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Isoindolone Formation via Intramolecular Diels–Alder Reaction

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ABSTRACT: The intramolecular Diels–Alder reaction provides a useful synthetic methodology to build biologically active and synthetically useful isoindolone ring systems. An application of this methodology, providing an efficient manufacturing route to an mGluR2 positive allosteric modulator via a 1,5,7-substituted isoindolone, is reported herein.

DISCUSSION

The compound **1** is a mGluR2 positive allosteric modulator, with a primary indication for schizophrenia. The original medicinal chemistry route proceeded via an 11-step linear synthesis, the disconnection of which is shown in Scheme 1. The isoindolone ring was constructed by transformation of 4-bromo-2,5-dimethylaniline (**3**) to the corresponding acid **9** over three steps, followed by bromination, ester formation, and reaction with 4-trifluoromethoxybenzylamine (**4**) to give **12**. Conversion of the bromo group to the acid via cyanation and hydrolysis gave the isoindolone **2**. The oxadiazole ring was formed next by reaction with the chloro-amidoxime, followed by alkylation with *N*-BOC-piperazine and deprotection. This route was considered undesirable for scale-up due to its long linear nature. Retrosynthetic analysis within our process chemistry group suggested that the molecule could be more usefully disconnected across the oxadiazole ring to yield a more convergent synthesis utilising the amidoxime **5** and isoindolone **6**, **7** fragments.

Synthesis of the amidoxime fragment **5** was achieved via a two-step telescoped procedure whereby the commercially available *N*-BOC-piperazine was reacted with bromoacetonitrile and hydroxylamine, yielding the amidoxime **5** in good yield with processing which appeared suitable for long-term commercial manufacture, as shown in Scheme 2. The reaction was performed successfully at 100 L scale to produce approximately 14 kg of amidoxime **5** in total.

To utilise this amidoxime fragment, it was important then to find a suitable commercial synthesis of the isoindolone fragment **2**. The original medicinal chemistry route (disconnection shown in Scheme 1) to **2** was shortened, by the use of the commercially available 4-bromo-2,5-dimethyliodobenzene (**8**) (Scheme 3). Simple Grignard chemistry was used to form the acid **9** in one step, which was then neatly cyclised to **10** by bromination (ring-closure occurring immediately on bromination) (Scheme 3). Conveniently, the overbrominated products could be reduced by treatment with sodium borohydride in the same step to also yield **10**. Ring-opening with trimethylaluminium and 4-trifluoromethoxybenzylamine (**4**) proceeded smoothly, giving **11** (Scheme 3); although the residual aluminium salts proved troublesome to remove, dissolution with Rochelles salt finally was favored. Activation of the alcohol **11**, followed by base-induced ring closure led to isoindolone **12** (Scheme 3), although this was problematic on scale when using LDA. Significant dimer **18** formation was observed, which appeared to be linked to temperature control in this cryogenic step. Ultimately, sodium *tert*-pentoxide was shown to give a much cleaner and more robust (noncryogenic) process with dimer levels being completely controlled. Small amounts (3%) of **10** were observed by HPLC, presumably due to competing *O*-alkylation and hydrolysis. Palladium-catalysed cyanation of **12** was also problematic—reactions stalled on scale, repeat charges of the catalyst were necessary, and yields were variable. Simple hydrolysis of **13** yielded **2** (Scheme 3). The route, having delivered 7.2 kg of API to satisfy the first manufacturing campaign, encountered significant problems during the second manufacturing campaign. Concerns over the robustness and long-term viability of the route prompted a screen of alternative routes to **2**.

A number of different approaches were attempted, but only one realistic alternative was found, utilising an intramolecular Diels–Alder approach[1] to build the isoindolone ring (Scheme 4). The initial Vilsmeier reaction,[2] whilst operationally straightforward, did present significant challenges due to the instability of the reaction mixture at higher temperatures, and the potential for exothermic runaway. Ultimately, a risk-based approach was used to enable manufacture, and automated systems to 'dump' a chilled diluent into the reaction mixture in the event of thermal runaway allowed 130 kg of material to be manufactured in 50 kg (input) batch sizes. It is intended that the work performed in the development, safety review, and scale-up of this stage will be covered in a separate publication.[3] Aldehyde **15** (as a mixture of isomers) was isolated as a stable

