# The Process Development of a Novel Aldose Reductase Inhibitor, FK366. Part 1. Improvement of Discovery Process and New Syntheses of 1-Substituted Quinazolinediones

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### Abstract:

This contribution describes part 1 of process development of a novel aldose reductase inhibitor FK366 (1). The original process applied on a laboratory scale was improved from the safety viewpoint to manufacture materials on 500-L scale suitable for toxicological and pharmacological evaluations. A new process, including regioselective alkylation of silylated quinazolinedione, provided a practical and cost-effective synthesis of FK366 in a dramatically increased yield.

## Introduction

Diabetic complications represented by neuropathy, cataract, and retinopathy are brought about by the overaccumulation of sorbitol in tissues. Aldose reductase inhibitors (ARIs) which inhibit an enzyme of the polyol pathway were explored for the remedy of diabetic complications (Figure 1).<sup>1</sup> 3-(4-Bromo-2-fluorobenzyl)-7-chloro-3,4-dihydro-2,4dioxo-1(2H)-quinazolineacetic acid (FK366, 1),<sup>2</sup> a potent ARI, was invented at Fujisawa laboratories.

The original process using an isatoic anhydride involved several problems in scale-up, and we improved it to the procedure applicable to pilot manufacturing of several 10 kilograms of drug substance. Whilst the improved eight-step synthesis was efficient enough to give a material suitable for toxicological studies on early stages, a more cost-effective process was required. During further studies we discovered that bis-silylated-2,4-quinazolinedione reacts with alkyl halides to give 1-substituted quinazolinediones exclusively.<sup>3</sup> We applied this reaction to the manufacture of FK366 and developed a straightforward five-step synthesis suitable for the production of FK366 on a commercial scale.

## **Results and Discussion**

**Original Process for FK366.** As for the introduction of carboxymethyl side chain to the quinazolinedione nucleus of FK366, the original route (Scheme 1) exploited an isatoic anhydride (4) derived from *N*-Cbz-anthranilic acid (3a). 4 was a useful intermediate not only for selective N-alkylation



Fidarestat

.CO2H

Figure 1. Aldose reductase inhibitors.

CH2CO2H

but also for protection (during N-alkylation) and activation (for amide formation) of carboxylic acid. However, the transformation of 3a to 4 afforded harmful benzylbromide as a byproduct.

The N-alkylation of **4** employed sodium hydride in dimethylformamide (DMF) system, which had a potential hazard for a large-scale synthesis.<sup>4</sup> The cyclization of anthranilamide (**5**) to quinazolinedione (**6**) with carbonyl-diimidazole (CDI) included another problem. A mixture of **5** and CDI in dioxane was heated, followed by distillation of dioxane under atmospheric pressure. A cyclization reaction suddenly occurred at the end of this procedure, and the reaction mixture solidified, accompanying severe exotherm. In the case where the reaction was conducted in the presence of solvent, the cyclization reaction proceeded sluggishly. The N3 benzylation of quinazolinedione nucleus also utilized sodium hydride in DMF.

**Process Improvements of Original Process.** Considering the mechanism of isatoic anhydride ring closure, the Cbz group of **3a** was substituted to ethoxycarbonyl group of **3b**, and the byproduct involved was the less harmful ethyl bromide (Scheme 2).

The investigations in the cyclization reaction indicated that the reaction was self-accelerated by imidazole liberated from CDI during the reaction. The reaction carried out in dioxane as a solvent in the presence of a catalytic amount of imidazole was easier to control.

For a large-scale synthesis, powdered potassium carbonate<sup>5</sup> in DMF was found to be a suitable alternative to the

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<sup>(5)</sup> Commercially available from Nippon Soda Co., Ltd.



#### Scheme 2. Ring closure to isatoic anhydride (4)



## Scheme 3. Retrosynthesis of FK366 (1)



potentially hazardous system of sodium hydride in DMF for the introduction of side chains.

