98 kDa receptors is increased at pHs lower than 8.8 (data not shown).

Discussion

Currently there exists only one electrophilic affinity label for glucocorticoid receptors. This is Dex-Mes, which displays irreversible antiglucocorticoid activity.[1,9,13] We have now prepared several new potential electrophilic affinity labels which could have irreversible agonist or antagonist activity. One of these, Dex-NCS (6 in (Scheme I) fulfills all of the requirements for being a new affinity label. (1) Dex-NCS has reasonable affinity for glucocorticoid receptors in cell-free extracts and in whole cells (Table I). (2) It is biologically active for the induction of the glucocorticoid-inducible enzyme TAT (Table I and Figure 1). (3) The apparent whole cell affinity of Dex-NCS for receptors is higher than the cell-free affinity (Table I), in keeping with the differences in off-rates of covalently vs noncovalently bound steroid being more noticeable at the higher temperatures of the whole-cell assay.[20] (4) Receptors prebound with Dex-NCS have a markedly reduced capacity to exchange–bind added [^{3}H]Dex (Figure 2). (5) The labeling of a species with the same molecular weight as the receptor (i.e., 98 kDa) by [^{3}H]Dex-NCS is covalent in that it is not dissociated on a denaturing SDS-polyacrylamide gel (Figure 3). (6) The covalent labeling by [^{3}H]Dex-NCS of only this 98 kDa species is inhibited by excess nonradioactive glucocorticoid steroid (Figure 3).

The labeling efficiency of the receptor by [^{3}H]Dex-NCS is currently low (7–16% at pH 7.5). However, it is also not clear that we have maximized the conditions for labeling. The results of the exchange binding assay suggest that ~45% of the receptors are being covalently labeled (Table II). Thus it is possible that the instability of covalent adduct under the conditions of analysis by SDS-PAGE (see above) may artifactually lower the yield of the covalently labeled receptors.

This same instability, however, provides a clue as to the functional group that is labeled by Dex-NCS. In particular, it would be predicted that, under weakly basic conditions, the instability of the reaction products with various functional groups would follow an order of instability of thiol ≈ acid > alcohol > amine.[35] Our observed order of chemical reactivity of various functional groups was thiol > amine ≫ alcohol ≥ acid. These two lines of evidence suggest that the amino acid of the receptor which most likely has been labeled by Dex-NCS (Figure 3) is a cysteine. Two lines of evidence argue that Cys-656, which is labeled by Dex-Mes,[9] is not being labeled by Dex-NCS. First, both Dex-Mes and Dex-NCS react essentially with only ionized thiols but the labeling by Dex-NCS increases at pH < 8.8 (Table II) while Dex-Mes labeling was maximal at pH 8.8.[2] Second, the reactive position of Dex-NCS is further away from the C-21 of Dex than is the reactive position of Dex-Mes. Thus it would appear that Dex-NCS is labeling a thiol group other than Cys-656. An attractive candidate is the second thiol that can be linked with Cys-656 with either MMTS[11] or arsenite.[36–38] Further work is required to confirm this hypothesis. Thus studies with Dex-NCS promise to expand our knowledge of the steroid binding cavity of glucocorticoid receptors.

Acknowledgment. S.L. is grateful to CICYT (Ministry of Education, Spain) for a postdoctoral fellowship. We thank Mr. Hung Luu for invaluable technical assistance and Dr. Kenner Rice for critical review of the manuscript.

Registry No. 1, 50-02-2; 1 21-S$(CH_2)_2NHCO_2$Bu-*t*, 73816-22-5; 1 21-S$(CH_2)_2NH_2$·HCl, 131567-17-4; 3, 131567-18-5; 4, 131567-19-6; 6, 131567-20-9; [^{3}H]dexamethasone 21-mesylate, 131567-21-0; [^{3}H]dexamethasone 21-S$(CH_2)_2NHCO_2$Bu-*t*, 131567-22-1; [^{3}H]-dexamethasone 21-S$(CH_2)_2NCS$, 131567-23-2; 2,6-bis(trifluoromethyl)benzoic acid, 24821-22-5; cysteamine hydrochloride, 156-57-0; 2-[(*tert*-butoxycarbonyl)amino]-1-ethanethiol, 67385-09-5.

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Synthesis and Antiviral Activity of 5-Heteroaryl-Substituted 2′-Deoxyuridines

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Received October 22, 1990

The synthesis of 5-heteroaryl-substituted 2′-deoxyuridines is described. The heteroaromatics were obtained from three different 5-substituted 2′-deoxyuridines. Cycloaddition reaction of nitrile oxides on the 5-ethynyl derivative 1 gave the isoxazoles **4a–e**. The thiazole derivatives **14a–c** were obtained from the 5-thiocarboxamide 11, while 5-pyrrol-1-yl-2′-deoxyuridine (17) could be synthesized directly from 5-amino-2′-deoxyuridine. The compounds were evaluated for antiviral activity. Selective activity against herpes simplex virus type 1 (HSV-1) and varicella zoster virus (VZV) was noted for 5-(3-bromoisoxazol-5-yl)-2′-deoxyuridine (**4c**). The compound was inactive against herpes simplex virus type 2, cytomegalovirus, and thymidine kinase (TK)-deficient mutants of HSV-1 and VZV, which indicates that, most likely, its antiviral activity depends on phosphorylation by the virus-specified TK.

