5-[(Aminoalkyl)amino]imidazo[4,5,1-*de*]acridin-6-ones as a Novel Class of Antineoplastic Agents. Synthesis and Biological Activity

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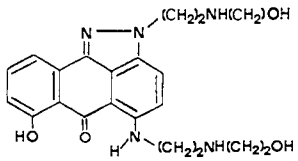
A new class of antineoplastic agents, the 5-substituted imidazo[4,5,1-*de*]acridin-6-ones with an (aminoalkyl)amino group in the side chain, has been made. These compounds were synthesized by reduction of 1-substituted 4-nitroacridin-9(10*H*)-ones and subsequent reaction of the derived amines with carboxylic acids. Their cytotoxic activity against $HeLaS_3$ cells in tissue culture and in vivo antitumor activity against P388 leukemia in mice was demonstrated. A strict relationship between the antineoplastic activity and the number of methylene spacers between proximal and distal nitrogens in the side chain was established.

Several classes of compounds including the anthracenediones, viz. ametantrone[1] and mitoxantrone,[2] anthrapyrazoles (e.g. 1),[3] 9*H*-thioxanthen-9-ones,[4] acridine-4-carboxamides,[5] phenazine-1-carboxamides,[6] substituted 1-amino-4-nitroacridinones[7] (e.g. 2), pyrazolo[3,4,5-*kl*]-



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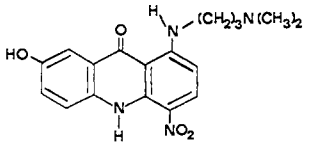

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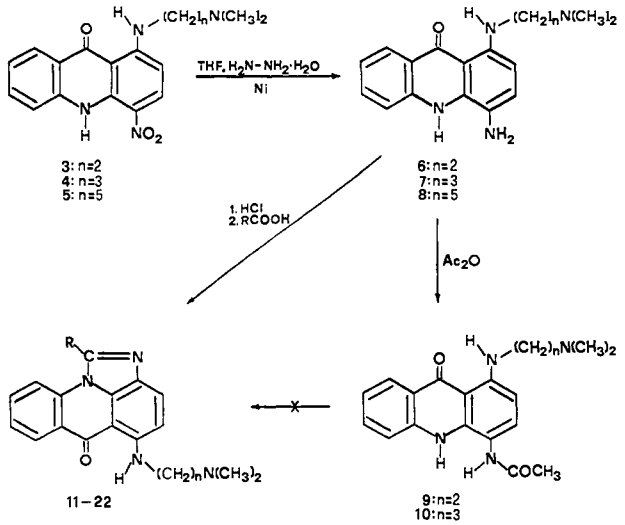
acridines,[8] benzothiopyrano[4,3,2-*cd*]indazoles,[9] and 1,8-naphthalimides[10] can be distinguished among the currently recognized synthetic antineoplastic compounds designated as "DNA complexing agents". These compounds are characterized by two common features which seem to determine their antineoplastic activity: a planar, polycyclic nucleus, capable of binding to DNA by intercalation, and the occurrence of one or two side chains containing polymethylenediamine fragments in a strictly defined orientation to the chromophore.

The structure–activity relationship studies for the side chains, particularly for the anthracenediones, point out the importance of the distance between both the amino groups and the type of substituents at the distal nitrogen for antineoplastic activity.[1,2a,6,11-13] It has been also suggested that the distal amino group binds electrostatically to the phosphate moieties of DNA[1,14] or that the side chain has the function of additionally stabilizing a drug–DNA complex.[15] The ethylenediamine moiety could also be important in cross-linking of DNA, according to the postulated mechanisms of action of anthracenediones.[16]

It is generally accepted that the mechanistic role of the chromophore of many antineoplastic DNA binders consists in DNA intercalation. A desirable property of the chromophore should be its ability to act as a charge-transfer acceptor.[5a] One of the most interesting chromophoric modifications of the basic tricyclic system has been the addition of another ring, leading to compounds with high antineoplastic activity. Anthrapyrazoles (1),[3] pyrazoloacridines,[8] and benzothiopyranoindazoles[9] constitute significant examples of such compounds. The hypothesized role of the added pyrazole ring is to increase the electron density of the π system and to make the chromophore more resistant to enzymatic reduction to radical species.[3c] These findings, as they relate to antitumor activity and cardiotoxicity, suggested to us that further similar modifications could be made.