Together with these major process improvements, each step was reexamined from the viewpoints of safety, yield, and operability. The improved process was successfully scaled up to 500 L, manufacturing 24 kg of drug substance suitable for toxicological studies. Overall yield from 2-amino-4-chlorobenzoic acid (2) to 1 was improved from 27% to 65%.

**Development of Silylquinazoline Method.** Although the improved original route was efficient enough to manufacture several tens of kilograms of drug substance, it consisted of eight manufacturing steps including purification of intermediates and final product. A more efficient and inexpensive process was still required for further stages.

As depicted in the retrosynthetic analysis, we envisaged a new method for selective introduction of alkyl chains to quinazolinedione (9), which was easily obtained from 2. The conceptually simple way to FK366 was selective introduction of a carboxymethyl group to N1 position followed by a halobenzyl group to N3 position (Scheme 3).

The reaction of 9 and ethyl bromoacetate with potassium carbonate as a base in DMF afforded a mixture of 9, mono-(6 and 10) and dialkylated products (11). The efforts to

Scheme 4. Direct alkylation of quinazolinedione (9)



**Table 1.** Alkylation of 9 with ethylbromoacetate in the presence of K<sub>2</sub>CO<sub>3</sub> in DMF

compound	9	6	10	11
peak area (%)	37.1	18.7	3.8	38.7

improve selectivity with the combinations of different bases, solvents, and temperature were in vain (Scheme 4, Table 1).

N1-selective alkylation of pyrimidinedione<sup>6</sup> is achieved via bis(trimethylsilyloxy)-pyrimidine intermediate which is commonly exploited for the synthesis of pyrimidine nucle-

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otides.<sup>7</sup> This procedure is also applied to the preparation of quinazoline nucleosides.<sup>8</sup> Thus, we applied these methodologies for the regioselective alkylation of quinazolinediones. We found that if bis(trimethylsilyloxy)quinazoline (**12**) derived from **9** was heated in ethyl bromoacetate, the desired 1-ethoxycarbonylmethyl derivative **6** was selectively obtained without involving other byproducts. The following introduction of 2-fluoro-4-bromobenzyl moiety at the N3 position using the corresponding benzylbromide and K<sub>2</sub>CO<sub>3</sub> as a base afforded the penultimate ethyl ester (**8**) in good yield (Scheme 5).

Thus, we developed a new silylquinazoline process for FK366 (Scheme 6).

Scale-Up Study of Silylquinazoline Process: Synthesis of 7-Chloroquinazoline-2,4-dione (9). The well-known procedure to manufacture quinazolinedione from anthranilic acid described in "Organic Synthesis"9 could not be directly applied for the synthesis of 4-chloroanthranilic acid since the initial urea formation reaction did not proceed due to the exceptionally low solubility in the reaction medium. After dissolving 4-chloroanthranilic acid as a sodium salt in water, potassium cyanate was added, and then diluted HCl was added in two portions to promote the ureide-forming reaction. To the obtained solution of 2-ureide benzoic acid was added sodium hydroxide for the cyclization to afford 7-chloroquinazolinedione sodium salt in good yield. We found that the ureide formation was highly dependent on the pH of the reaction mixture. Whilst the reaction proceeded sluggishly at the pH of >7, the decomposition of cyanate was predominant at the pH of <5. As a result, the reaction was susceptible to the mixing conditions and was not reproducible in the yield. Thus, the best result of the reaction in the yield and reproducibility was realized by continuously adjusting pH to 6-7 with HCl. As a result of this pH-controlling procedure, the amount of potassium cyanate was reduced



*Figure 2.* Ureide formation and pH in the reaction mixture (HCl added in two portions).

from 3 to 1.5 equiv, and the yield was improved from 85 to 94% on 500-L scale (Scheme 7, Figure 2, Figure 3).<sup>10</sup>

