receptors. QSAR analysis of the meta-substituted analogues 1 and 6-14 suggested that the substituent steric descriptor, MR,[16] accounts for most of the variance observed in the CCK-B receptor binding data for the parent indole analogues:

$$-\log (IC_{50}) = 0.089\ (\pm 0.017)MR + 5.99\ (\pm 0.14)$$

$$n = 10,\ s = 0.24,\ r = 0.88,\ F_{(1,8)} = 27.3,\ p < 0.001$$

A substituent at C-5 of the indole nucleus also incrementally enhanced receptor-blocking activity and this increase was additive to the effects observed with phenyl ring substitution. However, whereas meta or para monosubstitution (i.e. 19 and 30) provided approximately equipotent analogues, disubstitution (i.e. 29) appeared to be detrimental. In addition, increasing the alkoxyl substituent size to give 23 as suggested by the above relationship reduced receptor-binding activity relative to compound 22. Consequently, the isopropoxyl group may represent the maximum size for alkoxyl substituents on the pendant phenyl ring.

The CCK/gastrin receptor selectivity was subsequently investigated, and the data for a representative group of analogues appear in Table II. The compounds examined exhibit excellent selectivity for CCK-B over CCK-A receptors. Although the molecular basis for this observation is unclear, both the benzodiazepine and quinazolinone[17] antagonists possess structural features common to the quinazolino-1,4-benzodiazepine, asperlicin. These results are interesting since the natural product is a selective CCK-A receptor antagonist. The apparent modest selectivity between CCK-B and stomach gastrin receptors, on the other hand, is most likely attributable to a species difference. Since a species effect was not observed for L-365,260, the quinazolinone and benzodiazepine antagonists may interact with different regions and/or different amino acid residues associated with the CCK-B receptor. Nevertheless, these compounds, like other reported CCK-B antagonists,[9,18] do not discriminate between guinea pig CCK-B and gastrin receptors in vitro.

Since the methylene carbon attached to the quinazolinone ring of 1 is common to both the quinazolinone and benzodiazepine substructures in asperlicin (Scheme I),[19] we examined the effect of substitution at that position on CCK-B receptor binding and receptor subtype selectivity. However, only a minor difference in potency was observed for compound 25 relative to 24 with no apparent change in the receptor binding IC_{50} ratio (Table II).[20]

The receptor-binding assays were conducted as described in literature procedures: CCK-B receptor binding was performed with mouse brain membranes according to the method of Chang and Lotti.[21] CCK-A receptor binding was determined in rat pancreas with ^{3}H-labeled L-364,718 by the procedure described by Chang et al.[22] Finally, a modified procedure of Takeuchi et al. was used to measure gastrin binding to guinea pig stomach mucosal membranes.[23]

Certain benzodiazepine anxiolytics have been reported to functionally antagonize some of the peripheral[24] and central effects of CCK.[25] In addition, the benzodiazepine κ-opioid agonist tifluadom has been reported to be a CCK-A receptor antagonist.[26] Although 3-phenyl-4-(3*H*)-quinazolinones such as methaqualone have not to our knowledge been reported as CCK antagonists, our study raises the possibility that quinazolinones may, like the benzodiazepines, be amenable to structural modifications to yield nonpeptidal ligands for a specific peptide receptor.

Acknowledgment. We thank James Wikel for helpful discussions on QSAR analysis and Virginia Lucaites for the isolated guinea pig ileum study. We also thank Dr. Robert F. Bruns for his continued support of the CCK receptor binding assay.

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(17) Compound 12 (10^{-6} M) noncompetitively blocked the CCK-8S and CCK-4 induced contractile response in isolated guinea pig ileal longitudinal smooth muscle. No agonist activity was observed over the concentration range of 10^{-10} to 10^{-5} M. Additional studies are in progress to further elucidate the pharmacological properties of this series.

