7-Nitro-3-β-D-ribofuranosyl-3*H*-imidazo[4,5-*b*]pyridine (6). A solution of 4.5 g (10.6 mmol) of **5** in 135 mL of methanol saturated at 0 °C with ammonia was set aside at room temperature for 24 h. The solvent was removed in vacuo and the residue was chromatographed on a silica gel column eluting with EtOAc–MeOH (85:15) to give 2.7 g (86%) of **6** as a chromatographically pure solid: mp 142–146 °C dec; IR ν 1530 cm^{-1} (NO_2); ^1H NMR (Me_2SO-d_6) δ 3.68 (m, 2, CH_2-5′), 4.03 (m, 1, H-4′), 4.25 (m, 1, H-3′), 4.65 (m, 1, H-2′), 6.20 (d, 1, J = 5.4 Hz, H-1′) 8.05 (d, 1, $J_{5,6}$ = 5.4 Hz, H-5), 8.72 (d, 1, $J_{6,5}$ = 5.4 Hz, H-6), 9.12 (s, 1, H-2). Anal. ($C_{11}H_{12}N_4O_6$) C, H, N.

7-Amino-3-β-D-ribofuranosyl-3*H*-imidazo[4,5-*b*]pyridine (1-Deazaadenosine) (1). To a solution of 2.6 g (8.2 mmol) of **6** in 300 mL of MeOH was added 1.3 g of 10% Pd/C, and the mixture was shaken with hydrogen at 50 psi for 0.5 h. The catalyst was removed by filtration and the filtrate was evaporated to give 2.03 g (93%) of **1** as a chromatographically pure solid: mp 262–263 °C dec (lit.[5a] mp 263–264 °C).

Biological Studies. Cell Lines. The two human cell lines HeLa (human cervix carcinoma) and KB (human oral epidermid carcinoma) were routinely maintained in monolayer culture in minimum essential medium (Eagle) with nonessential amino acids and Earles' BSS, supplemented with 10% fetal calf serum and antibiotics (50 units/mL penicillin, 50 μg/mL streptomycin, and 100 μg/mL kanamycin). The three murine leukemia cell lines (P388, P388/DX, and L1210) were established in vitro as suspension cultures and maintained in APMI 1640 medium supplemented with 10% fetal calf serum, 20 μM 2-mercaptoethanol, 2 μM L-glutamine, and antibiotics. The cultures were incubated at 37 °C in a humidified atmosphere of 5% CO_2. The characteristics and the in vitro culture of these cell lines have previously been described.[8-10]

Antitumor Activity in Vivo. Animals and Tumors. Inbred DBA/2 and first generation hybrid (C57B1/6 × DBA/2)F_1 (BDF_1) and (Balb/c × DBA/2)F_1 (CDF_1) adult mice of both sexes were used for the evaluation of antitumor activity. All animals were obtained from Charles River Italia (Calco, Como, Italy). The animals were 2–3 months old, weighed 20–24 g, and were kept under standard laboratory conditions. The subline of P388 leukemia resistant to DX (P388/DX) was obtained by repeated exposure to the drug in Dr. F. M. Schabel's laboratory (Southern Research Institute, Birmingham, AL) and maintained in our facilities in BDF_1 mice given weekly ip passages of 10^7 cells/6 mg/kg ip of doxorubicin. For experimental purposes, 10^6 cells/mouse were transplanted ip in the same strain of animals. Ascitic L1210 leukemia was maintained by serial ip passages in DBA/2 mice, according to Geran et al.[9] For experimental purposes, 10^5 cells/mouse were inoculated ip in CDF_1 mice.

