NOVEL PRODRUGS OF AMIDE N-H BOND CONTAINING COMPOUNDS

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Many pharmaceutical compounds have physicochemical properties which create barriers to attaining their maximum therapeutic potential. Such adverse properties may be temporarily modified by attaching a promoiety to the compound. The compound-promoiety derivative is called a prodrug which is able to overcome the original barrier. Once the barrier is overcome, the prodrug reverts to the original compound through a process referred to as transformation or reversal.

Pharmaceutical compounds containing one or more N-H bonds tend to be poorly water- and lipid-soluble. In addition, these functional groups may lead to permeability problems and other poor pharmacokinetic and pharmaceutical properties including high polarity. The invention described in the present study is drawn to sulfenamide (N-S bond containing compounds) prodrugs of pharmaceutical compounds containing one or more N-H bonds. The unique utilization of N-S bond chemistry may also provide a means of drug targeting as the reversion of these compounds involves the reaction of the prodrug with free sulfhydryl containing compounds such as glutathione or biological cysteine. A number of aryl/alkyl sulfenyl prodrugs of amide group containing drugs such as acetanilide, linazolid carbamezepine and model amides were synthesized through a simple, novel route by use of Et_3N in the presence aryl/alkyl sulfenyl chloride, the latter being generated *in situ* by the treatment of the corresponding aryl/alkyl disulfides with sulfuryl chloride. The physicochemical properties of the drug linazolid improved upon prodrug formation, where its polarity decreased and oil solubility increased. Upon treatment with cysteine the prodrugs underwent reversion to the drug typically with a half life of 20-30 min.