Optimization of the Schiff Bases of N-Hydroxy-N'-aminoguanidine as Anticancer and Antiviral Agents

Anne T'ang,† Eric J. Lien,*† and Michael M. C. Lai‡

Section of Biomedicinal Chemistry, School of Pharmacy, and Department of Microbiology, School of Medicine, University of Southern California, Los Angeles, California 90033. *Received September 26, 1984*

Hydroxyurea, hydroxyguanidine, and some thiosemicarbazones have been shown to have anticancer and antiviral activities. One of their possible sites of action is the enzyme ribonucleotide reductase (RR). Combination of the structural features of these compounds led to the design and synthesis of the Schiff bases of *N*-hydroxy-*N'*-aminoguanidine. Synthesis and structure–activity studies of some of these compounds point to increased size and lipophilicity as important factors for activity. To optimize the activities of this series of compounds, 13 derivatives of high lipophilicity and molecular size have been synthesized and their biological activities studied. The most active anticancer compounds against L1210 in vitro (compounds **9** and **12**) are about 7 times more active than hydroxyguanidine and hydroxyurea. The most active antiviral compounds against Rous sarcoma virus transformation of chick fibroblasts in vitro (**7**, **9**) are about 40 times more active than hydroxyguanidine. One of the compounds (**4**) shows promising activity in vivo (% T/C = 140 against P388 leukemia in mice) and is undergoing further studies by the National Cancer Institute (NCI). Studies of the inhibition of transformation of chick embryo cells by Rous sarcoma virus show that all these compounds inhibit transformation while some compounds inhibit viral replication as well.

Ribonucleotide reductase (RR) is a key enzyme involved in DNA synthesis and cell replication. In comparison with several key enzymes studied, RR shows the greatest increase in activity in neoplastic tissues compared to normal tissues (20 800% of normal cells).[1-4] The activity of RR shows a very close correlation with cell replication. The pool size of deoxyribonucleotides is small and therefore cannot support DNA synthesis for long; they must be formed just prior to incorporation into DNA.[5] All this points to RR as a good target for developing agents whose ultimate goal is the inhibition of DNA synthesis.

Hydroxyurea, hydroxyguanidine, and some thiosemicarbozones, whose site of action is the enzyme RR, have good anticancer activities in vitro.[6-8] However, their in vivo effects are limited by one or more of the following: a short half-life, due to hydrophilicity and low molecular weight; rapid metabolic transformation to inactive forms; side-effects such as myelosuppression and gastrointestinal toxicity.[9-11] Guanidine and hydroxyguanidine are both active against several viruses.[7,12] Isatin-3-thiosemicarbazone inhibits pox viruses and influenza viruses.[13] It also inhibits Rous sarcoma virus and the enzyme reverse transcriptase.[12,14] Some other heterocyclic thiosemicarbazones have been shown to be active against vaccinia virus, HSV 1 and 2, and influenza virus, as well as against Rous sarcoma virus and reverse transcriptase.[15]

On the basis of the structures of the above compounds, some *N*-hdyroxy-*N'*-aminoguanidine derivatives with the combined structural features of both hydroxyguanidine and thiosemicarbazone have been synthesized. Previous structure–activity studies point to increased size and lipophilicity as important factors contributing to high anticancer activity.[16]

To optimize the anticancer and antiviral activities of these derivatives, 13 new compounds were designed. To explore electronic effects on activity, derivatives with electron-withdrawing and -donating groups at different positions were synthesized. These molecular modifications cover a wide range of physicochemical properties that will give more meaningful analysis so that the properties leading to the optimum compound can be determined (see Table I).

In order to study the anticancer activity of this series of compounds, their inhibition of L1210 leukemia cell growth was studied in vitro. To study the antiviral effects, the inhibition of transformation of chick embryo fibroblasts by Rous sarcoma virus was studied. Rous sarcoma virus is one of the best known and characterized RNA tumor viruses. It transforms cells in culture, causing the cells to round up and lose contact inhibition, forming discrete foci that can easily be quantitated.[17]

Results and Discussion

The ID_{50}s for the inhibition of L1210 leukemia cell growth are shown in Table II.

