Discovery & Back-up Research on Rescriptor (HIV-NNRTI, Non-Nucleoside Reverse Transcriptase Inhibitor)

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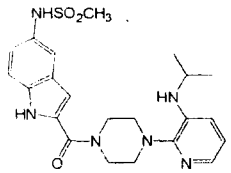
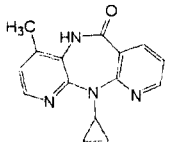
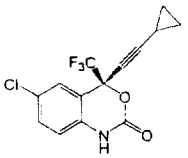
Although nucleoside reverse transcriptase inhibitors(NRTI) have been predominantly used to treat AIDS, non-nucleoside reverse transcriptase inhibitors(NNRTI) are demanded due to emergence of nucleoside drug resistance. The extensive research on NNRTI led to three new drugs for treatment of AIDS: Rescriptor (delavirdine mesylate, P&U, I)[1]; Viramune (nevirapine, BI, II)[2]; Sustiva (DMP-266, Merck, III)[3].



I, Rescriptor (P&U).



II, Viramune(BI)

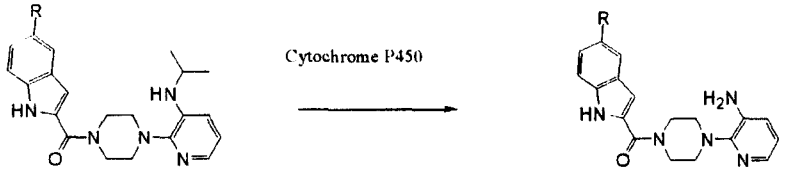


III, Sustiva (Merck)

P&U started NNRTI program for treatment of AIDS in 1988 and obtained FDA approval for Rescriptor to marketing in 1997. And back-up research has continued to enhance metabolic stability and activity against various mutants.

The major route of metabolism of Rescriptor *in vivo* is via oxidative N-dealkylation of the isopropylamino substituent by cytochrome P450 (Scheme I).

Scheme I. Metabolic pathway of BHAP

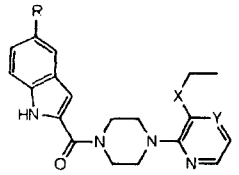


The metabolite is inactive in the *in vitro* enzyme assay. Therefore, our efforts went to replacing the isopropyl amino substituent with appropriate surrogates, ethoxy, ethylthio and others, in order to slow metabolic degradation (Figure I).

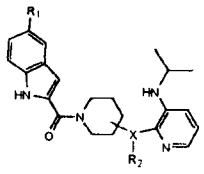
While, SAR(structure activity relationship)study has continued with parent BHAP to enhance the activity against various NNRTI resistant strains. The major mutant patterns are P235L and T181C for BHAPs and others(Nevirapine, TIBO, Pyrimidone) respectively.

BHAP analogs containing piperidine(C-C bond) and 3 or 4-(alkylamino)piperidine, (AAP-BHAPs, homologation)[4,5] in place of the piperazine of parent BHAPs were synthesized and 4-AAP-BHAPs are shown remarkable broad spectrum activity against NNRTI resistant strains (Figure I). Especially compound IV is shown good activity against P236L mutant (IC50= 0.7 uM) and Y181C mutant (IC50= 0. 8 uM).

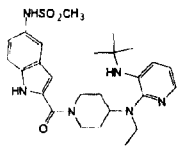
Figure I. Structures of BHAP analogues



X=O, S, SO, SO_2; Y = N, C.



X= C, N; R_2= alkyl.



IV

Conclusion:

Alkylthioether, alkylether and aminoalkylpiperidine BHAP analogs were designed and synthesized to enhance activity against NNRTI resistance strains and metabolic stability. 4-aminoalkyl BHAP with t-butyl amine on 3-position of pyridine ring (IV) is the most potent against NNRTI mutants and WT. and relatively stable in metabolism. In general, aminoalkyl BHAPs show good activity against WT and NNRTI mutants but metabolically degraded more rapidly than parent drug Rescriptor.

References:

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