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Anticoagulant Peptides: Nature of the Interaction of the C-Terminal Region of Hirudin with a Noncatalytic Binding Site on Thrombin

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A series of 20 C-terminal fragment analogues of the anticoagulant peptide hirudin were synthesized by solid-phase techniques in order to investigate the nature of the thrombin–hirudin interaction. Inhibition of plasma fibrin clot formation by thrombin in vitro was used as a measure of anticoagulant activity. In the minimum region necessary for detectable anticoagulant activity, $hirudin_{56-64}$, positions Phe^{56}, Glu^{57}, Ile^{59}, Pro^{60}, and Leu^{64} are sensitive to modification. These residues are apparently important for direct interaction with thrombin or for maintaining a favorable conformation for the interaction. On the basis of conformational analysis of this region by computational methods, a "kinked" amphipathic α-helical structure, which orients all of the residues most critical for activity on one face of the helix, is proposed.

Hirudin is a 65 amino acid anticoagulant peptide produced in the salivary glands of the medicinal leech (*Hirudo medicinalis*). It binds tightly to thrombin ($K_d \simeq 10^{-11}$ M) thereby inhibiting the cleavage of fibrinogen and subsequent fibrin clot formation.[1,2] Hirudin was originally isolated and named by Jacoby[3] in 1904 and purified to homogeneity and characterized in 1957 by Markwardt.[4] The amino acid sequence and covalent structure have been completed by Dodt et al. (Figure 1).[5,6] In addition, the nature of the thrombin–hirudin interaction has been partially characterized by semisynthetic modification of thrombin[1] and hirudin.[8] These studies indicate that the amino groups of thrombin and the carboxyl groups of hirudin are important for their interaction. Kinetic studies of the thrombin–hirudin complex at varying ionic strengths by Stone and Hofsteenge[2] suggest that the initial and rate-limiting interaction between hirudin and thrombin is diffusion controlled and possibly ionic in nature. Additionally, they noted that this initial interaction takes place at a site distinct from the catalytic site of the enzyme although hirudin additionally binds to the catalytic site. Chang[9] noted a reverse homology of the C-terminal 20 amino acids of hirudin to fibrinopeptides A and B. This coupled with semisynthetic C-terminal modifications of hirudin suggests that this region of hirudin might be in-

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Table I. Amino Acid Analyses

no.	Asx	Glx	Pro	Gly	Ala	Ile	Leu	Tyr	Phe
2	1.01 (1)	5.01 (5)	0.99 (1)	0.99 (1)		0.96 (1)	1.03 (1)	0.98 (1)	1.01 (1)
3	1.00 (1)	5.01 (5)	1.01 (1)			0.97 (1)	1.02 (1)	1.00 (1)	0.98 (1)
4	1.01 (1)	4.89 (5)	1.05 (1)			0.97 (1)	1.02 (1)	1.01 (1)	1.04 (1)
5	1.01 (1)	4.97 (5)	1.01 (1)			0.95 (1)	2.03 (2)	1.02 (1)	
6	1.03 (1)	5.94 (6)	1.02 (1)			0.98 (1)	1.03 (1)	0.98 (1)	
7	0.99 (1)	5.10 (5)	0.98 (1)	0.96 (1)		0.95 (1)	1.05 (1)	2.04 (2)	
8	1.01 (1	4.04 (4)	1.01 (1)		1.01 (1)	0.97 (1)	1.02 (1)	0.97 (1)	0.96 (1)
9	1.03 (1)	3.99 (4)	1.02 (1)		1.00 (1)	0.99 (1)	1.00 (1)	0.99 (1)	0.98 (1)
10	1.05 (1)	4.95 (5)	1.03 (1)		1.02 (1)		0.99 (1)	0.99 (1)	0.97 (1)
11	1.03 (1)	5.00 (5)			1.01 (1)	0.96 (1)	1.03 (1)	0.98 (1)	0.99 (1)
12	1.00 (1)	4.00 (4)	1.03 (1)		1.00 (1)	0.97 (1)	1.02 (1)	0.99 (1)	0.99 (1)
13	1.02 (1)	4.03 (4)	1.00 (1)		0.99 (1)	0.97 (1)	1.02 (1)	0.98 (1)	0.99 (1)
14	1.00 (1)	5.02 (5)	1.02 (1)		0.99 (1)	0.97 (1)	1.02 (1)		0.98 (1)
15	1.00 (1)	4.96 (5)	1.04 (1)		1.01 (1)	1.00 (1)		0.99 (1)	0.99 (1)
16	1.01 (1)	4.02 (4)	1.04 (1)		1.01 (1)	0.97 (1)	0.98 (1)	0.98 (1)	0.99 (1)
17	1.01 (1)	5.00 (5)	1.01 (1)	1.01 (1)			2.02 (2)	0.98 (1)	0.98 (1)
18	1.01 (1)	4.03 (4)	1.01 (1)		0.99 (1)		1.97 (2)	0.99 (1)	1.00 (1)
19	1.01 (1)	5.03 (5)		0.99 (1)	0.99 (1)	0.97 (1)	1.01 (1)	0.99 (1)	1.00 (1)
20	1.01 (1)	5.05 (5)		0.97 (1)		0.97 (1)	1.00 (1)	1.00 (1)	1.01 (1)
21	1.01 (1)	5.05 (5)	1.03 (1)		0.99 (1)	0.95 (1)	1.00 (1)		0.97 (1)

