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Articles

Optimization of the Reduction of a 5-Benzylidenethiazolidine-2,4-dione Derivative Supported by the Reaction Response Surface Analysis: Synthesis of Pioglitazone Hydrochloride

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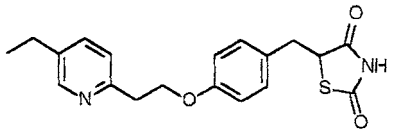
Abstract:

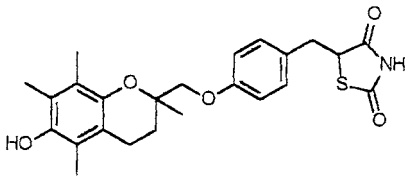
A reaction response surface analysis was applied to a series of experiments carried out under various conditions (temperature, time, amount of a catalyst and reduction reagents, purification of the substrate). Significant improvements were made in the C═C bond reduction in the benzylidene−thiazolidinedione intermediate in the synthesis of pioglitazone hydrochloride.

Introduction

A benzylthiazolidinonedione moiety represents the main common fragment of a class of antidiabetics for the treatment of noninsulin dependent diabetes mellitus (NIDDM),[1] such as pioglitazone (**1a**),[2−4] troglitazone (**1b**),[5] englitazone (**1c**),[6] and rosiglitazone (**1d**),[7−9] which have already been launched as approved drugs or which are still in clinical development.



1a



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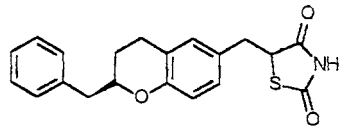

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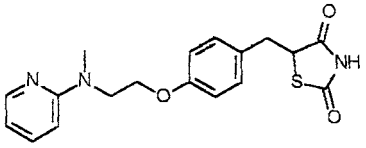
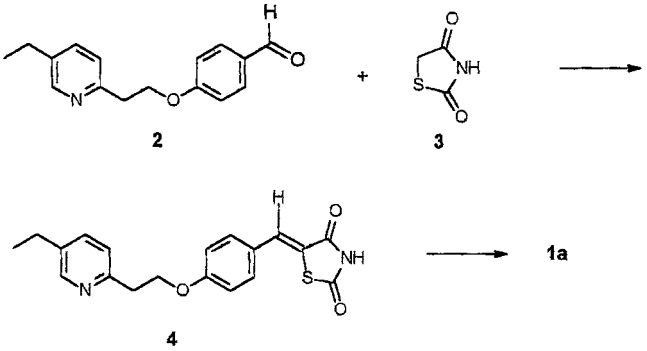


1d

Scheme 1



2 **3** **4** **1a**

Two final steps in the most often used synthetic strategy for the preparation of compounds **1** are exemplified in Scheme 1 by the synthesis of pioglitazone (**1a**). Knoevenagel condensation of the appropriately substituted benzaldehyde **2** with 2,4-thiazolidinedione **3** yields benzylidenethiazolidinedione derivative **4** which on reduction of the C═C bond affords pioglitazone (**1a**).

In the condensation step, the use of pyrrolidine as a catalyst of choice has been amply demonstrated.[15] With pyrrolidine, one can afford the yield of **4** somewhat above 90% and of considerably better purity than in the case of using piperidine. On the other hand, reduction of the double bond in benzylidenethiazolidinedione **4** and its analogues has opened more possibilities and consequently has been studied

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extensively. Accordingly, several methods of the reduction have been reported mostly in the patent literature. They comprise the use of sodium borohydride with cobalt ion complex catalyst,[10,11] lithium borohydride in pyridine,[12] lithium tri-*sec*-butylborohydride,[13] catalytic hydrogenation in the presence of Pd/C [14,15] (in *N*,*N*-dimethylformamide, acetic acid, and dioxane at elevated, i.e., 50−100 °C, temperatures and at a 50 kg/cm^2 pressure for 2 h with the yield of about 63%), $Pd(OH)_2C$,[16,17] or Raney nickel.[18,19] Reduction was also carried out with sodium sulfite,[20] activated aluminum,[21] sodium amalgam[22] as well as by reductive biotransformation.[9,23] Amongst foregoing methods, the procedure based on sodium borohydride and cobalt chloride−dimethylglyoxime ($CoCl_2$−DMG) catalyst emerged as the most convenient, safe, and amenable for scale-up. Therefore, developing laboratory-scale synthetic procedures for the synthesis of pioglitazone (**1a**), we have focused on this method.