Silylation of Quinazolinedione (9). The silylating agent was selected from the viewpoints of convenience and economy. Silvlation with trimethylchlorosilane and triethylamine in dichloromethane proceeded well, but the troublesome filtration of triethylamine hydrochloride was necessary. We used hexamethyldisilazane (HMDS) as a clean silylating agent and ammonium sulfate as a silylation catalyst. In early studies, the reaction speed was not consistent. For example, several hours were needed until the reaction was completed on a large scale, whilst an hour was needed on a small scale. We speculated that the removal of ammonia from the reaction mixture might be crucial for the silvlation with HMDS, and thus the agitation and reflux speed might be influential to the silvlation period. Figures 4 and 5 show the correlation between silvlation time and agitation speed or bath temperature at scale-down experiments on 500-mL scale using geometrically similar equipment. With stronger agitation and higher bath temperature, the silvlation smoothly proceeds to give a clear solution.

Next, we investigated more effective catalysts for the silylation. Pulverized ammonium sulfate ( $22 \mu m$ ) was a better catalyst than a regular granule ( $350 \mu m$ ), and to our surprise, sulfuric acid and methanesulfonic acid were highly efficient catalysts (Table 2).

#### Scheme 6. Silylquinazoline process for FK366 (1)





*Figure 3.* Ureide formation and pH in the reaction mixture (pH controlled to 6-7).



*Figure 4.* Effect of agitation speed on silvlation time. A mixture of 9 (20 g), HMDS (2 mol equiv) and  $(NH_4)_2SO_4$  (350  $\mu$ m, 0.15 mol equiv) were refluxed in toluene (60 mL). Bath temperature = 135 °C. The period to obtain a clear solution was regarded as a silvlation time.

#### Scheme 7. pH dependence of ureide formation



Whilst the granular ammonium sulfate tended to block up a bottom discharge valve of the reactor and to be contaminated in the product, the catalyst prepared in situ from sulfuric acid and HMDS did not involve such problems.

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**Figure 5.** Effect of bath temperature on silvlation time. A mixture of 9 (20 g), HMDS (2 mol equiv) and  $(NH_4)_2SO_4$  (350  $\mu$ m, 0.15 mol equiv) were refluxed in toluene (60 mL). Agitation speed = 400 rpm. The period to obtain a clear solution was regarded as a silvlation time.

Table 2	2.	Effects	of	catalysts	for	silylationa
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catalyst	amount of catalyst (equiv)	silylation time (min)
$(NH_4)_2 SO_4 (350 \mu m)$	0.15	90
$(NH_4)_2SO_4 (22 \ \mu m)$	0.15	70
p-TsONH <sub>4</sub>	0.15	90
$H_2SO_4$	0.15	50
$H_2SO_4$	0.08	50
MsOH	0.08	45

 $^a$  A mixture of 9 (20 g), HMDS (2 mol equiv), and catalyst were refluxed in toluene (60 mL) at bath temperature 135 °C.

*Caution!* As concentrated sulfuric acid and HMDS react violently, it must be added with greatest care on a large scale.

Alkylation of Bis-trimethysilyloxyquinazoline. Regioselective introduction of ethoxycarbonylmethyl group at the N1 position of the quinazolinedione nucleus was achieved using ethyl bromoacetate as a reagent/solvent. After the silylation with HMDS in toluene, the reaction mixture was concentrated under reduced pressure to give bis-trimethysilyl compound as a ceraceous solid, which was heated in the presence of 2 volumes of ethyl bromoacetate above 120 °C for several hours. To the reaction mixture was added dioxane to improve the agitation, and then methanol was added dropwise to quench the monosilylated intermediate, giving a slurry of the desired product **6**. Methanol also played a role of decomposing trimethylsilyl bromide, a byproduct of alkylation.

The reaction in the presence of other solvents such as toluene, DMF, or diglyme with ethyl bromoacetate to reduce the amount of this harmful reagent did not give the product in the acceptable yield since the reaction was retarded. The substitution of expensive and highly lachrymatory ethyl bromoacetate for ethyl chloroacetate was in vain since over 100 hours were required before the reaction led to completion at the same temperature.