Table II. Physical Data

					TLC[c]			HPLC[d]	
no.	calcd	FAB-MS[a]	ϵ_{280}	yield, %	I	II	III	tr gradient	k' (% CH_3CN)
2	1468	1468	1254	42	0.42	0.32	0.70	14.4	3.31 (22)
3	1411	1412	1395	15	0.44	0.39	0.74	14.2	3.21 (22)
4	1411	1412	1197	12	0.45	0.38	0.72	13.8	2.49 (22)
5	1377	1378	1320	9	0.44	0.38	0.72	14.0	2.82 (22)
6	1393	1394	1223	6	0.29	0.29	0.69	10.2	3.81 (18)
7	1484	1485	2694	14	0.41	0.44	0.77	12.6	3.20 (20)
8	1353	1376[b]	1379	10	0.53	0.74	0.83	14.8	3.21 (23)
9	1353	1354	1239	33	0.54	0.78	0.84	14.3	2.41 (23)
10	1369	1370	1153	22	0.42	0.66	0.82	11.0	3.52 (19)
11	1385	1386	1510	8	0.49	0.61	0.82	18.3	4.29 (26)
12	1353	1354	1302	9	0.51	0.72	0.83	14.2	2.29 (23)
13	1353	1354	1342	14	0.61	0.66	0.75	10.0	2.56 (22)
14	1319	1320		11	0.48	0.53	0.76	7.3	4.04 (20)
15	1369	1370	1253	18	0.40	0.52	0.80	10.1	1.65 (19)
16	1354	1355	1177	33	0.53	0.77	0.82	15.1	3.01 (23)
17	1468	1469	1320	32	0.54	0.64	0.76	14.0	3.69 (22)
18	1353	1354	1161	13	0.57	0.64	0.78	18.7	3.75 (26)
19	1441	1442	1284	9	0.56	0.55	0.77	15.5	6.47 (22)
20	1441	1442	1048	8	0.51	0.53	0.77	12.5	3.86 (20)
21	1319	1321		29	0.42	0.57	0.77	12.3	3.82 (20)

[a] (M + H) ± 1 mass unit. [b] (M ± Na). [c] Merck 20 × 20 silica gel 60 glass plates F_{254}, 0.22-mm thickness. I: *n*-BuOH/HOAc/H_2O/pyridine (60:12:48:60). II: *i*-PrOH/NH_4OH/H_2O (3:1:1). III: *n*-BuOH/HOAc/H_2O (4:5:5). [d] Vydac 218TP54 (4.6 × 250 mm) C18 column at 2 mL/min., t_0 = 1.9 min. Gradient: 15–40% acetonitrile in 0.1% trifluoroacetic acid.