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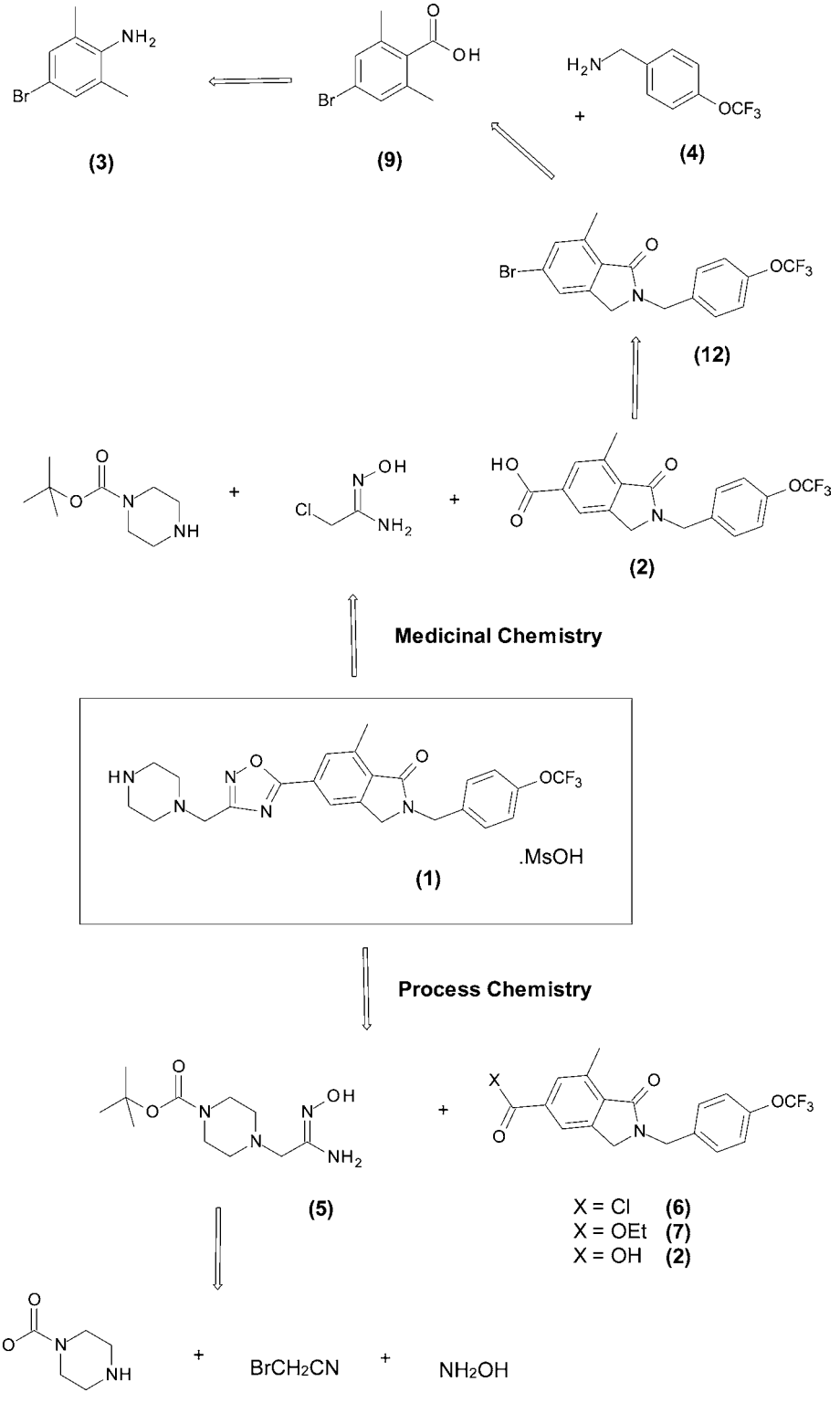
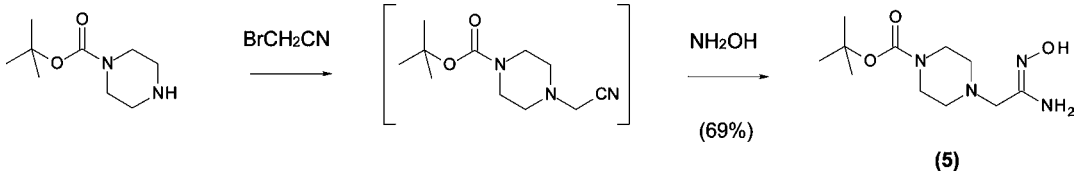
Scheme 1. Comparison of Medicinal and Process Chemistry disconnection strategies



Scheme 2. Synthesis of the amidoxime fragment



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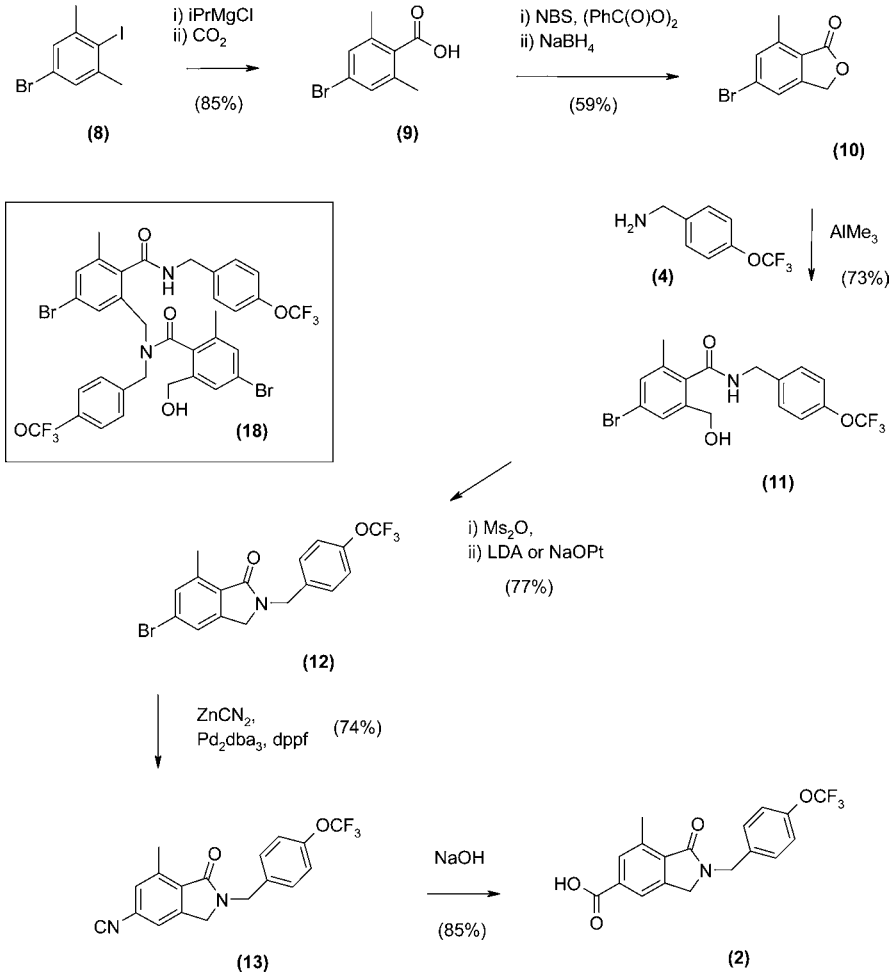
Scheme 3. Route used for first and second manufacturing campaigns



