Organic Process Research & Development **2001**, *5*, 9–15

Articles

The Process Development of RG 12525 (2-{[4-(Tetrazol-5-ylmethylphenyl)-methoxy]phenoxymethyl}quinoline)

Andrew W. Bridge,† Ronald H. Jones, Humayun Kabir, Alex A. Kee,* David J. Lythgoe, Mustafa Nakach,‡ Clive Pemberton, and John A. Wrightman

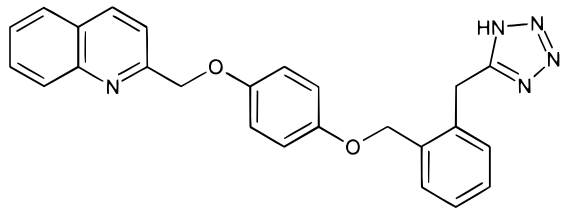
Process Development, Aventis Pharma Ltd.[1], Dagenham Research Centre, Rainham Road South, Dagenham, Essex RM10 7XS, UK and Centre-Researche Vitry-Alfortville, 13, Quai Jules Guesde, BP 14, Vitry-Sur-Seine, 94403 Cedex, France

Abstract:

This contribution describes process improvements to provide a practical and cost-effective synthesis for the manufacture of RG 12525 which resulted in a 3-fold increase in overall yield. Improved solvent systems for chlorination and azidation reactions are described. Adjustments to the tetrazole-forming step eliminated azide sublimation and minimised this risk on scale-up. A robust solvent system was found to control the polymorphic form during crystallisation, which had hitherto been difficult due to the near-equivalence of melting points (154 and 157 °C) of the two known forms.

Introduction

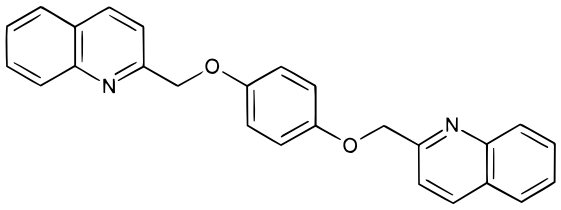
RG 12525 **1** was originally identified as a potent leukotriene D_4 receptor antagonist[2] but was later found to be a potent PPARγ (peroxisome proliferator-activated receptor) agonist with an additional indication for late onset diabetes.[3] The original synthetic route (Scheme 1) was used to prepare initial multikilogram quantities for clinical development, but process improvements were required to make further scale-up a viable proposition. Alternative routes have also been described[4] but were not deemed suitable, and therefore it was decided to identify potential improvements to the existing route. Quinaldine **2** was converted by in situ chlorination to 2-(chloromethyl)quinoline **3,** and treatment of this nonisolated intermediate with excess hydroquinone gave the phenol **4**. A large excess of α,α′-dichloroxylene ensured monoalkylation, and then cyanide displacement of the intermediate chloromethylbenzyl ether **5** gave the penultimate nitrile **6**. This was converted by azide treatment (NaN_3/NH_4Cl, DMF) to the tetrazole **1**. Although this



1

synthesis was short, the following selectivity and industrial hygiene/safety issues needed to be addressed:

(a) Significant amounts of the dimeric ether **7** are formed in the hydroquinone treatment of **3**.



7

(b) An excess of the lachrymatory α,α′-dichloroxylene was required to minimise dimer formation in the alkylation of **4**.

(c) Sublimation of ammonium azide was observed in the tetrazole step.

(d) Polymorphism of the final drug substance was difficult to control.[5]

(e) Colour and assay quality of the final drug substance was often variable.

Stage 1: Chlorination and Subsequent Alkylation of Quinaldine. Initial synthetic investigations utilising pure 2-(chloromethyl)quinoline hydrochloride (>99.8% normalised peak area by HPLC) established that the colour and assay problems inherent in the bulk API (active pharmaceutical ingredient) were associated with the use of crude

† Please send correspondence to: Andrew Bridge, Aventis Pharmaceuticals, Inc., Rt. 202−206, Bridgewater, NJ 08807.

‡ Centre-Researche Vitry-Alfortville.

(1) Formerly known as Rhône-Poulenc Rorer Ltd.

(2) Huang, Fu-Chih; Galemmo, Robert A.; Johnson, William H., Jr.; Poli, Gregory B., Jr.; Morrisette, Matthew M.; Mencel, James J.; Warus, James D.; Campbell, Henry F.; Nuss, George W.; Carnathan, Gilbert W.; Van Inwegen, Richard G. *J. Med. Chem.* **1990**, *33*, 3, 1194−1200

