in the neutral molecules. Consequently, both methyl derivatives of histamine possess the ability to be recognized at the histamine H_2-receptor and to activate it according to the proposed mechansm.[6,10,23]

The reduced potencies exhibited by 4-MeHA and 2-MeHA on the H_2-receptor are consistent with predictions from the recognition hypothesis proposed earlier,[6,10] which defined the N3-H tautomer of the monocation as the only recognizable species in this class of histamine congeners. Accordingly, the lower potencies of the methyl derivatives are explained by the increased fraction of their dicationic species compared to equimolar solutions of histamine. Moreover, our calculations indicate that 4-MeHA should be a more potent agonist at the histamine H_2-receptor than 2-MeHA. The rank order of potencies predicted from these calculations is in agreement with experimental observations, thus providing additional support for the mechanistic hypothesis describing the interactions of agonists at the histamine H_2-receptor.

Acknowledgment. We thank Drs. Jack Peter Green and Roman Osman for valuable discussions. This work was supported in part by NSF Grant BNS 83-03373, by a Research Scientist Development Award DA-00060 from the National Institute on Drug Abuse (to H.W.), and by an Irma T. Hirschl Career Scientist Award (to S.T. while at Mount Sinai). A generous grant of computer time from the University Computer Center of the City University of New York is gratefully acknowledged.

Registry No. 2-MeHA, 34392-54-6; 4-MeHA, 36507-31-0.

2,3-Dialkyl(dimethylamino)indoles: Interaction with $5HT_1$, $5HT_2$, and Rat Stomach Fundal Serotonin Receptors

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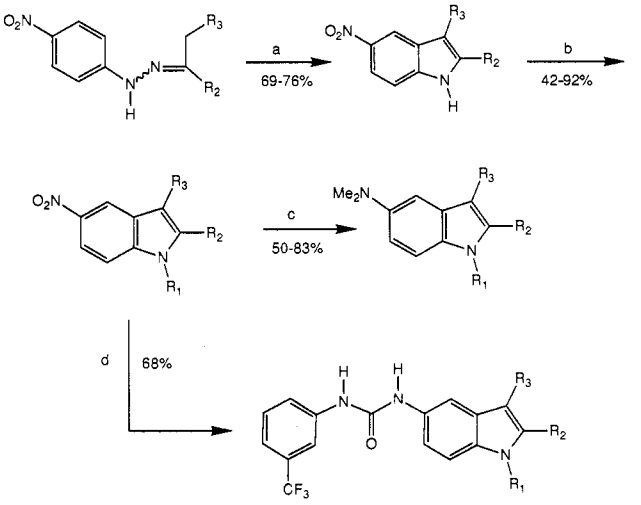
2,3-Dialkyl(dimethylamino)indoles, synthesized via the Fisher indole synthesis, were found to weakly bind to $5HT_1$ and $5HT_2$ sites in brain cortical membranes (IC_{50} greater than 1 μM at both sites for all compounds). These (dimethylamino)indoles were relatively potent antagonists of the serotonin receptor in the rat stomach fundus. At higher concentrations, several of the compounds were weak agonists at this receptor. For direct comparison with data obtained in the isolated rat fundus, antagonism of serotonin-induced contractions at $5HT_2$ receptors in the rat jugular vein was also examined. Several of the compounds showed good selectivity for the fundus receptor relative to the $5HT_2$ receptor; together with minimal affinity for $5HT_1$ and $5HT_2$ binding sites in brain cortical membranes, these results support the idea that the serotonin receptor in the stomach fundus is distinct from $5HT_1$ and $5HT_2$ binding sites.

In the mid-1950s, Shaw and Woolley reported that the indole derivative 2-methyl-3-ethyl-5-(dimethylamino)-indole (medmain) was a partial agonist at the serotonin receptor in certain isolated smooth muscle preparations such as sheep vascular tissue and the rat uterus.[1] In those tissues, now known to possess $5HT_2$ receptors,[2] the activity of medmain as both an agonist and antagonist was relatively weak. However, it has been our observation that medmain is a relatively potent antagonist of the serotonin receptor in the rat fundus. Serotonin receptors in the rat fundus preparation, originally described by Vane,[3] have recently been shown to be distinct from the serotonin receptor subtypes already described: $5HT_{1a}$, $5HT_{1b}$, or $5HT_2$.[4]

