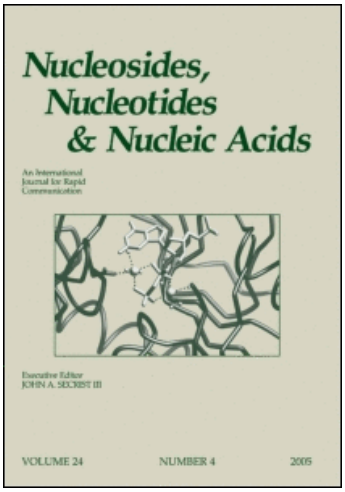

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Synthesis of Alkenyl Acyclonucleosides Derivatives of 5-Halogenouracil as Antiviral and Antitumoral Agents

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SYNTHESIS OF ALKENYL ACYCLONUCLEOSIDES DERIVATIVES OF 5-HALOGENOURACIL AS ANTIVIRAL AND ANTITUMORAL AGENTS

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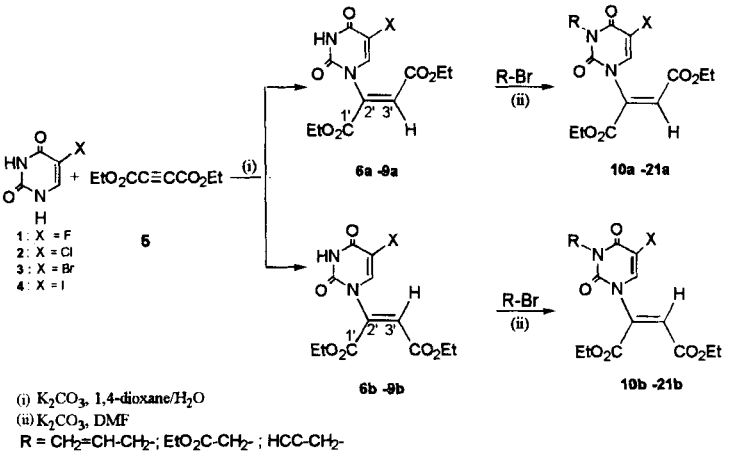
ABSTRACT: Alkenyl acyclonucleosides derivatives of 5-halogenouracil have been synthesized via Michael addition reaction. These compounds were treated by allylbromide, propargylbromide or ethylbromoacetate to give the corresponding N-1,N-3-disubstituted 5-halogenouracil.

We have recently reported the synthesis and biological activity of a series of α,β-unsaturated acyclonucleosides[1-4]. The antitumoral activity exibited by some of these compounds suggested that we should extend our studies to include novel analogues where 5-halogenouracil would be used as nucleobase. Indeed, 5-halogenouracil and their N1-substituted derivatives exhibit cytostatic, virostatic and immunosuppressive properties.[5] Thus, we undertook the synthesis of alkenyl acyclonucleosides dicarboxylate of 5-halogenouracil **6-9** (scheme). therefore to be able to introduce allyl, ethoxycarbonylmethyl or propargyl group at the N-3 position of the 5-halogenouracil moiety **10-21** (scheme).

The synthesis of products **6-9** involved Michael addition conditions. The reaction of heterocyclic bases **1-4** with diethyl acetylenedicarboxylate using potassium carbonate in 1,4-dioxan/H_2O gave a mixture of geometrical isomers **6a-9a** (Z) and **6b-9b** (E) in satisfactory overall yield (TABLE). N-3 alkylation of these compounds was carried out with potassium carbonate in DMF. The desired products were obtained in good yields

(TABLE). All isomers were separated on silica gel column chromatography. Confirmation of the isomery of these products was based on ^{1}H-NMR spectra study. In fact, the proton shifts of H_3' (Z) were lower than the corresponding H_3'(E).



SCHEME

TABLE 1: N1 and N3-alkylations of 5-halogenouracil.

	N-1-alkylation		N-3-alkylation					
Alkylating agent	EtO_2C-CC-CO_2Et		CH_2=CH-CH_2-Br		EtO_2C-CH_2-Br		HCC-CH_2-Br	
Nucleobase	t(h)	Yield %	t(h)	Yield %	t(h)	Yield %	t(h)	Yield %
5-Fluoruracil : **1**	2.5	84	2.5	87	2	91	2.5	95
5-Chlorouracil : **2**	2.5	87	3	85	3	87	2.5	90
5-Bromouracil : **3**	2	79	2	79	2.5	85	2	90
5-Iodouracil : **4**	2	85	2.5	86	2.5	92	2.5	97

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REFERENCES

1. Lazrek, H.B.; Khaider, H.; Rochdi, A., Barascut, J.L. Imbach, J.L.; *Nucl.Nucl.*, **1994**, *13*, 811-817.
2. Lazrek, H.B.;Redwane, N.; Rochdi, A., Barascut, J.L. Imbach, J.L.; *Nucl.Nucl.*, **1995**, *14*, 353-356
3. Lazrek, H.B.; Rochdi, A.; Khaider, H; Barascut, J.L.; Imbach J.L. *Tetrahedron.Letters*, **1996**, *37*, 4701-4704.
4. Lazrek, H.B.; Rochdi, A.; Khaider, H; Barascut, J.L.; Imbach J.L. *Tetrahedron*, **1998**, *54*, 3807-3816
5. Bibby, M.C.; Double, J.A.; McCormick, J.E.; McElhinney, R.S.; Radacie, M.; Pratesi, G.; Dumont, P. *Anti-Cancer Drug design*, **1993**, *8*, 115-128.