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The development of improved syntheses of PPARγ-sparing, insulin sensitizing thiazolidinedione-ketones

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ABSTRACT

Ketones **2** (**MSDC-0160**) and **3** (**MSDC-0602**) had been selected for clinical development, however their initial syntheses were considered suboptimal for application deep into clinical trials. Difficulties ranging from the nature of the starting material, alcohol oxidation problems, epoxide opening regioisomeric issues, and endgame ketone redox problems had been encountered. Direct ketone introduction/maintenance was desired for maximum efficiency and convergence was found to be critically dependent upon the acidity of the nucleophilic species (**13**, **18**) and the use of pre- or post-alkylative oximino-ether/oxime protection (*vide infra*). Improvements in overall yield for the syntheses of **2** (**MSDC-0160**) and **3** (**MSDC-0602**) from 20% (**2**) and 31% (**3**) respectively, to 44% (**2**) and 59% (**3**) were realized.

Introduction

Novel thiazolidinediones (TZDs) are now undergoing clinical development in multiple therapeutic areas based on their ability to reduce insulin resistance and metabolic dysfunction [1]. These new analogs have been designed based on the developing understanding that pharmacology against metabolic dysfunction is mediated by attenuation of pyruvate uptake through the mitochondrial pyruvate carrier (MPC); this recent understanding has opened up an alternate route into new insulin sensitizers [1,2]. We have summarized the medicinal chemistry approach to limit direct binding to the nuclear receptor PPARγ [3], which is known to drive dose-limiting side effects of the first generation TZDs. These efforts took advantage of the fact that marketed drug pioglitazone **1** (Actos®, Fig. 1) was known to be effective as anti-diabetic drug both in terms of treating the symptoms of diabetes and, more importantly, in reducing adverse cardiovascular outcomes; however, the use of pioglitazone is still limited by its additional effect of directly activating PPARγ, which drives the dose-limiting side effects of volume expansion, edema, and bone loss [4]. We reasoned that it made sense to look for modest changes in a proven structure that would maintain the interaction with the recently identified MPC and minimize interaction with the nuclear receptor. Several approaches were undertaken including introduction of polar substituents, but the successful effort involved introduction of a ketone functionality [3] and in the progressions of two clinical candidates shown in Fig. 1. Both of these clinical candidates have been shown to be stereoselectively converted to alcohol metabolites that also spare the direct activation of PPARγ [1,3,5]. Compound **1** (MSDC-0160) is progressing through clinical development as a potential treatment of neurodegeneration [6–8] and compound **2** (MSDC-0602) is currently in clinical development as a potential treatment for non-alcoholic steatohepatitis (NASH) [9,10].

As ketones **2** and **3** progressed into development we examined the fitness of the initial synthetic processes and found them wanting. Scheme 1 depicts the original synthesis of **2** which utilized pioglitazone as the starting material [11]. Pioglitazone **1** was oxidized (MCPBA) to afford the related N-oxide (**4**, 96%) which was smoothly rearranged and hydrolyzed to give the racemic hydroxyl compound **5** (74%), setting the stage for a simple benzylic alcohol oxidation to provide the target ketone **2**. That oxidation proved to be somewhat problematic with a wide variety of standard oxidation conditions [12a] leading to low yields and the production of considerable impurities. The modified DMSO/P_2O_5 oxidation reported by Taber [11,12b] resulted in a good yield (88%) of **2**.

