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*Full Papers*

# Process Development and Scale-Up of PPAR $\alpha/\gamma$ Dual Agonist Lobeglitazone Sulfate (CKD-501)

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**Abstract:**

**A scaleable synthetic route to the potent PPARα/γ dual agonistic agent, lobeglitazone (1), used for the treatment of type-2 diabetes was developed. The synthetic pathway comprises an effective five-step synthesis. This process involves a consecutive synthesis of the intermediate, pyrimidinyl aminoalcohol (6), from the commercially available 4,6-dichloropyrimidine (3) without the isolation of pyrimidinyl phenoxy ether (4). Significant improvements were also made in the regioselective 1,4-reduction of the intermediate, benzylidene-2,4-thiazolidinedione (10), using Hantzsch dihydropyridine ester (HEH) with silica gel as an acid catalyst. The sulfate salt form of lobeglitazone was selected as a candidate compound for further preclinical and clinical study. More than 2 kg of lobeglitazone sulfate (CKD-501, 2) was prepared in 98.5% purity after the GMP batch. Overall yield of 2 was improved to 52% from 17% of the original medicinal chemistry route.**

## Introduction

Type-2 diabetes is a polygenic and progressive metabolic disorder characterized by insulin resistance, hyperglycaemia, hypertriglyceridaemia, and low plasma HDL-cholesterol. It affects 5−10% of adults over the age of 30 in most populations.[1] Prevailing incidence of the disease is in the elderly population of developed countries with the main cause being a high-fat diet combined with a sedentary lifestyle.[2]

Peroxisome proliferator-activated receptors (PPARs) are transcription factors that belong to the nuclear hormone receptor superfamily. It has been reported in the literature that PPARs are bound and activated by the TZD (thiazolidine-2,4-dione) group and that this pharmacological activation enhances the action of insulin (insulin sensitizers) and promotes glucose utilization in peripheral tissues.[5−7] Until now, two PPAR agonists containing the TZD group, pioglitazone[8] and rosiglitazone,[9] have been launched in the market. Although tesaglitazar[10] and muraglitazar[11] were dropped during clinical trials, several PPAR dual agonists (e.g., netoglitazone (J&J)[12] and naveglitazar (Lilly)[13]] are currently being investigated in clinical trials.

Lobeglitazone (**1**) (Figure 1) which was reported in our previous works[14−16] belongs to the class of potent PPARα/γ dual agonists (PPARα $EC_{50}$: 0.02 μM, PPARγ $EC_{50}$: 0.018 μM, rosiglitazone; PPARα $EC_{50}$: >10 μM, PPARγ $EC_{50}$: 0.02 μM, pioglitazone PPARα $EC_{50}$: >10 μM, PPARγ $EC_{50}$: 0.30 μM). Lobeglitazone has excellent pharmacokinetic properties and was shown to have more efficacious in

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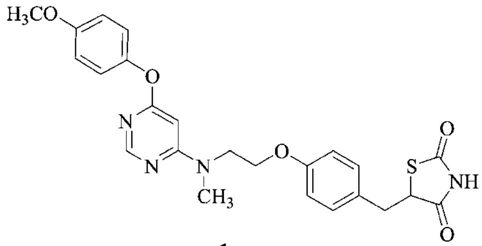

1
**Lobeglitazone**

***Figure 1.*** **Structure of the PPAR $\alpha/\gamma$ dual agonist lobeglitazone.**

vivo effects in KKA$^y$ mice than rosiglitazone and pioglitazone.[17] Due to its outstanding pharmacokinetic profile, lobeglitazone was chosen as a promising antidiabetes drug candidate. Thus, it was necessary to produce lobeglitazone in amounts ranging from several hundred grams to several kilograms for preclinical biological studies and additional toxicology tests in animal models. A GMP batch, preferably in the form of a pharmaceutically acceptable salt, to be used as the first human dose material in phase I studies was needed on a multi-100-g scale. It therefore became necessary to develop a scaleable synthesis that would provide the quantities needed for further development and to identify a pharmaceutically acceptable salt of lobeglitazone. Currently, lobeglitazone phase I clinical studies are completed , and phase II studies are scheduled to begin.

## Results and Discussion

**Review of Medicinal Chemistry Route.** Our initial medicinal chemistry (medchem) route is shown in Scheme 1. Basically, we followed the known procedure of rosiglitazone synthesis.[7,9] The medchem synthesis was performed with commercially available 4,6-dichloropyrimidine (**3**) in 10-g scale. **3** was reacted with *p*-methoxyphenol and NaH in DMF to afford the monosubstituted pyrimidine **4** in 65% yield. This low yield was deemed to be due to the remaining starting material and disubstituted byproduct **5**. The *N*-arylation of 2-methylaminoethanol with **4** gave the pyrimidinyl aminoalcohol **6** in 75% yield after $SiO_2$ chromatography. The aldehyde **7** was prepared by *O*-arylation of the aminoalcohol **6** with 4-fluorobenzaldehyde in the presence of NaH in DMF in 70% yield after chromatographic purification. Knoevenagel condensation[18] of **7** with 2,4-thiazolidinedione (TZD) in the presence of piperidine in EtOH afforded the alkene **10** in 68% yield after chromatography. The olefin moiety of the benzylidene-2,4-thiazolidinedione (**10**) was reduced with $NaBH_4$ or $LiBH_4$ in THF to give the benzyl-2,4-thiazolidinedione, lobeglitazone (**1**), in 75% purified yield after chromatography. The salt formation of **1** was performed using sulfuric acid in methanol to give the desired product, lobeglitazone sulfate (**CKD-501**, **2**), in quantitative yield. In summary, the target product, lobeglitazone sulfate, was obtained in 17% overall yield from **3**. However, this medchem route (Scheme 1) has a number of obstacles that need to be overcome before scaling. Furthermore, the numerous chromatographic purification steps were an obstacle to the production of lobeglitazone sulfate on the multi-hundred grams and kilograms scale. For GMP-kilogram-batch laboratory scaling, we had to optimize and modify the reaction conditions to overcome the obstacles we encountered in the medchem synthetic route, such as low conversion yields, inexpedient purification procedures, and the use of hazardous reagents.

**The Scaled GMP-Kilogram-Batch Laboratory Synthesis.** *Substitution of 3 with p-Methoxyphenol.* We first investigated the use other bases instead of NaH for the substitution reaction of **3**. Our initial substitution reaction afforded the desired compound **4** in 65% yield, while 15% of the starting **3** was remained and some byproducts were obtained.[19] Despite the longer reaction time and the use of excess NaH, the substitution was not complete. The most serious problem was the formation of the disubstituted compound **5** and unidentified byproducts (Scheme 2). We had to use chromatography to remove the starting material and byproducts, and these were the main causes for the low yield in this reaction. In addition, NaH poses a safety problem when used on a large scale.

To improve the yield and selectivity in the conversion of **3** to **4**, we modified the method previously reported by Miller[20] and Clark et al.[21] Several bases, KF, KF/18-C-6, CsF, TBAF, TEAF, and $K_2CO_3$, were tested in THF or in DMF. All reactions were monitored by HPLC analysis to decide the exact ending point in process control.[22]

Substitution reaction of **3** with *p*-methoxyphenol using CsF as base provided 58% yield of **4**. $K_2CO_3$ gave the worst result, with about 30% of the starting material remaining and over 10% of the byproduct **5** being produced. Although TBAF and TEAF gave good results with respect to the yield and selectivity, these could not be our option due to their high cost, hygroscopicity, and low thermal stability. KF gave an enhanced 90% yield without any starting material remaining or byproducts being produced. In addition, KF was less expensive, more thermally stable, more easily dried than any of the other bases. On the basis of the results shown in Table 1, KF was chosen as the most promising base for this reaction. The product **4** had high purity (>98% by HPLC), and could be used for the next step without further purification.