Scheme I



Taking into account these considerations, we synthesized and tested for antitumor activity a new class of compounds,

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Table I. Physical Properties and Cytotoxic and Antineoplastic Activities of 4-Substituted 1-[[(Dimethylamino)alkyl]-amino]acridin-9(10*H*)-ones and 1-Substituted 5-[[(Dimethylamino)alkyl]amino]imidazo[4,5,1-*de*]acridin-6-ones Hydrochlorides

compd[a]	n	R	% yield[b]	mp, °C	formula[c]	in vitro[d] HeLa S_3 IC_{50}, μg/mL	in vivo P388 leukemia[e] opt dose	in vivo P388 leukemia[e] % T/C[f]
amentantrone						0.17 ± 0.09	12.5	300 (3 cures)
3[g]	2	NO_2	94	250–252[h,i]	$C_{17}H_{18}N_4O_3 \cdot HCl \cdot 0.6H_2O$	0.15 ± 0.01	25	160, 166
4[g]	3	NO_2	86	250–255[h,j]	$C_{18}H_{20}N_4O_3 \cdot HCl \cdot 0.2H_2O$	0.04 ± 0.02	75	190
5	5	NO_2	77	248–250[h,k]	$C_{20}H_{24}N_4O_3 \cdot HCl \cdot 0.1H_2O$	0.13 ± 0.04	60	144
6	2	NH_2	92	226–230[h,l]	$C_{17}H_{20}N_4O \cdot 2HCl \cdot H_2O$	2.93 ± 0.15	100	toxic[m]
7	3	NH_2	85	221–224[h]	$C_{18}H_{22}N_4O \cdot 2HCl \cdot 0.9H_2O$	0.25 ± 0.07	25	toxic[m]
8	5	NH_2	81	207–211[h]	$C_{20}H_{26}N_4O \cdot 2HCl \cdot H_2O$	1.05 ± 0.15	not tested	
9	2	$NHCOCH_3$	86	166–170[n]	$C_{19}H_{22}N_4O_2 \cdot 2HCl \cdot 0.1H_2O$	>5	75	137
10	3	$NHCOCH_3$	88	179–182[o]	$C_{20}H_{24}N_4O_2 \cdot 2HCl \cdot 0.4H_2O$	>5	not tested	
11	2	H	83	267–269[h,p]	$C_{18}H_{18}N_4O \cdot 2HCl \cdot 1.5H_2O$	0.06 ± 0.05	150	180, 188
12	2	CH_3	54	259–262[q]	$C_{19}H_{20}N_4O \cdot 2HCl \cdot H_2O$	0.05 ± 0.02	50	190, 230
13	2	CH_2CH_3	57	223–226[r]	$C_{20}H_{22}N_4O \cdot 2HCl \cdot 2H_2O$	0.11 ± 0.01	100	200
14	2	$(CH_2)_2CH_3$	58	228–231[s]	$C_{21}H_{24}N_4O \cdot 2HCl \cdot 0.7H_2O$	0.20 ± 0.08	175	211, 233
15	2	$(CH_2)_7CH_3$	64	201–206[t]	$C_{26}H_{34}N_4O \cdot 2HCl \cdot 0.5H_2O$	0.20 ± 0.09	75	toxic[m]
16	2	$CH(CH_3)_2$	51	240–243[u]	$C_{21}H_{24}N_4O \cdot 2HCl \cdot 0.5H_2O$	0.37 ± 0.01	150	166
17	2	C_6H_5	48	226–228[v]	$C_{24}H_{22}N_4O \cdot 2HCl \cdot 0.5H_2O$	0.43 ± 0.02	50	150
18	3	H	76	260–264[h,w]	$C_{19}H_{20}N_4O \cdot 2HCl \cdot 1.5H_2O$	0.15 ± 0.08	100	133, 120
19	3	CH_3	51	230–236[h,x]	$C_{20}H_{22}N_4O \cdot 2HCl \cdot H_2O$	0.11 ± 0.03	150	122
20	3	CH_2CH_3	60	228–233[h,y]	$C_{21}H_{24}N_4O \cdot 2HCl \cdot H_2O$	0.25 ± 0.05	90	130
21	3	C_6H_5	52	216–221[h,z]	$C_{25}H_{24}N_4O \cdot 2HCl \cdot 0.5H_2O$	0.28 ± 0.08	30	110
22	5	H	71	225–228[aa]	$C_{21}H_{24}N_4O \cdot 2HCl \cdot 0.5H_2O$	0.50 ± 0.20	100	110

