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Supplementary Material Available: Spectral and analytical data for products **4–8**, **15–17**, **20**, **21**, **24**, and **25** (4 pages). Ordering information is given on any current masthead page.

Synthesis and Biological Evaluation of Poly-γ-glutamyl Metabolites of 10-Deazaaminopterin and 10-Ethyl-10-deazaaminopterin

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The chemical synthesis of a series of poly-γ-glutamyl metabolites of the experimental anticancer drugs 10-deazaaminopterin (10-DAAM) and 10-ethyl-10-deazaaminopterin (10-EDAAM) has been carried out by the solid-phase procedure. The synthetic products were identical with the poly-γ-glutamyl metabolites of radiolabeled 10-DAAM and 10-EDAAM produced by normal mouse tissues with regard to elution volume from [(diethylamino)ethyl]cellulose columns and susceptibility to hydrolysis by human plasma folylpolyglutamate hydrolase. Poly-γ-glutamyl metabolites with a glutamate chain length of up to four glutamate residues were detected in the tissues. The antifolate activity was evaluated with methotrexate (MTX) sensitive and MTX-resistant strains of *Lactobacillus casei* and *Streptococcus faecium*. In general, inhibitory potency decreases with increasing Glu chain length. However there are two exceptions. Addition of one Glu residue to 10-DAAM enhances its potency for MTX-resistant *L. casei* and addition of one Glu residue to 10-EDAAM enhances its potency for the MTX-sensitive *L. casei*. As shown earlier for MTX polyglutamates, polyglutamylation greatly enhances the inhibitory potency of 10-DAAM and 10-EDAAM for *L. casei* thymidylate synthase. MTX polyglutamates are 15–30 times more inhibitory than the corresponding 10-DAAM derivatives and 30–60 times more inhibitory than the corresponding 10-EDAAM derivatives. Polyglutamylation of 10-DAAM had little influence on its ability to inhibit *L. casei* dihydrofolate reductase; however, with 10-EDAAM, addition of one or two Glu residues enhanced its inhibitory potency 2.3-fold.

The coenzyme forms of folic acid exist in tissues as poly-γ-glutamyl derivatives.[1,2] In many folate-mediated enzymatic reactions, the polyglutamyl derivatives are preferred substrates.[1-3] Like folate, the well-known anticancer drug methotrexate (MTX) is metabolized to polyglutamyl derivatives in human red blood cells,[3,4] various animal tissues,[2-6] and tumors.[6,7] The chemical synthesis and preliminary biological evaluation of the polyglutamyl metabolites of MTX were reported from this laboratory in 1973.[5] MTX polyglutamates are relevant to cancer chemotherapy because: (1) their formation is related to cytotoxicity,[6,7] (2) they efflux from cells at a slower rate than MTX,[9] and (3) they are more inhibitory to thymidylate synthase[8,9] and AICAR transformylase[10,11] than the parent drug. The poly-γ-glutamyl derivatives of the antileukemic agent N^{10}-propargyl-5,8-dideazafolic acid (PDDF) were recently synthesized in this laboratory.[12] They were shown to be the most potent antifolate inhibitors of *Lactobacillus casei*,[12] L1210,[12] and human thymidylate synthase[13,14] yet described. Two analogues of aminopterin, 10-deazaaminopterin (10-DAAM) and 10-ethyl-10-deazaaminopterin (10-EDAAM),[15-19] exhibit superior antitumor activity compared to MTX in several murine tumor models. 10-EDAAM is presently undergoing advanced clinical trial at Memorial Sloan-Kettering Cancer Center. Quite recently, the polyglutamyl derivatives of both 10-DAAM and 10-EDAAM that were synthesized according to the procedures described in this paper (vide infra) were utilized to evaluate their inhibition of human thymidylate synthase.[20] In a related study, the synthetic polyglutamyl derivatives of MTX and 10-DAAM were tested as inhibitors of dihydrofolate reductase (DHFR) derived from sheep, chicken, and beef liver.[21] In this context, it was of interest to compare these synthetic compounds with the

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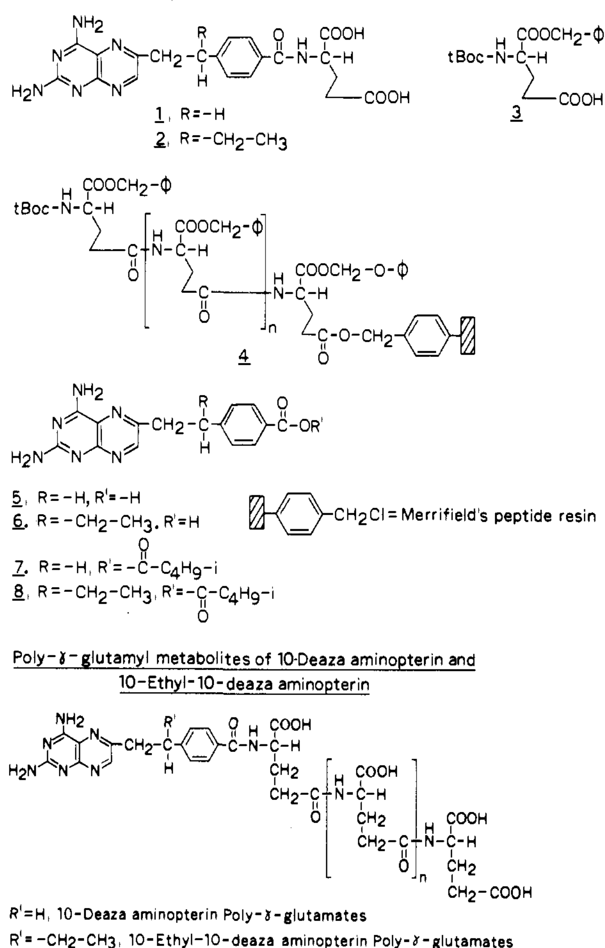