solution in toluene which could be used directly in the next stage without the need for purification. Reductive amination with 4-trifluoromethoxybenzylamine (**4**) and a $NaBH_4$/EtOH mixture worked well and, satisfyingly, gave an excellent purification procedure, the inseparable input mixture of 2-formyl-3-carboxylate and 5-formyl-3-carboxylate isomers, after reductive amination, crystallized exclusively as the desired isomer of the amine hydrochloride salt **16**. Scale-up to the pilot plant proceeded with no issues.

Treatment of this amine with crotonoyl chloride yielded the tertiary amide **19** (Scheme 5) in quantitative yield. After an aqueous wash, reflux of the resulting toluene solution[4] without isolation effected partial conversion (from **19**) to the tricyclic Diels–Alder product **20**, an equilibrium mixture held at roughly 75% conversion by the competing retro Diels–Alder reaction (Scheme 5). Addition of methanesulphonic acid to this mixture under Dean–Stark conditions effected conversion of **20** to the isoindolone ester species **7**, also forcing the equilibrium towards full consumption of the amide **19**. The Diels–Alder approach was trialled successfully at 2 L scale and was deemed suitable for long-term commercial manufacture. However, the project was discontinued before this stage could be scaled further.

Whilst it was found that the resulting isoindolone **7** could be converted easily to the corresponding acid **2** by simple hydrolysis, coupling to the amidoxime **5** could be achieved directly with better yield and processing by removing one synthetic step – addition of NaOEt/EtOH solution to a mixture of **5** and **7** in MeCN led to **17**, which could be isolated in excellent quality by addition of water. Subsequent treatment of **17** with MsOH simultaneously removed the BOC protection and furnished the API as the mesylate salt **1** to complete the four-stage synthesis in approximately 30% overall yield (from commercially available ethyl-3-furoate).

CONCLUSION

We report a highly efficient and low-cost four-stage synthesis of the API **1**, utilising intramolecular Diels–Alder chemistry to construct the isoindolone ring. Examples of this methodology have been growing in recent years but are still relatively rare in the literature[1] and limited in their scale of application and range of substitution patterns. Construction of isoindolones, on scale and with 1,5,7-substitution (derived from the cheap and readily available precursors), are hitherto unreported in the literature. This contribution demonstrates a useful addition to the application of this methodology. An optimised synthesis of ethyl 5-formylfuran-3-carboxylate has also been demonstrated on pilot-plant scale.

EXPERIMENTAL SECTION

Preparation of 4-Bromo-2,6-dimethylbenzoic Acid (9). A solution of 5-bromo-2-iodo-1,3-dimethyl-benzene (**8**) (10.0 g, 1.0 mol equiv) in methyl-*tert*-butyl ether (60 mL, 6.0 rel vol) was added to isopropylmagnesium chloride (2 M in THF, 2.0 mol equiv) in methyl-*tert*-butyl ether (20 mL, 2.0 rel vol),