Introduction

Substitution of the 5-methyl group of thymidine by other groups has led to a multitude of compounds with either cytostatic or antiviral properties,[1] i.e. 5-fluoro-2′-deoxyuridine, 5-ethyl-2′-deoxyuridine, 5-iodo-2′-deoxyuridine, and 5-(*E*)-(2-bromovinyl)-2′-deoxyuridine. The biological activity of these compounds is dependent on their conversion to the 5′-O-phosphorylated metabolites. The enzymes that convert these compounds to their 5′-*O*-monophosphates may be of either cellular or viral origin. 5′-O-Phosphorylation of 5-fluoro-2′-deoxyuridine affords the 5-fluoro-2′-deoxyuridine 5′-monophosphate, a potent inhibitor of thymidylate synthetase and a widely used

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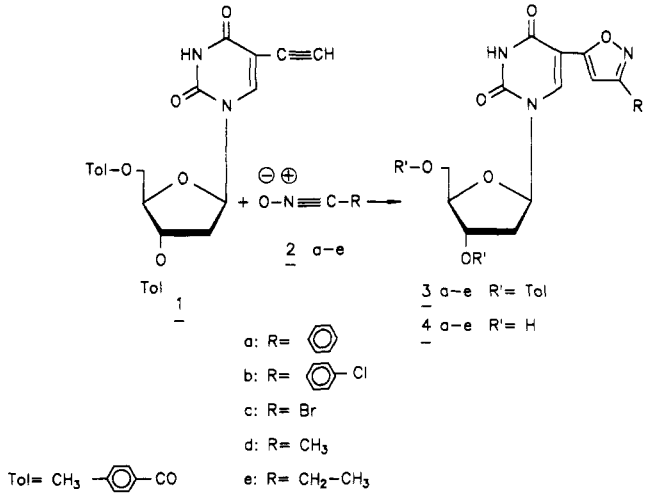
Scheme I



antitumor agent. 5′-O-Phosphorylation of 5-iodo-2′-deoxyuridine (IdUrd) by virus-encoded thymidine kinase gives 5-iodo-2′-deoxyuridine 5′-monophosphate and 5′-diphosphate, which is further converted to its 5′-triphosphate (IdUrdTP). IdUrdTP can serve either as a substrate or inhibitor of both the viral or cellular DNA polymerase. For maximal selectivity, the compound should be an inhibitor for the viral DNA polymerase rather than host DNA polymerase.

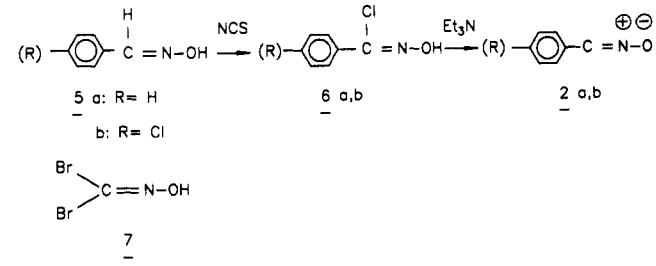
The most potent antiviral agent among the 5-substituted 2′-deoxyuridine derivatives is 5-(*E*)-(2-bromovinyl)-2′-deoxyuridine (BrVdUrd). Depending on the choice of the cell systems, BrVdUrd inhibits HSV-1 replication at a concentration of 0.001–0.1 μg/mL and varicella zoster virus (VZV) replication at a concentration of 0.001–0.01 μg/mL.[3] A structure–activity relationship (SAR) study with BrVdUrd as model compound has revealed that for optimum anti-HSV-1 activity the 5-substituent should be unsaturated, conjugated with the pyrimidine ring, not longer than four carbon atoms, not branched and endowed with an hydrophobic, electronegative function.[4] Various 5-membered heterocyclic compounds seem to fulfill these requirements. Here, we present our work on several isoxazol-5-yl, thiazol-2-yl, and pyrrol-1-yl substituted 2′-deoxyuridine derivatives, which should help in delineating the structural requirements for the HSV-1 activity of 5-substituted 2′-deoxyuridine derivatives.

Chemistry

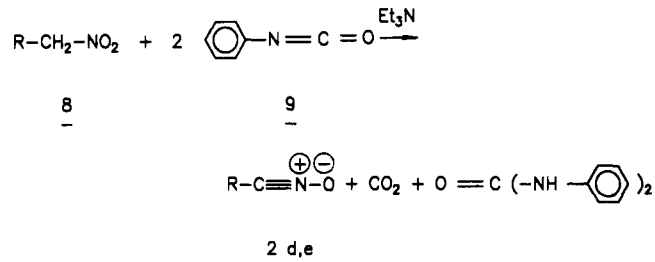
The 5-(isoxazol-5-yl) derivatives of 2′-deoxyuridine (**3a–e**) were synthesized from 5-ethynyl-3′,5′-di-*O*-toluoyl-2′-deoxyuridine[5] (**1**) (Scheme I). A convenient method to obtain isoxazole rings is the cycloaddition reaction of nitrile oxides (**2a–e**) with acetylenic functions. Nitrile oxides, especially aliphatic nitrile oxides, are unstable compounds and have to be generated "in situ".

The cycloaddition of the aromatic nitrile oxides **2a** and **2b** with 3′,5′-di-*O*-toluoyl-5-ethynyl-2′-deoxyuridine (**1**) was carried out by dropwise addition of triethylamine at −20 °C to the mixture of **1** and the chloroaldoximes **6a** and **6b**. Only the 3-phenylisoxazol-5-yl and 3-(*p*-chlorophenyl)-isoxazol-5-yl derivatives were formed. They were isolated in 35% and 60% yield, respectively. The starting chloroaldoximes were synthesized by chlorination of the benzaldoximes with *N*-chlorosuccinimide in dimethylformamide from which the aromatic nitrile oxides **2a** and **2b** were generated with triethylamine (Scheme II).[6]

Scheme II



Scheme III



The bromo nitrile oxide[7] **2c**, however, could not be obtained from dibromoformaldoxime **7**, when triethylamine was used as base (in tetrahydrofuran). The use of wet ethyl acetate as solvent and sodium bicarbonate as base did give the desired product **2c**. The cycloaddition of **2c** with **1** at 25 °C for 16 h gave 44% of 3′,5′-di-*O*-toluoyl-5-(3-bromoisoxazol-5-yl)-2′-deoxyuridine (**3c**). Attempts to remove the bromine atom of **3c** by catalytic hydrogenation (10% Pd/C, 50 psi) failed.

The aliphatic nitrile oxides (**2d** and **2e**) were generated as shown in Scheme III. Nitroethane and nitropropane react in a base-catalyzed dehydration reaction with 2 equiv of phenyl isocyanate with formation of the nitrile oxide and diphenylurea.[8] This side product (diphenylurea) disturbs the chromatographic purification of the reaction mixture. However, diphenylurea can be easily removed chromatographically when the nucleosides are first deprotected.

