Synthesis and Spectral Characterization of Impurities of a COX-2 Selective Drug, Celecoxib

Young Hee Lee,[†,‡,¶] Manjunatha Vishwanath,[‡,¶] Srinu Lanka,[‡] Eunhwa Lee,[†] Yongbin Park,[†] Sunhwan Lee,[†] Jaeuk Sim,[‡] Seohoo Lee,[‡] Kiho Lee,[§] Mayavan Viji,[‡,*] Heesoon Lee,[‡] and Jae-Kyung Jung[‡,*]

[†]*Samjin Central Research Institute, Samjin Pharma Co., LTD, Cheongju 28158, South Korea*
[‡]*College of Pharmacy, Chungbuk National University, Cheongju 28160, South Korea.*
**E-mail: cheviji@gmail.com; orgjkjung@chungbuk.ac.kr*
[§]*College of Pharmacy, Korea University, Sejong 30019, South Korea*
Received March 13, 2019, Accepted March 25, 2019

Keywords: Celecoxib, Impurities, Pyrazole, Active pharmaceutical ingredient, COX inhibitor

Introduction

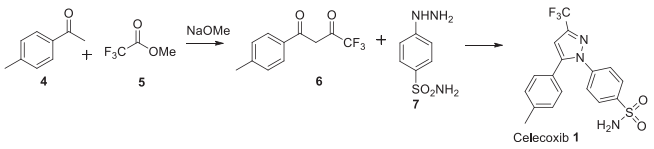
Rheumatoid arthritis is one of the omnipresent autoimmune disorders which leads to bone damage, skeletal disorders, and disability.[1] Celecoxib (**1**) the brand name Celebrex, is a selective cyclooxygenase (COX)-2 inhibitor (coxib) used for treatment of osteoarthritis, rheumatoid arthritis approved by the FDA.[2] Coxibs were developed to provide anti-inflammatory/analgesic activity similar to that of nonselective non-steroidal anti-inflammatory drugs (NSAIDs), but without gastrointestinal toxicity resulting from COX-1 inhibition.[3]

Impurities are the unwanted chemical entities that are formed during the process of synthesizing active pharmaceutical ingredients (APIs) or during formulation of the drug. Even in trace amounts the existence of the impurities may affect the efficacy and safety of the drug. As per guideline on impurities by International Conference on Harmonization (ICH), it is mandatory to identify and characterize all the impurities which are present 0.10% or more.[4] As a part of our continuing research on synthesis of pharmaceutically important molecules, we aimed at synthesis of process impurities of celecoxib.[5] During the HPLC analysis of crude celecoxib, two main impurities have been detected in the range of 0.01-0.15%, which originated from the manufacturing process of API. Initial analysis of HPLC and previous reports suggested that the impurities are the regioisomers of the celecoxib. Few reports are present in literature; however, these methods involve multistep synthesis with low yields and HPLC methods to identify these impurities are scarce.[6]

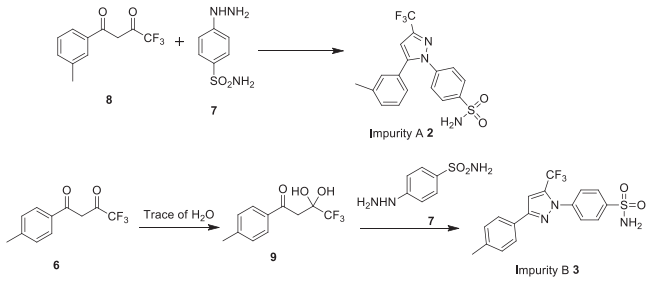
The synthetic strategy which is widely used to synthesize the diarylpyrazole ring of celecoxib as follows, the condensation reaction between hydrazine **7** with 1,3-dicarbonyl compound **6** produce **1** (Scheme 1). One of the demerits of this route was the formation of regioisomeric impurities.[7] Impurity A **2**, regioisomer is believed to originate from a starting material 1,3 dicarbonyl compound **8** (Scheme 2).[8] Whereas the impurity B **3**, formed due to reaction of 1,3 diketone **6** with traces of the water present in the reaction mixture, afforded hydrate **9**, which underwent condensation with hydrazine **7** resulting the impurity B **3** (Scheme 2).[9]

