# Implementation of a High-Temperature Claisen Approach for Early Phase Delivery of a Benzopyran Derivative

Andrew J. Walker,\*,\* Sven Adolph,† Richard B. Connell,\* Klaus Laue,† Michael Roeder,† Carsten J. Rueggeberg,§ Dirk Uwe Hahn,<sup>∥</sup> Kurt Voegtli,<sup>⊥</sup> and John Watson<sup>‡</sup>

Carbogen-AMCIS AG, Neulandweg 5, CH-5502, Hunzenschwil, Switzerland, GlaxoSmithKline Medicines Research Centre, Gunnels Wood Road, Stevenage, Herfordshire SG1 2NY, United Kingdom, Carbogen-AMCIS AG, Hauptstrasse 171, CH-4416, Bubendorf, Switzerland, and Carbogen-AMCIS AG, Schachenallee 29, CH-5001, Aarau, Switzerland

### Abstract:

Control of trace inorganics and an understanding of reaction kinetics and impurity generation proved critical in allowing safe and reliable scale-up of a high-temperature Claisen reaction in support of multikilogram manufacture of a key chromene intermediate 4. Implementation of a Medicinal Chemistry route allowed for rapid early phase delivery of 1 to support early clinical studies.

#### Introduction

5-Amino-6-bromo-N-[(1-(tetrahydro-2H-pyran-4-ylmethyl)-4-piperidinyl]methyl-3,4-dihydro-2H-chromene-8-carboxamide [1] is a 5-HT<sub>4</sub> receptor agonist discovered at GlaxoSmith-Kline<sup>1</sup> and has been evaluated in preclinical studies. Agonists for the 5-HT<sub>4</sub> receptor have potential utility in the treatment of a range of gastrointestinal disorders such as constipation, irritable bowel syndrome, and functional dyspepsia.<sup>1</sup>



Initial quantities of **1** were prepared using the Medicinal Chemistry route (Scheme 1) to support preliminary in vitro and in vivo studies, and there was a need for rapid scaleup of 1 to support further preclinical and early phase I clinical studies. Assessment of the Medicinal Chemistry route highlighted a number of key issues, and these were rapidly assessed to see if this route was amenable to the manufacture of multikilogram quantities of API. Herein, we report our results in this direction, and describe how we met the challenges of scaling up the Medicinal

<sup>II</sup> Current address: Solvias, WRO-1060.P.14, Postfach, 4002 Basel, Switzerland.

10.1021/op900193v © 2010 American Chemical Society Published on Web 12/07/2009

Chemistry route for large-scale synthesis to facilitate the most expedient supply of initial quantities of active pharmaceutical ingredient (API). In a subsequent article, we will relate our work on identification of improved alternative manufacturing routes to the benzopyran core.<sup>2</sup>

### **Results and Discussion**

A review of the Medicinal Chemistry route (Scheme 1) highlighted a number of key areas for further consideration: thermal stability of propargyl ether 3 and chromene 4, general operability of the Claisen reaction, chromatographic purification of 1 following capricious amide formation, and numerous concentrations to dryness from large [>100] volumes.

Use of chloro analogue 2 as starting material was driven by (i) the potential requirement for preparation of a chloro analogue of 1 at the outset of the project, (ii) literature precedent that the presence of a halogen atom at this position was beneficial to the thermal cyclisation,<sup>3</sup> and (iii) availability of this intermediate in large scale [>100 kg] from a related project. This approach gave us maximum flexibility to meet the overall needs of the program. The acetylene ether derivative of 3, in which the acetyl group is replaced by pivaloyl, was reported to give an improved profile for cyclisation,<sup>3</sup> but this was not evaluated due to lead time/availability of raw materials and the potential need for an additional deprotection stage.

The propargyl ether 3 was prepared using a modification of the Medicinal Chemistry process, wherein sodium hydride and DMF/THF at reflux was replaced by potassium carbonate in DMF at 70 °C. ARC data generated for the full batch reaction [-19 J/g] revealed this to be a safe and robust process for scale-up. Initial batches of propargyl ether 3 were isolated following a simple water drown-out and were found to contain significant levels of inorganics [1-2% w/w]. This reduced the thermal stability profile of 3, as judged by DSC, and resulted in significant levels of impurities and very poor isolated yield [<20%

<sup>\*</sup> To whom correspondence should be addressed. E-mail: Andrew.J.Walker@ gsk.com.

Carbogen-AMCIS AG, Hunzenschwil, Switzerland.

<sup>&</sup>lt;sup>‡</sup> GlaxoSmithKline Medicines Research Centre.

<sup>§</sup> Carbogen-AMCIS AG, Bubendorf, Switzerland.

<sup>&</sup>lt;sup>1</sup> Carbogen-AMCIS AG, Aarau, Switzerland.

<sup>(1) (</sup>a) Ahmed, M.; Miller, N. D.; Moss, S. F.; Sanger, G. J. WO 2007096352, 2007. (b) De Mayer, J.; Lefebvre, R.; Schuurkes, J. Neurogastroenterol. Motil. 2008, 20 (2), 99. (c) For tegaserod, see: Seerden, T. C.; De Man, J. G.; Holzer, P.; Van Den Bossche, R. M.; Herman, A. G.; Pelckmans, P. A.; De Winter, B. Y. Neurogastroenterol. Motil. 2007, 19 (10), 856.