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Melvin J. Yu,* K. Jeff Thrasher
Jefferson R. McCowan, Norman R. Mason
Laurane G. Mendelsohn
Lilly Research Laboratories
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285
Received October 26, 1990

Specific Anti-HIV-1 "Acyclonucleosides" Which Cannot Be Phosphorylated: Synthesis of Some Deoxy Analogues of 1-[(2-Hydroxyethoxy)methyl]-6-(phenylthio)thymine

Chemotherapy of AIDS (acquired immunodeficiency syndrome) is one of the most challenging scientific projects upon which much attention is currently focused. Although AZT (3′-azido-3′-deoxythymidine) is available as the sole compound formally approved for clinical use,[1,2] its serious

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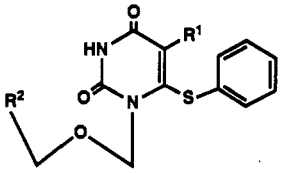
Table I. Inhibition of HIV-1 Replication in MT-4 Cells by "5'"-Deoxy HEPT Analogues and Related Compounds[a]



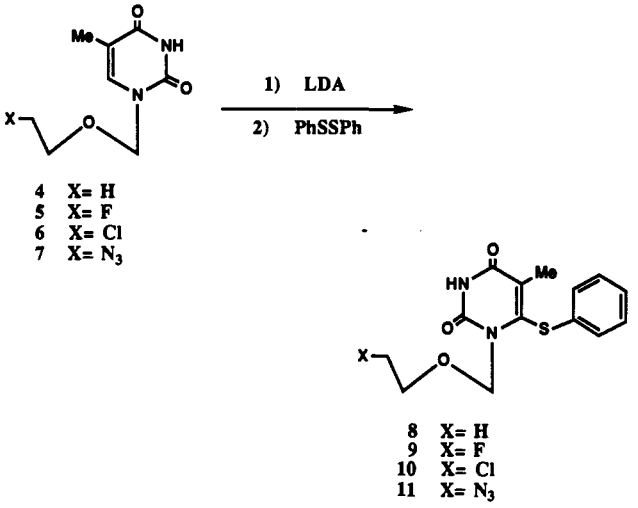
compd	R^1	R^2	EC_{50},[b] μM	CC_{50},[c] μM	SI[d]
HEPT (1)[e]	Me	CH_2OH	6.5 ± 1	>500	>77
2	Me	CH_2OMe	8.7 ± 0.1	299 ± 7	34
3	Me	CH_2OCH_2Ph	>20	45	<2.3
8	Me	Me	0.33 ± 0.3	231 ± 3	700
9	Me	CH_2F	1.1 ± 0.5	209 ± 17	190
10	Me	CH_2Cl	1.5 ± 0.3	196 ± 3	131
11	Me	CH_2N_3	5.8 ± 0.1	186 ± 17	32
12	Me	Ph	0.088 ± 0.012	95 ± 29	1080
13[e]	Et	CH_2OH	0.12 ± 0.045	400	3300
14	Et	Me	0.019 ± 0.002	161 ± 23	8500
15	Et	Ph	0.0059 ± 0.0013	34 ± 7	5800
AZT			0.0030 ± 0.0010	7.8 ± 1.0	2600

[a] All data represent mean values (± standard deviation or range) for at least two separate experiments. [b] Effective concentration of compound required to achieve 50% protection of MT-4 cells against the cytopathic effect of HIV-1. [c] Cytotoxic concentration of compound required to reduce the viability of mock-infected MT-4 cells by 50%. [d] Selectivity index: ratio of CC_{50}/EC_{50}. [e] Data are taken from ref 30.

side effects, suppression of bone marrow cell growth,[3] combined with the appearance of AZT-resistant HIV (human immunodeficiency virus) variants,[4] give an incentive to search for other promising AIDS drug candidates having a higher selectivity against HIV.

