Organic Process Research & Development **2002**, *6*, 767–772

The Process Development of a Scaleable Route to the PDE5 Inhibitor UK-357,903

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Abstract:

A case history is outlined for the development of a scaleable route to the drug candidate UK-357,903. Despite the partial structural similarities to those of sildenafil (Viagra), the introduction of the central pyridine moiety within UK-357,903 had a significant impact on the commercial process. In particular, the triply activated 2-alkoxy*pyridyl* moiety of UK-357,903 is much more susceptible to nucleophilic attack than the 2-ethoxy*phenyl* moiety of sildenafil, necessitating the development of new chemistry. Particular items of note are (i) the new six-step route to the advanced 2-ethoxy-5-(4-ethylpiperazinylsulfonyl)nicotinic acid intermediate and the subsequent telescoping to a two-pot process, (ii) the telescoping of the two steps from *N*-[3-carbamoyl-5-ethyl-1-(2-pyridylmethyl)-1*H*-pyrazol-4-yl]-2-ethoxy-5-(4-ethyl-1-piperazinylsulfonyl)nicotinamide to UK-357,903 to a single step, with the additional use of a hydroxide trapping agent to give an ambient pressure process yielding clinical quality product, and (iii) the introduction of process modifications to allow for the use of teratogenic 2-methoxyethanol, as both reagent and solvent, in the penultimate process step.

Introduction

UK-357,903 is a potent and selective phosphodiesterase 5 (PDE5) inhibitor which entered development for the potential treatment of male erectile dysfunction (impotence). It is thus of the same therapeutic class as sildenafil **(7)** (Viagra). Although at first sight they appear structurally similar (Figure 1), the introduction of the central pyridine moiety within UK-357,903 **(1)** had a significant impact on both the commercial process and the biological activity.

Results and Discussion

Pfizer's experience with the pyrazolopyrimidone class of PDE5 inhibitors extends over a decade and during this interim period, several synthetic approaches to this structural class have been demonstrated.[1,2] Following the commercial route development of sildenafil **(7)** previously outlined in this journal[3] (see Scheme 1), our Medicinal Chemistry colleagues used a closely analogous approach for the preparation of UK-357,903 **(1)**, albeit with the necessary introduction of a 2-methoxyethanol side chain as the final step (Scheme 2). An analogous convergent approach seemed appropriate for UK-357,903 **(1)**, but a new synthesis of the 2-alkoxypyridyl moiety together with improvements in the final two chemical steps was desirable.

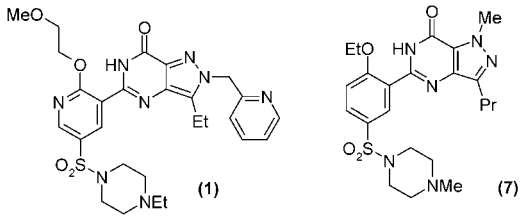
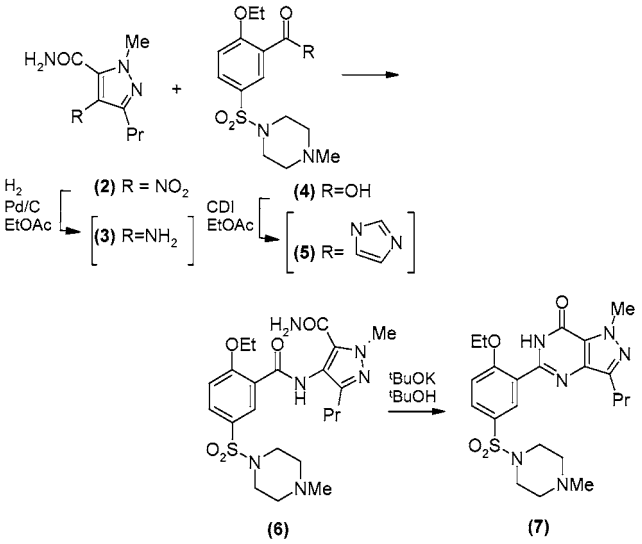


Figure 1.

