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Synthesis of 6-imino-5-tetrahydro-1*H*-2-pyrrolylidenhexahydro-2,4-pyrimidinediones as intermediates for the synthesis of C-azanucleosides

Ashot Martirosyan [a,*], Rafael Tamazyan [b], Sahak Gasparyan [a], Marina Alexanyan [a], Henry Panosyan [b], Vahan Martirosyan [a], Raymond Schinazi [c]

[a] Institute of Fine Organic Chemistry, National Academy of Sciences RA, Azatutyan Avenue 26, 0014 Yerevan, Armenia
[b] Molecular Structure Research Center, National Academy of Sciences RA, Azatutyan Avenue 26, 0014 Yerevan, Armenia
[c] Emory University School of Medicine, Veterans Affairs, Medical Center 1670, Clairmont Road, 151-H Decatur, Georgia 30033-4004, USA

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ABSTRACT

The method for the synthesis of 6-imino-5-tetrahydro-1*H*-2-pyrrolylidenhexahydro-2,4-pyrimidinediones is described. It is shown that the reaction of phosphorus trichloride, 2-pyrrolidones and 6-aminopyrimidines brings to condensation producing 6-imino-5-tetrahydro-1*H*-2-pyrrolylidenhexahydro-2,4-pyrimidinediones as intermediates for the synthesis of C-azanucleosides. The reaction of 6-imino-1,3-dimethyl-5-tetrahydro-2-pyrrolylidenhexahydro-2,4-pyrimidinedione with benzoyl chloride produces 10-benzoyl-2,4-dimethyl-6-phenyl-1,2,3,4,8,9-hexahydropyrimido[5,4-*e*]pyrrolo[1,2-*c*]pyrimidine-1,3-dione. A method for the selective reduction of the carbomethoxy group of methyl 5-(4-imino-1,3-dimethyl-2,6-dioxohexahydro-5-pyrimidinyliden)-2-pyrrolidine carboxylate by system $NaBH_4$/1,4dioxane/$CoCl_2$/PEG-400 is described.

1. Introduction

The modification of nucleosides has long been recognized as an important approach to improve their antiviral or anticancer activities.[1] In contrast to natural nucleosides, in C-nucleosides the ribofuranosyl moieties are linked to the heterocyclic base through a carbon–carbon bond and they possess a more stable glycosidic bond toward hydrolysis and enzymic reaction. Furthermore, the sugar residue of C-nucleosides where the oxygen is replaced by a nitrogen atom constitutes an another important class of C-azanucleosides able to inhibit glycohydrolases which are responsible for the cleavage of glycosidic bonds.[2]

The known methods for the synthesis of C-azanucleosides such as Heck-coupling reactions, 1,3-dipolar cycloadditions, Mannich-type C-nucleosidations, and Staudinger-aza-Wittig cyclization of γ-azido ketones have been described in the literature.[3] These methods are multistage and complicated. Consequently, development of new more readily accessible methods for their synthesis becomes actual.

In this Letter, we report a one-step simple synthesis of 6-imino-5-tetrahydro-2-pyrrolylidenhexahydro-2,4-pyrimidinediones as intermediates for the synthesis of C-azanucleosides and some further transformations specific for these systems. The proposed approach assumes the application of hydrogenation processes in the final stage of synthesis of C-azanucleosides.

The structural determination of the synthesized compounds was performed using X-ray crystallography, IR, and NMR spectroscopic methods.

2. Results and discussion

It is well known that the condensation of imino ethers or imino chlorides, particularly derived from pyroglutamic acid, with active methylene reagents such as Meldrum's acid and methyl cyanoacetate, lead to corresponding β-enaminoesters.[4] This precedent allowed us to postulate a one-step condensation of 2-pyrolidones with 6-aminopyrimidines **1a**–**b** to prepare 6-imino-5-tetrahydro-2-pyrrolylidenhexahydro-2,4-pyrimidinediones **2a–d** by interaction with phosphorus trichloride, probably through the formation of intermediates such as the corresponding imino chlorides and Vilsmeier-type complexes.[5](Scheme 1).

It should be noted that the usage of 2-pyrrolidone instead of 1,4-dioxane brings to small increase of yields of synthesis of **2a–b** (Table 1). We believe that the low yields of **2b** and **2d** are caused by bad solubility of the starting pyrimidines **1b**, while the compounds **2a** and **2c** were synthesized in good yields (Table 1).[6] The condensation of **1a–b** with 2-pyrrolidones gave only **2a–d**, and other isomers containing double bonds with the pyrrolidine ring were not detected.

