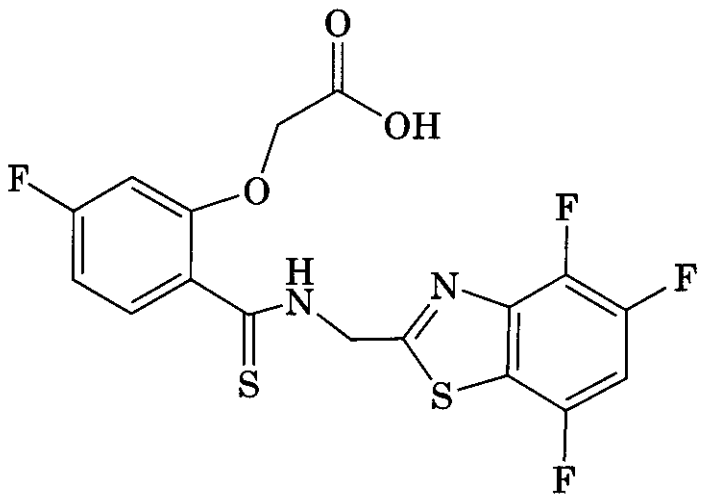
tors bind within the hydrophobic cleft and interact with the anionic site. The binding of potent inhibitors induces a conformational change, opening an adjacent hydrophobic pocket. The conformation induced by (**60**) differs from that caused by other, less selective inhibitors. This "specificity" pocket was thought to offer an opportunity for selective inhibition of aldose reductase while sparing aldehyde reductase. Hence, this structural study provided an initial pharmacophore for both potency and selectivity.

The SAR for this pharmacophore was developed with a series of synthetically accessible salicylic acid derivatives that were scored for potency and selectivity with the purified enzymes, and efficacy in a diabetic rat model **(137).** One of the most potent and selective of the derivatives was (**62**), containing the benz-



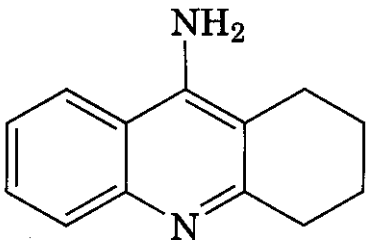
(62)

thiazole heterocycle. The SAR was employed, guided by the structures of selected inhibitor complexes, to design a novel indole scaffold to present the pharmacophoric elements (M. **Van** Zandt, personal communication). The optimization of this series provided the clinical candidate (**61**) (138).

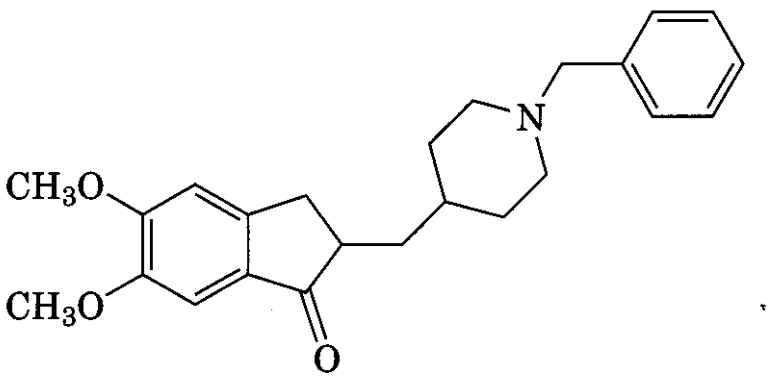
2.6 Hydrolases

Some other hydrolytic enzymes, in addition to proteases, that are important drug targets include protein phophatases, phosphodiesterases, nucleoside hydrolases, acetylhydolases, glycosylases, and phospholipases. Structure-based inhibitor design is currently being applied to a number of these enzymes. The last three mentioned have been successfully targeted in SBDD projects that have produced compounds that are either launched or in clinical trials.

2.6.1 Acetylcholinesterase. A pronounced decrease in the level of the neurotransmitter acetylcholine is one of the most pronounced changes in brain chemistry observed in the sufferers of Alzheimer's disease (139). Several drugs that are approved for the treatment of the dementia thought to result from this neurotransmitter deficit act by inhibiting acetylcholinesterase. These include (63) (tacrine, or

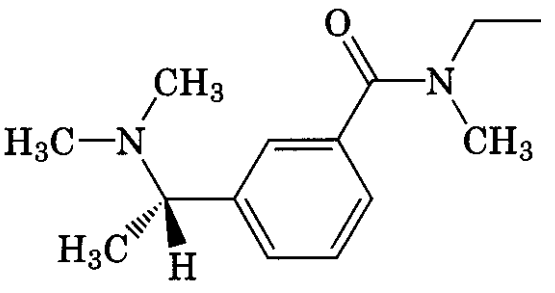


(63) tacrine



(64) donepezil

Cognex, a Pfizer drug that was the first such agent approved for this indication), (64) (donezepil), and (65)(rivastigmine). Several other agents are in clinical trials. Disappointing efficacy is observed with the existing drugs, arising from dose limitations that are likely attributable to the inhibition of acetylcholinesterase



(65) rivastigmine