Scheme 1. **Commercial route to sildenafil (7)**

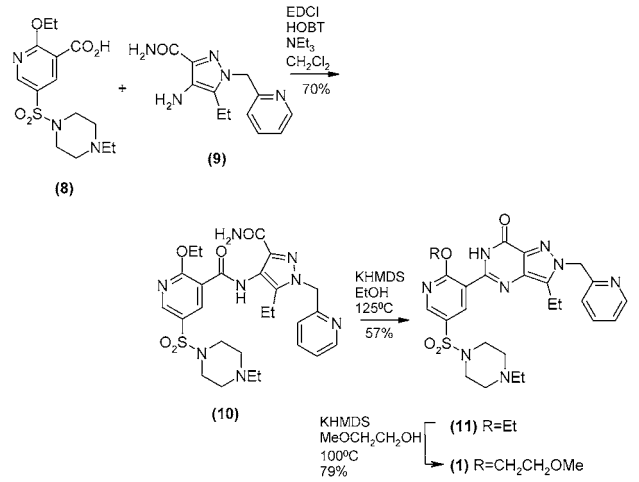


(a) Preparation of the Nicotinic Acid (8). In the sildenafil route the phenyl sulphonamide **(4)** was generated via chlorosulphonylation of 2-ethoxybenzoic acid. A literature search for chemistry analogous with that of 2-alkoxynicotinic acids proved fruitless, and the suggestion[4] that the more reactive 2-pyridone would not sulphonylate led to other approaches being considered. Therefore Medicinal Chemistry developed a novel route to sulphonamide **(8)**, which served

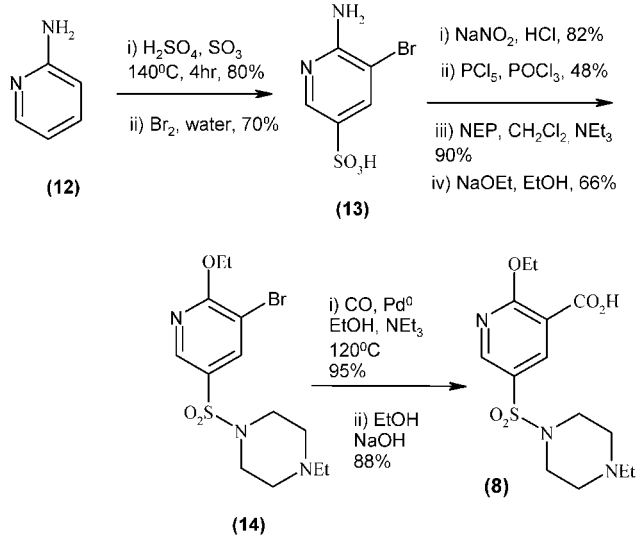
(1) Bell, A. S.; Brown, D.; Terrett, N. K. Eur. Pat. 463756 B1, April 19, 1995.
(2) (a) Bunnage, M. E.; DeVries, K. M.; Harris, L. J.; Levett, P. C.; Mathias, J. P.; Negri, J. T.; Street, S. D.; Wood, A. S. WO 01/27113, April 19, 2001. (b) Dunn, P. J.; Levett, P. C. Eur. Pat. Appl. 994115 A2, April 19, 2000 (c) DeVries, K. M.; Levett, P. C.; Negri, J. T.; Wood, A. S. Eur. Pat. Appl. 1092720 A2, April 18, 2001.
(3) Dale, D. J.; Dunn, P. J.; Golightly, C.; Hughes, M. L.; Levett, P. C.; Pearce, A. K.; Searle, P. M.; Ward, G.; Wood, A. S. *Org. Process Res. Dev.* **2000**, *4*, 17.
(4) Meislich, H. Pyridine and its Derivatives. In *Heterocyclic Compounds*; Interscience Publishers: New York-London, 1962; Part Three, Chapter XII, p 669.

10.1021/op0200468 CCC: $22.00
Published on Web 09/17/2002

Scheme 2. **Medicinal chemistry route to UK-357,903 (1)**



Scheme 3. **Medicinal chemistry route to nicotinic acid (8)**

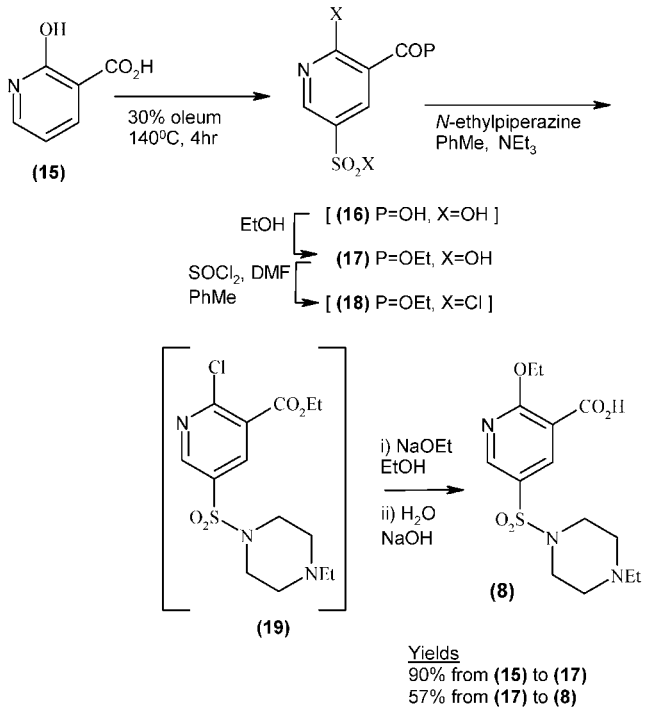


them well over the course of their discovery program (Scheme 3). This route was then successfully used within the Chemical R&D department for preparing the first 200 kg of sulfonamide **(8)**.

