This article was downloaded by:

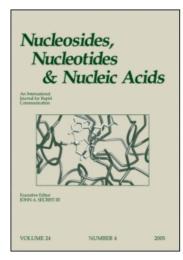
On: 26 January 2011

Access details: Access Details: Free Access

Publisher Taylor & Francis

Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-

41 Mortimer Street, London W1T 3JH, UK



# Nucleosides, Nucleotides and Nucleic Acids

Publication details, including instructions for authors and subscription information: http://www.informaworld.com/smpp/title~content=t713597286

# Reactivity Models of 1-N-Vinyluracil and Synthesis of a New Class of Potential Antiviral Agents by the Use of 1,3-Dipolar Cycloaddition Reactions

E. Colacino<sup>ab</sup>; G. De Luca<sup>a</sup>; A. Liguori<sup>a</sup>; A. Napoli<sup>a</sup>; C. Siciliano<sup>a</sup>; G. Sindona<sup>a</sup>

<sup>a</sup> Dipartimento di Chimica, Università della Calabria, Arcavacata di Rende, (CS), Italy <sup>b</sup> Labortoire de Chimie Organique Biomoleculaire de Synthèse, Université de Montpellier II, Montpellier Cedex 5,

Online publication date: 09 August 2003

**To cite this Article** Colacino, E. , De Luca, G. , Liguori, A. , Napoli, A. , Siciliano, C. and Sindona, G.(2003) 'Reactivity Models of 1-N-Vinyluracil and Synthesis of a New Class of Potential Antiviral Agents by the Use of 1,3-Dipolar Cycloaddition Reactions', Nucleosides, Nucleotides and Nucleic Acids, 22: 5, 743 - 745

To link to this Article: DOI: 10.1081/NCN-120022624 URL: http://dx.doi.org/10.1081/NCN-120022624

## PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: http://www.informaworld.com/terms-and-conditions-of-access.pdf

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

## NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS Vol. 22, Nos. 5–8, pp. 743–745, 2003

# Reactivity Models of 1-N-Vinyluracil and Synthesis of a New Class of Potential Antiviral Agents by the Use of 1,3-Dipolar Cycloaddition Reactions

E. Colacino,\* G. De Luca, A. Liguori, A. Napoli, C. Siciliano, and G. Sindona

Dipartimento di Chimica, Università della Calabria, Arcavacata di Rende, (CS), Italy

## **ABSTRACT**

By the use of a convergent approach based on 1,3-dipolar cycloaddition reactions between *N*-protected formylnitrones generated in situ and 1-*N*-vinyluracil, a new class of 4'-aza-analogues of 2',3'-dideoxynucleosides is synthesized. Competitive reaction for the endocyclic bond of uracil also brings to a new isoxazolidine derivative fused with the pyrimidine nucleus.

By a convergent approach based on 1,3-dipolar cycloaddition reactions between N-protected formylnitrones 1 generated in situ, starting from the corresponding hydroxylamines, and 1-N-vinylnucleobases 2 and 3, a new class of 4'-aza-2',3'-dideoxynucleosides 4 and 5 was synthesized<sup>[1,2]</sup> (Sch. 1).

743

DOI: 10.1081/NCN-120022624 Copyright © 2003 by Marcel Dekker, Inc. 1525-7770 (Print); 1532-2335 (Online) www.dekker.com



<sup>\*</sup>Correspondence: E. Colacino, Université de Montpellier II, Labortoire de Chimie Organique Biomoleculaire de Synthèse, CC008, Place E. Bataillon, F-34095 Montpellier Cedex 5, France; Fax: +33 4 6704 2029; E-mail: eveline.colacino@mailcity.com.

