CHAPTER I

INTRODUCTION

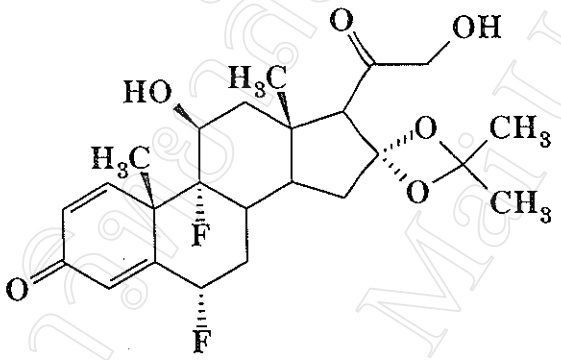
The process of lipid peroxidation initiated by free radical, contributes to cell aging and pathological disorders such as atherosclerosis, myocardial infarction, inflammation, and cancer (1-10). In order to control lipid peroxidation, a large number of antioxidant have been investigated. Vitamin E, vitamin C and uric acid analogues were synthesized. Also, natural products, some of them belonging to the flavonoid class, have been developed (1, 11-13).

Recent reports have shown that morin - a number of flavonoids found in plants such as Chlorophora tinctoria, Artocarpus integrifolia, Cudrania javanesis Trecule. and Morus alba - acts as broad-spectrum and non-toxic antioxidant (14-20).

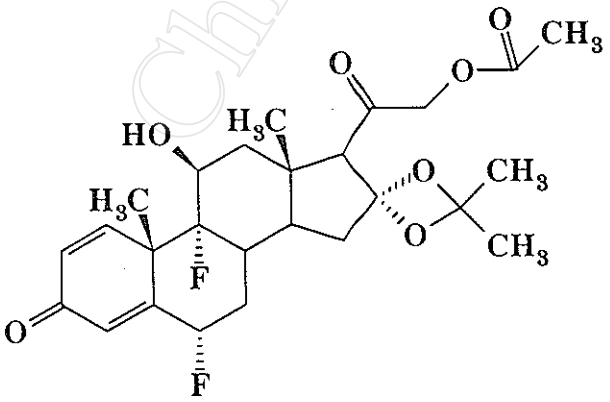
Unfortunately, morin is rapidly oxidized (14), and its very low lipophilicity results in poor absorption (21, 22). These disadvantages limit the clinical usefulness of morin. In order to develope the clinical usefulness such as antiaging; antiatherosclerosis; anti-inflammatoy and anticancer, stability and absorption properties of morin must be improved.

Many reports have shown that instability and poor absorption problems of parent drugs can be solved by "prodrug". For examples :

1. Fluocinolone acetonide, a corticosteriod for the topical treatment of inflammatory; allergic and pruritic skin condition, can be made more suitable for topical absorption by esterification to fluocinolone acetonide acetate (fluocinonide) as prodrug (23).

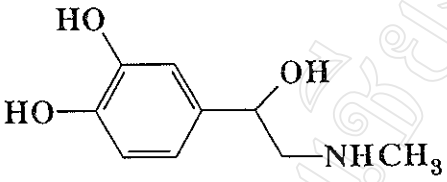


Fluocinolone acetonide

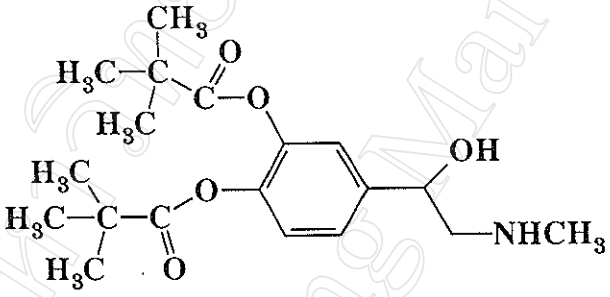


Fluocinolone acetonide acetate

2. Dipivaloylepinephrine (dipivefrin), an ester-prodrug for the antiglaucoma drug epinephrine, is better able to penetrate the cornea than is epinephrine (23).

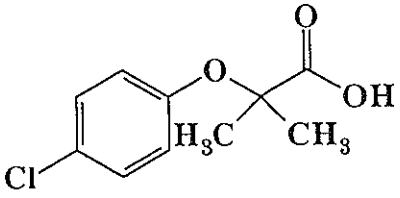


Epinephrine

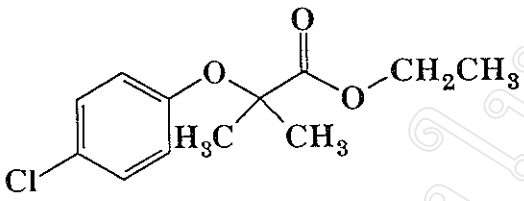


Dipivaloylepinephrine

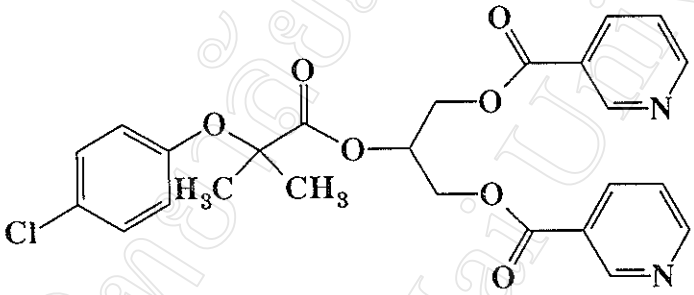
3. Clofibrate, binifibrate and etofibrate are rapidly and completely absorbed prodrugs of clofibric acid, antilipidemic drug (24).



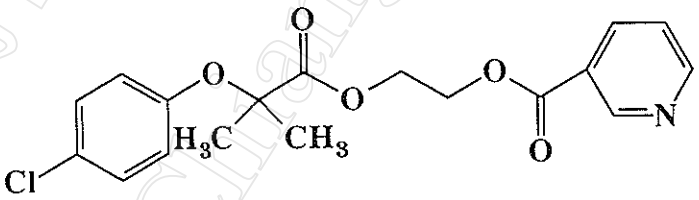
Clofibric acid



Clofibrate



Binifibrate



Etofibrate

Thus, prodrugs of morin - morin acetate, morin palmitate and morin nicotinate - were synthesized in this study. Prodrugs as ester form result in more difficult to oxidize. In addition, lipophilicity

increasing of prodrugs as acetate ester and palmitate ester results in higher lipid membrane absorption. Moreover, prodrug as nicotinate ester results in higher absorption, because of vasodilation property of nicotinate part.