*Substitution Reaction of Pyrimidinyl Phenoxy Ether **4**.* Our initial substitution reaction of **4** using *N*-methylaminoethanol was performed according to the previously reported rosiglitazone procedure.[7,9] This condition, without a solvent at 100 °C for 24 h, resulted in the conversion of **4** to **6** in moderate yield (75%) and produced an unknown byproduct. Furthermore, this harsh condition was considered to pose a

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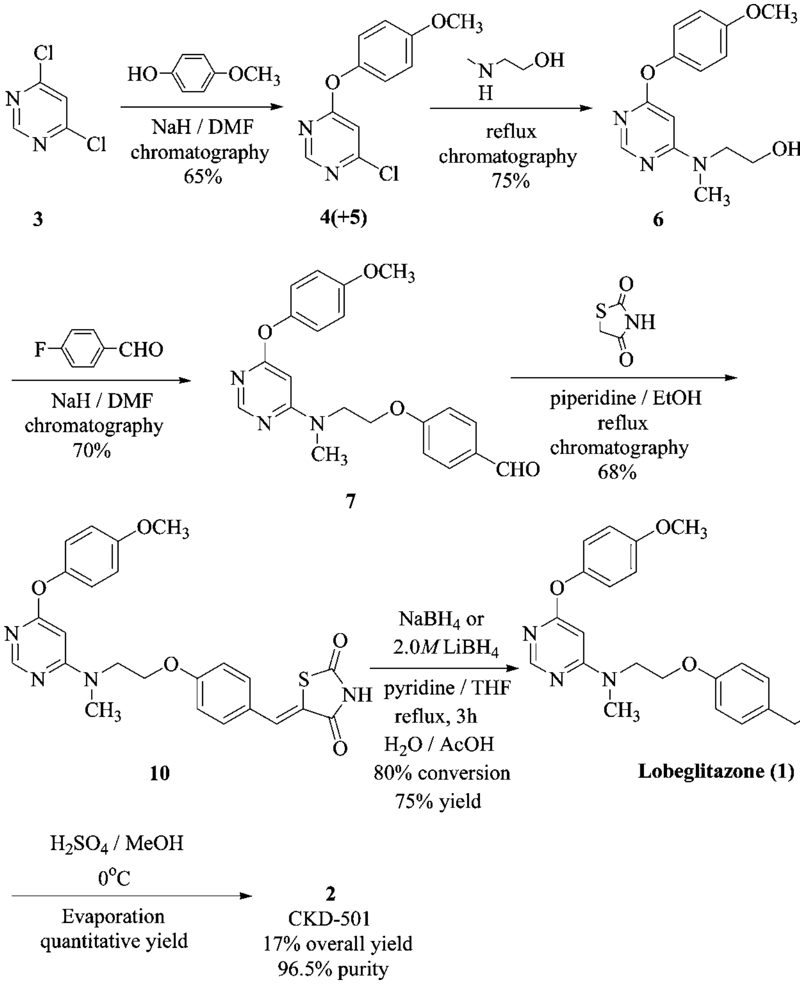
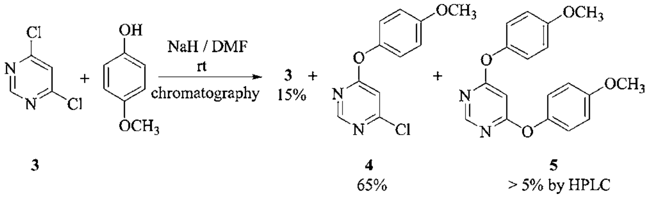
(22) HPLC analysis conditions: wavelength: 250 nm; flow rate: 1.5 mL/min; column: Kromasil $C_{18}$, UG 100 Å, 5 $\mu$m, 4.6 mm Ø × 250 mm; temperature: 40 °C; gradient: MeCN/buffer (45:55); buffer: 0.05 mM ammonium acetate (at adjusting pH 5.0); injection: 20 $\mu$L.

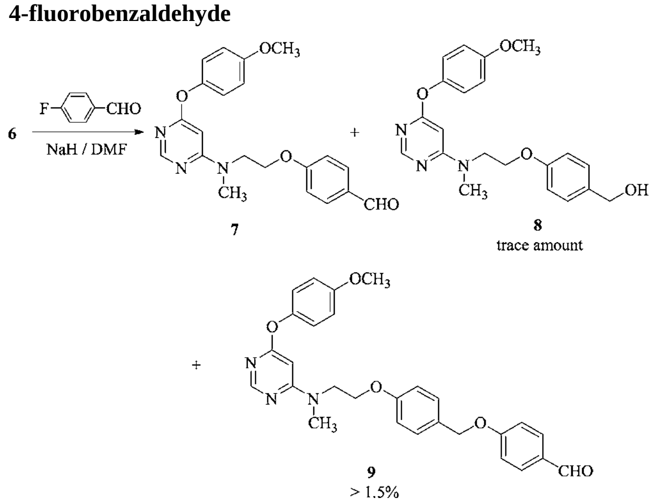
***Scheme 1.*** **Medicinal chemistry synthesis of the PPAR α/γ dual agonist CKD-501**



***Scheme 2.*** **Medicinal chemistry for substitution of 3 with *p*-methoxyphenol**



***Scheme 3.*** **Medicinal chemistry for *O*-arylation of 6 with 4-fluorobenzaldehyde**



safety problem, due to the high reaction temperature, and therefore, the reaction has to be carried out in a well-ventilated fume hood. In order to overcome these problems, several solvents, such as $CH_2Cl_2$, EtOH, toluene, and DMF, were tested to find the optimum solvent for the GMP-kilogram-batch preparation. In most cases, the substitution reaction would stall after about 80% conversion with some of the starting material **4** remaining except in the case of DMF at 80 °C and where 3.0 equiv of *N*-methylaminoethanol was used (Table 2). Under the optimized conditions using DMF, the desired product **6** was obtained in approximately quantitative yield with over 98% purity by HPLC analysis; especially, the starting material **4** disappeared completely (entry 3, Table 2). Although the substitution reaction was improved, this approach involved a cumbersome workup for the removal of DMF, and we tried to reduce the number of workups before scaling. Because the same solvent was used in two reactions (**3** → **4** and then **4** → **6**), we tried to eliminate the isolation procedure (workup) after the first reaction (**3** → **4**). As shown in entries 2 and 3 in Table 2, there were no differences in the purity and yield between the consecutive reaction (without the isolation of **4**) and the isolated reaction (with the isolation of **4**). This consecutive reaction was chosen for GMP-kilogram-batch laboratory scaling. These results are summarized in Table 2.