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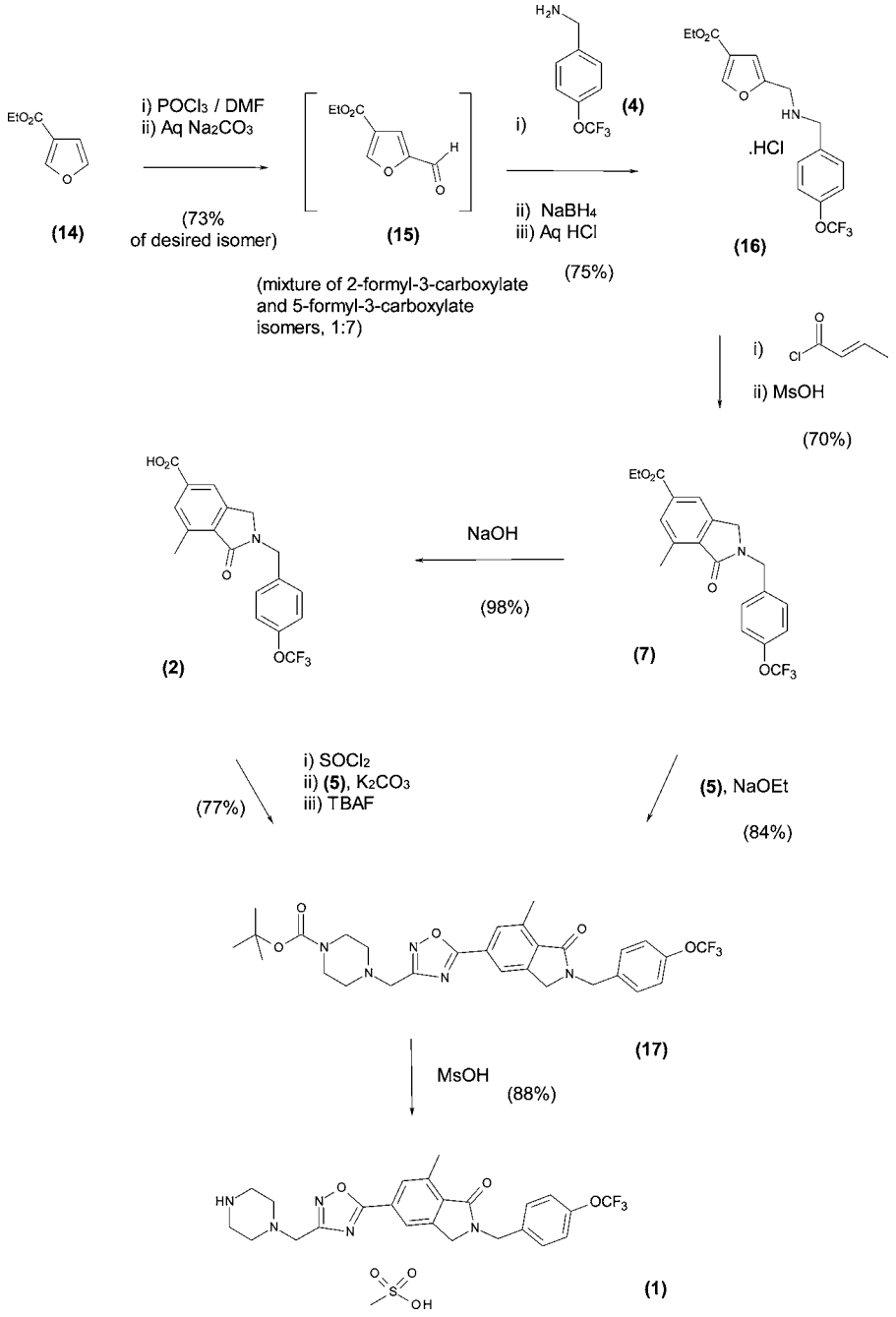
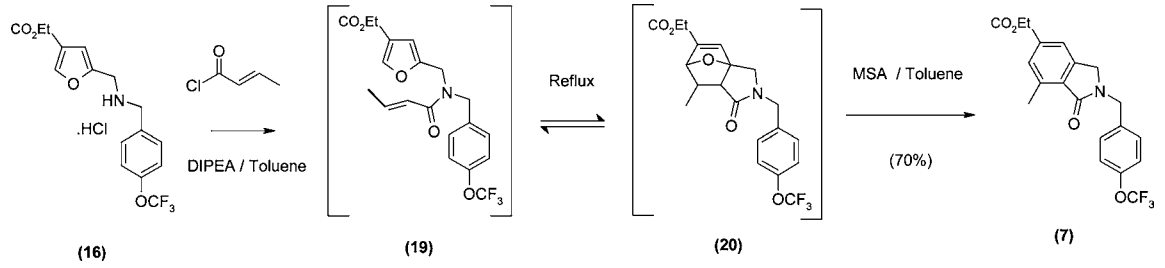
Scheme 4. Routes explored for third manufacturing campaign



Scheme 5. Intramolecular Diels–Alder reaction



maintaining <0 °C. Carbon dioxide gas was bubbled into the mixture until reaction was shown to be complete. Aqueous hydrochloric acid (2 N, 40 mL, 4.0 rel vol) was added to quench the reaction, the phases were separated, and the aqueous phase was discarded. The product was extracted into 1 M aqueous sodium hydroxide solution (65 mL, 6.5 rel vol) and

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then washed with methyl-*tert*-butyl ether (40 mL, 4.0 rel vol). The title compound **9** was precipitated by the addition of 2 N aq hydrochloric acid (45 mL, 4.5 rel vol) before being filtered, washed with water (20 mL, 2.0 rel vol) and then heptane (20 mL, 2.0 rel vol), and dried at 40 °C to yield a white crystalline solid (6.26 g, 85%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 2.28 (6 H, s), 7.35 (2 H, s), 13.30 (1H, s). Mp = 195 °C.

Preparation of 5-Bromo-7-methyl-2-benzofuran-1(3*H*)-one (10). A slurry of 4-bromo-2,6-dimethylbenzoic acid (**9**) (10 g, 1.0 mol equiv), *N*-bromosuccinimide (19.4 g, 2.5 mol equiv), and benzoyl peroxide (1.5 g, 0.1 mol equiv) in chlorobenzene (100 mL, 10 rel vol) was heated to >70 °C until the reaction was shown to be complete. A solution of 40% w/w aqueous sodium bisulfite (100 mL, 10.0 rel vol) was added to the reaction mixture, the phases were separated, and the aqueous phase was discarded. The organic phase was washed with saturated aqueous sodium bicarbonate (30 mL, 3.0 rel vol). The chlorobenzene phase was concentrated (to 30 mL, 3.0 rel vol) by vacuum distillation, and dimethylacetamide (25 mL, 2.5 rel vol) was added before adding this solution to a mixture of sodium borohydride (2.5 g, 1.6 mol equiv) in methyl-*tert*-butyl ether (40 mL, 4.0 rel vol) and dimethylacetamide (25 mL, 2.5 rel vol). The mixture was stirred until the reaction was shown to be complete. The mixture was then quenched with a solution of 36% w/w hydrogen chloride (25 mL, 2.5 mol equiv) in water (35 mL, 3.5 rel vol). Removing solvent by vacuum distillation precipitated the title compound **10** as a white crystalline solid, which was filtered and dried at 40 °C (5.9 g, 59%).

