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Rapid Scale-Up of the Matrix Metalloproteinase Inhibitor CH5902: Process Safety and Route Development Considerations

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Abstract:
The synthesis of the novel MMP inhibitor CH5902 is described. In this approach, the original discovery route has been streamlined and telescoped into a four-stage sequence, which has been demonstrated on a multikilogram scale. A number of issues arising from both process development and process safety concerns are discussed.

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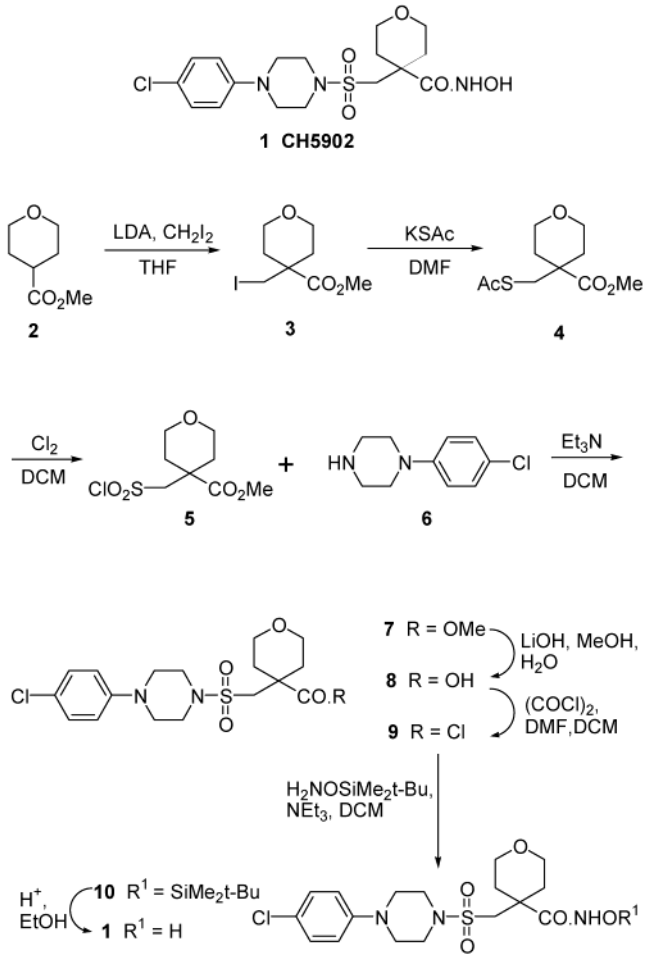
Introduction

Design of inhibitors of matrix metalloproteinase (MMP) enzymes has been a fertile area of pharmaceutical research, and a number of compounds have entered into development as putative treatments for cancer and/or inflammatory conditions (such as rheumatoid arthritis, age-related macular degeneration) thought to be mediated by such enzyme targets.[1] These have included the "first generation" inhibitors Marimastat and Batimastat (British Biotechnology) and follow-up compounds such as Trocade (Roche), Prinomastat (Agouron/Pfizer), and BMS275291 (Celltech/Bristol-Myers Squibb). We report here approaches to the synthesis of a novel MMP inhibitor CH5902 (**1**, 4-[4-(4-chlorophenyl)-piperazin-1-yl)sulfonylmethyl]-tetrahydropyran-4-carboxylic acid *N*-hydroxy amide) which was selected for further evaluation by Celltech. As in all such early-stage pharmaceutical development projects, compound supply is firmly on the critical path and process research and development chemists are charged with supplying kilogram quantities of material as soon as possible in order to initiate the preclinical work. This paper details our efforts, which resulted in the provision of kilo quantities of **1** within six months of project initiation. Of particular note is the input of both process safety and process development into the overall effort that facilitated the rapid scale-up to 50 L Kilo Lab reactors.

Medicinal Chemistry Route

The route used by the discovery chemists is shown in Scheme 1. As regards suitability for scale-up, it suffers from a number of obvious and practical drawbacks, notably (i) length, eight discrete steps involving product isolation, (ii) several steps require purification by chromatography, (iii) at least one of the intermediates is an oil, and (iv) a protecting group is used in the final coupling to form the hydroxamate which then requires deprotection. However, none of these problems were considered terminal, and with suitable modifications, this strategy formed the basis of our initial development thoughts.