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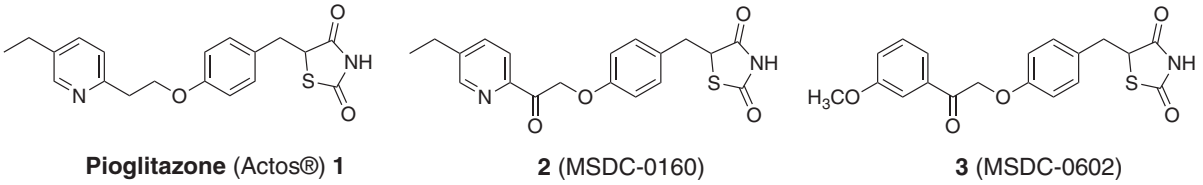
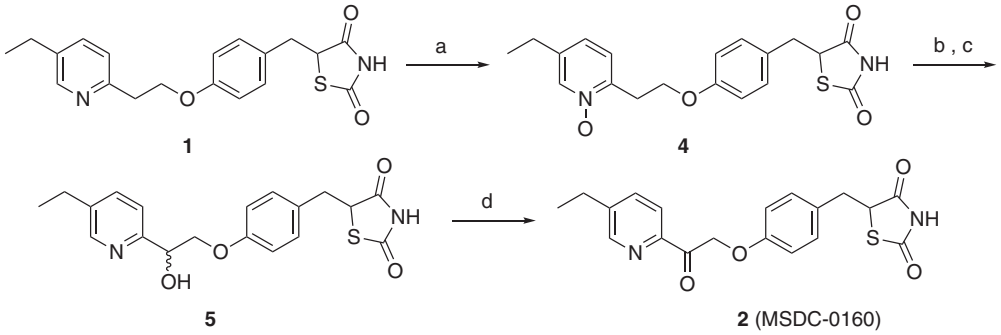


Fig. 1. Structures of Pioglitazone and Clinical Candidates **2** and **3**.



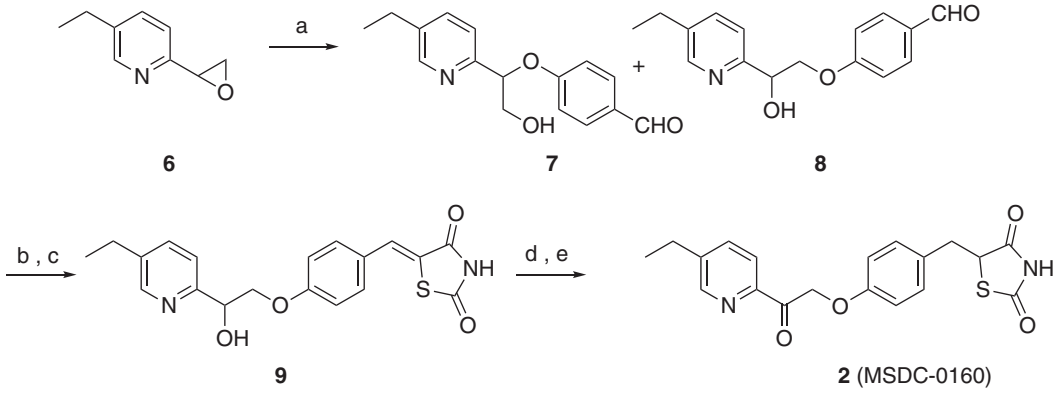
Scheme 1. (a) MCPBA, CH_2Cl_2, 96%; (b) TFAA, CH_2Cl_2, Δ; (c) aq. $NaHCO_3$, THF, 74%; (d) DMSO, P_2O_5 Et_3N, CH_2Cl_2, 88%.

An approach, starting from the pyridyl epoxide **6**, was the first synthesis to afford large quantities of **2** without starting from pioglitazone **1** (Scheme 2) [13]. Treatment of the epoxide with the sodium salt of 4-hydroxybenzaldehyde (phase transfer water-toluene, PEG 4000) gave (60%) a 1:4 mixture of **7** and **8**. Knoevenagel condensation with 2,4-thiazolidinedione afforded a mixture of **9** and the Knoevenagel product of **7**, leading to alcohol **9** (56%) after trituration with methanol. Alcohol **9** was transformed to ketone **2** upon cobalt mediated reduction [11] followed by an application of the Taber [11,12b] oxidation conditions. An overall yield of ca. 20% was realized, however the epoxide **6** is not readily available and its synthesis requires 4 steps from 2-methyl-5-ethyl pyridine.

Scheme 3 outlines our initial, more direct approach to ketone **3** [3]. Direct ketone introduction was accomplished by an alkylation of the readily available 3-methoxy-phenacyl bromide **10** to give **11** (62%). Knoevenagel condensation afforded **12** (76%), which, as expected, suffered double reduction when exposed to the conjugate reduction conditions to give **13** (85%). Benzylic alcohol oxidation in this non-pyridyl molecule was more readily accomplished with IBX to provide **3** (77%). An overall yield of 31% was realized in the Scheme 3 approach wherein the ketone was directly introduced.

