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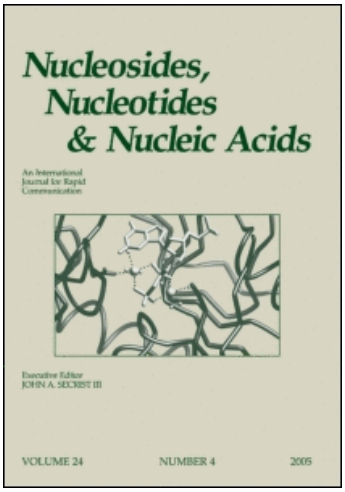

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Synthesis and Fluorescent Properties of the Tricyclic Analogues of Acyclovir Linked with Nitrogen Hetbrocyclic Units

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SYNTHESIS AND FLUORESCENT PROPERTIES OF THE TRICYCLIC ANALOGUES OF ACYCLOVIR LINKED WITH NITROGEN HETBROCYCLIC UNITS

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▫ *Tricyclic (T, 3,9-dihydro-9-oxo-5H-imidazo[l,2-α]purine) analogues of acyclovir (ACV,* ***1****), substituted in the 6 position with pyrid-4-yl, 4-(pyrid-4′-yl)Ph, 4-(pyrimidin-5′-yl)Ph and 4-(thiazol-2′-yl)Ph units were synthesized. For the synthesis ofthe heteroarylphenyl derivatives, a convenient general route was developed, i.e., Suzuki cross-coupling between protected 6-(4-dihydroxyborylphenyl) TACV and easily available bromoheterocycles. Fluorescent properties of newly synthesized TACV aoalogues strongly depend on the nature of a solvent. This sensitivity of fluorescence makes the compounds promising probes of H-bonding in the environment.*

Keywords Acyclovir, Tricyclic Analogues, Synthesis, Fluorescence Probe

INTRODUCTION

Our previous studies on the fluorescent, tricyclic (T, 3,9-dihydro-9-oxo-S*H*-imidazo[1,2-α] purine) analogues of two potent antivirals, acyclovir, ACV, 9-[(2-hydroxyethoxy)methyl] guanine, 1 and its (1,3-dihydroxy-2-propoxy) congener, ganciclovir, GCV, **2** have shown that the introduction of the 4-R-phenyl unit into 6

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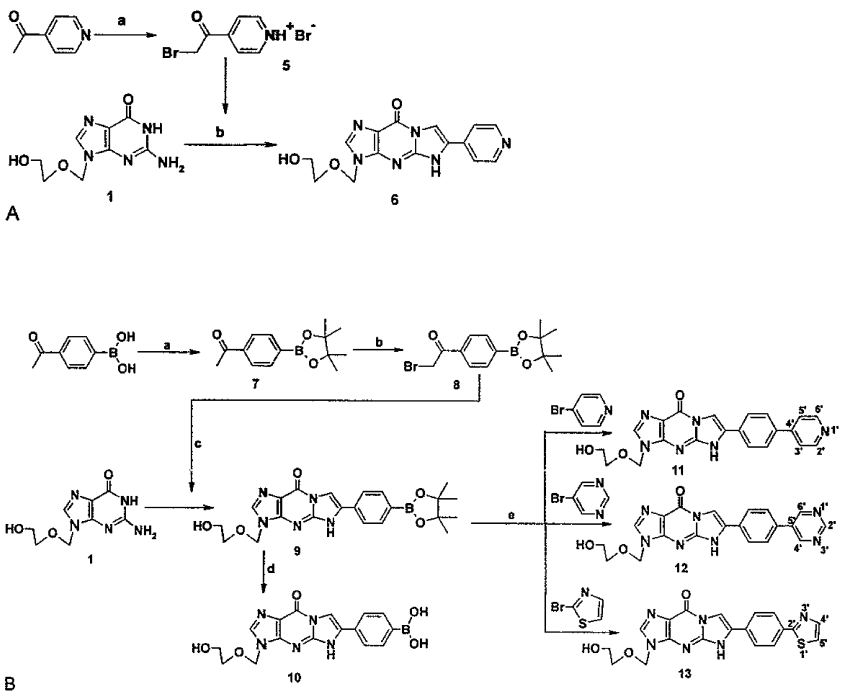
position of the tricycle is the most promising modification in terms of fluorescent and antiviral properties.[1–4]