[a] The compounds listed are hydrochlorides of the compounds listed in Scheme I. [b] Yields reported refer to the free base and were not optimized. [c] All compounds were analyzed for C, H, W. Values were within ±0.4% of the theoretical values. [d] Cytotoxic assay is based on a 72-h exposure time. For a detailed description of the assay, see: Pawlak, K.; Matuszkiewicz, A.; Pawlak, J. W.; Konopa, J. *J. Chem. Biol. Inter.* **1983**, *43*, 131. A criterion for significant cytotoxic activity is 50% inhibition at a concentration <1 μg/mL. Results represent the mean value from three independent experiments. [e] Group of eight BDF_1 mice were given 10^6 P388 cells ip on day 0. Twenty-four hours after tumor implantation, solutions of tested compounds in saline were given ip daily for five consecutive days. Control groups of 18 mice for each compound received saline. A compound is designated "toxic" if at a given dose T/C ≤85%. Values T/C ≥125% indicate statistically significant antitumor activity. For the general screening procedure, see: Geran, R. I.; Greenberg, N. H.; MacDonald, M. M.; Schumacher, A. M.; Abbot, B. J. *Cancer Chemother. Rep., Part 3* **1972**, *3*, 1. [f] When two values are given, the second one represents the result obtained during repeated independent multidose assay. [g] For compounds **3** and **4**, which were used as methane-sulphonate salts, the values of T/C = 185 at 50 mg/kg and T/C = 189 at 100 mg/kg were obtained, respectively. [h] With decomposition. [i] Free base mp 211–212 °C. [j] Free base mp 148–149 °C. [k] Free base mp 160–161 °C. [l] Free base mp 192–194 °C. [m] No activity was observed at doses lower than toxic ones. [n] Free base mp 248–250 °C. [o] Free base mp 208–210 °C. [p] Free base 219–220 °C. [q] Free base mp 199–201 °C. [r] Free base mp 166–167 °C. [s] Free base mp 173–174 °C. [t] Free base mp 163–164 °C. [u] Free base mp 187–188 °C. [v] Free base mp 199–201 °C. [w] Free base mp 148–149 °C. [x] Free base 139–140 °C. [y] Free base mp 109–110 °C. [z] Free base mp 148–149 °C. [aa] Free base mp 137–138 °C.

the 5-[(aminoalkyl)amino]imidazo[4,5,1-*de*]acridin-6-ones, in which we maintained the (aminoalkyl)amino side chain functionality that is apparently crucial for biological activity. This new class results from annulation of an imidazole ring onto an aminoacridone chromophore while retaining the C-6 oxo functionality (see Scheme I).

Chemistry

The synthetic pathway to imidazoacridinones **11–22** is shown in Scheme I. Compounds **3–5** were obtained by condensation of 1-chloro-4-nitroacridin-9(10*H*)-one with a suitable amine in DMF under conditions quite different from those reported in the literature.[7]

Reduction of these compounds with hydrazine monohydrate in the presence of Raney Ni in THF gave 4-amino derivatives **6–8** in excellent yields. Due to their instability (sensitivity to oxidation), these derivatives were isolated as hydrochlorides. Only compound **6** was obtained pure as a free base. Compounds **6** and **7** were directly converted, without isolation, into the stable 4-acetamido derivatives **9** and **10** with acetic anhydride.