The reactions of **2d** and **2e** with **1** were carried out in toluene at 80 °C under anhydrous conditions, and the isoxazolyl derivatives **3d** and **3e** were obtained in 70% yield. The toluoyl groups of **3a–e** were removed with methanolate in methanol to give the unprotected nucleosides **4a–e**.

The 5-(thiazol-2-yl) derivatives of 2′-deoxyuridine (**13a–c**) were synthesized from 3′,5′-di-*O*-benzoyl-5-cyano-2′-deoxyuridine (**10**).[9] The cyano function was first converted to a thiocarboxamide group, which was then reacted with different α-halogeno carbonyl synthons (Scheme IV).

When a solution of 3′,5′-di-*O*-benzoyl-5-cyano-2′-deoxyuridine in dimethylformamide, containing an excess of triethylamine, was saturated with hydrogen sulfide

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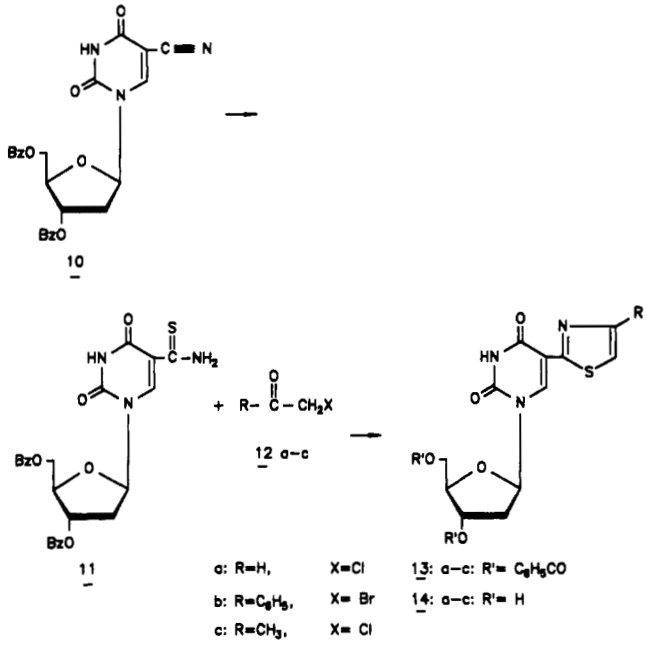
Table I. Antiviral Activity and Cytotoxicity in Vitro

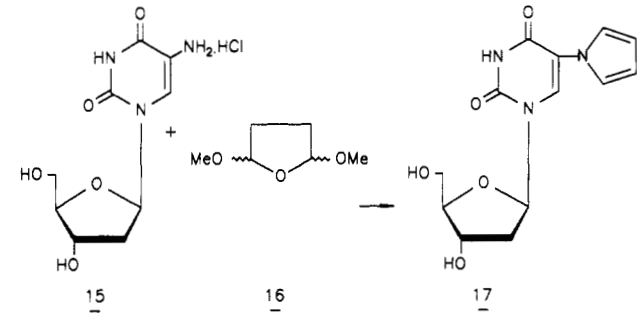
virus (strain)	cell culture	minimum inhibitory concentration,[a,b] μg/mL									
		BVdUrd	4a	4b	4c	4d	4e	14a	14b	14c	17
HSV-1 (KOS)	E_6SM	0.07	>40	>40	7	70	>200	20	>40	>400	20
HSV-1 (F)	E_6SM	0.07	>40	>40	2	40	150	7	>40	>400	70
HSV-1 (Mc Intyre)	E_6SM	0.07	>40	>40	2	70	>400	20	>40	>400	10
HSV-2 (G)	E_6SM	10	>40	>40	>200	>400	>400	>200	>40	>400	>400
HSV-2 (196)	E_6SM	>400	>40	>40	>400	>400	>400	>200	>40	>400	>400
HSV-2 (Lyons)	E_6SM	>400	>40	>40	>400	>400	>400	>20	>40	>400	>400
TK⁻ HSV-1 (B2006)	E_6SM	100	>40	>40	>400	>400	>400	>200	>40	>400	>400
TK⁻ HSV-1 (VMW1837)	E_6SM	>400	>40	>40	>400	>400	>400	>200	>40	>400	>400
VZV (YS)	HEL	0.003	73	>40	0.24	52	334	>100	>100	237	33
VZV (OKA)	HEL	0.003	38	9	0.09	87	>400	>100	>100	>400	42.3
TK⁻ VZV (YS-R)	HEL	0.4	>100	77	>100	>400	>400	>100	>100	>400	>100
TK⁻ VZV (07-1)	HEL	8.0	61	22	>100	>400	>400	>100	>100	>400	>100
CMV (Davis)	HEL	250	25	7	>100	250	250	>100	70	200	>100
CMV (AD169)	HEL	250	25	7	>100	N.D.[c]	250	>100	70	250	>100
VSV	E_6SM	>400	>40	>40	>400	>400	>400	>200	>40	>400	>400
VV	E_6SM	1	>40	>40	>400	>400	>400	>200	>40	>40	>400
morphologic alteration	E_6SM	>400	>40	>40	>400	>400	>400	>200	>40	>400	>400
cell growth	HEL	200	>200	>200	>50	>200	>200	>50	>200	>200	>50

[a] Concentration required to reduce virus-induced cytopathicity (HSV, VSV, VV) or plaque formation (VZV, CMV), or cell growth by 50%; for morphologic alteration, it corresponded to the minimum concentration required to cause a microscopically detectable change in normal cell morphology. [b] The results listed in the table are representative of a single experiment. The experiments were repeated several times. [c] Not determined.

Scheme IV



Scheme V



(H_2S) and stored overnight at room temperature, a more apolar compound was formed as judged by TLC analysis ($CHCl_3$–MeOH, 95/5). ^{13}C NMR analysis revealed the disappearance of the signal of the cyano group and appearance of a new signal at 191.4 ppm, indicating formation of the 5-thioamide function. Also, the ^1H NMR was indicative of the formation of a 5-thioamide function: the H-6 signal shifted from δ 8.68 ppm to 9.22 ppm and two (exchangeable) signals appeared at δ 9.79 ppm and 10.1 ppm. However, attempts to isolate unprotected 5-thiocarbamoyl-2'-deoxyuridine as a crystalline solid failed, as the crystallization solution always turned yellow and a second more polar compound was formed.

