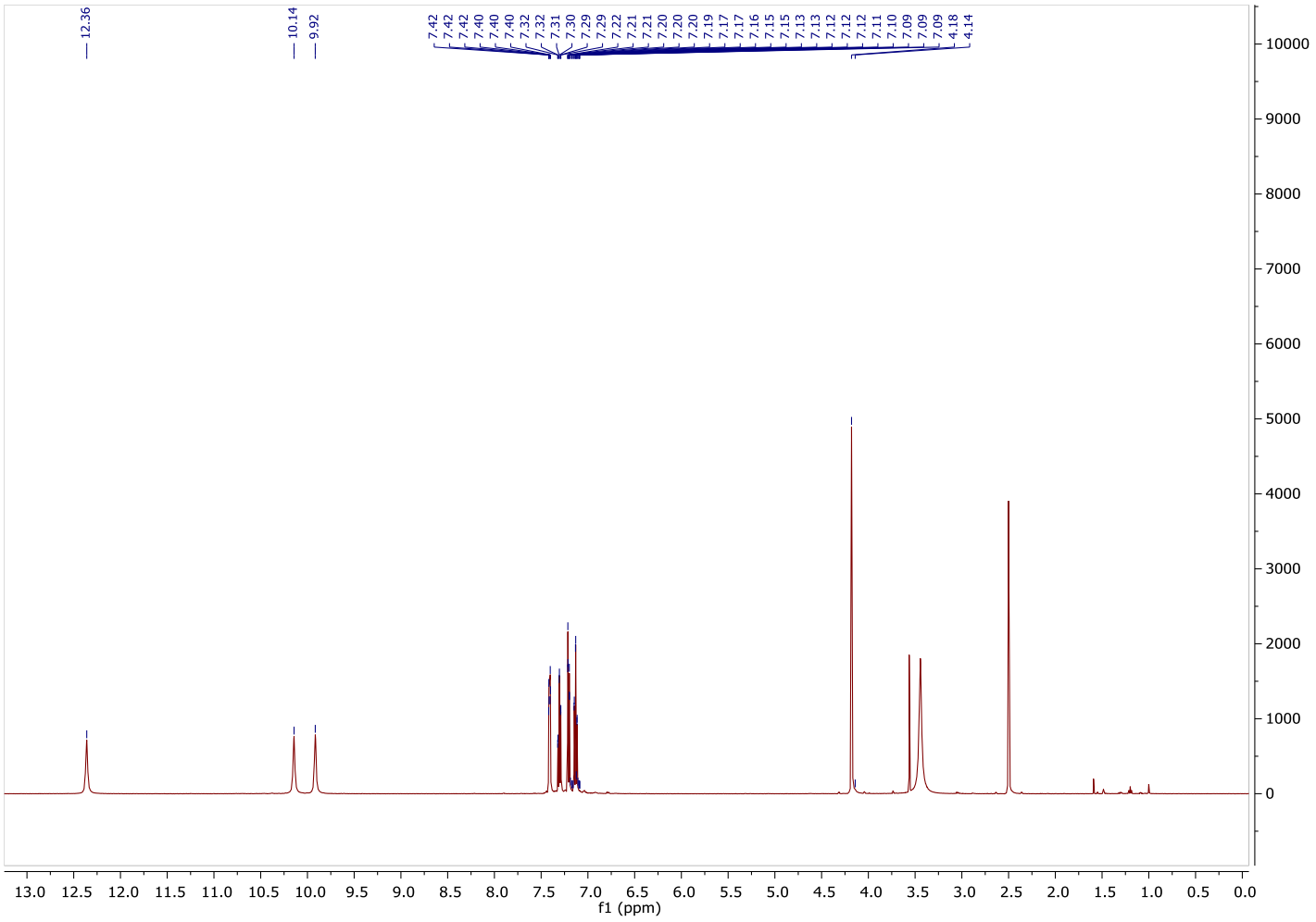
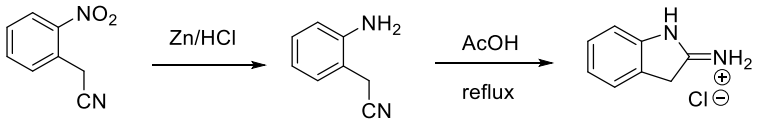


Figure 3. ^{1}H NMR spectrum of the crude reaction mixture of **15** (see **Scheme 5**).