**Table 1.** Effects of the various bases in the substitution reaction of 3[a]

| entry | base | solvent | temp (°C) | **3**:**4**:**5** ratio[b] (%) | yield[c] (%) |
|---|---|---|---|---|---|
| 1 | NaH[d] | DMF | rt | 15:73:>5 | 65 |
| 2 | KF | DMF | 80 | ND[e]:98:ND | 90 |
| 3 | KF/18-C-6[f] | DMF | 80 | ND:97:ND | 92 |
| 4 | CsF | DMF | 80 | >20:68:8 | 58 |
| 5 | TBAF[g] | THF | rt | <2:90:ND | 83 |
| 6 | TEAF[h] | THF | 80 | <5:85:ND | 78 |
| 7 | $K_2CO_3$ | DMF | 80 | >28:56:>10 | 48 |

[a] Conditions: starting material = 1.0 g (6.7 mmol, 1 equiv), base = 20 mmol (3 equiv), solvent = 8 ml/g. [b] Reactivity was monitored by HPLC, not isolated. [c] Isolated yield, about 10% of losses in yield arise during work-up procedure. [d] 60% NaH in mineral oil. [e] Not detected. [f] Commercially available KF/18-crown-6 ether complex. [g] Tetrabutyl ammonium fluoride. [h] Tetraethyl ammonium fluoride.

**Table 2.** Effect of the solvent and temperature on the substitution of 4[a]

| entry | solvent | MAE[b] (equiv) | temp (°C) | **4**:**6** ratio[c] (%) | yield[d] (%) |
|---|---|---|---|---|---|
| 1 | − | neat | 100 | ND:80 | 75 |
| 2 | DMF[e] | 3.0 | 80 | ND:97 | quantitative |
| 3 | DMF[f] | 3.0 | 80 | ND:97 | quantitative |
| 4 | $CH_2Cl_2$ | 2.0 | reflux | >10:85 | 75 |
| 5 | EtOH | 2.0 | reflux | 7.2:80 | 67 |
| 6 | THF | 2.0 | 0 | >15:75 | 62 |
| 7 | toluene | 1.5 | reluux | >9.1:75 | 62 |

[a] Conditions: starting material = 1.0 g (6.7 mmol, 1 equiv), solvent = 8 ml/g. [b] *N*-Methylaminoethanol. [c] All reactions were monitored by HPLC in-process. Ratio of the remaining starting material **4** to desired product **6** was determined by HPLC. [d] Isolated yield. [e] Consecutive process (**3** to **6**, without isolation of **4**). [f] Isolated process (**3** to **4**, and then **4** to **6**).

*Formation of the Intermediate 7.* Our first approach to the formation of the intermediate **7** was done from **6** with *p*-fluorobenzaldehyde using NaH in DMF by applying the procedure reported by Lohray et al.[23] The preliminary results were disappointing due to the formation of the unexpected byproducts **8** and **9**, as shown in Scheme 3. The formation of **8** was probably not caused by the Cannizzaro reaction,[24] since the use of NaOH in methanol for the substitution reaction produced such byproducts in much smaller amounts. To minimize the formation of the byproducts, we tried to use other bases to avoid the hydride sources. The results are summarized in Table 3.

Desired product **7** was not observed with the use of KF and $K_2CO_3$. Stronger bases were introduced to overcome the problem probably associated with the weak basicity. With the use of KOH or NaOH, compound **8** was not observed, and only byproduct **9** was detected, with its amount being about 1.5% in the case of KOH and 5% in the case of NaOH as determined by HPLC (entries 4 and 5, Table 3).[22] Considering the improved yield and easy handling, KOH was selected as the most practical and effective base in this substitution for GMP-kilogram-batch scaling. The product **7** could be used in the next step without further purification.


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**Table 3.** Influence of the base on the formation of 7[a]

| entry | base | solvent | temp (°C) | **8**:**9** ratio[b] (%) | yield[c] (%) |
|---|---|---|---|---|---|
| 1 | NaH[d] | DMF | 60 | >10:10 | 61 |
| 2 | KF | DMF | 80 | trace:trace | NR[e] |
| 3 | $K_2CO_3$ | DMF | 80 | ND:ND[f] | NR |
| 4 | KOH | DMF | 80 | trace:<1.5 | 80 |
| 5 | NaOH | DMF | 80 | trace:<5 | 72 |

[a] Conditions: starting material = 1.0 g (3.6 mmol, 1 equiv), base = 11 mmol (3 equiv), solvent = 5 mL/g. [b] All reactions were monitored by HPLC. [c] Not purified yield. [d] 60% NaH in mineral oil. [e] No reaction. [f] Not detected.

**Table 4.** Effect of the acid catalysts for Knoevenagel condensation[a]

| entry | base | solvent | temp[c] (°C) | reaction time[d] (h) | yield[e] (%) |
|---|---|---|---|---|---|
| 1 | pyrrolidine[f] | EtOH[b] | reflux | 10 | 61 |
| 2 | piperidine[f] | EtOH | reflux | 12 | 60 |
| 3 | piperidine/acetic acid | toluene | reflux | 3 | 90 |
| 4 | piperidine/acetic acid | benzene | reflux | 4 | 89 |
| 5 | piperidine/benzoic acid | toluene | reflux | 6 | 87 |

[a] Conditions: starting material = 1.0 g (2.6 mmol, 1 equiv), thiazolidine-2,4-dione = 2.6 mmol (1.0 equiv), piperidine = 0.79 mmol (0.3 equiv), acetic acid = 0.79 mmol (0.3 equiv), benzoic acid = 0.79 mmol (0.3 equiv). All reactions were monitored by HPLC and TLC. [b] This solvent was not for recrystallization but for reaction. [c] Moisture was removed using Dean−Stark azeotropic water trapping apparatus. [d] End point was determined by HPLC and TLC. [e] Isolated yield, used EtOH as recrystallization solvent. [f] Three equivalents of base used.

*Knoevenagel Condensation.* For the Knoevenagel condensation of substrate **7**, we first tried the previously reported methods, such as the rosiglitazone methodology reported by Willson et al.[25] and the pioglitazone methodology reported by Sohda et al.[26,27] Willson's procedure called for treating an aldehyde with thiazolidine-2,4-dione (TZD) using piperidine or pyrrolidine as a base in alcoholic solvent under reflux conditions. However, in the case of compound **7**, it showed an unsatisfactory 60% yield after recrystallization with EtOH, which was lower than the 68% yield after column chromatography in the medchem synthesis. For the GMP-kilogram-batch base scaling, the reaction conditions had to be modified. We replaced the solvent, EtOH, by other aprotic solvents and introduced the acid catalyst, acetic acid or benzoic acid, as depicted in the JTT-501 synthesis previously reported by Shinkai et al.[28] As summarized in Table 4, the best result was obtained with piperidine and acetic acid in toluene under reflux conditions.

The benzylidene compound **10** was obtained from **7** with the optimized reaction conditions (entry 3, Table 4) in 90% yield and 95% purity by HPLC analysis. Furthermore, the HPLC analysis indicated that 0.85% of impurity **11** together with two unknown impurities with amounts of 1.5 area % and 1.7 area % were observed during this reaction (Scheme


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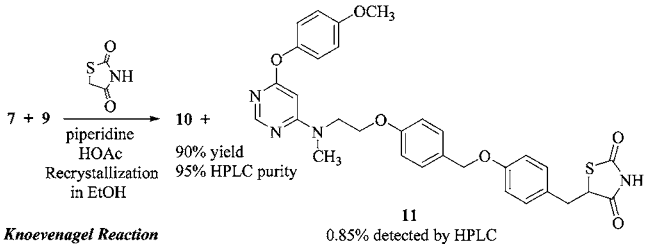
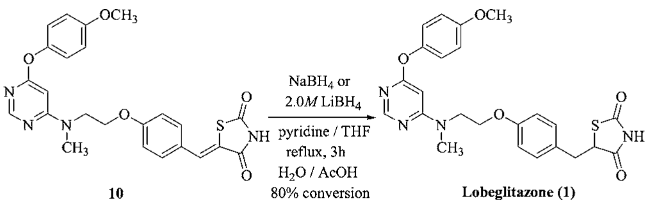
***Scheme 4.*** **Scaled GMP-kilogram-batch laboratory synthesis of the benzylidene 10**




***Scheme 5.*** **Medicinal chemistry scheme of reduction process with benzylidene 10**




4). This contaminated **10** after recrystallization in EtOH was used in the next step without further purification.