Encouraged by the antagonist activity of medmain at the serotonin receptor in the fundus, we made several derivatives to explore the nature of this receptor. Specifically, we examined both the agonist and antagonist activity of medmain at this receptor, as well as the specificity for the serotonin receptor in the fundus over the other serotonin receptors already described. In addition, we explored the effect of fundus activity/selectivity imparted by adding substituents at N-1, or by varying the alkyl groups at the 2- and 3-position, or finally, by moving the dimethylamino group from the 5-position to the 7-position. In this paper, we describe a series of 2,3-dialkyl(dimethylamino)indole derivatives and their agonist and antagonist activity at the fundus receptor, as well as their activity at other serotonergic receptors. Activity at $5HT_2$ receptors was examined in the rat jugular vein, a

Scheme I[a]



[a] (a) Concentrated HCl, reflux overnight; (b) NaH in 5/1 PhMe/DMF, R_1I, room temperature or 80 °C; (c) H_2, 5% Pd/C, formalin solution in EtOH; (d) H_2, 5% Pd/C in EtOH, followed by m-$CF_3C_6H_4NCO$ in EtOH, then chromatography.

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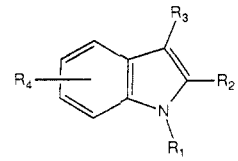
Table I. 2,3-Dialkylindoles



no.	R_1	R_2	R_3	R_4	formula[a]	mp, °C	recrystn solvent
1	H	Me	Et	5-NMe_2	$C_{13}H_{18}N_2$	100–101	*i*-PrOH
2	H	Me	Et	4-Cl, 5-NMe_2	$C_{13}H_{17}ClN_2$	133–136	*i*-PrOH
3	Me	Me	Et	5-NMe_2	$C_{14}H_{20}N_2$·maleate	133–135	EtOAc/MeOH
4	Et	Me	Et	5-NMe_2	$C_{15}H_{22}N_2$·maleate	86–88.5	EtOAc/MeOH
5	*n*-Pr	Me	Et	5-NMe_2	$C_{16}H_{24}N_2$·maleate	118–120	EtOAc/MeOH
6	*i*-Pr	Me	Et	5-NMe_2	$C_{16}H_{24}N_2$	71–73	EtOAc/MeOH
7	*p*-FC_6H_4CO	Me	Et	5-NMe_2	$C_{20}H_{21}FN_2O$·maleate	135–138	EtOAc/MeOH
8	Me	Et	Me	5-NMe_2	$C_{14}H_{20}N_2$·maleate	153–157	EtOAc/MeOH
9	Me	Me	Me	5-NMe_2	$C_{13}H_{18}N_2$·maleate	179–182	EtOAc/MeOH
10	Me	Me	Et	5-*m*-$CF_3C_6H_4NHCONH$	$C_{20}H_{20}F_3N_3O$	216–218.5	*i*-PrOH
11	Me	Me	Et	7-NMe_2	$C_{14}H_{20}N_2$·TsOH	142–145	EtOAc/MeOH

[a] All compounds gave satisfactory (±0.4%) C, H, N analysis.

tissue established to contract to serotonin via activation of $5HT_2$ receptors.[5]

Chemistry

The indoles (Table I) were prepared by the Fisher indole synthesis (Scheme I). The requisite hydrazones were prepared in 80–90% yields by condensation of (*p*-nitrophenyl)hydrazine [(*o*-nitrophenyl)hydrazine for indole **11**] with the appropriate ketone in refluxing ethanol overnight. The crude hydrazones were subjected directly to refluxing concentrated HCl, to give the indoles in 40–70% yield. The indoles were deprotonated with NaH in 5/1 toluene/DMF and then alkylated with the desired alkyl iodide.[6] Alternatively, N-1 could also be acylated with *p*-fluorobenzoyl chloride, to give the N-1 *p*-fluorobenzoyl substituted indole in 77% yield.

For the completion of the synthetic sequence, we initially followed a two-step procedure: reduction of the nitro group to the amine with $TiCl_3$,[7] followed by a permethylation/demethylation sequence[6] to give the 5-(dimethylamino)-indoles. However, the $TiCl_3$ reduction gave variable yields, as well as formation of a 4-chloroindole byproduct in minor amounts. Furthermore, the permethylation/demethylation sequence proceeded in low yields. Ultimately, we found that the nitro group could be directly converted to the dimethylamino group by catalytic hydrogenation in the presence of formalin solution. Alternatively, the hydrogenation could be done in the absence of formalin solution, to give the primary amine which was reacted with *m*-(trifluoromethyl)phenyl isocyanate to give the urea **10**.