The reaction was repeated but this time the reaction mixture was concentrated directly and the resulting dark solid analysed by ^{1}H NMR spectroscopy. The ^{1}H NMR spectrum was very clean **(Figure 3)** but was clearly not the target carboxylic acid. ^{1}H NMR spectroscopic analysis and comparison with literature values indicated the product to be the hydrochloride salt **15** following decarboxylation, whose previously reported synthesis is shown in **Scheme 6**.[9] Due to the facile nature of the reaction, requiring no purification other than concentration of the reaction mixture, **15** and the reaction itself should hold interest to the synthetic community.



Scheme 6. Previously reported synthesis of **15**.

In an attempt to avoid this decarboxylation, deprotection of the *tert* butyl ester was attempted using thionyl chloride, in the hopes we could trap the carboxylic acid as the acid chloride. However, the reaction led to a high number of intractable products following addition of an amine. Finally, direct amide coupling from the ethyl ester was attempted using trimethyl aluminium. Despite extended reaction times and elevated

temperatures, no reaction whatsoever was observed, again pointing towards the low electrophilicity of this ester.

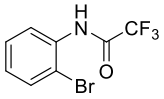
Conclusions

The studies detailed in this manuscript explain why 2-amino-1*H*-indole-3-carboxylic acid has not been reported in the literature, despite multiple reports on how to prepare the corresponding esters. Attempts at ester deprotection under both acidic and basic conditions failed to yield the carboxylic acid. We hope this will guide researchers on suitable routes to such amides in the future. Additionally, two unexpected products of interest are reported, one of which, 2-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-1-yl)phenol, is a compound with axial chirality properties in the form of atropisomerism.

Experimental Section

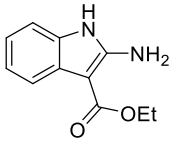
General. Unless otherwise explicitly stated, all starting materials, reagents and solvents were purchased from commercial suppliers and used as received without further purification. UPLC-MS refers to ultra-performance liquid chromatography-mass spectrometry analysis, using a Waters Acquity H-class plus UPLC coupled to a Waters Acquity UPLC PDA detector and a Waters Acquity QDa API-ES mass detector. Samples were eluted through a BEH C_{18} 2.1 × 50 mm, 1.7 µm column using water and acetonitrile acidified by 0.1% formic acid. The gradient runs water:MeCN:formic acid 90:10:0.1 to 10:90:0.1 over 3 min at 1.5 mL/min and detected at 254 nm. Retention times (Rt) correspond to the ones recorded by the UV detector. NMR were recorded on a Bruker Avance III HD 500 MHz equipped with a Prodigy cryoprobe. Chemical shifts are reported in parts per million (ppm) in the scale relative to residual solvent signals. Multiplicities are abbreviated according to the traditional convention (s, singlet; d, doublet; dd, double doublet; m, multiplet; etc.). Automated flash column chromatography was performed in a Teledyne ISCO CombiFlash NextGen 300+ system using a 12 g prepacked silica gel cartridge.

***N*-(2-Bromophenyl)-2,2,2-trifluoroacetamide (8)**[10]



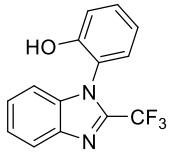
A solution of 2-bromoaniline (500 mg, 2.91 mmol) and pyridine (0.29 mL, 3.63 mmol) in CH_2Cl_2 (6.15 mL) was cooled to -5 - 0°C in an ice/acetone bath. Trifluoroacetic anhydride (0.44 mL, 3.2 mmol) was added dropwise over a period of 20 min, keeping the reaction mixture temperature below 5°C. The ice-bath was removed and the mixture was stirred at room temperature overnight. The reaction mixture was poured into water (6 mL) and extracted CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with 0.5M HCl (20 mL), water (20 mL) and brine (20 mL), then dried over Na_2SO_4, filtered and concentrated under reduced pressure to give *N*-(2-bromophenyl)-2,2,2-trifluoro-acetamide **8** (648 mg, 2.298 mmol, 83% yield) as a colourless solid which was used without purification in the next reaction. ^{1}H NMR (500 MHz, d_4-MeOD) δ 7.71 (ddd, *J* = 8.1, 1.4, 0.4 Hz, 1H), 7.53 – 7.48 (m, 1H), 7.47 – 7.40 (m, 1H), 7.31 – 7.24 (m, 1H). ACQUITY UPLC® BEH C_{18} 1.7µm: Rt = 1.62 min; 267.9 m/z $[MH]^-$

Ethyl 2-amino-1*H*-indole-3-carboxylate (6)[11]