Synthesis. Condensation of aldehyde **2** with thiazolidinedione **3** was carried out as recommended in the presence of pyrrolidine in methanol solution proceeded smoothly affording high yield (92%) of crystalline benzylidenethiazolidinedione derivative **4**, which was used in the next step after recrystallization from 1,2-dichloroethane. Reduction of compound **4** with sodium borohydride in the presence of cobalt chloride−dimethylglyoxime ($CoCl_2$−DMG) complex was reported[10] to afford pioglitazone (**1a**) in >90% yield. In our hands the literature procedure (THF/H_2O 1 M NaOH solution at 15 °C for 3 h) gave pioglitazone (**1a**) only in 72% yield and of 96.6% (HPLC) purity, containing >2.5% of staring material **4**. On the other hand, it transpired from the preliminary experiments that the removal of the unreduced material (**4** hydrochloride) from the final product, pioglitazone (**1a**) hydrochloride, by crystallization is cumbersome and gives a low yield. Therefore, to obtain the latter efficiently and the one of pharmaceutical quality, it was essential not only to improve the yield of the reduction step (Scheme 1) but also to drive the reaction to completion, leaving less than 1% of the substrate **4**. To achieve identification of a set of conditions, for this particular transformation, affording product **1a** with high yield and of better than 99% purity, we carried out optimization experiments with reaction response surface techniques.

For the optimization study, literature recipes were adjusted and simplified. THF is commonly used for this type of reduction but was deemed to be unsuitable because of the potential for peroxide formation. After screening several solvents, methanol was substituted for it. It was also noticed that addition of sodium borohydride solution is accompanied only by a small exothermic effect and could be carried out conveniently in one batch. We did not observe any indication of a possible reaction of methanol with $NaBH_4$. A series of experiments was performed under various conditions determined by a suitable choice of temperature, reaction time, amount of catalyst and reduction reagents, as well as purification of a substrate. The results of the experiments were used for the computation of the reaction response surfaces depending on selected process parameters (vide infra). The analysis of these surfaces aimed at identification of the optimal conditions for the reaction studied.

Table 1. **Variables and responses considered and their ranges**

	variables	range
x_1	time (hours)	⟨1;4⟩
x_2	amount of a catalyst (mL)[a]	⟨0,2;5.0⟩
x_3	temperature (°C)	⟨10;50⟩
x_4	amount of $NaBH_4$ [mMol]	⟨8;21⟩
x_5	purified[b] ($x_5 = -1$) or recrystallized[c] ($x_5 = 1$) substrate	{−1,1}
	responses	**range**
y_1	yield (%)	⟨0;100⟩
y_2	impurity level (%)	⟨0;100⟩

[a] Solution of 42 mg of $CoCl_2 \cdot 6H_2O$ and 250 mg of dimethylglyoxime in 5 mL of DMF. [b] Crude **4** was dissolved in a methanol−triethylamine mixture and then precipitated with hydrochloric acid. [c] Crude **4** was recrystallized from 1,2-dichloroethane.

Table 2. **Experimental data[a] used as input for theoretical analysis**

	variable					response	
expt no.	x_1	x_2	x_3	x_4	x_5	y_1	y_2
1	3	1	15	17.6	1	72	0.10
2	3	0.5	15	17.6	1	70	0.88
3	3	1	30	17.6	1	83	0.45
4	3	5	30	17.6	1	80	0.25
5	3	1	45	19.7	−1	69.5	8.5
6	3	0.8	40	15.4	−1	79.4	7.4
7	3	0.3	40	16.8	−1	75.3	8.0
8	3	1.5	50	21.0	−1	71.6	13.2
9	2	1	35	21.0	−1	94.2	3.5
10	3	1	30	8.8	1	74.9	17.3
11	2	1	35	17.6	1	93.7	0.16
12	1	1	40	17.6	1	91.3	0.21
13	1.5	1	40	17.6	1	94.6	0.36

[a] The experimental data expressed in terms of the u_1−u_5 variables (that belong to the ⟨−1;1⟩ interval) are given in the Experimental Section.