Scheme 1. **Discovery Route to CH5902**



Towards a Multikilogram Synthesis

Clearly the first objective was to minimize the number of isolated stages, preferably avoiding the isolation of intermediates that are oils or that are potentially unstable to ambient conditions (e.g., materials that are moisture sensitive). This immediately precludes both the acid chlorides (**5** and **9**) and the iodide **3**, which is an oil. The route then naturally simplifies to four discrete stages: formation of the thioacetate **4** (stage 1), oxidation and coupling to form the

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(1) (a) Marshall, J. L.; Baidas, S.; Bhargava, P.; Rizvi, N. *Idrugs* **2000**, *3*, 518. (b) Whittaker, M. F.; Christopher D.; Brown, P.; Gearing, A. J. H. *Chem. Rev.* **1999**, *99*, 2735.

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Figure 1.

sulphonamide ester **7** (stage 2), hydrolysis to the corresponding acid **8** (stage 3), and finally conversion to the required hydroxamic acid **1** (stage 4). This strategy formed the basis of our approach to a scaleable synthesis.

Stage 1. Preparation of the thioacetate **4** from tetrahydropyran-4-carboxylic acid methyl ester (THPE, **2**) is now two consecutive reactions where the intermediate iodide **3** is not isolated but formed in situ and then reacted with potassium thioacetate.

The original discovery route involved generation of the anion from THPE (**2**) by the addition of commercial lithium diisopropylamide (LDA) followed by the addition of diiodomethane. Under these conditions, the iodide **3** can be obtained in ~50% yield after chromatography. Although the product **11** (see Figure 1) resulting from the bis-alkylation of diiodomethane was not found, considerable yield (equivalent to 22% THPE input) was lost due to the formation of the acylated compound **12**. In addition, we found that the activity of commercial LDA was variable and hence the use of freshly prepared LDA (from diisopropylamine and *n*-butyllithium) was preferred.

The formation of the impurity **12** can be eliminated simply by the reverse addition, that is, addition of **2** to preformed LDA, followed by the addition of diiodomethane, and this was essentially the method chosen for scale-up. Initially this involved formation of the THPE (**2**) anion at −10 °C followed by addition of diiodomethane at the same temperature and then warming to give the condensation product **3**. However, when this was performed in a reaction calorimeter (Mettler RC1), only a minor exotherm was observed following the diiodomethane addition, but the heat evolution increased substantially when the reaction mixture was heated (Figure 2). Approximate calculations showed that an adiabatic temperature rise of 82 °C could be expected from this reaction indicating that there was sufficient energy liberated to raise the reaction temperature above reflux. As the safety of scale-up operations has to account for a reduction in cooling capability per unit volume and the possibility of credible plant failure (e.g., cooling systems), it was felt that, due to the high level of accumulation of unreacted reagent, there was an appreciable risk that this reaction could run out of control on scale-up with hazardous consequences.

The kinetics of this reaction were analysed using a second-order reaction kinetic model. The values obtained for the heat evolution were corrected for the degree of conversion by dividing the heat output rate by the degree of thermal conversion (heat evolved at time *t* divided by the total heat evolved). This gave values for the normalized heat output rate, and these were used to calculate the time required for two reaction half-lives as a function of temperature (Figure 3). After this time, the rate of reaction heat evolution would be $^1/_{16}$ of its initial rate and the potential temperature rise at $^1/_4$ of its initial level (i.e., ~20 °C in this case).

These data indicated that acceptable operating conditions might exist when the reagent addition time was the time taken for two reaction half-lives. This conclusion was confirmed by performing a second isothermal reaction calorimetry experiment in which the diiodomethane was added to the anion at 0 °C over 2 h and then the resulting mixture was heated to 20 °C. The heat evolved during this experiment was used to calculate the maximum possible batch temperature due to an adiabatic temperature rise (e.g., in the event of coolant failure with simultaneous cessation of the addition). These values are summarized in Figure 4, which shows that safe operating conditions are possible with a 2 h addition at 0 °C since the maximum possible excursion temperature of 15 °C is less than the final batch temperature of 20 °C. The rate of heat output was compared to that expected for isothermal second-order reaction kinetics with a constant rate constant. As the observed rate matched the prediction

