Neuroleptics from the 4a,9b-*trans*-2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4,3-*b*]indole Series. 3. Carboxamidoalkyl Derivatives

Willard M. Welch,*† Charles A. Harbert,† Reinhard Sarges,† Albert Weissman,‡ and B. Kenneth Koe‡

Departments of Medicinal Chemistry and Pharmacology, Pfizer Central Research Laboratories, Groton, Connecticut 06340.
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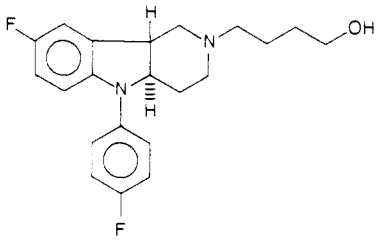
Substitution of position 2 of the 4a,9b-*trans*-2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4,3-*b*]indole nucleus with ω-carboxamidoalkyl substituents leads to compounds with exceedingly potent neuroleptic activity in in vitro and in vivo models. Although duration of activity is not as long as that of the analogous 4-hydroxy-4-(4-fluorophenyl)butyl derivatives reported previously, the absolute potency in vivo is greater. The ability of these compounds to bind with great affinity to dopamine (DA) receptors further defines the nature of the DA receptor auxiliary binding site as a hydrogen-bond donating site in addition to or instead of a lipophilic site as has been previously proposed.

In previous papers,[1,2] we have disclosed the discovery of potent neuroleptic activity in a series of 4a,9b-*trans*-2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4,3-*b*]indole derivatives commonly known as and hereafter referred to as *trans*-hexahydro-γ-carbolines. The activity of these compounds is highly stereospecific in that only one enantiomer of each resolved pair is active in vitro and in vivo and the intrinsic activity derives from the tricyclic carboline portion of the molecule as shown by the fact that the tricyclic nucleus substituted with H or simple alkyl is potently active in displacing [^{3}H]spiroperidol from dopamine receptors in vitro. Compounds that contain more complex side chains at position 2, particularly those side chains derived from the 4-aryl-4-oxobutyl moiety, not only potently displace [^{3}H]spiroperidol in vitro but also are extremely active neuroleptics in vivo. This latter observation may be attributed to the enhanced lipophilicity of these substituted compounds or may be due to interaction with an auxiliary binding site at or near the dopamine (DA) receptor the occupation of which is necessary to show potent activity as postulated by Humber et al.[3] We have observed that the most potent derivative in the *trans*-hexahydro-γ-carboline series above was the simple 4-hydroxybutyl derivative I and have suggested[2] that the auxiliary binding



I

site is more likely a hydrogen-bonding site rather than a lipophilic binding site as proposed by Humber et al.[3] We also noted, in conjunction with SAR studies in the hexahydro-γ-carbolines series above, that all neuroleptics have a hydrogen-bond accepting site located some 3–5 Å from the basic nitrogen component and that this site can be an oxygen functionality as in I above and its derivatives or as in butaclamol and haloperidol or may be a nitrogen-containing moiety as illustrated by thiothixene, octoclothepine, and fluspirilene as well as by the benzamides and clozapine. It is the tertiary amine derivatives among these latter compounds that suggest that this site is hydrogen-bond accepting rather than donating. This realization led directly to an investigation of the effect of incorporating amine-derived side chains into *trans*-hexahydro-γ-carbolines. The compounds prepared and testing results are summarized in Tables I–III.

Chemistry

All of the compounds discussed in this paper were prepared from the racemic 4a,9b-*trans*-4′,8-difluoro-2,3,4,4a,5,9b-hexahydro-γ-carboline nucleus, the preparation of which has previously been described.[4] Alkylation of this nucleus with ω-haloalkyl nitriles provided the nitrile derivatives that were reduced to the requisite primary amines with lithium aluminum hydride. These amines were then acylated with a variety of acid chlorides. Compounds **11**, **12**, **14**, and **15** were synthesized by first reacting the cyclic amides with 1,4-dichlorobutane to give the ω-chlorobutyl amides,[5] which were then reacted with the tricyclic nucleus. Although this latter method was not particularly efficient, adequate yields of pure final products were obtained following column chromatography and/or crystallization.