In this series, compounds **9** and **12** are the most active compounds ($ID_{50} = 2.70 \times 10^{-6}$ and 3.3×10^{-6} M, respectively). This makes them about 6–7 times more active than hydroxyurea ($ID_{50} = 2.16 \times 10^{-5}$ M) and guanazole ($ID_{50} = 1.68 \times 10^{-5}$ M), the known inhibitors of RR that have been used clinically, and hydroxyguanidine ($ID_{50} = 1.67 \times 10^{-5}$ M). Another RR inhibitor, 5-hydroxy-2-formylpyridine thiosemicarbazone has also undergone clinical trials. The results for the inhibition of cell transformation by Rous sarcoma virus are shown in Table III. The inhibition of viral replication is given in Table IV. The ID_{50}s

† Section of Biomedicinal Chemistry.
‡ Department of Microbiology.

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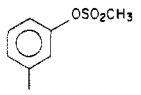
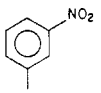
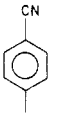
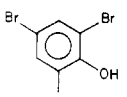
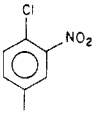
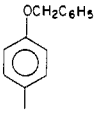
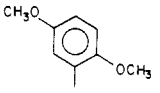
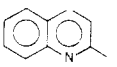
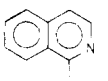
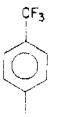
Table I. Schiff Bases of *N*-Hydroxy-*N'*-aminoguanidine ($RCH{=}NNHC(=NH)NHOH{\cdot}CH_3C_6H_4SO_3H$)

compd R	recryst solvent	mp, °C	% yield	empirical formula[a]
	EtOH–ether (1:1)	143–146	54.2	$C_9H_{12}N_4O_4S{\cdot}CH_3C_6H_4SO_3H$
	EtOH	205–207	65.8	$C_8H_9N_5O_3{\cdot}CH_3C_6H_4SO_3H$
	EtOH–ether (2:1)	206–208	82.9	$C_9H_9N_5O{\cdot}CH_3C_6H_4SO_3H$
	EtOH–ether (2:1)	214	73.2	$C_8H_8N_4O_2Br_2{\cdot}CH_3C_6H_4SO_3H$
	EtOH	202–207	69.4	$C_8H_8N_5O_3Cl{\cdot}CH_3C_6H_4SO_3H$
	EtOH–ether (4:1)	165–167	74.7	$C_{15}H_{16}N_4O_2{\cdot}CH_3C_6H_4SO_3H$
	IPA–petroleum ether (2:1)	131–136	43.0	$C_{10}H_{14}N_4O_3{\cdot}CH_3C_6H_4SO_3H$
	EtOH–$CHCl_3$–ether (1:4:2)	104–106	38.3	$C_9H_{14}N_4O{\cdot}CH_3C_6H_4SO_3H$
	EtOH–ether (2:1)	159–161	42.7	$C_7H_{11}N_5O{\cdot}CH_3C_6H_4SO_3H{\cdot}1/2H_2O$[b]
	EtOH–benzene (2:1)	126–128	60.4	$C_7H_9N_5O{\cdot}CH_3C_6H_4SO_3H{\cdot}1/2H_2O$
	EtOH	149–153	92.3	$C_{11}H_{11}N_5O{\cdot}CH_3C_6H_4SO_3H$[c]
	EtOH	165–168	64.8	$C_{11}H_{11}N_5O{\cdot}CH_3C_6H_4SO_3H$
	EtOH	195–198	86.5	$C_9H_9N_4OF_3{\cdot}CH_3C_6H_4SO_3H$[d]

[a] All compounds were analyzed for C, H, and N and analyses were within ±0.4% of theoretical values except where indicated. [b] N: calcd, 19.32; found, 18.65. [c] C: calcd, 53.85; found, 54.31. [d] N: calcd, 13.39; found, 12.65.

for all the compounds fall in the range of 10^{-5}–10^{-6} M. The most active compounds, **7** and **9** ($ID_{50} = 2.7 \times 10^{-6}$ and 4.5×10^{-6} M, respectively), are significantly more active than hydroxyguanidine ($ID_{50} = 1.05 \times 10^{-4}$ M).

