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Full Paper

Nucleoside Synthesis

4-Heterosubstituted Cyclopentenone Antiviral Compounds: Synthesis, Mechanism, and Antiviral Evaluation

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Abstract: Racemic 4-oxocyclopent-2-en-1-yl acetate was used in a short synthesis of nucleoside analogues with pyrimidine and purine heterobases. The protocol is based on a typical nucleophilic substitution process. Uracil, thymine, 6-chloropurine, and some adenines gave the expected 4-heterosubstituted products along with the isomeric 2-heterosubstituted compounds as minor components. Samples of selected products were evaluated for their antiviral activity in a primary screening against a variety of viruses belonging to different classes. One of the compounds was found to be highly active against human papilloma virus (HPV).

Introduction

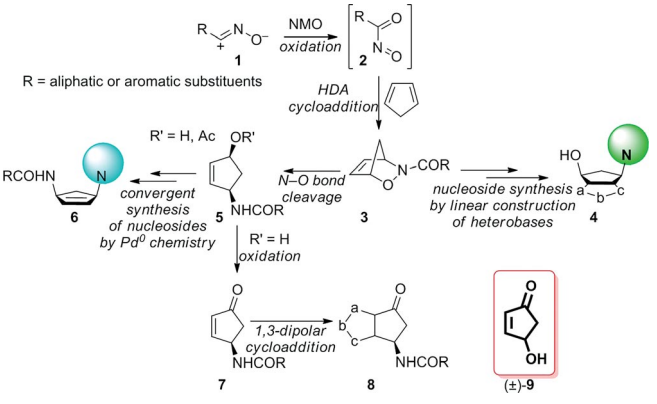
The search for new compounds for the treatment of viral diseases and for selective antiviral chemotherapy is being actively pursued in our group, and various scaffolds have been used in working towards this goal. Recently, we have revised our synthetic approach to achieve the entire synthesis in a few steps, taking advantage of peculiarities of the starting materials and intermediates, maximizing the yields and decreasing the time required to reach the final products.[1]

Nitrile oxides **1** and transient nitrosocarbonyl intermediates **2** derived from them by oxidation are the synthetic tools that we have used extensively to obtain a variety of different nucleoside analogues (Scheme 1).[2]

Nitrosocarbonyl compounds **2** have found wide applications in nucleoside synthesis because of their high reactivity in hetero-Diels–Alder (HDA) cycloaddition reactions with cyclopentadiene and dienes in general, and because of the synthetic potential of the HDA cycloadducts (i.e., **3**), which were elaborated into the desired nucleosides (i.e., **4**) through linear construction of the heterobases.[3]

Alternatively, cycloadducts **3** can undergo mild reductive N–O bond cleavage to give the corresponding hydroxycyclopentene amides (i.e., **5**), which have been used in a Pd^0-catalysed convergent approach to nucleoside analogues of type **6**.[4]

The dipolarophilic properties of substrates **5** have also been investigated in the presence of nitrile oxides as well as their oxidized derivatives, cyclopentenone amides **7**, which gave the



Scheme 1. Nitrile oxides and nitrosocarbonyl compounds in the synthesis of nucleoside analogues: an overview. NMO = *N*-methylmorpholine *N*-oxide.

hydrogen-bonding-stereocontrolled cycloadducts **8**.[5] To gain further insight into the selectivity of the 1,3-dipolar cycloadditions of nitrile oxides with these substrates under hydrogen-bonding-directed conditions[6] and also in metal-mediated reactions,[7] we investigated the 1,3-dipolar cycloaddition reactions of racemic 4-hydroxy-2-cyclopentenone (±)-**9**.[8]

The chemistry of this scaffold has been extensively investigated and reviewed, as the hydroxycyclopentenone moiety often appears in natural products and biologically active compounds, or constitutes the privileged starting material for their synthesis.[9] Recently, Reiser and co-workers used the chemistry of 4-hydroxy-2-cyclopentenone for the enantioselective synthesis of *ent*-norarisateromycin[10] and other enantiopure guaianes and pseudoguaianolides.[11]

We also took the opportunity to reinvestigate the synthetic utility of racemic 4-hydroxy-2-cyclopentenone (±)-**9** in a short approach to nucleoside analogues by using pyrimidine and purine heterobases. Intriguing mechanistic insights were obtained by performing the syntheses with selected heterobases

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as well as with enantiomerically enriched 4-hydroxy-2-cyclopentenone acetate.

Samples of some pyrimidine and purine derivatives were sent for antiviral in-vitro testing, and the results are briefly discussed.

Results and Discussion

Synthesis of the Uracil and Thymine Derivatives

Racemic 4-oxocyclopent-2-en-1-yl acetate [(±)-**10**] was prepared by acetylation[12] of 4-hydroxy-2-cyclopentenone [(±)-**9**][10,13] in the presence of acetic anhydride and pyridine in THF as solvent.

The coupling reactions were carried out by the in situ generation of the conjugate bases of benzoyl-protected uracil and thymine bases, obtained according to literature procedures,[14] by treatment with NaH (95 %) in dry acetonitrile. The reaction mixtures were stirred under an inert gas for 3.5 h, and after this time they were quenched with ice, and CH_2Cl_2 was added. From the organic phase, crude products were obtained, which were then submitted to chromatographic separation to isolate the products (Scheme 2).

The regioisomeric adducts **12a**,**b** and **13a**,**b** were obtained in very good yields; the uracil derivatives were obtained in an 89:11 ratio, while the thymine derivatives were obtained in a 92:8 ratio. The structures were assigned on the basis of analytical and spectroscopic data.

^{1}H NMR spectroscopy was used for the structure determination and for distinguishing the regioisomeric compounds; Table 1 collects the diagnostic signals, which clearly differentiate the two types of structures.

Table 1. ^{1}H NMR diagnostic signals (δ, [D$_6$]DMSO) of compounds **12a**,**b** and **13a**,**b**.

12	CH_2	CH–N	CH=CH–C=O[a]		CH=CH(Me)[b]
a	2.55 (dd)	5.69 (m)	7.82 (dd)	6.49 (dd)	7.68 (d)
	2.83 (dd)				5.86 (d)
b	2.53 (dd)	5.71 (m)	7.92 (dd)	6.49 (dd)	6.55 (s)
	2.84 (dd)				(1.82, d)
13	CH_2–CH_2		CH=C–N		CH=CH(Me)
a	2.45 (m)		6.57 (s)		8.18 (d)
	3.10 (m)				6.11 (d)
b	2.44 (m)		6.55 (s)		8.06 (s)
	3.12 (m)				(1.95, s)

[a] Cyclopentene moiety. [b] Pyrimidine moiety.