Results and Discussion

Neuroleptic activity of the compounds listed in Tables I–III was assessed in vitro by their ability to displace [^{3}H]spiroperidol from labeled receptors of corpus striatum by a method adapted from that of Burt, Creese, and Snyder[6] and in vivo by their ability to antagonize the stereotypy induced in rats by *d*-amphetamine sulfate (5 mg/kg, ip). Both methods have been described fully in an earlier paper from these laboratories.[7]

Having found that the *trans*-hexahydro-γ-carboline nucleus substituted at position 2 with a 4-hydroxybutyl group (compound I) was among the most potent in vivo and in vitro DA antagonists known,[2] we elected to synthesize the corresponding 4-amino derivative **2** via the intermediate nitrile **1**. As will be noted in Table I, the amine **2** is potently active in the [^{3}H]spiroperidol displacement assay but is virtually inactive in the anti-amphetamine screen at all three time points. This result suggests that concentrations of compound **2** at central DA receptors high enough to exert a physiological response are

† Department of Medicinal Chemistry.
‡ Department of Pharmacology.

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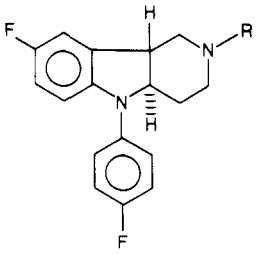
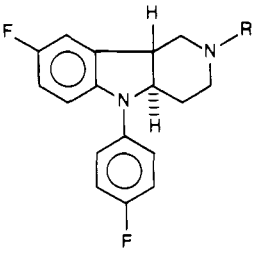
Table I. Neuroleptic Activity of Nitrogen-Containing Side Chains



compd	R	mp, °C	formula[a]	antag of amphetamine (rat): ED_{50},[b] mg/kg ip 1 h	5 h	24 h	inhibn of [^{3}H]-spiroperidol binding: IC_{50},[c] nM
1	$CH_2CH_2CH_2CN$	245–249	$C_{21}H_{21}N_3F_2$·HCl	0.1–0.32	0.45	5.6	
2	$CH_2CH_2CH_2CH_2NH_2$	224–227	$C_{21}H_{25}N_3F_2$·2HCl	17.7	7.22	17.7	28
3	$CH_2CH_2CH_2CH_2NHCOCH_3$	245–248	$C_{23}H_{27}ON_3F_2$·HCl	0.02	0.006	0.66	15
I				0.03	0.009	~1.0	7.4
(±)-butaclamol				0.38	0.37	>3.2	12
chloropromazine				5.3	8.5	>32	51

[a] All compounds were analyzed for C, H, and N; values were within ± 0.4% of calculated values. [b] The effects of each compound on prominent amphetamine-elicited symptoms were studied in rats by using the rating scale and method reported by Weissman et al.[8] Groups of five rats were treated with compounds at doses separated by 0.5 log unit (i.e., ..., 0.32, 1.0, 3.2, 10, ... mg/kg) and were then treated with *d*-amphetamine sulfate, 5 mg/kg ip, 1, 5, and 24 h later. ED_{50} values were determined from the tables of Weil.[9] [c] [^{3}H]Spiroperidol binding to rat striatal membranes using 0.5 nM ligand was performed by the method of Burt et al.[6] IC_{50} values were determined graphically from four drug concentrations separated by 0.5 log unit. Entries are means of two to three determinations.