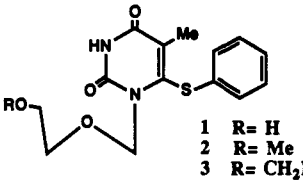
We have recently synthesized some 6-substituted acyclouridines[5] on the basis of our own strategy using LDA (lithium diisopropylamide) which has been proved to be a general method for the modification of the base moiety of nucleosides.[6-15] 1-[(2-Hydroxyethoxy)methyl]-6-(phenylthio)thymine (1, HEPT) was found to be a specific anti-HIV-1 agent.[5] In contrast to 2',3'-dideoxyribonucleoside analogues, HEPT has no inhibitory activity against other retro viruses such as SIV_{MAC} (simian immunodeficiency virus), SRV (simian AIDS-related virus), MSV (murine Moloney sarcoma virus), and even against HIV-2.[16,17] The "5'"-triphosphate of HEPT however does

Scheme I



4 X= H
5 X= F
6 X= Cl
7 X= N_3

8 X= H
9 X= F
10 X= Cl
11 X= N_3



1 R= H
2 R= Me
3 R= CH_2Ph

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not inhibit HIV-1 reverse transcriptase at concentrations much higher than the EC_{50} of HETP for HIV-1 replication in MT-4 cells.[5] Consequently, the presence of an hydroxyl group in HEPT may not be necessary for its anti-HIV-1 activity. In addition HEPT does not compete with [^{3}H-*Me*]thymidine for phosphorylation by thymidine kinase derived from MT-4 cells.[5,16] Our recent studies have suggested that modification of the base moiety of HEPT by substituting at C-2 or C-5 might enhance activity.[18,19]

In the present communication, we describe the synthesis and anti-HIV-1 activity of HEPT analogues, the acyclo portions of which were altered so they could not be phosphorylated. Furthermore, we show a dramatic improvement in the activity by replacing the 5-substituent with an ethyl group.

Initially, preparation of *O*-alkyl derivatives of 1 was carried out. Lithiation of 1-[(2-methoxyethoxy)methyl]-thymine[20] with LDA (2.5 equiv, in THF, below −70 °C for 1 h) and subsequent reaction with $(PhS)_2$ (2.0 equiv, for 40 min) gave the *O*-methyl derivative **2** in 51% yield.[21] The *O*-benzyl derivative **3**[22] was prepared in 80% yield by a selective alkylation of 1 using 1.0 equiv of benzyl bromide in the presence of NaH (2.1 equiv) in THF at room temperature. The anti-HIV-1 activity and cytotoxicity of these compounds are listed in Table I (also included in the table are those of HEPT, its "5′"-deoxy analogues, and AZT).[23] Although the presence of the bulky *O*-benzyl group results in an almost complete loss of activity, the *O*-methyl derivative **2** appeared to retain the activity accompanied by a slight increase in cytotoxicity.

As a result of these experiments, we then synthesized some "5′"-deoxy analogues of HEPT from the thymine derivatives (**4**–**7**)[20,24-26] (Scheme I). The LDA lithiation

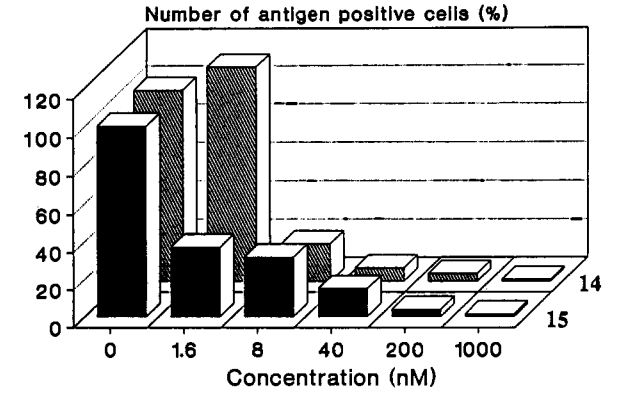
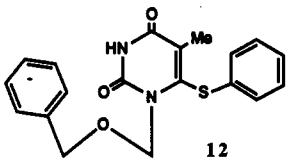
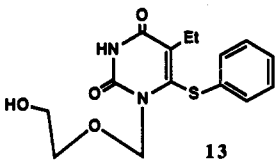