^{1}H NMR (400 MHz, d_6-DMSO) δ_H 2.57 (s, 3H), 5.32 (s, 2H), 7.60 (s, 1H), 7.73 (s, 1H). Mp = 97 °C.

Preparation of 4-Bromo-2-(hydroxymethyl)-6-methyl-*N*-[4-(trifluoromethoxy)benzyl]benzamide (11). 4-(Trifluoromethoxy)-benzylamine (3.0 g, 1.2 mol equiv) was added to a solution of 5-bromo-7-methyl-2-benzofuran-1(3*H*)-one (**10**) (3.0 g, 1.0 mol equiv) in 2-methyltetrahydrofuran (30 mL, 10.0 rel vol) and inerted. Trimethylaluminium (2 M in toluene, 7.9 mL, 1.2 mol equiv) was added and the resulting solution heated to >40 °C until the reaction was complete. The organic solution was then added to a cooled solution of potassium sodium tartrate (4.2 g, 1.5 mol equiv) in water (15 mL, 5.0 rel vol) and stirred. This biphasic mixture was separated and the aqueous phase discarded. The organic phase was washed with water (10 mL, 3.33 rel vol); then nonane (30 mL, 3.0 rel vol) was added and the 2-methyltetrahydrofuran removed by vacuum distillation to yield **11** as a white crystalline solid, which was filtered, washed with nonane (6 mL, 2.0 rel vol), and dried at 40 °C (73.5%).

^{1}H NMR (400 MHz, d_6-DMSO) δ_H 2.19 (s, 3H), 4.43 (d, 2H, 5.9 Hz), 4.45 (d, 2H, 6.0 Hz), 5.33 (t, 1H, 5.76 Hz), 7.34 (s, 1H), 7.35 (s, 2H), 7.47 (s, 1H), 7.49 (s, 2H), 8.85 (t, 1H, 5.76 Hz). Mp = 116 °C.

Preparation of 5-Bromo-7-methyl-2-[4-(trifluoromethoxy)benzyl-2,3-dihydro-1*H*-isoindol-1-one (12). Triethylamine (2.25 mL, 1.4 mol equiv) was added to 4-bromo-2-(hydroxymethyl)-6-methyl-N-[4-(trifluoromethoxy)benzyl]benzamide (**11**) (5.0 g, 1.0 mol equiv) in 2-methyltetrahydrofuran (25 mL, 5.0 rel vol). Methanesulphonyl chloride (0.98 mL, 1.1 mol equiv) was added to this solution, maintaining <5 °C. This was stirred until the reaction was shown to be complete. 35%w/w sodium *tert*-pentoxide in THF (9.1 mL, 2.5 mol equiv) was added maintaining <5 °C and the reaction stirred until reaction was shown to be complete. Water (50 mL, 10 rel vol) was added and the resulting biphasic mixture separated, discarding the aqueous phase. 2.7 M aqueous hydrochloric acid (20 mL, 4.0 rel vol) was added, the phases separated, discarding the aqueous phase. The organic phase was concentrated to dryness and the resulting wax recrystallised in heptane (20 mL, 4.0 rel vol). Filtering, washing with heptane (10 mL, 2.0 rel vol) and drying at 40 °C yields **12** as a white solid (77%).

^{1}H NMR (400 MHz, d_6-DMSO) δ_H 2.64 (s, 3H), 4.33 (s, 2H), 4.73 (s, 2H), 7.34 (d, 2H, 8.40 Hz), 7.42 (d, 2H, 8.40 Hz), 7.47 (s, 1H), 7.59 (s, 1H).

Preparation of 7-Methyl-1-oxo-2-[4-(trifluoromethoxy)benzyl]-2,3-dihydro-1*H*-isoindole-5-carbonitrile (13). 5-Bromo-7-methyl-2-[4-(trifluoromethoxy)-benzyl-2,3-dihydro-1*H*-isoindol-1-one (**12**) (40.0 kg, 1.0 mol equiv), zinc cyanide (0.6 mol equiv), 1,1′-bis-(diphenylphospino)ferrocene (0.012 mol equiv), tris-(dibenzylideneacetone)dipalladium(0) (0.005 mol equiv), dimethylformamide (5 rel vol) and water (0.25 mol equiv) were charged to a vessel and thoroughly inerted with nitrogen before heating to >90 °C until the reaction was shown to be complete. The reaction was cooled and *tert*-methyl butyl ether (13 rel vol) added with subsequent filtration. The organic phase obtained was washed twice with 8.75% w/w aqueous ammonium hydroxide (14 rel vol). Heptane (14 rel vol) was added to crystallize. Washing with a 9:1 heptane/MTBE mix and drying at 40 °C afforded (**13**) as a brown solid (74%).

