The 48 siblings of Ibuprofen

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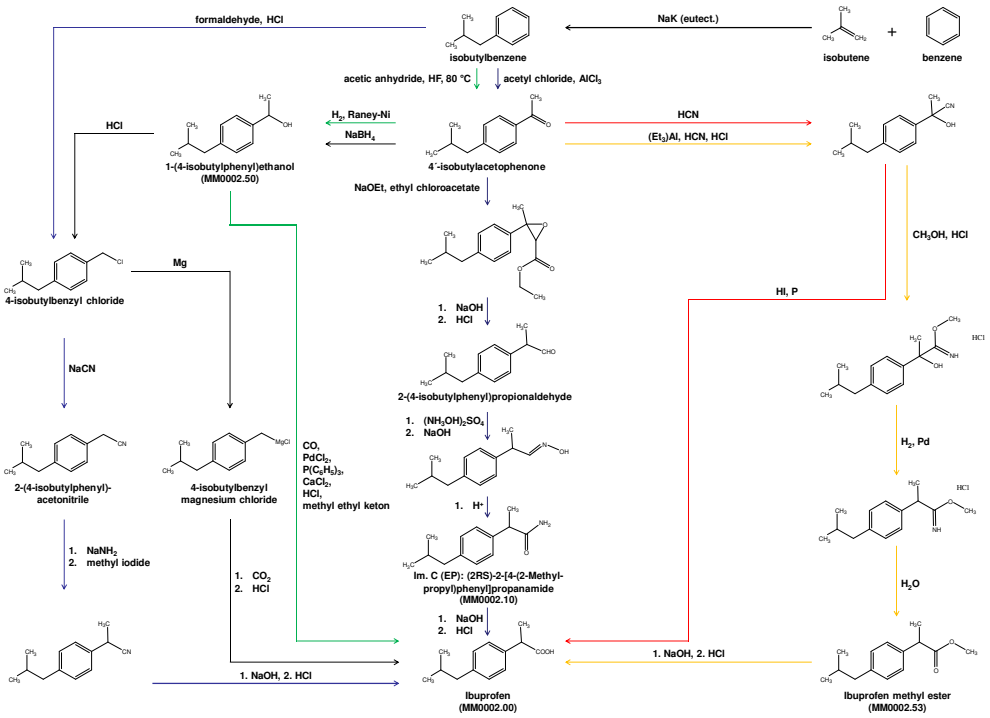
Introduction

Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) that is used for treating pain, fever, and inflammation.[1] It is classed as essential medicine by the World Health Organization, the most effective and safe medicines needed in a health system.[2] Ibuprofen was first synthesised in 1961 by the Boots group (Stewart Adams and John Nicholson) and marketed as Brufen.[3] It is available under a number of trade names, e.g. Aktren, Dolormin, Ibuflam, Nurofen, Brufen, Motrin and others.[4] Like other NSAIDs, it works by inhibiting the production of prostaglandins by decreasing the activity of the enzyme cyclooxygenase.[1]

Synthesis of Ibuprofen

Ibuprofen can be synthesised on various routes as you can see on the scheme below. The historical Boots process is marked blue, whereas the green arrows show the BHC (Boots-Hoechst-Celanese) process which is also an industrial route of synthesis. The ethyl process is illustrated with orange arrows.[4] A laboratory synthesis can be carried out by following the black arrows. Using 4´-isobutylacetophenone as starting material Ibuprofen can be synthesised in three steps, namely the reduction of the ketone with $NaBH_4$, subsequent nucleophilic substitution of the hydroxyl group with hydrochloric acid, and finally a Grignard reaction with CO_2 including acidic hydrolysis.[5]