The above experiment shows that the compounds inhibit cell transformation by Rous sarcoma virus. To further elucidate the mechanism of action, an experiment was designed to determine whether the compounds inhibit viral transformation only or if they inhibit viral replication as well. The compounds were tested at the concentrations at which they were active in inhibiting cell transformation. The results are shown in Table IV. Four out of the five compounds studied inhibited viral replication. In contrast, one compound, **9**, and hydroxyguanidine did not significantly inhibit virus production. This points to the possibility that this series of compounds act by a different mechanism of action from hydroxyguanidine. Further biochemical studies are needed to determine the exact step(s) in the virus life cycle that is(are) affected.

The in vivo toxicity of two of the compounds was studied (**3** and **9**). The LD_{50}s are 156.49 and 322.19 mg/kg, respectively. The compounds showed similar toxic effects. The animals became less active, showed signs of breathing difficulty, rapid and heavy breathing, salivation, abnormal gait at high doses, and intermittent tremors. Death occurred within 2 h and was due to asphyxia and convulsions. All the mice in the control group survived.

The in vivo anticancer activities of five of the compounds were studied. Four out of the five compounds studies were inactive at 100 mg/kg and toxic at 200 mg/kg. One compound (**4**) shows promising activity, with a % T/C median survival time of 140% at 100 mg/kg against P 388 leukemia in mice. This compound is undergoing further studies at NCI.

Experimental Section

Chemistry. Melting points were determined in open capillary tubes with a Thomas-Hoover melting point apparatus and are

Table II. Inhibition of L1210 Leukemia Cell Growth by *N*-Hydroxy-*N'*-aminoguanidine Derivatives

compd	ID_{50}, × 10^{-5} M	pI_{50}	±SE[a]
1-[[3-(methylsulfonyl)benzylidene]amino]-3-hydroxyguanidine tosylate (1)	1.48	4.83	0.55
1-[(3-nitrobenzylidene)amino]-3-hydroxyguanidine tosylate (2)	0.76	5.12	0.77
1-[(4-cyanobenzylidene)amino]-3-hydroxyguanidine tosylate (3)	0.94	5.03	0.85
1-[(3,5-dibromo-2-hydroxybenzylidene)amino]-3-hydroxyguanidine tosylate (4)	1.65	4.78	1.22
1-[[(4-chloro-3-nitrobenzylidene)amino]-3-hydroxyyguanidine tosylate (5)	1.27	4.90	0.26
1-[[4-(benzloxybenzylidene]amino]-3-hydroxyguanidine tosylate (6)	2.53	4.60	0.97
1-[(2,5-dimethoxybenzylidene)amino]-3-hydroxyguanidine tosylate (7)	0.71	5.15	0.73
1-[(5-norbonen-2-ylmethylene)amino]-3-hydroxyguanidine tosylate (8)	1.06	4.97	0.40
1-[(*N*-methyl-2-pyrrolidinylmethylene)amino]-3-hydroxyguanidine tosylate (9)	0.27	5.57	0.77
1-[(3-pyridylmethylene)amino]-3-hydroxyguanidine tosylate (10)	2.31	4.64	0.96
1-[(2-quinolylmethylene)amino]-3-hydroxyguanidine tosylate (11)	0.68	5.17	0.38
1-[(1-isoquinolymethylene)amino]-3-hydroxyguanidine tosylate (12)	0.33	5.48	0.34
1-[[4-(trifluoromethyl)benzylidene]amino]-3-hydroxyguanidine tosylate (13)	0.92	5.04	0.16
hydroxyguanidine sulfate	1.67	4.78	0.42
hydroxyurea	2.16	4.67	1.06

[a] Standard error = $1/b(S_{nw})^{1/2}$, where b = the slope of the best fit regression line, n = number of readings obtained from each drug concentration, w = weight coefficient (see ref 19), and S_{nw} = summation of $n \times w$.