The method for selective reduction of amide and nitrile groups by $NaBH_4$/CH_3OH/$CoCl_2$ is well established.[7] On the other hand, it is known that cyclic polyethers (crown ethers) are able to accelerate the reaction rates and induce high selectivity in reactions by

* Corresponding author.
E-mail address: ashot@enzymebiosystems.com (A. Martirosyan).

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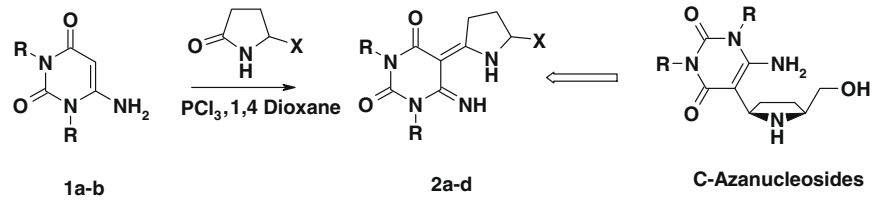


Scheme 1.

Table 1
Synthesis of 6-imino-5-tetrahydro-2-pyrrolylidenhexahydro-2,4-pyrimidinediones **2a–d**

Compd no.	Solvent	Yield (%)
2a	1,4-Dioxane	75
2a	2-Pyrrolidone	80
2b	1,4-Dioxane	30
2b	2-Pyrrolidone	35
2c	1,4-Dioxane	70
2d	1,4-Dioxane	28

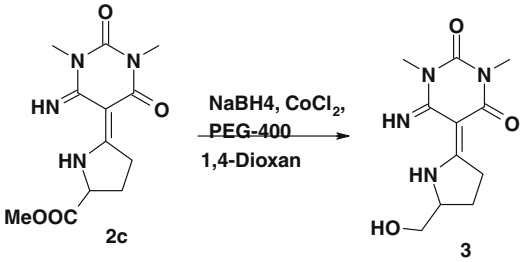
the crown ether-activated anion species. Polyethylene glycol (PEG-400) is an excellent substitute for crown ethers and it has been used as a co-solvent in the reduction of carbon–carbon triple or double bonds by $NaBH_4/PdCl_2$ in PEG-400/CH_2Cl_2, where $PdCl_2$ is used in catalytic quantities.[8] Using the system of $NaBH_4$/1,4-dioxane/$CoCl_2$/PEG-400 we anticipated a simple and selective reduction of the 6-imino group of **2c**.

However, the 6-imino group of **2c** had shown stability in the conjugated system with carbon–carbon double bond, we observed the reduction of the ester moiety of **2c** with 3 equiv of $NaBH_4$/1,4-dioxane/$CoCl_2$/PEG-400 in 80% yield (Scheme 2).[9]

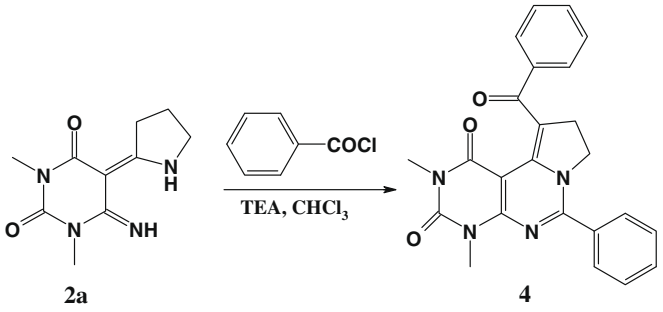
In an attempt to increase the reductive activity of the 6-imino group we used benzoyl chloride to acylate **2a**. Surprisingly, we found that a double incorporation of the benzoyl moiety had occurred involving migration of C–C double bond into pyrrolidine ring accompanied by an acylation of the enamine and condensation to give **4** (Scheme 3).[10]

It should be noted that a thin layer chromatography (TLC) control of the course of the reaction shows only the presence of the starting and the final compounds. The final compound **4** was consumed completely after the addition of 2 equiv of benzoyl chloride. This observation allows supposing that all the above-mentioned processes take place simultaneously.