Table II. Effect of Side-Chain Length on Neuroleptic Activity



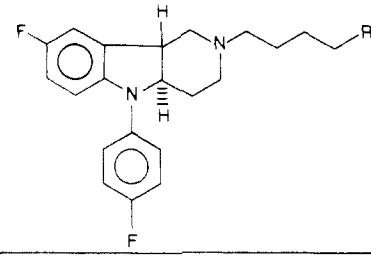
compd	R	mp, °C	formula[a]	antag of amphetamine (rat): ED_{50},[b] mg/kg ip 1 h	5 h	24 h	inhibn of [^{3}H]-spiroperidol binding: IC_{50},[c] nM
4	$(CH_2)_2NHCOCH_3$	229–233	$C_{21}H_{23}ON_3F_2$·HCl	0.11	0.36	>1.0	16
5	$(CH_2)_3NHCOCH_3$	224–227	$C_{22}H_{25}ON_3F_2$·HCl	0.03–0.1	0.03	0.32–1.0	10
3	$(CH_2)_4NHCOCH_3$	245–248	$C_{23}H_{27}ON_3F_2$·HCl	0.02	0.006	0.66	15
6	$(CH_2)_5NHCOCH_3$	237–240	$C_{24}H_{29}ON_3F_2$·HCl	0.01	0.004	0.04	9
7	$(CH_2)_6NHCOCH_3$	204–208	$C_{25}H_{31}ON_3F_2$·HCl	0.02	0.002	0.03	8
8	$(CH_2)_7NHCOCH_3$	217–221	$C_{26}H_{33}ON_3F_2$·HCl	0.09	0.02	0.05	9
I				0.03	0.009	~1.0	7.4
(±)-butaclamol				0.38	0.37	>3.2	12
chlorpromazine				5.3	8.5	>32	51

[a] All compounds were analyzed for C, H, and N; values were within ± 0.4% of calculated values. [b] The effects of each compound on prominent amphetamine-elicited symptoms were studied in rats by using the rating scale and methods reported by Weissman et al.[8] Groups of five rats were treated with compounds at doses separated by 0.5 log unit (i.e., ..., 0.32, 1.0, 3.2, 10, ... mg/kg) and were then treated with *d*-amphetamine sulfate, 5 mg/kg ip, 1, 5, and 24 h later. ED_{50} values were determined from the tables of Weil.[9] [c] [^{3}H]Spiroperidol binding to rat striatal membranes using 0.5 nM ligand was performed by the method of Burt et al.[6] IC_{50} values were determined graphically from four drug concentrations separated by 0.5 log unit. Enties are means of two to three determinations.

not achieved. At the present time, there are insufficient data to determine whether the inactivity of **2** is due to rapid metabolism or to failure of the primary amine derivative to cross the blood–brain barrier. Interestingly, acetylation of the amine group yielded the acetamide **3**, which was found to be an exceedingly potent compound both in vitro and in vivo. Modification of the amino group in this way apparently makes this molecule more able to penetrate to the central nervous system where the intrinsic activity is expressed at the receptor.

Having discovered a new side chain with interesting potent in vivo and in vitro neuroleptic activity, we then developed SAR in several ways, as illustrated in Tables II and III. Table II illustrates that potency is dependent to some extent on chain length. In this homologous series, both in vitro and in vivo activity increase with chain length from the two-carbon analogue **4** to the six-carbon compound **7**. Compound **8**, with a seven-carbon side chain, is marginally less active than is **7** in vivo although it is still very potent in vitro. The remarkable in vivo potency of compound **7** (comparing 5-h activity) exceeds that of the 4-hydroxybutyl derivative I by 1 order of magnitude and suggests that an optimum combination of lipophilicity and hydrogen-bonding ability has been achieved in this compound. The relatively small activity differences between the four-carbon side chain compound **3** and the seven-

Table III. Effect of Amide Type on Neuroleptic Activity



compd	R	mp, °C	formula[b]	antag of amphetamine (rat): ED_{50},[b] mg/kg ip 1 h	5 h	24 h	inhibn of [^{3}H]-spiroperidol binding: IC_{50},[c] nM
9	$H_2NCOCH_2CH_3$	amorph	$C_{24}H_{29}O_2N_3F_2 \cdot HCl$	0.05	0.02	>0.32	11
10	$HNCC_6H_5$	259–262	$C_{28}H_{29}ON_3F_2 \cdot HCl$	0.28	0.02	0.57	19
11		197–199	$C_{24}H_{27}O_2N_3F_2 \cdot HCl$	0.06	0.008	0.06	10
12		amorph	$C_{26}H_{31}ON_3F_2 \cdot HCl$	0.02	0.1–0.032	0.06	6.2
13	$HNSO_2C_6H_4CH_3$	amorph	$C_{28}H_{31}O_2N_3F_2S \cdot HCl$	>1.0	>1.0	NT	27
14		230–233	$C_{28}H_{27}O_2N_3F_2 \cdot HCl$	>1.0	0.32–1.0	3.2	28
15		169–171	$C_{29}H_{27}O_2N_3F_2 \cdot HCl$	3.6	1.1	0.57	27
I				0.03	0.009	~1.0	7.4
(±)-butaclamol				0.38	0.37	>3.2	12
chlorpromazine				5.3	8.5	>32	51