When the pyrimidine ring is attached to the C-4 carbon atom of the 2-cyclopentenone moiety, signals of two olefinic protons are found: a doublet (J = 6 Hz) at δ = 6.49 ppm for both compounds, and a doublet of doublets (J = 6, 3 Hz) at δ = 7.82 and δ = 7.92 ppm, respectively, for **12a** and **12b**. The deshielded olefinic protons are also coupled with the CH–N proton with a signal at $\delta \approx$ 5.7 ppm, which couples further with the methylene group of the cyclopentenone ring. This situation is not found in compounds **13**, where the lack of signals attributable to the CH–N protons indicates that the uracil or thymine ring is directly connected to an sp^2 carbon atom. Moreover, signals of two methylene groups are found at δ = 2.4–3.1 ppm and of a single olefinic proton at $\delta \approx$ 6.6 ppm for both adducts.

These results have clear and quite predictable mechanistic implications; the investigation of the mechanism will be presented and discussed in a specific section of this paper.

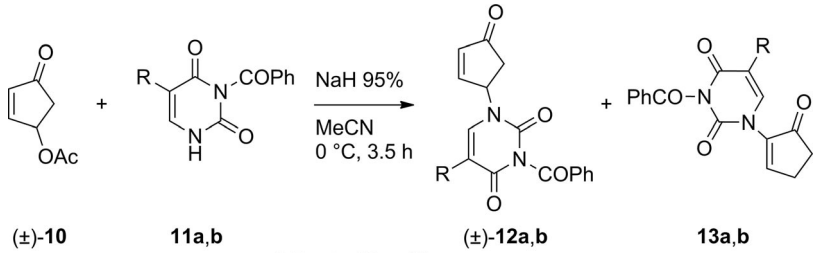
From an experimental point of view, further details can be added to those given above. The reactions were also carried out in other anhydrous solvents such as CH_2Cl_2 and THF. The results were similar in terms of the regioisomeric ratio of the products **12a**,**b** and **13a**,**b**. However, the products were obtained in lower yields (25–35 %), because the nucleophiles were not generated efficiently in those solvents.

Racemic 4-oxocyclopent-2-en-1-yl mesylate could also be used as the starting material instead of acetate (±)-**10**. When the reactions were run in anhydrous acetonitrile under the same experimental conditions, products **12a**,**b** and **13a**,**b** were obtained again in lower yields (44–49 %) and with similar regioisomeric ratios. Being a better leaving group, the mesylate is presumably prone to undergo fast elimination to give the cyclopentadienone (vide infra).

Synthesis of the 6-Chloropurine Derivatives

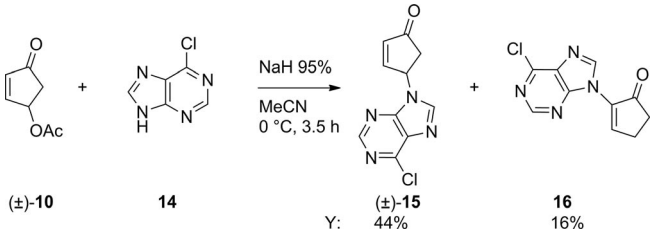
Under the same experimental conditions, the coupling reaction of 6-chloropurine (**14**) with oxocyclopentenyl acetate (±)-**10** was carried out by in situ generation of the conjugate base in the presence of NaH (95 %) in dry acetonitrile. After 2 h at 0 °C under an inert gas, the residue, obtained from the usual workup procedure, was submitted to chromatographic separation to give the products (Scheme 3).

Regioisomeric adducts **15** and **16** were obtained in moderate yields in a 73:27 ratio. The structure of adduct **15** was found to be identical to that reported in the literature,[10] while the



	R	12	13
a	H	75%	9%
b	Me	85%	7%

Scheme 2. Synthesis of uracil and thymine derivatives.



Scheme 3. Synthesis of 6-chloropurine derivatives.

structure of its regioisomer **16** was assigned on the basis of analytical and spectroscopic data.

As in the previous cases of the pyrimidine derivatives, compound **16** differs from the parent **15** because of the presence of signals of the two methylene groups at δ = 2.72 and 3.39 ppm and of a single olefinic proton at δ = 7.28 ppm.

Because of the overall lower yields of the products compared to the analogous reactions with pyrimidines, we briefly investigated carrying out the reactions in the presence of alternative bases to promote the in situ generation of the conjugate base of 6-chloropurine (**14**).

DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) gave interesting results at different reaction temperatures. Figure 1 shows the quantitative determination by HPLC analysis of the ratio of compounds **15**/**16** in the reactions carried out in the presence of DBU using a ratio of reagents **10**/**14** = 1:1 at 0 °C and –20 °C in anhydrous acetonitrile.

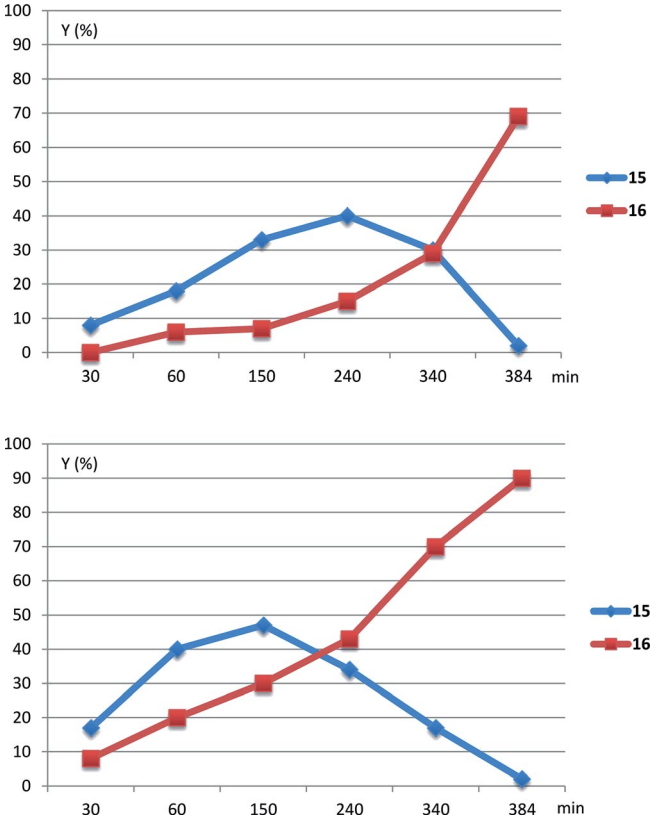


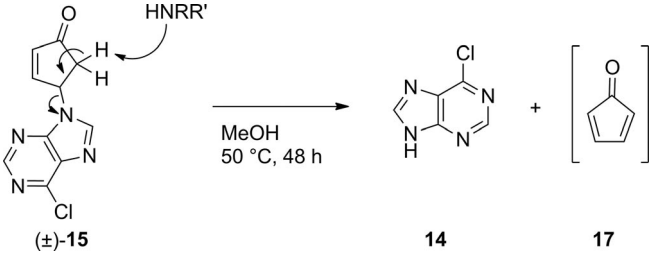
Figure 1. Coupling reaction of cyclopentenone **10** and 6-chloropurine (**14**) in the presence of DBU at 0 °C (top) and –20 °C (bottom).