Table III. Inhibition of Cell Transformation by Rous Sarcoma Virus by *N*-Hydroxy-*N'*-aminoguanidine Derivatives (Names Given in Table II)

compd	ID_{50}, × 10^{-5} M	pI_{50}	±SE[a]
1	3.52	4.45	0.40
2	3.57	4.45	0.42
3	9.72	4.01	0.92
4	0.65	5.19	0.92
5	0.96	5.02	0.54
6	0.81	5.09	0.62
7	0.27	5.57	1.02
8	6.94	4.16	0.43
9	0.45	5.35	1.24
10	8.10	4.09	0.83
11	4.38	4.36	0.35
12	1.58	4.80	0.46
13	1.18	4.93	0.32
hydroxyguanidine sulfate	10.5	3.98	0.24

[a] See the footnotes of Table II.

Table IV. Inhibition of Viral Replication by *N*-Hydroxy-*N'*-aminoguanidine Derivatives

compd	concn, M	virus yield,[a] ffu/mL	% inhibn
control		1.6×10^5	0
3	1×10^{-6}	3.1×10^4	80
4	7×10^{-6}	9.3×10^3	94
9	5×10^{-6}	9.0×10^4	44
11	2×10^{-5}	2.5×10^4	84
12	3×10^{-6}	3.4×10^4	79
hydroxyguanidine sulfate	1×10^{-4}	1.6×10^5	0

[a] ffu = focus-forming units.

corrected. Elemental analyses were performed by the Department of Chemistry, Chun Shan Institute of Science and Technology, Taiwan, or by C. F. Geiger, Ontario, California; results were within 0.4% of theoretical values except where noted. All compounds were dried in a drying pistol with P_2O_5 before analysis. The drying temperature used was 110 ° except for low-melting compounds (7, 8, 10), which were dried at 78 °C.

Infrared spectra were obtained from a Beckman IR-4210 spectrophotometer using KBr pellets. Proton NMR spectra were performed on a Varian XL 200-MHz spectrometer in collaboration with Dr. Prakash and Dr. Krishnamurthy at the Hydrocarbon Research Institute, University of Southern California. The samples were prepared in Me_2SO-d_6.

Thin-layer chromatography was performed on precoated silica gel 60 F254 chromatographic sheets (20 × 20 cm; 0.2 mm) (Merck) with two different solvent systems: *tert*-butyl alcohol–acetic acid–water (3:1:1) and butanol–acetic acid–water (65:13:22).

Ultraviolet absorption spectra were obtained from a Varian/Cary Model 219 UV spectrophotometer.

Syntheses of *N*-Hydroxy-*N'*-aminoguanidine Derivatives. Thirteen new compounds were synthesized according to the procedure reported previously.[16] Thiosemicarbazide (0.5 mol) and methyl *p*-toluenesulfonate (0.5 mol) in methanol (500 mL) was refluxed for 18 h to form *S*-methylisothiosemicarbazide tosylate. *S*-methylisothiosemicarbazide tosylate (0.4 mol) was reacted with hydroxylamine (0.5 mol) at room temperature for 48 h to give *N*-hydroxy-*N'*-aminoguanidine tosylate. The final substituted *N*-hydroxy-*N'*-aminoguanidine tosylate derivatives were prepared via Schiff base formation by reacting *N*-hydroxy-*N'*-aminoguanidine tosylate with the appropriate aldehydes. The aldehydes used to prepare the final substituted derivatives were obtained commercially except for quinaldehyde and isoquinaldehyde, which were prepared in our laboratories. The structures of the target compounds are given in Table I.

Preparation of Quinaldehyde. Quinaldehyde was prepared by the method of Barrows and Lindwall.[18] Quinaldine (0.175 mol) in 42.5 mL of dioxane was added dropwise to selenium dioxide (0.2 mol) in 225 mL of dioxane to give a cloudy mixture. The mixture was warmed gently for 0.5 h to give a clear brown solution. This was heated with agitation in a steam bath for 3 h. The selenium formed was filtered off and the filtrate concentrated in vacuo to give a reddish brown gum. The aldehyde was purified by steam distillation and cooled to give white needles: mp 50–57 °C; yield 23.3%.