**Benzylation at the N3 Position.** In the early process, N-benzylation was conducted using the NaH/DMF system. To avoid this potentially hazardous system, we explored other



Figure 6. XRPD pattern of FK366: Form A (left), Form B (right).

reaction conditions. Further investigations indicated that powdered potassium carbonate in acetone was an excellent alternative for this reaction. **6** in acetone was then refluxed with 4-bromo-2-fluorobenzylbromide (**7**) in the presence of powdered  $K_2CO_3$  as a base<sup>5</sup> for several hours to give **8** in high yield. After the completion of the reaction, acetic acid was added to decompose excess potassium carbonate, and then the mixture was refluxed again to decompose excess benzylbromide by the reaction with potassium acetate to avoid hazardous exposure to personnel during workup and filtration. To the reaction mixture was added methanol<sup>11</sup> to improve stirrability, and crystals were collected, followed by drying under reduced pressure to give **8**.

**Hydrolysis and Purification.** Hydrolysis of ethyl ester was conducted with sodium hydroxide in aqueous methanol. After the completion of the reaction, the reaction mixture was acidified with concentrated hydrochloric acid (HCl) to precipitate crude FK366. Purified FK366 was obtained by recrystallization of crude material in aqueous 2-propanol. After dissolution in hot aqueous 2-propanol, the product was treated by charcoal and then filtered. To the filtrate was added purified water, and then the solution was cooled to give purified FK366 as white crystals.

The corresponding methyl and isopropyl esters were major impurities in FK366 drug substance involved in these steps. The amount of HCl, the water—solvent ratio, and crystallization temperature were studied to reduce these byproducts.

**Emergence of a New Polymorph.** In early studies, only one crystal form (**A**) was identified for FK366. However a new crystal form (**B**) was obtained in the course of further development of new silylquinazoline process (Figure 6), and precipitation of the B-form crystal was problematic on a large-scale synthesis due to highly thick slurry and poor filterability.

The crystal form was difficult to control in early studies since the form varied from lot to lot and seemed independent from the quality of the product. However, detailed investigations into impurities included in FK366 revealed that N,N'-di-benzyl compound (13), which had originated from the bisbenzylation of incorporated intermediate 9 in 6, played an important role for the crystallization of the polymorph (Scheme 8).

Recrystallization of FK366 with a spiked amount of 0.5– 1% of **13** led to consistent precipitation of the B-form crystal even though original FK366 never arose as B-form to any





*Table 3.* Effect of spiked amount of 13 and seed crystal toward crystal form of FK366

seed crystal	spiked amount (wt %)	crystal form obtained
none	0.1	А
	0.5	А
	1.0	В
А	0	А
В	0	А
А	0.5	А
В	0.5	В
А	2.0	В
В	2.0	В

degree. Table 3 shows the correlation of crystal form with the spiked amount of **13**. Addition of 1% of **13** resulted in precipitation of the B-form crystal in the absence of seed crystal. On the other hand, A-form material was always obtained independently from the seed crystal without **13**. With 0.5% of **13**, the crystal form depended on the seed crystal form, and with 2% of **13**, the B-form was always obtained independently from the seed form.<sup>12</sup>

There is a high possibility that this impurity was involved in the new process, and thus we endeavored to control the amount of dibenzyl compound. To control the contamination of this impurity below 1%, the alkylation reaction was monitored by HPLC, confirming the residual amount of unreacted **9** was below 1% as well.

**Selective Monoalkylation of Quinazolinediones.** We examined the synthetic applicability of selective N1 alkylation of quinazolinedione via bis-trimethylsilylated intermediates. As shown in Table 4, several 1-substituted quinazolinediones were obtained in high yields. We believe the reaction is a convenient general method to manufacture N1 substituted quinazolinediones.<sup>3</sup>

<sup>(11)</sup> If the methanol was added without decomposing excess potassium carbonate, a considerable amount of methylester was contaminated.