<sup>(2)</sup> Rassias, G.; Stevenson, N. G.; Curtis, N. R.; Northall, J. M.; Gray, M.; Prodger, J. C.; Walker, A. J. Org. Process Res. Dev. 2010, 14, DOI: 10.1021/op900188v.

<sup>(3) (</sup>a) Kakigami, T.; Baba, K.; Usui, T. Heterocycles 1998, 48 (12), 2611-2619. (b) Baba, Y.; Usui, T.; Kakiue, T.; Baba, K. JP 08157466, 1996.

Scheme 1. Medicinal Chemistry route to 1



th] in the subsequent high-temperature cyclisation.<sup>4</sup> Consequently, an additional extractive water wash, followed by solvent exchange, was incorporated for scale-up to give **3** of high purity and low residual inorganic content [<0.1% w/w]. This was scaled up to 25 kg input to give **3** in 70% th, >99.5% by HPLC.

Ether **3** was initially subjected to the existing thermal cyclisation conditions [Dowtherm A, 220 °C] to assess the reaction profile.



Time /h

*Figure 1.* HPLC plot of the high-temperature cyclisation of alkyne ether 3 to give chromene 4.

HPLC timecourse analysis revealed that the chromene 4 was unstable at the temperature required for cyclisation, with a maximum of 67% (Figure 1, % a/a by HPLC) observed after approximately 1 h. This decreased on isothermal ageing to 39% after 4 h with an increase in known impurities, benzofuran 12 and indole 13 (Scheme 2, as suggested by MS and literature<sup>3</sup>) alongside numerous unknown low-level by-products. 3 was not completely consumed until ~2 h at 220 °C, but impurities 12 and 13 were much more difficult to purge from the product at this, and downstream, stages. Consequently, we focused our efforts on minimising levels of these impurities at the expense of conversion in the initial campaigns.

Scheme 2. Impurities from Claisen rearrangement



Use of alternative high-boiling solvents [NMP, DMSO, dimethylacetamide, or ethylene glycol<sup>5</sup>] preferentially generated different products [including **12** and **13**] rather than the desired product, and we reverted to Dowtherm A to assess the potential of this system to provide a safe and scaleable process. An isothermal kinetic study at 180-240 °C demonstrated that a minimum of >200 °C was required to generate useful levels of the chromene **4** within a reasonable time frame for processing [<3 h] without extensive concomitant decomposition of the product.

A continuous chemistry approach to this stage was also considered, as this had the potential to minimise the time during which the reaction mixture was held at elevated temperature. Unfortunately, levels of impurities rose in parallel with conversion to **4**, and dilution [required to provide a window for solution flow chemistry] had a deleterious effect on the impurity profile.

The optimum conditions were established for a standard batch process using Dowtherm A (5 vol) as solvent and heating at 220–230 °C. Further profiling of the reaction generated consistent results in lab experiments for both reaction conversion and impurity profile, and provided confidence in the time required to hold the reaction at 220–230 °C [45–60 min] prior to workup. The observed decomposition of the reaction mixture with extended heating required the batch to be cooled down

<sup>(4)</sup> Ishii, H.; Ishikawa, T.; Takeda, S.; Ueki, S; Suzuki, M.; Harayama, T. *Chem. Pharm. Bull.* **1990**, *38* (6), 1775–1777 for an example of a basemediated alternative pathway.

<sup>(5) (</sup>a) Ariamala, G.; Balasubramanian, K. K. *Tetrahedron* **1989**, *45* (1), 309–318. (b) Rao, U.; Balasubramanian, K. K. *Tetrahedron Lett.* **1983**, 24 (45), 5023–5024.

rapidly after this time point. Given this narrow time-window, it was recognised that on scale there would be insufficient time to take an in-process check for HPLC conversion without compromising the quality of the isolated product, and in-line monitoring was not an option. After the in-process samples were taken for retrospective analysis, the product was isolated by addition of heptane to the Dowtherm mixture at 40 °C to precipitate the product. Analysis demonstrated that yields of 50-60% could be obtained with an HPLC purity of 80% a/a. Levels of unreacted **3** were typically 10-15% a/a in the isolated product, and we also observed up to 10% mass balance discrepancy between HPLC purity [80-90% a/a] and NMR % w/w assay [70-80% w/w]. Downstream assessment showed that we were able to proceed with this quality of intermediate for initial supplies. This was demonstrated across a number of lab batches to provide assurance in the proposed operating conditions for the Claisen process. Recrystallisation of chromene 4 was evaluated, but the product could only be isolated in poor overall yield and with modest improvement in purity [20-30%]th overall, 90-93% a/a] and was therefore not implemented on scale.