744 Colacino et al.

(i) p-TsOH, MeOH, CHCl $_3$ ; (ii) HClO $_4$  60%, MeOH, CHCl $_3$ ; (iii) POCl $_3$ , TEA, 1,2,4-(1H)-triazole, CH $_3$ CN (quantitative yield); (ii) R = CH $_3$  92% yield; R = H 88% yield; (iv) NH $_3$ , 1,4-dioxane; (v) POCl $_3$ , 4-nitrophenol, N-methylpytrolidine, 1,4-dioxane (90% yield)

## Scheme 1.

The tandem mass spectra<sup>[3]</sup> of these compounds were similar to those of the wild-type nucleosides but all the protonated isoxazolidinyl nucleosides present a retrocycloaddition process, which can be considered a 'marker' of the chemistry of this class of compounds. The application of the convertible nucleoside approach (Sch. 1) was achieved in order to prepare 4'-aza-2',3'-dideoxynucleosides 9 and 10. A competitive reaction for the endocyclic bond of 1-N-vinyluracil 3 during 1,3-dipolar cycloaddition process, characterised by site selectivity affords a new isoxazolidinyl derivative fused with the pyrimidine nucleus (Sch. 1). The regiochemistry of nitrone attack on double bond C(5)–C(6) was demonstrated by two dimensional NMR and MS/MS experiments.<sup>[4]</sup>

On the bases of the above mentioned promising results, some other fused *N*, *O*-heterocycles (Table 1) have been prepared, using as dipolarophiles, modified uracils on 1-*N*-position by tetrahydropyranyloxyethyl and 2-benzyloxy-ethoxymethyl moieties. (Sch. 2).

Table 1.

	$R_1$	PG	Solvent	Yield (%)
13	BnOCH <sub>2</sub> CH <sub>2</sub> OCH <sub>2</sub> -	THP	Toluene	20
14	BnOCH <sub>2</sub> CH <sub>2</sub> OCH <sub>2</sub> -	Benzyl	Toluene	25
15	THPOCH <sub>2</sub> CH <sub>2</sub> -	THP	CHCl <sub>3</sub>	15
16	THPOCH <sub>2</sub> CH <sub>2</sub> -	Benzyl	CHCl <sub>3</sub>	19
17	BnOCH <sub>2</sub> CH <sub>2</sub> OCH <sub>2</sub> -	_	MeOH/CHCl <sub>3</sub>	72
18	HOCH <sub>2</sub> CH <sub>2</sub> OCH <sub>2</sub> -	_	MeOH	85
19	HOCH <sub>2</sub> CH <sub>2</sub> -	_	MeOH/CHCl <sub>3</sub>	70
20	THPOCH <sub>2</sub> CH <sub>2</sub> -	_	MeOH	92



(i) 1,3,5-trioxane, HCl<sub>(p)</sub>, 1,2-DCE, 0°C, 4h; (ii) (Bu<sub>t</sub>)N<sup>t</sup>Γ cat., 1,2-DCE, reflux; (iii) DMF, NaOH, 1.5 h, reflux; (iv) p-TsOH, rt 16h, 1,4-Dioxane; (v) HClO<sub>4</sub> 60%, MeOH/CHCl<sub>3</sub>; (vi) H<sub>2</sub>, Pd/C 10%, MeOH, rt, 20 h.

#### Scheme 2.

The subsequent reductive opening of fused isoxazolidine rings brought to some new acyclic uridine derivatives functionalised on C(5) by a methylamino group.

## REFERENCES

- Colacino, E.; Sindona, G.; Converso, A.; De Nino, A.; Leggio, A.; Liguori, A.; Maiuolo, L.; Napoli, A.; Procopio, A.; Siciliano, C. Synthesis of isoxazolidino analogues of 2',3'-dideoxynucleosides. Nucleosides Nucleotides 1999, 18, 581– 583.
- 2. Colacino, E.; Converso, A.; Liguori, A.; Napoli, A.; Siciliano, C.; Sindona, G. Simple and efficient routes for the preparation of isoxazolidinyl nucleosides containing cytosine and 5-methyl-cytosine as new potential anti-HIV drugs. Tetrahedron **2001**, *57*, 8551–8557.
- 3. Colacino, E.; Giorgi, G.; Ligouri, A.; Napoli, A.; Romeo, R.; Salvini, L.; Siciliano, C.; Sindona, G. Structural characterization of fast atom bombardment tandem mass spectrometry. J. Mass Spectrom. **2001**, *36*, 1220–1225.
- 4. Colacino, E.; De Luca, G.; Liguori, A.; Napoli, A.; Siciliano, C.; Sindona, G. Modelli di Reattività di 1-*N*-viniluracile nella Sintesi di Potenziali Antivirali, XXVI Convegno Nazionale della Divisione di Chimica Organica della Società Chimica Italiana, Folgaria (TN), Italy, Sep. 7–12, 1999.