The thiocarboxamide function reacted readily with chloroacetaldehyde (**12a**), 2-bromoacetophenone (**12b**), and chloroacetone (**12c**) to afford the thiazol-2-yl (**13a**), 4-phenylthiazol-2-yl (**13b**), and 4-methylthiazol-2-yl (**13c**) derivatives of 3',5'-di-*O*-benzoyl-2'-deoxyuridine, respectively. These nucleosides were deprotected with ammonia in methanol to **14a–c**.

The 5-pyrrol-1-yl-2'-deoxyuridine **17** could be obtained by reaction of the hydrochloric salt of 5-amino-2'-deoxyuridine[10] **14** with dimethoxytetrahydrofuran (**16**). The amino function in the 5-position of pyrimidine nucleosides is strongly deactivated so that rather drastic conditions were necessary for this reaction (1.5 h, 100 °C). As a consequence, the 5-amino function of 5-amino-2'-deoxyuridine did not react with either diformylhydrazine or *N,N'*-dimethylformamide azine hydrochloride.[11]

Assignments of the ^{13}C NMR signals to the different carbon atoms of the pyrimidine and isoxazole rings were made and indicated the position of the substituents. The carbon-4 of an isoxazole resonates at a higher field than the carbon-5 atom of the isoxazole. If the other isomer is formed (i.e. isoxazol-4-yl), the carbon-5 should be the unsubstituted one. However, the signal at δ 102.8 ppm (^{13}C NMR) was coupled with the signal appearing at ±6.69 (^1H NMR) ppm, which is indicative for an isoxazol-5-yl structure. Thus, the ^{13}C NMR off-resonance spectrum was in agreement with the proposed structures. Assignment of the sugar signals C-4' and C-1' of the final products was proven by selective carbon–proton coupling experiments.

Antiviral Activity

Of the 5-substituted 2'-deoxyuridine derivatives evaluated for antiviral activity, only 5-(3-bromoisoxazol-5-

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yl)-2′-deoxyuridine (**4c**) showed a marked activity against HSV-1 in both embryonic skin muscle (E_6SM) cells (Table I) and primary rabbit kidney (PRK) cells (data not shown). However, as compared to the reference compound BrVdUrd, compound **4c** was about 100-fold less active. The 5-(3-methylisoxazol-5-yl) (**4d**), 5-thiazol-2-yl (**14a**), and 5-pyrrol-1-yl (**17**) derivatives showed slight activity against HSV-1, but only in E_6SM cells (Table I). Pronounced activity was found with **4c** against the TK^+ strains YS and OKA of VZV (Table I). Also, compounds **4d** and **17** were slightly active against these two VZV strains, while **14a** was inactive.

As could be expected from the results recently obtained with other 5-substituted 2′-deoxyuridines,[12,13] none of the compounds that were subject of the present study proved active against thymidine kinase deficient (TK^-) HSV or VZV. Apparently, the presence of a bromine atom in the isoxazole ring (**4c**) does not allow any activity against TK^- viruses. This contrasts with the behavior of 5-fluoro-2′-deoxyuridine, which is active against TK^- HSV.[14]

None of the test compounds at a concentration up to 40 μg/mL showed cytotoxicity, whether monitored by alteration of cell morphology or inhibition of cell growth. It may be assumed that the inactive compounds are most probably not phosphorylated by either viral TK or cellular kinases as it has been clearly demonstrated previously with other 2′-deoxyuridine derivatives. However, failure of phosphorylation of the inactive compounds has not been directly demonstrated, and hence, it cannot be entirely ruled out that the lack of antiviral activity may be the result of phosphorylated anabolites of these nucleosides failing to inhibit the target viral function (presumably the viral DNA polymerase).

The compounds with the smaller substituents (**4d**, **14a**, and **17**) show some inhibition of HSV-1 replication and might be good starting products for further structure–activity relationship studies. Introduction of the electronegative and hydrophobic bromine in the isoxazole ring potentiates the antiviral activity, whereas introduction of an alkyl substituent (**4e**) seems to reduce the antiviral activity. Surprisingly, introduction of a *p*-chlorophenyl group on the isoxazole ring yielded a compound [5-[3-(*p*-chlorophenyl)isoxazol-5-yl]-2′-deoxyuridine, **4b**] with distinct anti-CMV activity (Table I). Compound **4b** was more effective in this regard than the other compounds tested and might represent a new lead for the development of CMV inhibitors.

Experimental Section

Melting points were determined in capillary tubes with a Büchi-Tottoli apparatus and are uncorrected. Ultraviolet spectra were recorded with a Philips PU 8700 UV/vis spectrophotometer. The ^{1}H NMR and ^{13}C NMR spectra were determined with a JEOL FX 90Q spectrometer with tetramethylsilane as internal standard for the ^{1}H NMR spectra and DMSO-d_6 (39.6 ppm) for the ^{13}C NMR spectra (s = singlet, d = doublet, t = triplet, br s = broad signal, m = multiplet). Precoated Merck silica gel F254 plates were used for TLC, and the spots were examined with UV light and sulfuric acid–anisaldehyde spray. Column chromatography was performed on Merck silica gel (0.060–0.200 mm). Anhydrous solvents were obtained as follows: tetrahydrofuran was refluxed overnight on lithium aluminum hydride; dichloromethane was stored for 1 week on anhydrous calcium chloride, filtered, and distilled; water was removed from *N*,*N*-dimethylformamide by distillation with benzene followed by distillation in vacuo.