When the reaction was run at 0 °C, the two regioisomeric products were formed together, and the yields increased with time up to a reaction time of 3.5–4.0 h; from this point on, the overall yields increased, but adduct **15** seems to give way to its regioisomer **16**. Similar behaviour was found when the reaction was run at –20 °C; the overall yields were slightly higher, but after 3–4 h compound **16** overtook **15** in terms of yield.

Control experiments demonstrated that bases had a detrimental effect on compound **15**, favouring regioisomer **16**. Hence, prolonged reaction times have to be avoided so that the synthesis will be directed towards the 4-heterosubstituted cyclopentenones as the major products. These results parallel those observed with NaH when used in typical syntheses.

The introduction of a 6-chloropurine ring onto a carbocyclic moiety sets up the functionalization of the 6-position of the heterocyclic ring with a variety of substituents, mainly amines, to give a library of adenine derivatives. Tentative experiments conducted by treatment of adduct **15** with amines in methanol solution at 50 °C for 48 h revealed an unexpected behaviour of the compound to be functionalized. Only the heterobase was recovered from the reaction mixture, and total degradation of the starting compound was observed.

Scheme 4 shows our interpretation of these results. The acidic protons located on the sp^3 C-5 carbon atom in **15** can be easily removed by the amines, and an elimination cascade reaction leads to the loss of heterocyclic base **14** and formation of the transient intermediate cyclopentadienone **17**. Structure **17** is known to be an antiaromatic intermediate, highly unstable, and prone to dimerize in a bis(pericyclic) Diels–Alder (DA) reaction or to decompose.[15]



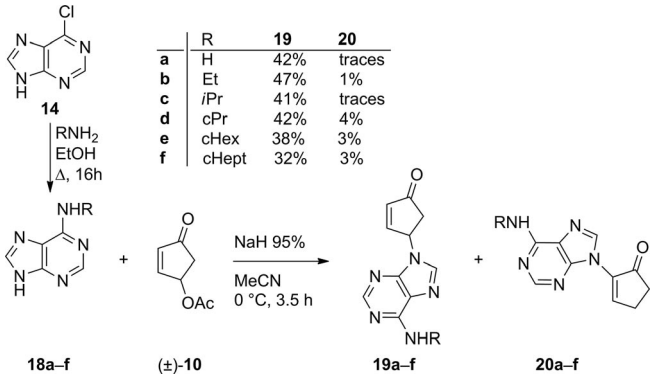
Scheme 4. Elimination mechanism in the reactions of compound **15** with amines.

The same behaviour was also observed for the pyrimidine derivatives when treated with amines. For these reasons, an alternative protocol for the synthesis of adenine derivatives had to be used.

Synthesis of the Adenine Derivatives

6-Chloropurine (**14**) was preliminary derivatized with some primary amines according to literature procedures by treatment with an excess (3 equiv.) of amines in ethanol at reflux overnight.[16] Adenine and some other derivatives are also commercially available.

Once isolated and purified, adenines **18a**–**18f** were used to functionalize oxocyclopentenyl acetate (±)-**10** under the typical conditions already described to give regioisomeric adducts **19a**–**19f** and **20a**–**20f** (Scheme 5).



	R	19	20
a	H	42%	traces
b	Et	47%	1%
c	*i*Pr	41%	traces
d	cPr	42%	4%
e	cHex	38%	3%
f	cHept	32%	3%

Scheme 5. Synthesis of adenine derivatives.

Adducts **19a**–**19f** were isolated in fair yields in keeping with previous results. From the reaction mixtures, only adducts **20b** and **20d**–**20f** were isolated and fully characterized, and the reported structures were assigned accordingly. Compounds **20a** and **20c** were observed only in trace amounts, and they were not isolated or characterized. Table 2 reports the diagnostic NMR signals of those protons that define the structures as shown in Scheme 5.

Table 2. ^{1}H and ^{13}C NMR diagnostic signals (δ, [D$_6$]DMSO) of compounds **19a**–**19f** and **20b**, **20d**–**20f**.

19	*CH*–N	*CH*=*CH*–C=O	N=*CH*$_{Het}$[a]	*CH*–N
a	5.91 (dt)	7.86–6.51 (dd)	8.12, 8.16	54.0
b	5.92 (dt)	7.86–6.51 (dd)	8.15, 8.18	54.4
c	5.91 (dt)	7.85–6.51 (dd)	8.15, 8.17	54.0
d	5.92 (dt)	7.86–6.51 (dd)	8.16, 8.22	54.0
e	5.91 (dt)	7.85–6.51 (dd)	8.15, 8.16	54.0
f	5.91 (dt)	7.84–6.51 (dd)	8.14, 8.17	54.0
20		CH=C–N	N=*CH*$_{Het}$[a]	
b		6.97 (s)	8.35, 8.65	
d[b]		6.25 (s)	8.07, 8.55	
e		6.98 (s)	8.32, 8.60	
f		6.97 (s)	8.35, 8.65	

[a] Singlets. [b] (δ, $CDCl_3$).

It is known that the conjugate bases of adenines **18a**–**18f** can adopt two possible orientations in the final products; the heterocyclic ring can be attached through either the N-7 or the N-9 nitrogen atom, giving rise to the structures shown in Figure 2 for the cases in question.

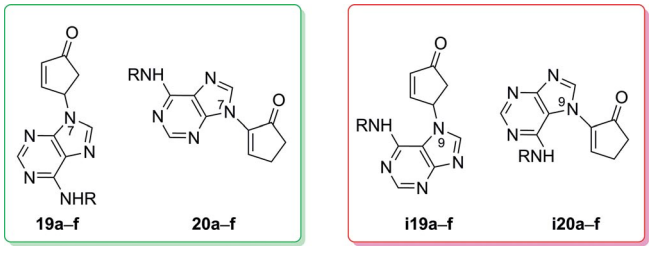


Figure 2. Possible orientations of the adenine ring in adducts **19** and **20**.

In previous work, we have investigated this dichotomy by NMR spectroscopy (NOESY and HMBC experiments). The proton signals of the adenine N=CH differ in their chemical shifts by just 0.11 ppm or even less than this value when the heterocycle is N-7-linked to the carbocyclic moiety. The chemical shift difference for these protons increases to δ = 0.58 ppm for N-9-linked derivatives. These values are calculated on the basis of results obtained for benzamide-cyclopentene adenine derivatives.[4]

Looking at the chemical shifts reported in Table 2 for compounds **19a**–**19f**, the differences between the N=CH chemical shifts lie in the range 0.01–0.06 ppm, whereas for compounds **20b**, **20e**, and **20f** the corresponding figure is ca. 0.3 ppm. These observations allow to exclude the presence of the isomeric compounds **i19a**–**i19f** and compounds **i20b**, **i20d**–**i20f**.

A final confirmation of the general structure of compounds **19** came from X-ray analysis of ethyl derivative **19b**, whose ORTEP structure is reported in Figure 3.