The assignment of the structure was further confirmed by X-ray structure analysis of **4** as shown in Figure 1. The diffraction experiment was carried out on CAD4 'Enraf-Nonius' diffractometer. The compound **4** $C_{24}H_{20}N_4O_3$ is crystallized in monoclinic C 2/*c* space group (a = 36.230(7) Å, b = 5.4187(11) Å, c = 21.741(4) Å, β = 110.43(3)°). A total of 9159 reflections were collected and 4763 are unique (R_{int} = 0.057). R_1 and wR_2 are 0.0549 [$I > 2\sigma(I)$] and 0.1188 (all data), respectively. All observed interatomic distances were in good agreement with their mean statistical values.[11]



Scheme 2.



Scheme 3.

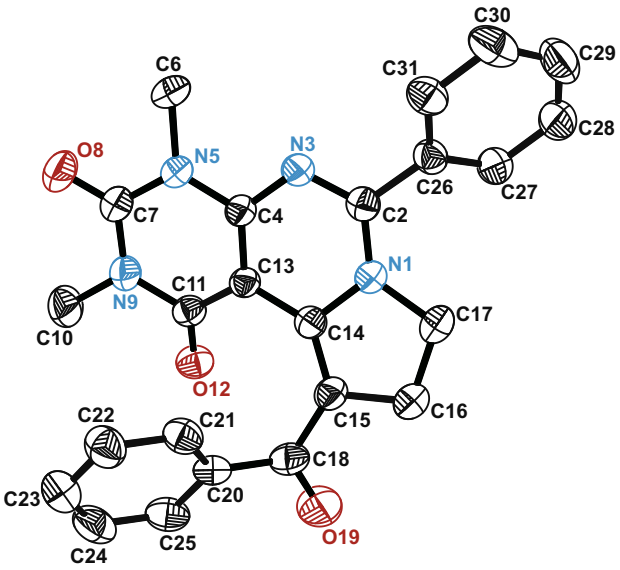


Figure 1.

It should be noted that all these compounds showed moderate activity in primary lymphocytes infected with human immunodeficiency virus type 1 (HIV-1).[12] HIV drug susceptibility assay was done as previously described.[13]

3. Conclusion

The synthesis of novel 6-imino-5-tetrahydro-2-pyrrolylidenhexahydro-2,4-pyrimidinediones as intermediates for the synthesis of C-azanucleosides has been accomplished. The application

of hydrogenation on the final stage of the synthesis of C-azanucleosides provides wide choice of catalysts for stereo selective and asymmetric synthesis.

Described above, examples of transformations specific for these systems **(2a–d)** such as the reaction of 6-imino-1,3-dimethyl-5-tetrahydro-2-pyrrolylidenhexahydro-2,4-pyrimidinedione with benzoyl chloride and a method for the selective reduction of the carbomethoxy group of methyl 5-(4-imino-1,3-dimethyl-2,6-dioxohexahydro-5-pyrimidinyliden)-2-pyrrolidine carboxylate by system $NaBH_4$/1,4dioxane/$CoCl_2$/PEG-400 may play an essential role in understanding and planning future investigations of similar systems.

Studies on the extension of these reactions for the synthesis of various C-aza nucleoside derivatives and 1,2,3,4,8,9-hexahydropyrimido[5,4-*e*]pyrrolo[1,2-*c*]pyrimidine-1,3-diones are in progress.

Acknowledgment

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Supplementary data

^{13}C and ^{1}H NMR spectra[14] for the compounds **2a–d**, **3**, **4** are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.11.010.