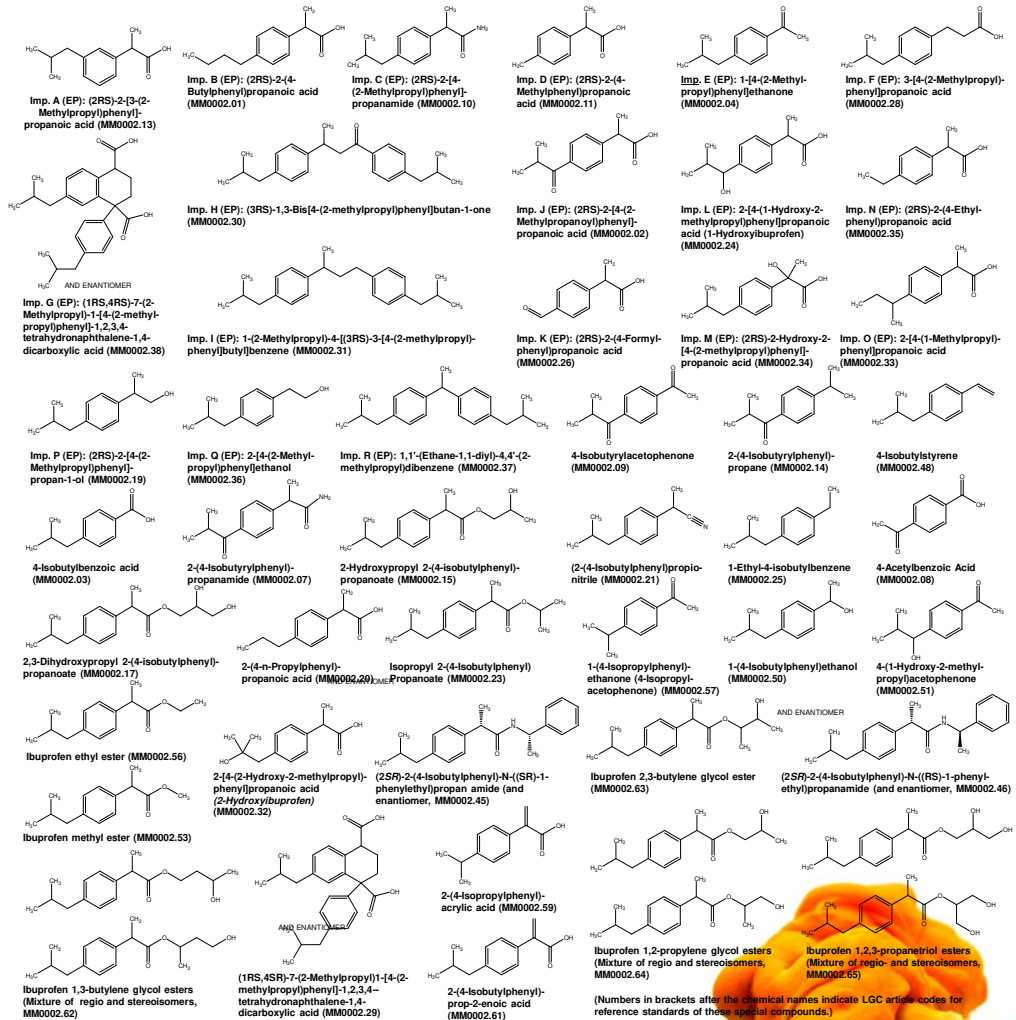


References

[1] Ibuprofen. The American Society of Health-System Pharmacists. Retrieved 2017-08-14.
[2] WHO Model List of Essential Medicines (19th List). *World Health Organization*. April 2015, Amended November 2015, Retrieved 2017-08-14.
[3] Halford, GM; Lordkipanidzé, M; Watson, SP (2012). 50th anniversary of the discovery of ibuprofen: an interview with Dr Stewart Adams. *Platelets*. 23 (6): 415–22.
[4] Kleemann A, Engel J, Kutscher B, Reichert D, Pharmaceutical Substances, Syntheses, Patents and Applications of the most relevant APIs. 5th Edition, 2009, Thieme Verlag, Germany
[5] Kjonaas RA, Williams PE, Counce DA and Crawley LR (2011) Synthesis of Ibuprofen in the Introductory Organic Laboratory, J. Chem. Educ., 88, 825–828
[6] ICH Q3A(R2) Impurities in New Drug Substances. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, October 2006, Retrieved 2017-08-14
[7] ICH Q3B(R2) Impurities in New Drug Products. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, June 2006, Retrieved 2017-08-14

Degradation products and impurities

During production and storage of Ibuprofen and its drug products, plenty of impurities and degradation products can be formed. Below 48 of those are shown. Development, validation and implementation of analytical methods to correctly identify and quantify these compounds is key, to fulfil the relevant ICH guidelines Q3A[6] and Q3B[7]. The use of the reference standards is supporting the fulfilment of these analytical requirements.



(Numbers in brackets after the chemical names indicate LGC article codes for reference standards of these special compounds.)

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