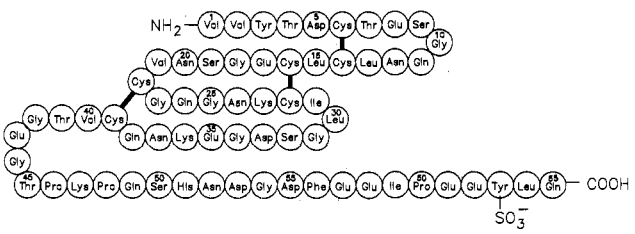

Figure 1. Sequence and structure of hirudin as reported by Dodt et al.[5,6] Mao et al.[7] reported residue 33 as Asn instead of Asp.

volved in binding to the extended binding site of fibrinogen on thrombin. A recent study has shown that a synthetic 21 amino acid C-terminal fragment of hirudin, unsulfated N^{α}-acetylhirudin$_{45-65}$ (1), inhibits fibrin clot formation without inhibiting the amidase activity of thrombin toward small peptidic substrates.[10] Since this peptide did not appear to be interacting with the catalytic site, as Chang's hypothesis suggests for Lys[46], shorter fragments were examined in order to establish the minimum active sequence at this noncatalytic binding site.[11] This was found to be hirudin$_{56-64}$. This paper reports the synthesis of several series of C-terminal hirudin analogues and their ability to inhibit thrombin-induced fibrin clot formation for the purpose of establishing the nature of the hirudin$_{56-64}$ interaction with its noncatalytic binding site of thrombin.

Results and Discussion

Peptides **2–21** were synthesized by solid-phase methods using an Applied Biosystems Model 430A peptide synthesizer. Cleavage and deprotection were accomplished with liquid HF at 0 °C. Purification by gel filtration and reverse-phase high-performance liquid chromatography yielded the desired products (Tables I and II). Inhibition of fibrin clot formation was measured as the inhibition of turbidity of a plasma solution to which thrombin had been added.[10]

Hirudin$_{55-63}$ contains six negatively charged groups (including a sulfated tyrosine) over a span of nine residues (Figure 1); thus, the expectation was that this region represents the proposed ionic binding component of hi-

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Table III. Fibrin Clot Inhibition

no.	compd	rel potency[a]	IC_{50},[b] μM
1	N^{α}-acetylhirudin$_{45-65}$[c]	444	1.6
2	hirudin$_{54-65}$	192	3.7
3	hirudin$_{55-65}$	100	7.1
4	[D-Phe^{56}]hirudin$_{55-65}$	<2	>200
5	[Leu^{56}]hirudin$_{55-65}$	<2	>200
6	[Glu^{56}]hirudin$_{55-65}$	<2	>200
7	[Tyr^{56}]hirudin$_{54-65}$	215	3.3
8	[Ala^{57}]hirudin$_{55-65}$	<3	>200
9	[Ala^{58}]hirudin$_{55-65}$	53	13.3
10	[Ala^{59}]hirudin$_{55-65}$	<3	>200
11	[Ala^{60}]hirudin$_{55-65}$	<3	>200
12	[Ala^{61}]hirudin$_{55-65}$	38	18.5
13	[Ala^{62}]hirudin$_{55-65}$	17	42.8
14	[Ala^{63}]hirudin$_{55-65}$	52	13.6
15	[Ala^{64}]hirudin$_{55-65}$	<3	>200
16	[Ala^{65}]hirudin$_{55-65}$	38	18.5
17	[Leu^{59}]hirudin$_{54-65}$	86	8.3
18	[D-Leu^{59},Ala^{65}]hirudin$_{55-65}$	<3	>200
19	[D-Ala^{60}]hirudin$_{54-65}$	26	27.0
20	[Sar^{60}]hirudin$_{54-65}$	41	17.3
21	[Glu^{63},Ala^{65}]hirudin$_{55-65}$	12	59.1

[a] Relative potency, with that of hirudin$_{55-65}$ being equal to 100. [b] IC_{50} = molar dose of peptide that results in 50% inhibition of fibrin clot formation relative to a blank control after thrombin addition to plasma. [c] Ref 10.