Figure 1. Inhibitory effect of **14** and **15** on HIV-1 antigen expression in CEM cells, the number of antigen-positive cells is expressed as a percentage of untreated virus-infected cells.

reaction was found to work even when the starting material included a halogeno or azido functionality. From the EC_{50} values of the resulting 6-phenylthio analogues (**8**–**11**)[27] in Table I, it can be concluded that the hydroxyl function of HEPT does not contribute to its anti-HIV-1 activity. Another possible conclusion to be drawn from the data is that the value of the EC_{50} may correlate with the size of the substituent in the acyclo portion. Thus, this hypothesis was examined by the introduction of an aralkyl side chain. Compound **12**[28] synthesized in this context was found to be much more active than **8** which corresponds to the genuine deoxy analogue of HEPT. However, due to the



12



13

increased toxicity, the selectivity index (SI) of **12** remained much the same as that of **8**.

In the course of our studies, aimed at increasing the anti-HIV-1 activity of HEPT,[18,19] we recently found that replacement of the 5-methyl group in HEPT with an ethyl group enhanced activity to a greater extent, as illustrated by the EC_{50}, CC_{50}, and SI of **13** (see Table I). This combined with the present results led us to synthesize **14** and

(17) Recently reported tetrahydroimidazo[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-one and -thione (TIBO) derivatives have a similar antiviral spectrum: Pauwels, R.; Andries, K.; Desmyter, J.; Schols, D.; Kukla, M. J.; Breslin, H. J.; Raeymaeckers, A.; Van Gelder, J.; Woestenborghs, R.; Heykants, J.; Schellekens, K.; Janssen, M. A. C.; De Clercq, E.; Janssen, P. A. J. *Nature* **1990**, *343*, 470–474.

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(19) Manuscripts in preparation.

(20) Detailed procedure for the preparation of compounds involved in the present study, including derivatives with no substituent at the 6-position, will be described in forthcoming complete manuscripts.

(21) Elemental analyses of 6-phenylthio derivatives described in this communication are available as supplementary material (see the paragraph at the end of this paper).

(22) Physical data for compounds **2** and **3** are as follows. Compound **2**: mp 102–104 °C (EtOH–H_2O); MS *m/z* 322 (M^+); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.03 (s, 3 H, 5-Me), 3.33 (s, 3 H, OMe), 3.40–3.50 and 3.68–3.78 (m, 4 H, OCH_2CH_2O), 5.60 (s, 2 H, OCH_2N), 7.16–7.37 (m, 5 H, SPh), 8.50 (bs, 1 H, NH). Compound **3**: mp 107–109 °C (Et_2O–hexane); MS *m/z* 398 (M^+); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.00 (s, 3 H, 5-Me), 3.46–3.60 and 3.70–3.86 (m, 4 H, OCH_2CH_2O), 4.50 (s, 2 H, OCH_2Ph), 5.61 (s, 2 H, OCH_2N), 7.12–7.38 (m, 10 H, SPh and CH_2Ph), 8.93 (bs, 1 H, NH).

(23) The procedure to measure anti-HIV-1 activity in MT-4 cells has been described previously: Pauwels, R.; Balzarini, J.; Baba, M.; Snoeck, R.; Schols, D.; Herdewijn, P.; Desmyter, J.; De Clercq, E. *J. Virol. Methods* **1988**, *20*, 309–312.

(24) Compound **5** was obtained from 1-[(2-hydroxyethoxy)-methyl]thymine[25] by reacting with (diethylamido)sulfur trifluoride in CH_2Cl_2.

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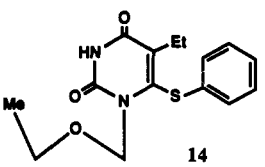
(26) Compounds **6** and **7** were prepared according to the published procedure: Abrams, H. M.; Ho, L.; Chu, S. *J. Heterocycl. Chem.* **1981**, *18*, 947–951.