However, this eight-step linear process utilised oleum sulfonylation, bromination, diazotisation, chlorination, and high-pressure carbonylation chemistry and yielded **8** in just 11% overall yield. Since there were a number of hazardous reactions in this route and the high-temperature carbonylation required specialised plant equipment, we were encouraged to search for a new route.

Despite the discouraging literature claim,[4] we decided to investigate the sulfonylation of the inexpensive, agrochemical intermediate, 2-hydroxynicotinic acid (Scheme 4), since we believed success here could lead to a superior commercial manufacturing process. Not surprisingly, we found that sulfonylation of 2-hydroxynicotinic acid **(15)** did not occur in concentrated sulphuric acid. In light of the harsher conditions that were required to sulfonylate 2-aminopyridine (as outlined above), we progressed to a successful reaction with stoichiometric 30% oleum at 140 °C, yielding sulfonic acid **(16)** in 90% yield. Catalytic oleum was not a viable

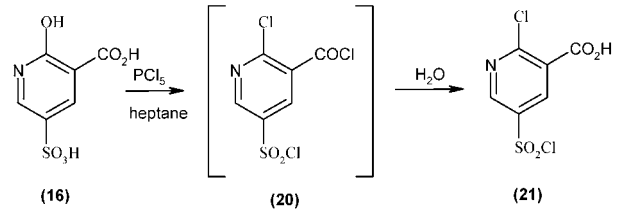
Scheme 4. **Chemical R&D route to nicotinic acid (8)**



option, since use of substoichiometric sulfur trioxide in concentrated sulfuric acid failed to effect reaction completion. Reaction calorimetry data showed the addition of the 2-hydroxynicotinic acid **(15)** to oleum at 40 °C generated −60.1 kJ/mol based on nicotinic acid which could produce an adiabatic temperature rise of 93 °C. Upon heating the reaction mixture to 140 °C over 2 h to effect reaction completion, calorimetry data showed further exothermic activity both during the linear ramp, and after reaching the final temperature (Total ΔT_{ad} = 53 °C). It was therefore important to make sure the heat from the nicotinic acid addition had dissipated before slow heating of the reaction to ∼140 °C commenced to reduce this possible temperature rise. Reaction calorimetry was also used to examine the quench of the reaction at 55 °C with water which was added over 1 h. This quench liberated −100 kJ/mol based on the nicotinic acid, which was equivalent to an adiabatic temperature rise of 88 °C (i.e., would cause boiling of the reaction mixture). However, whilst it is not normal practice to quench oleum reactions with water addition, this did allow the reaction to be handled much more easily. Therefore, provided adequate mixing (to avoid local boiling) is used and the quench carefully controlled, the process was deemed safe to run in this way.

To minimise the total number of steps, progression of nicotinic acid **(16)** through to nicotinic acid **(8)** would ideally have carried the 3-carboxyl functionality through unchanged. This strategy was shown to be feasible (Scheme 5), with a phosphorus pentachloride/heptane-mediated trichlorination of **16** to **20**, followed by a selective hydrolysis of the unisolated nicotinoyl chloride **(20)** back to the nicotinic acid **(21)**, occurring in up to 64% yield. Unfortunately this was a particularly capricious reaction, with over-hydrolyzed sulfonic acid impurities being generated in up to 20%.

Scheme 5. **Trichlorination approach to (21)**



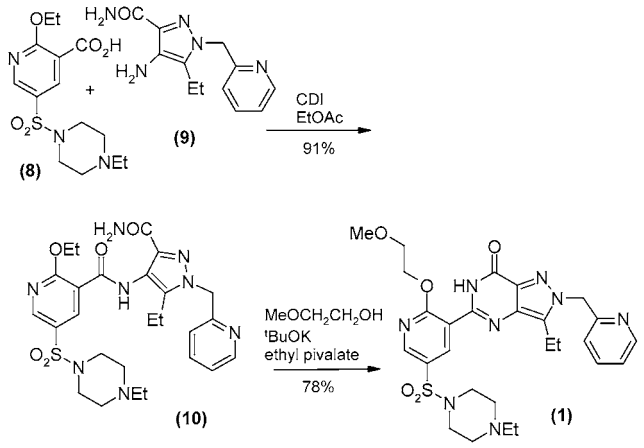
To compensate for this, a facile protecting-group strategy was employed, whereby nicotinic acid **(16)** was first protected as the ethyl nicotinoate **(17)** in 74% yield over two crops. To drive this condensation reaction to completion, azeotropic removal of the generated water was required. Interestingly, no additional acid catalysis was required for this reaction, presumably due to the presence of the 5-sulfonic acid functionality. A further process modification allowed the telescoping of steps **(15)** to **(17)** in 90% yield by quenching the oleum reaction directly into ethanol, although controlling the simultaneous generation of diethyl sulfate clearly had to be engineered into the process.

