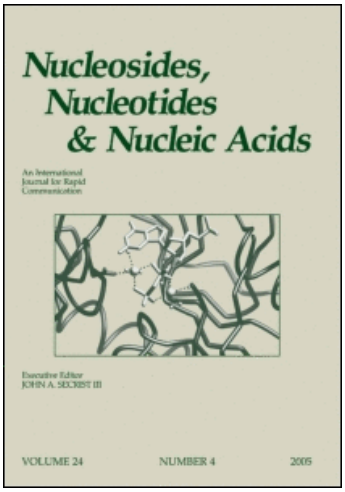

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Omar Moukha-chafiq[a]; Mohamed Labd Taha[a]; Abdelmalek Mouna[a]
[a] Facultes des Sciences, Laboratoire de Chimie Bio-Organique Appliquée, Agadir, Maroc

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SYNTHESIS AND ANTI-HSV ACTIVITY OF NEW N_1-ACYCLIC C_4 AND C_6-DISUBSTITUTED PYRAZOLO[3,4-D]PYRIMIDINE NUCLEOSIDES

Omar Moukha-chafiq, Mohamed Labd Taha, and Abdelmalek Mouna □
Laboratoire de Chimie Bio-Organique Appliquée, Facultes des Sciences, Agadir, Maroc

□ *Several N_1-(2-hydroxyethoxy)methyl, (4-hydroxybutyl) and (2,3-dihydroxy-1-propoxy)methyl-C_4,C_6-disubstituted-1H-pyrozolo[3,4-d]pyrimidines were synthesized. Some of them were evaluated against herpes simplex virus 1 and 2 replications in E_6 SM cells.*

Keywords Pyrazolo[3,4-d]pyrimidines; acyclonucleoside analogues

Recently, there have been considerable advances in the chemotherapy of virus infections. Nevertheless, with the increase in the use of antiviral drugs, a development of resistance to antivirals has been observed. In the chemotherapy of herpes simplex virus infections, acyclovir is used clinically as an anti-herpes drug. However, herpes viruses may sometimes acquire resistance to acyclovir in immunocompromised patients.[1] Many research approaches currently are aimed at developing new types of antiviral agents that have a wide range of efficacy without serious adverse effects and are potent against viral strains resistant to current antiviral agents. The search for more effective antiviral agents has so far developed only a few compounds that have reached prominence at clinical level.

Acyclic nucleosides are of interest because of the antiviral activity of a large number of this class of compounds.[2] Up to now, there have been only a few reports regarding the synthesis of pyrazolo[3,4-d]pyrimidine acyclonucleosides. As an extension of our studies on mono di and trisubstituted pyrazolo[3,4-d]pyrimidine derivatives[3] in which some of them showed an interesting antiviral, antitumor and/or antituberculosis activity, we describe

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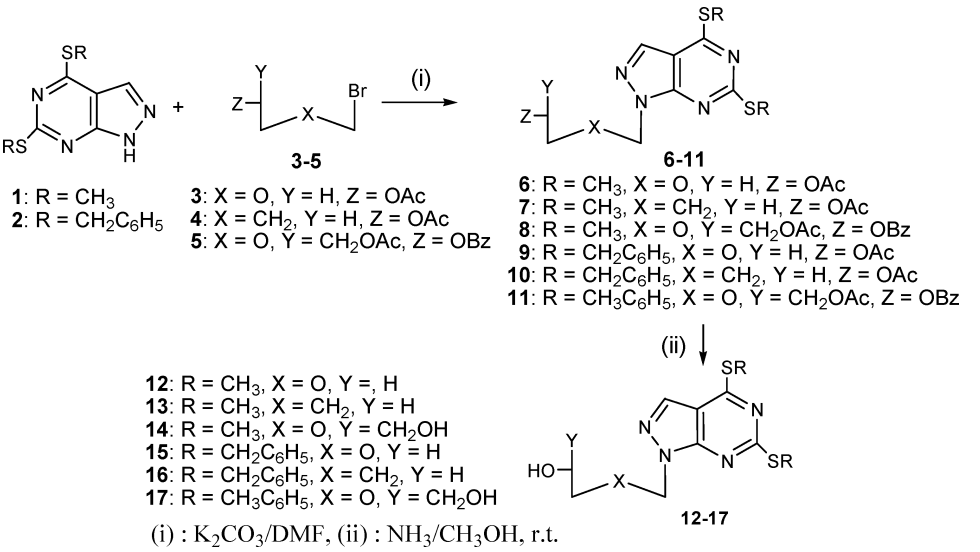
Address correspondence to Omar Moukha-chafiq, Drug Discovery Division, Southern Research Institute, 2000 Ninth Avenue South, Birmingham, AL 35205. E-mail: moukhachafiq@sri.org



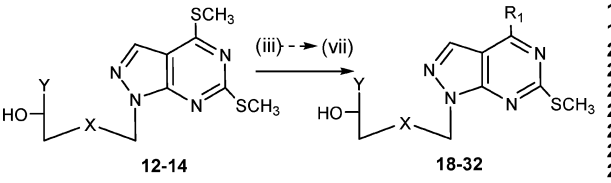
SCHEME 1

herein the synthesis of the anti-herpes acyclovir, HBG and iso-DHPG 4,6-disubstituted pyrazolo[3,4-d]pyrimidinic analogues. We also have studied the effects of some of these acyconucleosides on herpes simplex virus type 1 and 2 replications in E_6SM cells.