Preparation of Isoquinaldehyde. Isoquinaldehyde was prepared by the same method as for quinaldehyde except that 1-methylisoquinoline was used in place in quinaldine: mp 45–50 °C; yield 26.7%.

Biological Procedure. In Vitro Inhibition of L1210 Leukemia Cell Growth. The compounds were dissolved in growth medium (Roswell Park Memorial Institute RPMI1640) containing up to 1% Me_2SO and filtered through 0.22 μm × 13 mm cellulose acetate/nitrate filters (Millipore GSWP). The concentration of drug before and after filtration was checked by UV absorption. There was no loss of drug due to filtration. Cells were grown in RPMI1640 media supplemented with 10% fetal calf serum and seeded in test tubes at (3–4) × 10^4 cells/mL. The drugs were added to the cells to give final concentrations between 10^{-3} and 10^{-6} M. Each concentration was run in duplicate. Untreated and Me_2SO-treated sets of controls were used. The initial cell numbers were counted, and the cells were placed in a humidified incubator at 37 °C and supplied with 95% air/5% CO_2. The cell numbers were counted after 24 and 48 h by a Coulter Counter (Models TAII, ZBI).

The percent inhibition of cell growth was calculated as follows:

$$\% \text{ inhibition} = (1-(T - N_0)/(C - N_0)) \times 100\%$$

where T = number of cells/mL in treated samples at 48 h, C = number of cells/ml in control samples at 48 h, and N_0 = number of cells/ml at zero time.

The dose required for 50% inhibition of cell growth (ID_{50}) for each compound was calculated at 48 h by using probit analysis.[19,20]

Inhibition of Cell Transformation by Rous Sarcoma Virus—Focus Assay. The preparation of the growth medium and the agar media used in the assays was described previously.[16]

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The compounds were dissolved in Hams (F-10, 1X) medium containing up to 1% Me_2SO to give concentrations between 10^{-2} and 10^{-6} M. Chick embryo fibroblasts were grown as monolayer cells at 5×10^5 cells/60 mm petri dish. The medium was removed by suction. Virus was diluted to give approximately 200 focus-forming units/0.1 mL. To the cells were added 2.6 mL of fresh medium, 0.3 mL of drug, and 0.1 mL of virus so that final drug concentrations were between 10^{-3} and 10^{-6} M. Three controls were used: cell control (no virus, no drug); virus control (no drug); cytotoxicity control (no virus). The cells were incubated at 37 °C for 8–16 h, and the mediun was removed by suction. The cells were overlaid with 4.5 mL of agar medium and 0.5 mL of drug solution and incubated for 4 days. A second agar overlay (5 mL) was performed. The foci were counted between days 7 and 10.

The % inhibition of transformation was calculated as follows:

$$\% \text{ inhibition} = (1-(T/C)) \times 100\%$$

where T = number of foci in treated samples and C = number of foci in control samples.

The results were calculated by using probit analysis.[19,20]

Inhibition of RSV Replication. The medium used in this experiment is the same as for the focus assay.

Compounds were prepared in Hams 1 × F10 medium so that the final concentrations were their approximate ID_{50}s in the viral transformation assay. Chick embryo cells were grown at 5×10^5 cells/60-mm petri dish. The old medium was removed by suction and replaced with 4.5 mL of new medium, 0.5 mL of drug solution, and virus. The control consisted of medium and virus only. On days 3 and 6, the medium was removed by suction and replaced with another 4.5 mL of new medium and 0.5 mL of drug solution. Two days later, the medium was harvested. The virus titers in each harvest were then tested by standard focus assays as described above, without the presence of any drug.

The virus titers in the treated samples were compared to that in the control. A decrease in number points to an inhibition of viral replication. The results are summarized in Table IV.