The dichlorination to the sulfonyl chloride **(18)** was effected successfully in thionyl chloride with catalytic DMF in quantitative yield (SAFETY NOTE: this generates the known animal carcinogen dimethylcarbamoyl chloride).[5] Subsequent formation of the sulfonamide **(19)**, in the presence of *N*-ethylpiperazine and triethylamine in ethyl acetate, could also be achieved in quantitative yield once all traces of thionyl chloride had been removed from the previous step. The final introduction of the 2-ethoxy side chain with ethanolic sodium ethoxide and subsequent ester saponification to nicotinic acid **(8)** could then be effected in a one pot process.

At this stage we had effectively telescoped the process down to three isolation stages; **(15)** to **(17)**, **(17)** to **(19)** and **(19)** to **(8)**, each being two synthetic transformations. The final process, that has delivered multikilogam quantities of nicotinic acid **(8)**, further telescoped together the four transformations **(17)** to **(8)** using a toluene solution without intermediate isolation. Use of toluene as solvent in the chlorination step, [**(17)** to **(18)]**, allowed for facile azeotropic removal of excess thionyl chloride, whilst also allowing the thionyl chloride charge to be reduced from reaction solvent to 5 equiv. The product sulfonyl chloride **(18)** was then taken through to the sulfonamide-forming step as the toluene solution, whereby the triethylamine hydrochloride generated could be readily aqueous washed from the less dense toluene layer rather then filtered, as had been the case previously. The use of ethyl acetate as solvent was no longer required and the water wet toluene solution of product **(19)** could be readily azeotropically dried in the same vessel for the subsequent water sensitive step. The sodium ethoxide mediated introduction of the 2-ethoxy side chain could also be effected in toluene with the subsequent ester saponification utilising addition of aqueous sodium hydroxide. This two-phase hydrolysis had the advantage of minimising generation of the 2-pyridone impurity, with product isolation readily

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

Scheme 6. **Chemical R&D route to UK-357, 903 (1)**



achieved via extraction into the basic aqueous phase with product crystallisation after pH adjustment to the isoelectric point. This "four-into-one" step telescoped process generates the nicotinic acid **(8)** in 54% yield (i.e., 51% from 2-hydroxynicotinic acid **(15)**, compared to 11% for the Discovery route), with the *overall* cost reduced to one-quarter compared to the route starting from 2-aminopyridne.

(b) Preparation of Amide (10). As outlined in Scheme 2, the Medicinal Chemistry route utilised a hydroxybenzotriazole/1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (EDCI) coupling system with nicotinic acid **(8)** and aminopyrazole **(9)**[9] to generate amide **(10)** in ~70% yield. The moderate yield coupled with the knowledge that EDCI was both a suspect sensitizer and expensive encouraged us to switch to the *N*,*N*-carbonyldiimidazole/ethyl acetate approach (Scheme 6), as previously utilised in the commercial route for the preparation of sildenafil. This approach allowed crystallised product amide **(10)** to be filtered directly from the reaction mixture in 91% yield, with the imidazole byproduct remaining in the ethyl acetate solution. The formation of the imidazolide generates carbon dioxide and hence represents a potential overpressure hazard. Safety work showed that the rate of gas evolution could be controlled to acceptable levels by performing the CDI addition at 25 °C and then heating the reaction in steps as described in the Experimental Section. Off-gas measurement data showed that when the reaction was heated at 1 °C/min the maximum rate of off-gassing was 0.85 litre/min (per litre of batch) occurring at ~38 °C. To provide an adequate margin for scale-up, it was a requirement to only use 50% vessel fills and control the heat up rate to a maximum of 1 °C/min.

(c) Preparation of UK-357,903 (1). The two-step Medicinal Chemistry process to convert amide **10** to UK-357,-903 **(1)** by cyclisation and then displacement (Scheme 2)

(6) Salmi, E. J.; Leimu, R. *Suom. Kemistil.* **1947**, *20B*, 43. For abstract, see: *Chem. Abs.* **1947**, *41*, 5370c.
(7) Urban, P. *Bretherick's Handbook of Reactive Chemical Hazards*, 5th ed.; Butterworth Heinemann: Woburn, MA, 1995; Vol. 2, p 193.
(8) Au, W.; Ahmed, E.; Chiechanwit, T.; Hsie, W.; Ma, H.; Moslen, T. *Occup. Hyg.* **1996**, *2*, 177.
(9) For preparation of amino pyrazole **(9),** see ref 2c above, examples 1a to 1f, inclusive.