Recently we have found that the replacement of 6-phenyl with 6-[(4′-hydroxymethyl)-4-biphenylyl] substituent results in the compounds 6-[(4′-$HOCH_2$)PhPh]-TACV **3** and -TGCV **4** with advantageous flourescense characteristics (emission in visible region, little overlap with absorption) together with selective activity against herpes simplex virus type 1 (HSV-1).[5] In continuation of the above approach to improve the fluorescent properties of the tricyclic analogues, we synthesized a series of nitrogen containing 6-heteroaryl and 6-heteroarylphenyl TACV derivatives and characterized their fluorescence as well as biological activity.

SYNTHESIS

The synthetic route to the nitrogenheteroaryl substituted TACV analogues is depicted in Scheme 1. The target compounds were prepared by reacting-the l-sodium derivative of acyclovir with an appropiate bromoketone according to an alkylation-condensation reaction using simpler reagents.[1–3,5] When using known bromoketone 5,6-(pyrid-4-yl)TACV **6** was smoothly obtained in 75% yield. In order to have a broad access to a variety of the heteroarylphenyl TACV derivatives, a



SCHEME 1 A: Reagents and conditions: (a) Br_2, HBr, 0 → 20°C;[6] (b) NaH/DMF, r.t., 30 min. B: Reagents and conditions: (a) DMF, pinacol, 20°C, 1–3 h; (b) Br_2, $AlCl_3$, THF, 0–20°C, 1.5 h; (c) NaH, DMF, 20°C, h; (d) H_2O, 100°C, 10 min; (e) DMF-H_2O (5:3 or 1:1), $Pd(Ph_3P)_4$, K_2CO_3 or Na_2O_3, 75–85°C.

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general route was developed. Commercially available 4-acetylphenyldihydroxyborane was transformed into a pinacol ester **7** and then into a bromoketone **8**, phenacyl bromide carrying the protected dihydroxyborane function. Acyclovir subjected to the alkylation-condensation reaction with **8** provided a TACV substituted reagent **9** for the Suzuki cross-coupling with diverse, inexpensive, commercially available bromoheterocycles. Hydrolytic deprotection of **9** resulted in 6-(4-dihydroxyborylphenyl) TACV **10**. The reconnaissance reactions, presently performed with **9**, provided TACV analogues linked in 6 position with 4-(pyrid-4′-yl)Ph **11**,4-(pyrimidin-5′-yl)Ph **12** and 4-(thiazol-2′-yl)Ph **13** units in 84, 27, and 50% yield, respectively. The target derivatives **6**,**9**-**13** were fully characterized by elemental analyses, ^{1}H and ^{13}CNMR spectra, as well as absorption and fluorescence spectra.

FLUORESCENCE

The Effect of Heterocyclic Substituent on the Absorption and Fluorescence Characteristics of 6-(4-RPh)TACV

The location of absorption maxima and the shape of the absorption bands of synthesized heteroaryl or heteroarylphenyl substituted compounds do not significantly differ from those of their appropriate hydrocarbon analogs: 6-(4′-R-Ph-Ph)TACV and 6-PhTACV.[5,7] Out of 6-heteroaryl and Gheteroarylphenyl synthesized compounds, only 6-[4-(thiazol-2′-yl)Ph] TACV showed some fluorescence in aqueous solution (Table 1). Unlike their hydrocarbon analogues, the remaining heteroaryl or heteroarylphenyl substituted derivatives of TACV do not show any measurable fluorescence in this medium ($\phi^F < 0.0001$). In order to reveal

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TABLE 1 Absorption (λ^A_{max}) and Fluorescence Maxima (λ^F_{max}), Fluorescence Quantum Yields (ϕ^F) and Lifetimes (τ^F) of 6-[4-(Pyrid-4′-yl)Ph]TACV and 6-[4-(Thiazol-2′-yl)Ph]TACV in Selected Solvents