rudin upon binding to thrombin. Table III shows the effect of single Ala substitutions for residues 57–65. Glu^{57}, Ile^{59}, Pro^{60}, and Leu^{64} are sensitive to the removal of functionality. Glu^{58}, Glu^{61}, Glu^{62}, Tyr^{63}, and Gln^{65} are less critical. The lipophilic residues' importance is noteworthy in view of the highly charged nature of the C-terminal peptide. Position 56 requires an aromatic L-amino acid (compounds **3–7**). Position 59 also requires an L-amino acid (compounds **17** and **18**), but Pro^{60} can be replaced by D-Ala (**19**) or sarcosine (**20**) while L-Ala results in an inactive compound (**11**). The presence of Pro at position 60 and the activity of **19** present the possibility of a reverse turn at residues 59–62.

Unexpectedly, only the acidic residue Glu^{57} is essential for activity. Removal of the acidic functionality of Glu^{58}, Glu^{61}, and Glu^{62} affects potency to varying degrees, but the carboxylate at these positions is not essential. The effect of Tyr^{63} sulfation, which is reported to result in a 10-fold increase in the binding affinity of hirudin,[2] has not been determined for these fragments, but replacement of Tyr^{63} by Glu (compound **21**) results in an active analogue, although less potent (Table III).

These results have bearing on Chang's hypothesis[9] of hirudin's reverse homology to the fibrinopeptides. The fibrinopeptides B do not contain a phenylalanine or the other lipophilic residues that have been shown in this paper to be important for hirudin–thrombin interaction. The fibrinopeptides A do contain a phenylalanine residue followed in the C- to N-terminal direction by an acidic residue, but they do not contain the other features necessary for activity of the hirudin fragments. On the basis of these observations it is not clear whether or not the C-terminal region of hirudin binds to the proposed extended binding region of fibrinogen on thrombin. Even if the same binding site were being utilized, the mode of interaction would appear to be different for hirudin and the fibrinopeptides. Fenton has proposed that hirudin's acidic C-terminus interacts with a positively charged region on thrombin that is on the fibrin side of the fibrinogen binding channel and not the fibrinopeptide side.[12] Evidence for this comes from the observation that hirudin can block the chemotactic activity of thrombin.[13] A portion of the chemotactic domain, the insertion region Tyr^{59b}-Pro-Pro-Trp, should be close to this positively charged region, assuming that thrombin is structurally similar to other serine proteases.[14]

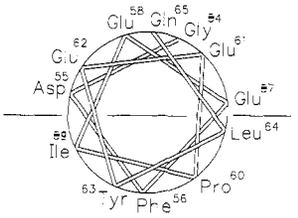

Figure 2. Edmundson wheel[17] diagram of hirudin$_{54-65}$. This represents the arrangement of amino acids of the peptide in an α-helical conformation as viewed down the axis of core. In addition to its amphipathic character, residues 56, 57, 59, 60, and 64, which are important for activity, are all present on one face of the α-helix.

Conformational analysis of hirudin$_{54-65}$ by Chou–Fasman analysis[15] suggests the potential for an α-helical conformation (⟨Pa⟩ = 1.06, ⟨Pb⟩ = 0.72, ⟨Pt⟩ = 0.84). The hydrophobic moment of this peptide has a maximum value of 3.20 at a frequency of 98° as determined by the method of Eisenberg et al.[16] This correlates to a periodicity of the hydrophobicity of 3.7, which corresponds well with the 3.6 residues/turn of an α-helix. Depiction of hirudin$_{54-65}$ as an Edmundson wheel reveals as amphipathic α-helix (Figure 2). Neither the fibrinopeptides A nor B are amphipathic when they assume an α-helical conformation. A more interesting observation than the mere grouping of hydrophilic and lipophilic residues on opposing sides of an α-helix is that all of the residues most important for the activity of these peptides, including the polar residues, are grouped together when the peptide is α-helical. This model for the thrombin-bound conformation of hirudin's C-terminal region would suggest the thrombin binding site as being a groove with a lipophilic lining and positively charged residues along the outer edges. One would not expect that replacement of Pro^{60} by Ala would disrupt an α-helical conformation; thus, the inactivity of compound 11 would seem to indicate that a typical α-helical conformation does not completely describe the active conformation of hirudin$_{54-65}$. However, the possibility that the active conformation is a distorted or "kinked" helix cannot be discounted at this time. Conformationally restricted analogues will be necessary to answer this question since NMR[18] and CD data (unpublished results) do not give evidence of an ordered structure for the C-terminal region of hirudin.