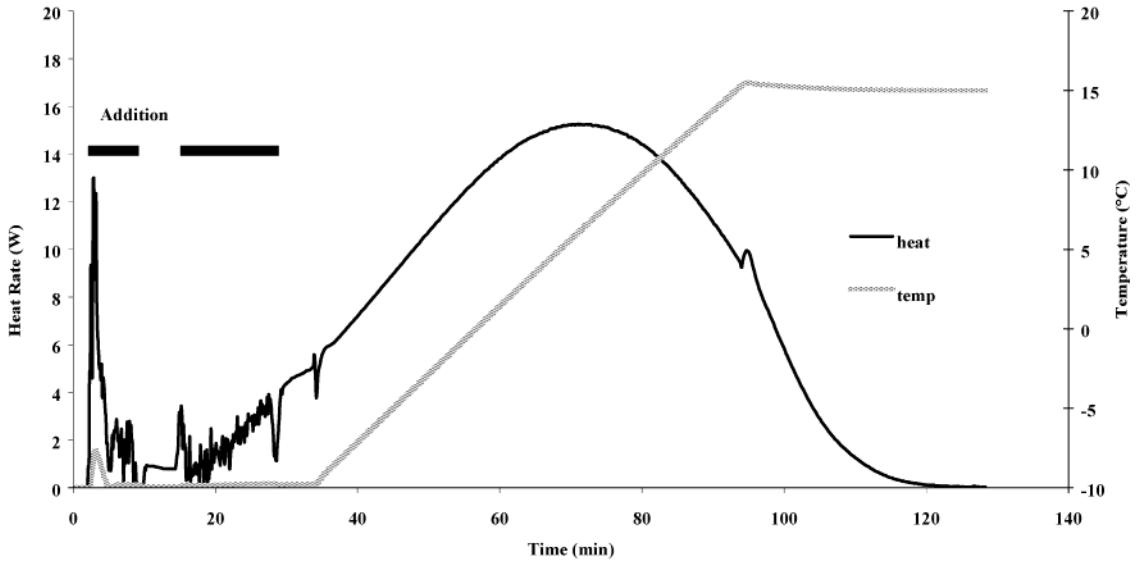


Figure 2. **Rate of heat evolution during reaction with diiodomethane.**

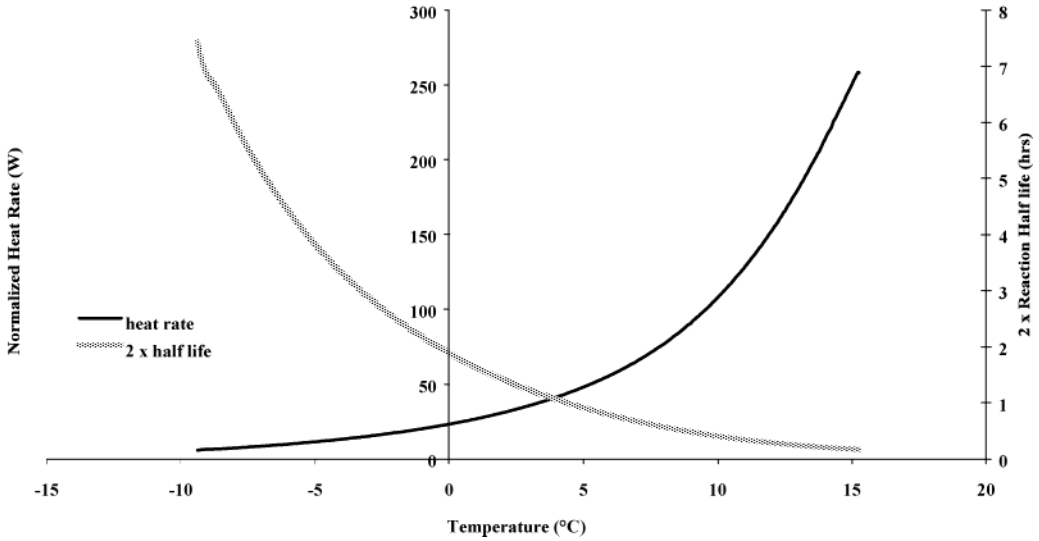


Figure 3. **Normalized heat rate and time for two half-lives.**

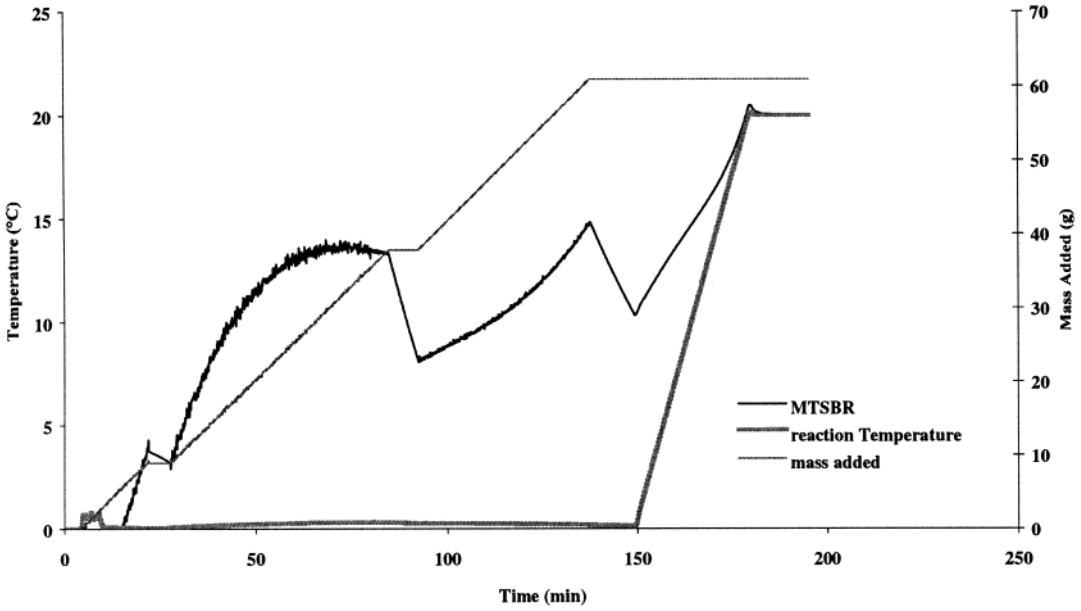


Figure 4. **Maximum temperature of semibatch reaction.**

consistently over the course of the reaction, it was felt that the assumption of second-order reaction kinetics was justified.

On scale-up of this process to 50 L vessels, the addition of diiodomethane was strictly controlled such that the reaction temperature was maintained at 0−10 °C with a minimum addition time of 1.5 h. At the completion of the iodomethylation reaction, the intermediate **3** was extracted into toluene prior to a solvent swap into dimethylformamide (DMF) for the displacement reaction with potassium thioacetate. Isolation of the thioacetate **4** was then achieved by aqueous drown-out and filtration of the product, which is a low melting solid (mp 63 °C). This procedure was scaled up to the 50 L Kilo Lab for a run of five batches. In one such batch, the product **4** failed to precipitate after the water drown-out, producing only an immiscible oil. Subsequent investigation showed the presence of residual toluene resulting from an incomplete solvent swap into DMF. Although this does not interfere with the reaction of **3** with potassium thioacetate, the resulting product **4** is sufficiently soluble in toluene so as to prevent effective crystallization. This is an aspect that is very often overlooked during the rapid development of a process but can be as critical as the extent of chemical conversion. Subsequent batches incorporated an in-process check to control the level of residual toluene, and no further problems were encountered. An average isolated yield of 57%, over the two reactions, was obtained on scale-up to the Kilo Lab.

Stages 2 and 3 (Scheme 2). Oxidation of the thioacetate **4** to the corresponding sulphonyl chloride **5** was accomplished using chlorine gas in dichloromethane (DCM) and water.[2] The reaction is exothermic, and reaction calorimetry measurements[3] clearly showed that heat evolution

(2) King, J. F.; Rathore, R. *Phosporus Sulfur Relat. Elem.* **1987**, *33*, 165.

(3) In this experiment, chlorine (56.1 g) was slowly added to a mixture of compound **4** (30.3 g), dichloromethane (150 mL), and water (150 mL) stirred at 10 °C in a Mettler RC1 reaction calorimeter. The heat evolved during the chlorination was determined using the calorimeter software and was found to be 72 kJ.