5-(3-Phenylisoxazol-5-yl)-2′-deoxyuridine (4a). To a solution of 200 mg (0.41 mmol) 3′,5′-di-*O*-toluoyl-5-ethynyl-2′-deoxyuridine and 280 mg (1.80 mmol) of benzohydroximoyl chloride in 20 mL of THF, cooled at −20 °C, was added dropwise a solution of 2 mL of Et_3N (14.3 mmol) in 10 mL of THF. The temperature was raised slowly (2 h) up to room temperature; TLC evaluation ($CHCl_3$–MeOH, 95/5) revealed that all starting material had been transformed to a more lipophilic product. The mixture was evaporated and taken up in 20 mL of a 0.1 M solution of sodium methoxide in MeOH. After 2 h, 5 mL of acetic acid was added and the mixture was evaporated. Chromatographic purification yielded 90 mg (59%) of the phenylisoxazolyl derivative, which was crystallized from acetone: mp >250 °C; UV (MeOH) λ_{max} 237 nm (ϵ = 20 250), 303 (ϵ = 18 450); ^{1}H NMR δ 2.27 (t, 2 H, H-2′), 3.68 (br s, 2 H, H-5′), 3.85 (m, 1 H, H-4′), 4.33 (m, 1 H, H-3′), 5.23 (br s, 2 H, 3′-OH and 5′-OH), 6.23 (t, 1 H, H-1′), 7.26 (s, 1 H, H-4″), 7.51 and 7.86 (2 × br s, 5 H, aromatic H), 8.76 (s, 1 H, H-6), 11.81 (br s, 1 H, NH) ppm; ^{13}C NMR δ 40.5 (C-2′), 60.9 (C-5′), 70.2 (C-3′), 85.4 (C-1′), 87.9 (C-4′), 99.4 (C-4″), 102.7 (C-5), 126.6, 128.5, 129.1 and 130.1 (aromatic C), 139.5 (C-6), 149.4 (C-2), 162.0, 159.7, and 163.6 (C-4, C-3″, and C-5″) ppm. Anal. $C_{18}H_{17}N_3O_6$ (C, H, N).

5-[3-(*p*-Chlorophenyl)isoxazol-5-yl]-2′-deoxyuridine (4b). To a solution of 250 mg (0.51 mmol) of 3′,5′-di-*O*-toluoyl-5-ethynyl-2′-deoxyuridine and 1.9 g (10 mmol) of *p*-chlorobenzohydroximoyl chloride in 20 mL of THF, cooled at −20 °C, was added dropwise a solution of 2 mL (14.3 mmol) of triethylamine in 10 mL of THF. The mixture was kept for 2 h at −20 °C and slowly warmed up to room temperature (2 h). After evaporation, the protective groups were removed by treatment with 20 mL of 0.1 M NaOMe in MeOH during 2 h. The solution was neutralized with 0.5 M HCl and evaporated. Column chromatography yielded 70 mg of 5-[3-(*p*-chlorophenyl)isoxazol-5-yl]-2′-deoxyuridine, which was crystallized from acetone: mp 229–231 °C; UV (MeOH) λ_{max} 242 nm (ϵ = 21 000), 305 (ϵ = 17 600); ^{1}H NMR (DMSO-d_6) δ 2.26 (t, 2 H, H-2′), 3.70 (br s, 2 H, H-5′), 3.87 (m, 1 H, H-4′), 4.23 (m, 1 H, H-3′), 5.03 (t, 1 H, 5′-OH), 5.19 (d, 1 H, 3′-OH), 6.21 (t, 1 H, H-1′), 7.28 (s, 1 H, H-4″), 7.58 and 7.95 (2×) (d, 2 H, J = 8.7 Hz, aromatic H), 8.76 (s, 1 H, H-6), 11.79 (br s, 1 H, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 42.0 (C-2′), 61.1 (C-5′), 70.3 (C-3′), 85.8 (C-1′), 88.0 (C-4′), 99.7 (C-4″), 102.0 (C-5), 127.4, 128.4, 129.1, and 135.2 (aromatic C), 139.7 (C-6), 149.5 (C-2), 161.1, 159.7, and 163.9 (C-4, C-3″, and C-5″) ppm. Anal. $C_{18}H_{16}N_3O_6Cl \cdot {}^3/_4H_2O$ (C, H, N).

5-(3-Bromoisoxazol-5-yl)-2′-deoxyuridine (4c). 3′,5′-Di-*O*-toluolyl-5-ethynyl-2′-deoxyuridine (700 mg, 1.43 mmol) was dissolved in 100 mL of EtOAc with gentle heating. To this solution were added 3 mL of H_2O, 700 mg (2.3 mmol) of dibromoformaldoxime (**7**), and 700 mg (7 mmol) of potassium bicarbonate. The mixture was stirred vigorously during 16 h. TLC analysis ($CHCl_3$–MeOH, 95/5) revealed the disappearance of all starting material and the formation of a more lipophilic product. This product was isolated by column chromatography (390 mg, 44% yield), and the protective groups were removed by treatment with a 0.1 M sodium methoxide solution in methanol at room temperature for 8 h. Column chromatography yielded 5-(3-bromoisoxazol-5-yl)-2′-deoxyuridine in 92% yield (220 mg). The product was recrystallized from acetone: mp 170–172 °C; UV (MeOH) λ_{max} = 248 nm (ϵ = 10 400), 302 (ϵ = 18 000); ^{1}H NMR (DMSO-d_6 + D_2O) δ 2.25 (t, 2 H, H-2′), 3.66 (br s, 2 H, H-5′), 3.89 (m, 1 H, H-4′), 4.31 (m, 1 H, H-3′), 6.18 (t, 1 H, H-1′), 6.94 (s, 1 H, H-4″), 8.76 (s, 1 H, H-6) ppm; ^{13}C NMR (DMSO-d_6) δ 40.6 (C-2′), 60.8 (C-5′), 70.0 (C-3′), 85.7 (C-1′), 88.0 (C-4′), 101.2 (C-5), 104.5 (C-4″), 140.5 (C-6), 140.5 (C-3″), 149.3 (C-2), 159.6 (C-4), 165.0 (C-5″) ppm. Anal. $C_{12}H_{12}N_3O_6Br$ (C, H, N).