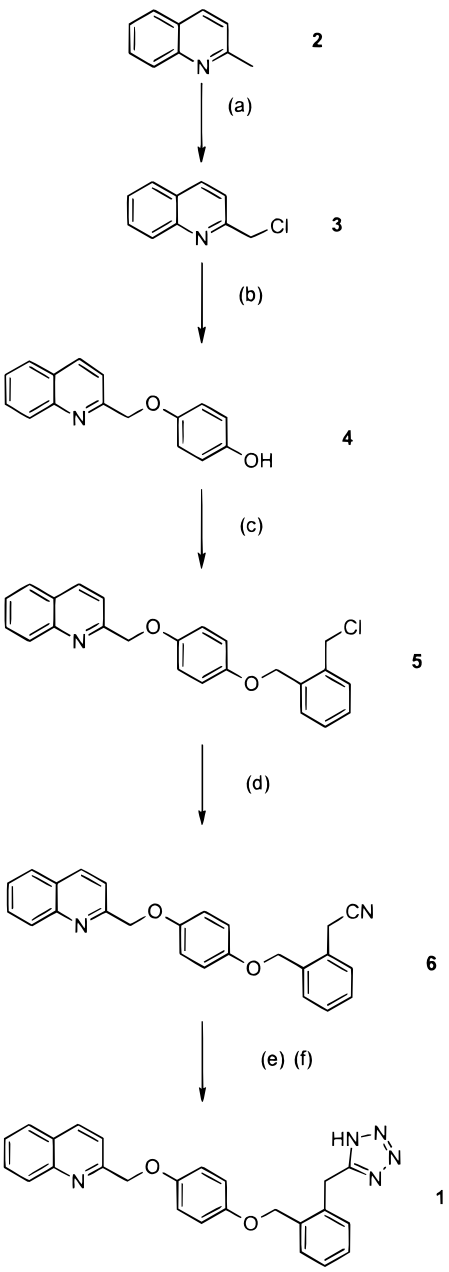
(3) Jayyosi, Zaid; McGeehan, Gerard M.; Kelley, Michael F. PPAR-g-binding quinoline derivatives, their preparation, and their therapeutic use. PCT Int. Appl. 1999, 125 pp. CODEN: PIXXD2 WO 9920275 A1 19990429 CAN 130:320864 AN 1999: 282096.

(4) O'Brien, M. K.; Sledeski, A. W.; Truesdale, L. K. *Tetrahedron Lett.* **1997**, *38*, 509−512; Sledeski, A. W.; O'Brien, M. K.; Truesdale, L. K. *Tetrahedron Lett.* **1997**, *38*, 1129−1132.

(5) (a) Thompson, M. D.; Authelin, J.-R. Chemical Development of the Drug Substance Solid Form. In *Process Chemistry in the Pharmaceutical Industry*; Gadamasetti, K. G., Ed.; Marcel-Dekker: New York, 1999; p 371−388; ISBN 0-8247-1981-6. (b) Carlton, R. A.; Difeo, T. J.; Powner, T. H.; Santos, I.; Thompson, M. D. *J. Pharm. Sci.* **1996**, *85*, 461−467.

10.1021/op0000677 CCC: $20.00 © 2001 American Chemical Society and The Royal Society of Chemistry
Published on Web 12/30/2000

Scheme 1[a]

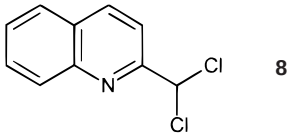


[a] Original conditions: (a) chlorine, Na_2CO_3, water, 1,2,4-trichlorobenzene; (b) hydroquinone, methanol, water, NaOH; (c) α,α′-dichloroxylene, NaOH, tetrabutylammonium hydrogen sulphate, xylene, water; (d) NaCN, xylene, water; (e) sodium azide, DMF, ammonium chloride, 130 °C; (f) recrystallisation from methanol.

2-(chloromethyl)quinoline **3**. However, this material is a severe skin irritant, and supply difficulties and the cost of the material meant that an in situ preparation and purification of the (chloromethyl)quinoline free base **3** was necessary. Chlorination of the cheap and readily available quinaldine **2** with chlorine and anhydrous sodium carbonate as base in either carbon tetrachloride[6] or chloroform[7] has been reported, but for health and environmental reasons we chose to examine alternative solvents. The addition of water (0.5 equiv) was also found to be important for safety reasons, since this promotes the formation of oxygen dichloride OCl_2 as opposed to the more explosive chlorine dioxide ClO_2.[8] This water could be conveniently provided by using the requisite amount of the sodium carbonate monohydrate. Alternatively the use of sodium bicarbonate precluded the need for any added water as it is probable that under the reaction conditions sodium carbonate is initially converted to sodium bicarbonate. The use of dichloromethane resulted in chlorination of the solvent to give some chloroform and carbon tetrachloride. 1,2,4-Trichlorobenzene handled well, but its high melting point (16 °C) and inclusion on the UK Red List[9] of chemicals led us to consider alternative solvents. Benzotrifluoride and 4-chlorobenzotrifluoride proved viable alternatives, but the former was chosen on the grounds of ease of solvent recovery and cost. Under the established reaction conditions no chlorination of this solvent was observed. The optimum temperature was found to be 30−35 °C; lower temperatures gave a sluggish reaction, whilst higher temperatures gave higher levels of the dichlorinated impurity **8**. Small-scale experiments suffered from blockage of the dip tube, but this was alleviated at larger scale by the higher chlorine gas flow rates.

Table 1: **Extraction composition by HPLC (% npa)**

extract	quinaldine **2**	monochloro salt **3**	dichlorinated **8**
reaction mixture	1.8	91.4	6.1
1st aqueous extract	3.6	96.0	0
organic layer	0	75.5	24.5
2nd aqueous extract	1.9	97.7	0
organic layer	0	61.3	38.6



8

Typically, on bubbling 1.4 equiv of chlorine over 4 h, the reaction was shown to be complete by HPLC (quinaldine < 2%) with the monochloro **3**-to-dichloro **8** ratio being 92:5. Any attempt to continue the chlorination beyond this point would result in lower yield as the product **3** is then chlorinated faster than the residual quinaldine **2**. After degassing, the inorganics were dissolved by addition of water. Following charcoal treatment and filtration, extraction of the organic layer with dilute hydrochloric acid was discovered to preferentially extract the desired product **3**, leaving the dichloro impurity **8** in the organic phase (Table 1).