^{1}H NMR (400 MHz, d_6-DMSO) δ_H 2.69 (d, 3H), 4.41 (s, 2H), 4.76 (s, 2H), 7.33 (d, 2H, J = 8.2 Hz), 7.42 (d, 2H, J = 8.4 Hz), 7.74 (s, 1H), 7.86 (s, 1H); Mp = 104 °C.

Preparation of 7-Methyl-1-oxo-2-[4-(trifluoromethoxy)benzyl]-2,3-dihydro-1*H*-isoindole-5-carboxylic Acid (2). 7-Methyl-1-oxo-2-[4-(trifluoromethoxy)-benzyl]-2,3-dihydro-1*H*-isoindole-5-carbonitrile (5.0 g) (**13**) was mixed with methanol (50 mL, 10 rel vol) and 49% aqueous potassium hydroxide (3.31 mL, 3.0 mol equiv) and heated until reaction was complete. The mixture was concentrated under vacuum to remove the methanol and then added to dilute aq hydrochloric acid to precipitate the product, which was extracted with isopropyl acetate. The organic phase was concentrated to remove solvent and then triturated with heptane, filtered, and dried at 40 °C to yield the title compound **2** (85%). Mp = 205 °C.

^{1}H NMR (400 MHz, d_6-DMSO) δ 2.71 (s, 3H), 4.42 (s, 2H), 4.77 (s, 2H), 7.35 (d, 2H, 8.73 Hz), 7.43 (d, 2H, 8.73 Hz), 7.81 (s, 1H), 7.91 (s, 1H), 13.19 (s, 1H, br). HRMS Calcd for $C_{18}H_{15}F_3NO_4$: 366.0948; HRMS found $[M + H]^+$: 366.0946.

Preparation of Ethyl 5-Formylfuran-3-carboxylate (15). To a solution of ethyl-3-furoate (**14**) (50 kg, 1 mol equiv) in *N*,*N*-dimethyl formamide (104.4 kg, 4 mol equiv) was cautiously added phosphoryl chloride (218.8 kg, 4 mol equiv). The resulting solution was heated to 60 °C until reaction was deemed complete. The reaction mixture was then added to a solution of sodium carbonate (312.1 kg, 8.25 mol equiv) in water (900 L, 18.0 rel vol). Toluene (350 L, 7.0 rel vol) was added, and the phases separated. The organic phase was concentrated (to 210 L, 4.2 rel vol total volume) under atmospheric pressure. This afforded a 22.1% w/w solution of the title compound **15** in toluene (73% of desired isomer).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.37 (3 H, t, 7.2 Hz), 4.33 (2 H, q, 7.2 Hz), 7.54 (1 H, m), 8.22 (1 H, m) and 9.69 (1 H,

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m). ^{13}C NMR (400 MHz, $CDCl_3$) δ 177.8, 161.6, 153.2, 151.4, 122.0, 119.7, 61.3, 14.2.

Preparation of Ethyl 5-{[(4-Trifluoromethoxybenzyl)-amino]methyl}-furan-3-carboxylate Hydrochloride (16). To a solution of ethyl 5-formylfuran-3-carboxylate (**15**) (63.9 kg, 1.0 mol equiv) in toluene (208 L, 3.0 rel vol), 4-(trifluoromethoxy)benzylamine (79.9 kg, 1.1 mol equiv) was added, stirring until the reaction was shown to be complete. Sodium borohydride (18.0 kg, 1.25 mol equiv) was added and the resulting slurry cooled to −5 °C. Ethanol (480 L, 7.5 rel vol) was added, and the resulting solution was quenched into aqueous hydrochloric acid (415 L, 6.5 mol equiv) to crystallise. This slurry was heated to >55 °C and then cooled to room temperature. Filtering and washing with aqueous ethanol and drying at 40 °C afforded the title compound **16** as a crystalline white solid (75%).

^{1}H NMR (400 MHz, d_6-DMSO) δ_H 1.28 (3 H, t, 7.2 Hz), 4.24 (6 H, m), 6.97 (1 H, s), 7.44 (2 H, d, 7.9 Hz), 7.70 (2 H, d, 8.6 Hz), 8.46 (1 H, d, 1.0 Hz). ^{13}C NMR (400 MHz, DMSO) δ 162.0, 149.0, 148.6, 147.6, 132.4, 131.3, 121.0, 120.0, 119.8, 111.7, 60.3, 48.6, 41.8, 14.1. Mp = 158 °C.