In Vivo Acute Toxicity (LD_{50}) Studies. The toxicities of two of the compounds (3, 9) were studied in Swiss-Webster male mice. The compounds were suspended with 2.5% acacia in normal saline. Six mice were used for each dose. The mice were weighed and the appropriate doses injected intraperitoneally. Control mice were injected ip with a 2.5% acacia suspension in normal saline. The LD_{50} of each compound was calculated by using probit analysis.[19,20]

In Vivo Anticancer Activity against P388 Leukemia. The activities of the compounds against P388 leukemia in vivo in mice were studied by the National Cancer Institute, Bethesda, Md. The drugs were given by the intraperitoneal injection. The activity was expressed as the percentage increase in median survival time of treated cancer-bearing mice over control cancer-bearing mice.

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Supplementary Material Available: Appendix 1, thin-layer chromatography R_f values, and Appendix 2, proton NMR chemical shifts in Me_2SO-d_6 (Varian 200 MHz) (6 pages). Ordering information is given on any current masthead page.

Substituted 2-Pyrones, 2-Pyridones, and Other Congeners of Elasnin as Potential Agents for the Treatment of Chronic Obstructive Lung Diseases†

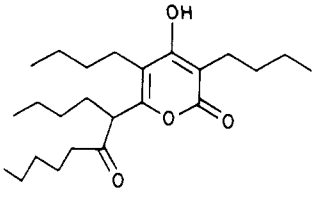
William C. Groutas,* Michael A. Stanga, Michael J. Brubaker, Tien L. Huang, Min K. Moi, and Robert T. Carroll

Department of Chemistry, Wichita State University, Wichita, Kansas 67208. *Received August 17, 1984*

Several congeners of elasnin (I) have been synthesized and shown to inhibit human leukocyte elastase (HLE). The C-3 alkyl substituted 2-pyrones **11** and **12** were found to be the most effective inhibitors of the enzyme. These compounds are highly specific in their inhibitory activity.

More than 48 000 people die each year in the U.S. from chronic obstructive lung disease (emphysema and bronchitis).[1] Furthermore, the disabling nature of these diseases results in a formidable economic cost in terms of lost wages and other medical expenses. The destruction of lung tissue by leukocyte elastase has been postulated to occur whenever a proteinase–proteinase inhibitor imbalance exists.[2] This imbalance can, in principle, be overcome either by replenishing the amount of α-1-proteinase inhibitor (α-1-PI) or by inhibiting selectively human leukocyte elastase (HLE).

We have recently reported preliminary findings related to the use of substituted α-pyrones as selective inhibitors of HLE.[3] These compounds resemble elasnin (I), a 2-pyrone elaborated by *Streptomyces noboritoensis*.[4-7] Elasnin has been reported to exhibit selective inhibitory activity toward HLE and to be devoid of toxic side effects.[4] In pursuing our objectives in this general area,[8,9] we have synthesized several congeners of elasnin and have examined their inhibitory activity toward HLE.



I

Chemistry. The substituted 2-pyrones and 2-pyridones were prepared according to Scheme I. Alkylation of the

† A portion of this work was presented at the 19th National Symposium in Medicinal Chemistry, University of Arizona, Tucson, AZ, June 17–21, 1984.

(1) U.S. Department of Health and Human Services, Public Health Service (1980), National Institutes of Health, Publication No. 81-2105.
(2) "Biochemistry, Pathology and Genetics of Pulmonary Emphysema"; Bignon, J., Scarpa, G. L., Eds.; Pergamon Press: New York, 1981.
(3) Groutas, W. C.; Abrams, W. R.; Carroll, R. T.; Moi, M. K.; Miller, K. E.; Margolis, M. T. *Experientia* **1984**, *40*, 361–362.
(4) Omura, S.; Ohno, H.; Saheki, T.; Yoshida, M.; Nakagawa, A. *Biochem. Biophys. Res. Commun.* **1978**, *83*, 704–709.
(5) Omura, S.; Nakagawa, A.; Ohno, H. *J. Am. Chem. Soc.* **1979**, *101*, 4386–4388.
(6) Nakagawa, A.; Ohno, H.; Miyano, K.; Omura, S. *J. Org. Chem.* **1980**, *45*, 3268–3274.

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