Results and Discussion

The goal of the present study was to capitalize on the previous observation[1] that 2,3-dialkyl(dimethylamino)-indoles possess affinity for serotonin receptors as defined in the sheep carotid artery and rat uterus (two tissues now known to possess $5HT_2$ receptors). Table I contains a series of 2,3-dialkylindoles bearing a dimethylamino group at the 5- or 7-position. These indoles were prepared by the classical Fisher indole synthesis. In general, these compounds bound weakly to $5HT_1$ and $5HT_2$ sites in brain cortical membranes (IC_{50} greater than 1 μM at both $5HT_1$ and $5HT_2$ sites for compounds **1–11** in Table I). On the basis of these binding results, the 2,3-dialkylindoles showed affinity lower than that previously described for potent piperazine or ergoline derivatives.[8] Thus, compounds in this series interacted with certain serotonin receptor sites, albeit only weakly based on binding affinities.

Table II. Affinity of 2,3-Dialkylindoles at $5HT_2$ and Rat Stomach Fundal Serotonin Receptors

no.	rat fundus $-\log K_B$ (*n*)	rat jugular ($5HT_2$) $-\log K_B$ (*n*)
1	7.30 ± 0.29 (6)	4.93 ± 0.08 (3)
2	6.86 ± 0.15 (8)	
3	7.32 ± 0.08 (3)	6.51 ± 0.17 (3)
4	7.01 ± 0.10 (6)	6.45 ± 0.09 (7)
5	6.57 ± 0.12 (3)	
6	7.00 ± 0.13 (12)	7.28 ± 0.15 (3)
7	<5.0 (4)	
8	6.69 ± 0.15 (3)	6.48 ± 0.12 (4)
9	6.71 ± 0.13 (3)	
10	7.16 ± 0.29 (3)	5.18 ± 0.09 (3)
11	<5.5 (3)	

On the basis of the weak interaction with $5HT_1$ and $5HT_2$ serotonergic receptors, we explored the possibility that modification of this series might permit the development of compounds showing relatively high affinity at another serotonin receptor, the receptor responsible for the contractile response to serotonin in the rat stomach fundus. This receptor is clearly distinct from either $5HT_1$ or $5HT_2$ binding sites.[4] In this regard, we were encouraged by the initial observation that although medmain (**1**) only weakly antagonized serotonin-induced contractions at $5HT_2$ receptors in the rat jugular vein, it was a more potent antagonist of serotonin-induced contractions in the rat stomach fundus ($-\log K_B = 7.30$ in the fundus) (Table II).

However, as we modified medmain (**1**), no dramatic improvement in affinity for the serotonin receptor in the fundus occurred; rather, increased affinity at $5HT_2$ receptors, as determined in the rat jugular vein, was observed (Table II). For example, increasing the size of the alkyl substituent at N-1 (i.e., Me, Et, *n*-Pr, *i*-Pr; compounds **3–6**) seemed to increase affinity at $5HT_2$ receptors in the rat jugular vein with little effect on affinity toward serotonin receptors in the rat stomach fundus. Minor variation of the alkyl substituents at the 2- and 3-position of the indole nucleus (compounds **8** and **9**) did not enhance affinity for serotonin receptors in the fundus. This series of com-

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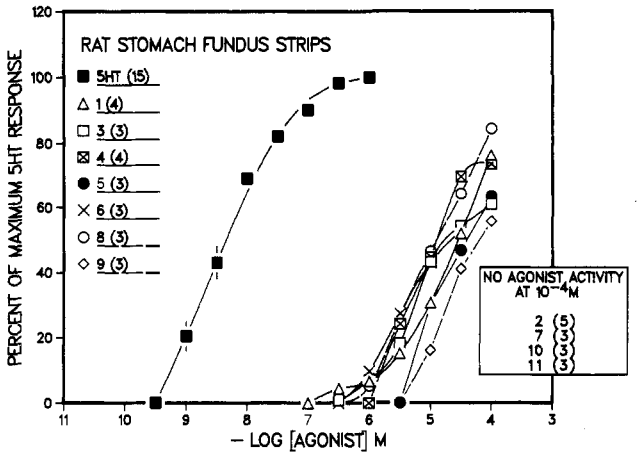