[a] All compounds were analyzed for C, H, and N; values were within ± 0.4% of calculated values. [b] The effects of each compound on prominent amphetamine-elicited symptoms were studied in rats by using the rating scale and method reported by Weissman et al.[8] Groups of five rats were treated with compounds at doses separated by 0.5 log unit (i.e., ..., 0.32, 1.0, 3.2, 10, ... mg/kg) and were then treated with *d*-amphetamine sulfate, 5 mg/kg ip, 1, 5, and 24 h later. ED_{50} values were determined from the tables of Weil.[9] [c] [^{3}H]Spiroperidol binding to rat striatal membranes using 0.5 nM ligand was performed by the method of Burt et al.[6] IC_{50} values were determined graphically from four drug concentrations separated by 0.5 log unit. Entries are means of two to three determinations.

carbon side chain compound **8** in both the in vivo and in vitro screens suggest that the distance between the basic nitrogen atom and the DA receptor auxiliary binding site must be the approximate length of a four-carbon bridge, the three-carbon bridge being too short and the six being able to fold upon itself to fit the distance parameter. A seven-carbon chain (compound **8**) is less active in vivo (but not in vitro) and suggests that, beyond a certain point, lipophilicity of the molecule becomes detrimental to transport of the molecule into the CNS. The extreme potency of these compounds supports arguments for an interaction of the amido hydrogen-bonding moiety in these molecules with an auxiliary site corresponding to that suggested by Humber et al.[3] on or near the DA receptor. These results demonstrate that a hydrogen-bonding site must be present in addition to, or instead of, a lipophilic site since none of the present compounds possess very lipophilic (i.e., *tert*-butyl) or aromatic (i.e., phenyl)pharmacophores within their structures.

A study of the effect of amide type is presented in Table III. In this table, it will be noted that the amide type has little effect on in vitro activity but that significant differences between derivatives with respect to distribution are seen. Thus, the urethane derivatives **9** and **11**, the benzamide **10**, and the piperidone **12** are potently active in vivo as well as in vitro, but the activity profiles of the more delocalized tosylamide **13**, the benzoxazolinone **14**, and the phthalimide **15** are more similar to that of the amine **2** in that they are active in vitro but lose substantial activity in the in vivo model. This result again suggests that these latter three compounds, like **2**, are not transported well into the CNS. That the tertiary amides **11** and **12** retain potent in vitro and in vivo activity demonstrates that a free amide proton is not necessary for interaction with the auxiliary receptor site and provides support for our previous observation that this auxiliary receptor site is hydrogen-bond accepting, rather than donating.[2]

Many compounds in the 4-hydroxy-4-(substituted aryl)butyl series from the preceding paper[2] appear to have been successfully protected from rapid metabolism by a suitable choice of substituents, as is illustrated by their unchanged potency in vivo at 5- and 24-h test points. The amidoalkyl derivatives appear to be more susceptible to metabolic elimination, since activity at the 24-h point was reduced to $^1/_5$–$^1/_{20}$ of the 5-h values in all compounds. This finding suggests that hydrolysis and/or conjugative elimination of these compounds, while not particularly facile, is an ongoing process in vivo.

In conclusion, we have discovered that substitution of position 2 of the 4a,9b-*trans*-2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4,3-*b*]indole nucleus with ω-carboxamidoalkyl substituents led to compounds with exceedingly potent neuroleptic activity in vitro and in vivo models. The potent activity of these compounds suggests that a hydrogen-bond accepting moiety is a critical element of the auxiliary binding site of the DA receptor in addition to or instead of lipophilic binding site in the same region.

Experimental Section

Melting points (uncorrected) were taken with a Thomas-Hoover capillary apparatus. NMR spectra were recorded on Varian T-60 and XL-100 spectrometers with Me_4Si as an internal standard. IR spectra were determined with a Perkin-Elmer Model 21 spectrometer. Mass spectra were obtained with a Perkin-Elmer RMU-6E mass spectrometer. Microanalyses were performed by the Pfizer Analytical Department.