Great care is always required when evaluating high temperature scale-up reactions involving highly-energetic groups such as acetylenes. Initial thermal screening by DSC of ether **3** isolated from the Medicinal Chemistry process had highlighted significant exothermic activity from 140-300 °C [877 J/g, with sharp exotherm at 258 °C]. Implementation of the revised process for preparation of 3 gave an improvement in its thermal stability as a solid by DSC [exothermic activity from 181-299 °C, 453 J/g] due to the removal of inorganic impurities. Subsequent ARC assessment of the final batch process [in 5 vol of Dowtherm A] indicated we had a safe and robust system for operation on scale using inorganic-free 3. An exotherm of 95 J/g was observed at 180 °C, broadly consistent with the onset for rearrangement, and no other thermal activity was observed until 298 °C [exotherm of 35 J/g]. Twothirds of this initial energy was used to warm up the reaction back up to 220 °C following addition of 3 to hot Dowtherm A. The remaining low energy  $[\sim 30 \text{ J/g}]$ associated with the desired reaction in the ARC experiment and the boiling barrier at 257 °C indicated that the process was suitable for scale-up to 10 kg and beyond. However, the sensitivity of the quality of the isolated product to prolonged heating/cooling probably limits the utility of this process for further scale-up.

The batch process was successfully operated on multiple 10-kg scale to give the chromene **4** in the expected yield and quality [53-59% th uncorr., 82-92% a/a, 75-84% w/w by NMR assay].

With the key fragment **4** in hand, we were able to assess the remainder of the route to anilinoacid **7**. Hydrogenation to remove the double bond and effect dechlorination was readily achieved using a modified EtOH/THF/Et<sub>3</sub>N system. These solvents allowed for a much-simplified isolation of benzopyran **5** *via* concentration and water antisolvent addition. This also effectively removed residual triethylamine hydrochloride which was a problem in the original process. Interestingly, residual propargyl ether **3** was converted to phenol **14** in this step rather than the propyl ether analogue, and this was readily removed in the following steps (Scheme 3). The purity of **5** could be improved further by recrystallisation from *tert*-butyl methyl ether, but since impurities were purged in the following steps, it was decided to proceed directly with the bromination using this quality of material.

# *Scheme 3.* Tracking process impurities through the synthesis



Modification to the bromination conditions involved addition of a solution of **5** in dichloromethane to a suspension of NBS in acetic acid. Impurity **14** was converted to the dibromophenol **15** which was effectively removed following isolation of **6** from TBME (Scheme 3). On scale-up to plant, a delay in charging **5** to the NBS solution resulted in partial degradation of the reagent, resulting in incomplete conversion. However, addition of further NBS and workup gave **6** in good quality and assay on 13-kg scale [96.5% a/a, 95.4% w/w assay, 63% th]. Importantly, we were now able to re-establish good analytical agreement between HPLC and NMR assay of **6** at this point in the synthesis. No benzylic bromination was observed during this reaction.

Final saponification to cleave ester and amide protecting groups was achieved in one pot using potassium hydroxide in aqueous dioxane. Any remaining dibromo impurity **16** was efficiently purged during this process (Scheme 3), and traces of any residual acetanilide acid were removed following pH adjustment and isolation. The product **7** was washed with ethyl acetate/heptane to provide control of residual water in anticipation of the amide coupling [77% th, 0.16% KF, 99.35% a/a by HPLC].

The diamine side chain 11 was prepared from 4-cyanopiperidine 9 and 4-formylpyran using a telescoped reductive amination-nitrile reduction. Initial attempts to perform this via sequential hydrogenation were unsuccessful, and we reverted to the use of LiAlH<sub>4</sub> for reduction of nitrile 10 to the primary amine 11. This was best achieved using THF as solvent, and this solvent was integrated into the reductive amination to provide a streamlined process. Removal of aluminium salts and isolation as its dihydrochloride salt from dioxane gave 11 in excellent yield and quality across three batches [77-87% th, 96-98% w/w by NMR assay, 1.6-2.9% w/w dioxane]. [Note - whilst the use of solvents such as dichloromethane and dioxane are unsuitable for longerterm manufacture due to their toxicity and environmental impact, their utility as general process solvents for phase I supply are considered acceptable.]

With quantities of the amine and acid in hand, we examined the final amide coupling of **7** with **11**. This was originally achieved in Medicinal Chemistry using EDCI and catalytic



DMAP, and the crude free base required extensive chromatography to reduce levels of the related *N*-acylurea impurity (Scheme 4).

This was typically formed in  $\sim 10\%$  during the reaction, and it was also noted that conversion of 7 was also incomplete. A number of standard peptide coupling agents were evaluated [activation using SOCl<sub>2</sub>, cyanuric chloride, CDI] before 2-chloro-4.6-dimethoxy-1,3,5-triazine (CD-MT<sup>6</sup>) was selected on the grounds of optimum conversion and operational simplicity. Initial solvent screening identified nitromethane and acetonitrile as preferred solvents, and acetonitrile also facilitated the direct isolation of the HCl salt of 1 from the reaction mixture by filtration, removing the need for chromatography. A limited DoE study [stoichiometry of amine (1-1.5 equiv), NEM (3-7 equiv), and CDMT (1-1.6 equiv), and temperature (25-45 °C) in MeCN] indicated a maximum conversion of 98% could be obtained at higher loadings of CDMT and NEM, although in practice this did not translate to a very high isolated yield in verification experiments. This implied that there were additional factors that were not considered in the initial design or in the workup, and will be the subject of further work. Whilst conversion was not complete, isolated yield and purity of the isolated HCl salt was acceptable for onward processing, and this was scaled-up to give the HCl salt, 8 in 76% th, 96.1% a/a on a 9-kg scale.