The syntheses presented in Schemes 2 (for **2**) and Scheme 3 (for **3**) had been utilized to provide clinical supplies to date. As we anticipated possible transition into Phase 3 clinical development, we felt that these routes presented issues which would make further scale-up difficult. The direct ketone introduction in Scheme 3 is noteworthy, however Scheme 3 does not deal with the undesired reduction of an installed ketone and a subsequent re-oxidation, resulting in a modest 31% overall yield. Improved syntheses of **2** and **3** must be higher in yield, they should be more convergent, and direct ketone introduction would be desirable as long as we avoid ketone red-ox in the end game. Success in these endeavors would enable facile production of needed clinical supplies.

More concise syntheses of **2** and **3** might result if a reduced 5-(4-hydroxybenzyl)-2,4-thiazolidinedione [14] *right-hand half* moiety **14** could be directly alkylated with a phenacylhalide such as the commercially available 3-methoxy-phenacyl bromide **10** of Scheme 3, leading directly to **3**, or 2-bromo-1-(5-ethyl-2-pyridinyl)-ethanone **15**, not reported before these studies, which would afford **2** as shown in Scheme 4.



Scheme 2. (a) NaOH, 4-HO-PhCHO, $PhCH_3$, PEG 4000 60% **7**:**8** 1:4; (b) 2,4-thiazolidinedione, pyrrolidine, CH_3OH, Δ; (c) separate, 56%; (d) $CoCl_2$-$6H_2O$, dimethylglyoxime, $NaBH_4$, THF, aq. NaOH; (e) P_2O_5, DMSO, Et_3N, CH_2Cl_2 75%

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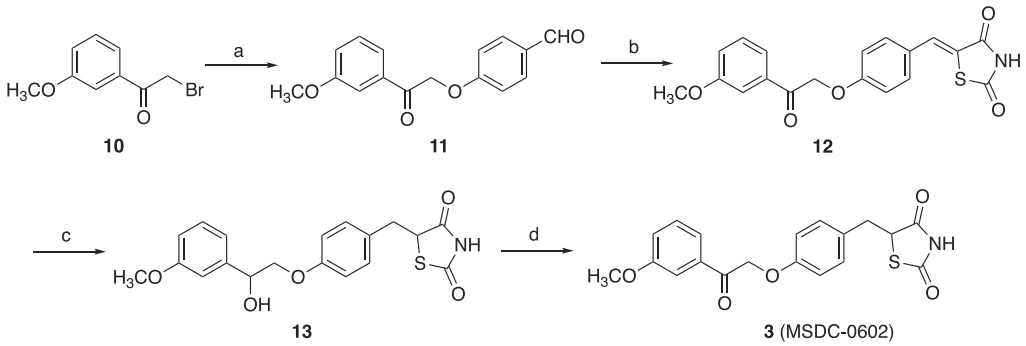
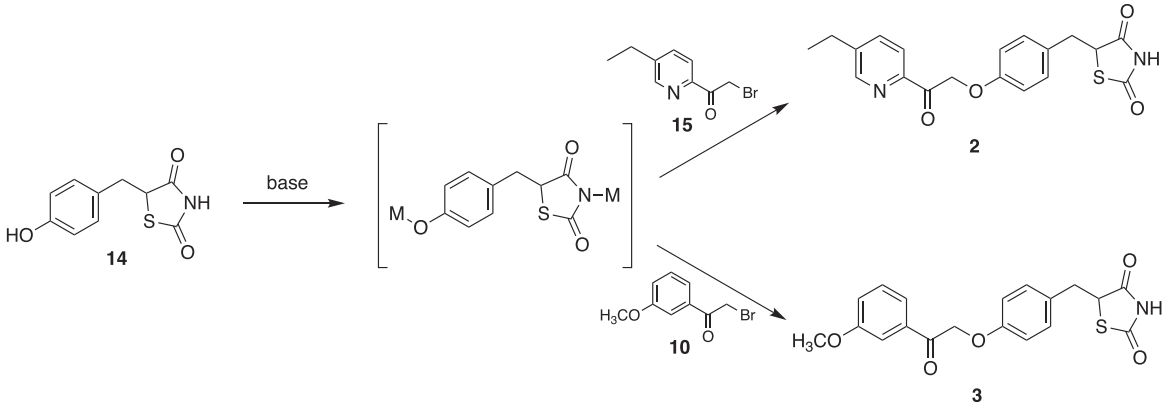
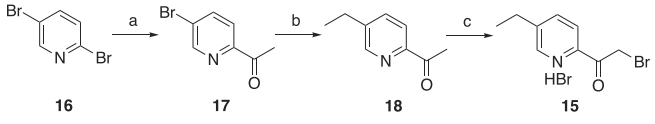