The combined aqueous phase was washed with TBME (to remove any benzotrifluoride, the presence of which causes the product in the next step to form large agglomerates). This aqueous phase can then be used directly in the next step and can be stored at ambient temperature for 48 h without significant decomposition of **3** (<1%).

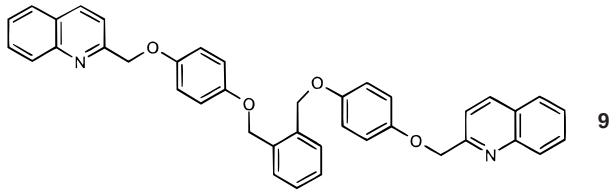
(6) Mathes, W.; Schüly, H. *Angew. Chem., Int. Ed. Engl*. **1963**, *2*, 144.
(7) Nakanishi, S.; Saito, T. (Sumika Fine Chemicals Co. Ltd.). Jpn. Kokai Tokkyo, Koho JP 92-360753, 1994.
(8) Hain, J.; McGee, H. A. *Ind. Eng. Chem. Prod. Res. Dev*. **1984**, *23*, 490.
(9) Department of the Environment, Transport and the Regions, Greening Government Operations available from http://www.environment.detr.gov.uk/greening/greenpro/gguide/gg2annc.htm.

This purification procedure was found to be essential to eliminate colour that would otherwise be carried through the process until the final step. Also polymeric material which is not detected by HPLC but which is carried through to the final product is removed in this protocol. As a demonstration of the validity of the purification regime, commercial 2-(chloromethyl)quinoline hydrochloride (>99.8% normalised peak area by HPLC) was taken through to RG 12525 **1** to give product quality comparable to that obtained by the new process.

Alkylation of the (chloromethyl)quinoline **3** solution by hydroquinone (3 equiv) in the presence of excess sodium hydroxide solution in aqueous methanol was straightforward and gave a 9:1 ratio[10] of the desired phenol **4** to the dimer **7**.

The crude product could be purified by dissolution in hot sodium hydroxide solution (70 °C) and filtration to remove the insoluble dimer **7**. The quality of this product is high (assay > 99.5%, <0.1% dimer) with a yield of 59% over 2 steps.

Stage 2: Alkylation with α,α′-Dichloroxylene and Subsequent Cyanation. Initially, alkylation of **4** was carried out in a xylene and water mixture with tetrabutylammonium hydrogen sulphate as phase transfer catalyst, sodium hydroxide as base, and an excess of α,α′-dichloro-*o*-xylene (DCX) (1.7 equiv) to favour monoalkylation. The cyanation was carried out without isolation to avoid handling the intermediate **5**. This process gave highly coloured product, low yield and assay necessitating improved conditions. The main impurity in the alkylation with DCX was the dialkylated product **9**.



9

The first modification increased the DCX to 2 equiv and utilised a 2-propanol/water mix (3:1) at 60 °C to give product **5**/dimer **9** ratio of 70/30. Attempts to reduce the formation of dimer **9** by slow addition of **4** to DCX failed.

A statistical model (using MODDE)[11] was set up to examine the important parameters with the goal of maximizing product/dimer ratio. The model used 19 experiments taking DCX, temperature, excess of sodium hydroxide, water, and 2-propanol as factors. A reasonable fit was initially obtained, but the prediction fit was poor. Subsequent elimination of insignificant factors and factor interactions led to a good fit for predictions. This showed that the favoured conditions were:

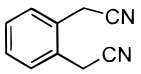
(a) large excess DCX,
(b) minimum NaOH excess,
(c) maximum water content, and
(d) low temperature.

(10) Based on isolated yields.
(11) MODDE is a registered trademark of UMETRI AB, Box 7960, S-907 19 Umeå, Sweden.

Table 2: **Effect of DCX level**

	product assay (% w/w)		
equiv of DCX	product **5**	dimer **9**	yield (%) of **5**
2.5	86	11	81
2.0	85	12	71
1.5	87	10	75
1.05	75.7	19.3	63.6

The model favoured a high water content (detrimental to solubility) and lower temperatures which might cause the DCX to be present as a solid (mp = 55 °C). Further experiments to refine the model produced a product: dimer ratio of 87.5/12.5 using 2.5 equiv of DCX, 1.05 equiv of sodium hydroxide, 10 vol of IPA and 7 vol of water. To minimise raw material, disposal and environmental costs we were keen to recycle the excess DCX but were unable to obtain satisfactory recovery. This approach was abandoned on the grounds of minimising exposure to this material and the intermediate **5**, both being strong irritants. Consequently it was decided to carry out the next step (reaction with cyanide) without isolation of the product and to destroy the excess DCX with cyanide to give α,α′-dicyano xylene **10**.



10

This pathway rendered recycling obsolete and increased the pressure to reduce DCX usage to minimise cost. It was found that limiting the DCX level to 1.5 equiv gave the best compromise (Table 2).