The tosylate salt had previously been selected as the version for development. Initially, this was prepared by regeneration of the free base followed by salt formation in acetonitrile. However, the lack of solubility of the tosylate salt of **1** in acetonitrile precluded the development of a controlled crystallisation, and we had additional concerns regarding the use of acetonitrile in the final stage [ICH class 2 solvent].<sup>7</sup> Solvent screening identified DMSO and isopropyl acetate as an appropriate binary system that gave control of form and purity. A charcoal treatment to reduce colour was also incorporated into the final process. This was successfully scaled to 9 kg scale and provided the desired salt of **1** in excellent overall yield and quality to support phase I clinical supplies.

In summary, scaleable processes using the existing Medicinal Chemistry route were developed for the synthesis of 1 on multikilogram scale. This addressed a number of issues that

(7) ICH Harmonised Tripartite Guideline: Impurities: Guideline for Residual Solvents Q3C, (R3), Step 4; International Conference on Harmonisation, 2005. http://www.ich.org/LOB/media/MEDIA423.pdf. were identified at the outset of the project, notably safety and purity concerns about the high-temperature Claisen reaction and a capricious amide formation, as well as isolation and purification procedures. This was supported by a good understanding of purity using NMR assay as well as HPLC, and knowledge of process impurities and their fate through the synthetic sequence. This enabled rapid delivery of initial quantities of **1** in modest overall yield and excellent purity, and allowed us to investigate alternative routes off the critical path for delivery. These were focused on identification of improved routes to the key benzopyran core and will be detailed in the subsequent paper.<sup>2</sup>

### **Experimental Section**

### **General Remarks**

The NMR spectra were recorded on 400 MHz Bruker Advance for <sup>1</sup>H NMR and 100 MHz for <sup>13</sup>C NMR. HPLCs were measured on Agilent Series 1100 (Agilent) or TSP (Thermo) HPLC systems at 277 nm. Accurate MS spectra were recorded on a Waters Micromass Q-ToF Ultima mass spectrometer. The ionisation technique was positive ion electrospray with external lockmass correction. DSC analysis was performed on the Mettler Toledo DSC 822e instrument.

Methyl 4-(Acetylamino)-5-chloro-2-(2-hydroxy)benzoate, 2 [CAS Registry no. 24190-77-0, prepared according to ref 1a]. NMR data for 2: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz, 300 K): 10.56–10.47 (s, 1H, NH), 9.55–9.45 (s, 1H, 2-OH), 7.80–7.77 (s, 1H, 6-H), 7.74–7.71 (s, 1H, 3-H), 3.86–3.81 (s, 3H, <u>H</u><sub>3</sub>COC(O)), 2.22–2.12 (s, 3H, <u>H</u><sub>3</sub>CC(O)NH); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 400 MHz, 300 K): 167.7, 159.3 (C-2), 141.0 (C-4), 130.5 (C-6), 114.2 (C-5), 111.5 (C-1), 110.1 (C-3), 52.8 (H<sub>3</sub>COC(O)), 2.4.4 (H<sub>3</sub>CC(O)NH), 93–95% a/a by HPLC.

Methyl 4-(Acetylamino)-5-chloro-2-(2-propynyloxy)benzoate, 3. A suspension of methyl 4-(acetylamino)-5-chloro-2hydroxybenzoate 2 (24.78 kg, 101.7 mol) and potassium carbonate (16.85 kg, 121.9 mol) in DMF (247 L) was treated with propargylbromide (80% in toluene, 15.87 kg, 106.7 mol) at rt. The resulting reaction mixture was stirred at rt before warming to 70 °C and ageing for 5.5 h (98% conversion by HPLC). The reaction mixture was cooled to 35 °C and treated with water (295 L). The resulting suspension was cooled to rt and stirred overnight. The product was filtered off, and the filter cake was rinsed three times with water (3× 25 L).

The resulting wet cake was dissolved in dichloromethane (245 L) and methanol (12 L) and washed with water (2× 42 L). The organic solution was concentrated to ~75 L, and a solvent switch from dichloromethane to TBME was performed using  $3\times 51$  L. The resulting suspension was stirred at rt and filtered off. The filter cake was twice rinsed with TBME (21 L) and dried to give **3** as a pale-brown solid (19.73 kg, 99.8% a/a, <0.1% ROI), DSC mp: 145.2 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, 300 K):  $\delta$  8.54–8.41 (s, 1H, NH), 7.96–7.86 (s, 1H, 6-H), 7.86–7.64 (br s, 1H, 3-H), 4.89–4.77 (d, J = 4 Hz, 2H, OCH<sub>2</sub>CCH), 3.95–3.82 (s, 3H, H<sub>3</sub>COC(O)), 2.62–2.51 (t, J = 4 Hz, 1H, OCH<sub>2</sub>CC<u>H</u>),  $\delta = 2.36-2.22$  (s, 3H, H<sub>3</sub>CC(O)NH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 400 MHz, 300 K):  $\delta$ 

<sup>(6) (</sup>a) Kaminski, Z. J. Synthesis 1987, 917–920. (b) Garrett, C. E.; Jiang, X.; Prasad, K.; Repic, O. Tetrahedron Lett. 2002, 43, 4161–4165. (c) Kaminski, Z. J.; Paneth, P.; Rudzinski, J. J. Org. Chem. 1998, 63, 4248–4255. (d) Review: Blotny, G. Tetrahedron 2006, 62, 9507–9522.