Figure 3. ORTEP view of the structure of compound **19b**.

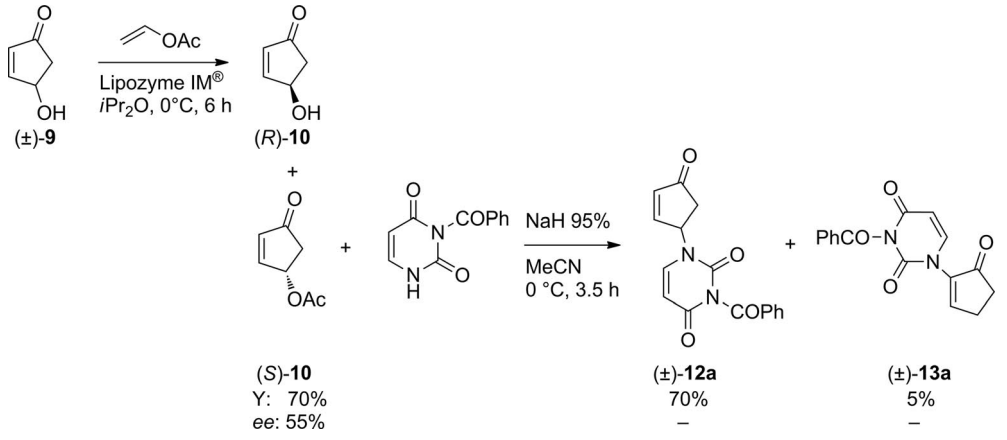
Mechanistic Proposal

To gain further insight into the mechanism of the reaction between oxocyclopentenyl acetate (±)-**10** and the selected pyrimidine and purine heterobases, we prepared enantiomerically enriched oxocyclopentenyl acetate (*S*)-**10** by enzymatic kinetic resolution of racemic acetate (±)-**10**. The kinetic resolution was carried out in organic solvent (anhydrous diisopropyl ether) with vinyl acetate (5 equiv.) in the presence of Lipozyme IM® (10 mol-%).[17] Oxocyclopentenyl acetate (*S*)-**10** was obtained in 70 % yield with a good 55 % *ee* (Scheme 6).

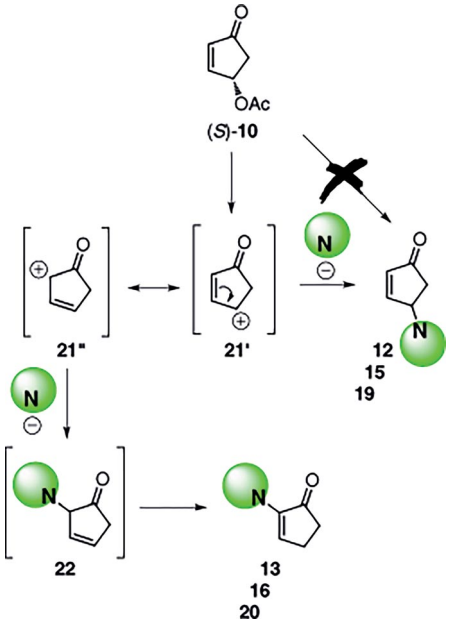
The coupling reaction of (*S*)-**10** with uracil **11a** gave the expected compounds (i.e., **12a** and **13a**), which were found to be racemates.

This result, and the constant presence of the regioisomeric 2-heterosubstituted cyclopentenones, allows us to suggest that the reactions may reasonably be expected to proceed via a stabilized allylic cation of type **21′** in resonance with **21″** (Scheme 7). These cationic species are responsible for the formation of the regioisomeric compounds: products **12**, **15**, and **19** derive directly from the primary cationic form **21′**, while products **13**, **16**, and **20** derive from **21″** by isomerization via **22**.

Although we cannot exclude the possibility that other processes or mechanisms take place under the optimized experimental conditions described, these observations clearly indicate that the protocol based on the nucleophilic substitution with heterobases onto the enantiomerically pure or enantiomerically enriched oxocyclopentenyl acetates is unfit for carrying out an enantioselective synthesis. Only racemic compounds can be easily obtained.



Scheme 6. Reaction between uracil **11a** and enantiomerically enriched oxocyclopentenyl acetate (*S*)-**10**.



Scheme 7. Proposed substitution mechanism.

Antiviral Evaluation

Samples of selected stable compounds were sent to the NIAID (NIH, USA)[18] for in-vitro testing against a variety of viruses for an initial screening study. Products **12a**, **12b**, **15**, **16**, **19a**, and **20b** were tested against a group of viruses belonging to the herpesviridae family: herpes simplex 1 (HSV1; virus strain E-377; cell line HFF), herpes simplex 2 (HSV2; virus strain G; cell line HFF), and human cytomegalovirus (HC; virus strain AD169; cell line HFF). The tests against hepatic viruses were done on hepatitis B (HBV; virus strain ayw; cell line 2.2.15) and hepatitis C (HCV; virus strain CON-1; cell line 2.2.15). From the respiratory viruses, the following were selected: influenza A virus H1N1 (IV/H1N1; virus strain influenza A/California/7/2009; cell line MDCK), adenovirus 5 (AD5; virus strain Type 5; cell line HeLa), neuroamidase (NA; virus strain NA; cell line HFF). From the flaviridae group, West Nile virus (WNV; virus strain Kern 515 WN02; cell line Vero 76) and yellow fever virus (YFV; virus strain 17D; cell line Vero) were tested. From the poxviridae, vaccinia virus (VV; virus strain Copenhagen; cell line HFF) was tested. From picornaviridae, Coxsackie virus B3 (CVB3; virus strain Nancy; cell line LLC-MK2) was chosen. Finally, some tests were carried out on a group of viruses of the bunyaviridae family: Punta Toro virus (PTV; virus strain Adames; cell line Vero 76), Rift Valley fever virus (RVFV; virus strain MP-12; cell line Vero 76); and from the papovaviridae, the human papilloma virus (HPV; virus strain HPV-11; cell line HEK 293).

All the tested compounds were found to be inactive against HSV1 and HSV2, HC, HBVC, HCV, IV/H1N1, AD5, NA, WNV, YFV, VV, and CVB3, with in general high values of EC_{50} and EC_{90} (EC = effective concentration), and low values of CC_{50} (cytotoxicity concentration). Details of the results obtained in all these cases are reported in the Supporting Information.

Interesting and promising results were obtained in the tests against the viruses of the bunyaviridae and papovaviridae families.