	6-[4-(pyrid-4′-yl)Ph]TACV					6-[4-(thiazol-2′-yl)Ph]TACV			
Solvent	ε_r[b]	λ^A_{max} [nm]	λ^F_{max} [nm]	ϕ^F[c]	τ^F[d] [ns]	λ^A_{max} [nm]	λ^F_{max} [nm]	ϕ^F[c]	τ^F[d] [ns]
[a]H_2O	78.3	270; 318	[e]	[e]	[e]	250; 280; 322	505	0.005	nd
MeOH	32.6	269; 327	480	0.001	<0.5	250; 282; 308; 332	490	0.020	0.7
MeCN	35.9	271; 325	482	0.097	3.2	250; 281; 310; 336	480	0.106	3.9
EtOAc	6.0	273; 332	445	0.396	nd	[f]; 282; 309; 344	445	0.335	nd

[a]Contains ca 15% MeOH.
[b]Relative permittivity (dielectric constant).
[c]λ_{exc} = 320 nm.
[d]λ_{exc} = 320 nm; emission at λ^F_{max} was monitored.
[e]Non-fluorescent ($\phi^F < 0.0001$).
[f]Overlapped with solvent absorption; nd–not determined.

the factors that may be responsible for the very inefficient emissive process, we measured the fluorescence.quantum yields and lifetimes of selected compounds: 6-[4-(pyrid-4′-yl)Ph]TACV **11** and 6-[4-(thiazol-2′-yl)-Ph]TACV **13** in protic and aprotic organic solvents of various polarity. The results are presented in Table 1.

Their analysis indicates that the molecules are sensitive to both polarity and hydrogen-bonding ability of a solvent. In a less polar, aprotic solvent, ethylacetate, fluorescence is strong. In a solvent with higher polarity, acetonitrile, fluorescence becomes weaker. In a hydroxylic solvent, MeOH, despite its polarity similar to MeCN (expressed by c, Table 1), fluorescence quantum yield is significantly lowered compared to aprotic, polar MeCN. The solvent induced fluorescence quenching is even more pronounced in aqueous medium. The reduction of ϕ^F value is accompanied by the shortening of fluorescence lifetime. It may be suggested that the sharp decrease of fluorescence quantum yield in hyroxylic solvents is due to the formation of hydrogen bonded pairs: excited fluorophore (H bonding acceptor)–solvent (H bonding donor). It was demonstrated that the intermolecular interaction of a fluorophore with hydroxylic solvents is an efficient channel of the excited state deactivation in several systems, e.g., azaaromatics,[8] quinones,[9] and fluorenone.[10]

The formation of H-bonded solute-solvent complexes in the ground state is not indicated by UV spectroscopy. Except for small (<4 nm) solvatochromic shift, the shape of the absorption bands of 6-[4-(pyrid-4′-yl)Ph]TACV and 6-[4-(thiazol-2′-yl)-Ph]TACV in MeCN and MeOH is very similar.

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BIOLOGICAL ACTIVITY AND PROSPECTS OF APPLICATION IN BIOLOGICAL SYSTEMS

New heteroaryl TACV derivatives **6**, **11**, **12**, and **13** were evaluated against herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2), vaccinia virus, vesicular stomatitis virus, and herpes simplex-l TRKOS. All compounds showed SI below 10. Also the compounds demonstrated very weak inhibitory effect on the proliferation of osteosarcoma cells (OST TK^+, OST TK/HSV-1 TK^+). However, sensitivity of fluorescence of TACV analogues linked with nitrogen heteroaryl units makes them promising probes of H-bonding in the environment. Such probes upon incorporation or conjugation to macromolecules provide information about the presence of hydrogen bonding groups, local concentration, and dynamics of water in the close vicinity of the fluorophore. In biological systems fluorescein dianion was reported to be a useful probe of hydrogen bonding in environment. In this case, however, fluorescence maximum is an indicator.[11]

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