168.7, 164.7, 156.9 (C-2), 138.8, 132.0, 115.9, 113.6 (C-1), 106.2 (C-3), 77.5 (CH<sub>2</sub>CCH), 76.4 (CH<sub>2</sub>CCH), 57.1 (H<sub>3</sub>COC(O)), 52.2 (OCH<sub>2</sub>CCH), 25.2 (H<sub>3</sub>CC(O)NH). MS calculated for  $C_{13}H_{12}CINO_4$  282.0533 (MH<sup>+</sup>), found 282.0534.

Methyl 5-(Acetylamino)-6-chloro-2H-chromene-8-carboxylate, 4. Dowtherm A (36.8 kg diphenylether and 15.8 kg biphenyl) was heated to 220 °C and 3 (9.61 kg, 35.5 mol) was added via a hastelloy drum in a single solid addition, causing a temperature drop down to 195 °C. The mixture was heated up to 220 °C over 11 min, and the solution was maintained at 220 °C for 50 min before it was cooled down to 40 °C. Heptane (96 L) was added at 40 °C, and the resulting suspension was cooled to 20 °C and stirred overnight at this temperature. The product was filtered, washed with heptane (2  $\times$  6.8 L) and MIBK (2  $\times$ 6.8 L), and dried under a nitrogen stream gave 4 as a brown solid (5.44 kg, 92.3% a/a, 84.3% w/w NMR assay). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, 300 K): δ 7.75–7.71 (s, 1H, NH), 7.15–7.03 (br s, 1H, 7-H), 6.38–6.28 (d, J = 12Hz, 1H, 4-H), 5.97-5.86 (m, 1H, 3-H), 4.95-4.88 (t, J = 4 Hz, 2H, 2-H), 3.89–3.87 (s, 3H, H<sub>3</sub>COC(O)), 2.30-2.25 (s, 3H, H<sub>3</sub>CC(O)NH). DSC melt: Peak 189.2 °C. MS calculated for  $C_{13}H_{12}CINO_4$  282.0533 (MH<sup>+</sup>), found 282.0522.

Methyl 5-(Acetylamino)-3,4-dihydro-2H-chromene-8-carboxylate, 5. A suspension of 4 (22.31 kg, 79.4 mol) and 10% Pd/C (Degussa E101 R/W, 50% wet, 4.45 kg) in absolute ethanol (223 L) and THF (223 L) was dosed with triethylamine (8.42 kg, 83.7 mol), the mixture was purged with hydrogen ( $\leq 1200$  mbar) and stirred for 18 h at 20 °C. The reaction mixture was filtered through prewashed Celite (22.3 kg) and washed with ethanol/THF (46 L, 1:1). The filtrate was concentrated to  $\sim$ 70 L vol at 45–50 °C under reduced pressure, cooled to 20 °C, and treated with water (225 L). The resulting suspension was stirred at this temperature for 2 h before cooling further to 5-10 °C. The suspension was filtered, washed with water (45 L) and ethyl acetate/heptane (1:3 ratio,  $2 \times 46$  L), and dried to give 5 as a pale-brown solid (13.22 kg, 67% th, 81.9% a/a, 84.5% w/w NMR assay). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz, 300 K): δ 9.36-9.25 (s, 1H, NH), 7.48-7.43 (d, J = 12 Hz, 1H, 8-H), 7.22-7.12 (d, J = 8 Hz, 1H, 7-H), 4.18–4.10 (t, J = 4 Hz, 2H, OCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 3.78–3.70 (s, 1H, H<sub>3</sub>COC(O)), δ 2.68–2.58 (m, 2H, OCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>),  $\delta$  2.12–2.07 (s, 3H, H<sub>3</sub>CC(O)NH),  $\delta$  1.94–1.86 (t, J = 4Hz, 2H, OCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 400 MHz, 300 K): δ 168.9, 166.3, 154.9 (a-C), 141.0 (C-5), 128.6 (C-7), 116.9 (C-8), 115.6 (C-6), 115.3 (b-C), 66.1 (OCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 23.9 (OCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 21.2 (OCH<sub>2</sub>CH<sub>2</sub>-CH<sub>2</sub>), 20.9 (<u>H</u><sub>3</sub>CC(O)NH). DSC melt: Peak 171.8 °C. MS calculated for C<sub>13</sub>H<sub>15</sub>NO<sub>4</sub> 250.1079 (MH<sup>+</sup>), found 250.1069.