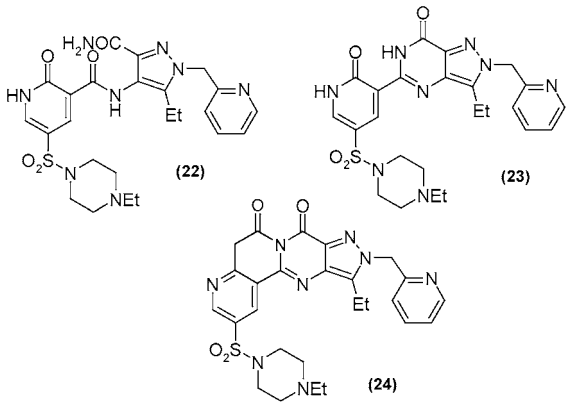


Figure 2.

was suboptimal as a commercial process for the following reasons:

(1) The cyclisation of amide **10** to pyrimidone **11** gave a 35% combined level of the 2-pyridone impurities **22** and **23** (Figure 2). In contrast, the in-process reaction assay of the analogous sildenafil cyclisation step showed >95% sildenafil present (with very low levels of any impurities in the reaction mixture), thus demonstrating the large difference in electrophilicity between 2-ethoxypyridine and 2-ethoxybenzene derivatives.

(2) Use of KHMDS as the base in alcoholic solvents for both the cyclisation and displacement steps liberated stoichiometric quantities of ammonia, which would require process engineering to scrub. Furthermore, the liberated ammonia reacted with the reactive 2-alkoxy substituent of **10**, **11**, and **1)**to yield the analogous 2-aminopyridine impurities.

(3) The cyclisation to pyrimidone **11** required the reaction to be run in KHMDS/ethanol at 125 °C, thus necessitating the use of a high-pressure reactor (~60 psi).

We reasoned that the source of the 2-pyridone impurities **22** and **23** was the mole of potassium hydroxide generated during the cyclisation of the bisamide **10** to the pyrimidone **11**. We investigated a number of experimental approaches to minimise the impact of potassium hydroxide. Several were tried, but we surprisingly found that the best results were obtained utilising an ester as a hydroxide-trapping reagent. Initial efforts utilising ethyl acetate were very encouraging with the impurities **22** and **23** reduced to a combined level of ~8% (from ~35%). Further analysis of the isolated product revealed the presence of the fused tetracyclic impurity **24**, presumably generated via acyl transfer from ethyl acetate. To prevent formation of impurity **24**, a nonenolisable ester was used as a hydroxide-trapping agent. Ethyl pivalate gave a further improvement, with no pivalated impurities detected, and levels of the 2-pyridones **22** and **23** were reduced further to ~6%, thus improving the isolated yield.

Switching the base from KHMDS required the use of a nonnucleophilic base to prevent undesired exchange at the reactive 2-alkoxy site. For the cyclisation step, **10** to **11**, this could be best achieved with potassium ethoxide in ethanol (since an ethoxy-for-ethoxy exchange would give the same product), giving an 80% yield in the pilot plant (compared with 45% with KHMDS). For the displacement step **11** to **1**, the use of potassium *tert*-butoxide in 2-methoxyethanol again improved the yield to 97% (compared to 79% with KHMDS), albeit now in the presence of an hydroxide-trapping agent. ***These reactions should be charged and conducted under nitrogen, since Bretherick[7] highlights the danger of metal alkoxides hydrolysing in moist air, whereby the exotherm may ignite the solids.***

Removing the need to run the cyclisation step at high pressures (i.e., ethanol at 125 °C) conceptually seemed quite straightforward, given that the medicinal chemists had already demonstrated that a temperature of ~125 °C was required to effect cyclisation. As such, a range of higher-boiling solvents was investigated, including hindered tertiary alcohols (to prevent 2-ethoxy displacement). However in-process HPLC assays revealed a maximum of 64% product was achievable. The solution to this problem was particularly satisfying. By telescoping together both the cyclisation and displacement reactions, bisamide **10** could be converted directly to UK-357,903 **(1)** using 2-methoxyethanol as both the high-boiling solvent (for the cyclisation) and the reagent (for the displacement) in the presence of potassium *tert*-butoxide and ethyl pivalate. Unfortunately, filtration and drying of the precipitated product after pH adjustment to the isoelectric point was extremely slow (5 h and 4 days, respectively). After laboratory evaluation we found that after pH adjustment the product could be directly extracted into warm methyl isobutyl ketone (MiBK) and then crystallised at reduced volume to furnish a 78% yield of high,quality UK-357,903 **(1)** which could be rapidly filtered and dried.