Experimental Section

Synthesis, Purification, and Characterization. The peptides were synthesized by solid-phase methods on an Applied Biosystems Model 430A peptide synthesizer. Boc-Gln-PAM resin (Applied Biosystems; 0.64 mmol/g), Boc-Glu(Bzl)-PAM resin (0.70 mmol/g), or Boc-Ala-PAM resin (0.76 mmol/g) was utilized with double symmetrical anhydride couplings except for Asn, which was coupled by the DCC/HOBT method. N^{α}-*t*-Boc amino acids

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were used with the following side-chain protection: Asp(Chx), Glu(Chx), His(Tos), Tyr(2-BrZ), Ser(Bzl). Upon completion of the synthesis, the peptide was cleaved from the resin with liquid HF containing 5% anisole at 0 °C for 40 min. Upon removal of the HF in vacuo, the peptide was precipitated with ether and extracted with 30% aqueous acetic acid or dilute sodium bicarbonate with a small amount of dimethylformamide. The extract was lyophilized, and the residue was desalted on a Sephadex G-15 column (2.6 × 90 cm) in 5% aqueous acetic acid. The peptide was then purified by reverse-phase high-performance liquid chromatography (RP-HPLC) on a Rainin Dynamax C18 column (21.4 × 250 mm) at 10 mL/min using acetonitrile/0.1% aqueous TFA mobile phases. The major peak was collected, and the fraction was lyophilized. The resultant peptide was analyzed for homogeneity by RP-HPLC and TLC (Table II) and for identity by amino acid analysis using a Beckman Model 6300 amino acid analyzer (Table I) and FAB-MS on a Finnigan TSQ-46 instrument (Table II).

Anticoagulant Assay. Inhibition of fibrin clot formation was determined as previously described.[10] Briefly, 50 μL (0.2 pmol) of bovine thrombin (Sigma) was added to the wells of a microtiter plate (Falcon) containing 50 μL of a solution of the synthetic peptide to be tested (0–25 nmol). After a 1-min agitation and an additional incubation fr 10 min at 24 °C, 100 μL of diluted human plasma (1:10) in 0.1% EDTA was added and vortexed for 20 s. The turbidity of the solution was monitored by an autoreader (EL 309, Bio-Tek Instruments) at 405 nm at 5-min intervals. All of the above reagents were diluted in an assay buffer containing 0.12 M sodium chloride, 0.01 M sodium phosphate, 0.01% sodium azide, and 0.1% bovine serum albumin, pH 7.4.

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Registry No. **2**, 109528-49-6; **3**, 109528-50-9; **4**, 109528-51-0; **5**, 109528-52-1; **6**, 109528-53-2; **7**, 109528-54-3; **8**, 109528-55-4; **9**, 109528-56-5; **10**, 109528-57-6; **11**, 109528-58-7; **12**, 109528-59-8; **13**, 109528-60-1; **14**, 109528-61-2; **15**, 109552-33-2; **16**, 109528-62-3; **17**, 109528-63-4; **18**, 109528-64-5; **19**, 109528-65-6; **20**, 109528-66-7; **21**, 109528-67-8; thrombin, 9002-04-4.

Book Reviews

Organometallic Chemistry. Volume 14. Edited by E. W. Abel and F. G. A. Stone. The Royal Society of Chemistry, Burlington House, London, WIV OBN. 1986. xvi + 503 pp. 14 × 22 cm. $96.00.