The synthesis of the imidazo[4,5,1-*de*]acridin-6-ones by reaction of 4-aminoacridin-9(10*H*)-ones with boiling acetic anhydride was unsuccessful by the reported literature procedure.[17] However, heating of the hydrochlorides of **6–8** with a suitable carboxylic acid gave the desired imidazoacridin-6-ones **11–22**, the 4-acylamino derivatives (e.g., **9** and **10**) always being side products of the reaction. In the cyclization reaction, the highest yields were obtained with formic acid. The reactions with nonanoic and benzoic acids were carried out in boiling bromobenzene. The remaining reactions were performed with an excess of acids at their boiling points. The structures of these compounds were established on the basis of NMR studies, using spin-decoupling methods for proton assignments, microanalyses, and mass spectra.

All the derived imidazoacridinones show intense green-bluish fluorescence under long-wave UV light. For biological evaluation, all the obtained compounds were converted into water-soluble hydrochlorides by dissolution in

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chloroform–MeOH or dioxane–MeOH followed by treatment with gaseous HCl. Their physicochemical properties are reported in Table I.

Results and Discussion

The results of cytotoxic and antineoplastic activities of all the synthesized imidazoacridinones and of some of the acridone intermediates are reported in Table I. Biological data for the latter compounds were acquired to determine the effect of chromophore modifications of the acridone derivatives on biological activity. Ametantrone was used in our test as positive control. All the imidazoacridinones (**11–22**) showed significant cytotoxic activity, comparable to that of ametantrone, against the $HeLaS_3$ cells in tissue culture. Similar cytotoxic activity was shown by the 1-substituted 4-nitroacridinones **3–5**, while the respective 4-amino and 4-acetamidoacridinone derivatives **6–10** were not cytotoxic.

4-Nitroacridinones **3** and **4** demonstrated similar in vivo activity to that reported for them by Capps.[7] 4-Aminoacridinones **6** and **7** were totally inactive.

The following conclusions can be made about the structure–activity relationships.

1. A key role in the antineoplastic activity of the imidazoacridinones is played by the distance between the amino moieties in the side chain at the 5-position. The highest antineoplastic activity is shown by the compounds containing two carbon spacers between proximal and distal nitrogens in the side chain. An increase in the number of methylene units between nitrogen atoms resulted in a significant decrease or loss of antineoplastic activity. Such a dependence is similar to that found in the anthracenediones[11-13] and 1,8-naphthalimides.[10b]

2. The type of substituent in the 1-position of imidazoacridinones exerts weaker, although significant, influence on antineoplastic activity. The observed total loss of activity for compound **15** can be ascribed to the pronounced change of lipophilic character of the molecule and to this effect on transport and distribution.

3. The synthesized imidazoacridinones and 4-nitroacridinones show similar antineoplastic activity. Also, ^1H NMR studies point out a similar modifying influence of the imidazole ring and of the nitro group on chemical shifts of the protons on ring C. For example, the two corresponding protons on ring C of the nitroacridinone **3** and of imidazoacridinone **11** have similar chemical shifts: δ 6.59 and 8.38 versus δ 6.83 and 8.00, respectively. This suggests that both the nitro group and the imidazole ring could modify in a similar way the electron density on the acridine chromophore, particularly the ring C and, consequently, the physicochemical properties related to the antineoplastic activity.

Conclusions

The results reported here demonstrate that the substituted 5-[[2-(dimethylamino)ethyl]amino]imidazo[4,5,1-*de*]acridin-6-ones constitute a novel class of antineoplastic compounds. They confirm the hypothesis that modification of the acridine chromophore, while maintaining the C-6 oxo group and the polymethylenediamine side chain in the peri position, can result in biologically active compounds.