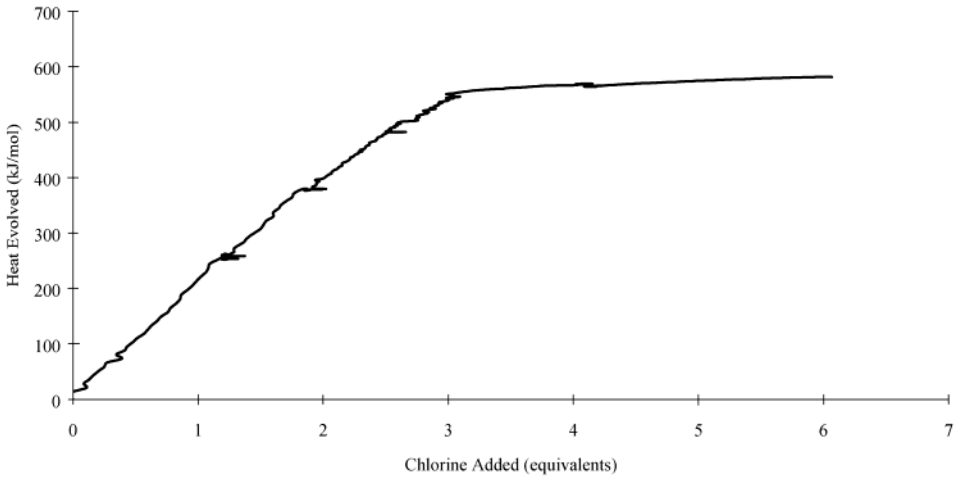
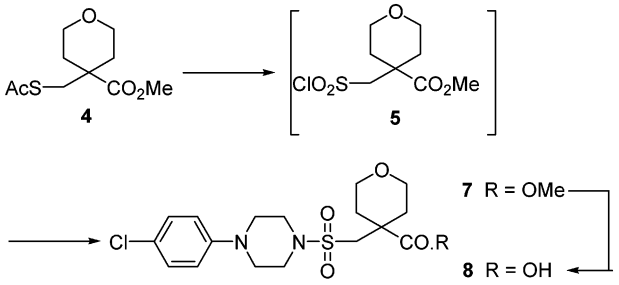


Figure 5. **Heat evolution during chlorine addition.**

Scheme 2. **Oxidation and Sulphonamide Formation**



was closely controlled by the rate of chlorine addition and also that heat evolution stopped after 3 equiv of chlorine had been added (Figure 5). In fact this was a useful indicator, since, at reaction completion, the temperature dropped rapidly and this correlated with the absence of starting material by HPLC. At a 50 L scale, the actual chlorine charge corresponded very closely with the theoretical 3 equiv required.

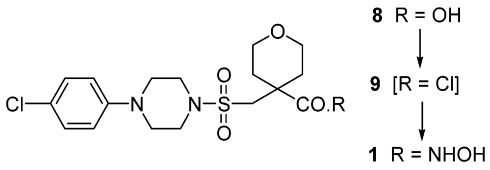
The resulting solution of **5** in DCM was washed with water and then azeotropically dried by atmospheric distillation which also removed the acetyl chloride produced as a byproduct. An aliquot of this solution was then evaporated to dryness to obtain a yield estimate, which determined the batch charge of 4-chlorophenylpiperazine hydrochloride (**6**) required for the subsequent coupling reaction. The ester (**7**) was obtained in moderate yield (47−53%) after workup.

Hydrolysis of **7** (stage 3) was achieved using lithium hydroxide in methanol and water. The carboxylic acid **8** was isolated by filtration after removal of the methanol and subsequent acidification.

Stage 4. The final stage of any synthesis where the product is intended for pharmaceutical (i.e., clinical), use is always critical, especially as regards the selection of solvents/reagents and so forth which can impact the overall quality, and hence acceptability, of the product. In this case, the final stage is the conversion of the carboxylic acid **8** to the corresponding hydroxamic acid **1** via the intermediate acid chloride **9** (Scheme 3).

The first problem was the use of an *O*-protected hydroxylamine derivative (*O*-*tert*-butyldimethylsilyl) in the original discovery strategy (Scheme 1). This obviously is a disadvantage not only from cost/availability considerations but also because it necessarily introduces an additional deprotection step into the sequence. In fact, *O*-protection is unnecessary because hydroxylamine itself reacts with acyl halides preferentially through nitrogen to give hydroxamic acids directly. For this campaign, CH5902 (**1**) was prepared by quenching the acid chloride **9** directly with an aqueous solution of hydroxylamine.

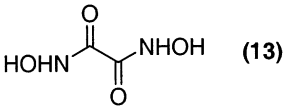
Scheme 3. **Hydroxamate Formation**



Of greater concern, was the method for generating the acid chloride **9**. The original discovery route utilized the common laboratory procedure of reaction of a carboxylic acid with oxalyl chloride catalyzed by DMF. This gives virtually quantitative conversion to the acid chloride under mild conditions, normally at ambient temperature. However, it has been reported[4] that dimethylcarbamoyl chloride (DMCC) is produced as a minor reaction byproduct during this procedure. DMCC is a known animal carcinogen and a potential human carcinogen necessitating control of exposure to very stringent standards. Our concerns with this information were two-fold: first, protection of operators during processing and, second, the possible implications for the quality of the product, which is final API, and which would thus require analytical evidence for the absence of this material, probably down to exacting levels. With this in mind, we opted to avoid the issue completely and perform the carboxylic acid chlorination in the absence of DMF, that is, *un*catalyzed. The immediate consequence is that the reaction no longer proceeds satisfactorily at ambient temperature but requires an extended period at reflux for completion. The optimal conditions are 2−4 h in refluxing THF using an excess (1.2 equiv) of oxalyl chloride.