Figure 1. Comparative concentration–response curves for contractile effects of serotonin and 2,3-dialkyl(dimethylamino)indoles in the rat stomach fundus. Compounds were examined at a maximum concentration of 10^{-4} M. Points are mean values and vertical bars represent the standard error of the mean for the number of tissues indicated in parentheses.

pounds, however, was sensitive to the incorporation of electron-withdrawing substituents. Thus, incorporation of a chlorine at the 4-position (**2**) diminished the activity at the fundus receptor, and acylation of N-1 (**7**) markedly reduced affinity at this receptor. Finally, the location, but not necessarily the electronic nature, of the amine substituent appears to be important for affinity to the serotonin receptor in the fundus. Relocation of the dimethylamino moiety from the 5-position (**3**) to the 7-position (**11**) led to a marked reduction in affinity for the fundus receptor. However, relacement of the dimethylamino moiety (**3**) with a [*m*-(trifluoromethyl)phenyl]urea derivative (**10**) led to no loss of affinity for the fundus receptor, but interestingly, led to a decrease in $5HT_2$ receptor affinity as measured in the rat jugular vein. In sum, medmain (**1**), with no substituent at N-1 and a dimethylamino group at the 5-position, had the highest affinity and selectivity for the serotonin receptor in the rat stomach fundus.

With regard to agonist activity in the rat stomach fundus, compounds **2**, **7**, **10**, and **11** in concentrations as high as 10^{-4} M showed no agonist activity (Figure 1). On the basis of the affinity of these agents as antagonists of serotonin-induced contractions, it would appear that compounds **2**, **7**, and **11** simply have little affinity for serotonin receptors. Most of the compounds that showed some affinity for serotonin receptors in the stomach fundus possessed partial agonist activity and, in higher doses, contracted the rat stomach fundus (Figure 1). It is of interest to note that compound **10**, which possessed reasonable affinity for the serotonin receptors, in the stomach fundus when examined as an antagonist ($-\log K_B = 7.16$), showed no agonist activity. This result suggests that, unlike the case of antagonist activity, the electronic nature of the amine substituent at the 5-position of the indole is important for agonist activity. Thus, when the dimethylamino substituent (**3**) is replaced with a [*m*-(trifluoromethyl)phenyl]urea (**10**), agonist activity is lost although affinity for the serotonin receptor in the fundus is retained.

Affinity determined by antagonism of serotonin-induced contractions in the jugular vein agreed with the affinities determined at $5HT_2$ binding sites in rat cortical membranes, an observation previously reported for other compounds.[5] However, using this 2,3-dialkylindole series of compounds, we further confirm that the affinities determined for serotonin receptors in the stomach fundus do not correlate with affinity determined at either $5HT_1$ or $5HT_2$ binding sites in rat cortical membranes. This observation with 2,3-dialkylindoles confirms and extends our previous observations with other antagonists and supports the idea that the serotonin receptor in the stomach fundus is distinct from $5HT_1$ and $5HT_2$ binding sites.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Identities of all compounds were confirmed by ^1H NMR, mass spectra, and combustion analysis. All reactions were followed by TLC carried out on Merck F254 silica gel plates. Microanalyses were provided by the Physical Chemistry Department of the Lilly Research Laboratories. The experimental procedures described below are representative of the procedures used to prepare the indoles listed in Table I.

Synthesis of the (*p*-Nitrophenyl)hydrazone of 2-Pentanone. 2-Pentanone (44.7 g, 0.52 mol) and (*p*-nitrophenyl)-hydrazine (79.5 g, 0.52 mol) were refluxed overnight in 95% ethanol (400 mL) and then diluted with water (200 mL). The solution was allowed to cool (12 h) and the crude hydrazone collected by filtration, yield 97.8 g (85%). ^1H NMR analysis indicated a mixture of syn and anti isomers.

Synthesis of 2-Methyl-3-ethyl-5-nitroindole. The crude (*p*-nitrophenyl)hydrazone above (97.8 g, 0.44 mol) was dissolved in concentrated HCl (1200 mL). The solution was refluxed overnight and allowed to cool, and the resulting indole was collected by filtration, yield 62.0 g (69%). The indole was alkylated without further purification.