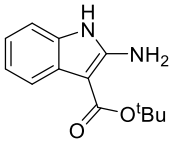
A Biotage microwave vial containing a magnetic stirrer, DMSO (3.4 mL) , substituted *N*-(2-bromophenyl)-2,2,2-trifluoro-acetamide **8** (1.00 g, 3.54 mmol), *L*-proline (81.6 mg, 0.71 mmol) potassium carbonate (980 mg, 7.09 mmol) and ethyl cyanoacetate (0.45 mL, 4.25 mmol) was degassed with nitrogen over a period of 15 min. Copper iodide (67.5 mg, 0.35 mmol) was added to the flask, the mixture degassed again for 5 min and the mixture heated to 60°C for 6 h before water (3.40 mL) was added and the mixture left to stir overnight at room temperature. The resulting mixture was filtered and the solid washed with MeOH (2 × 3 mL), and the combined filtrate concentrated under reduced pressure. The residue was redissolved in EtOAc (30 mL) and washed with brine (5 × 20 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product, which was purified by automated column chromatography on silica (12 g, ISCO, gradient from petroleum ether to 30% EtOAc over 30CV) to give ethyl 2-amino-1*H*-indole-3-carboxylate **6** (326 mg, 1.52 mmol, 46% yield) as an off-white solid and 2-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-1-yl)phenol **9** (10 mg, 1%) as a colourless solid. ^{1}H NMR (500 MHz, d_6-DMSO) δ 10.62 (s, 1H), 7.54 (d, *J* = 7.6 Hz, 1H), 7.10 (ddd, *J* = 7.7, 1.2, 0.7 Hz, 1H), 6.93 (td, *J* = 7.5, 1.2 Hz, 1H), 6.89 – 6.84 (m, 1H), 6.65 (s, 2H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.32 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H). ACQUITY UPLC® BEH C_{18} 1.7 µm: Rt = 1.59 (broad) min; m/z 205.2 $[M+H]^+$

2-(2-(Trifluoromethyl)-1*H*-benzo[*d*]imidazol-1-yl)phenol (9)



^{1}H NMR (500 MHz, d_6-DMSO) δ 10.25 (s, 1H), 7.93 – 7.87 (m, 1H), 7.47 – 7.39 (m, 4H), 7.16 – 7.08 (m, 2H), 7.03 (ddd, *J* = 7.9, 7.4, 1.3 Hz, 1H). ^{13}C NMR (126 MHz, d_6-DMSO) δ 153.6 (C), 140.3 (C), 140.2 (q, *J* = 38 Hz, C) 136.8 (C), 136.8, 131.6 (CH), 129.3 (CH), 125.8 (CH), 123.7 (CH), 120.8 (CH), 119.5 (CH), 118.8 (q, *J* = 278.5 Hz, CF_3), 116.8 (CH), 111.5 (CH). ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.0. Assignment supported by crystallographic data **(Figure 2)**. ACQUITY UPLC® BEH C_{18} 1.7 µm: Rt = 1.64 min; m/z 279.1 $[M+H]^+$ HRMS(EI) $C_{13}H_{17}N_2O_4$ requires 279.0745, found 279.0741 $[M+H]^+$

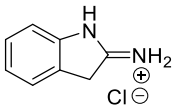
***Tert*-butyl 2-amino-1*H*-indole-3-carboxylate (7)**[3]



A Biotage microwave vial containing a magnetic stirrer, DMSO (27 mL) , substituted *N*-(2-bromophenyl)-2,2,2-trifluoro-acetamide **8** (7.61 g, 26.98 mmol), *L*-proline (621.3 mg, 5.40 mmol) potassium carbonate (7.459 g, 53.97 mmol) and *tert*-butyl cyanoacetate (3.86 mL, 26.98 mmol) was degassed with nitrogen over a period of 15 min. Copper iodide (0.514 g, 2.70 mmol) was added to the flask, the mixture degassed again for 5 min and the mixture heated to 60°C for 6 h before water (27 mL) was added and the mixture left to stir overnight at room temperature. The resulting mixture was filtered and the solid washed with MeOH (2 × 30 mL), and the

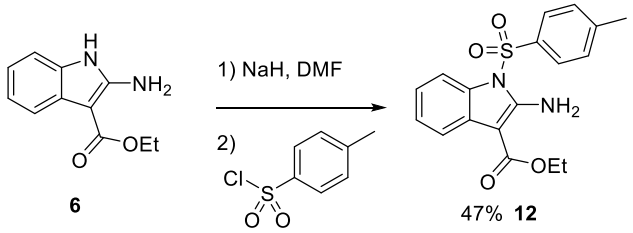
combined filtrate concentrated under reduced pressure. The residue was redissolved in EtOAc (100 mL) and washed with brine (5 × 60 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product, which was purified by automated column chromatography on silica (24 g, ISCO, gradient from petroleum ether to 30% EtOAc over 30CV) to give ethyl 2-amino-1*H*-indole-3-carboxylate **6** (2.90 g, 1.52 mmol, 47% yield) as an off-white solid. ^{1}H NMR (500 MHz, d_4-MeOD) δ 7.63 (d, *J* = 7.7 Hz, 1H), 7.07 – 7.03 (m, 1H), 6.96 (td, *J* = 7.6, 1.2 Hz, 1H), 6.90 (ddd, *J* = 7.3, 1.3 Hz, 1H), 1.62 (s, 9H). ACQUITY UPLC® BEH C_{18} 1.7 µm: Rt = 1.82 min; m/z 231.1 $[M-H]^-$