<sup>(12)</sup> Influences of impurities or additives to the plymorph control were reported in the following literature: (a) Ebian, A. R.; Moustafa, M. A.; Khalil, S. A.; Motawi, M. M. J. Pharm. Pharmacol. 1973, 25, 13–20. (b) Hasegawa, M.; Fukuda, N.; Higuchi, H.; Noguchi, S.; Matsubara, I. Agric. Biol. Chem. 1977, 41, 49. (c) Kitamura, M.; Funahara, H. J. Chem. Eng. Jpn. 1994, 27, 124–126. (d) Davey, R. J.; Blagden, N.; Potts, G. D.; Docherty, R. J. Am. Chem. Soc. 1997, 119, 1767–1772.

Table 4. Selective N1 alkylation of quinazolinediones



## Conclusions

A concise five-step sequence has been developed and demonstrated for the preparation of FK366 on 20–30 kg scale in 80% overall yield. This new process is characterized by the selective monoalkylation of the quinazolinedione nucleus and has led to dramatic improvement in overall yield in comparison to that of the original method (27%). The reported methods are practical, inexpensive, and suitable for a large-scale synthesis.

## **Experimental Section**

Solvents and reagents were obtained from commercial sources and were used without any purification. The melting points were uncorrected. IR spectra were recorded on a SensIR Technologies Travel*IR* spectrometer. <sup>1</sup>H NMR spectra were obtained on a Brucker DPX200 using tetramethylsilane as internal standard. Mass spectra were recorded on a Hewlett-Packard 1100LC/MSD mass spectrometer using EI for ionization. Elemental analyses were carried out on a Perkin-Elmer CHN elemental analyzer. HPLC analyses were performed using a YMC gel ODS 120 Å S-7 column and a CH<sub>3</sub>CN- or CH<sub>3</sub>OH-buffer phase. Reactions were carried out in 200–1000-L glass-lined carbon steel reactors. The intermediates and the drug substance were isolated in a stainless steel centrifuge (30-in. i.d.) using a polypropylene filter bag and dried in a vacuum tray dryer.

7-Chloro-3,4-dihydro-2,4-dioxo-1(2H)-quinazoline (9). To a suspension of 2-amino-4-chlorobenzoic acid 2 (18.0 kg) in water (100 L) was added aqueous sodium hydroxide solution (4.6 kg in 20 L) to give a clear solution. To the reaction mixture was added aqueous sodium cyanate solution (11.8 kg in 240 L). A process pH electrode was immersed into the vessel, and the pH value of the solution was adjusted to 6.5 with 35% HCl at room temperature to give a porridgy suspension. The pH of the reaction mixture was maintained at 6.5  $\pm$  0.2 with 35% HCl for 5 h with stirring at 30  $\pm$  2 °C. After the completion of the ureide formation, to the reaction mixture was added sodium hydroxide (16.8 kg). The reaction mixture was heated to 60-65 °C and stirred for 2 h at this temperature (sodium salt of quinazoline dione precipitates). After cooling below 5 °C, the precipitates were collected by a centrifuge to give sodium salt as a white mass.

Sodium salt thus obtained was returned to the vessel and was suspended in acetone (180 L) and water (180 L). The

pH of the suspension was adjusted to 1.0-1.5 with 35% HCl at  $30 \pm 2$  °C, and stirring was continued 2 h. After cooling below 5 °C, the precipitates were collected by a centrifuge, washed with water (40 L), and dried in a vacuum tray dryer to give **9** (19.4 kg, 94.0% yield) as a white powder: mp 231–233 °C.