Synthesis of 1,2-Dimethyl-3-ethyl-5-nitroindole. Under a nitrogen atmosphere, NaH (1.6 g of 60% NaH, 40 mmol, 2.3 equiv) was washed twice with petroleum ether and then suspended in toluene (50 mL). 2-Methyl-3-ethyl-5-nitroindole (3.5 g, 17 mmol) was added as a solid, followed by the addition of DMF (10 mL) as a cosolvent, which made the reaction a homogeneous solution. The reaction was stirred at room temperature for 30 min; methyl iodide (11.4 g, 80 mmol, 4.7 equiv) was added, and stirring was continued for 2 h. The reaction was carefully quenched with water and extracted (×3) with chloroform. The combined chloroform extracts were washed twice with water and dried over sodium sulfate. Removal of the solvent with a rotary evaporator gave the crude product, yield 3.3 g (89%). No further purification was necessary before the next reaction.

Note that, with alkylating agents other than methyl iodide, it was necessary to warm the reaction to 80 °C for several hours in order for the reaction to proceed.

Synthesis of 1,2-Dimethyl-3-ethyl-5-(dimethylamino)-indole (3). To the crude 5-nitroindole (3.3 g, 15 mmol) in 95% ethanol (50 mL) was added an excess of formaldehyde (37% in water), followed by 5% Pd/C (3.3 g). The solution, under 60 psi of H_2, was stirred overnight at room temperature. Removal of the catalyst by filtration followed by rotary evaporation of the solvent gave the crude product, yield 2.72 g (89%), which was dissolved in ethyl acetate (10 mL). A stoichiometric amount of maleic acid and methanol (2 mL) were added, and the mixture was warmed to solution. After partial evaporation and cooling, the maleate salt of the product was collected by filtration, yield 2.85 g, mp 133–135 °C.

Isolation of Smooth Muscle Preparations. Male Wistar rats (150–375 g; Laboratory Supply, Indianapolis, IN) were sacrificed by cervical dislocation, and longitudinal sections of the stomach fundus were prepared for in vitro examination. Four preparations were obtained from one rat fundus. Ring preparations of the external jugular vein were prepared as previously described.[9] Tissues were mounted in organ baths containing 10 mL of modified Krebs solution of the following composition (millimolar concentrations): NaCl, 118.2; KCl, 4.6; $CaCl_2 \cdot 2H_2O$, 1.6; KH_2PO_4, 1.2; $MgSO_4$, 1.2; dextrose, 10.0; and $NaHCO_3$, 24.8. Tissue bath solutions were maintained at 37 °C and equilibrated with 95% O_2 and 5% CO_2. Tissues were placed under optimum

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resting force (4 g) and were allowed to equilibrate for approximately 1 h before exposure to drugs. Isometric contractions were recorded as changes in grams of force on a Beckman Dynograph with Statham UC-3 transducers.

Determination of Apparent Antagonist Dissociation Constants. Noncumulative contractile concentration–response curves for serotonin in the fundus and cumulative concentration response curves in the jugular vein were obtained by a stepwise increase in concentration after washing out the preceding concentrations every 15–20 min. Each agonist concentration remained in contact with the tissue for approximately 2 min and maximum response to each agonist concentration was measured. ED_{50} values were taken as the concentration of agonist that produced half-maximal contraction. After control responses were obtained, tissues were incubated with an appropriate concentration of buffer or antagonist for 1 h. Responses to serotonin were then repeated in the presence of antagonist. Concentration responses utilized only one agonist and one antagonist concentration per tissue. In general, successive agonist responses in the presence of buffer treatment were unaltered (average dose ratio was 1.28 ± 0.21 [8]).

Apparent antagonist dissociation constants (K_B) were determined for each concentration of antagonist according to the following equation:[10]

$$K_B = [B]/(\text{dose ratio} - 1)$$

where [B] is the concentration of the antagonist and dose ratio is the ED_{50} of the agonist in the presence of the antagonist divided by the control ED_{50}. Generally, parallel shifts in the concentration–response curves occurred in the presence of antagonists. These results were then expressed as the negative logarithm of the K_B (i.e., $-\log K_B$). Calculations were done as described previously.[11]