Methyl 5-(Acetylamino)-6-bromo-3,4-dihydro-2*H*chromene-8-carboxylate, 6. A solution of 5 (13.21 kg, 53.1 mol) in dichoromethane (132 L) was prepared in the feed tank and added over 3 h to a fine pale-yellow suspension of *N*-bromosuccinimide (10.40 kg, 58.4 mol) in acetic acid (66 L), prepared at 20 °C. The clear orange-red solution was stirred overnight at 20 °C, and HPLC analysis revealed only 71% a/a conversion. Further N-bromosuccinimide was added (2.34 kg, 13.1 mol), and the mixture was further stirred for 2 h, giving 90% a/a conversion according to HPLC. Water (66 L) was added, and the resulting organic phase was washed further with dichloromethane (66 L) and water (66 L). The organic phase was concentrated under reduced pressure at 40  $^\circ$ C to  $\sim$ 66 L, and TBME (132 L) was added to give an off-white suspension. This was cooled further to 0-5 °C, filtered, washed with TBME ( $2 \times 40$  L), and dried under nitrogen to give **6** as an off-white solid (10.93 kg, 63% th, 96.1%)a/a, 95.4% w/w NMR assay). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz, 300 K): δ 9.72-9.63 (s, 1H, NH), 7.75-7.66 (s, 1H, 8-H), 4.23-4.04 (t, J = 4 Hz, 2H, OC<u>H</u><sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 3.80-3.75 (s, 3H, H<sub>3</sub>COC(O)), 2.69-2.54 (m, 2H,  $OCH_2CH_2CH_2$ ),  $\delta$  2.11–1.98 (s, 3H, <u>H</u><sub>3</sub>CC(O)NH),  $\delta$ 1.94-1.79 (t, J = 4 Hz, 2H, OCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>, 400 MHz, 300 K): δ 168.2, 165.1, 153.9 (a-C), 139.4 (C-5), 131.1 (C-7), 124.8 (C-6), 119.7 (b-C), 112.1 (C-8), 66.4 (OCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 52.5 (H<sub>3</sub>COC(O)), 22.9  $(H_3\underline{C}C(O)NH)$ , 22.3  $(OCH_2CH_2\underline{C}H_2)$ , 20.8  $(OCH_2\underline{C}H_2$ -CH<sub>2</sub>). DSC melt: Peak 199.7 °C. MS calculated for  $C_{13}H_{14}BrNO_4$  328.0184 (MH<sup>+</sup>), found 328.0191.

5-Amino-6-bromo-3,4-dihydro-2H-chromene-8-carboxylic Acid, 7. A suspension of 6 (10.86 kg, 33.1 mol) in dioxane (55 L) and water (55 L) was treated with a solution of potassium hydroxide (15.3 kg, 272.7 mol) in water (117 L) at ambient temperature, and the resulting suspension was heated to 90 °C overnight. The solution was cooled to 20 °C and treated with 5 N HCl (47 L) to pH 5.6 to give a white suspension. This was cooled, filtered, and washed with water  $(2 \times 55 \text{ L})$  and then ethyl acetate/heptane ( $4 \times 5$  vol, 1:3 mixture). The cake was dried in a conical dryer at 50 °C under vacuum to give 7 as an off-white solid (6.93 kg, 77% th, 99.4% a/a, 99.4% w/w NMR assay, KF 0.03% w/w), <sup>1</sup>H NMR (DMSO- $d_6$ , 400 MHz, 300 K): δ 11.88–11.76 (s, 1H, COOH), 7.70-7.60 (s, 1H, 8-H), 5.78-5.60 (br s, 2H, NH<sub>2</sub>), 4.18-4.00 (t, J = 4 Hz, 2H, OCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 2.48-2.40(m, 2H, OCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 2.01-1.84 (t, J = 4 Hz, 2H, OCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 400 MHz, 300 K): δ 165.9 (<u>C</u>OOH), 155.7 (*a*-C), 148.0 (C-5), 133.3 (C-7), 108.5 (C-6), 107.9 (C-8), 97.8 (b-C), 65.8 (OCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 21.5 (OCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 21.0 (OCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>). DSC melt: Peak 220.3 °C. MS calculated for C<sub>10</sub>H<sub>10</sub>BrNO<sub>3</sub> 271.9922 (MH<sup>+</sup>), found 271.9918.

