Chapter 3

The role of the enantiomers of ibuprofen and deprenyl in pharmaceutical industry

3.1 Ibuprofen enantiomers

The IUPAC name for ibuprofen is 2-(4-isobutyl-phenyl)-propionic acid. Figure 3.1 depicts a two dimensional structure of ibuprofen. Ibuprofen is an aromatic compound with a *para*-sustituted benzene ring. In the upper right of the structure is a carboxylic acid functional group, specifically a propionic acid. Attached to the second carbon is a phenyl group. Attached to the phenyl group, *para* to the propionic acid group, is an isobutyl group which leads to the beginning of its common name. Ibuprofen is a small organic compound composed of 13 carbon atoms, 18 hydrogen atoms and 2 oxygen atoms.

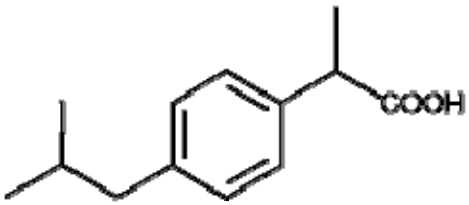
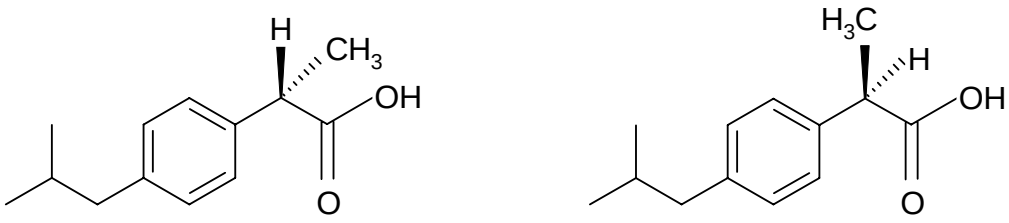


Figure 3.1 Ibuprofen

Ibuprofen, like other 2-arylpropionate derivatives (including ketoprofen, flurbiprofen, naproxen, etc) contains a chiral carbon in the α-position of the propionate moiety. As such there are two possible enantiomers of ibuprofen with the potential for different biological effects and metabolism for each enantiomer. It was found that the S-

enantiomer of ibuprofen was the active form both *in vitro* and *in vivo* [1-3]. However, most of the ibuprofen formulations that are currently marketed are a racemic mixture of both enantiomers (including ibuprofen drug). Figure 3.2 (a) and (b) shows a three-dimensional (3D) representations of S-ibuprofen and R-ibuprofen, respectively.



(a) (b)

Figure 3.2 Ibuprofen enantiomers (a) S-ibuprofen; (b) R-ibuprofen

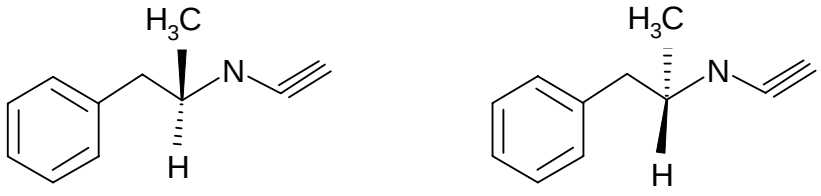
Ibuprofen is a nonsteroidal anti-inflamatory drug (NSAID) that is widely marked under various trademarks including Act-3, Advil, Brufen, Mortin, Nuprin, Nurofen and Myprodol. Ibuprofen is used to relieve the pain, tenderness, inflammation (swelling), and stiffness caused by arthritis and gout. It is also used to reduce fever and to relieve headaches, muscle aches, menstrual pain, aches and pains from the common cold, backache, and pain after surgery or dental work. It was shown that only the S-enantiomer is responsible for the desired therapeutic effects [4], while the R-enantiomer displays toxicity due to its storage in fatty tissue as a glycerol ester, whose long-term effects are not known [5]. Despite this fact, the ibuprofen is currently administered as racemate.

3.1.1 Current analytical methods used for the determination of ibuprofen

Proton-NMR [6] HPLC and GC-MS [7] techniques were used for the identification of ibuprofen and its degradation products of ibuprofen. Novel ibuprofen potentiometric membrane sensors based on tetraphenylporphyrinato indium (III) were developed for use in the quantification and quality control assessment of ibuprofen in pharmaceutical preparations, but not for enantioanalysis of ibuprofen [8].

3.2 Deprenyl enantiomers

Deprenyl, an irreversible inhibitor of monoamine oxidase enzyme (MAO), was first described by Knoll *et al* [9]. R-deprenyl selectively inhibits MAO type B [10,11]. Figure 3.3 (a) and (b) shows 3D structures of R-deprenyl and S-deprenyl respectively.



(a) (b)

Figure 3.3 Enantiomers of deprenyl. (a) R-deprenyl; (b) S-deprenyl

The main metabolites of deprenyl are desmethyldeprenyl, methamphetamine, and amphetamine formed by N-dealkylation [12-15]. R-deprenyl and its metabolites also inhibit the monoamine transpoters in the brain [16-18]. Based on its dopamine sparing effect, S-deprenyl is used worldwide in the treatment of Parkinson `s disease [19], as well as other neurodegenerative disorders. Neuroprotective and neuronal rescue effects of R-deprenyl, unrelated to MAO-B inhibition but also highly stereoselective,

have also been reported [20-25]. Furthermore, R-deprenyl has been found to exert neuroprotection against toxic insult [26-28], as well as have anti-apoptotic [29,30] and anti-tumor effects [31] and, in low concentrations, it has been shown to increase the lifespan of laboratory animals [32,33]. The S-enantiomer has strong psychostimulant effects than the R-enantiomer [34].

3.2.1 Current analytical methods used for the determination of deprenyl

The methods available for determination of deprenyl are based on the enantioseparation of its enantiomers as well as of the metabolits of S- and R-deprenyl. The chromatographic methods proposed for the enantioanalysis of deprenyl are: thin layer chromatography (TLC) [35,36], High performance liquid chromatography (HPLC) [37,38] and capillary electrophoresis (CE) [39,40].

3.3 References

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