References and notes

1. (a) Slater, M. J.; Amphlett, E. M.; Andrews, D. M. *J. Med. Chem.* **2007**, *50*, 897; (b) Butora, G.; Olsen, D. B.; Carroll, S. S. *Bioorg. Med. Chem.* **2007**, *15*, 5219; (c) Guntaka, R. V.; Varma, B. R.; Weber, K. T. *Int. J. Biochem. Cell Biol.* **2003**, *35*, 22.
2. (a) Yokoyama, M.; Toyoshima, H.; Shimizu, M.; Togo, H. *J. Chem. Soc., Perkin Trans. 1* **1997**, 29; (b) Ganem, B.; Papandreou, G. *J. Am. Chem. Soc.* **1991**, *113*, 898; (c) Schramm, V. L. *Annu. Rev. Biochem.* **1998**, *67*, 693.
3. (a) Furneaux, R. H.; Limberg, G.; Tyler, P. C.; Schramm, V. L. *Tetrahedron* **1997**, *53*, 2915; (b) Yokoyama, M.; Ikeue, T.; Ochiai, Y. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2185; (c) Wong, C.-H.; Provencher, L.; Poroco, J. A. *J. Org. Chem.* **1995**, *60*, 1492; (d) Chen, X. Y.; Link, T. M.; Schramm, V. L. *J. Am. Chem. Soc.* **1996**, *118*, 3067; (e) Hainke, S.; Arndt, S.; Seitz, O. *Org. Biomol. Chem.* **2005**, *3*, 4233; (f) Wellington, K. W.; Benner, S. A. *Nucleosides, Nucleotides, Nucleic Acids* **2006**, *25*, 1309; (g) Häberli, A.; Leumann, C. J. *Org. Lett.* **2001**, *3*, 489; (h) Kim, D. C.; Yoo, K. H.; Kim, D. J.; Chung, B. Y.; Park, S. W. *Tetrahedron Lett.* **1999**, *40*, 4825.
4. Fasseur, D.; Rigo, B.; Leduc, C.; Cauliez, P.; Couturier, D. *J. Heterocycl. Chem.* **1992**, *29*, 1285.
5. Black StC, D.; Bowyer, C. M.; Ivory, A. J.; Jolliffe, K. A.; Kumar, N. *Tetrahedron* **1996**, *52*, 4687.
6. *Typical experimental procedure for preparation of* **2a–d**: To a 1,4-dioxane (10 mL) solution of 2-pyrrolidone or pyroglutamic acid methyl ether (0.3 mmol) at 0–5 °C was added PCl_3 (0.3 mmol). The mixture was stirred at room temperature for 10 min, and **1a–b** (2 mmol) in 1,4-dioxane (10 mL) was added over a period of 10 min. The stirring was continued at 90–95 °C for 5 h. The mixture was concentrated under reduced pressure. To the crude mixture was added 20 mL of ice water, filtered, and neutralized with 30% NH_4OH. The residue was separated by filtration and purified by crystallization from the convenient solvent. *6-Imino-1,3-dimethyl-5-tetrahydro-1H-2-pyrrolylidenhexahydro-2,4-pyrimidinedione* (**2a**): Product **2a** was prepared in 75% of yield. Mp = 214–215 °C; ^{1}H NMR (DMSO-d_6/CCl_4 1/3), δ, ppm (*J*, Hz): 12.22 (1H, br, NH); 7.51 (1H, br, NH); 3.79 (2H, tt, J_1 = 7.5, J_2 = 1.7, NCH_2); 3.35 (3H, s, CH_3); 3.17 (3H, s, CH_3); 3.12 (2H, tt, J_1 = 8.2, J_2 = 1.7, $CH_2C{=}N$); 1.82 (2H, J_1 = 8.2, J_2 = 7.5, $CH_2CH_2CH_2$); ^{13}C NMR (DMSO-d_6/CCl_4 1/3), δ, ppm (*J*, Hz): 21.5 (CH_2); 27.0 (CH_3); 28.9 (CH_3); 38.1 (CH_2); 57.0 (NCH_2); 83.8 (*C*–CO); 149.7 (NC); 155.6 (NC); 160.4 (NC); 173.2 (NC). IR (FT-IR Necsus Nicolet spectrometer, thin film):3320, 3297, 1699, 1620, 1567, 1528, 1470, 1385 cm^{-1}. Anal. Calcd for $C_{10}H_{14}N_4O_2$: C, 54.04; H, 6.35; N, 