Results and Discussion

Our program of work comprised four basic steps presented in chronological order in Tables 1 and 2: (i) preliminary study (experiments no. 1−4), (ii) search for conditions

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appropriate for the use of a more economical substrate (the "purified" form of benzylidenethiazolidinedione **4** is less expensive than its "recrystallized" form, experiments no. 5-8), (iii) experiments (no. 9−11) with a new factor (shorter time of reaction, a factor omitted in experiments no. 1−8) and a trial to reduce the amount of reducing agent ($NaBH_4$), and (iv) final refinement (experiments no. 12 and 13).

A series of experiments started with experiment no. 1 corresponding to process variables described in ref 10. Due to an unsatisfactory yield at our hands ($y_1 = 72\%$), we tried to modify two parameters, i.e., the amount of catalyst (x_2) and the temperature (x_3), expected to be most important. A simple linear regression applied to the logit-transformed y_1 and y_2 responses of experiments no. 1−4 directed us to use considerably higher temperatures in all experiments that followed. In experiments no. 5−8, a more economic substrate (**4**) was used at conditions slightly different from those of experiment no.1 and comprising a variation of three process parameters simultaneously: x_2 , x_3, and x_4 (amount of catalyst, temperature, amount of $NaBH_4$, respectively). From this trial, we deduced that we should go back to the "recrystallized" form of the substrate and search for some other, not yet included process parameter(s) that may have become important. And indeed, in refs 11 and 13, we found a similar reduction reaction conducted in a relatively short time (2 h) that has encouraged us to apply a shorter time of the present reduction step. Rather unexpectedly, we discovered (experiments no. 9 and 11) that by reducing the reaction time to 2 h we got the reaction yield y_1 increased to above 90%. At this point, we constructed two kinds of the response surfaces, i.e., the first one based on the multiple linear regression (MLR) method with a stepwise forward/backward elimination of nonsignificant variables[26] and the second one based on the partial least-squares (PLS) method of projections to latent structures.[25] To establish an approximate functional dependence of reaction yield (%) and impurity level (%) responses, y_1 and y_2, respectively, on the reaction conditions, five independent variables (process parameters), time (x_1), amount of a catalyst (x_2), temperature (x_3), amount of sodium borohydride (x_4), and substrate purification (x_5), were selected. The variables chosen and their minimum and maximum acceptable values are shown in Table 1. The range of parameters corresponds to border values estimated based on our own experience. A scan of the experimental space is summarized in the Table 2. In the present approach, the theoretical analysis is performed after most of the experiments were completed (i.e., the experiments labeled 1−11). Thus, the primary goal would be a prediction of interesting (perhaps larger than those already recognized) regions of experimental space taking into account all the available experimental knowledge. Therefore, our approach constitutes a refinement of experiment rather than construction of the plan of experiment from the very beginning following an elegant mathematical fractional factor design (FFD). A similar approach has been used previously by our team for a design of new experiments and optimization of esterification of terephthalic acid by methanol in industrial reactors[24] (comments in English are available upon request).

In the present approach, a search for a suitable functional form of response surfaces was initiated with a logit-transform of y_1 and y_2 variables in order to ensure that the theoretically predicted values fall into the $\langle 0;100 \rangle$ [%] interval. The logit-transformed responses, $z = \mathrm{logit}(y)$, were approximated with the use of a quadratic form of u_1-u_5 variables:

$$z = b_0 + \Sigma_i b_i u_i + \Sigma_{i \le j} b_{ij} u_i u_j \quad (1)$$

The u-variables that belong to the $\langle -1;1 \rangle$ interval are obtained from x-variables by the so-called orthogonal scaling transformation:[25] $u = (x - M)/R$, where M = midrange and R = range/2. After the right-hand side of eq 1 is established, the theoretical (predicted) y-responses can be obtained via inverse logit-transform of the calculated (predicted) z-responses.