Preparation of Ethyl 7-Methyl-1-oxo-2-[4-(trifluoromethoxy)benzyl]-2,3-dihydro-1*H*-isoindole-5-carboxylate (7). Crotonoyl chloride (26.8 mL, 1.05 mol equiv) was added to a mixture of ethyl 5-{[(4-trifluoromethoxybenzyl)amino]methyl}-furan-3-carboxylate hydrochloride (**16**) (100 g, 1.0 mol equiv), diisopropylethylamine (113.5 mL, 2.5 mol equiv), and toluene (1 L, 10.0 rel vol) at ambient temperature. On complete reaction, the mixture was washed with water (500 mL, 5 rel vol), concentrated (to 5.0 rel vol total volume), and heated to reflux for >12 h under Dean−Stark conditions. Methanesulphonic acid (16.9 mL, 1.0 mol equiv) was added, and the reaction was then heated to reflux (Dean−Stark) until reaction was deemed complete (~24 h). The solution was then washed with 1.0 N aqueous sodium hydroxide solution (500 mL, 5.0 rel vol) and then water (500 mL, 5.0 rel vol). Heptane (1 L, 10.0 rel vol) was added, and the mixture was cooled to ambient temperature to crystallise. The mixture was filtered, washed with heptane (200 mL, 2.0 rel vol), and dried (55 °C) to yield the title compound **7** as a white crystalline solid (76.2 g, 74%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.40 (t, 3H, 7.12 Hz), 2.81 (s, 3H), 4.27 (s, 2H), 4.39 (q, 2H, 7.12 Hz), 4.78 (s, 2H), 7.18 (d, 2H, 8.60 Hz), 7.35 (d, 2H, 8.19 Hz), 7.87 (s, 1H), 7.90 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 168.4, 166.0, 148.7, 141.5, 138.0, 135.6, 133.2, 132.8, 131.3, 129.5, 121.4, 121.3, 120.4, 61.4, 48.9, 45.6, 17.1, 14.2; Mp = 135 °C.

Preparation of 7-Methyl-1-oxo-2-[4-(trifluoromethoxy)benzyl]-2,3-dihydro-1*H*-isoindole-5-carboxylic Acid (2). Ethyl 7-methyl-1-oxo-2-[4-(trifluoromethoxy)benzyl]-2,3-dihydro-1*H*-isoindole-5-carboxylate (**7**) (2.5 g, 1.0 mol equiv) was mixed with 2-propanol (10 mL, 4.0 rel vol) and 49% aqueous potassium hydroxide (0.67 mL, 1.5 mol equiv) and heated until reaction was complete. To this was added 36% w/w aqueous hydrochloric acid (1.0 mL, 2.0 mol equiv); the mixture was cooled to ambient temperature, and water was added (12.5 mL, 5.0 rel vol). The title compound **2** was then filtered and dried at 40 °C (98%).

^{1}H NMR (400 MHz, d_6-DMSO) δ 2.71 (s, 3H), 4.42 (s, 2H), 4.77 (s, 2H), 7.35 (d, 2H, 8.73 Hz), 7.43 (d, 2H, 8.73 Hz), 7.81 (s, 1H), 7.91 (s, 1H), 13.19 (s, 1H, br). HRMS Calcd for $C_{18}H_{15}F_3NO_4$: 366.0948; HRMS found $[M + H]^+$: 366.0946. Mp = 205 °C.

Preparation of *tert*-Butyl 4-[(2*Z*)-2-amino-2-hydroxyimino)ethyl]-piperazine-1-carboxylate (5). Bromoacetonitrile (0.531 L, 1.20 mol equiv) was charged to a cooled solution of *tert*-butyl piperazine-1-carboxylate (1.181 kg, 1.00 mol equiv) and tetramethylguanidine (1.157 L, 1.45 mol equiv) in tetrahydrofuran (4.25 L, 3.6 rel vol). When the reaction was complete, the mixture was warmed, 2-methyltetrahydrofuran (5.9 L, 5.0 rel vol) was added, and then the mixture was washed with water (1.77 L, 1.50 rel vol). The organic solution was concentrated by vacuum distillation before methanol (1.3 L, 1.10 rel vol) was charged, and the mixture was then cooled. Hydroxylamine hydrochloride (0.749 kg, 1.70 mol equiv), tetramethylguanidine (1.356 L, 1.70 mol equiv), and water (0.3 L, 0.25 mol equiv) were added, and the mixture was heated. When the reaction was complete, the mixture was charged with sodium chloride (0.18 kg, 0.15 rel wt) and allowed to separate into two phases. The lower phase was removed and back-extracted twice with 2-methyltetrahydrofuran (1.65 L, 1.40 rel vol). The combined organic phases were charged with heptane (9.45 L, 8.0 rel vol), cooled, and then charged with seed. The mixture was held before cooling further and charging more heptane. The title compound **5** was collected by filtration, washed once with cold water and twice with heptane, and then dried at 40 °C under vacuum (69%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.46 (s, 9H), 2.42 (m, 4H), 3.00 (s, 2H), 3.43 (m, 4H), 5.10 (s, 2H). HRMS Calcd for $C_{11}H_{23}N_4O_3$: 259.1765; HRMS found $[M + H]^+$: 259.1756; Mp = 154 °C.

Preparation of *tert*-Butyl 4-[(5-{7-Methyl-1-oxo-2-[4-(trifluoromethoxy)benzyl]-2,3-dihydro-1*H*-isoindol-5-yl}-1,2,4-oxadiazol-3-yl)methyl]piperazine-1-carboxylate (17). *tert*-Butyl 4-[(2*Z*)-2-amino-2-hydroxyimino)ethyl]-piperazine-1-carboxylate (**5**) (5.26 g, 1.0 mol equiv) and ethyl 7-methyl-1-oxo-2-[4-(trifluoromethoxy)benzyl]-2,3-dihydro-1*H*-isoindole-5-carboxylate (**7**) (8.31 g, 1.0 mol equiv) were mixed in acetonitrile (111 mL, 14 rel vol) at 60 °C. Sodium ethoxide (21%w/w in EtOH) (1.51 mL, 0.2 mols) was added over 20 min and the reaction held at 60 °C until reaction was complete. Water (83.1 mL, 10 rel vol) was added and the mixture cooled to ambient temperature. The title compound **17** was filtered and washed with water before being dried at 40 °C (84%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.46 (9 H, s), 2.58 (4 H, m), 2.84 (3 H, s), 3.50 (4 H, m), 3.79 (2 H, s), 4.33 (2 H, s), 4.81 (2 H, s), 7.20 (2 H, m), 7.36 (2 H, m), 7.99 (1 H, s), 8.04 (1 H, s). ^{13}C NMR (400 MHz, $CDCl_3$) δ 174.3, 168.2, 167.6, 166.6, 154.7, 148.9, 139.3, 136.0, 134.7, 133.4, 131.8, 130.3, 128.7, 121.4, 121.3, 120.5, 79.8, 52.9, 43.5, 41.0, 28.3, 17.6. HRMS Calcd for $C_{29}H_{33}F_3N_5O_5$: 588.2428; HRMS found $[M + H]^+$: 588.2432; Mp = 174 °C.

