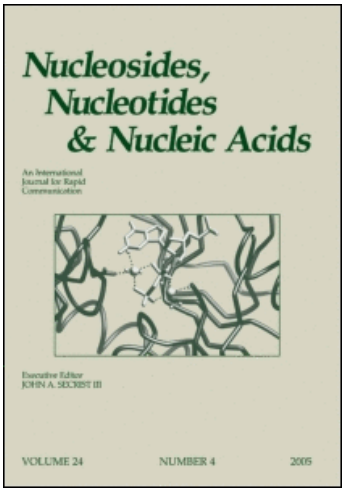

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

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C. Congiatu[a]; C. McGuigan[a]; W. G. Jiang[b]; G. Davies[b]; M. D. Mason[c]
[a] Welsh School of Pharmacy, Cardiff University, Cardiff, UK [b] Metastasis Research Group, University of Wales College of Medicine, Cardiff, UK [c] Section of Oncology, University of Wales College of Medicine, Cardiff, UK

To cite this Article Congiatu, C. , McGuigan, C. , Jiang, W. G. , Davies, G. and Mason, M. D.(2005) 'Naphthyl Phosphoramidate Derivatives of BVdU as Potential Anticancer Agents: Design, Synthesis and Biological Evaluation', Nucleosides, Nucleotides and Nucleic Acids, 24: 5, 485 — 489
To link to this Article: DOI: 10.1081/NCN-200061774
URL: http://dx.doi.org/10.1081/NCN-200061774

Nucleosides, Nucleotides, and Nucleic Acids, 24 (5–7):485–489, (2005)

ISSN: 1525-7770 print/ 1532-2335 online
DOI: 10.1081/NCN-200061774

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NAPHTHYL PHOSPHORAMIDATE DERIVATIVES OF BVdU AS POTENTIAL ANTICANCER AGENTS: DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION

C. Congiatu and C. McGuigan ▫ *Welsh School of Pharmacy, Cardiff University, Cardiff, UK*

W. G. Jiang and G. Davies ▫ *Metastasis Research Group, University of Wales College of Medicine, Cardiff, UK*

M. D. Mason ▫ *Section of Oncology, University of Wales College of Medicine, Cardiff, UK*

▫ *The phosphoramidate technology we have developed has been recently applied to BVdU, leading to NB1011 (NewBiotics Inc., California), a novel potential anticancer compound recently entered into phase 2 of the clinical trials for colon cancer. We report in this work a new series of derivatives containing naphthol as aryl masking group on the phosphate moiety, which has shown a significant increase in anticancer activity in preliminary biological evaluations.*

Keywords Phosphoramidate, Protide, Anticancer

INTRODUCTION

The phosphoramidate approach was conceived as a means to improve cellular penetration of nucleotides and to bypass the first step of kinase-mediated activation of nucleosides. It has been observed that the ability of phosphoramidate protides to deliver the monophosphate derivative can lead to an impressive boost in activity compared with the corresponding nucleoside.[1] NewBiotics discovered a surprising anticancer activity in a phosphoramidate derivative of the anti-herpetic (E)-5-(2-bromovinyl)-2′-deoxyuridine (BVdU)[2,3] that we synthesized and tested only as potential antiviral prodrug[4] (Figure 1).

Address correspondence to C. Congiatu, Welsh School of Pharmacy, Redwood Building, King Edward VII Ave., Cardiff CF10 3XF, UK; Fax: +44-2920874537; E-mail: sphcc3@cf.ac.uk

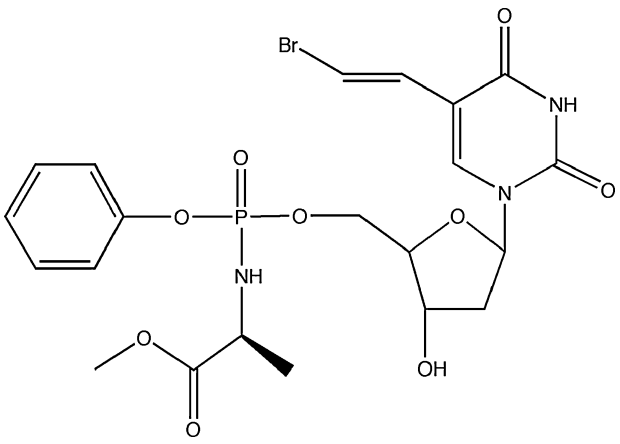


FIGURE 1 NB1011.

Following this, a new series of BVdU phosphoramidates was designed considering naphthol as a new aromatic moiety, and the effect of an electron withdrawing and a donating substituent has also been investigated (Table 1 and Figure 2).

Furthermore, in order to identify structure-activity relationshi ps, different amino acids containing alternative ester moieties have been investigated (Table 2 and Figure 3).

The synthesis of BVdU-5′-phosphoramidate compounds follows the procedure of Van Boom et al.,[5] further developed by McGuigan.[1] Phosphorylation of the corresponding naphthol derivatives with phosphorus oxychloride, followed by coupling with different esterified amino acid salts, gave aryloxy-phosphochloridates, which were generally purified by flash chromatography and then coupled with BVdU in the presence of 1-methylimidazole (NMI). Due to the chirality of the phosphorus center, the final products were obtained as mixtures of two diastereoisomers. In the following scheme, CPF 98 has been chosen to show the standard procedure used for the synthesis of naphthyl-phosphoramidates (Scheme 1).