Scheme 3. (a) 4-HO-benzaldehyde, K_2CO_3, acetone 62%; (b) 2,4-thiazolidinedione, piperidine, abs. EtOH, Δ, 76%; (c) $CoCl_2$-$6H_2O$, 2,2′-bipyridine, 1 N aq. NaOH, THF, $NaBH_4$ 85%; (d) IBX, EtOAc, Δ, 77%



Scheme 4. An idealized convergent approach to **2** and **3**.



Scheme 5. (a) i. *n*-BuLi, $PhCH_3$, −40 °C, ii. N,N-dimethylacetamide, 80%; (b) $PdCl_2$-DPPF, Et_2Zn, dioxane, 50 °C, 88%; (c) Br_2, HBr-HOAc, 80%.

The required 2-bromo-1-(5-ethyl-2-pyridinyl)-ethanone **15** was prepared as shown in Scheme 5 [15]. 2,5-Dibromopyridine **16** is selectively lithiated (*n*-BuLi) at the 2 position and reacted with dimethylacetamide to afford **17** (80%) [16]. The 5-position ethyl is then installed by a palladium mediated reaction with Et_2-Zn [17] to give **18** and then bromination (Br_2, HBr/HOAc) provides the HBr salt of the desired pyridyl bromoketone **15** (80%) [18].

The direct coupling of phenacyl halides with 5-(4-hydroxybenzyl)-2,4-thiazolidinedione **14** (c-pKa = 6.38 (TZD) and 9.92 (phenol), calculated in water) [14,19] will require the proper selection of reaction conditions in order to promote O- *vs* N-alkylation. A brief base survey, using the commercially available **10**, was performed to set the conditions for the chemistry of Scheme 6. As illustrated, by the graphic in panel A, (Scheme 6) **14** was exposed to a variety of base/solvent conditions: 2 eq. K_2CO_3 in DMSO (N-alkylation), 2 eq. KOH in EtOH (decomposition, N-alkylation), phase transfer conditions (NaOH, *n*-Bu_4NBr, $PhCH_3$; decomposition), and 2 eq. of KOtBu in DMSO (15–30% **3**). These results suggested that the stronger base system KOtBu/DMSO, to insure complete deprotonation of **14**, was needed for the chemistry of Scheme 6. When **15** free base was employed as the electrophile in Path A, Scheme 6, with KOtBu in DMSO as the base/solvent system, poor 0–20% yields of **2** were observed with extensive decomposition of the more reactive **15** observed. When the more acidic phenol **19** [14,19] (c-pKa = 9.14, calculated in water) was employed in this reaction (Scheme 6, panel B), a good yield (85%) of **12** (Scheme 3) was obtained and a poor yield of **20** in the pyridyl series (0–20%), again with extensive decomposition of **15**, was realized.

Clearly, the acidity of the phenol had a major impact on the alkylation in the phenyl series.