This volume, which is the 14th in a series, is an annual review of the 1984 organometallic chemistry literature. The chapters are organized into discussions of metallic types and the metals are classified by periodic group. Additional chapters deal with the generalities of organometallic structure and are organized with respect to ligand type and structure. Several chapters present overviews of organometallic reactions, such as "Ligand Substitution" and "Homogeneous Catalysis". The final and exceedingly useful chapter is a compilation of metal complexes whose structures have been determined by X-ray, neutron, or electron diffractometry.

This volume represents an excellent attempt to review and critically report on the more than 4000 original organometallic chemistry articles which appeared in 1984. While the discussion of some areas is necessarily terse, the volume offers a balanced overview. Chapter 9 (by W. E. Lindsell) on "Organometallic Compounds Containing Metal–Metal Bonds" is particularly interesting in its treatment of the physical and spectroscopic properties of these complexes.

Chapter 15 (by M. E. Fakley), which reviews homogeneous catalysis by transition metal complexes, is a useful overview of redox, metathesis, polymerization, and addition reactions.

A brief perusal of this volume is all that is required to recognize the valuable summary and compilation of the literature contained therein. This book will clearly be of use to organometallic chemists as a reference volume and probably of occasional use to organic or medicinal chemists.

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The Frythe, Welwyn, England **Lawrence I. Kruse**

New Cardiovascular Drugs 1986. Edited by Alexander Scriabine. Raven, New York. 1986. xi + 274 pp. 16 × 24 cm. ISBN 0-88167-209-2. $65.00.

This is the fourth annual volume of a series that began in 1983 which was titled "New Drugs Annual: Cardiovascular Drugs". The title changed to its present form in 1985. Similar to previous editions, this book contains major therapeutic theme areas which this year include: antihypertensive, cardiac stimulant, antiarrhythmic, antithrombotic, and cardioprotective drugs. The last chapter, "Regulatory Aspects of Drug Development", is similar to a chapter that appeared in the first volume of this series. The five therapeutic areas contain a total of 13 chapters ranging in length from 11 to 24 pages. Each chapter describes the preclinical pharmacology, toxicology, metabolism, pharmacokinetics, and clinical pharmacology. The drugs discussed are presently in clinical trials in the United States. A number of the drugs, including cibenzoline, terazosin, carteolol, and suloctodil, are already marketed in various countries.

The presence of chemistry and toxicology sections are welcome additions to what is essentially a pharmacology book since these important elements of a drug's profile are often ignored in standard pharmacology books. What is missing in most of the chapters is a description of any side effects or toxicity observed in clinical trials. Perhaps this is due to the fact that nearly all the chapters are written by representatives of the companies who are developing the drug and the companies, understandably, do not want to divulge any minor toxicity that could stigmatize their drug.

The book is essentially well-written and the similar format for each chapter makes it easy to follow. The use of appropriate standards aids in the understanding of the drugs discussed. The biggest disappointment in the book is a lack of novelty of some of the compounds discussed. Unfortunately, several of the compounds are pharmacologically indistinct from already marketed drugs. I think this book would benefit if newer compounds were included, even if there were no clinical data reported.

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CN 800, Princeton, New Jersey 08543-0340 **Dennis M. Ackerman**

Flavonoids and Bioflavonoids, 1985. Edited by L. Farkas, M. Gabor, and F. Kallay. Elsevier, Amsterdam. 1986. xxii + 466 pp. 16 × 24 cm. ISBN 0-444-41737-0 (Series) and 0-444-99520-X (Vol. 23). $109.25.

This book summarizes the proceedings of the 7th Hungarian Bioflavonoid Symposium held in Szeged in May, 1985. Forty-four lectures have been outlined, with their authorship emanating mostly from European laboratories. The latest trends in flavonoid chemistry are adequately described. Some of the most interesting presentations are those dealing with the pharmacology of the flavonoids and related compounds. The pharmacological effects are varied enough and of sufficient interest to warrant continued