***trans*-(±)-2-(3-Cyanopropyl)-8-fluoro-5-(4-fluorophenyl)-2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4,3-*b*]indole Hydrochloride (1).** A suspension of 8.7 g (30.4 mmol) of

(±)-4a,9b-*trans*-8-fluoro-5-(4-fluorophenyl)-2,3,4,4a,5,9a-hexahydro-1*H*-pyrido[4,3-*b*]indole, 8.5 g (42.5 mmol) of 4-bromobutyronitrile, 19.1 g (182 mmol) of anhydrous Na_2CO_3, and 100 mg of KI in 100 mL of methyl isobutyl ketone was heated at 70 °C overnight. The cooled reaction mixture was poured into 200 mL of water, and the resulting mixture was extracted twice with 200-mL portions of $CHCl_3$. The combined organic extracts were dried over $MgSO_4$ and evaporated to a yellow oil. This oil was dissolved in acetone, and a solution of HCl(g) in acetone was added, precipitating a white solid. This solid was separated by filtration and washed well with acetone to give 8.5 g (72%) of the desired product, mp 245-249 °C.

***trans*-(±)-2-(4-Aminobutyl)-8-fluoro-5-(4-fluorophenyl)-2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4,3-*b*]indole Dihydrochloride (2).** A 1.82-g (48-mmol) portion of lithum aluminum hydride (LAH) was stirred under N_2 while 8.5 g (21.8 mmol) of compound 1 was added portionwise over a 1-h period. The resulting reaction mixture was allowed to stir at room temperature for 1 h. An excess of Glauber's salt was added carefully and stirred until the excess LAH had decomposed, and then the salts were filtered off and washed with dry ether. A solution of HCl(g) in ether was added, and the solid that precipitated was collected by filtration and dried to give 706 mg (90%) of the desired product, mp 224-227 °C.

***trans*-(±)-2-(4-Acetamidobutyl)-8-fluoro-5-(4-fluorophenyl)-2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4,3-*b*]indole Hydrochloride (3).** A suspension of 315 mg (0.8 mmol) of compound 2 in 10 mL of CH_2Cl_2 was stirred with 0.44 mL (32.1 mmol) of triethylamine to give a pale yellow solution. To this was added, under N_2, 0.063 mL (0.88 mmol) of acetyl chloride in 5 mL of CH_2Cl_2. This solution was allowed to stir at ambient temperature for 2 h and was then poured into 20 mL of saturated $NaHCO_3$ solution. The product was extracted into CH_2Cl_2, and the extracts were dried over $MgSO_4$ and evaporated. The residual yellow gum was dissolved in ether and treated with a saturated solution of HCl(g) in ether. A gummy tan solid precipitated. The solvent was evaporated, and the residual solid was slurried with acetone to give a white crystalline solid in 82% yield. An analytical sample was crystallized from hot acetonitrile, mp 245-248 °C.

***trans*-(±)-8-Fluoro-5-(4-fluorophenyl)-2,3,4,4a,5,9b-hexahydro-2-[4-(2-oxo-3-oxazolidinyl)butyl]-1*H*-pyrido[4,3-*b*]indole Hydrochloride (11).** A suspension of 1 g (3.49 mmol) of *trans*-(±)-8-fluoro-5-(4-fluorophenyl)-2,3,4,4a,5,9b-hexahydropyrido[4,3-*b*]indole, 0.93 g (5.23 mmol) of 3-(4-chlorobutyl)oxazolidin-2-one, 1.46 g (14 mmol) of anhydrous Na_2CO_3, and a trace of KI in 50 mL of methyl isobutyl ketone was heated at 95 °C overnight. A second 0.93 g (5.73 mmol) of oxazolidinone was added, and the reaction was heated a further 24 h at 95 °c. The solvent was then evaporated in vacuo, and the residues were partitioned between 100 mL of CH_2Cl_2 and 100 mL of H_2O. The aqueous layer was extracted with a second 100-mL portion of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and evaporated to a yellow gum, which was dissolved in 30 mL of 2:1 2-propanol/acetone. An ethereal solution of HCl(g) was added, and a white crystalline product separated. This was filtered off to give the desired product: 1.1 g (74%); mp 197-199 °C.