Table 3 reports the values obtained against the PTV for the tested compounds. Compound **16** was found to be more promising than the other products; the EC_{50} values are low enough with CC_{50} far from the required values. Analogously, Table 4 reports the values collected for the tested compounds against

Table 3. Antiviral activities against Punta Toro virus (PTV).[a]

Compound	EC_{50}	CC_{50}	SI_{50}[b]
12a[c]	>100	>100	0
12a[d]	>100	>100	0
12b[c]	3.2	3.6	1.1
12b[d]	>2.8	2.8	0
15[c]	>100	>100	0
15[d]	>100	>100	0
16[c]	*3.7*	*36*	*9.7*
16[d]	*3.4*	*30*	*9*
19b[c]	3.2	3.6	1.1
19b[d]	3.2	3.2	1
20b[c]	72	>100	>1.4
20b[d]	83	>100	>1.2
Ribavirin[c]	*11*	*>1000*	*>92*
Ribavirin[d]	*12*	*>1000*	*>81*

[a] Drug conc. range: 0.1–100 μg/mL; control conc. range: 1–1000 μg/mL. [b] SI = selectivity index. [c] Control assay name: visual (cytopathic effect/toxicity). [d] Control assay name: neutral red (cytopathic effect/toxicity).

the RVFV. Again, compound **16** was found to be more promising than all the other products; the EC_{50} values are lower than the previous tests with CC_{50} far from the required values.

Table 4. Antiviral activities against Rift Valley fever virus (RVFV).[a]

Compound	EC_{50}	CC_{50}	SI_{50}
12a[b]	>100	>100	0
12a[c]	>100	>100	0
12b[b]	>7.5	7.5	0
12b[c]	>6.4	6.4	0
15[b]	>100	>100	0
15[c]	>100	>100	0
16[b]	*1.7*	*36*	*21*
16[c]	*1.3*	*26*	*20*
19b[b]	3.2	3.6	1.1
19b[c]	3.1	3.2	1
20b[b]	>100	>100	0
20b[c]	>100	>100	0
Ribavirin[b]	*8.3*	*>1000*	*>120*
Ribavirin[c]	*8.7*	*>1000*	*>110*

[a] Drug conc. range: 0.1–100 μg/mL; control conc. range: 1–1000 μg/mL. [b] Control assay name: visual (cytopathic effect/toxicity). [c] Control assay name: neutral red (cytopathic effect/toxicity).

Table 5 reports the activities from the tests against HPV. Compounds **12b**, **15**, **16**, **19a**, and **20b** were found to be inactive, whereas compound **12a** was found to be highly active against HPV. The CC_{50} value is high enough given the effective dose concentrations of EC_{50} = 9.82 and EC_{90} = 36.79, values which, remarkably, are lower than those of the control drug Cidofovir.

Table 5. Antiviral activities against human papilloma virus (HPV).[a]

Compound[b]	EC_{50}	EC_{90}	CC_{50}	SI_{50}	SI_{90}
12a	9.82	36.79	>100	>10	>3
12b	32.09	>100	>100	>3	1
15	63.83	>100	>100	>1	1
16	62.90	>100	>100	>1	1
19b	62.85	>100	>100	>2	1
20b	41.80	96.90	>100	>2	>1
Cidofovir	148.00	>200	>200	>1	1

[a] Drug conc. range: 1–100 μM; control conc. range: 50–200 μM. [b] Control assay name: quantitative polymerase chain reaction (qPCR) DNA/trypan blue (toxicity).

It is worth noting that the presence of the methyl group in the thymine base in compound **12b** is enough to make the compound inactive.

It is known that HPV has a complex replication machinery starting with the specific binding of protein E2 to the viral DNA, and recruitment of protein E1, which is the replicative helicase protein of HPV. E1 rapidly oligomerizes to form a hexamer (around the nucleic acid), a central origin-DNA-binding domain, and an N-terminal regulatory region that is essential for replication in vivo.[19]

The literature reports a variety of compounds belonging to different classes of organic molecules, with different structural features and different mechanisms of inhibition of HPV.[20]

The structure of compound **12a** is now added to this large family, and further investigations will include both structural variations and docking studies to shed some light onto the mechanism of its activity.

Conclusions

Racemic 4-oxocyclopent-2-en-1-yl acetate [(±)-**10**] was used in a short synthesis of nucleoside analogues with pyrimidine and purine heterobases. The protocol is based on a typical nucleophilic substitution process and is not applicable to an enantioselective approach to the desired products, as indicated by experiments conducted on the enantiomerically enriched starting material.

Uracil, thymine, and 6-chloropurine gave the expected 4-heterosubstituted products of type **12a**,**b** and **15**, along with the isomeric 2-heterosubstituted compounds **13a**,**b** and **16** as minor products. 6-Chloropurine derivatives **15** and **16** could not be used for further functionalization with amines because of a rapid elimination reaction that gave 6-chloropurine and the transient cyclopentadienone intermediate. A modified protocol was planned by using adenine derivatives, either prepared or from a commercial source, which were coupled with 4-oxocyclopent-2-en-1-yl acetate [(±)-**10**] under the same experimental conditions to give mixtures of the 4-substituted and 2-substituted adenine derivatives.

Samples of selected products were evaluated for their antiviral activity in an initial screening against a variety of viruses belonging to different classes. Products **12a**, **12b**, **15**, **16**, **19a**, and **20b** were found to be mainly inactive against the majority of the viruses. Moderate activities were, however, observed for compound **16** against PTV and RVFV. Interesting high and promising activity was observed against HPV for compound **12a**; structural changes and docking studies will be carried out to understand the mechanism of activity against HPV, and for the further improvement of the field.

Experimental Section

General Remarks: Elemental analyses were carried out with a C. Erba 1106 elemental analyser. IR spectra (Nujol mulls for solids) were recorded with an FTIR Perkin–Elmer RX-1 instrument. ^1H and ^{13}C NMR spectra were recorded with Bruker Avance 400 and 300 instruments in the specified deuterated solvents. Chemical shifts are expressed in ppm from internal tetramethylsilane (δ). HPLC analyses were carried out with a Waters 1525 instrument, equipped with a UV2487 detector (λ = 266 nm), both controlled by Breezee software, and an RP C-18 Intersil ODS-2 column; a mixture of H_2O/CH_3CN (60:40) was used as eluent. Column chromatography and TLC were carried out on silica gel 60 (0.063–0.200 mm; Merck) by using mixtures of cyclohexane/ethyl acetate from 9:1 to 5:5 as eluent. MPLC chromatographic separations were carried out with a Biotage Flash Master Personal apparatus by using mixtures of cyclohexane/ethyl acetate from 9:1 to 5:5 as eluent.

Materials: Furfuryl alcohol, uracil, thymine, 6-chloropurine, and all the required reagents for the syntheses were purchased from Sigma–Aldrich. All other reagents and solvents were purchased from Sigma–Aldrich and Alfa–Aesar and were used without any further purification.