As shown in Scheme 6 (panel A and B), the reactivity of the pyridyl-phenacyl bromide precluded a successful alkylation. As the reactions shown in Scheme 6 are conducted in DMSO, a pKa comparison of the phenol nucleophiles employed (**14** and **19**) and the electrophiles utilized (**10** and **15**) will assist in our analysis of the Scheme 6 data. 4-Methylphenol has a reported DMSO pKa = 18.9 [20a] suggesting the pKa of **14** in DMSO should be approximately 18.9, with no direct DMSO comparator for **19**, the Δ value for the water calculated pKa value (ca. 0.8) will be applied to suggest a DMSO pKa = 18.1 for **19**. The DMSO pKa values for **10** and **15** were suggested by the DMSO pKa of 3-methoxy-acetophenone (24.5) [20b], 2-acetyl-pyridine (DMSO pKa = 23.6) [20c], and 2-fluoro-1-phenylethanone (DMSO pKa = 21.7) [20c]. Assuming that the reduction in measured pKa from 3-methoxy-acetophenone (24.5) to 2-fluoro-1-phenylethanone (DMSO pKa = 21.7), ca. 3 pK units, can be applied to **10**, a suggested pKa = 21.7 results. Similarly, the 2-acetyl-pyridine (DMSO pKa = 23.6) conversion to **15** leads to a projected DMSO pKa = 20.6. These calculated and suggested pKa values suggest proton transfer and decomposition as an issue for **15** (DMSO pKa = 20.6) with phenols **14** (DMSO pKa = 18.9) and **19** (DMSO pKa = 18.1), while the larger spread in DMSO pKa values for **19** (DMSO pKa = 18.1) and **10** (DMSO pKa = 21.7) allows a successful alkylation leading to **12** in 85% yield.

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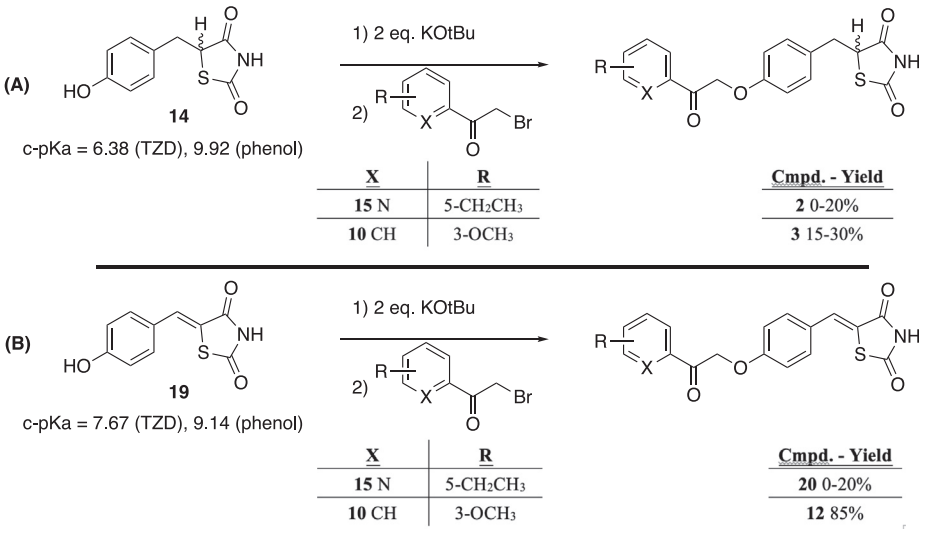
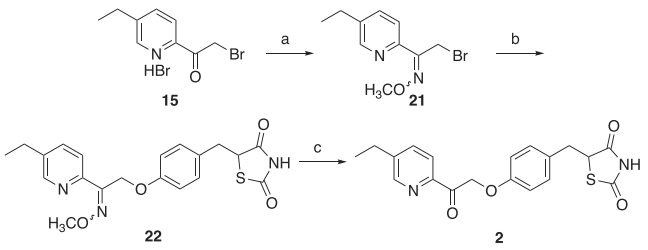


Scheme 6. More convergent synthetic studies. Impact of nucleophile acidity.



Scheme 7. (a) i. CH_3ONH_2-HCl, EtOH, ii. aq. $NaHCO_3$, 85%; (b) i. 14, 2 eq. KOtBu, DMSO, ii. **21**, 74%; (c) 6 N aq. HCl, pyruvic acid, Δ, 70%.