The b-coefficients (eq 1) were calculated with the use of a standard multiple linear regression (MLR) theory supplemented by a procedure of a stepwise forward/backward selection of nonsignificant terms.[26] At the first step of this procedure (forward), candidate terms entered stepwise the linear model equation (eq 1) at the 0.50 significance level. At the second step (backward), from a set of candidate terms, certain terms (not significant at the 0.10 level) were stepwise eliminated while the entire model was refitted. As a result, the following model equations were obtained ($z_i = \mathrm{logit}(y_i)$, $i = 1,2$):

$$z_1 = b_0 + b_1 u_1 + b_{33} u_3^2 \quad (2)$$

$$z_2 = d_0 + d_{45} u_4 u_5 + d_{44} u_4^2 \quad (3)$$

The linear coefficients of eqs 2 and 3 are given in the Experimental Section. The present approach to constructing model equations does not alleviate the significant correlation between u-variables. From the right-hand side of eqs 2 and 3, it can be deduced only that the primary variables determining the reaction yield (y_1) are x_1 (the reaction time) and x_3 (the temperature inside the reactor). The impurity level (y_2) is controlled likely by x_4 (the amount of sodium borohydride) and, to a lesser extent, by the form of a substrate (represented by x_5). The influence of x_2 (the amount of a catalyst) can be disregarded at the 0.10 significance level. An analysis of the y_1 response obtained with the use of eqs 1 and 2 and visualized in Figure 1 also leads us to the conclusion that high yields (y_1 above 95%) can be expected in a narrow region (window) of x_1 (time) and x_3 (temperature): $x_1 < 1.8$ h and 20 °C $< x_3 <$ 40 °C. With the use of eq 3, a low impurity level (y_2 below 1%) is expected for $x_4 > 16$ mmol of $NaBH_4$ (for "recrystallized" substrate **4**, $x_5 = 1$).

For experiments no. 1−11, the y_1 and y_2 response surfaces were approximated also with the use of the partial least-squares (PLS) method of projections to latent structures applied to the z-responses in the form of eq 1. Four independent components (score vectors, being linear combinations of x-variables) were determined by cross validation

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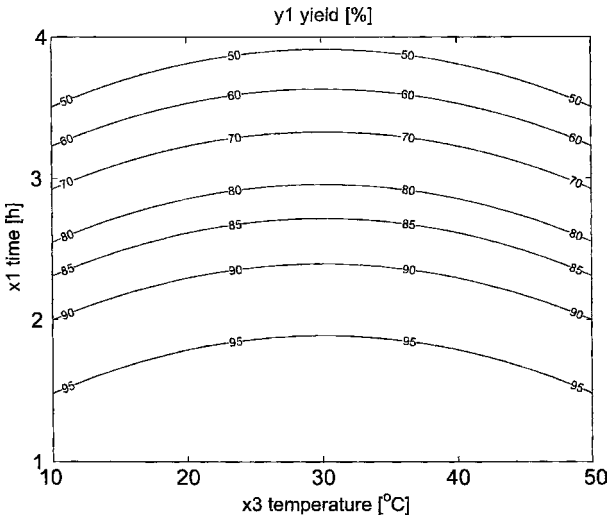

Figure 1. **y_1 (contour plot) based on experiments no. 1−11 (MLR, eqs 1 and 2).**

and by the comparison of the PRESS values (the prediction residual sum of squares computed for each model dimension) with the algorithm implemented in the Modde 6.0 software.

Some features of model y_1 and y_2 surfaces that emerge from the forward/backward MLR approach can be recognized also in the PLS responses. In particular, the y_1 PLS response becomes fairly large for a region corresponding to $x_1 < 2.0$ h and $x_3 > 20$ °C. Another PLS response, y_2 , reveals even broader regions where one can expect the impurity level to be below 1%. The results of the PLS prediction must be viewed with caution due to a possible overfitting and, therefore, can be used as an auxiliary indication in concordance with the MLR prediction that the search for the optimal condition should be continued for relatively short reaction times (somewhat below 2.0 h) and at elevated temperatures (above 20 °C). Taking into account rather difficult experimental conditions of the reaction at low temperature (solubility problems occur at temperatures below 30 °C), one should conduct the reaction above 30 °C. In fact, reduction of **4** performed in the course of two additional experiments (entries no. 12 and 13 in the Table 2) according to the suggested conditions yielded pioglitazone (**1a**) in 94.65% yield of higher than 99% purity (see Table 2, entry no. 13) contaminated only by 0.36% of substrate **4**. Moreover**,** from the sample of pioglitazone (**1a**) of such purity, its hydrochloride of pharmaceutical quality (*high purity*) was readily obtained (see Experimental Section). A repetition of the PLS calculations for y_1 and y_2 including all 13 experiments lead to the reaction response surfaces y_1 and y_2 presented in Figures 2−4. From Figures 2 and 3, it is clearly seen that the optimal conditions should correspond to the reaction time of about 1.5−2.0 h and the temperature of about 40−45 °C, i.e., to the conditions sampled already at the experiment no. 11 (Table 2). As seen from Figure 4, the reaction conditions corresponding to high reaction yield simultaneously correspond to a low impurity level. The results presented in Figures 2 and 3 constitute an indication that no further improvement of the reaction yield is expected. In the course of the experiments conducted at the elevated temperatures (40−50 °C), we observed a significant foaming of the