Synthesis of Protected Uracil and Thymine Derivatives 12 and 13: An excess of the protected uracil or thymine (1.5 equiv.) was

dissolved in anhydrous acetonitrile (8 mL), and NaH (95 %; 1.7 equiv.) was added portionwise while stirring the mixture under an inert gas. After 2 h, 4-oxocyclopent-2-en-1-yl acetate [(±)-**10**] (1 g, 7.14 mmol) was dissolved in the minimum amount of anhydrous acetonitrile, and the resulting solution was added dropwise to the reaction mixture under vigorous stirring at 0 °C. The temperature was allowed to rise to ambient temperature over the reaction time of 3.5 h after the reagent addition. The reaction was then quenched with ice, and CH_2Cl_2 was added. The organic phase was dried with Na_2SO_4, and the solvent was evaporated. The residue was submitted to chromatographic separation to isolate the products. Regioisomers **12a**,**b** and **13a**,**b** were obtained and fully characterized.

Compound 12a: Yield 1.59 g (75 %). M.p. 170–172 °C (diisopropyl ether/ethanol). IR: $\tilde{\nu}$ = 1755, 1729 (C=O) cm^{-1}. ^1H NMR (400 MHz, [D_6]DMSO, 25 °C): δ = 2.55 and 2.83 (dd, J = 19, 7 Hz, 2 H, CH_2), 5.69 (m, 1 H, CH–N), 5.86 (d, J = 8 Hz, 1 H, =CH–CO), 6.49 (dd, J = 6, 2 Hz, 1 H, CH=), 7.62 (m, 3 H, arom.), 7.68 (d, J = 8 Hz, 1 H, CH=), 7.82 (d, J = 6, 3 Hz, 1 H, =CH), 8.02 (d, J = 8 Hz, 2 H, arom.) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO, 25 °C): δ = 59.2, 103.8, 131.8, 132.8, 133.5, 137.9, 139.4, 146.3, 151.8, 162.7, 164.3, 171.9, 207.8 ppm. $C_{16}H_{12}N_2O_4$ (296.28): calcd. C 64.86, H 4.08, N 9.46; found C 64.86, H 4.10, N 9.42.

Compound 12b: Yield 1.88 g (85 %). M.p. 179–182 °C (diisopropyl ether/ethanol). IR: $\tilde{\nu}$ = 1755, 1747 (C=O) cm^{-1}. ^1H NMR (400 MHz, [D_6]DMSO, 25 °C): δ = 1.83 (d, J = 7 Hz, 3 H, CH_3), 2.53 and 2.84 (dd, J = 16, 2 Hz, 2 H, CH_2), 5.71 (m, 1 H, CH–N), 6.49 (dd, J = 6, 2 Hz, 1 H, CH=), 6.55 (s, 1 H, =CH–CO), 7.61 (m, 3 H, arom.), 7.94 (d, J = 8 Hz, 1 H, CH=), 7.79 (m, 2 H, arom.), 8.08 (d, J = 7 Hz, 1 H, CH=) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO, 25 °C): δ = 11.8, 56.0, 109.6, 129.5, 130.2, 130.4, 131.2, 135.5, 137.2, 139.1, 149.3, 160.6, 162.6, 167.2, 169.7, 205.5 ppm. $C_{17}H_{14}N_2O_4$ (310.30): calcd. C 65.80, H 4.55, N 9.03; found C 65.85, H 4.51, N 9.02.

Compound 13a: Yield 0.19 g (9 %). M.p. 174–177 °C (diisopropyl ether/ethanol). IR: $\tilde{\nu}$ = 1744, 1724 (C=O) cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO, 25 °C): δ = 2.45 and 3.10 (m, 2 H + 2 H, CH_2CH_2), 6.11 (d, J = 8 Hz, 1 H, =CH–CO), 6.57 (s, 1 H, CH=), 7.62 (m, 2 H, arom.), 7.82 (t, J = 8 Hz, 1 H, arom.), 8.09 (d, J = 8 Hz, 2 H, arom.), 8.18 (d, J = 8 Hz, 1 H, CH=) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO, 25 °C): δ = 28.8, 33.3, 103.2, 119.8, 129.5, 130.6, 130.8, 135.8, 142.0, 147.9, 161.1, 166.9, 168.9, 206.3 ppm. $C_{16}H_{12}N_2O_4$ (296.28): calcd. C 64.86, H 4.08, N 9.46; found C 64.84, H 4.11, N 9.44.

Compound 13b: Yield 0.16 g (7 %). M.p. 164–167 °C (diisopropyl ether/ethanol). IR: $\tilde{\nu}$ = 1747, 1723 (C=O) cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO, 25 °C): δ = 1.95 (s, 3 H, CH_3), 2.45 and 3.10 (m, 2 H + 2 H, CH_2CH_2), 6.55 (s, 1 H, CH=), 7.61 (m, 2 H, arom.), 7.81 (t, J = 8 Hz, 1 H, arom.), 8.06 (d, J = 8 Hz, 1 H, CH=), 8.07 (d, J = 8 Hz, 2 H, arom.) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO, 25 °C): δ = 11.9, 29.0, 33.3, 111.4, 119.3, 129.5, 130.6, 130.8, 135.7, 137.3, 147.9, 161.9, 167.2, 168.9, 206.3 ppm. $C_{17}H_{14}N_2O_4$ (310.30): calcd. C 65.80, H 4.55, N 9.03; found C 65.83, H 4.52, N 9.05.

Synthesis of 6-Chloropurine Derivatives 15 and 16: An excess of 6-chloropurine (**14**) (1.5 equiv.) was dissolved in anhydrous acetonitrile (8 mL), and NaH (95 %; 1.7 equiv.) was added portionwise while stirring under an inert gas. After 2 h, 4-oxocyclopent-2-en-1-yl acetate [(±)-**10**] (1 g, 7.14 mmol) was dissolved in the minimum amount of anhydrous acetonitrile, and the resulting solution was added dropwise to the reaction mixture under vigorous stirring at 0 °C. The temperature was allowed to rise to ambient temperature over the reaction time of 3.5 h after the reagent addition. The reaction was quenched with ice, and CH_2Cl_2 was added. The organic phase was dried with Na_2SO_4, and the solvent was evaporated. The residue was submitted to chromatographic separation to isolate the products. Adduct **15** was found to be identical to the product described in the literature,[10] while its regioisomer **16** was fully characterized.

Compound 16: Yield 0.27 g (16 %). M.p. 210–215 °C (diisopropyl ether/ethanol). IR: $\tilde{\nu}$ = 1753 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.72 and 3.40 (m, 2 H + 2 H, CH_2CH_2), 7.28 (s, 1 H, CH=), 8.43 (s, 1 H, N=CH), 8.91 (s, 1 H, N=CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 27.7, 33.4, 119.6, 132.8, 138.3, 141.3, 151.3, 152.3, 153.3, 156.8, 161.2, 204.8 ppm. $C_{10}H_7ClN_4O$ (234.64): calcd. C 51.19, H 3.01, N 23.88; found C 51.13, H 3.02, N 23.85.