(d) The 2-Methoxyethanol Issue. The one downside of this process was that 2-methoxyethanol is a teratogenic solvent, with an OEL of 5 ppm.[8] Hence, the process was carefully designed to introduce a 2-methoxyethanol side chain into our drug candidate, whilst safely controlling 2-methoxyethanol levels in the manufacturing plant, in the waste streams, and in the final isolated UK-357,903 **(1)**.

(1) Significant effort was put into finding a stoichiometric 2-methoxyethanol process that utilised an inert high-boiling cosolvent. Dibutyl ether was our best option, but with just a 29% UK-357,903 yield (unisolated), this was clearly not viable.

(2) Introduction of the 2-methoxyethanol side chain earlier in the process would have prevented 2-methoxyethanol contamination of the isolated UK-357,903 **(1)**, but the highly labile nature of this side chain meant this could not be carried through the synthetic sequence successfully. Literature precedent demonstrates[6] the facile leaving group potential of the 2-methoxyethanol side chain, whereby the saponification of a 2-methoxyethanol ester was shown to proceed at a rate twice that of the ethoxy analogue—presumably due to the neighbouring group participation of the β-methoxy substituent.

As a consequence we looked to engineering and process optimisation within our current process to overcome the 2-methoxyethanol issues:

(1) Extensive vapour monitoring work was undertaken using 3M passive diffusion monitors. Analysis by the Institute of Occupational Medicine showed that at all stages of the process within the pilot plant, levels were below the MEL of 5 ppm except within 1 m of the chargehole during the solids charging to reactors. Monitors within the operators' airsuits always gave a "nondetected" reading.

(2) The process was optimised to ensure the 2-methoxyethanol was contained within this single step and not forwarded to the final salt-forming step. During the workup, to separate the 2-methoxyethanol from the product it was necessary to optimise the level of 2-methoxyethanol remaining in the aqueous phase. Optimal results were achieved by ensuring most of the ethanol (a byproduct from the displacement component of the reaction) was azeotropically removed, during the reaction, with several 2-methoxyethanol strip-and-replace cycles. This minimised the effect of ethanol solubilising the 2-methoxyethanol from the aqueous to the MiBK phase after pH adjustment. This had the additional benefit of driving the reaction further to completion, an added bonus since the intermediate pyrimidone **11** was a difficult impurity to purge. Furthermore. it was found that a MiBK strip (to 3 mL/g) followed by three aqueous washes of the MiBK phase would lower the 2-methoxyethanol levels to a nondetectable level within the isolated UK-357,903 **(1)**. All waste streams were subsequently incinerated.

(3) As a consequence of the optimisation work presented above, our manufacturing division was prepared to run the 2-methoxyethanol process within a modified containment facility.

(e) The Salt-Forming Step. Salt-selection work early in the development cycle for UK-357,903 **(1)** identified the benzenesulfonate monohydrate as the solid form of choice over the anhydrous P255 form. Judicious process optimisation was then required to ensure dehydration to an anhydrous benzene sulfonate salt did not occur:

(1) 8% water in MEK was optimal, allowing the speck-freeing operation at 50 °C. Increasing the water level lowered the yield, whilst reducing the water level to <5% water yielded the anhydrous salt.

(2) Benzenesulfonic acid in 8% water wet MEK was added to the solvated UK-357,903 **(1)** at 35 °C. An addition temperature >50 °C yielded the anhydrous salt, as could a concentration gradient if 8% wet MEK was not employed in both the header tank and the main vessel.

(3) Drying the salt necessitated a temperature of around 40 °C, with full vacuum at high humidity (i.e., using a tray of water in the bottom of the oven) to give the hydrated benzene sulfonate in 87% yield. *Unfortunately after many successful batches, the process failed at 50 °C, producing* ~10% contamination with undesired anhydrous benzenesulfonate salt.

(4) A stability trial at 50 °C/20% RH also produced ~5% conversion to an anhydrous benzene sulfonate salt.

These two final results showed that we did not have control of the process to guarantee generation of the besylate monohydrate salt. Therefore, as we had lost confidence in the processability and stability of this solid form, the salt screen was re-run with a wider range of counterions. This ultimately resulted in the anhydrous *p*-toluenesulfonate salt being selected, which could be reproducibly prepared in 98% yield.

Conclusions

Despite the partial structural similarity between sildenafil **(7)** and UK-357,903 **(1)**, the scaleable route described in this paper demonstrates the significant process variations required to overcome the fundamental reactivity differences between a 2-ethoxyphenyl and a 2-ethoxypyridyl derivative. The high yielding, operationally streamlined, convergent route described (36% yield from 2-hydroxynicotinic acid **(15)**, compared with the overall medicinal chemistry route yield of 3.5% from 2-aminopyridine) allowed this new PDE5 inhibitor to be prepared on a multikilogram, large pilot-plant scale.

Experimental Section

Proton NMR data were recorded on a Varian Unity 300 spectrometer operating at 300 MHz. Melting points were determined on a Buchi melting point apparatus and are uncorrected.