<sup>1</sup>H NMR (200 MHz, DMSO- $d_6$ ,  $\delta$ ) 7.17 (1H, d, J = 1.8 Hz), 7.22 (1H, dd, J = 8.3, 1.8 Hz), 7.88 (1H, d, J = 8.3 Hz), 11.26 (1H, brs), 11.42 (1H, brs); IR (ATR) 3042, 2841, 1679, 1617, 1428, 1285, 1081 cm<sup>-1</sup>; MS (EI) m/z 196 (M+).

Anal. Calcd for  $C_8H_5N_2O_2Cl$ : C, 48.88; H, 2.56; N, 14.25. Found: C, 48.89; H, 2.59; N, 14.14.

# Ethyl 7-Chloro-3,4-dihydro-2,4-dioxo-1(2H)-quinazolineacetate (6)

To a suspension of **9** (18.25kg) in toluene (54.8L) and hexamethyldisilazane (HMDS; 36.0kg) was added sulfuric acid (0.73kg) with greatest cautions. The mixture was heated to reflux and stirred under heavy refluxing for 8 h till clear solution was obtained. After the removal of toluene and excess HMDS with vacuum distillation, ethyl bromoacetate (36.5L) was added to the residue. The reaction mixture was heated to 115–130 °C and was stirred at this temperature for 3 h. After checking the completion of the reaction with HPLC, the reaction mixture was diluted with 1,4-dioxane (36.5 L) at 100 °C, and then methanol (54.8 L) was added at 70 °C for 30 min.

The suspension was cooled below 5 °C and precipitates were collected by a centrifuge. After washing with methanol (20 L) and water (90 L), the wet crystals were dried in a vacuum tray dryer to afford **6** (25.4kg, 96.8%) as a white powder: mp 253-255 °C.

<sup>1</sup>H NMR (200 MHz, DMSO- $d_6$ ,  $\delta$ ) 1.22 (3H, t, J = 7.2 Hz), 4.17 (2H, q, J = 7.2 Hz), 4.91 (2H, s), 7.35 (1H, dd, J = 8.5, 1.6 Hz), 7.61 (1H, d, J = 1.6 Hz), 8.01 (1H, d, J = 8.5 Hz), 11.89 (1H, br s); IR (ATR) 3042, 1737, 1679, 1366, 1081, 842 cm<sup>-1</sup>; MS (EI) m/z 282 (M<sup>+</sup>). Anal. Calcd for C<sub>12</sub>H<sub>11</sub>N<sub>2</sub>O<sub>4</sub>Cl: C,50.99; H, 3.92; N, 9.91. Found: C, 50.94; H, 3.86; N, 9.83.

**Ethyl 3-(4-Bromo-2-fluorobenzyl)-7-chloro-3,4-dihydro-2,4-dioxo-1(2H)-quinazoline Acetate (8).** To a suspension of **6** (25.0 kg) in acetone (125 L) were added pulverized potassium carbonate (14.7 kg) and 4-bromo-2-fluorobenzylbromide (30.8 kg) at ambient temperature. The reaction mixture was heated to reflux and stirred for 5 h.

After checking the end of the alkylation, acetic acid (12.5 kg) was added at 40–45 °C, and stirring was continued for 2 h under reflux to decompose excess benzylbromide. To the reaction mixture was added methanol (200 L) at 55–60 °C for 30 min, and then it was cooled below 5 °C. Precipitates were collected by centrifuge and washed with methanol (50 L) and water (250 L). The wet crystals were dried in a vacuum tray drier to afford **8** (39.5kg, 95.1%) as white crystals: mp 160–161 °C.

<sup>1</sup>H NMR (200 MHz, DMSO- $d_6$ ,  $\delta$ ) 1.20 (3H, t, J = 7.1 Hz), 4.17 (2H, q, J = 7.1 Hz), 4.99 (2H, s), 5.13 (2H, s), 7.15 (1H, t, J = 8.3 Hz), 7.32–7.42 (2H, m), 7.55 (1H, dd, J = 8.5, 1.6 Hz), 7.71 (1H, d, J = 1.6 Hz), 8.08 (1H, d, J = 8.5 Hz); IR (ATR) 3042, 2841, 1737, 1679, 1617, 1366, 1227

cm<sup>-1</sup>; MS (EI) m/z 492 (M + 23). Anal. Calcd for C<sub>19</sub>H<sub>15</sub>N<sub>2</sub>O<sub>4</sub>BrClF: C, 48.59; H, 3.22; N, 5.96. Found: C, 48.70; H, 3.16; N, 5.88.