Because of the enhancement of antineoplastic activity by the addition of certain A-ring substituents, primarily hydroxyls, as has been observed in other classes of DNA-binding agents,[1,3d,7] we are currently studying the effects of such substitutions on biological activity in the further development of this new class of antineoplastic agents. Furthermore, a modification of the substituents in the 1-position to increase their hydrophilicity is warranted.

Experimental Section

Melting points were determined with a Boetius PHMK 05 apparatus and are uncorrected. NMR spectra were obtained with a Varian VXR-300 spectrometer using tetramethylsilane (TMS) as internal standard and are reported as ∂ (ppm). NMR abbreviations used are as follows: s (singlet), d (doublet), t (triplet), qu (quartet), qt (quintuplet), m (multiplet), and ex (exchangeable with deuterium oxide). Coupling constants are given in hertz. Quartets which by addition of deuterium oxide are transformed into triplets are labeled with an asterisk. Microanalytical results, indicated by atomic symbols, are within ±0.4% of the theoretical values and were obtained from Department of Elemental Microanalysis, Institute of Organic Chemistry, Polish Academy of Sciences, Warsaw and from Microanalytical Laboratory of the University of Camerino. Reaction products were purified by crystallization or, in necessary cases, by column chromatography on silica gel. The course of the reactions and the purity of products were controlled by TLC on silica gel, using the $CHCl_3$–MeOH (4/1) system.

General Procedure for the Preparation of 1-[[2-(Dimethylamino)alkyl]amino]-4-nitroacridin-9(10*H*)-ones (3–5). A mixture of 6.87 g (0.025 mol) of 1-chloro-4-nitroacridin-9-(10*H*)-one[18] and 80 mL of DMF was heated until the solid was totally dissolved. Then, 0.065 mol of the suitable amine was added to the hot solution, which was subsequently stirred and left at room temperature for 4 h. Addition of 100 mL of EtOH and thorough mixing gave a yellow precipitate, which was filtered, washed with EtOH, water, and again with EtOH. **3**: ^1H NMR (DMSO) 12.42 (1 H, ex, s, N10-H), 11.80 (1 H, ex, t, -N*H*CH_2-), 8.38 (1 H, d, J = 9.8, C3-H), 8.22 (1 H, d, C8-H), 7.92 (1 H, d, C5-H), 7.77 (1 H, t, C6-H), 7.40 (1 H, t, C7-H), 6.59 (1 H, d, J = 9.9, C2-H), 3.52 (2 H, qu*, -NHC$H_2$$CH_2$-), 2.60 (2 H, t, CH_2C$H_2$$NMe_2$), 2.26 (6 H, N($CH_3$)$_2$).

General Procedure for the Synthesis of 4-Amino-1-[[3-(dimethylamino)alkyl]amino]acridin-9(10*H*)-ones Dihydrochloride (6–8). To a mixture of nitro derivatives **3–5** (0.01 mol), 100 mL of THF, and about 1.5 g of Raney Ni was added with stirring at room temperature 1.8 mL of hydrazine monohydrate, and stirring was continued for about 30 min. The catalyst was filtered off over Celite and washed with 50 mL of THF. The resulting filtrate was treated with 5 mL of concentrated HCl and stirred for 10 min. The yellow precipitate obtained was collected and washed with THF. The products were recrystallized from a solution of MeOH (90%)–dioxane made acidic (pH ~2). **7**: ^1H NMR (DMSO) 11.64 (1 H, ex, s, NH), 10.22 (5 H, ex, br s, NH), 8.18 (1 H, d, C8-H), 7.81–7.71 (2 H, m, C5-H and C6-H), 7.53 (1 H, d, J = 8.8, C3-H), 7.29 (1 H, t, C7-H), 6.37 (1 H, d, J = 8.7, C2-H), 3.62 (2 H, t, -NHC$H_2$$CH_2$-), 3.16 (2 H, t, CH_2C$H_2$$NMe_2$), 2.78 (6 H, s, N($CH_3$)$_2$), 2.08 (2 H, qt, -$CH_2CH_2$$CH_2$-). Free base **6** was obtained by concentration of the filtered reaction mixture to about 40 mL. The resulting precipitate, redissolved by heating in the liquor mother, crystallized on cooling and by addition of hexane to give red needles.