Registry No. (±)-1, 77378-64-4; (±)-1·HCl, 77378-79-1; (±)-2, 98651-79-7; (±)-2·HCl, 103422-28-2; (±)-3, 77378-66-6; (±)-3·HCl, 77378-81-5; (±)-4, 103422-29-3; (±)-4·HCl, 77378-69-9; (±)-5, 103422-30-6; (±)-5·HCl, 77400-06-7; (±)-6, 103422-31-7; (±)-6·HCl, 77400-07-8; (±)-7, 103422-32-8; (±)-7·HCl, 77378-70-2; (±)-8, 103422-33-9; (±)-8·HCl, 77378-71-3; (±)-9, 103422-34-0; (±)-9·HCl, 77378-75-7; (±)-10, 103422-35-1; (±)-10·HCl, 77378-74-6; (±)-11, 103422-36-2; (±)-11·HCl, 83502-51-6; (±)-12, 103437-39-4; (±)-12·HCl, 83502-34-5; (±)-13, 103422-37-3; (±)-13·HCl, 77378-77-9; (±)-14, 103422-38-4; (±)-14·HCl, 83502-53-8; (±)-15, 103422-39-5; (±)-15·HCl, 83514-69-6; $Br(CH_2)_4CN$, 5332-06-9; (±)-4a,9b-*trans*-8-fluoro-5-(4-fluorophenyl)-2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4.3-*b*]indole, 69623-07-0; 3-(4-chlorobutyl)oxazolidin-2-one, 15026-71-8.

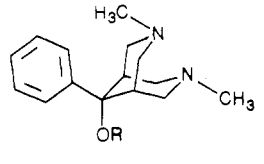
3,7-Diazabicyclane: A New Narcotic Analgesic

Paul S. Salva,*† Gilbert J. Hite,† Richard A. Heyman,‡ and Gerald Gianutsos‡

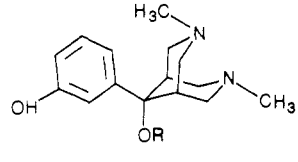
Sections of Medicinal Chemistry and Pharmacology, School of Pharmacy, The University of Connecticut, Storrs, Connecticut 06268. *Received January 21, 1986*

The synthesis of a series of 9-phenyl-3,7-diazabicyclanes and 9-(*m*-hydroxyphenyl)-3,7-diazabicylanes is described. Members of both series were tested for antinociception in rat tail withdrawal and mouse acetic acid writhing assays. Their affinities for opiate receptors in rat brain homogenate were also determined. The 9-phenyl compounds, **1a-c**, were inactive. However, the 9-(*m*-hydroxyphenyl) analogues, **2a-c**, were found to possess significant activity in the writhing assay, comparable to that of morphine. All activity was reversed by naloxone.

In 1976, the 3,7-dimethyl-9-phenyl-3,7-diazabicyclo[3.3.1]nonane compounds **1a-c** were reported to be devoid of antinociceptive activity in the Haffner tail clamp test at doses of up to 100 mg/kg po.[1] However, this diazabicyclane structure continues to appear in the literature as a model to explain the different activity profiles of narcotic analgesics that have their aromatic rings in a phenyl-equatorial rather than a phenyl-axial orientation.[2-6] In this model, the aromatic ring is considered to be the most important element for binding to the narcotic receptor. Acting as the anchor, it determines the orientation of the rest of the molecule at the receptor. The protonated nitrogens can still interact with a common anionic site, albeit from different directions, but their alkyl substituents would be projected to very different areas of the receptor. This model can also explain why N-allyl and similar groups induce opiate antagonist activity in phenyl-axial opiates but not phenyl-equatorial opiates.[7-9] If this model is valid,



1a-c



2a-c

* Address correspondence to this author at the Department of Anesthesiology, Texas Tech University Health Sciences Center, Lubbock, TX 79430.

† Section of Medicinal Chemistry.

‡ Section of Pharmacology.

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