5-(3-Methylisoxazol-5-yl)-2′-deoxyuridine (4d). 3′,5′-Di-*O*-toluolyl-5-ethynyl-2′-deoxyuridine evaporated three times with 25 mL of toluene, was dissolved in 50 mL of toluene with heating. To this solution were added 150 μL (2.10 mmol) of nitroethane, 600 μL (5.25 mmol) of phenyl isocyanate, and 2 drops of triethylamine. The mixture was heated for 16 h at 90 °C under an inert atmosphere. After cooling and evaporation, the remaining oil was taken up in 50 mL of 0.1 M NaOMe in MeOH. The

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deprotection was completed within 2 h. After the usual workup procedure and purification step, 210 mg (69%) of 5-(3-methylisoxazol-5-yl)-2'-deoxyuridine was obtained. This product crystallized from acetone: mp 237 °C; UV (MeOH) λ_{max} = 244 nm (ϵ = 11900), 301 (ϵ = 16000); ^{1}H NMR (DMSO-d_6) δ 2.26 (br s, 5 H, H-2' and CH_3), 3.65 (br s, 2 H, H-5'), 3.89 (m, 1 H, H-4'), 4.31 (m, 1 H, H-3'), 5.27 (t, 1 H, 5'-OH), 5.49 (d, 1 H, 3'-OH), 6.20 (t, 1 H, H-1'), 6.69 (s, 1 H, H-4''), 8.61 (s, 1 H, H-6), 11.26 (s, 1 H, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 11.3 (CH_3), 40.7 (C-2'), 61.2 (C-5'), 70.5 (C-3'), 85.8 (C-1'), 88.0 (C-4'), 102.8 (C-4''), 102.9 (C-5), 139.6 (C-6), 149.7 (C-2), 160.1, 160.4, and 162.5 (C-4, C-3'', and C-5'') ppm. Anal. $C_{13}H_{15}N_3O_6 \cdot {}^1/_4H_2O$ (C, H, N).

5-(3-Ethylisoxazol-5-yl)-2'-deoxyuridine (4e). 3',5'-Di-*O*-toluoyl-5-ethynyl-2'-deoxyuridine (1) (500 mg, 1.02 mmol), dried by coevaporation with toluene, was dissolved in 100 mL of toluene with gentle heating. Nitropropane (135 μL, 1.5 mmol), 328 μL (3 mmol) of phenyl isocyanate, and 3 drops of Et_3N were added. The mixture was heated for 16 h at 80 °C under anhydrous conditions. At that moment TLC revealed that all starting material had disappeared. The mixture was cooled, and the volatiles were evaporated. The resulting oil was taken up in 50 mL of 0.1 M sodium methanolate in MeOH and kept for 2 h at room temperature. The reaction mixture was neutralized, evaporated, and purified, yielding 212 mg (64%) of **4e** as a foam. The compound was recrystallized from acetone: mp 193–195 °C; UV (MeOH) λ_{max} = 244 nm (ϵ = 13350), 301 (ϵ = 17900); ^{1}H NMR (DMSO-d_6) δ 1.20 (t, 3 H, CH_3), 2.21 (t, 2 H, H-2'), 2.64 (q, 2 H, CH_2CH_3), 3.63 (br s, 2 H, H-5'), 3.87 (m, 1 H, H-4'), 4.28 (m, 1 H, H-3'), 5.02–5.40 (br s, 2 H, D_2O exchangeable, 3'-OH and 5'-OH), 6.18 (t, 1 H, H-1'), 6.71 (s, 1 H, H-4''), 8.61 (s, 1 H, H-6), 11.75 (s, 1 H, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 12.5 (CH_3), 19.0 (CH_2CH_3), 40.5 (C-2'), 61.0 (C-5'), 70.3 (C-3'), 85.4 (C-1'), 87.9 (C-4'), 101.2 (C-4''), 102.5 (C-5), 139.0 (C-6), 149.4 (C-2), 159.8 (C-4), 162.2 (C-5''), 165.1 (C-3'') ppm. Anal. $C_{14}H_{17}N_3O_6$ (C, H, N).

5-Thiocarbamoyl-3',5'-di-*O*-benzoyl-2'-deoxyuridine (11). To a solution of 1 g (2.16 mmol) of 5-cyano-3',5'-di-*O*-benzoyl-2'-deoxyuridine in 20 mL of DMF was added 3 mL of Et_3N. The solution was saturated with H_2S (0.5 h). The reaction vessel was closed and kept for 24 h at room temperature. The mixture was neutralized with acetic acid, evaporated, and purified by column chromatography (CH_2Cl_2–CH_3CN, 90/10), giving 970 mg (90%) of **2** as a foam: ^{1}H NMR (DMSO-d_6) δ 2.75 (m, 2 H, H-2'), 4.61 (br s, 3 H, 2 × H-5' and H-4'), 5.64 (m, 1 H, H-3'), 6.25 (t, 1 H, H-1'), 7.04–8.82 (br s, 10 H, aromatic H), 9.22 (s, 1 H, H-6), 9.79 (s, 1 H, NH_2), 10.1 (s, 1 H, NH_2), 11.97 (s, 1 H, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 64.4 (C-5'), 74.6 (C-3'), 82.4 (C-1'), 87.3 (C-4'), 109.3 (C-5), 128.5, 128.7, 129.3, and 133.6 (aromatic C), 148.9 and 149.9 (C-6 and C-2), 162.4 (C-4), 165.2 and 165.5 (C=O), 191.4 (C=S) ppm.

5-Thiazol-2-yl-2'-deoxyuridine (14a). To a solution of 400 mg (0.87 mmol) of the protected thioamide **11** in 45 mL of a mixture of THF and EtOH (2/1) were added 2 mL (15 mmol) of a chloroacetaldehyde solution (50% in H_2O). This mixture was refluxed for 6 h. TLC (CH_2Cl_2–CH_3CN, 80/20) revealed that about 20% of the starting material was transformed, another 6 mL (45 mmol) of the chloroacetaldehyde solution was added, and the mixture was refluxed overnight (total 24 h). After evaporation and chromatographic purification, 230 mg (51%) of 3',5'-dibenzoyl-5-thiazol-2-yl-2'-deoxyuridine (**13a**) was obtained as an oil. The protective groups were removed by treatment with methanol saturated with ammonia (16 h); column chromatography yielded 120 mg (70%) of 5-thiazol-2-yl-2'-deoxyuridine (**14a**). The compound was recrystallized from isopropanol: mp 217–219 °C; UV (MeOH) λ_{max} 320 nm (ϵ = 14100); ^{1}H NMR (DMSO-d_6) δ 2.23 (t, 2 H, H-2'), 3.63 (br s, 2 H, H-5'), 3.89 (m, 1 H, H-4'), 4.30 (m, 1 H, H-3'), 5.01 (t, 1 H, 5'-OH), 5.30 (d, 1 H, 3'-OH), 6.22 (t, 1 H, H-1'), 7.46 (d, 1 H, 3.3 Hz, H-5''), 7.85 (d, 1 H, 3.3 Hz, H-4''), 8.83 (s, 1 H, H-6), 11.90 (s, 1 H, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 40.3 (C-2'), 61.4 (C-5'), 70.5 (C-3'), 85.4 (C-1'), 87.9 (C-4'), 107.7 (C-5), 119.8 (C-5''), 138.6 (C-6), 141.9 (C-4''), 149.4 (C-2), 159.1 and 161.3 (C-2'' and C-4) ppm. Anal. $C_{13}H_{13}N_3O_5S$ (C, H, N).