25.21. Found: C, 54.22; H, 6.57; N, 25.03. *6-Imino-5-tetrahydro-1H-2-pyrrolylidenhexa hydro-2,4-pyrimidinedione* (**2b**): Product **2b** was prepared in 30% of yield. Mp = 300–305 °C; ^{1}H NMR (DMSO-d_6/CCl_4 1/3), δ, ppm (*J*, Hz): 11.62 (1H, br, NH); 11.34 (1H, br, NH); 8.28 (2H, br, NH_2); 3.76 (2H, t, J = 7.5, NCH_2); 3.30 (2H, t, J = 7.5, CH_2); 2.08 (2H, k, J = 7.5, $CH_2CH_2CH_2$): ^{13}C NMR (DMSO-d_6/CCl_4 1/3), δ, ppm (*J*, Hz): 20.0 (CH_2); 35.6 (CH_2); 50.4 (br, NCH_2); 83.2 (*C*–CO); 147.9 (NC); 158.7 (NC); 164.0 (NC); 173.9 (NC). IR (thin film): 3330, 3295, 3110, 1736, 1709, 1651, 1529, 1467, 1384 cm^{-1}. Anal. Calcd for $C_8H_{10}N_4O_2$: C, 49.48; H, 5.19; N, 28.85. Found: C, 49.77; H, 5.35; N, 28.73. *Methyl 5-(4-imino-1,3-dimethyl-2,6-dioxohexahydro-5-pyrimidinyliden)-2-pyrrolidine carboxylate* (**2c**): Product **2c** was prepared in 70% of yield. Mp = 220–221 °C; ^{1}H NMR (DMSO-d_6/CCl_4 1/3), δ, ppm (*J*, Hz): 11.92 (1H, br, NH); 7.72 (1H, br, =NH); 4.64 (1H, ddt, J_1 = 8.8, J_2 = 6.6, J_3 = 1.5, NCH); 3.69 (3H, s, OCH_3); 3.37 (3H, s, NCH_3); 3.18 (3H, s, NCH_3); 3.22 (1H, m) and 3.16 (1H, m, CH_2); 2.15 (1H, m) and 1.90 (1H, m, CH_2CH): ^{13}C NMR (DMSO-d_6/CCl_4 1/3), δ, ppm (*J*, Hz): 25.6 (CH_2); 27.1 (CH_3); 29.0 (CH_3); 38.5 (CH_2); 51.0 (OCH_3); 70.3 (CH); 83.7 (*C*–CO); 149.5 (NC); 155.7 (NC); 160.4 (NC); 172.8 (NC); 175.6 (OCO). IR (thin film): 3500–3100 (br, s), 1743, 1700, 1610, 1568, 1534, 1460, 1380 cm^{-1}. Anal. Calcd for $C_{12}H_{16}N_4O_4$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.67; H, 5.61; N, 20.12. *Methyl5-(4-imino-2,6-dioxohexahydro-5-pyrimidinyliden)-2-pyrrolidine-carboxylate* (**2d**): Product **2d** was prepared in 28% of yield. Mp = 280–281 °C; ^{1}H NMR (DMSO-d_6/CCl_4 1/3), δ, ppm (*J*, Hz): 10.71 (1H, br, NH); 10.54 (1H, br, NH); 10.41 (1H, br, NH); 7.03 (1H, br, =NH); 4.63 (1H, dd, J_1 = 8.6, J_2 = 6.4, NCH); 3.65 (3H, s, OCH_3); 3.35–2.97 (2H, m, $CH_2C{=}$); 2.08 (1H, m, $CHCH_2$); 1.82 (1H, m, $CHCH_2$). ^{13}C NMR (DMSO-d_6/CCl_4 1/3), δ, ppm (*J*, Hz): 25.5 (CH_2); 38.4 (CH_2); 51.7 (OCH_3); 70.8 (NCH); 83.0 (*C*–CO); 149.2 (NC); 156.5 (NC); 163.0 (NC); 175.1 (NC). IR (thin film):3520, 3380, 3290, 3110, 1746, 1663, 1631, 1602, 1520, 1460, 1384 cm^{-1}. Anal. Calcd for $C_{10}H_{12}N_4O_4$: C, 47.62; H, 4.80; N, 22.21. Found: C, 47.84; H, 4.67; N, 22.08.
7. (a) Satoh, T.; Suzuki, S. *Tetrahedron Lett.* **1969**, 1931; (b) Shinichi, I.; Yoshiki, S.; Koichi, I. *Synthesis* **1988**, 995; (c) Akabori, S.; Takanoshi, Y. *J. Chem. Soc., Perkin Trans. 1* **1991**, 479.
8. Suzuki, N.; Kaneko, Y.; Tsukanaka, T.; Nomoto, T.; Ayaguchi, Y.; Izawa, Y. *Tetrahedron* **1985**, *41*, 2387.