*Reduction of Benzylidene TZD **10***. At this point in the synthesis, we applied the conditions previously developed in-house for the synthesis of rosiglitazone to reduce **10** to **1**.[29] Rosiglitazone was synthesized as a reference compound in order to evaluate the biological activity of lobeglitazone. However, the initial reduction of the benzylidene **10** using the rosiglitazone procedure proved to be problematic, in that the reaction would stall after 80% conversion and gave **1** in 75% yield (Scheme 5). Adding more $NaBH_4$ or $LiBH_4$ in THF to the reaction mixture did not consume the remaining **10** (up to around 15%). Another approach using 10% Pd−C or 20% $Pd(OH)_2$ under an $H_2$ atmosphere gave a good result, viz. the completion of the reaction with moderate yield (about 75%). However, this hydrogenation required a prolonged reaction time (about 60−72 h) together with potential safety problems. Also, the generation of an undesired product derived from both the 1,2- and 1,4-reduction of the thiazolidinedione moiety makes this approach less attractive. Search for more selective reduction conditions allowing an expedient workup procedure was performed.

Initial study for the reduction of the benzylidene compound **10** focused on the work reported by Mashraqui et al.,[30] in which Hantzsch ester **12** was used with ruthenium chloride as a catalyst. Although the reduction of **10** using **12** showed a somewhat improved result without any of the starting **10** remaining and no over-reduction product being produced, other problems occurred because of the small amounts of ruthenium metal remaining after workup. Efforts had been focused on searching for a better catalyst to be used for the reduction with Hantzsch ester **12**. As shown in Scheme 6, the best result was obtained with the use of silica gel as the catalyst and 1.3 equiv of **12** in toluene.[31] This reduction was carried out under anhydrous conditions by removing the moisture with the use of a Dean−Stark water-trapping

***Scheme 6.*** **Scaled GMP-kilogram-batch laboratory synthesis of lobeglitazone (1)**

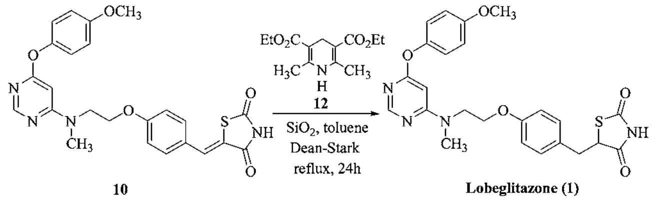



***Table 5.*** **Influence of the weight ratio of the benzylidene compound 10 to silica gel on the reduction of 10 using Hantzsch ester**

| | | | reaction condition[c] | | |
|---|---|---|---|---|---|
| entry | benzylidene **10** vs $SiO_2$ (w/w) ratio | solvent[b] | temp (°C) | time (h) | yield[d] (%) |
| 1 | 1:3 | toluene | reflux | 12 | 90 |
| 2 | 1:3 | toluene[e] | reflux | 12 | 58 |
| 3 | 1:1.5 | toluene | reflux | 24 | 88 |
| 4 | 1:1 | toluene | reflux | 38 | 89 |
| 5 | 1:0.5 | toluene | reflux | 60 | 72 |
| 6 | − | toluene | reflux | 72 | ND[f] |
| 7 | 1:1.5 | benzene | reflux | 30 | 60 |
| 8 | 1:1.5 | THF | reflux | 48 | ND |

[a] Conditions: substrate, **10** = 1.0 mmol, Hantzsch ester, **12** = 1.3 mmol, at reflux conditions under $N_2$ atm and monitored by HPLC, NMR, and TLC. [b] All solvents were not dried. [c] Reactions were carried out under azeotropic conditions. [d] Isolated yield. [e] Azeotropic condition was not applied. [f] Not detected.

apparatus (azeotropic conditions) under a nitrogen atmosphere. Since the ester **12** is sensitive to light and moisture, it was necessary to perform this reduction under dark and anhydrous conditions.

For further optimization of the reduction, we next tried to change the weight ratio between the benzylidene compound **10** and silica gel. It was essential to use the Dean−Stark apparatus to prevent the influence of moisture on the reduction process. The result indicated in entry 1 (see Table 5) showed that the reduction was accelerated by the added silica gel and gave a good yield of 90%. When the azeotropic apparatus was not used, the moisture contained in the silica gel tended to decrease the yield (entry 2, Table 5). The water molecules binding to the silica gel are possibly deteriorating the role of silica gel as an acid catalyst. When the reduction of **10** was carried out in the absence of silica gel or when THF was used as a solvent, the reduction did not proceed at all (entries 6 and 8, Table 5).

The reduction system composed of the Hantzsch ester and silica gel is an excellent tool for the chemo- and regioselective reduction of $\alpha,\beta$-unsaturated TZD, due to its simplicity compared with other methods described in the recent literature.[32,33] The crude product mixture was hot filtered to get rid of the silica gel and was concentrated in vacuo. The resulting crude cake was purified by triturating by stirring in hexane/EtOAc (4:1, v/v) and filtering. The precipitates were dissolved in $CH_2Cl_2$/ethanol (4:1, v/v), and this mixture was then concentrated to an inner volume of approximately

(29) Giles, R. G.; Lewis, N. J.; Sasse, M. J.; Urquhart, M. W. J.; Youssef, L. *Tetrahedron* **2000**, *56*, 4531−4537.
(30) Mashraqui, S. H.; Karnik, M. A. *Tetrahedron Lett.* **1998**, *39*, 4895−4898.
(31) Silica gel (230−400 mesh) was purchased from Merck Co. Ltd.
(32) Alba, A.; Aramendia, A.; Borau, V.; Gabcia-Raso, A.; Jimenez, C.; Marinas, J. M. *J. Am. Chem. Soc.* **1986**, *108*, 7314−7325.
(33) Stamm, H.; Sommer, A.; Onistschenko, A.; Woderer, A. *J. Org. Chem.* **1986**, *51*, 4979−4983.