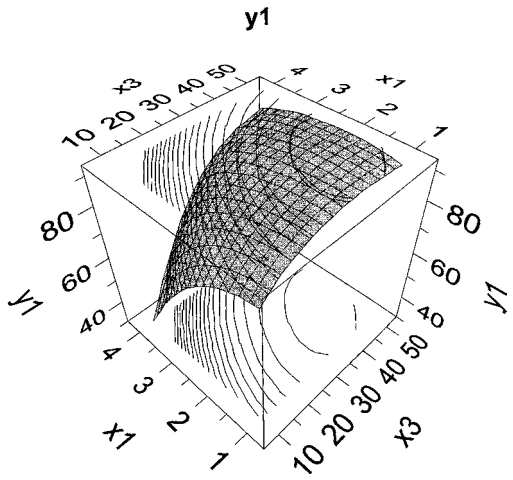

Figure 2. **y_1 (3D plot) based on experiments no. 1−13 (PLS, $x_2 = 1$, $x_4 = 17.6$, $x_5 = 1$).**

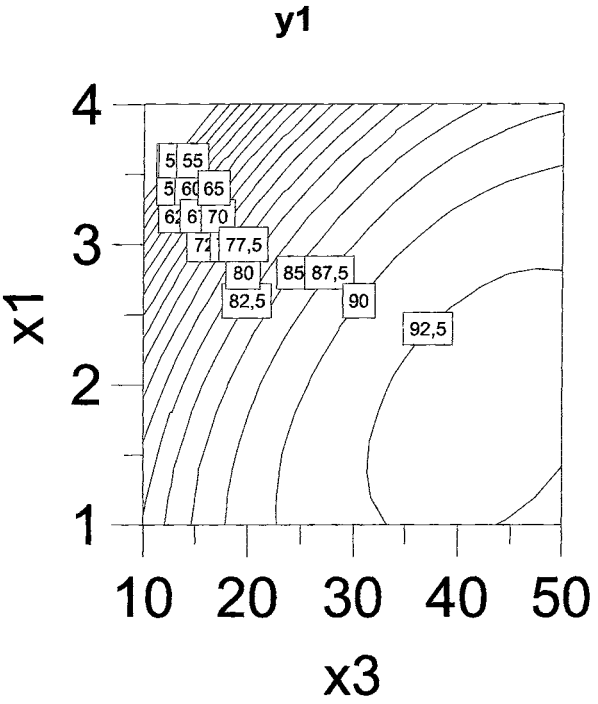

Figure 3. **y_1 (contour plot) based on experiments no. 1−13 (PLS, $x_2 = 1$, $x_4 = 17.6$, $x_5 = 1$).**

reaction mixtures that becomes unacceptable for the future large-scale synthesis. Thus, we can argue we encountered a new experimental factor (i.e., foaming) that should be included when planning scale amplification of the present process.

Conclusions

It has been demonstrated that a scan of experimental conditions (process parameters), supported by the subsequent analysis of the reaction response surface, allows us to identify the regions of optimal conditions for the given transformation efficiently and can be used as the method for testing the results of the optimization process. The present approach allowed us to increase the reaction yield for the reduction of the benzylidenethiazolidinedione derivative from 72% to about 95% and to obtain the product of the purity above 99%.