5-(4-Phenylthiazol-2-yl)-2'-deoxyuridine (14b). To a solution of 643 mg (1.39 mmol) of 5-thiocarbamoyl-3',5'-di-*O*-benzoyl-2'-deoxyuridine in a mixture of THF and EtOH (2/1) was added 300 mg (1.5 mmol) of 2-bromoacetophenone. The mixture was refluxed for 6 h, cooled, and evaporated. Chromatographic purification yielded 710 mg (88%) of 3',5'-dibenzoyl-5-(4-phenylthiazol-2-yl)-2'-deoxyuridine as an oil, which was deprotected with 0.1 M sodium methoxide in MeOH (20 mL, 6 h). After neutralization, evaporation, and purification 338 mg (71%) of **14b** was obtained. The product was recrystallized from MeOH: mp >250 °C; UV (MeOH) λ_{max} = 230 nm (ϵ = 18900), 254 (ϵ = 20500), 334 (ϵ = 13500); ^{1}H NMR (DMSO-d_6) δ 2.27 (t, 2 H, H-2'), 3.70 (br s, 2 H, H-5'), 3.92 (m, 1 H, H-4'), 4.33 (m, 1 H, H-3'), 5.10 (t, 1 H, 5'-OH), 5.28 (d, 1 H, 3'-OH), 6.31 (t, 1 H, H-1'), 7.37 (br s, 3 H, aromatic H), 8.00 (br s, 3 H, aromatic H), 9.06 (s, 1 H, H-6), 12.03 (br s, 1 H, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 40.5 (C-2'), 61.3 (C-5'), 70.4 (C-3'), 85.1 (C-1'), 88.0 (C-4'), 107.5 (C-5), 114.0 (C-5''), 126.1, 127.8, 128.7, and 134.1 (aromatic C), 139.1 (C-6), 149.3 (C-2), 143.1 (C-4''), 158.1 and 163.3 (C-2'' and C-4) ppm. Anal. $C_{18}H_{17}N_3O_5S$ (C, H, N).

5-(4-Methylthiazol-2-yl)-2'-deoxyuridine (14c). 5-Thiocarbamoyl-3',5'-dibenzoyl-2'-deoxyuridine (238 mg, 0.51 mmol) was dissolved in 20 mL of a mixture of THF and EtOH (2/1); 2 mL of chloroacetone (25 mmol) was added and the mixture was refluxed overnight. The solution was cooled and evaporated to an oil, which was taken up in 20 mL of methanol saturated with ammonia and kept at room temperature overnight. The mixture was evaporated and purified by column chromatography. It yielded 97 mg of **14c** as a foam; the compound was recrystallized from acetone: mp 245–247 °C; UV (MeOH) λ_{max} = 256 nm (ϵ = 6500), 326 (ϵ = 14700); ^{1}H NMR (DMSO-d_6) δ 2.22 (t, 2 H, H-2'), 2.39 (d, 3 H, 0.9 Hz, CH_3), 3.60 (br s, 2 H, H-5'), 3.88 (m, 1 H, H-4'), 4.28 (m, 1 H, H-3'), 4.98 (t, 1 H, 5'-OH), 5.30 (d, 1 H, 3'-OH), 6.19 (t, 1 H, H-1'), 7.17 (d, 1 H, 0.9 Hz, H-5''), 8.76 (s, 1 H, H-6), 11.88 (br s, 1 H, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 17.0 (CH_3), 40.3 (C-2'), 61.3 (C-5'), 70.4 (C-3'), 85.5 (C-1'), 87.8 (C-4'), 107.8 (C-5), 114.6 (C-5''), 138.5 (C-6), 149.4 and 151.2 (C-2 and C-4''), 157.4 and 161.3 (C-2'' and C-4) ppm. Anal. $C_{13}H_{14}N_3O_5S \cdot {}^1/_4H_2O$ (C, H, N).

5-Pyrrol-1-yl-2'-deoxyuridine (17). To a solution of 210 mg (0.63 mmol) of the hydrochloride salt of 5-amino-2'-deoxyuridine (**15**) in 20 mL of DMF was added 0.5 mL (3.8 mmol) of 2,5-dimethoxytetrahydrofuran (**16**). The solution was heated for 1.5 h at 100 °C, cooled, and evaporated. The reaction mixture was purified twice by column chromatography before an analytical pure compound was obtained; 70 mg (38%) of 5-pyrrol-1-yl-2'-deoxyuridine was yielded as a foam: UV (MeOH) λ_{max} = 228 nm (ϵ = 7250), 287 (ϵ = 8100); ^{1}H NMR (DMSO-d_6) δ 2.20 (m, 2 H, H-2'), 3.60 (br s, 2 H, H-5'), 3.81 (m, 1 H, H-4'), 4.27 (m, 1 H, H-3'), 5.11 (t, 1 H, 5'-OH), 5.25 (d, 1 H, 3'-OH), 6.13 (br s, 3 H, H-1', H-3'', and H-4''), 6.93 (t, 2 H, J = 2.2 Hz, H-2'' and H-5''), 11.72 (s, 1 H, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 40.1 (C-2'), 60.9 (C-5'), 70.1 (C-3'), 84.7 (C-1'), 87.6 (C-4'), 108.7 (C-3'' and C-4''), 116.4 (C-5), 121.4 (C-2'' and C-5''), 133.3 (C-6), 149.3 (C-2), 159.6 (C-4) ppm. Anal. $C_{13}H_{15}N_3O_5 \cdot {}^1/_2H_2O$ (C, H, N).