The approach to the synthesis of acyclonucleosides **12–17** involves coupling pyrazolo[3,4- d]pyrimidines **1** and **2** with acyclic chain moieties **3–5** (Scheme 1).

The coupling pseudo-sugars **3**, **4**, and **5** can be synthesized from 1,3-dixolane, tetrahydrofuran and glycerol, respectively, as previously describe.[4–6] The bases used for the direct coupling 4,6-dimethyl pyrazolo[3,4-d]pyrimidine **1** and 4,6-dibenzyl pyrazolo[3,4-d]pyrimidine **2** were synthesized in 6 steps from commercially available malononitrile and triethyl orthoformate following a synthetic pathway previously described by Robins et al.[7] Nucleophilic displacement of the bromine group of the **3–5** with **1–2** in the presence of potassium carbonate in DMF gave regioselectively, **6–11** and small trace of their N_2-isomers which easily could be separated by silica gel column chromatography. The two regioisomers could be easily distinguished by their UV spectra. Treatment of the desired isomers **6–11** with methalonic ammonia at room temperature afforded the target compounds **12–17**.

Compounds **12–14** served as precursors for the synthesis of acyclonucleosides **18–32** (Scheme 2). When compounds **12–14** were treated with methanolic ammonia in a sealed reacting vessel at 100°C, the 4-amino derivatives **18–20** were obtained in 86%, 88% and 80% yield, respectively. Condensation of **12–14** with methyl amine in aqueous solution or benzyl



18: $R_1 = NH_2$, X = O, Y =, H
19: $R_1 = NH_2$, X = CH_2, Y = H
20: $R_1 = NH_2$, X = O, Y = CH_2OH
21: $R_1 = NHCH_2C_6H_5$, X = O, Y = H
22: $R_1 = NHCH_2C_6H_5$, X = CH_2, Y = H
23: $R_1 = NHCH_3C_6H_5$, X = O, Y = CH_2OH
24: $R_1 = NHCH_3$, X = O, Y =, H
25: $R_1 = NHCH_3$, X = CH_2, Y = H
26: $R_1 = NHCH_3$, X = O, Y = CH_2OH
27: $R_1 = OCH_3$, X = O, Y = H
28: $R_1 = OCH_3$, X = CH_2, Y = H
29: $R_1 = OCH_3$, X = O, Y = CH_2OH
30: R_1 = OH, X = O, Y = H
31: R_1 = OH, X = CH_2, Y = H
32: R_1 = OH, X = O, Y = CH_2OH

(iii): $NH_3/MeOH/_{100}$ oC, (iv): $NHCH_3$/reflux, (v): $NH_2CH_2C_6H_5$/ethanol/reflux, (vi): NaOMe/MeOH, (vii): NaOH

SCHEME 2

amine in ethanol at reflux afforded **21–26** in good yields. Products **27–29** were synthesized in 83%, 87%, and 82% yield, respectively, via treatment of **12–14** with $NaOCH_3/CH_3OH$ solution at room temperature. Reaction of **12–14** with sodium hydroxide solution (2N) at room temperature during 4–6 hours gave compounds **30–32** in 70%, 72%, and 78% yield respectively. All structures of the synthetic products were identified by ^1H NMR, mass spectra, UV and/or elemental analysis as for example compound **12**.[8]

ANTI-HSV ACTIVITY

The antiviral activity effect of some of the target acyclonucleosides on herpes simplex virus type 1 (HSV-1) (KOS) and (HSV-2) (G) replications was determined (Table 1).

TABLE 1 Cytotoxicity and antiviral activity in E_6SM cells

		Minimum inhibitory concentration[b] (μg/ml)	
Compound	MCC[a] (μg/ml)	HSV-1 (KOS)	HSV-2 (G)
12	400	>80	>80
14	400	>80	>80
15	80	>16	>16
16	400	240	240
17	16	>3.2	>3.2
18	80	>80	>80
19	>400	>400	240
21	>400	>400	240
22	400	240	240
24	>400	>80	>80
27	400	240	240
28	>400	>400	400
Ribavirine	>400	400	400
ACV	>100	0.0064	0.0192

[a]Inhibitory concentration required to reduce virus plaque formation by 50%. Virus input was 100 plaque forming units (PFU).

[b]Minimum cytotoxic concentration required to cause a microscopically detectable alteration of normal cell morphology.

Data for ribavirine, and ACV are shown for comparison. Our results show that none of the tested compounds showed any significant activity except for compounds **16, 19, 21, 22, 27**, and **28**, which are slightly active against HSV-1 and/or HSV-2 (Table 1).

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8. **1-(2-hydroxyethxy)meythl-4,6-dimethylthio-1*H*-pyrazolo[3,4-d]pyrimidine 12.** R_f: 0.52 ($CHCl_3$: CH_3OH, 90:10). M.p.: 71–72°C (ethanol). UV (ethanol) λ_{max}: 249 nm (ε: 7 800). ^{1}H-NMR (Me_2SO-d_6) δ: 2.53 (s, 3H, 6-SCH_3), 2.65 (s, 3H, 4-SCH_3), 3.34–3.51 (m, 4H, OCH_2CH_2O), 4.61 (t, *J*: 5.39 Hz, 1H, HO, D_2O exchangeable), 5.66 (s, 2H, OCH_2N), 8.26 (s, 1H, H_3). MS (FAB^+, GT) *m/z:* 287 $[M+H]^+$. Elem. Anal. Calcd. for $C_{10}H_{14}N_4O_2S_2$ (286.38): C 41.94%, H 4.93%, N 19.56%, Found: C 42.26%, H 5.14%, N 19.82%.