Synthesis of 6-Chloropurine Derivatives 15 and 16 in the Presence of DBU (HPLC Analyses): 6-Chloropurine (**14**) (50 mg, 1 equiv.) was dissolved in anhydrous acetonitrile (6 mL), and DBU (1 equiv.) was added portionwise while stirring under an inert gas. After 2 h, 4-oxocyclopent-2-en-1-yl acetate [(±)-**10**] (1 equiv.) was dissolved in the minimum amount of anhydrous acetonitrile, and the resulting solution was added dropwise to the reaction mixture under vigorous stirring at 0 °C or at –20 °C. Samples of the reaction mixtures (1 mL) were taken after 30–384 min, quickly quenched with ice, and analysed by HPLC. Quantitative determinations were done in duplicate.

Synthesis of Adenine Derivatives 19 and 20: An excess of adenines **18a**–**18f** (1.5 equiv.) was dissolved in anhydrous acetonitrile (8 mL), and NaH (95 %; 1.7 equiv.) was added portionwise while stirring under an inert gas. After 2 h, 4-oxocyclopent-2-en-1-yl acetate [(±)-**10**] (1 g, 7.14 mmol) was dissolved in the minimum amount of anhydrous acetonitrile, and the resulting solution was added dropwise to the reaction mixture under vigorous stirring at 0 °C. The temperature was allowed to rise to ambient temperature over the reaction time of 3.5 h after the reagent addition. The reaction was quenched with ice, and CH_2Cl_2 was added. The organic phase was dried with Na_2SO_4, and the solvent was evaporated. The residues were submitted to chromatographic separation to isolate the products. Regioisomers **19a**–**19f** and **20b**, **20d**–**20f** were obtained and fully characterized.

Compound 19a: Yield 0.65 g (42 %). M.p. 202–206 °C (diisopropyl ether/ethanol). IR: $\tilde{\nu}$ = 3250, 3320 (NH_2), 1686 (C=O) cm^{-1}. ^1H NMR (400 MHz, [D_6]DMSO, 25 °C): δ = 2.72 and 2.99 (dd, J = 18, 7, 3 Hz, 1 H + 1 H, CH_2), 5.91 (m, 1 H, CH–N), 6.51 (dd, J = 6, 2 Hz, 1 H, =CH–CO), 7.25 (s, 2 H, NH_2), 7.86 (dd, J = 6, 2 Hz, 1 H, CH=), 8.12 (s, 1 H, N=CH), 8.16 (s, 1 H, N=CH) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO, 25 °C): δ = 41.1, 54.0, 116.1, 119.0, 136.0, 138.6, 139.5, 149.2, 152.4, 153.9, 156.0, 160.8, 205.6 ppm. $C_{10}H_9N_5O$ (215.21): calcd. C 55.81, H 4.22, N 32.54; found C 55.83, H 4.22, N 32.55.

Compound 19b: Yield 0.82 g (47 %). M.p. 178–179 °C (diisopropyl ether/ethanol). IR: $\tilde{\nu}$ = 3288 (NH), 1718 (C=O) cm^{-1}. ^1H NMR (400 MHz, [D_6]DMSO, 25 °C): δ = 1.17 (t, J = 7 Hz, 3 H, CH_3), 2.72 and 2.99 (dd, J = 18, 7, 3 Hz, 1 H + 1 H, CH_2), 3.51 (br. s, 2 H, CH_2N), 5.92 (m, 1 H, CH–N), 6.51 (dd, J = 6, 2 Hz, 1 H, =CH–CO), 7.78 (br. s, 1 H, NH), 7.86 (dd, J = 6, 2 Hz, 1 H, CH=), 8.15 (s, 1 H, N=CH), 8.18 (s, 1 H, N=CH) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO, 25 °C): δ = 15.1, 41.5, 54.4, 114.1, 118.0, 136.4, 139.6, 144.0, 152.8, 154.8, 158.8, 161.2, 206.1 ppm. $C_{12}H_{13}N_5O$ (243.26): calcd. C 59.25, H 5.39, N 28.79; found C 59.23, H 5.32, N 28.75.

Compound 20b: Yield 0.02 g (1 %). M.p. >240 °C (dec.) (diisopropyl ether/ethanol). IR: $\tilde{\nu}$ = 3280 (NH), 1698 (C=O) cm^{-1}. ^1H NMR (400 MHz, [D_6]DMSO, 25 °C): δ = 1.06 (t, J = 7 Hz, 3 H, CH_3), 1.77 and 1.89 (m, 2 H + 2 H, CH_2CH_2), 4.18 (br. s, 2 H, CH_2N), 6.97 (s, 1 H, =CH), 7.90 (d, J = 7 Hz, 1 H, NH), 8.35 (s, 1 H, N=CH), 8.65 (s, 1

H, N=CH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 25.0, 27.5, 33.2, 48.8, 116.2, 119.8, 138.3, 148.8, 153.9, 164.5, 189.5, 205.8 ppm. $C_{12}H_{13}N_5O$ (243.26): calcd. C 59.25, H 5.39, N 28.79; found C 59.28, H 5.35, N 28.78.

Compound 19c: Yield 0.75 g (41 %). M.p. 154–156 °C (diisopropyl ether/ethanol). IR: $\tilde{\nu}$ = 3286 (NH), 1707 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.21 (d, J = 7 Hz, 6 H, CH$_3$), 2.72 and 2.99 (dd, J = 18, 7, 3 Hz, 1 H + 1 H, CH$_2$), 4.42 (br. s, 1 H, CH-N), 5.91 (m, 1 H, CH–N), 6.51 (dd, J = 6, 2 Hz, 1 H, =CH–CO), 7.52 (d, J = 7 Hz, 1 H, NH), 7.85 (dd, J = 6, 2 Hz, 1 H, CH=), 8.15 (s, 1 H, N=CH), 8.17 (s, 1 H, N=CH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 22.3, 41.1, 54.0, 119.2, 136.0, 139.2, 148.6, 152.4, 153.8, 160.8, 205.7 ppm. $C_{13}H_{15}N_5O$ (257.29): calcd. C 60.69, H 5.88, N 27.22; found C 60.63, H 5.87, N 27.25.

Compound 19d: Yield 0.71 g (42 %). M.p. 220 °C (dec.) (diisopropyl ether/ethanol). IR: $\tilde{\nu}$ = 3283 (NH), 1693 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 0.61 and 0.71 (m, 4 H, CH$_2$CH$_2$ cyclopropyl), 2.72 and 3.03 (dd, J = 18, 7, 3 Hz, 1 H + 1 H, CH$_2$), 3.04 (br. s, 1 H, CH–N), 5.92 (m, 1 H, CH–N), 6.51 (dd, J = 6, 2 Hz, 1 H, = CH–CO), 7.86 (dd, J = 6, 2 Hz, 1 H, CH=), 7.91 (d, J = 7 Hz, 1 H, NH), 8.16 (s, 1 H, N=CH), 8.22 (s, 1 H, N=CH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 6.4, 23.8, 41.1, 54.0, 119.4, 136.0, 139.4, 148.9, 152.3, 155.6, 160.8, 205.7 ppm. $C_{13}H_{13}N_5O$ (255.28): calcd. C 61.17, H 5.13, N 27.43; found C 61.13, H 5.17, N 27.45.