At completion, the composition of this reaction consists of the acid chloride **9** plus residual unreacted oxalyl chloride (nominally 0.2 equiv). Quench of this mixture with an

(4) Levin, D. *Org. Process. Res. Dev.* **1997**, *1*, 182.



(13)

Figure 6. **Bis-Hydroxamate.**

aqueous solution of hydroxylamine gives both the required hydroxamic acid **1** and a byproduct resulting from the reaction of oxalyl chloride with hydroxylamine, presumably the bis-hydroxamate (**13**). This latter material is much less soluble than the required product, CH5902 (**1**), and consequently difficult to remove by recrystallization. The preferred option is to prevent formation in the first place. In the laboratory, excess oxalyl chloride can be removed by concentrating the reaction mixture under vacuum, but this is not ideal for scale-up. Our solution was to destroy the excess oxalyl chloride by addition of a measured equivalent of water *prior* to the addition of aqueous hydroxylamine. The level of residual oxalyl chloride remaining at the end of the reaction was determined by a derivatization/GC analysis method. A weighed aliquot of the reaction mixture was quenched into methanol which converts the residual oxalyl chloride to dimethyl oxalate, a stable derivative which can be analyzed by an appropriate GC method. The amount of dimethyl oxalate observed can then be related to the quantity of oxalyl chloride remaining by means of a calibration graph, prepared by measuring the GC response (peak area) of a series of standard solutions of dimethyl oxalate of appropriate concentrations. Following this estimation of the level of residual oxalyl chloride (typically 0.05−0.20 equiv), a corresponding equivalent of water was added to the reaction mixture, which was then allowed to stir out at ambient temperature overnight. Repeat analysis showed ≤0.01 equiv of oxalyl chloride present at this point. In addition, the aqueous quench did not significantly affect the level of unreacted acid **8** remaining in the reaction mixture.

Although a number of assumptions and approximations are inherent in this approach (e.g., it is assumed that the reaction volume equals the original volume of THF and that no solvent is lost during subsequent processing), the method worked well as demonstrated by the near absence of an oxalate-related impurity present in the final isolated product.

Conversion of the acid chloride **9** to the required hydroxamic acid **1** was accomplished by addition of the reaction mixture to an aqueous solution of hydroxylamine (50% w/w; 6-fold excess), the accompanying exotherm being controlled by the rate of addition. Workup of the reaction was achieved by distillation of the THF and replacement with water, during which the product precipitates. The main impurity present at this point is unreacted carboxylic acid **8**. This can be reduced in the isolated product by pH adjustment (7.5−8.5) of the slurry with aqueous ammonia prior to filtration. Using this approach at a 50 L scale, the final material CH5902 (**1**) was obtained in an average yield of 82% and with a minimum purity of 98.4% (HPLC). No more than 0.5% of the parent carboxylic acid **8** remained in the final isolated solid.

Summary

The original discovery route was streamlined to form the basis for a practical and safe synthesis of the target compound **1**. The approach was demonstrated on a multikilogram scale in order to provide material suitable for toxicological and initial clinical studies.

Experimental Section

General. Reactions at the multikilogram scale were run in glass-lined steel reactors; a basket centrifuge was used to isolate solid products, which were dried in a tray drier under vacuum. ^{1}H NMR spectra were obtained at 200 MHz using tetramethylsilane as a reference. Gas chromatographic (GC) analysis was performed on a BP-5, 25 m × 1 mm capillary column using helium as carrier gas (75−280 °C). HPLC analysis was performed on a Luna II C18 column (5 μm, 4.6 × 150 mm) using water (containing 0.1% trifluoroacetic acid) and acetonitrile with UV detection (215 nm).