3-(4-Bromo-2-fluorobenzyl)-7-chloro-3, 4-dihydro-2, 4-dioxo-1(2H)-quinazolineacetic Acid (1). To the suspension of 8 (39.0kg) in methanol (546 L) was added aqueous sodium hydroxide solution (4.98 kg in 156 L) at 30-40 °C. The reaction mixture was heated to reflux and stirred for 45 min until the completion of the reaction. The hot solution was filtered to remove insoluble particulate, and the vessel, the filter, and the connecting piping were rinsed with aqueous methanol (methanol 78 L + water 78 L). The filtrate and the rinse solution were combined and diluted with water (78 L). The solution was cooled to 30 °C, and 35% HCl (19.5L) was added for the crystallization at 30-35 °C. After stirring for 30 min at this temperature, the suspension was cooled below 5 °C. The precipitates were collected by centrifuge and washed with aqueous methanol (methanol 117 L + water 117 L). The wet crystals were dried in a vacuum tray dryer to afford crude 1 (36.15kg, 98.6%) as a white powder.

The crude crystals of FK366 (1) thus obtained (36.0 kg) were suspended in aqueous 2-propanol (2-propanol 360 L + purified water 72 L). The suspension was heated to reflux to give a clear solution and was treated with charcoal (1.08 kg) for 30 min. The charcoal was filtered off, and the filter cake was washed with 2-propanol (72 L). To the filtrate was added purified water (72 L) at 75–80 °C and then cooled to 45 °C for the crystallization. The resulting slurry was reheated up to 65 °C to facilitate stirrability and to obtain better filterability of crystals, and then it was cooled to 0–5 °C.

The precipitates were collected by centrifuge, washed with aqueous 2-propanol (2-propanol 36 L + purified water 36 L), and dried in a vacuum tray dryer to give **1** (34.7kg, 96.4%) as a white crystalline powder: mp 222.5-223 °C.

<sup>1</sup>H NMR (200 MHz, DMSO- $d_6$ ,  $\delta$ ) 4.91 (2H, s), 5.14 (2H, s), 7.15 (1H, t, J = 8.3 Hz), 7.31–7.41 (2H, m), 7.55 (1H, dd, J = 8.5, 1.6 Hz), 7.67 (1H, d, J = 1.6 Hz), 8.08 (1H, d, J = 8.5 Hz), 13.28 (1H, br s); IR (ATR) 3042, 2841, 1737, 1679, 1617, 1594, 1428, 1227 cm<sup>-1</sup>; MS (EI) *m*/*z* 441 (M<sup>+</sup>). Anal. Calcd for C<sub>17</sub>H<sub>11</sub>N<sub>2</sub>O<sub>4</sub>BrClF: C, 46.23; H, 2.51; N, 6.34. Found: C, 46.24; H, 2.47; N, 6.32.

General Procedures for the Selective Alkylation of Quinazolinedione. To a suspension of quinazolinedione in toluene and HMDS was added sulfuric acid at room temperature. The reaction mixture was refluxed till the clear solution was obtained. The solution was concentrated under vacuum to give a ceraceous solid. The residue was combined with an alkyl halide, leading to alkylation under elevated temperature. After the completion of the reaction, methanol was added to the reaction mixture to crystallize 1-substituted quinazolinedione.

#### Acknowledgment

We thank Dr. Zanka of Chemical Development Laboratories for helpful discussions and documentation.

Received for review May 28, 2003. OP0340661