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Synthesis of Novel Uracil Non-nucleosides Analogues of the Reverse Transcriptase Inhibitors Emivirine and TNK-651

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Abstract : 6-Benzyl-1-(ethoxymethyl)-5-isopropyluracil (Emivirine) and its corresponding 1-benzyloxymethyl analogue (TNK-651) showed high activity against HIV-1. The present study describes synthesis of novel emivirine analogues by reaction of chloromethyl ethyl ether with uracils having 5-ethyl / isopropyl and 6-(3,5-dimethoxybenzyl) substituents. A series of new TNK-651 analogues substituted at N-1 with phenoxyethoxymethyl moiety was prepared on treatment of the corresponding uracils with bis(phenoxyethoxy) methane. The newly synthesized non-nucleosides were tested for biological activity against wild type HIV-1 IIIB as well as the resistant strains N119 (Y181C), A17 (K103N + Y181C), and the triple mutant EFVR (K103R + V179D + P225H) in MT-4 cells. Some of the tested compounds showed good activities. Among them 6-(3,5-dimethylbenzyl)-5-ethyl-1-[2-(phenoxyethyl) oxymethyl]uracil which showed inhibitory potency higher than emivirine against both wild type HIV-1 and the tested mutant strains.

Keywords : Emivirine, HIV, non-nucleoside reverse transcriptase, uracils
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