2-Hydroxy-5-sulfonicotinic Acid (16). 2-Hydroxynicotinic acid (27 kg, 194.2 mol) was added portionwise to 30% oleum (58.1 kg) at 50 °C over 1 h resulting in an exotherm to 82°C. The reaction mixture was heated further to 140 °C. After maintaining this temperature for 12 h the reactor contents were cooled to 15 °C, quenched with water (25 L) and filtered. The filter cake was then re-slurried with acetone (33 kg) at room temperature, filtered, and dried to afford the title compound (35.3 kg, 83%) as a white solid: mp 273 °C dec. (DMSO-d_6) δ 7.93 (1H, d), 8.42 (1H, d). *m*/*z* (Found: 220 $[M + H]^+$, 100%. $C_6H_6NO_6S$ requires 220).

Ethyl 2-hydroxy-5-sulfonicotinoate (17). 2-Hydroxy-5-sulfonicotinic acid **(16)** (500 g, 2.28 mol) was dissolved in ethanol (2.5 L) with stirring and was heated to 80 °C. After 30 min, 0.5 L of solvent was distilled off and replaced with fresh ethanol (0.5 L) and then reheated to 80 °C. After a further 60 min 1.0 L of solvent was distilled off and then replaced with fresh ethanol (1.0 L) and reheated to 80 °C. After a further 60 min, 1.0 L of solvent was distilled off, and the reaction was cooled to 22 °C and stirred for 16 h. The precipitated product was filtered, washed with ethanol (0.5 L), and dried at 50 °C under vacuum to afford the title compound (416 g, 74%) as a white solid: mp 237 °C (dec). (DMSO-d_6) δ 1.25 (3H, t), 4.19 (2H, q), 7.66 (1H, d), 8.13 (1H, d). *m*/*z* (Found: 248 $[M + H]^+$, 100%. $C_8H_{10}NO_6S$ requires 248).

2-Ethoxy-5-(4-ethyl-1-piperazinylsulfonyl)nicotinic Acid (8): Telescoped Process in Toluene from (17). Ethyl 2-hydroxy-5-sulfonicotinoate **(17)** (441.5 g, 1.79 mol) was dissolved in toluene (1.77 L); thionyl chloride (1.06 kg, 8.93 mol) and dimethylformamide (71.3 mL) were then added. The stirred suspension was then heated to reflux for 3 h to yield a yellow solution. Thionyl chloride (2.87 L) was distilled with continual replacement with toluene (2.15 L). The pale yellow solution was cooled to 10 °C, and a stirred

solution of *N*-ethylpiperazine (198.9 g, 1.66 mol) and triethylamine (392.2 g, 3.88 mol) in toluene (700 mL) was added dropwise over 90 min, keeping the reaction mixture below 10 °C. The reaction was stirred at ambient temperature for 18 h and washed with water (2 × 700 mL) and brine (2 × 350 mL). The toluene phase was azeotropically dried by distilling off 1750 mL, which was continuously replaced by dry toluene (1750 mL). The remaining brown solution was cooled to 10 °C, and sodium ethoxide (178.0 g) was added portionwise, keeping the temperature below 10°C. The reaction was stirred at 10 °C for 1 h and then warmed to ambient temperature and stirred for 18 h. Sodium hydroxide (34.9 g, 0.87mol) dissolved in water (1.5 L) was added to the toluene mixture, and the two-phase mixture was vigorously stirred for 18 h at 40 °C. Once cooled to ambient temperature, the aqueous phase was separated off and adjusted to pH 3 with concentrated hydrochloric acid. The precipitated solid was granulated for 2 h with ice cooling and then filtered, washed with water (300 mL), and dried in vacuo at 50 °C to afford the title compound (338.4 g, 57.4%) as an off-white solid: mp 206−207 °C. ($CDCl_3$) δ 1.25 (3H, t), 1.39 (3H, t), 2.82 (2H, q), 3.03 (4H, m), 3.25 (4H, m), 4.50 (2H, q), 8.25 (1H, d), 8.56 (1H, d). *m*/*z* (Found: 344 $[M + H]^+$, 100%. $C_{14}H_{22}N_3O_5S$ requires 344).

