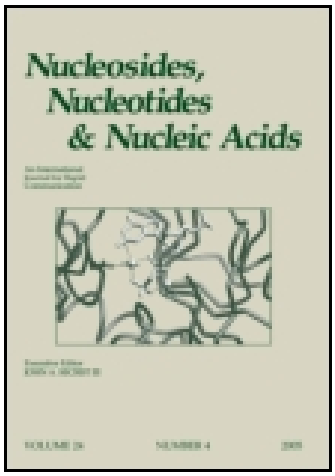

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lncn20

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Published online: 31 Aug 2006.

To cite this article: Tomasz Goslinski, Grazyna Wenska, Bozenna Golankiewicz, Jan Balzarini & Erik De Clercq (2003) Synthesis and Fluorescent Properties of 6-(4-Biphenylyl)-3,9-dihydro-9-oxo-5H-imidazo[1,2-A]purine Analogues of Acyclovir and Ganciclovir, Nucleosides, Nucleotides and Nucleic Acids, 22:5-8, 911-914, DOI: 10.1081/NCN-120022684

To link to this article: http://dx.doi.org/10.1081/NCN-120022684

NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS
Vol. 22, Nos. 5–8, pp. 911–914, 2003

Synthesis and Fluorescent Properties of 6-(4-Biphenylyl)-3,9-dihydro-9-oxo-5*H*-imidazo[1,2-*A*]purine Analogues of Acyclovir and Ganciclovir

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ABSTRACT

Tricyclic (T) analogues of acyclovir (ACV, **1**) and ganciclovir (GCV, **2**) carrying the 3,9-dihydro-9-oxo-5*H*-imidazo[1,2-*a*]purine system [i.e., 6-(4-BrPh)TACV, **5** and 6-(4-BrPh)TGCV, **6**] were transformed into 6-[(4′-R^2)-4-biphenylyl] derivatives of TACV (**7**–**9**) and TGCV (**10**–**12**) by Suzuki cross coupling with 4-substituted phenylboronic acids. Compound **11** ($R^2 = CH_2OH$) showed a high (~1000) selectivity index against herpes simplex virus type 1 (HSV-1) together with advantageous fluorescence properties (emission in visible region, little overlap with absorption and moderate intensity).

Key Words: Acyclovir; Ganciclovir; Tricyclic analogues; Fluorescent properties.

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DOI: 10.1081/NCN-120022684
1525-7770 (Print); 1532-2335 (Online)

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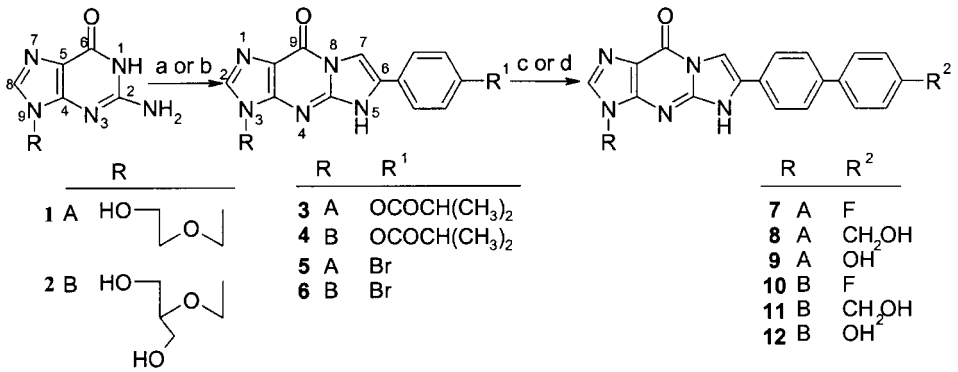
We have previously reported that two potent antivirals, acyclovir, ACV, 9-[(2-hydroxyethoxy) methyl]guanine, **1** and its (1,3-dihydroxy-2-propoxy) congener, ganciclovir, GCV, **2** may be rendered intrinsically fluorescent by conversion of their guanine moiety into the tricyclic 3,9-dihydro-9-oxo-6-phenyl-5*H*-imidazo[1,2-*a*]purine system to form 6-PhTACV and 6-PhTGCV derivatives.[1] Appropriate substitution in the 4 position of 6-phenyl group resulted in 6-(4-R^1Ph) TACV and –TGCV, with antiviral activity comparable to that of parent compounds **1** and **2**.[2] The presence of an acyloxy group such as the 4-R^1 substituent provided strong fluorescence, as with derivatives **3**, **4**.[3]

In order to further improve the fluorescence characteristics of the TACV and TGCV analogues, we synthesized a series of 6-[(4′-R^2)-4-biphenylyl] derivatives. Parent compounds **1** and **2** were converted into 6-(4-BrPh) TACV **5**, and 6-(4-BrPh) TGCV **6**, respectively, according to a previously described method for an alkylation-condensation reaction using appropriate bromoketone[1] followed by Suzuki cross-coupling[4] with 4-substituted phenylboronic acids (Sch. 1). The target biphenylyl derivatives **7**–**12**, obtained in approximately 50% yield after chromatographic purification (silica gel, CH_2Cl_2/MeOH gradient) and recrystallization (i-PrOH/H_2O) were fully characterized by elemental analyses, ^{1}H and ^{13}C NMR spectra as well as absorption and fluorescence spectra.