***Table 6.*** **Comparision of first-round lobeglitazone salt candidates**

| test items | sulfate | HCl | mesylate | maleate | besylate |
|---|---|---|---|---|---|
| appearance | pale-yellowish white | off-white | pale yellow | pale yellow | yellow |
| mp DSC onset (°C) | 111.5 | 105.5 | 104.2 | 120.1 | 107.2 |
| hygroscopicity | nonhygroscopic | hygroscopic | nonhygroscopic | nonhygroscopic | hygroscopic |
| solubility($\mu$g/mL) | 33.5 | 13.3 | 11.9 | 11.8 | 11.7 |
| deliquescence | at RH 94−96% | at RH 76−82% | at RH 53−58% | at RH 55−60% | at RH 62−66% |
| other thermal behavior | not detected | not detected | not detected | not detected | not detected |
| four-week stability[44] | stable under 40 °C and light | stable at 40 °C light sensitive 18% decrease | stable at 40 °C light sensitive 4−6% decrease | stable at 40 °C light sensitive 6−10% decrease | stable at 40 °C light sensitive 10−12% decrease |

3.5−4 L by evaporation in vacuo. The condensed mixture was stirred for 24 h at room temperature, and the yellowish solid formed was collected by filtration. To meet the requirements of the ICH guideline on residual solvents, we dried the filter cake in a vacuum-dry oven for 24 h (inner temperature range of about 85 °C, vacuum capacity −30 in. of Hg by Fischer Scientific Instruments). Unfortunately, we found that the amount of the unknown impurity, detected by NMR signals and not by the UV detector in HPLC, was increased. Another procedure to remove the residual solvent without generating this unknown impurity had to be found. We used isopropyl ether for additional trituration to reduce the level of residual ethanol and other solvents, and this procedure gave a good result which met the requirement of the ICH guideline. After the vacuum drying, the purified lobeglitazone (**1**) was obtained in 90% yield with 98% purity and was found to contain 1500 ppm of ethanol, 800 ppm of isopropyl ether, and 500 ppm of dichloromethane by GLC analysis. In conclusion, we developed a scaleable GMP-kilogram-batch laboratory method for the regioselective reduction of the benzylidene **10** to afford **1** using Hantzsch ester and $SiO_2$ catalyst.

*Salt Assessment and Preparation.* The choice of a suitable salt of lobeglitazone (**CKD-501** free base) was important for the success of the project. The selection of the salt form was considered from several viewpoints, such as the purification of the final product by crystallization and the development of a pharmaceutical dosage form.[34,35] Pharmaceutically available acids were screened for salt formation with the **CKD-501** free base. Salt forms of lobeglitazone on the gram scale were obtained with hydrochloric acid, sulfuric acid, methanesulfonic acid, benzenesulfonic acid, maleic acid, and oxalic acid. To elucidate the thermal properties of the salt forms (melting point, crystallinity, and hygroscopicity) differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), and dynamic vapor sorption (DVS) were performed. The apparent solubilities in water were determined for 7 days at room temperature, and the pH rate profiles were tested at 55 °C in acidic, neutral, and basic buffer solutions for the estimation of the degradation rate constant, $K_{obs}$, in accordance with the pH conditions. Accelerated testing was conducted at 40 °C without a light source to assess the solid stability of the salt forms, and the photostability was tested with a light source of no less than 10,000 lux. Additionally, the acidity−basicity constant (p$K_a$) and partition coefficient (Log $P$) of the **CKD-501** free base form were determined by the potentiometric titration method with GLp$K_a$. Five crystalline salts (sulfate, hydrochloride, mesylate, maleate, and besylate) were selected as the first-round salt candidates on the basis of their crystal and thermodynamic properties, hygroscopicity, and aqueous solubilities. During the progression of the **CKD-501** project, more data relevant to salt selection were generated in parallel, and the final salt candidate was elected: On the basis of the results of 4 weeks stability data, the hydrochloric acid salt of lobeglitazone showed greater instability than the other salts under the light-stability test and was excluded from the list of candidates. The HCl and besylate salts were revealed to have higher hygroscopicity, lower solubility, and relatively poorer stability than the sulfate salt. Due to their high deliquescence and degradation resulting from their keen susceptibility towards light exposure, as shown in Table 6, the HCl and besylate salts were discarded.[36]

The sulfate salt of lobeglitazone was chosen as the preferred candidate for further pharmaceutical evaluation. Its good melting point together with the demonstrated integrity of the crystalline pulverized form, good chemical stability,[37] and nonhygroscopicity made it appropriate for tablet formulation.[38] Various solvents, viz. EtOAc, EtOH, MeOH, *i*-PrOH, acetone, $CH_3CN$, *n*-hexane, and isopropyl ether, were tested to find the optimum solvent for the preparation and crystallization of **CKD-501** (lobeglitazone sulfate), first on a milligram and then on a multigram scale. All of the tested solvents, except methanol, showed poor solubility for lobeglitazone itself. A small-scale (about 10 g) attempt for the salt formation in methanol is shown in scheme 7. The residual methanol contained in the obtained lobeglitazone sulfate (**CKD-501**) amounted to $<$3−4%, as determined by GLC analysis. To get rid of this residual methanol, the final desired product **2** was dried at a temperature of 45−50 °C

(34) Stahl, H. W.; Wermuth, C. G. *Handbook of Pharmaceutical Salts, Properties, Selection, and Use*; Wiley-VCH: Weinheim, 2002.

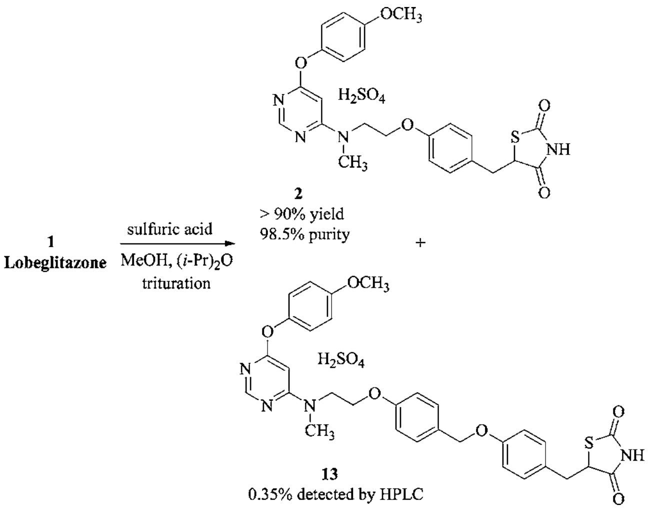
(35) Bastin, R. J.; Bowker, M. J.; Slater, B. J. *Org. Process Res. Dev.* **2000**, *4*, 427−435.

(36) Performed at three different conditions: (i) accelerated stability: 45 ± 2 °C/75% ± 5% relative humidity, (ii) long term stability: 25 ± 2 °C/60% ± 5% relative humidity, (iii) photostability: ambient temperature and humidity/fluorescence lamp exposure (light source: 10,000 Lux), and analyzed by XRD, Karl Fischer, HPLC purity and assay, DSC, and TGA.

(37) Long-term chemical stability observed at ambient temperature and humidity in aluminum foil package storage for two years.

(38) A mechanical grinding stability experiment and a six-month stability study under accelerated storage conditions (45 ± 2 °C/75% ± 5% relative humidity monitoring by HPLC) were performed after the preparation of the GMP batch confirmed the selection of the lobeglitazone sulfate (**CKD-501**) as the development candidate.