***N*-[3-Carbamoyl-5-ethyl-1-(2-pyridylmethyl)-1H-pyrazol-4-yl]-2-ethoxy-5-(4-ethyl-1-piperazinylsulfonyl)nicotinamide (10).** 2-Ethoxy-5-(4-ethyl-1-piperazinylsulfonyl)-nicotinic acid **(8)** (0.875kg, 2.55mol) was dissolved in ethyl acetate (7 L, 8 mL/g), and 2 mL/g was distilled off at atmospheric pressure to ensure the reaction system was dry. The slurry was cooled to room temperature under a nitrogen atmosphere, and *N*,*N*′-carbonyldiimidazole (0.43 kg, 2.65 mol) was added in one portion. The slurry was heated at 35 °C for 30 min, at 45−50 °C for a further 30 min, and finally at reflux for 1 h. On confirmation of complete imidazolide formation the reaction was cooled to 45−50 °C under nitrogen, and 4-amino-5-ethyl-1-(2-pyridylmethyl)-1*H*-pyrazole-3-carboxamide **(9)**[7] (0.59 kg, 2.42 mol) was charged in one portion before returning to reflux; a further 1 mL/g was distilled off at atmospheric pressure. The reaction was stirred at reflux for 16 h and then cooled to 10−15 °C and granulated for 1 h. The reaction slurry was filtered, washed (ethyl acetate), and finally dried in vacuo at 50 °C to afford the title compound (1.252 kg, 90.7%) as a white solid: mp 178−179 °C. ($CDCl_3$) δ 1.04 (3H, t), 1.06 (3H, t), 1.59 (3H, t), 2.40 (2H, q), 2.50 (4H, m), 2.90 (2H, q), 3.08 (4H, m), 4.78 (2H, q), 5.35 (1H, s), 5.48 (2H, s), 6.68 (1H, s), 6.92 (1H, d), 7.22 (1H, m), 7.65 (1H, m), 8.58 (1H, d), 8.64 (1H, d), 8.83 (1H, d). *m*/*z* (Found: 571 $[M + H]^+$, 100%. $C_{26}H_{35}N_8O_5S$ requires 571).

1-Ethyl-4-{5-[3-ethyl-6,7-dihydro-7-oxo-2-(2-pyridylmethyl)-2H-pyrazolo[4,3-d]pyrimidin-5-yl]-6-(2-methoxyethoxy)-3-pyridylsulfonyl}piperazine (1). *N*-[3-Carbamoyl-5-ethyl-1-(2-pyridylmethyl)-1*H*-pyrazol-4-yl]-2-ethoxy-5-(4-ethyl-1-piperazinylsulfonyl)nicotinamide **(10)** (500 g, 0.876 mol) was added under nitrogen in one portion to 2-methoxyethanol (2.5L, 5 mL/g), and the reaction was stirred at ambient temperature for 10 min. The addition of potassium *tert*-butoxide (236 g, 2.103 mol), added portionwise under nitrogen over 10 min to the stirred reaction mixture, was found to produce an exotherm (Δ = 20−50 °C). The reaction was stirred until a steady temperature was obtained, giving a clear pale yellow solution. Ethyl pivalate (285 g, 2.19 mol) was then washed in with 2-methoxyethanol (0.3 L). The reaction mixture was heated to reflux temperature (115−125 °C) and maintained at reflux temperature for 6 h, removing the ethanol and *tert*-butyl alcohol byproducts by distillation and replacing with 2-methoxyethanol. The remaining solvent is then reduced under vacuum distillation to a volume of 2 mL/g. The viscous solution was stirred and cooled to ambient temperature. Water (3 L) was added to the viscous solution and stirred to produce a homogeneous solution. Dilute aqueous hydrochloric acid was added to adjust the pH of the reaction mixture from about pH = 13 to 8, slowly over 1 h. MiBK (3 L) was added and the mixture heated to 55 °C. The lower aqueous layer was separated off, whilst the remaining organic layer was washed with warm water (500 mL). The organic layer was removed and 1 L distilled under vacuum. The remaining solution was cooled to 50 °C, and the resulting precipitate, granulated at 50 °C for 1 h, was filtered, washed with MiBK (1 L), and dried under vacuum at 50 °C to afford the title compound (400.3 g, 78.4%) as a white solid: mp 157−158 °C. ($CDCl_3$) δ 1.02 (3H, t), 1.30 (3H, t), 2.40 (2H, q), 2.55 (4H, m), 3.03 (2H, q), 3.12 (4H, m), 3.55 (3H, s), 3.85 (2H, m), 4.77 (2H, m), 5.66 (2H, s), 7.10 (1H, d), 7.21 (1H, m), 7.63 (1H, m), 8.57 (1H, d), 8.62 (1H, d), 8.97 (1H, d). *m*/*z* (Found: 583 $[M + H]^+$, 100%. $C_{27}H_{35}N_8O_5S$ requires 583).

Acknowledgment

We acknowledge the advice and assistance of many Pfizer colleagues throughout this development work. In particular we thank Richard Storey for his assistance with the solid-form work, Steven Galvin and Sandra Mullane for their helpful suggestions around transfer to production, and Wiebke Bahker, Rob Savage, Richard Shannon, Angela Shaw, Zena Smith, and Geoff Walker for their analytical support.

Received for review April 26, 2002.

OP0200468