Once the reaction was complete, the crude reaction mixture was reacted with sodium cyanide (2.5 equiv, 3 h at reflux). The reaction was clean and facile. The product was isolated by cooling to ambient temperature and filtration. The crude product which contained the dimer **9** was used without purification in the next step.

Stage 3: Formation of Tetrazole. The tetrazole **1** was originally obtained using ammonium chloride and sodium azide in DMF heating at 130 °C for 5 h, but a copious sublimate of ammonium azide was formed in the condensor. The explosive potential of this material (shock-sensitive)[12] made it prudent to find alternative ways to effect this transformation. In addition, this solvent led to a protracted work-up involving dilution with water and multiple extractions.

The replacement of ammonium chloride by triethylamine hydrochloride reduced the sublimate, and this held true using NMP as solvent. The most successful procedure involved in situ generated triethylammonium acetate (by addition of triethylamine and acetic acid) which gave an equivalent reaction rate in NMP. The reaction could be applied in xylene but the limited solubility of the tetrazole as sodium salt made the work-up more difficult.

(12) The relationship between the kinetic data of the low-temperature thermolysis and the heats of explosion of inorganic azides. Zeman, Svatopluk; Dimun, Milan; Truchlik, Stefan; Kabatova, Viera. *Thermochim. Acta* **1984**, *80 (1)*, 137−41.

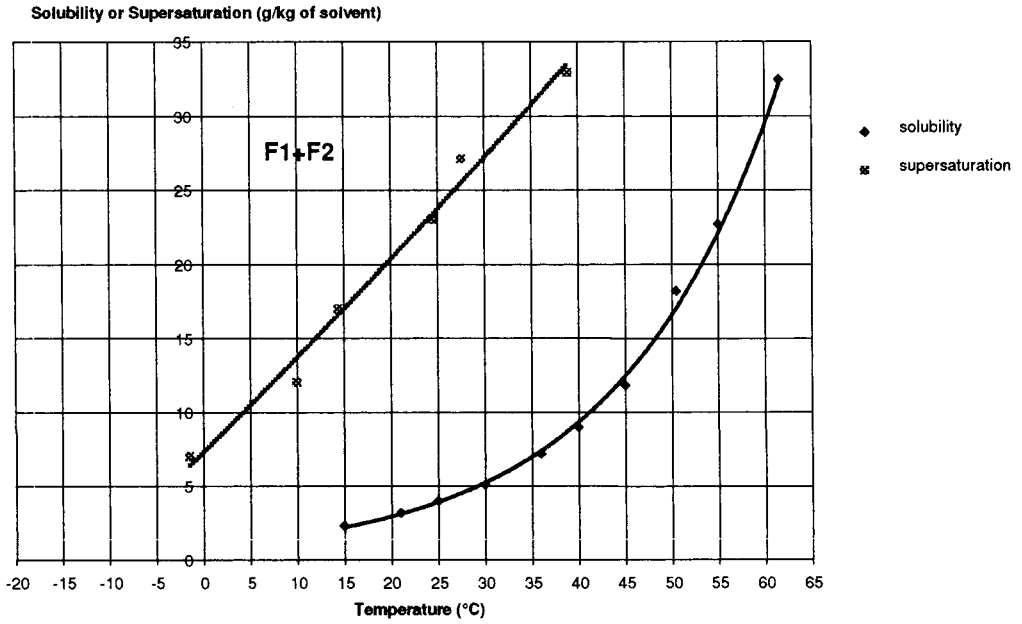


Figure 1. **Solubility and supersaturation vs temperature in methanol.**

Table 3: **Effect of solvent on tetrazole formation**

solvent	yield (%)	assay (% w/w)
DMF	72.5	99.0
NMP	92.4	98.5
xylene	89.0	92.8
cyclohexanone	89.6	88.8
acetophenone	93.2	98.6
anisole	95.4	99.1
hexan-1-ol	89.9	99.0

Cyclohexanone, acetophenone, anisole, and hexan-1-ol were found to facilitate complete reaction and also avoid formation of sublimate (See Table 3).

Anisole was chosen as optimal solvent because it provides a number of advantages over the other alternatives:

(a) a reaction temperature of 130 °C and a 6 h reaction period,

(b) sublimation was avoided,

(c) it is a recoverable solvent,

(d) immisibility with water facilitates removal of inorganics leaving the product in anisole,

(e) the stability of the solvent to base allows the organic solvent to be added directly to hot alkali for extraction of product as the sodium salt into the aqueous layer, leaving the dimer **9** in the anisole layer,

(f) the solvent is unreactive towards azide.

This combination provided the product in the best yield and quality.

Stage 4: Recrystallisation. With the original overall synthetic procedure, which did not involve an extraction into acid of the (chloromethyl)quinoline at stage 1, it was necessary to employ at least two recrystallisations of crude product **1** to achieve the requisite specification both in colour[13] and assay.

The improvements described in this paper gave product that was now of a good colour specification and assay (>99.0% w/w by HPLC) after only a single recrystallisation. However polymorphism was a major issue. It has been shown that RG 12525 exists as two polymorphs.[5] Form I (needles, mp 154 °C) had been selected as the form required for development over Form II (rhombs, mp 157 °C) on the basis of stability.