TABLE 1 BVdU-Phosphoramidates

Compound	α/β Naphthol	X	R
CPF 96	α	H	Me
CPF 97	α	H	Et
CPF 98	α	H	Bn
CPF 99	β	–	Me
CPF 100	β	–	Et
CPF 101	β	–	Bn
CPF 102	α	Cl	Me
CPF 104	α	MeO	Me

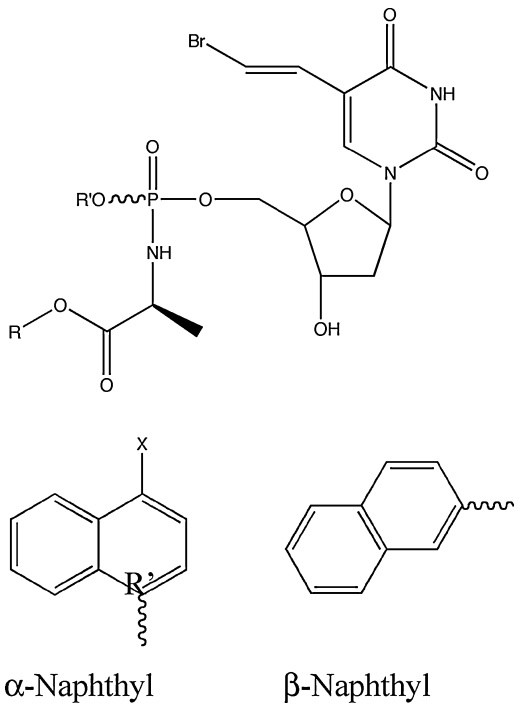
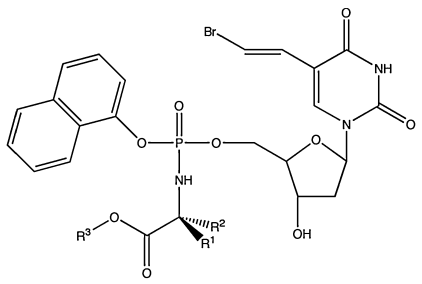


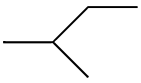
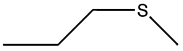
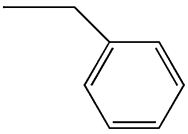
FIGURE 2 BVdU-phosphoramidates.

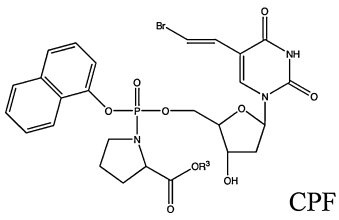
Compounds CPF 96-102 and 104 have been tested against two different tumor cell lines, MCF7 (breast cancer) and PC-3 (prostate cancer), showing a general increase in activity over the lead compound NB1011 (Table 3). In particular, this preliminary evaluation reveals a 100-fold increase in potency against prostate cancer achieved with the compound **CPF 98**.

TABLE 2 BVdU-Phosphoramidates, Amino Acid Moiety Tuning

Compound	Amino acid	R^3
CPF 127	Dimethylglycine	Me
CPF 156	L-Isoleucine	Me
CPF 146	L-Isoleucine	Bn
CPF 147	Dimethylglycine	Bn
CPF 149	L-Phenylglycine	Me
CPF 165	L-Valine	Bn
CPF 166	L-Proline	Me
CPF 167	L-Methionine	Me
CPF 168	D-Alanine	Bn
CPF 169	L-Phenylalanine	Me
CPF 170	L-Phenylalanine	Bn
CPF 171	L-Alanine	tBu
CPF 172	L-Valine	Me

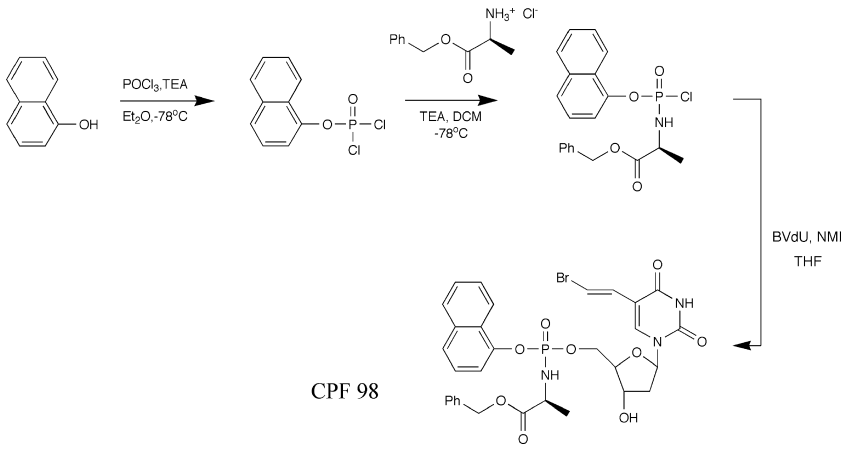


R^1	R^2	Amino acid
	H	L-Isoleucine
	H	L-Valine
	H	L-Methionine
	H	L-Phenylalanine
CH_3	CH_3	Dimethylglycine
Ph	H	L-Phenylglycine
H	CH_3	D-Alanine



CPF 166

FIGURE 3 BVdU-phosphoramidates, amino acid moiety tuning.



SCHEME 1 Synthesis of phosphoramidates.

TABLE 3 Preliminary Biological Evaluations

Compound	Breast cancer (MCF7) EC_{50} (μM)[a]	Prostate cancer (PC-3) EC_{50} (μM)[a]
NB1011	200	155
CPF 96	78	90
CPF 97	46	18
CPF 98	24	1.6
CPF 99	80	70
CPF 100	22	17
CPF 101	14	3.5
CPF 102	22	13
CPF 104	22	26

[a]EC_{50}: effective concentration required to cause 50% inhibition of cell growth.

Following this, derivatives containing modifications to the amino acid moiety are appealing targets in an attempt to further improve anticancer activity and these are currently under biological evaluation.

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