Results and Discussion

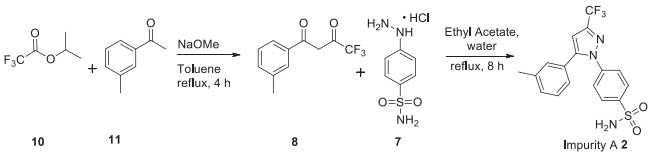
After identifying the cause for the formation of these impurities, we set out our goals to synthesize these molecules. Synthesis of impurity A **2** was achieved by using a twostep straight forward strategy (Scheme 3). Initially isopropyl trifluoroacetate **10** was reacted with 3′-methylacetophenone **11** in toluene with sodium methoxide as a base to afford



Scheme 1. Commercial process for the synthesis of celecoxib (**1**).

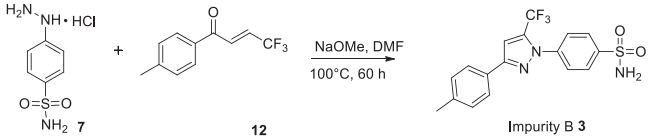


Scheme 2. Pathways for the formation of impurities A (**2**) and B (**3**).



Scheme 3. Synthetic route of impurity A.

[¶]These authors equally contributed in this work.



Scheme 4. Synthetic route of impurity B.

4,4,4-trifluoro-1-(*m*-tolyl)butane-1,3-dione, **8** with a good yield (87%). Further, **8** was added to 4-hydrazinobenzenesulfonamide hydrochloride **7** in ethyl acetate, the impurity A **2** was obtained as white solid (5.15 g) with an excellent yield of 92.0%.

Impurity B was synthesized in a single step by using mild condition (Scheme 4). To a solution of (*E*)-4,-4,4-trifluoro-1-(*p*-tolyl)but-2-en-1-one **12** and 4-hydrazinobenzenesulfonamide hydrochloride **7** in DMF sodium methoxide in methanol was added. After the addition, reaction mixture was heated to 100 °C till the starting materials are consumed. The impurity B **3** was isolated and purified by column chromatography as an off-white solid (120 mg, 22.5%) with high purity. ^{19}F NMR confirms that the impurities were regio-isomers of celecoxib (see supporting information).