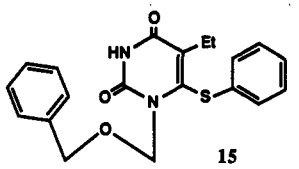
(27) Physical data for compounds **8**–**11** are as follows. Compound **8**: mp 134 °C (EtOH); MS *m/z* 292 (M^+); ^{1}H NMR ($CDCl_3$, 100 MHz) δ 1.14 (t, 3 H, *J* = 6.8 Hz, OCH_2Me), 2.03 (s, 3 H, 5-Me), 3.59 (q, 2 H, *J* = 6.8 Hz, OCH_2Me), 5.55 (s, 2 H, OCH_2N), 7.26 (m, 5 H, SPh), 9.45 (bs, 1 H, NH). Compound **9**: mp 136–137 °C (EtOH); MS *m/z* 310 (M^+); ^{1}H NMR ($CDCl_3$, 100 MHz) δ 2.06 (s, 3 H, 5-Me), 3.83 (dt, 2 H, *J* = 29.3 and 3.9 Hz, OCH_2CH_2F), 4.45 (dt, 2 H, *J* = 47.4 and 3.9 Hz, OCH_2CH_2F), 5.62 (s, 2 H, OCH_2N), 7.27 (m, 5 H, SPh), 9.31 (bs, 1 H, NH). Compound **10**: mp 123–124 °C (EtOH); MS *m/z* 328 and 326 (M^+); ^{1}H NMR ($CDCl_3$, 100 MHz) δ 2.06 (s, 3 H, 5-Me), 3.51 (t, 2 H, *J* = 5.4 Hz, OCH_2CH_2Cl), 3.84 (t, 2 H, *J* = 5.4 Hz, OCH_2CH_2Cl), 5.62 (s, 2 H, OCH_2N), 7.27 (m, 5 H, SPh), 9.14 (bs, 1 H, NH). Compound **11**: mp 91–92 °C (EtOH–H_2O); IR ($CHCl_3$) 2240 cm^{-1}; MS *m/z* 333 (M^+); ^{1}H NMR ($CDCl_3$, 100 MHz) δ 2.07 (s, 3 H, 5-Me), 3.28 (t, 2 H, *J* = 5.4 Hz, $OCH_2CH_2N_3$), 3.74 (t, 2 H, *J* = 5.4 Hz, $OCH_2CH_2N_3$), 5.61 (s, 2 H, OCH_2N), 7.28 (m, 5 H, SPh), 9.78 (bs, 1 H, NH).

(28) Physical data for **12** are as follows: mp 157–161 °C (EtOH–H_2O); MS *m/z* 354 (M^+); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.00 (s, 3 H, 5-Me), 4.64 (s, 2 H, OCH_2Ph), 5.63 (s, 2 H, OCH_2N), 7.03–7.37 (m, 10 H, 2Ph), 8.87 (br, 1 H, NH).

15[29] by the method described. Their activity shown in



14



15

Table I, together with that of HEPT, clearly indicates that the initial activity of HEPT has been dramatically improved at this stage. In particular, the EC_{50} value of 15 is comparable to AZT. It should be emphasized that, in terms of CC_{50}, both 5-ethyl analogues are much less cytotoxic than is AZT. When the activity was examined with some AZT-resistant HIV-1 strains, both compounds were equally effective.[30] Their anti-HIV-1 activities were further confirmed by monitoring viral antigen expression in CEM cells as shown in Figure 1.[31] HIV-1 antigen expression was almost completely suppressed at concentrations of 40–800 nM.

It should be mentioned that the analogues synthesized in this study are uniformly inactive against HIV-2,[30] following the original specificity of HEPT. Our recent observation using reverse transcriptase (RT) indicates that 14 and 15 were potent inhibitors of HIV-1 RT, irrespective of the source of enzymes.[30] However, reflecting their lack of activity against HIV-2 in cell cultures, these compounds did not prove inhibitory to HIV-2 RT. These results suggest their mode of action against HIV-1 at RT is clearly distinct from that of AZT. Another point to be emphasized is the effect of the compounds on bone marrow cell proliferation. In our preliminary experiments, AZT suppressed approximately 50% of the colony formation of murine bone marrow progenitor cells at concentration of 1 μM, whereas no such inhibition was observed with 14 and 15 even at 10 μM.