Recrystallisation from methanol, the original choice, was associated with several drawbacks:

(a) The solubility of RG 12525 in methanol is poor needing 30 volumes of solvent to achieve solution.

(b) Attempts to recover a second crop from methanol were unsuccessful.

LC−MS analysis of the liquors showed a high content of a compound corresponding to the addition of methanol to the product **1**. Efforts to produce this compound by boiling RG 12525 in methanol alone proved fruitless, indicating that the process is probably catalysed by charcoal used in the procedure.

Pilot plant batches achieved recrystallisation returns of only 80% and these contained up to 4% of Form II. Solubility studies in methanol (Figure 1) showed that at low supersaturation (i.e., the region above the supersaturation curve) both Form I (F1) and Form II (F2) are present during primary nucleation (i.e., in the absence of seeding) so that there will be no control of polymorphic form on crystallisation.

Solubility studies identified 10% aqueous acetone (i.e., 1 vol of water/9 vol of acetone) as a better solvent with this combination giving the maximum solubility at 50 °C. Only Form I (F1) is produced during primary nucleation in the region of supersaturation so that control of polymorph is possible by selection of solvent. The return on material was 85% (See Figures 2 and 3). In addition, a much higher throughput could be achieved as only 10 vol of solvent were required leading to adoption as the solvent of choice. A comparison between methanol and acetone/water is shown in the Van't Hoff diagram (Figure 4).

(13) Colour as determined by solution colour; Y6 or higher was acceptable.

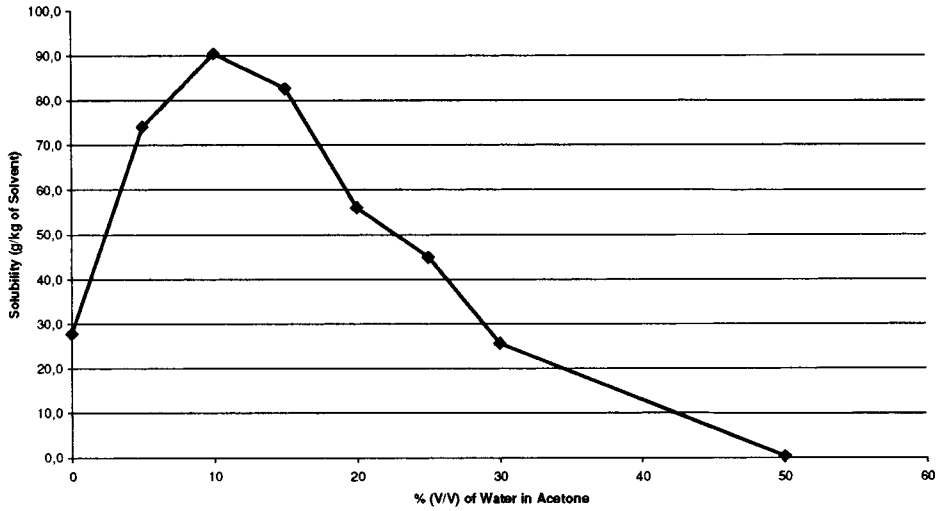


Figure 2. **Solubility vs % of water in acetone at 50 °C.**

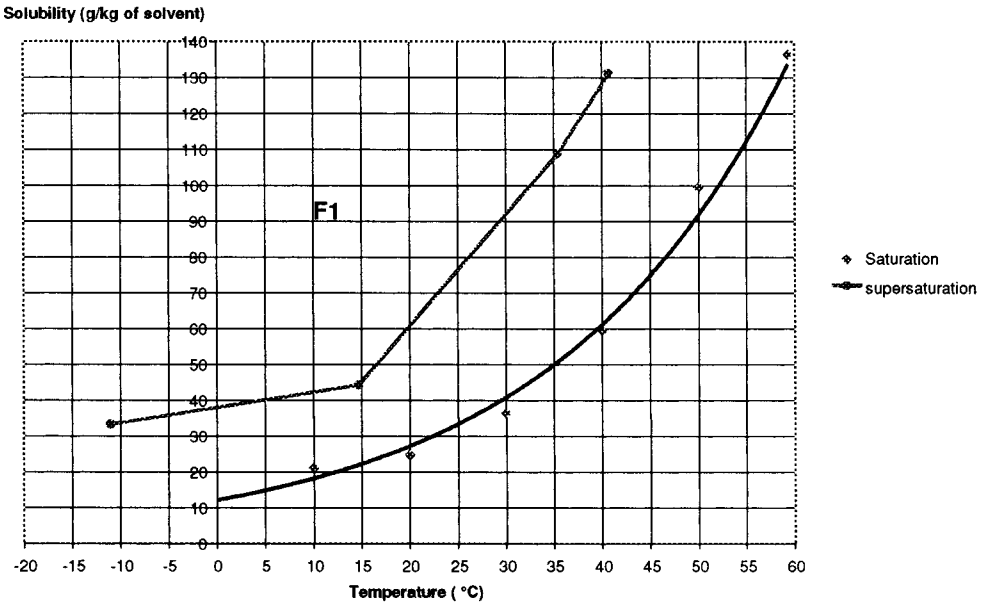


Figure 3. **Solubility vs temperature in acetone−water (90−10 v/v).**

As a final comparison the yields before and after the described process improvements are given in Table 4.