Cortical Binding to $5HT_2$ and $5HT_1$ Receptors. Brain tissue was obtained from 150–200-g male Wistar rats. The cerebral cortex was dissected, homogenized, and prepared according to the method described by Nelson, using a preincubation in buffer without added monoamine oxidase inhibitors in order to eliminate endogenous 5HT.[12] For receptor binding, an amount of membrane preparation equivalent to 250–350 mg of protein was used per sample in 1 mL of Tris buffer. The assay for 5HT binding ($5HT_1$ site) was done following the method of Bennett and Snyder[13] and that for spiperone binding ($5HT_2$ site) according to Peroutka and Snyder.[14] Nonspecific binding of [^{3}H]-5HT and [^{3}H]spiperone was determined in the presence of 10^{-5} M 5HT or 10^{-6} M lysergic acid diethylamide, respectively, and specific binding was calculated as the difference between total binding without added nonradioactive compound and the nonspecific binding. The IC_{50} values were determined as the amount of substance causing 50% inhibition of the specific binding with use of 10 different concentrations in the range of 10^{-9} to 10^{-4} M. The concentration of [^{3}H]-5HT (sp act. 17.6 Ci/mmol; Amersham Corp., Arlington Heights, IL) in each sample was 2.3–2.6 nM and that of [^{3}H]spiperone (sp act. 20 Ci/mmol; Amersham) was 0.5–0.7 nM. For 5HT, the IC_{50} at $5HT_1$ and $5HT_2$ sites was 4 and 5000 nM, respectively, and for spiperone, the IC_{50} at $5HT_1$ and $5HT_2$ sites was 400 and 1.0 nM, respectively.

Acknowledgment. We thank Dr. Michael Flaugh for preparing "medmain" and for helpful discussions, Dr. Norman Mason for determining the binding affinities to brain cortical membranes, and Jack Campbell and David Vogt for their expert technical assistance in performing the hydrogenation experiments. Finally, we thank Ann McKenney for her assistance in the preparation of this manuscript.

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Book Reviews

Annual Reports in Medicinal Chemistry. Volume 20. Edited by Denis M. Bailey. Academic, Orlando, FL. 1985. xiii + 352 pp. 17 × 25.5 cm. ISBN 0-12-040520-2. $35.00.

The 20th publication of *Annual Reports in Medicinal Chemistry* continues the traditionally high caliber of well-selected topics that reflect the major current areas of interest in medicinal chemistry in a concise, yet thorough, detailed and timely fashion. Clearly the editor and the contributing experts are to be commended for the continuation of the excellence and value of this series. For this reviewer, it is *the* most eagerly anticipated yearly publication in its field. This is because of the in-depth treatment afforded specialized areas coupled with a state-of-the-art reflection of therapeutic advances and the presentation of newer thought-provoking approaches to medicinal chemistry and directions toward the development of potential drug products.

The current volume continues the format of this established series. It consists of short, but comprehensive, thoroughly referenced chapters restricted to 10 pages or less, including references. Each of the chapters covers advances in the area since it was last reviewed in the series. The 32 chapters in this volume, as those in its predecessor, are grouped into seven sections: CNS Agents, Metabolic and Endocrine Function, Topics in Biology, Topics in Chemistry and Drug Design, and Worldwide Market Introductions. In addition to summaries of recent advances in the more stable fields of antianxiety, anticonvulsant, analgesic, dopaminergic, antihypertensive, pulmonary, gastrointestinal, and antineoplastic medicinal chemistry, an excellent balance has been achieved by introducing many highly specialized and newly emerging technologies that may provide a basis for future drug discoveries. Topics reviewed for the first time in the initial three sections of the book are as follows: "Cotransmitters in the CNS", "Antiglaucoma Agents", "Plasminogen Activators", "Determinants of Microbial Resistance to β-Lactam Antibiotics", "Quinolone Antibacterial Agents", and "Nonclassical Targets for Antibacterial Agents". The next three sections are all devoted to developing areas of science that may provide a basis for drug discoveries. These include chapters "Interleukin", "Growth Hormone Releasing Factors", "Platelet-Activating Factor" (a second update), "Luteininizing Hormone Releasing (LHRH) Analogues", "Sodium/Calcium Exchange and Calcium Homeostasis in Excitable Tissue", "Possible Roles of Protein Kinases C in Cell Function", "Neutrophil Elastase", "Sickle Cell Anemia", "Renin Inhibition" (a second update), "NMR Spectroscopy in Biological Systems", "Contrast Enhancing Agents in NMR Imaging", "Solid-State Organic Chemistry and Drug Stability", "Altered Drug Action in the Elderly", and "Strategies for Delivery of Drugs Through the Blood–Brain Barrier". The final section consists of one chapter, "To Market, To Market". This part, introduced for the first time in last year's volume, is a compilation (drug name, structure, country of origin, originator, country of introduction, distributor, trade name, a brief summary of properties, one or more references) of new chemical entities (NCEs) introduced in the world market in 1984. This summary reveals that NCEs for