4-Acetamido-1-[[2-(dimethylamino)alkyl]amino]acridin-9(10*H*)-ones (9 and 10). The reaction was performed as for **6**. After filtration of the catalyst, the filtrate was treated, with stirring at room temperature, with 3 mL (0.03 mol) of acetic anhydride and the resulting mixture was stirred for 30 min. After addition of 50 mL of 10% aqueous NaOH, the solution was concentrated under vacuo. The resultant yellow precipitate was collected, washed with water, and crystallized from EtOH–water. **9**: ^1H NMR (DMSO) 10.20 (1 H, ex, s, N10-H), 10.03 (1 H, ex, t, -N*H*CH_2-), 9.17 (1 H, ex, s, N*H*$COCH_3$), 8.14 (1 H, d, C8-H), 7.71 (1 H, d, C5-H), 7.64 (1 H, t, C6-H), 7.22 (1 H, d, J = 8.6, C3-H), 7.18 (1 H, t, C7-H), 6.18 (1 H, d, J = 8.7, C2-H), 3.23 (2 H, qu*, -NHC$H_2$$CH_2$-), 2.54 (2H, t, CH_2C$H_2$$NMe_2$), 2.21 (6 H, s, N($CH_3$)$_2$), 2.09 (3 H, s, NHCOC$H_3$).

General Procedure for the Synthesis of 5-[[(Dimethylamino)alkyl]amino]imidazo[4,5,1-*de*]acridin-6-ones (Table I). (a) Example: 5-[[2-(Dimethylamino)ethyl]amino]-imidazo[4,5,1-*de*]acridin-6-one (11). A mixture of 1.85 g (0.003

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mol) of **6** and 10 mL of HCOOH was heated at reflux for 14 h. Then, 200 mL of water was added and the solution was made basic (pH 9) by addition of sodium carbonate. The resulting solution was extracted with benzene (2 × 150 mL); the organic extracts were dried (Na_2SO_4) and evaporated to give a residue, which crystallized as yellow needles from acetone–hexane. **11**: ^{1}H NMR (DMSO) 9.22 (1 H, s, C1-H), 8.97 (1 H, ex, t, N*H*CH_2), 8.40 (2 H, t, C10-H and C7-H), 8.00 (1 H, d, J = 8.6, C3-H), 7.92 (1 H, t, C9-H), 7.59 (1 H, t, C8-H), 6.83 (1 H, d, J = 9.0, C4-H), 3.46 (2 H, qu*, -NHC*H*$_2$CH_2-), 2.62 (2 H, t, $CH_2CH_2NMe_2$), 2.28 (6 H, s, N(CH_3)$_2$).

Compounds **12**, **13**, and **16–22** were obtained in an analogous manner. Compound **14** required a refluxing time of 28 h.

(b) 5-[[2-(Dimethylamino)ethyl]amino]-1-octylimidazo-[4,5,1-*de*]acridin-6-one (15). A mixture of 1.48 g (0.004 mol) of hydrochloride **6**, 8 mL (0.045 mol) of nonanoic acid, and 10 mL of bromobenzene was heated at reflux for 12 h. After cooling, the solution was diluted with $CHCl_3$ (100 mL) and extracted with 5% aqueous HCl. The aqueous extracts were made basic with NaOH and extracted with benzene. The organic extracts, dried with $CaCl_2$, were evaporated to dryness, and the crude product was crystallized from benzene–heptane. **15**: ^{1}H NMR (CD_3OD) 8.56 (1 H, d, C7-H), 8.20 (1 H, d, C10-H), 7.92 (1 H, t, C9-H), 7.88 (1 H, d, J = 8.8, C3-H), 7.59 (1 H, t, C8-H), 6.84 (1 H, d, J = 8.9, C4-H), 3.66–0.88 (27 H, m, series of overlapping signals relative to the aliphatic moieties).