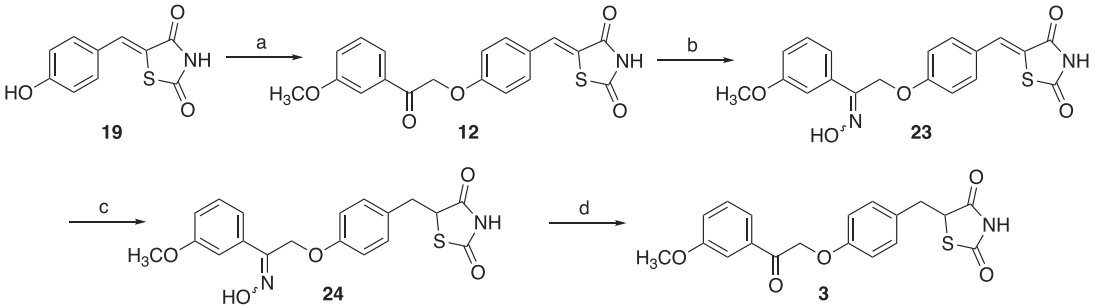
These outcomes render the direct Scheme 6, Panel A approach non-operative as depicted. As an alternative we considered the potential utility of a pre-alkylation protection/stabilization in the pyridyl **15**) series to prepare **2**, and a post-alkylation protection/deprotection (Scheme 5, Panel B), avoiding the Scheme 3 type red-ox protocol to achieve a synthesis of **3**.

Prior utilization of a phenacyl bromide protected as an O-methyl-oxime in a phenol alkylation [21] suggested the potential of that blocking group for the present issue. In the event, bromide **15** (Scheme 7) was reacted with CH_3ONH_2-HCl in ethanol to provide the relatively stable methoxime **21** (85%) after neutralization. The reaction of **21** with the dianion of **14**, in DMSO, proceeded smoothly to give **22**, a protected variant of **2**, in 74% yield, a dramatic improvement over the results presented in Scheme 6. After some experimentation, a mixture of pyruvic acid [22] and 6 N aq. HCl at 75 °C was found to efficiently cleave the methoxime, giving **2** in 70% yield, 44% overall from **21**.

The success (Scheme 6 – Panel B) of the coupling of **19** with 3-methoxy-phenacyl bromide **10** to give **12** suggested that a post-alkylative transitory carbonyl protection might facilitate a more convergent synthesis of **3**. Toward that end (Scheme 8) we elected to examine the utility of a standard oxime as the blocking function. As alluded to in Scheme 6, Panel B, the alkylation of **19** with 2-bromo-1-(3-methoxyphenyl)-ethanone **10** proceeds smoothly (KOtBu) to give **12** in 85% yield. The oxime blocking group is easily introduced ($HONH_2$-HCl, THF, DMF) to afford **23** (93%) and this function remains intact during the cobalt mediated conjugate reduction, leading to **24** in 90% yield. Acidic hydrolysis then affords **3** (83%), with an overall yield of 59% (*vs* 31% in Scheme 3) for the more convergent Scheme 8 approach.

Conclusion

Convergent and efficient syntheses of the clinical candidates **2** (MSDC-0160) and **3** (MSDC-0602) were realized after careful consideration/pairing of the c-pKa of the thiazolidinedione right hand half entities **14** and **19** with either a methoxime-blocked pyridyl phenacyl halide **21** (paired with **14** leading to **2**) or a phenacyl halide **10** (paired with **19** leading to **3**). Judicious use of pre-alkylative or post-alkylative ketone protection led to improved syntheses of **2** (20%–44%) and **3** (31%–59%), potentially setting the stage for more facile syntheses of **2** and **3** as clinical development progresses toward Phase 3.



Scheme 8. (a) i. KOtBu, DMSO, ii.**10**, 85%; (b) $HONH_2$-HCl, THF, DMF, 93%; (c) $CoCl_2$-$6H_2O$, 2,2′bipyridyl, $NaBH_4$, 90%; (d) 6 N aq. HCl, THF, Δ, 83%.

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Declaration of Competing Interest

JRC has an interest in Metabolic Solutions Development Co. and in Cirius Therapeutics.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.07.022.