Methyl 4-(Acetylsulfanylmethyl)tetrahydropyran-4-carboxylate (4). A solution of diisopropylamine (2.11 kg, 20.85 mol) in THF (13.5 L) was cooled to between −5 and −10 °C under a nitrogen atmosphere. A solution of *n*-butyllithium in hexanes (23.2% w/w, 5.26 kg, 19.0 mol) was then added maintaining the temperature at ≤0 °C during the addition. The resulting solution was cooled to −5 to −10 °C, and methyl tetrahydropyran-4-carboxylate (2.5 kg, 17.34 mol) was added slowly over approximately 2 h such that the temperature did not exceed −5 °C. The batch temperature was adjusted to −5 to 0 °C when diiodomethane (4.65 kg, 17.36 mol) was added at sufficient rate to maintain the reaction temperature between 0 and 10 °C (∼1.75 h). When the addition was complete, the batch was warmed to 20−25 °C and then stirred out for 16 h. After this time, the reaction was chilled to ∼10 °C and quenched by the addition of a solution of ammonium chloride (3.05 kg) in water (11.25 L). The layers were separated, and the aqueous phase re-extracted with toluene (20 L). The combined organic extracts were concentrated to ∼15 L by distillation at atmospheric pressure, washed twice with water (5 L), and then azeotropically dried by the addition and subsequent atmospheric distillation of toluene (7.5 L). DMF (21.8 L) was added to the resulting solution which was then concentrated to ∼15 L by distillation under reduced pressure (100 mbar). The effectiveness of the solvent swap from toluene to DMF was assessed by GC analysis of an aliquot of the reaction mixture. If necessary, additional DMF (in 5.3 L portions) was added and then subsequently distilled (100 mbar) until less than 4% toluene was present.

The resulting solution of methyl 4-(iodomethyl)tetrahydropyran-4-carboxylate (**3**) in DMF was cooled to 15 °C when potassium thioacetate (2.38 kg, 20.8 mol) was charged, maintaining the temperature at less than 30 °C. After stirring out overnight, the reaction mixture was cooled to 10 °C and water (27 L) was added carefully over at least 30 min to initiate crystallization. The crude product was isolated by filtration and washed with water. The damp cake was reslurried in heptane (12.2 L) and then filtered, washed with heptane, and dried at 40−45 °C under vacuum to give **4** as a pale brown solid (2.24 kg, 55.6%): ^{1}H NMR ($CDCl_3$) δ

1.56 (m, 2H), 2.08 (m, 2H), 2.36 (s, 3H), 3.20 (s, 2H), 3.47 (m, 2H), 3.73 (s, 3H), 3.83 (m, 2H); gas chromatography 98.8 area %.

Methyl 4-[4-(4-Chlorophenyl)piperazin-1-yl)sulfonylmethyl]tetrahydropyran-4-carboxylate (7). Compound **4** (3.8 kg, 16.4 mol) was dissolved in a mixture of DCM (19.1 L) and water (11.4 L), and the resulting mixture was cooled to 0 °C. Chlorine gas was introduced into the reaction mixture at such a rate as to maintain the temperature at less than 10 °C. The reaction was continued and sampled periodically until no starting material was detected by HPLC assay. The reaction was complete in ~1.75 h requiring the addition of 3.56 kg (50.1 mol) of chlorine. The layers were separated, and the organic phase was washed twice with water (11.4 L) and then concentrated to ~15 L by distillation at atmospheric pressure. The solution was azeotropically dried by the addition and subsequent distillation of an additional portion of DCM (13.3 L). A sample of the resulting solution of methyl 4-(chlorosulfonylmethyl)tetrahydropyran-4-carboxylate (**5**) in DCM was stripped under vacuum in order to estimate yield for the next part of the process (2.91 kg, 69.2%).

The above solution of **5** was added to a cooled (0 °C) mixture of 1-(4-chlorophenyl)piperazine hydrochloride (**6**, 2.65 kg, 11.4 mol) and triethylamine (2.53 kg, 25 mol) in DCM (14.6 L), maintaining the temperature at less than 10 °C. The batch was allowed to warm to 20−25 °C and stirred for a further hour. Water (8.7 L) was added, and the layers were separated. The organic phase was washed successively with dilute aqueous hydrochloric acid (twice with a solution of 0.29 kg of concentrated HCl in 8.7 L of water) and water (8.7 L). The solution was concentrated by distillation to ~15 L, and a solvent swap was effected by the addition of *tert*-butyl methyl ether (23.5 L) and atmospheric pressure distillation until a pot temperature of ≥51 °C was achieved. The product crystallized during the distillation, and the resulting slurry was stirred for 18 h during which time it had cooled to 24 °C. After this time, the mixture was further cooled to less than 5 °C and then filtered. The cake was washed with cold (<10 °C) *tert*-butyl methyl ether (5.8L) and then dried under vacuum at 40−50 °C to provide the *title compound* (**7**) as an off-white solid (3.84 kg, 56.2%): ^{1}H NMR ($CDCl_3$) δ 1.80 (m, 2H), 2.27 (m, 2H), 3.25 (m, 6H), 3.40 (m, 4H), 3.67 (m, 2H), 3.80 (m, 2H), 3.84 (s, 3H), 6.87 (d, 2H), 7.27 (d, 2H); HPLC 99.2 area %.