Conclusions

A route suitable for scale-up of RG 12525 has been described with a 3-fold improvement in yield. Benzotrifluoride was demonstrated to be a solvent suitable for chlorination reactions. Extraction of the chlorination product into aqueous acid was found to be the key to downstream improvements in colour and assay. The use of statistical methods and the need to minimise the usage of dichloroxylene gave the optimal conditions for step 2. Anisole in combination with acetic acid/triethylamine/sodium azide was established as the best conditions for tetrazole formation in this system. Finally, a single recrystallisation with 10% aqueous acetone provided a high return and complete control over the polymorphic form.

Experimental Section

General. Reactions were carried out under a nitrogen atmosphere except in the case of the chlorination.

NMR spectra were recorded on a Varian Unity Inova 400 spectrometer in $CDCl_3$ or d_6-DMSO solutions and TMS as internal standard for calibration, mass spectra on a Bruker Daltonics BioApex 30esICR spectrometer, infrared on a Nicolet 20SXB spectrometer, the sample being dispersed in a KBr disk. Elemental analysis were conducted using a Carlo Erba 1108 elemental analyser.

HPLC used a Hewlett Packard HP-1100 using a Hichrom NC100-5C18-2874 column. The mobile phase was acetonitrile/water/phosphoric acid (70/30/0.1) with detection at 230 nm, and flow rate at 1 mL/min.

DSC was run on a Mettler DSC20 in aluminium crucibles with a heating rate of 6 °C min^{-1}.

4-(Quinolin-2-yl)methoxyphenol, 4. Quinaldine (25.0 g, Fluka > 90.0%, 175 mmol), benzotrifluoride (150 mL) and sodium carbonate (10.2 g, 96.3 mmol) and sodium carbonate monohydrate (11.9 g, 96.3 mmol) were charged to a 250 mL round-bottom flask and the mixture stirred (200 rpm)

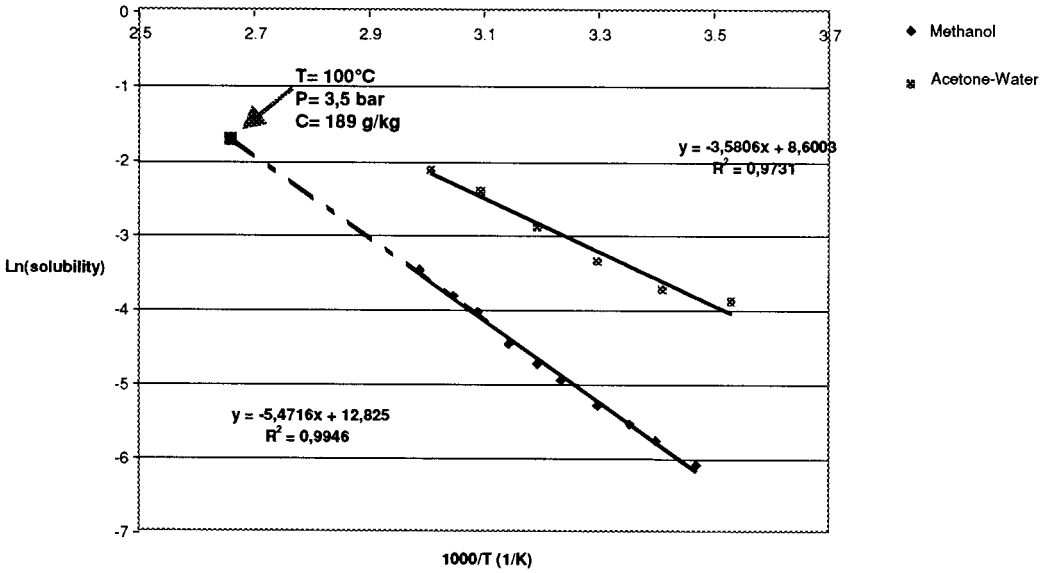


Figure 4. **Vant'Hoff diagram.**

Table 4: **Summary of effect of process changes on yield**

	original conditions	new
stage 1[a]	54.6% (91.0% w/w)	57. 0% (99.0% w/w)
stage 2[b]	45.9% (59.6% w/w)	75.0% (87.0% w/w)
stage 3[c]	68.8% (99.0% w/w)	94.9% (99.5% w/w)
stage 4[d]	75.5% (99.5%)	85.0% (99.9% w/w)
total	9.7%	34.9%

[a] Summary of new conditions. Stage 1: (a) Benzotrifluoride, **2**, sodium carbonate monohydrate (1.1 equiv) and chlorine (1.4 equiv), 35 °C− 40 °C. (b)1 M HCl (1.4 equiv). (c) Hydroquinone (3 equiv), methanol, water, aq sodium hydroxide (4.4 equiv), **3**. [b] Stage 2: (a) α,α′-Dichloro-*o*-xylene (1.5 equiv), **4,** sodium hydroxide, water, 60 °C. (b) Sodium cyanide (2.5 equiv), 2-propanol, reflux. [c] Stage 3: Anisole, **6**, triethylamine (2.2 equiv), acetic acid (2.2 equiv), sodium azide (1.6 equiv), 130 °C, 7 h. [d] Stage 4: **1**, Acetone:water (9:1), acticarbone 3SA.

