



A new concept for controlled release of hydrophobic drugs from water soluble prodrugs

During 2008-2009 YKI has focussed internal resources on development of a concept for controlled delivery and release of hydrophobic substances. The concept can be viewed upon as a prodrug (pro-fragrance/pro-aroma/pro-insecticide) concept, where a water soluble pro-molecule controllably breaks down to the desired compound which is thereby released.

The prodrug concept is **applicable to parent drugs having a ketone function in the molecular structure**, which is the case for at least 5 % of today's commercially available pharmaceuticals, and **allows up to 30 times increased solubility of poorly soluble drugs**.

It has also been demonstrated, for a commercial drug and a model drug, that the corresponding prodrug breaks down into its parent drug in blood at physiological conditions, at a pharmaceutically relevant rate. The water soluble prodrugs are storage stable when stored in the dry state, but breakdown to the desired drug starts immediately upon dissolution in water or in blood.

A patent application has been filed on the technology, covering several areas of use, including release of drugs, fragrances, aromas and insect repellents. The following has been included in the patent application:

- Controlled release of drug molecules, demonstrated in-vitro in blood at physiological conditions
- Several (>100) listed derivatives of known molecules **including e g the two Novartis pipeline molecules Patupilone (EPO906) and Everolimus** and many more (for examples, see Table 1 below). Many of the derivatives are new molecules.
- In-vitro demonstrations showing that solubility of poorly soluble drugs can be increased up to at least 30 times when the drug is present in its proposed prodrug form.
- Demonstration of storage stability of the prodrugs when stored at dry conditions, followed by onset of breakdown after dissolution.

Table 1. Parent-drugs for which prodrug derivatives have been claimed.

Parent drug	Company	Parent drug	Company
Nabumetone	Today generic, originally GlaxoSmithKline	Ebastine	Nycomed
Propafenone1	Abbott	Warfarin	Nycomed
Pentoxifylline1	Aventis	Haloperidol	Janssen-Cilag
Idarubicin	Pfizer	Daunomycin	Sanofi-Aventis
Ketobemidone	Pfizer	Propiomazine	Sanofi-Aventis
Medroxyprogesterone	Pfizer	Rimexolone	Schering-Plough
Megestrol	Bristol Myers Squibb	Everolimus	Novartis
Alclometasone	GlaxoSmithKline	Patupilone	Novartis
Clobetasone	GlaxoSmithKline		

YKI's desire is now to sell or license the technology to relevant partners.

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