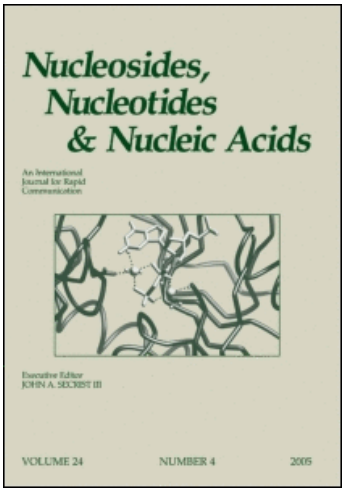

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Potential Inhibitors of HIV Integrase

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POTENTIAL INHIBITORS OF HIV INTEGRASE

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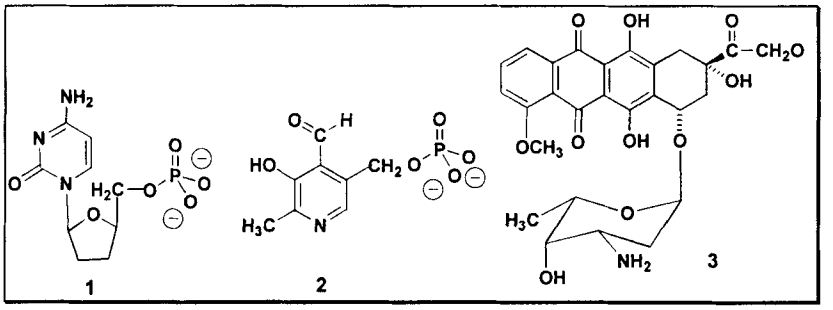
ABSTRACT: In the search for inhibitors of HIV integrase, the enzyme involved in the integration of viral DNA into host DNA, we have synthesized and studied a number of analogs of the heterocyclic molecule, chloroquine.

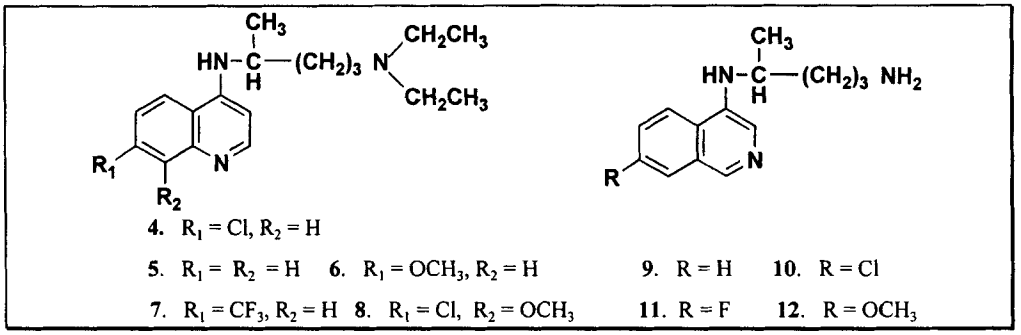
The viral enzyme, HIV integrase, is involved in the integration of viral DNA into host cell DNA.[1] In the first step of integration called 3'-processing, specific endonuclease activity removes two nucleotides from each end of the double helical viral DNA producing new 3'-hydroxyl ends (CAOH-3'). This truncated viral DNA is coupled in the next steps to host cell DNA (integration), which includes the DNA strand transfer reaction.

A number of compounds including nucleotides, oligonucleotides, and heterocyclic molecules are known to inhibit HIV integrase activity (e.g. L-ddCMP (**1**), pyridoxal phosphate (**2**), doxorubicin (**3**), and T30177 (G quartet) (see Table 1). This paper focuses on analogs of chloroquine (**4**) as inhibitors of HIV integrase and a comparison of their inhibitory data with that of nucleotides (Table 1).



The structures of the various analogs chosen for study are shown below. These compounds were synthesized from 7-substituted isoquinolines through established

literature procedures. The data in Table 1 show that chloroquine and primaquine exhibit good inhibition activity against HIV integrase as their phosphate salts (IC_{50} values were 31, 25 μM and 24, 11 μM, respectively). Analogs of chloroquine with other substitution or no substitution at the 7-position or 7,8-disubstitution (compounds **5-8**) or which are iso-quinoline analogs (compounds **9-12**) were inactive (IC_{50} values were >300 μM). The reasons for the lack of activity of these closely related analogs of chloroquine are unclear.



4. $R_1 = Cl, R_2 = H$

5. $R_1 = R_2 = H$ **6.** $R_1 = OCH_3, R_2 = H$ **9.** R = H **10.** R = Cl

7. $R_1 = CF_3, R_2 = H$ **8.** $R_1 = Cl, R_2 = OCH_3$ **11.** R = F **12.** $R = OCH_3$

Table 1. Inhibition of 3′-Processing and DNA Strand Transfer Steps of HIV Integrase

Compound	IC_{50} μM	IC_{50} μM	References
	3'-Processing	Strand Transfer	
Doxorubicin	0.9	2.4	2
L-ddCMP	50	45	3
Pyridoxal Phosphate	25	18	3
G Quartet (T30177)	0.08	0.05	4
Chloroquine (**4**)	30.5	24.5	
Primaquine	23.5	11.1	
Compounds **5-8**	>300	>300	
Compounds **9-12**	>300	>300	

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