and heated to 35 °C. Chlorine (20.3 g, 286 mmol)[14] was bubbled into the reaction mixture via a subsurface dip-tube over a period of 180 min, ensuring that the temperature remained between 35− 40 °C. After the reaction was complete (by HPLC quinaldine < 2.0%), nitrogen was bubbled through the mixture for 1 h. To the reaction mixture was added water (130 mL) followed by charcoal (acticarbone ENO, 1.54 g), and the mixture stirred for 15 min. The mixture was filtered through a pad of Hyflo (12.0 g) and washed with benzotrifluoride (2 × 25 mL). The organic layer was separated and extracted with 1 M hydrochloric acid (175 mL then 75 mL), and the combined aqueous layer was washed with TBME (15 mL) to give a solution of 2-(chloromethyl)quinoline hydrochloride (267.8 g).

Hydroquinone (57.7 g, 524 mmol) was charged to a 1 L reaction flask containing methanol (174 mL) and water (125 mL) under nitrogen atmosphere and the resulting solution cooled to 10 °C. To the reaction mixture was added a solution of sodium hydroxide (30.9 g, 773 mmol) in water (31 mL) over 10 min, followed by the solution of the 2-(chloromethyl)quinoline hydrochloride salt (267.8 g) over 5 min. The reaction mixture was heated to 50 °C for 3 h (HPLC shows <1% of 2-(chloromethyl)quinoline) and then allowed to cool to room temperature. The reaction mixture was filtered and washed with water (2 × 150 mL). The damp solid (24.7 g) was returned to a 250 mL flask containing sodium hydroxide (5.2 g) in water (158 mL) and heated to 70 °C for 15 min. The suspension was then filtered (yield of dimer (**7**) = 2.2 g, 6.3%) and washed with water (30 mL). The combined aqueous filtrate was returned to the reaction vessel and cooled to <30 °C. Concentrated hydrochloric acid (20.2 g, 37%, 205 mmol) was added over 1 h, keeping the temperature <30 °C (pH = 5). The product was filtered, washed with water (40 mL), and dried in an oven at 55 °C.

Yield = 26.0 g (59.2%).

^{1}H NMR ($CDCl_3$) 5.3 (2 H, s), 6.7−6.9 (4 H, AB quartet), 7.6 (1 H, t), 7.7−7.8 (2 H, 2t), 7.85 (1 H, dd), 8.05 (1 H, d), 8.2 (1 H, d), 8.25 (1 H, s, OH).

^{13}C NMR ($CDCl_3$) 71.5, 115.9, 116.0, 119.5, 126.5, 127.3, 128.6, 129.8, 136.9, 147.1, 151.1, 151.8, 158.2; IR (cm^{-1}) 3600−2500, 1515, 1460, 1231, 1200, 1064; MS 252 (M + H, 100%).

$C_{16}H_{13}NO_2$ requires C 76.48, H 5.21, N 5.57. Found C 76.08, H 5.12, N 5.69%.

Dimer 7: ^{1}H NMR (DMSO) 5.30 (4 H, s), 7.01 (4 H, s), 7.62 (2 H, m), 7.66 (2 H, d), 7.78 (2 H, m), 7.99 (2 H, d), 8.01(2 H, d), 8.41 (2 H, d); IR (cm^{-1}) 3100−2900 (C−H), 1505 (C═C), 1429, 1241(C−O), 1225 (C−O); MS (ES^+) 393 (M + H, 55%), 250 (100%), 143 (25%).

2-[4-(Quinolin-2-yl-methoxy)phenoxy]methylphenyl Acetonitrile, 6. A 2 L flask was charged with α,α′-dichloro-*o*-xylene (78.4 g, 448 mmol) and 2-propanol (225 mL) and the mixture heated to 50 °C to give a solution. 4-(Quinolin-2-yl)methoxyphenol **4** (75.0 g, 299 mmol) was charged followed by a solution of sodium hydroxide (13.8 g, 345 mmol) in water (510 mL) and the mixture heated to 60 °C for 2.5 h. (HPLC analysis shows 4-(quinolin-2-yl)methoxyphenol **4** < 1.0%). Sodium cyanide (36.6 g, 746 mmol) was added to the reaction mixture followed by 2-propanol (450 mL) and the mixture heated to reflux (84 °C) for 4 h.

(14) Of this quantity 3.03 g was collected in a sodium hypochlorite trap so that only 17.27 g of chlorine (243 mmol, 1.39 equiv) is required for reaction.

(HPLC shows stage 2A < 1.0%). The batch was cooled to 70 °C and seeded with 2-[4-(quinolin-2-yl-methoxy)phenoxy]-methylphenyl acetonitrile **6** (0.56 g). Then it was cooled to 25 °C over 5 h and stirred at this temperature for 16 h. The material was filtered and washed with 2-propanol (450 mL) and hot water (70 °C, 750 mL) and then dried in an oven at 60 °C to constant weight.

Yield = 98.2 g, 75.3% corrected yield.[15]

^{1}H NMR (DMSO) 4.09 (2 H, s), 5.09 (2 H, s), 5.32 (2 H, s), 6.97−7.05 (4 H, m), 7.36−7.41 (2 H, m), 7.46−7.50 (2 H, m), 7.62 (1 H, t), 7.67 (1 H, d), 7.79 (1 H, t), 8.00 (2 H, t), 8.41 (1 H, d); IR (cm^{-1}) 3100−2900 (CH), 2220 (CN), 1507 (C═C), 1217 (C−O), 1070 (C−O), MS: 381 (M^+ + H, 100%), 272 (15%).