***Scheme 7.*** **Scaled GMP-kilogram-batch laboratory synthesis of the lobeglitazone sulfate (2)**



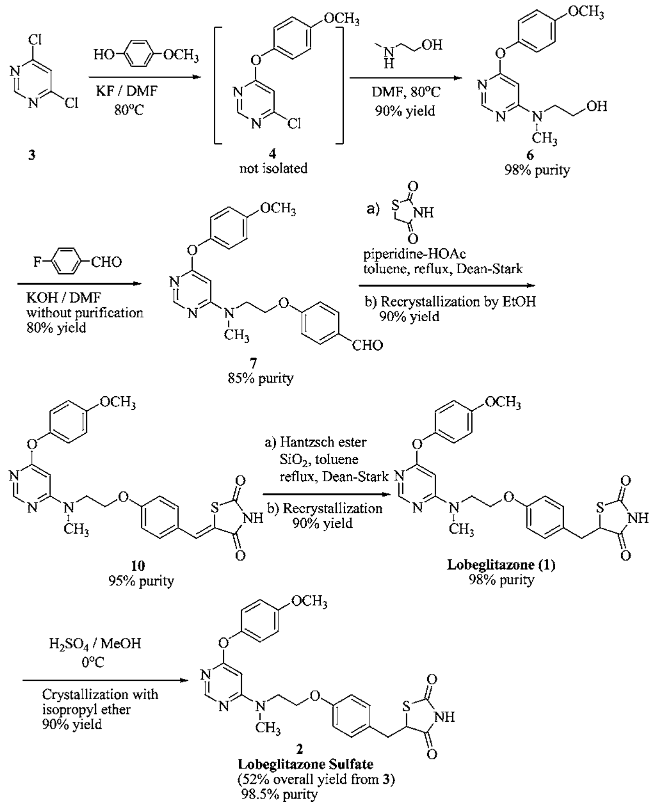

for 24−36 h, using a vacuum pump (−30 in. of Hg by Fischer Scientific). Unfortunately, we found that the dried product **2** contained 2.5−4% of the sulfuric acid monomethyl ester ($CH_3SO_4H$) by NMR analysis. The integration ratio between the monomethyl ester and product **2** determined by NMR seemed to be dependent on the temperature of the drying oven and the time spent in it. That is, the higher the temperature, the greater the increase in the monomethyl ester ratio observed. To overcome these problems, we tried to triturate the product **2** with several solvents, such as pentane, hexane, petroleum ether, and dichloromethane, expecting the easy removal of the residual solvent at room temperature in a vacuum system. A similar crystal form was always obtained, independent of the conditions and solvent. Finally, isopropyl ether was selected as the best solvent for the trituration and crystallization of the crude lobeglitazone sulfate.

The trituration and crystallization procedure with ($i$-Pr)$_2$O enhanced the relative purity of the desired product **2**, less than 0.35% of impurity **13** being included, the sulfuric acid monomethyl ester ($CH_3SO_4H$) not being detected,[39] and the amount of methanol being less than 3000 ppm so as to meet the ICH methanol specifications.[40] Therefore, lobeglitazone **1** was transformed into lobeglitazone sulfate **2** in >90% yield and 98.5% HPLC purity. This allowed us to explore the use of the final salt form in the preclinical development stage and the phase I/II clinical trials.

## Conclusions

A scaleable synthetic route to lobeglitazone sulfate was developed on the basis of a modified medicinal chemistry route. More than 2 kg of compound **2** was finally synthesized in approximately 52% overall yield starting from 1.0 kg of the commercially available dichloropyrimidine **3** under GMP-kilogram-batch laboratory conditions. The overall yield of

***Scheme 8.*** **Scaled GMP-kilogram-batch laboratory synthesis of the lobeglitazone sulfate (2)**




the desired compound **2** was enhanced to 52% with 98.5% purity in comparison to the yield of 17% for the medicinal chemistry route, as summarized in scheme 8. The major improvements in the GMP-kilogram-batch scaling process were made in the following two steps. First, the facile consecutive reaction from **3** to **6** was achieved by substituting KF for NaH, thereby suppressing the generation of the undesired compound **5**. Compound **6** was obtained in a higher yield of around 90% with 98% purity. Second, Hantzsch ester used for the reduction of compounds with the $\alpha,\beta$-unsaturated thiazolidinedione was proven to be the remarkable regioselective reducing agent for the benzylidene compound **10** without generating any other byproducts. The uses of $SiO_2$ as an acid catalyst and an azeotropic Dean−Stark water trap for the removal of moisture were found to be essential for the successful regioselective reduction. Therefore, Hantzsch ester was found to be the most effective and convenient reducing agent in this reductive conversion. After the reduction, the purified lobeglitazone was obtained by recrystallization in ethanol without resorting to $SiO_2$ chromatography. It was obtained in approximately 90% yield with 98% purity. The quantity and quality of the lobeglitazone sulfate **(CKD-501**) obtained under the GMP-kilogram-batch laboratory conditions were sufficient to allow it to be used for a complete preclinical study of its toxicology and the phase I/II clinical studies. The optimized process for lobeglitazone sulfate was transferred to Kyoung Bo pharmaceutics for future market manufacturing.

(39) One major impurity, compound **13**, showed a lasting retention time about 45 min exhibiting 0.35 % by HPLC analysis, HR-MS; 586, $C_{31}H_{30}N_4O_6S$ by EA.

(40) Methanol is being classified as a class 2 (<3000 ppm) solvent in ICH guidelines.

## Experimental Section

**General Procedure.** The experimental details are given for the largest scale that was carried out. All solvents and reagents were obtained from commercial sources and were used without further purification. Melting points were determined on a Buchi 510 capillary apparatus and are uncorrected. IR spectra were recorded on a Bruker Vector 22 FT-IR spectrometer. NMR spectra were recorded on a Bruker DPX 400 MHz instrument operating at 400 MHz for proton and 100 MHz for carbon NMR and were performed in DMSO-$d_6$ solutions using tetramethylsilane as the internal reference, except where otherwise indicated. The coupling constants ($J$) are reported in Hz. Mass spectra were recorded on an LC/MSD SL 1100 series (Agilent Technologies), and the data system was an HP Chemstation. HPLC: all compounds are measured under the same conditions; wavelength: 250 nm; flow rate: 1.5 mL/min; column: Kromasil $C_{18}$ (UG 100 Å, 5 $\mu$m, 4.6 mm Ø × 250 mm); temperature: 40 °C; isocratic elution: MeCN, 0.05 M ammonium acetate buffer, pH 5.0 (45:55, v/v). The differential scanning analysis (DSC) used for melting-point determination was performed with an SSC 5000 (SEIKO), TA Instruments. The sample (approximately 5 mg) was heated in pinhole-crimped aluminum pans from 25 to 300 °C at a rate of 5 °C/min. The DSC measuring chamber was continuously purged with dry nitrogen during the runs, and the instrument was routinely calibrated with indium and tin. The DSC used for the safety evaluation was conducted from 25 to 500 °C at a rate of 10 °C/min without nitrogen purging under air. The thermogravimetric analysis (TGA) experiment was performed on a Thermo Gravimetric Analyzer. The sample (approximately 5 mg) was heated in an open platinum pan from 25 to 300 °C at a rate of 5 °C/min. The TGA measuring chamber was continuously purged with dry nitrogen during the runs, and the instrument was routinely calibrated with indium and aluminum. The pH solubility profile of the lobeglitazone sulfate and the corresponding p$K_a$ value were calculated by means of a p$K_a$ and log $P$ autotitrator (GLp$K_a$-01). The gas chromatogram of the final compound was recorded on a GC-17A (Shimadzu). Gas flow: 60 mL (He)/min. Column: DB-624 30 m × 0.32 mm, column temperature 40 °C.