Indolin-2-imine hydrochloride (15)



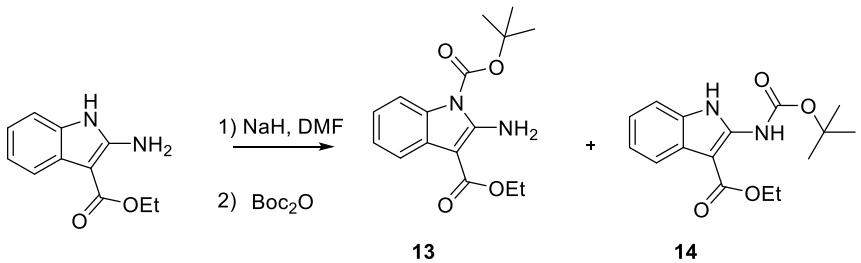
Tert-Butyl 2-amino-1*H*-indole-3-carboxylate **6** (329 mg, 1.42 mmol) was dissolved in 4M HCl in dioxane (5.0 mL) and left to stir at room temperature for 3 h. The reaction mixture was concentrated directly under reduced pressure in a fumehood and the resulting solid dried to give indolin-2-ylideneammonium hydrochloride **15** (240 mg, 1.344 mmol, quantitative yield). ^{1}H NMR (500 MHz, d_6-DMSO) δ 12.36 (s, 1H), 10.14 (s, 1H), 9.92 (s, 1H), 7.41 (dt, *J* = 7.5, 1.0 Hz, 1H), 7.31 (td, *J* = 7.7, 1.2 Hz, 1H), 7.21 (dt, *J* = 7.8, 0.8 Hz, 1H), 7.13 (td, *J* = 7.5, 1.1 Hz, 1H), 4.18 (s, 2H). In accordance with literature precedents.[9]

Preparation of **12**



A solution of ethyl 2-amino-1*H*-indole-3-carboxylate **6** (20 mg, 0.1 mmol) in anhydrous DMF (0.3 mL) was added dropwise to an ice cold suspension of sodium hydride (4.7 mg, 0.2 mmol) in anhydrous DMF (0.2 mL). The reaction was stirred at 0°C for 2h and then at room temperature for 4.5h. After UPLC-MS analysis evidenced product formation, the mixture was poured onto a saturated aqueous NH_4Cl solution (10 mL) and extracted with DCM (3 × 10 mL). The organic phase was concentrated under reduce pressure to afford the crude ethyl 2-amino-1-(p-tolylsulfonyl)indole-3-carboxylate **12** (22 mg, 0.046mmol, 47% yield) as a brown oil that was analysed via NMR. NMR analysis showed roughly a 75% conversion of starting material to product. Ester deprotection was conducted on this material without further purification. UPLC X-Select CSH C_{18} 50x3.0mm, 2.5u: Rt = 1.88 min; 359.2 m/z $[M+H]^+$

Preparation of **13** and **14**



A solution of ethyl 2-amino-1*H*-indole-3-carboxylate (12 mg, 0.06 mmol) in anhydrous DMF (0.3 mL) was added dropwise to a suspension of sodium hydride in anhydrous DMF (0.2 mL). The reaction mixture was stirred at room temperature for 1h. After UPLC-MS analysis showed product formation, the mixture was poured onto water (10 mL) and extracted with dichloromethane (3 × 20 mL). The organic phase was concentrated under reduced pressure to afford a 2:1 (estimated) mixture of ethyl 2-(tert-butoxycarbonylamino)-1*H*-indole-3-carboxylate **13** and **14** as a brown oil. Mixture of products observed by UPLC-MS (retention times: 1.93 and 2.00) and NMR. The mixture was subjected to attempted ester hydrolysis without further purification.

Acknowledgements

This research has been partly funded by the Coleg Cymraeg Cenedlaethol and the Harrington Rare Disease Scholar Award. We wish to extend our thanks to Prof. Thomas Wirth for use of equipment for chiral HPLC.

Supplementary Material

Characterisation data of synthesised compounds are available in the Supplementary Material file associated with this manuscript.

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