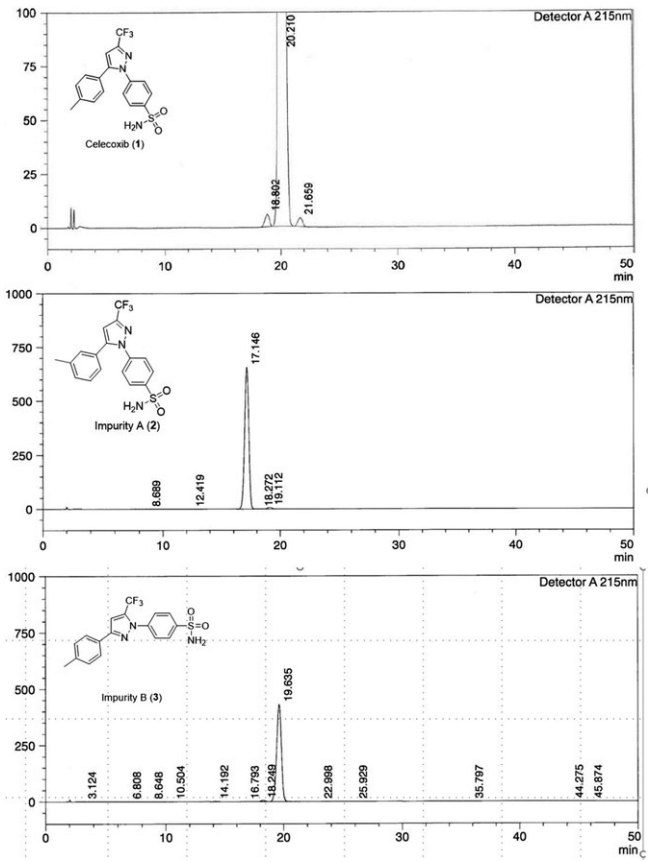


Figure 1. HPLC chromatogram for celecoxib (**1**), impurity **A** (**2**) and impurity **B** (**3**).

HPLC Analysis of the Compounds. The HPLC analysis of crude celecoxib drug in our method showed the targeted impurities were present in trace amounts which were taken up for further HPLC analysis. In the initial analysis, crude celecoxib drug has the assay of 99.12% at retention time of 20.21 min, whereas the impurity A and impurity B were observed at retention times 18.80 and 21.66 min, respectively (Figure 1). HPLC analysis of the impurities synthesized were matched with the impurities in the drug, the synthesized molecules were highly pure with assay of 98.63% and 98.30% for impurity A and impurity B, respectively.

In summary, the origins for the formation of these impurities **A** & **B** during process development were hypothesized, synthesized and characterized in this report; which were obtained with the overall yield of 80% and 23%, respectively. A robust HPLC method also has been developed to calculate the assay of these impurities as 98.6% and 98.3%.

Acknowledgment. This work was supported by the National Research Foundation of Korea grants funded by the Korea Government (MSIP) (MRC 2017R1A5A2015541, and Basic Science Research Program 2017R1D1A1B03) and the International Science and Business Belt Program through the Ministry of Science, ICT and Future Planning (2017K000490). This work was also supported by Post-doctoral Fellowship program funded by the Ministry of Education of the Republic of Korea through the Chungbuk National University in 2018 (M. V).

Supporting Information. Experimental section along with ^{1}H, ^{13}C, ^{19}F NMR, HRMS, and HPLC spectral data are available at the online version of this communication.

References

1. M. Cross, E. Smith, D. Hoy, L. Carmona, F. Wolfe, T. Vos, B. Williams, S. Gabriel, M. Lassere, N. Johns, R. Buchbinder, A. Woolf, L. March, *Ann. Rheum. Dis.* **2014**, *73*, 1316.
2. D. Clemett, K. L. Goa, *Drugs* **2000**, *59*, 957.
3. J. T. Birch, S. Bhattacharya, *Prim. Care Clin. Office Pract.* **2010**, *37*, 779.
4. R. Holm, D. P. Elder, *Eur. J. Pharm. Sci.* **2016**, *87*, 118.
5. Y. H. Lee, M. Viji, E. Lee, H. Jo, K. Yoo, J. Sim, S. Lee, K. Lee, H. Lee, J. K. Jung, *Tetrahedron Lett.* **2017**, *58*, 2614.
6. R. N. Rao, S. Meena, D. Nagaraju, A. R. Rao, S. Ravikanth, *Anal. Sci.* **2006**, *22*, 1257.
7. A. R. Reddy, A. Sampath, G. Goverdhan, B. Yakambaram, K. Mukkanti, P. P. Reddy, *Org. Process. Res. Dev.* **2009**, *13*, 98.
8. Y. Zhang, Y. Cui, L. Chen, Zhongnuo Pharmaceutical Shijiazhuang Co., Ltd., PR China. **2012**, pp. 11.
9. V. M. Muzalevskiy, A. Y. Rulev, A. R. Romanov, E. V. Kondrashov, I. A. Ushakov, V. A. Chertkov, V. G. Nenajdenko, *J. Org. Chem.* **2017**, *82*, 7200.