**Preparation of 2-[6-(4-Methoxyphenoxy)pyrimidin-4-yl]methylaminoethanol (6).** To a dry, nitrogen-purged 70-L (Buchi) reactor with a mechanically stirred solution of anhydrous DMF (8 L) (previously dried by stirring for 24 h with anhydrous sodium sulfate and filtering) were successively added 4,6-dichloropyrimidine **3** (1.00 kg, 6.7 mol), potassium fluoride (1.17 kg, 20 mol), and $p$-methoxyphenol (0.83 kg, 6.7 mol) at ambient temperature. After the additions, the reaction mixture was heated to 80 °C and stirred for 3−4.5 h, at which time the reaction was assayed by monitoring TLC and HPLC, indicating that none of the starting material **3** remained. Once complete, the reaction mixture was cooled to room temperature (*HPLC retention time; starting material **3**: 5.1 min, compound **4**: 12.5 min, desired product **6**: 2.9 min*). 2-Methylaminoethanol (1.6 L, 20 mol) was added to the mixture, which was then stirred with a mechanical stirrer at 80 °C. After approximately 1−1.5 h, the reaction mixture was monitored by TLC and HPLC, which indicated that no **4** remained. The reaction was then cooled to room temperature and was carefully quenched for 40 min with 50 L of distilled water (DW) at a rate sufficient to maintain the internal temperature below 30 °C. Because the total amount of the solutions for the workup exceeded the capacity of the reactor, the workup process was divided into two parts. Each part of the divided mixture was diluted with 35 L of ethyl acetate. The organic layer was washed four times with brine (30 L each) and twice with DW (7 L each). The organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo. The obtained syrup-like product was completely dried in a vacuum system to give 1.66 kg of the desired product **6** (90% yield, corrected for 98% purity by HPLC) as a light-yellow oil (containing <1.4% of three minor unknown impurities, but no starting materials or intermediate **4**). The desired product **6** was used for the next step without further purification. $SiO_2$ TLC $R_f$ = 0.2 (Detection: Iodine char chamber, $p$-anisaldehyde solution, developing solvents: EtOAc/hexanes, 1:1); IR ($CHCl_3$) $\nu$ 3355, 2935, 1592, 1546, 1504 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 3.03 (s, 1H), 3.74 (m, 2H), 3.82 (m, 5H), 5.81 (s, 1H), 6.92 (d, 2H, $J$ = 3.61 Hz), 7.04 (d, 2H, $J$ = 3.67 Hz), 8.24 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 37.5, 53.4, 55.9, 62.2, 86.0, 115.1, 122.8, 146.6, 157.3, 157.9, 164.9, 170.9; MS (ESI) $m/z$ 276.30 (M + 1); Anal. Calcd for $C_{14}H_{17}N_3O_3$: C, 61.08; H, 6.22; N, 15.26. Found: C, 60.98; H, 6.05; N, 15.15.

**Preparation of 4-(2-{[6-(4-Methoxyphenoxy)pyrimidin-4-yl]methylamino}ethoxy)benzaldehyde (7).** To a dry, nitrogen-purged 70-L reactor (Buchi) with a mechanically stirred solution of **6** (1.66 kg, 6.0 mol) in anhydrous DMF (8 L) were successively added potassium hydroxide (1.19 kg, 18 mol) and 4-fluorobenzaldehyde (0.71 L, 6.6 mol) at ambient temperature. After the completion of the additions, the reaction mixture was stirred at room temperature for 6 h, at which time the disappearance of the starting material **6** was confirmed by monitoring TLC and HPLC (*HPLC retention time; starting **6**: 2.9 min, product **7**: 12.5 min*). Once the reaction was complete, the reaction mixture was filtered to remove any remaining insoluble potassium hydroxide. The filtrate was diluted with 40 L of ethyl acetate. Because the total amount of the solutions for the workup exceeded the capacity of the reactor, the workup process was divided into three parts. Each part of the reaction mixture (30 L) was washed twice with 30-L portions of brine and twice with 7-L portions of DW. The combined organic layers were dried over sodium sulfate, filtered, and condensed under reduced pressure. The obtained yellowish syrup-type oil was dried in vacuo to give 1.82 kg of the desired product **7** (80% yield based on 85% purity by HPLC), as a pale-yellow oil (containing a trace amount of impurity **8**, and <1.5% of impurity **9**). The aldehyde **7** was used in the next step without further purification. $SiO_2$ TLC $R_f$ = 0.48 (detection: Iodine char chamber, $p$-anisaldehyde solution, developing solvents: EtOAc/hexanes, 1:1); IR ($CHCl_3$) $\nu$ 2947, 2834, 1692, 1590, 1506, 1440 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 3.14 (s, 3H), 3.83 (s, 3H), 4.30 (m, 2H), 4.67 (m, 2H), 5.86 (s, 1H), 6.94 (m, 2H), 7.02 (m, 2H), 7.08 (m, 2H), 7.84 (m, 2H), 8.32 (s, 1H), 9.90 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 3706, 53.4, 56.1, 62.5, 86.1, 115.1, 122.8, 128.5, 130.8, 146.7, 157.3, 157.9, 164.8, 170.9, 174.9; MS (ESI) *m*/*z* (M + 1) 380.41; Anal. Calcd for $C_{21}H_{21}N_3O_4$: C, 66.48; H, 5.58; N, 11.08. Found: C, 66.31; H, 5.42; N, 10.95.

**Preparation of 5-[4-(2-{[6-(4-Methoxyphenoxy)pyrimidin-4-yl]methylamino}ethoxy)benzylidene]thiazolidine-2,4-dione (10).** To a dry, nitrogen-purged 70-L reactor (Buchi) with a mechanically stirred solution of **7** (1.8 kg, 4.8 mol) in 30 L of toluene were successively added 2,4-thiazolidinedione (0.48 kg, 4.8 mol), acetic acid (70 mL, 1.44 mol), and piperidine (0.12 L, 1.4 mol), and then the reaction mixture was stirred at reflux temperature for 5 h with a Dean−Stark water trap (the amount of condensed water was about 86 mL). The disappearance of the starting material **7** was detected by monitoring HPLC (*HPLC retention time; starting **7**: 12.5 min, product **10**: 13.5 min*). Once the reaction was completed, the mixture was cooled to room temperature, and the precipitates formed were collected by filtration and washed twice with fresh anhydrous toluene.