Dimer 9: ^{1}H NMR (DMSO) 5.14 (4 H, s), 5.30 (4 H, s), 6.95−7.00 (8 H, m), 7.34 (2 H, m), 7.49 (2 H, m), 7.61 (2 H, dt), 7.66 (2 H, d), 7.78 (2 H, m), 7.99 (2 H, d), 8.02 (2 H, d), 8.40 (2 H, d); IR (cm^{-1}) 3100−2900 (CH), 1510 (C═C), 1250 (C−O), 1075 (C−O), MS 627 (M + Na^+, 100%), 605 (M + H, 58%).

2-[4-(2-chloromethylphenylmethoxy)phenoxymethyl]-quinoline, 5: ^{1}H NMR (DMSO) 4.88 (2 H, s), 5.18 (2 H, s), 5.32 (2 H, s), 6.99−7.05 (4 H, m), 7.35−7.40 (2 H, m), 7.49 (2 H, m), 7.62 (1 H, m), 7.67 (1 H, d), 7.79 (1 H, dt), 8.00 (2 H, t), 8.41 (1 H, d); IR (cm^{-1}) 3100−2900 (C−H), 1500 (C═C), 1250 (C−O); MS 392(M + H, 55%), 390 (M + H, 100%).

2-{[4-(Tetrazol-5-ylmethylphenyl)-methoxy]phenoxy-methyl}quinoline (RG 12525) 1. Anisole (85 mL) and 2-[4-(quinolin-2-yl-methoxy)phenol]methylphenyl acetonitrile **6** (30.0 g) (assay = 87% w/w) were charged to a 500 mL flask and heated to 60 °C under nitrogen. Triethylamine (16.1 g, 160 mmol) was added, followed by acetic acid (9.6 g, 160 mmol), then sodium azide (7.62 g, 116 mmol) and the mixture heated to 130 °C for 7 h. (HPLC analysis indicates (6) < 4.0%). The reaction mixture was cooled to 90 °C, and then water (100 mL) was added, stirring for 5 min at 60−70 °C. An additional charge of anisole (25 mL) was added and the aqueous phase separated. The organic phase was washed with water (100 mL) and separated. The organic phase was added to a hot (80 °C) solution of sodium hydroxide (6.45 g, 157 mmol) in water (360 mL) and stirred for 15 min. The aqueous phase was separated, keeping the temperature at 60−65 °C. The solution was washed with anisole (3 × 100 mL). The aqueous solution was cooled to 52 °C and then acidified to pH 5 by the addition of water/hydrochloric acid (3:1, 60 mL) over 40 min. The product was filtered, washed with water (2 × 100 mL), and dried to constant weight at 55 °C.

Yield = 26.2 g (90.2%, corrected for assay). Assay = 99.5% w/w.

Recrystallisation. Crude RG 12525 **1** (10.0 g), acetone (90 mL), and water (10 mL) were heated to 58 °C to ensure complete dissolution. Then charcoal (acticarbone 3SA, 0.5 g) was added and the mixture heated to reflux for 20 min. The mixture was cooled to 58 °C and then filtered, rinsing with 10% acetone/water (5 mL), and the filtrate was heated to 55 °C. RG12525 Form 1 (0.1 g) was added as seeds and the mixture cooled to 20 °C over 1 h. The product was isolated on a filter, washed with 10% acetone/water (2 × 10 mL), and dried to constant weight in an oven at 55 °C.

Yield = 8.4 g (84.3%). Assay = 99.9%. Mp = 153.5 °C (Form 1).

^{1}H NMR (DMSO) 4.40 (2 H, s), 5.05 (2 H, s), 5.30 (2 H, s), 6.9−7.0 (4 H, AB quartet, ArH), 7.22 (1 H, q), 7.30 (2 H, m), 7.5 (1 H, d), 7.63 (1 H, t), 7.70 (1 H, d), 7.77 (1 H, t), 8.0 (2 H, dd), 8.4 (1 H, d).

^{13}C NMR 26.0, 67.9, 71.2, 115.6 (x2), 119.5, 126.5, 127.1, 127.3, 127.9, 128.4, 128.5, 129.8 (×2), 134.5, 135.3, 136.9, 146.9, 152.4, 155.0, 157.8; IR (cm^{-1}) 3140 (NH), 3060 (CH), 2900 (CH), 1507 (C═C), 1217 (C−O), 1070 (C−O); MS (ES) 424 (M + H, 100%); $C_{25}H_{21}N_5O_2$ requires C 70.91, H 5.00, N 16.54. Found C 70.83, H 4.78, N 16.60%.

(15) The isolated yield represents 86.5%; the assay of the material is 87.6%; hence, corrected yield = 86.5 × 0.876 = 75.7%

Acknowledgment

We thank Ron Cook, Kiran Virji, Peter Shade, Dave Thomas, and Mike Podmore for analytical support and Drs. Michel Mulhauser and Jean-Réne Authelin for stimulating discussions.

Received for review June 15, 2000.

OP0000677