In conclusion, the present study demonstrates the anti-HIV-1 activity originally found in HEPT can be retained, or improved in certain cases, by removing the hydroxyl group. The 5-ethyl-"5'"-deoxy analogues (14 and 15) obtained by further modification at the base moiety are much less toxic than AZT and, in particular, 15 is almost as active as AZT. Considering their effectiveness against AZT-resistant strains of HIV-1 and also their lower toxicity to bone marrow cells, we believe these compounds may constitute highly promising candidates for the chemotherapy of AIDS.

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Supplementary Material Available: Elemental analyses of compounds 2, 3, 8–12, 14, and 15 (1 page). Ordering information is given on any current masthead page.

* The author to whom correspondence should be addressed.
† Showa University.
‡ Fukushima Medical College.
§ Mitsubishi Kasei Corporation.
∥ University of Birmingham.
⊥ Rega Institute for Medical Research.

Hiromichi Tanaka,† Masanori Baba,‡ Shigeru Saito†
Tadashi Miyasaka,*,† Hideaki Takashima§
Kouichi Sekiya,§ Masaru Ubasawa,§ Issei Nitta§
Richard T. Walker,∥ Hideki Nakashima⊥
Erik De Clercq⊥

School of Pharmaceutical Sciences
Showa University
Hatanodai 1-5-8
Shinagawa-ku, Tokyo 142, Japan
Fukushima Medical College
Fukushima 960-12, Japan
Mitsubishi Kasei Corporation Research Center
Yokohama 227, Japan
Department of Chemistry
University of Birmingham
Birmingham B15 2TT
United Kingdom
Rega Institute for Medical Research
Katholieke Universiteit Leuven
B-3000 Leuven, Belgium

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Novel Synthesis and Biochemical Properties of an [^{125}I]-Labeled Photoaffinity Probe for Thromboxane A_2/Prostaglandin H_2 Receptors

Thromboxane A_2 (TXA_2) and prostaglandin H_2 (PGH_2) posses potent proaggregatory, vasoconstrictor, and bronchoconstrictor activities. TXA_2 has been implicated as a pathophysiological mediator in a variety of cardiovascular disorders.[1] As a consequence, there has been considerable interest in the development of TXA_2/PGH_2 receptor antagonists for potential use in some of these pathophysiological disorders. In addition, characterization of TXA_2/PGH_2 receptors at the structural-functional level has begun to be pursued.[2,3] In the past few years, a number of radioligands have been synthesized and used for the characterization of TXA_2/PGH_2 receptors.[4-7] Of the various radioligands, 7-[(2*R*,2*S*,3*S*,5*R*)-6,6-dimethyl-

(29) Physical data for 14 and 15 are as follows. Compound 14: mp 123–125 °C (EtOAc–acetone); MS *m/z* 306 (M^+); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.99 (t, 3 H, *J* = 7.4 Hz, 5-CH_2CH_3), 1.10 (t, 3 H, *J* = 7.0 Hz, OCH_2CH_3), 2.67 (q, 2 H, *J* = 7.4 Hz, 5-CH_2CH_3), 3.56 (q, 2 H, *J* = 7.0 Hz, OCH_2CH_3), 5.45 (s, 2 H, OCH_2N), 7.13–7.39 (m, 5 H, SPh), 8.41 (br, 1 H, NH). Compound 15: mp 110–112 °C (EtOAc–hexane); MS *m/z* 368 (M^+); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.98 (t, 3 H, *J* = 7.5 Hz, 5-CH_2CH_3), 2.63 (q, 2 H, *J* = 7.5 Hz, 5-CH_2CH_3), 4.63 (s, 2 H, OCH_2Ph), 5.52 (s, 2 H, OCH_2N), 7.08–7.37 (m, 10 H, 2Ph), 8.25 (br, 1 H, NH).

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