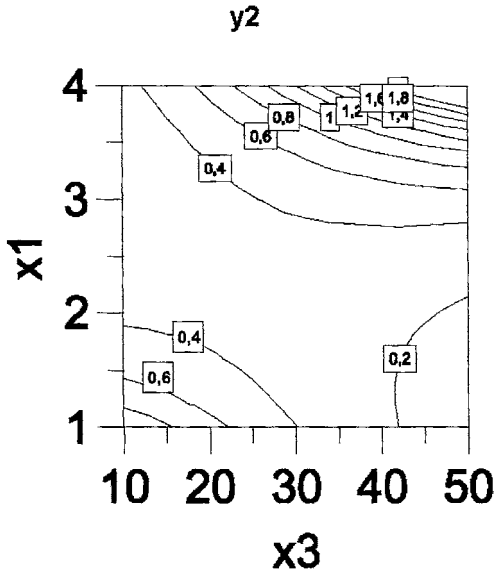

Figure 4. **y_2 (contour plot) based on experiments no. 1−13 (PLS, $x_2 = 1$, $x_4 = 17.6$, $x_5 = 1$).**

Table 3. **Experimental data expressed in terms of the u_1−u_5 variables**

	variable					response	
expt no.	u_1	u_2	u_3	u_4	u_5	y_1	y_2
1	0.333	−0.667	−0.75	0.477	1	72	0.1
2	0.333	−0.875	−0.75	0.477	1	70	0.88
3	0.333	−0.667	0	0.477	1	83	0.45
4	0.333	1	0	0.477	1	80	0.25
5	0.333	−0.667	0.75	0.8	−1	69.5	8.5
6	0.333	−0.75	0.5	0.138	−1	79.4	7.4
7	0.333	−0.958	0.5	0.354	−1	75.3	8
8	0.333	−0.458	1	1	−1	71.6	13.2
9	−0.333	−0.667	0.25	1	−1	94.2	3.5
10	0.333	−0.667	0	−0.877	1	74.9	17.3
11	−0.333	−0.667	0.25	0.477	1	93.7	0.16
12	−1.000	−0.667	0.5	0.477	1	91.26	0.21
13	−0.667	−0.667	0.5	0.477	1	94.65	0.36

Experimental Section

General Procedures. Commercially available solvents and reagents were used without further purification. Reversed-phase HPLC elutions were performed on a Phenomenex Synergi Max RP (150 × 4.6 mm^2) column with acetonitrile−water mixtures. TLC chromatography was performed on silica gel 60 F_{254} Merck plates. ^{1}H NMR spectra were recorded on a Varian-GEMINI 200 MHz spectrometer with TMS as internal standard in DMSO-d_6 solution. Chemical shifts are reported in δ scale (ppm). Mass spectra were measured on an AMD 604 mass spectrometer. IR spectra were recorded on a Perkin-Elmer FTIR 1725X spectrometer in KBr pellets. Melting points were determined in open capillaries and are uncorrected.

Computational Section. The experimental data expressed in terms of the u_1−u_5 variables are given in Table 3. The u_1−u_5 variables are obtained from x-variables by an orthogonal scaling,[25] $u = (x - M)/R$, where M = midrange and R = range/2. The linear parameters, b and d, of eqs 1 and 2, respectively, are estimated to be $b_0 = 0.90$, $b_1 = -0.95$, $b_{33} = -0.25$; $d_0 = -1.40$, $d_{45} = -1.75$, $d_{44} = -1.43$. The z-response is related to the y-response by the following logit-transform: $z = 10 \log(y/(100 - y))$. The b- and d-coefficients were obtained with the multiple linear regression (MLR) theory[26] with a stepwise selection of terms significant at the $\alpha = 0.50$ level (forward step, to collect candidate terms) and at the $\alpha = 0.10$ level (backward step, to eliminate nonsignificant terms, refitting the model equations for each set of candidate variables). The partial least squares (PLS) method of projections to latent structures[25] was applied to the y_1 and y_2 responses expressed in terms of all linear and quadratic terms of x_1−x_5 variables (x_5^2 term was not included) by means of four components (score vectors) when applied to experiments no. 1−11 and six components (score vectors) when applied to experiments no. 1−13. The number of significant components (latent vectors) was determined by cross validation using the PRESS values (the predictive residual sum of squares). The MODDE 6.0 program[25] selects automatically the number of PLS components that give the smallest PRESS.