FLUORESCENCE

The absorption and emission spectra of selected acyclovir analogues are presented in Fig. 1. Identical spectral changes were observed for ganciclovir derivatives **10**–**12**. Replacement of 6-phenyl with 6-biphenylyl substituent resulted in *ca.* 10 nm batochromic shift of the lowest energy absorption band and a substantial increase in its intensity. The value of ε_{max} determined for the compound **9** at $\lambda_{max} = 320$ nm equals to 27,600 $dm^3\,mol^{-1}\,cm^{-1}$. The effect of 6-biphenylyl substituent on the



Scheme 1. Reagents and conditions: (a) NAH/DMF, 4-BrPhCOCH$_2$Br, room temp, 4 h, then NH_4OHaq; (b) NAH/DMF, 4-[$(CH_3)_2$CHCOO]PhCOCH$_2$Br, room temp, 4 h; (c) **5** or **6**, DMF-H2O, $Pd(Ph_3P)_4$, 4-$(HO)_2$BPhF or 4-$(HO)_2$BPhCH$_2$OH, K_2CO_3, 85–90°C, 3–5 h; (d) **5** or **6**, DMF-H_2O, $Pd(Ph_3P)_4$, 4-[$(CH_3)_4C_2O_2$B]PhOH, K_2CO_3, 85°C, 2–4 h.

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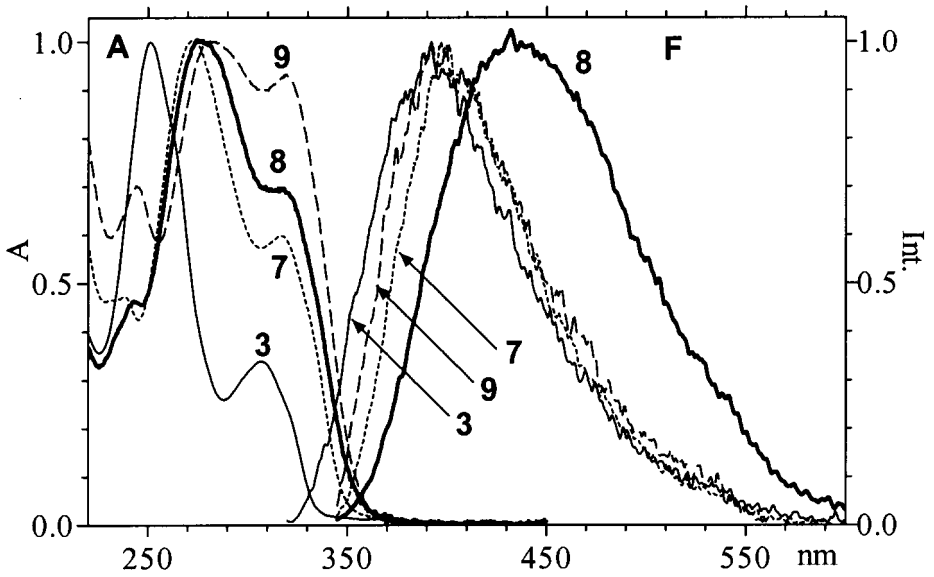

Figure 1. Normalized absorption (A) and fluorescence (F) spectra of compounds **3**,**8**,**9** in H_2O-CH_3OH (10:1; v:v) and compound **7** in CH_3OH; (**7**,**8**,**9**: $\lambda_{exc} = 340$ nm; **3**: $\lambda_{exc} = 310$ nm).

position and intensity of the fluorescence band was similar (Fig. 1). Among the compounds studied the 4′-hydroxymethylbiphenylyl derivatives **8** and **11** exhibited the most advantageous fluorescence properties. The emission of **11** was moderately intense ($\varphi = 0.15$), relatively long-lived ($\tau = 3.9$ ns), extended into the visible region, and the emission band was well separated from absorption band.

BIOLOGICAL ACTIVITY

The novel TACV and TGCV derivatives were evaluated against herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2), varicella-zoster virus (VZV) and cytomegalovirus (CMV) in human embryonic lung (HEL) cell cultures. The effects of the compounds on cell morphology were evaluated in parallel with their antiviral activity according to procedures described previously.[5] The insertion of an additional phenyl ring into the substituent at the 6 position generally reduced the antiviral activity and selectivity. However, this reduction in activity was less pronounced for HSV-1 and HSV-2 than for VZV and CMV. Compound **11**, advantageous from the fluorescence viewpoint was inhibitory to TK^+ HSV-1 and TK^+ HSV-2 within the concentration range of 0.08–0.4 μg/mL, well below the cytotoxicity threshold (80 μg/mL). It could be considered as an antiherpetic drug candidate worthy of further evaluation from both a therapeutic as well as diagnostic viewpoint, for the treatment and non-invasive diagnosis of HSV infections, the latter because of its fluorescent properties.

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