Compound 20d: Yield 0.07 g (4 %). M.p. 218 °C (dec.) (diisopropyl ether/ethanol). IR: $\tilde{\nu}$ = 3285 (NH), 1694 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ = 0.73 and 0.99 (m, 4 H, CH$_2$CH$_2$ cyclopropyl), 2.67 and 3.34 (m, 2 H + 2 H, CH$_2$CH$_2$), 3.11 (br. s, 1 H, CH-N), 6.25 (s, 1 H, =CH), 7.28 (s, 1 H, NH), 8.07 (s, 1 H, N=CH), 8.55 (s, 1 H, N=CH) ppm. ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 7.2, 29.3, 30.6, 107.8, 118.4, 120.5, 136.4, 153.9, 164.5, 189.5, 205.8 ppm.

Compound 19e: Yield 0.81 g (38 %). M.p. 168–172 °C (diisopropyl ether/ethanol). IR: $\tilde{\nu}$ = 3288 (NH), 1698 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.34, 1.73 and 1.87 (m, 6 H + 2 H + 2 H, cyclohexyl), 2.72 and 2.99 (dd, J = 18, 7, 3 Hz, 1 H + 1 H, CH$_2$), 4.09 (br. s, 1 H, CH–N), 5.91 (m, 1 H, CH–N), 6.51 (dd, J = 6, 2 Hz, 1 H, =CH–CO), 7.85 (dd, J = 6, 2 Hz, 1 H, CH=), 7.54 (d, J = 7 Hz, 1 H, NH), 8.15 (s, 1 H, N=CH), 8.16 (s, 1 H, N=CH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 25.0, 25.2, 32.3, 41.1, 54.0, 135.9, 139.1, 152.4, 160.8, 205.7 ppm. $C_{16}H_{19}N_5O$ (297.35): calcd. C 64.63, H 6.44, N 23.55; found C 64.63, H 6.47, N 23.54.

Compound 20e: Yield 0.06 g (3 %). M.p. >240 °C (dec.) (diisopropyl ether/ethanol). IR: $\tilde{\nu}$ = 3460 (NH), 1706 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.34, 1.70 and 1.77 (m, 6 H + 2 H + 2 H, cyclohexyl), 1.91 and 2.49 (dd, J = 18, 7, 3 Hz, 1 H + 1 H, CH$_2$), 4.11 (br. s, 1 H, CH–N), 6.98 (s, 1 H, =CH), 7.75 (d, J = 7 Hz, 1 H, NH), 8.32 (s, 1 H, N=CH), 8.60 (s, 1 H, N=CH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 25.1, 27.0, 34.9, 49.7, 51.2, 118.7, 140.4, 156.2, 166.7, 170.4, 208.1 ppm. $C_{16}H_{19}N_5O$ (297.35): calcd. C 64.63, H 6.44, N 23.55; found C 64.65, H 6.42, N 23.56.

Compound 19f: Yield 0.71 g (32 %). M.p. 132–133 °C (diisopropyl ether/ethanol). IR: $\tilde{\nu}$ = 3298 (NH), 1685 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.3–1.7 (m, 10 H, cycloheptyl), 1.89 (m, 2 H, CH$_2$ cycloheptyl), 2.72 and 2.99 (dd, J = 18, 7, 3 Hz, 1 H + 1 H, CH$_2$), 4.27 (br. s, 1 H, CH–N), 5.91 (m, 1 H, CH–N), 6.51 (dd, J = 6, 2 Hz, 1 H, =CH–CO), 7.84 (dd, J = 6, 2 Hz, 1 H, CH=), 7.55 (d, J = 7 Hz, 1 H, NH), 8.14 (s, 1 H, N=CH), 8.17 (s, 1 H, N=CH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 20.7, 27.7, 34.2, 50.7, 54.0, 119.3, 136.0, 139.1, 148.6, 152.4, 153.5, 160.8, 205.7 ppm. $C_{17}H_{21}N_5O$ (311.38): calcd. C 65.57, H 6.80, N 22.49; found C 65.53, H 6.77, N 22.44.

Compound 20f: Yield 0.07 g (3 %). M.p. >250 °C (dec.) (diisopropyl ether/ethanol). IR: $\tilde{\nu}$ = 3466 (NH), 1686 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.3–1.7 (m, 10 H, cycloheptyl), 1.89 (m, 2 H, CH$_2$ cycloheptyl), 2.49 and 3.30 (m, 2 H + 2 H, CH$_2$CH$_2$), 4.30 (br. s, 1 H, CH–N), 6.97 (s, 1 H, =CH), 7.95 (d, J = 7 Hz, 1 H, NH), 8.35 (s, 1 H, N=CH), 8.65 (s, 1 H, N=CH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 26.2, 29.9, 30.1, 35.6, 36.5, 53.3, 118.6, 122.3, 140.6, 151.2, 156.0, 156.3, 167.0, 208.2 ppm. $C_{17}H_{21}N_5O$ (311.38): calcd. C 65.57, H 6.80, N 22.49; found C 65.56, H 6.79, N 22.50.

X-ray Crystallographic Analysis of 19a: Colourless, needle-like crystals of compound **19b** were obtained by slow recrystallization from a diisopropyl ether/ethanol solution. Accurate unit-cell parameters were obtained by least-squares fit of the 2θ values for 25 reflections measured with a Nonius CAD-4 diffractometer with graphite-monochromated Mo-K_α radiation. Corrections were applied for Lorentz and polarization effects. An approximate absolute scale and a mean thermal factor of 3.347 Å^2 were determined by Wilson's statistics.[21] The structure was solved by direct methods, and the *E*-map correctly revealed all the non-hydrogen atoms in the molecule. The positions of the hydrogen atoms were checked in a final difference-Fourier map and were refined with isotropic thermal parameters in a subsequent least-squares refinement. The experimental single-crystal X-ray data are summarized in Tables S1 and S2 in the Supporting Information. All calculations were carried out with the SHELX93 computing package[22] and with local programs. ORTEP software was used to generate the structure in Figure 3.[23] CCDC 1430693 (for **19a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Antiviral Assays: The National Institute of Allergy and Infectious Diseases (NIAID) provides free and confidential services for suppliers who are interested in submitting compounds to be evaluated for antiviral activity. Tested compounds were delivered in standard DMSO solutions. The methods used for the different assays can be found at http://niaid-aacf.org/. For the types of viruses, virus strains, cell lines, and control assays, see the main article text. Complete data on the initial screening are given in the Supporting Information.

Supporting Information (see footnote on the first page of this article): Crystallographic analysis of compound **19b**; ^{1}H and ^{13}C NMR spectra of all synthesized compounds; antiviral screening data.

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Keywords: Carbocycles · Nucleosides · Nucleobases · Nucleophilic substitution · Biological activity · Antiviral agents

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