Representative Procedure for the Synthesis of 5-{[4-[2-(5-Ethylpyridin-2-ylo)ethoxy]phenyl]methyl}thiazolidine-2,4-dione (Pioglitazone, 1a). To a 500 mL round-bottom flask equipped with a mechanical stirrer was added **4** (15.3 g, 42.4 mmol), water (45 mL), methanol (30 mL), and 1 M sodium hydroxide solution (33,9 mL, 33.9 mmol), and the resultant mixture was stirred for 15 min at ca. 23 °C. Then, 1 mL of the $CoCl_2$−DMG complex solution (42 mg of $CoCl_2 \cdot 6H_2O$ and 250 mg of dimethylglyoxime in 5 mL of DMF) was added, and the stirring was continued. After 15 min, sodium borohydride (2.00 g, 52.89 mmol) in water (45 mL) was added in a single portion. The blue-purple solution was warmed to 35 °C and stirred for 3 h. Then the reaction mixture was cooled to room temperature and brought to pH 6−7 with 1 M hydrochloric acid (70 mL), and the deposited precipitate of **1a** was filtered off. Crude product **1a** was dissolved in methanol (60 mL) and 1 M sodium hydroxide (45 mL), treated with active carbon, filtered through a Celite pad, precipitated with 1 M hydrochloric acid (45 mL), and filtered off. The solid was washed with water (60 mL) and cold methanol (60 mL) and dried to give pioglitazone (**1a**) (12.7 g, 83% yield of 99.16% (HPLC) purity) (cf. Table 2, entry 3); mp 174.3 °C (lit.[14] mp 173−174 °C). ^{1}H NMR (DMSO-d_6, TMS, 200 MHz) δ (ppm): 1.18 (t, 3H, $J = 7.6$ Hz), 2.59 (q, 2H, $J = 7.6$ Hz), 3.00−3.35 (m, 4H), 4.30 (t, 2H, $J = 6.6$ Hz), 4.85 (dd, 1H, $J_1 = 9.0$, $J_2 = 4.4$ Hz), 6.86 (d, 2H, $J = 8.6$ Hz), 7.14 (d, 2H, $J = 8.6$ Hz), 7.27 (d, 1H, $J = 7.9$ Hz), 7.56 (dd, 1H, $J_1 = 7.9$, $J_2 = 2.4$ Hz), 8.36 (d, 1H, $J = 2.0$ Hz), 12.00 (bs, 1H) (lit.[15]). IR (KBr) ν cm^{-1}: 1706, 1515, 1254.

Pioglitazone (1a) Hydrochloride. To a suspension of pioglitazone (**1a**) (4.0 g, 11.2 mmol) obtained in the optimized experiment (see Table 2, entry 12) in methanol (10 mL) concentrated hydrochloric acid (1.03 mL, 12.3 mmol) in methanol (10 mL) was added, and the mixture was stirred at room temperature until a clear solution resulted. Then propan-2-ol (20 mL) was added; the mixture was stirred for 2 h at room temperature and left for 18 h at 4 °C. The deposited solid was filtered off, washed with cold methanol (5 mL), and dried (60 °C, 24 h) to afford the first crop of

pioglitazone hydrochloride (**4**) (3.36 g, 76% yield) of 99.85% (HPLC) purity. Crystallization from methanol−propan-2-ol (1:1, v/v), mp 191 °C (dec). ^{1}H NMR (DMSO-d_6, TMS, 200 MHz) δ (ppm): 1.23 (t, 3H, J = 7.7 Hz), 2.77 (q, 2H, J = 7.7 Hz), 3.05 (dd, 1H, J_1 = 14.1, J_2 = 9.0 Hz), 3.29 (dd, 1H, J_1 = 14.1, J_2 = 4.4 Hz), 3.47(t, 2H, J = 6.2 Hz), 4.39(t, 2H, J = 6.2 Hz), 4.87 (dd, 1H, J_1=8.8, J_2=4.4 Hz), 6.87 (d, 2H, J = 8.6 Hz), 7.14 (d, 2H, J = 8.6 Hz), 7.96 (d, 1H, J = 8.2 Hz), 8.40 (dd, 1H, J_1 = 8.2, J_2 = 2.0 Hz), 8.72 (d, 1H, J = 2.0 Hz), 12.04 (s, 1H) (lit.[15]). Anal. HRMS (LSIMS-(+)): calcd for $C_{19}H_{21}N_2O_3S$, 357.12729; found, 357.12736; m/z 357 $[M + H]^+$. IR (KBr) ν cm^{-1}: 1743, 1693, 1511, 1244. Anal. Calcd for $C_{19}H_{21}N_2O_3SCl$ (392.90): C, 58.08; H, 5.39; N, 7.13; S, 8.16; Cl, 9.02. Found: C, 57.89; H, 5.37; N, 7.12; S, 8.13; Cl, 8.90.

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