1-Tetrahydro-2*H*-pyran-4-ylmethyl-4-piperidinemethanamine Dihydrochloride, 11. A solution of 4-cyanopiperidine 9 (5.08 kg, 46.1 mol) and 4-formyltetrahydropyran (5.26 kg, 46.1 mol) in THF (102 L) was treated with acetic acid (1.0 L) at 22 °C and aged for 30 min. Ten percent Pd/C (1.02 kg) was added, the reactor was purged with hydrogen, and the mixture was hydrogenated at 20 °C overnight. Anhydrous Na<sub>2</sub>SO<sub>4</sub> (5.09 kg) was added to the purged reaction mixture; the mixture was stirred for 30 min and then filtered off using prewashed Celite (5.09 kg), washing through with further THF (10 L). The filtrate was cooled to 0-5 °C and dosed with 2.4 M lithium aluminium hydride in THF solution (26.2 kg) over  $\sim$ 2 h and warmed to ambient overnight. Analysis indicated incomplete conversion, and thus further 2.4 M lithium aluminium hydride in THF solution (8.76 kg) was added at 0-5 °C. The mixture was warmed to ambient temperature and stirred for a further 1 h, giving full conversion by GC. The reaction mixture was cooled down to -5 °C, and water (9.6 L) was added carefully. The quenched reaction mixture was warmed to ambient, and 30% NaOH solution (1.5 L) was added. Anhydrous Na<sub>2</sub>SO<sub>4</sub> (10.17 kg) was charged to the purged reactor and was stirred for 30 min, filtered, and washed with THF ( $2 \times 31$  L). A solvent switch from THF to dioxane was performed at 40 °C under reduced pressure, and the resulting suspension was cooled to 10 °C and treated with 4 M HCl in dioxane (35 L) to give the salt as a white suspension. The white suspension was stirred and warmed to ambient temperature and was filtered and washed with dioxane ( $2 \times 20$  L). The product was dried on a rotary evaporator at 40 °C to give 11 as a white solid (11.51 kg, 87% th, 98.4% w/w NMR assay, residual dioxane 2.8% w/w, <0.1% ROI). <sup>1</sup>H NMR (D<sub>2</sub>O, 400 MHz, 300 K):  $\delta$  3.89–3.81 (dd, J = 4 Hz, 2H, 2-H<sub>a</sub>,  $6-H_a$ ), 3.59-3.47 (dd, J = 4 Hz, 2H,  $2-H_b$ ,  $6-H_b$ ), 3.40-3.31 (t, J = 8 Hz, 2H, tetrahydropyran-CH<sub>2</sub>-bridge), 3.31-3.00 (2× dd, J = 4 Hz, 1H, CHCH<sub>2</sub>CH<sub>2</sub>O), 2.94-2.82 (m, 5H, 8-H<sub>a</sub>, 12-H<sub>a</sub>, 8-H<sub>b</sub>, 12-H<sub>b</sub>, CHCH<sub>2</sub>NH<sub>2</sub>), 2.15-2.00 (m, 2H, 9-H<sub>b</sub>, 12-H<sub>b</sub>), 1.99-1.84 (m, 2H, piperidine-CH<sub>2</sub>-bridge), 1.62-1.56 (d, J = 12 Hz,  $3-H_b$ , 5-H<sub>b</sub>), 1.52-1.34 (d, J = 12 Hz, 9-H<sub>a</sub>,  $11-H_a$ ), 1.30-1.17(m, 2H, 3-H<sub>a</sub>, 5-H<sub>a</sub>); <sup>13</sup>C NMR (D<sub>2</sub>O, 400 MHz, 300 K):  $\delta$  67.1 (2× CHCH<sub>2</sub><u>C</u>H<sub>2</sub>O), 62.5 (piperidine-<u>C</u>H<sub>2</sub>-bridge), 52.7 (2× CHCH<sub>2</sub>CH<sub>2</sub>N), 49.6 (H<sub>2</sub>NCH<sub>2</sub>-), 43.7 (CHCH<sub>2</sub>-CH<sub>2</sub>O), 31.8 (CHCH<sub>2</sub>CH<sub>2</sub>N), 29.8  $(1 \times CHCH_2CH_2O)$ , 29.7 ( $1 \times CH\underline{C}H_2CH_2O$ ), 26.6 ( $2 \times CH\underline{C}H_2CH_2N$ ). DSC melt: Broad peak 90 °C. MS calculated for C12H24N2O 213.1967 (MH<sup>+</sup> for parent), found 213.1958.

5-Amino-6-bromo-N-[(1-(tetrahydro-2H-pyran-4-ylmethyl)-4-piperidinyl]methyl-3,4-dihydro-2H-chromene-8-carboxamide, Monohydrochloride, 8. A suspension of 2H-chromene-8-carboxylic acid 7 (6.85 kg, 25.17 mol), diamine • 2HCl 11 (9.09 kg, 31.87 mol), and 2-chloro-4,6-dimethoxy-1,3,5-triazine (ex AlzChem, >98% purity, 7.03 kg, 40.04 mol) in acetonitrile (130.3 kg) was treated with Nethylmorpholine (20.2 kg, 175.2 mol) over 23 min at 23 °C, and the mixture was allowed to stir for 16 h at 22–25 °C. The mixture was filtered, washed with acetonitrile  $(3 \times$ 27.6 kg), and dried in vacuo at 40 °C to give 8 as a beige solid (8.93 kg, 76% th, 96.1% a/a HPLC). <sup>1</sup>H NMR (DMSO- $d_6$ , 400 MHz):  $\delta$  10.23 (broad s, 1H, R<sub>3</sub>NH<sup>+</sup>), 8.04 (t, J = 4 Hz, 1H, amide N<u>H</u>), 7.73 (s, 1H, H8), 5.52 (s, 2H, aryl NH<sub>2</sub>), 4.21 (t, J = 5 Hz, 2H, H2), 3.83 (dd, J = 12 Hz, J = 2 Hz, 2H, H22, H24), 2.97–3.51 (m, 6H, H15, H17, H19, H22, H24), 2.76-2.94 (m, 4H, H12, H15, H17), 2.49 (t, J = 6 Hz, 2 H, H4), 2.01–2.14 (m, 1 H, H13), 1.96 (dt, *J* = 5 Hz, 2H, H3), 1.57–1.85 (m, *J* = 10 Hz, 7H, H14, H18, H20, H21, H25), 1.16-1.29 (m, 2H, H14, H18). <sup>13</sup>C NMR (DMSO- $d_6$ , 100 MHz):  $\delta$  164.0 