References

[1] J.R. Colca, S.P. Tanis, W.G. McDonald, R.F. Kletzien, Expert Opin. Investig. Drugs 23 (2014) 1–7.
[2] J.R. Colca, Expert Opin. Drug Discov. 2015 (10) (2015) 1259–1270.
[3] S.P. Tanis, J.R. Colca, T.T. Parker, G.D. Artman III, S.D. Larsen, W.G. McDonald, R. C. Gadwood, R.F. Kletzien, J.B. Zeller, P.H. Lee, W.J. Adams, Bioorg. Med. Chem. 26 (2018) 5870–5884.
[4] R.A. DeFronzo, S. Inzucchi, M. Abdul-Ghani, S.E. Nissen, Diabet. Vasc. Dis. Res. (2019) 1–11.
[5] W.J. Adams, H.M. Dotzauer, T. VanNoord, J.R. Colca, 17th North American Regional ISSX Meeting 16-20 October 2011, Abstract – p307.
[6] J.R. Colca, J.T. VanderLugt, W.J. Adams, A. Shashlo, W.G. McDonald, J. Liang, R. Zhou, D.G. Orloff, Clin. Pharmacol. Ther. 93 (2013) 352–359.
[7] R.C. Shah, D.C. Matthews, R.D. Andrews, A.W. Capuano, D.A. Fleischman, J.T. VanderLugt, J.R. Colca, Curr. Alzheimer Res. 11 (2014) 564–573.
[8] E. Quansah, W. Peelaerts, J.W. Langston, D.K. Simon, J. Colca, P. Brundin, Mol. Neurodegener. 13 (2018) 28/1-28/12.
[9] J.R. Colca, W.G. McDonald, W.J. Adams, Expert Opin. Investig. Drugs 27 (2018) 631–636.
[10] J.R. Colca, W.G. McDonald, K.S. McCommis, B.N. Finck, Hepatol. Commun. 1 (2017) 193–197.
[11] S.P. Tanis, T.T. Parker, J.R. Colca, R.M. Fisher, R.F. Kletzien, J. Med. Chem. 39 (1996) 5053–5063.
[12] (a) For a review of oxidation conditions which have been run on process scale (≥100g) see: S. Caron, R.W. Dugger, S.G. Ruggeri, J.A. Ragan, D.H.B. Ripin Chem. Rev. 106 (2006) 2943–2989;
(b) D.F. Taber, J.C. Amedio Jr., K.-Y. Jung, J. Org. Chem. 52 (1987) 5621–5622.
[13] D.E. Carpenter, R.J. Imbordino, M.T. Maloney, J.A. Moselein, M.R. Reeder, A. Scott, Org. Proc. Res. Dev. 6 (2002) 721–728.
[14] T. Storr, D. Mitchell, P. Buglyo, K.H. Thompson, V.G. Yuen, J.H. McNeill, C. Orvig, Bioconj. Chem. 14 (2003) 212–221.
[15] S.P. Tanis, T. Parker, R.C. Gadwood, J.R. Zeller, G.D. Artman III, S.D. Larsen, A process for the preparation of thiazolidinedione derivatives for use as PPARγ receptor modulators WO2012021467.
[16] B. Abarca, R. Ballesteros, R. Ballesteros-Garrido, F. Colobert, F.R. Leroux, Tetrahedron 64 (2008) 3794–3801.
[17] B. Pelcman, A. Sanin, P. Nilsson, T. Groth, H. Kromann, Preparation of pyrazole-3-carboxamide derivatives useful in the treatment of inflammation WO2007051981.
[18] K. Nakao, R.W. Stevens, K. Kawamura, C. Uchida, H. Koike, S. Caron, 2-3-Substituted indole compounds as cox-2 inhibitors WO9935130.
[19] Calculated using ACD Labs Structure Designer V12.0.
[20] (a) F.G. Bordwell, R.J. McCallum, W.N. Olmstead, J. Org. Chem. 49 (1984) 1424–1427;
(b) F.G. Bordwell, F.J. Cornforth, J. Org. Chem. 43 (1978) 1763–1768;
(c) F.G. Bordwell, Acc. Chem. Res. 21 (1988) 456–463.
[21] G.T. Kim, Hee O. Han, J.S. Koh, Seung H. Kim, K.-H. Kim, H.-K. Chung, Ok K. Park, S.K. Jeon, S.H. Woo, H.J. Yim, G.-C. Hur, S.W. Hong, K.D. Koo, C.-S. Lee, M.S. Chang, S.-Y. Koo, H.W. Joo, J.U. Song, S.P. Moon, Song-mi-a, Novel compounds as agonist for PPAR gamma and PPAR alpha, method for preparation of the same, and pharmaceutical composition containing the same WO2007058504.
[22] E.B. Hershberg, J. Org. Chem. 13 (1948) 542–546.

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