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Registry No. **3**, 99139-99-8; **3**·HCl, 123381-64-6; **3**·$MeSO_3H$, 99140-00-8; **4**, 99140-23-5; **4**·HCl, 123381-65-7; **4**·$MeSO_3H$, 99140-24-6; **5**, 123381-83-9; **5**·HCl, 123381-66-8; **6**, 123381-84-0; **6**·2HCl, 123381-67-9; **7**, 123381-85-1; **7**·2HCl, 123381-68-0; **8**, 123381-86-2; **8**·2HCl, 123381-69-1; **9**, 123381-87-3; **9**·2HCl, 123381-70-4; **10**, 123381-88-4; **10**·2HCl, 123381-71-5; **11**, 123381-89-5; **11**·2HCl, 123381-72-6; **12**, 123381-90-8; **12**·2HCl, 123381-73-7; **13**, 123381-91-9; **13**·2HCl, 123381-74-8; **14**, 123381-92-0; **14**·2HCl, 123381-75-9; **15**, 123381-93-1; **15**·2HCl, 123381-76-0; **16**, 123381-94-2; **16**·2HCl, 123381-77-1; **17**, 123381-95-3; **17**·2HCl, 123381-78-2; **18**, 123381-96-4; **18**·2HCl, 123411-29-0; **19**, 123381-97-5; **19**·2HCl, 123381-79-3; **20**, 123381-98-6; **20**·2HCl, 123381-80-6; **21**, 123381-99-7; **21**·2HCl, 123381-81-7; **22**, 123382-00-3; **22**·2HCl, 123381-82-8; $Me_2N(CH_2)_2NH_2$, 108-00-9; $Me_2N(CH_2)_3NH_2$, 109-55-7; $Me_2N(CH_2)_5NH_2$, 3209-46-9; $EtCO_2H$, 79-09-4; $PrCO_2H$, 107-92-6; Me_2CHCO_2H, 79-31-2; $PhCO_2H$, 65-85-0; 1-chloro-4-nitroacridin-9(10*H*)-one, 20621-51-6; nonanoic acid, 112-05-0.

Synthesis and Biological Activity of New HMG-CoA Reductase Inhibitors. 1. Lactones of Pyridine- and Pyrimidine-Substituted 3,5-Dihydroxy-6-heptenoic (-heptanoic) Acids

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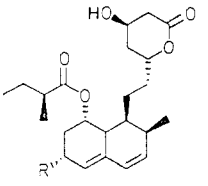
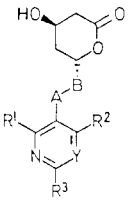
Lactones of pyridine- and pyrimidine-substituted 3,5-dihydroxy-6-heptenoic (-heptanoic) acids **2–4** have been synthesized. Extensive exploration of structure-activity relationships led to several compounds exceeding the inhibitory activity of mevinolin (**1b**) on HMG-CoA reductase, both in vitro and in vivo. First clinical trials with **2i** (HR 780) are in preparation.

Only a few years after the discovery of the LDL receptor by Brown and Goldstein in 1973,[1] the fungal metabolites compactin (**1a**)[2,3] and mevinolin (**1b**)[4,5] have been isolated. Both compounds are potent inhibitors of cholesterol biosynthesis at the level of the major rate-limiting enzyme 3-hydroxy-3-methylglutaryl-CoA reductase (HMG-CoA reductase). Through a feedback mechanism, inhibition of HMG-CoA reductase results in an increase of LDL-receptor synthesis with subsequent removal of LDL from the bloodstream.[6]



1a: R = H

1b: R = CH_3



2: A–B = (E)-CH=CH; Y = CH, N

3: A–B = (Z)-CH=CH; Y = CH, N

4: A–B = CH_2-CH_2; Y = CH, N

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