4-[4-(4-Chlorophenyl)-piperazin-1-yl)sulfonylmethyl]-tetrahydropyran-4-carboxylic Acid (8). A mixture of **7** (3.84 kg, 9.2 mol) and lithium hydroxide monohydrate (0.77 kg, 18.3 mol) in methanol (19.2 L) and water (19.2 L) was heated to reflux for 2 h. After this time, the methanol was removed by atmospheric pressure distillation and replaced with water (32.1 L in total). Whilst maintaining the batch temperature between 40 and 60 °C, the reaction was acidified to pH 5.5−6.5 by the careful addition of aqueous hydrochloric acid (1.86 kg of concentrated HCl in 5.74 L of water) over approximately 2.5 h. The product precipitated during the acidification, and the resulting slurry (pH 6) was allowed to cool to 20 °C over 14 h. The mixture was filtered, and the cake was washed with water (2 × 7.7 L). The product was dried under vacuum at 50−60 °C to afford **8** as an off-white solid (3.60 kg, 97.5%): ^{1}H NMR (d_6-DMSO) δ 1.70 (m, 2H), 1.98 (m, 2H), 3.25 (m, 8H), 3.43 (s, 2H), 3.50 (m, 2H), 3.67 (m, 2H), 6.98 (d, 2H), 7.27 (d, 2H), 12.80 (br s, 1H); HPLC 98.7 area %.

4-[4-(4-Chlorophenyl)-piperazin-1-yl)sulfonylmethyl]-tetrahydropyran-4-carboxylic Acid *N*-Hydroxy Amide (1). A solution of **8** (3.30 kg, 8.2 mol) in THF (32.5 L) was heated to reflux whilst oxalyl chloride (1.24 kg, 9.8 mol) was added carefully over approximately 1 h. The resulting mixture was maintained at reflux and monitored periodically by HPLC analysis until less than 3% starting material (**8**) remained and the reaction was deemed complete. Typically, this required an additional 2−3 h at reflux. The progress of acid chloride formation was followed by quenching an aliquot of the reaction mixture into aqueous hydroxylamine and analyzing for conversion to the corresponding hydroxamic acid (i.e., **1**). At completion, the batch was cooled to ~20 °C and then sampled for the determination of residual oxalyl chloride (see main text). A measured equivalent of water was then added to the mixture, which was allowed to stir at ambient temperature (15−25 °C) for 16 h prior to a repeat analysis. In this batch, the amount of oxalyl chloride remaining was determined as 0.101 equiv (0.83 mol) requiring the addition of 14.9 g (0.83 mol) of water. The oxalyl chloride level reduced to <0.01 equiv after the stir-out period.

The above prepared slurry of 4-[4-(4-chlorophenyl)-piperazin-1-yl)sulfonylmethyl]tetrahydropyran-4-carbonyl chloride (**9**) in THF was added in portions to a cooled (5 °C) mixture of 50% aqueous hydroxylamine (3.27 kg, 49.5 mol) and THF (9.9 L), maintaining the temperature at less than 20 °C. The mixture was stirred at 10 °C for a further hour when the THF was removed by distillation at atmospheric pressure, the batch volume being maintained by the addition of water (37.7 L in total). The product precipitated during the solvent swap, and the resulting slurry was cooled to 20 °C over ~1 h when dilute aqueous ammonia (~17.5%) was added to adjust the pH to between 7.5 and 8.5. The reaction mixture was stirred at 18−24 °C for 14 h after which time the solid product was isolated by filtration. The cake was washed with water (2 × 13.2 L) and dried under vacuum at 35−45 °C to give CH5902 (**1**) as an off-white solid (2.88 kg, 84.1%): ^{1}H NMR (d_6-DMSO) δ 1.70 (m, 2H), 1.98 (m, 2H), 3.23 (br s, 8H), 3.40 (s, 2H), 3.45 (m, 2H), 3.65 (m, 2H), 6.97 (d, 2H), 7.25 (d, 2H), 8.75 (br s, 1H), 10.58 (s, 1H); HPLC 98.9 area %.

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