5-Amino-6-bromo-N-[(1-(tetrahydro-2H-pyran-4-ylmethyl)-4-piperidinyl]methyl-3,4-dihydro-2H-chromene-8-carboxamide, Monotosylate, 1. The HCl salt 8 (8.89 kg, 17.68 mol) was stirred for 2 h at ambient temperature in deionised water (51 L), and the brown turbid solution was filtered. The filtrate was cooled to 3 °C, and an aqueous sodium carbonate solution (13.73% w/w; 20 L) was added over 70 min to adjust the pH to 10. The resulting suspension was transferred in two portions to the filter, and the cake was rinsed with water  $(3 \times 39.5 \text{ L})$ . The resulting free base was dried at 53 °C to give a residual water content of 9.6% w/w by KF. The free base was dissolved out of the filter using acetonitrile (30.3 kg), and the solution was treated with activated carbon (0.17 kg) whilst warming to 69 °C. The charcoal was removed by filtration and rinsed with hot acetonitrile (5 kg). A solution of 4-toluene sulfonic acid monohydrate (3.15 kg, 16.56 mol) in acetonitrile (22.7 kg) was added to the filtrate at 68-73 °C over 60 min. The reaction mixture was cooled to 10 °C over 2 h and filtered, washing the cake with acetonitrile (26.2 kg). The crude tosylate salt was dried at 50 °C in vacuo and then dissolved on the filter in dimethyl sulfoxide (60.4 kg) directly on the nutsche at 90 °C. The solution was filtered, and the filter was rinsed with hot dimethyl sulfoxide (6 kg). DMSO filtrates were combined and heated to 80 °C. Isopropyl acetate (71.5 kg) was added at 78-80 °C, and the clear solution was seeded with a suspension of 1 (20 g) in isopropyl acetate (0.3 kg). The turbid solution was aged for 23 min, and further isopropyl acetate was added (51.2 kg) at 79-81 °C. The resulting suspension was cooled to 20 °C, aged, and then filtered. The cake was rinsed with isopropyl acetate (2× 13.7 kg) and dried at 50 °C in vacuo to give 1 as a slightly coloured crystalline solid in (8.91 kg, 79% th, 99.8% a/a HPLC, 0.29% w/w DMSO, 0.03% w/w IPAc). <sup>1</sup>H NMR (DMSO- $d_6$ , 400 MHz):  $\delta$  8.69 (broad s, 1H, R<sub>3</sub>NH<sup>+</sup>), 8.03 (t, J = 6 Hz, 1H, amide NH), 7.74 (s, 1H, H8), 7.49 (d, 2H, H29, H31), 7.12 (d, J = 8 Hz, 2H, H23, H32), 5.52 (broad s, 2H, aryl NH<sub>2</sub>), 4.20 (t, J = 5 Hz, 2H, H2), 3.79–3.87 (m, 2H, H22, H24), 3.49 (d, *J* = 12 Hz, 2H, H15, H17), 3.15–3.35 (m, 4H, H19, H22, H24), 2.80–2.96 (m, J = 6 Hz, 4H, H12, H15, H17), 2.48 (t, J = 6 Hz, 2H, H4), 2.29 (s, 3H, H26), 1.99–2.09 (m, 1H, H13), 1.96 (dt, J = 6 Hz, 2H, H3), 1.72–1.84 (m, 3H, H20, H21, H25), 1.62 (d, J = 11 Hz, 2H), 1.40–1.54 (m, 2H, H21, H25), 1.14–1.27 (m, 2 H, H14, H18). <sup>13</sup>C NMR (DMSOd<sub>6</sub>, 100 MHz): δ 164.1 (C11), 153.1 (C10), 146.4 (C6), 145.6 (C27), 137.7 (C30), 131.8 (C8), 128.0 (C23, C32), 125.5 (C29,

C31), 111.1 (C5), 107.5 (C7), 98.5 (C9), 66.2 (C22, C24), 65.9 (C2), 61.4 (C12), 52.3 (C15, C17), 43.6 (C19), 33.7 (C20), 30.2 (C14, C18), 29.6 (C13), 26.7 (C21, C25), 21.0 (C4), 20.7 (C3, C26). DSC melt: Peak 229.4 °C.



### Acknowledgment

We thank Fabian Hunziker, Peter Lazar, and Marco Roth (Carbogen AMCIS) for their technical assistance.

## **Supporting Information Available**

DOE results for CDMT amide coupling screen. This material is available free of charge via the Internet at http://pubs.acs.org.

Received for review July 27, 2009. OP900193V