Preparation of *tert*-Butyl 4-[(5-{7-Methyl-1-oxo-2-[4-(trifluoromethoxy)benzyl]-2,3-dihydro-1*H*-isoindol-5-yl}-1,2,4-oxadiazol-3-yl)methyl]piperazine-1-carboxylate (17). A slurry of 2-(4-hydroxylbenzyl)-7-methyl-1-oxo-2,3-dihydro-1*H*-isoindole-5-carboxylic acid (**2**) (2.2 kg, 1.00 mol equiv) in toluene (17.6 L, 8.0 rel vol) was heated, and thionyl chloride (0.66 L, 1.50 mol equiv) was added. When reaction was complete, excess thionyl chloride and toluene were removed by atmospheric distillation. This solution was charged to a slurry of *tert*-butyl 4-[(2*Z*)-2-amino-2-hydroxyimino)-ethyl]-piperazine-1-carboxylate (**5**) (1.716 kg, 1.1 mol equiv) and potassium carbonate (1.043 kg, 1.25 mol equiv) in 2-methyl tetrahydrofuran (41.8 L, 19.0 rel vol). Tetrabutylam-

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monium fluoride (1 M in THF) (6.04 L, 1.0 mol equiv) was charged, and the contents were heated until the cyclisation was complete. After cooling the organic phase was washed with water before being concentrated by distillation. Methyl-*tert*-butyl ether was added to induce crystallization. After cooling, the title compound **17** was filtered, washed with methyl-*tert*-butyl ether and dried at 40 °C to constant weight in the vacuum oven (77%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.46 (9 H, s), 2.58 (4 H, m), 2.84 (3 H, s), 3.50 (4 H, m), 3.79 (2 H, s), 4.33 (2 H, s), 4.81 (2 H, s), 7.20 (2 H, m), 7.36 (2 H, m), 7.99 (1 H, s), 8.04 (1 H, s). ^{13}C NMR (400 MHz, $CDCl_3$) δ 174.3, 168.2, 167.6, 166.6, 154.7, 148.9, 139.3, 136.0, 134.7, 133.4, 131.8, 130.3, 128.7, 121.4, 121.3, 120.5, 79.8, 52.9, 43.5, 41.0, 28.3, 17.6.

HRMS Calcd for $C_{29}H_{33}F_3N_5O_5$: 588.2428; HRMS found $[M + H]^+$: 588.2432. Mp = 174 °C.

Preparation of 7-Methyl-5-[3-piperazin-1-ylmethyl)-1,2,4-oxadiazol-5-yl-]-2-[4-(trifluoromethoxy)benzyl]-2,3-dihydro-1*H*-isoindol-1-one Methanesulphonate (1). To a solution of *tert*-butyl 4-[(5-{7-methyl-1-oxo-2-[4-(trifluoromethoxy)benzyl]-2,3-dihydro-1*H*-isoindol-5-yl}-1,2,4-oxadiazol-3-yl)methyl]piperazine-1-carboxylate (**17**) (0.170 mol), in a mixture of 1-butanol (250 mL) and water (30 mL) at 85 °C, was added methanesulfonic acid (0.187 mol). After addition of further water (10 mL), the reaction mixture was held at 85 °C until reaction was complete. The reaction mixture was cooled to 65−70 °C before conducting a screening filtration into the crystalliser. The reaction vessel and the line into the crystalliser were then washed with hot (80 °C) 1-butanol (1 × 200 mL). The resulting reaction mixture was then held at 85 °C before adding 1-butanol (800 mL), then cooling to 78 °C, and seeding with **1** (0.1 g, 1% w/w). The reaction mixture was cooled to 15 °C. The reaction mixture was then temperature cycled to 65−70 °C twice, before filtration to afford the title compound **1** which was washed with 1-butanol (2 × 200 mL) before drying at 40 °C under vacuum to afford the title compound as a white solid (87.38 g, 88.0% yield). ^{1}H NMR (400 MHz, d_6-DMSO) δ 2.36 (3 H, s), 2.81 (4 H, m), 3.15 (4 H, m), 3.91 (2 H, s), 4.46 (2 H, s), 4.78 (2 H, s), 7.37 (2 H, m), 7.45 (2 H, m), 8.00 (1 H, m), 8.12 (1 H, m), and 8.59 (1H, br s). HRMS Calcd for $C_{24}H_{25}F_3N_5O_3$: 488.1904; HRMS found $[M + H]^+$: 488.1887. Mp = 225 °C.

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Notes

The authors declare no competing financial interest.

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