In vitro antiviral assays were performed as described previously.[15,16] The origin of the viruses [herpes simplex virus type 1 (HSV-1 strain KOS, F, and McIntyre], thymidine kinase deficient (TK$^-$) strains B2006 and VMW1837), herpes simplex virus type 2 (HSV-2, strains G, 196 and Lyons), varicella-zoster visus (VZV, strains Oka and YS), TK$^-$ VZV (strains 07-1 and YS-R), vaccinia virus (VV), vesicular stomatitis virus (VSV) and cytomegalovirus (CMV, strains AD169 and Davis) has been described.[14,15] Cytotoxicity measurements were based on either microscopically detectable alteration of normal cell morphology or inhibition of cell growth. The antiviral activity and cytotoxicity assays were performed in primary rabbit kidney (PRK), human embryonic skin-nude (E_6SM) or human embryonic lung (HEL) cells seeded in 96-well microtiter plates.

Acknowledgment. This study was supported by grants from the Belgian Fonds voor Geneeskundig Wetenschappelijk Onderzoek (Project no. 3.0040.83 and 3.0097.97). Robert Snoeck is a senior research assistant from the

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Belgian National Fund for Scientific Research. We thank Dominique Brabants for her dedicated editorial assistance and Anita Van Lierde, Frieda De Meyer and Anita Camps for their efficient technical assistance.

Registry No. 1, 69075-43-0; **3a**, 133040-26-3; **3b**, 133040-27-4; **3c**, 133040-28-5; **3d**, 133040-29-6; **3e**, 133070-82-3; **4a**, 133070-83-4; **4b**, 133040-30-9; **4c**, 133040-31-0; **4d**, 133040-32-1; **4e**, 133040-33-2; **6a**, 698-16-8; **6b**, 28123-63-9; **7**, 74213-24-4; **8** (R = CH_3), 79-24-3; **8** (R = C_2H_5), 25322-01-4; **9**, 103-71-9; **10**, 133040-34-3; **11**, 133040-35-4; **12a**, 107-20-0; **12b**, 70-11-1; **12c**, 78-95-5; **13a**, 133040-40-1; **13b**, 133040-41-2; **13c**, 133040-42-3; **14a**, 133040-36-5; **14b**, 133040-37-6; **14c**, 133040-38-7; **15**, 73446-40-9; **16**, 696-59-3; **17**, 133040-39-8.

Substituent Effect on the Stereochemistry of H_2-Receptor Antagonists of the Phenylformamidine Series. A Conformation-Dependent Mode of Interaction with the H_2 Receptor

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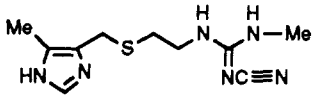
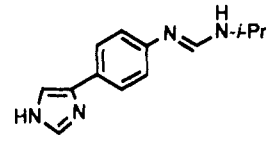
The influence of alkyl substitution on the stereoisomerism of the formamidine cation (*E,E* vs *E,Z*) of several N-substituted (imidazolylphenyl)formamidines (**1–10**) was investigated. As (imidazolylphenyl)formamidines having alkyl substituents of more than three carbon atoms bind to H_2-receptor preparations in a pseudoirreversible mode causing unsurmountable antagonism, the four isomeric butylformamidines (**5–7** and **9**) having comparable lipophilic character but different *E,E*/*E,Z* composition were investigated in H_2-receptor assays to determine quantitatively any difference in their pseudoirreversible inhibitory pattern. It was found that the geometry of the formamidine cation is affected by the steric bulk of the substituent on the formamidine nitrogen. A relationship between the percentage of the *E,E* conformation of the formamidine cation and degree of pseudoirreversible antagonism was also found. The present studies support the hypothesis that bidentate hydrogen bonding plays an important role in the interaction of (imidazolylphenyl)formamidines with the H_2 receptor.

The search for H_2 antagonists by the structural modification of cimetidine has led to the discovery of a number



cimetidine



mifentidine (1)

of new compounds.[1] Chemical variations of this prototype structure have focused mainly on the two molecular determinants for H_2-receptor antagonism, i.e. the imidazole ring and the cyanoguanidine moiety.

While the imidazole ring was amenable to replacement only by a limited number of moieties (e.g. aminomethylfuran, guanidinothiazole, aminomethylbenzene), manipulation of the cyanoguanidine part has led to a wide variety of amidine-type structures which were introduced on structural parts of classical H_2-receptor antagonists.[1,2] Thiourea, cyanoguanidine, nitroethenediamine, and sulfamoylamidine are examples of acyclic amidine systems. Aminopyrimidones, -thiadiazoles, -thiatriazines, and -thiazoles (benzo- or thieno-fused) may be considered cyclized amidine correspondents. Most of them possess a reduced basicity conferred by the presence of electronegative substituents or by the inherent sp^2 character of their nitrogens' lone pairs.

Ganellin and co-workers,[3] in a study aimed at analyzing quantitatively differences in the antagonist activity associated with these moieties, have pointed out the importance of the orientation of the dipole moment associated with these amidine systems. Their findings suggest that interaction of these structural parts with the H_2 receptor might be largely determined by their hydrogen-bonding ability. Recent studies[2,4] on mifentidine (**1**),[5] a new type of H_2-receptor antagonist having a phenylformamidine structure, have led us to suggest a general model for the interaction of amidino groups with the H_2 receptor. The model proposes that these moieties bind to a common binding site in two possible modes, as depicted in Figure 1.

It is implicit from this model that in order to establish an effective bidentate coupling, a syn relationship of the two hydrogens on the amidine nitrogens is required. The model also implies that the formation of the cyclic complex is energetically compatible and that the amidine group is present at the receptor in a proper alignment. Provided the latter condition is fulfilled, whether the formamidine binds in its protonated form to an ionized acidic moiety, as in Figure 1 (part a), or in its neutral form to an unionized acidic counterpart (part b), the energy of binding will be influenced by its steric bias to assume the required syn relationship of NH bonds (i.e. the *E,E* configuration

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