**Recrystallization of Crude 10.** To a dry, nitrogen-purged 70-L glass-lined reactor were added the crude **10** and ethanol (10 L). The resulting slurry was then heated at 35−40 °C for about 5 h (*Note: Not all of the solid cakes were dissolved after this time*). The reaction mixture was then cooled to ca. 25 °C for at least 3 h and stirred for 20 h at the same temperature. The resulting solid was collected by filtration and washed with precooled ethanol (5 L, about 5 °C in a refrigerator) (*Note: Through the recrystallization process, the major impurities (compounds **6**, **8**, **9**, and **11**) were effectively removed, as confirmed by HPLC analysis*). To a dry 20-L glass reactor was added the obtained yellowish solid **10** followed by trituration with (*i*-Pr)$_2$O (15 L) for 12 h at room temperature. The resultant solids were collected by filtration and washed with (*i*-Pr)$_2$O (2 × 5 L), and dried in a vacuum oven to afford 2.06 kg of the purified **10** (90% yield based on 95% HPLC purity) as a light-yellow solid (containing 0.85% of the impurity **11**), which was used in the next reaction without further purification. Silica gel TLC $R_f$ = 0.32 (detection: Iodine char chamber, ninhydrin solution, developing solvents: $CH_2Cl_2$/MeOH, 20:1); mp 194−195 °C; IR (KBr) $\nu$ 3428, 2948, 2748, 1741, 1704, 1591, 1508, 1292, 1257 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 3.07 (s, 3H), 3.75 (s, 3H), 3.94 (m, 2H), 4.23 (m, 2H), 6.05 (s, 1H), 6.95 (d, $J$ = 8.84 Hz, 2H), 7.00 (m, 4H), 7.54 (d, $J$ = 8.86 Hz, 2H), 7.73 (s, 1H), 8.16 (s, 1H); $^{13}$C-NMR (100 MHz, DMSO-$d_6$) $\delta$ 37.3, 48.9, 56.2, 66.5, 86.4, 115.4, 116.2, 121.3, 123.3, 126.5, 132.5, 132.9, 146.9, 157.2, 158.1, 160.8, 164.5, 168.4, 168.8, 170.6; MS (ESI) *m*/*z* (M + 1) 479.51; Anal. Calcd for $C_{24}H_{22}N_4O_5S$: C, 60.24; H, 4.63; N, 11.71; S, 6.70. Found: C, 60.11; H, 4.49; N, 11.65; S, 6.52.

**Preparation of 5-(4-{2-[6-(4-Methoxyphenoxy)pyrimidin-4-yl]methylamino ethoxy}benzyl)thiazolidine-2,4-dione (1).** To a dry, nitrogen-purged 70-L reactor (Buchi) with a mechanically stirred suspension of compound **10** (2.1 kg, 4.3 mol) in toluene (50 L) were successively added the Hantzsch ester (1.4 kg, 5.6 mol) and silica gel (6 kg). After each addition, the reaction mixture was stirred at reflux temperature for 12 h, at which point HPLC showed the complete conversion of **10** to **1** in the case where a Dean−Stark water trap was used **(***HPLC retention time; starting material **10**: 13.5 min, desired product **1**: 12.5 min*). The mixture was hot filtered to remove the silica gel (*Note: In order to ensure safe handling, a good exhausting hood and sufficient caution are required*). The filter cake was washed with ethyl acetate (2 × 5.0 L), and the filtrate was concentrated in vacuo.

**Recrystallization of Crude 1.** To a dry, 70-L glass reactor was added the oily residue in anhydrous ethyl acetate (5 L) followed by stirring at 25 °C for about 3.5 h until the residue was clearly dissolved, and then hexanes (20 L) was added. The reaction mixture was stirred at 25 °C for 10 h, allowed to stand for 24 h at room temperature, and then filtered to afford a yellowish solid. The resulting solid was completely dissolved in 15 L of mixed solvent (dichloromethane/ethanol = 12:3) with stirring for about 5 h, and the reaction solution was concentrated in vacuo to an inner volume of approximately 3.5−4 L. The condensed organic mixture was stirred for 1 day at room temperature, and the yellowish solid formed was collected by filtration. The obtained solid was triturated with isopropyl ether (15 L) for 1 day at ambient temperature, filtered, and dried in a vacuum oven at 85 °C for 10 h to afford the desired product 1 as a light yellow solid. $SiO_2$ TLC $R_f$ = 0.35 (detection: Iodine char chamber, ninhydrin solution, developing solvents: $CH_2Cl_2$/MeOH, 20:1); mp 145−146 °C; IR (KBr) $\nu$ 3427, 3112, 2924, 2835, 2752, 1749, 1693, 1590, 1545, 1506, 1444, 1363 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 3.12 (m, 4H), 3.45 (m, 1H), 3.83 (s, 3H), 4.00 (m, 2H), 4.16 (m, 2H), 4.50 (m, 1H), 5.84 (bs, 1H), 6.83 (m, 2H), 7.06 (m, 2H), 7.15 (m, 2H), 8.31 (s, 1H), 8.89 (bs, NH); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 37.9, 38.1, 49.7, 54.0, 55.9, 66.6, 85.9, 115.0, 122.8, 128.8, 130.7, 146.7, 157.3, 157.9, 158.4, 164.2, 170.8, 171.1, 174.9; MS (ESI) *m*/*z* (M + 1) 481.5; Anal. Calcd for $C_{24}H_{24}N_4O_5S$: C, 59.99; H, 5.03; N, 11.66; S, 6.67. Found: C, 60.11; H, 5.05; N, 11.67; S, 6.50.

**Preparation of 5-(4-{2-[6-(4-Methoxyphenoxy)pyrimidin-4-yl]methylamino ethoxy}benzyl)thiazolidine-2,4-dione sulfate (2).** To a dry, nitrogen-purged 20-L glass reactor was added compound **1** (1.87 kg, 3.89 mol) in 15 L of anhydrous methanol (obtained by passage through Linde-type 4 Å molecular sieves) and then stirred at 0 °C until it was clearly dissolved. While the temperature was maintained at 0−5 °C, sulfuric acid (96%, 216 mL, 3.89 mol) was added dropwise for 30 min to the reaction mixture, and then the resulting mixture was stirred for 1−1.5 h more. The mixture was condensed to one tenth of its original volume in vacuo maintaining the water bath temperature less than 10 °C (*Note: with higher bath temperature, a gradual increase, up to <3%, in the amount of CKD-501-monomethyl sulfate was observed by HPLC analysis*).

**Crystallization of Crude Lobeglitazone Sulfate (CKD-501).** The residual pale-yellow syrup was crystallized with isopropyl ether (20 L) at room temperature for 24 h, and then the collected solid was filtered to give a pale-yellow solid. The obtained solid was slurried twice with isopropyl ether ($2 \times 20$ L). The resulting pale-yellow solid was dried in a vacuum oven for 24 h at room temperature. The isolated yield was 90% (2.03 kg), the purity of **2** (lobeglitazone sulfate) was >98.5% (containing 0.35% impurity **13** by HPLC analysis), and the contents of residual solvents in this final material were 3900 ppm of isopropyl ether, 86 ppm of EtOH, and 480 ppm of MeOH (by GLC head space method). Silica gel TLC $R_f = 0.35$ (detection: iodine char chamber, ninhydrin solution, developing solvents: $CH_2Cl_2$/MeOH, 20:1); mp 111.4 °C; IR (KBr) $\nu$ 3437, 3037, 2937, 2775, 1751, 1698, 1648, 1610, 1503, 1439, 1301, 1246, 1215, 1183 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 3.09 (m, 4H), 3.29 (m, 1H), 3.76 (s, 3H), 3.97 (m, 2H), 4.14 (m, 2H), 4.86 (m, 1H), 6.06 (bs, 1H), 6.86 (m, 2H), 7.00 (m, 2H), 7.13 (m, 4H), 8.30 (s, 1H), 11.99 (s, NH); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 37.1, 38.2, 53.7, 53.8, 56.3, 62.2, 65.8, 86.0, 115.1, 116.0, 123.0, 129.8, 131.2, 145.7, 153.4, 157.9, 158.1, 161.1, 166.5, 172.4, 172.5, 176.3, 176.5; MS (ESI) $m/z$ (M + 1) 481.5; Anal. Calcd for $C_{24}H_{26}N_4O_9S_2$: C, 49.82; H, 4.53; N, 9.68; S, 11.08. Found: C, 49.85; H, 4.57; N, 9.75; S, 11.15.

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