9. *5-(5-Hydroxymethyltetrahydro-1H-2-pyrrolyliden)-6-imino-1,3-dimethylhexahydro-2,4-pyrimidinedione* **3**: The mixture of **2c** 2.8 g (10 mmol), $NaBH_4$ 1.1 g (30 mmol), $CoCl_2{\cdot}6H_2O$ 0.35 g (1.5 mmol), and PEG-400 4 g (10 mmol) in 10 mL of 1,4-dioxane was stirred under reflux for 2 h. The mixture was concentrated under reduced pressure. To the crude mixture was added 10 mL of ice water and filtered. The residue was purified by crystallization from ethanol to give 2.0 g of **3** in 80% yield. Mp = 174–175 °C: ^{1}H NMR (DMSO-d_6/CCl_4 1/3), δ, ppm (*J*, Hz): 12.31 (1H, br, NH); 7.49 (1H, br, =NH); 4.23 (1H, t, J = 5.5, OH); 4.04 (1H, m, NCH); 3.44 (2H, m, OCH_2); 3.35 (3H, s, NCH_3); 3.17 (3H, s, NCH_3); 3.21 (1H, m) and 3.06 (1H, m, $CH_2C{=}$); 1.90 (1H, m) and 1.58 (1H, m, $CHCH_2$): ^{13}C NMR (DMSO-d_6/CCl_4 1/3), δ, ppm (*J*, Hz): 23.97 (CH_2); 27.02 (CH_3); 28.78 (CH_3); 37.96 (CH_2); 65.10 (OCH_2); 70.43 (CH); 83.82 (=C); 149.78 (N–C=); 155.68 (N=C); 160.59 (CO); 173.17 (CO). IR (thin film): 3345, 3270, 3190, 1703, 1624, 1560, 1549, 1470, 1380 cm^{-1}. Anal. Calcd for $C_{11}H_{16}N_4O_3$: C, 52.37; H, 6.39; N, 22.21; Found: C, 52.22; H, 6.45; N, 22.50.
10. *10-Benzoyl-2,4-dimethyl-6-phenyl-1,2,3,4,8,9-hexahydropyrimido[5,4-e]pyrrolo-[1,2-c]pyrimidine-1,3-dione* **4**: To a $CHCl_3$ (20 mL) solution of **2a** 2.2 g (10 mmol) and TEA 1.0 g (10 mmol) at room temperature was added benzoyl chloride 2.8 g (20 mmol). The mixture was stirred under reflux for 2 h. The organic solution was washed with water, dried with $MgSO_4$, and concentrated under reduced pressure. The crude mixture was purified by crystallization from methanol to give 2.7 g of **4** in 67% of yield. Mp = 249–250 °C: ^{1}H NMR (DMSO-d_6/CCl_4 1/3), δ, ppm (*J*, Hz): 7.74 (2H, m, H_{aryl}); 7.63 (2H, m, H_{aryl}); 7.58–7.50 (3H, m, H_{aryl}); 7.38–7.27 (3H, m, H_{aryl}); 4.14 (2H, t, J = 9.2, NCH_2); 3.45 (3H, s, CH_3); 3.02 (2H, dd, J_1 = 9.8, J_2 = 8.4, CH_2); 1.82 (3H, s, CH_3). ^{13}C NMR (DMSO-d_6/CCl_4 1/3), δ, ppm (*J*, Hz): 27.1 (CH_3); 28.9 (CH_3); 29.3 (CH_2); 49.2 (NCH_2); 104.7 and 104.8 (*C*–CO); 126.9, 127.2, 127.6 and 128.0 (*ortho* and *meta* CH); 129.8 and 130.5 (para-CH); 132.8; 139.4; 140.8; 150.1; 154.9; 157.0; 160.7; 190.7 (CO-Ph). IR (thin film):1704, 1669, 1604, 1560, 1501, 1468, 1380 cm^{-1}. Anal. Calcd for $C_{24}H_{20}N_4O_3$: C, 69.89; H, 4.89; N, 13.58. Found: C, 69.72; H, 4.93; N, 13.75.
11. CCDC 655561 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
12. The antiviral 50% effective concentration (EC_{50}) was determined from the concentration–response curve using the median effect method. EC_{50} for compounds **2a**––57 μM, **2b**––>100 μM, **2c**––32 μM, **2d**––>100 μM, **3**––>100 μM, **4**––4.5 μM.
13. Schinazi, R. F.; Sommadossi, J. P.; Saalmann, V.; Cannon, D. L.; Xie, M.-W.; Hart, G. C.; Smith, G. A.; Hahn, E. F. *Antimicrob. Agents Chemother.* **1990**, *34*, 1061.
14. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury-300Vx instrument (300.077 and 75.462 MHz, respectively) at 30 °C.