Figure 1.

natural metabolites formed in normal mammalian tissues and to evaluate their antifolate activities. As part of a continuing program aimed at the development of antifolate drugs,[22] this paper details the chemical synthesis and evaluation of antifolate activity of the poly-γ-glutamyl metabolites of 10-DAAM and 10-EDAAM.

Chemistry

10-DAAM (1) and 10-EDAAM (2), labeled uniformly with ^{14}C at the glutamate moiety, were synthesized as described.[23] Starting from Merrifield chloromethyl peptide resin and *tert*-Boc-L-glutamic acid α-benzyl ester (**3**), a series of resin-bound *tert*-Boc-L-glutamyl-γ-(L-glutamyl)$_n$-γ-L-glutamyl-α-benzyl esters (**4**) with varying glutamate chain lengths were prepared.[12] 4-Amino-4-deoxy-10-deazapteroic acid (**5**) and 4-amino-4-deoxy-10-ethyl-10-deazapteroic acid (**6**) were prepared by procedures previously developed in this laboratory.[16] Pteroic acids **5** and **6** were converted to their corresponding mixed anhydrides **7** an **8** (Figure 1) by treatment with isobutyl chloroformate in the presence of 4-methylmorpholine. Treatment of the poly-L-glutamyl peptide resin **4** with 20% TFA in CH_2Cl_2 permitted the selective removal of the *tert*-butoxycarboxyl protective group without affecting the α-benzyl esters. The deprotected resin was reacted with the mixed anhydride **7** or **8**. The resin-bound polyglutamyl derivatives of 10-DAAM and 10-EDAAM were treated with a 1:1 mixture of *p*-dioxane and 2 N NaOH to cleave the product from the resin and simultaneously deprotect the α-carboxyl groups. The crude polyglutamyl derivatives were purified by DEAE-cellulose chromatography and stored as ammonium salts in water. As observed with the polyglutamyl metabolites of folates and other antifolates, these compounds elute serially from DEAE-cellulose, and their elution volumes were directly related to the number of glutamyl residues.

Table I. Inhibition of Bacterial Growth by Antifolyl Polyglutamates

	IC_{50}, nM		
total Glu residues	MTX	10-DAAM	10-EDAAM
(A) *Lactobacillus casei* (ATCC 7469)			
1[a]	0.03	0.08	0.63
2	0.09	0.09	0.16
3	0.20	0.60	1.00
4	0.80	3.00	9.00
5	2.20	14.00	90.00
6	27.00	90.00	
(B) *Streptococcus faecium* (ATCC 8043)			
1[a]	0.85	0.75	7.00
2	3.40	7.20	67.00
3	560.00	560.00	1800.00
4	2600.00	930.00	9400.00
5	1200.00	980.00	10400.00
6	>8000	>3000	

[a] Parent compound.

Results and Discussion

The chemical structures of the polyglutamyl metabolites of 10-DAAM and 10-EDAAM used in this study are shown in Figure 1. The biochemical and pharmacological properties of these derivatives described in this paper and elsewhere[20,21] were determined with these synthetic samples. Therefore, it was of importance to establish that the synthetic products are structurally identical with the natural metabolites. It has been shown previously that racemization of the glutamate moieties of the polyglutamates does not occur during the solid phase synthetic sequence described here.[5,24] Human plasma conjugase (folylpolyglutamate hydrolase, FPGH) is specific for the cleavage of the γ peptide bonds of pteroyl polyglutamates and analogues.[4,5] All the synthetic polyglutamates of the two 10-deazaaminopterins were completely hydrolyzed to their parent compounds by FPGH. The susceptibility of our synthetic polyglutamates and the radiolabeled metabolites of both 10-DAAM or 10-EDAAM to FPGH established that the synthetic and natural derivatives possess the γ-glutamyl peptide linkages. Furthermore, the chain length of each radiolabeled natural metabolite was established by cochromatography with the synthetic derivative of identical glutamate chain length. Confirmation of the chain length of each synthetic derivatives used as standard was further obtained independently by FAB mass spec-

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trometry. These results clearly established the identity and authenticity of the synthetic samples with the natural radiolabeled metabolites. It should be pointed out, however, that unlike 10-DAAM the synthetic polyglutamyl derivatives of 10-EDAAM were mixtures of two diastereomers, due to the asymmetry introduced by the ethyl group at the 10-position. It is quite possible that the natural polyglutamyl metabolites of 10-EDAAM may be asymmetrically enriched due to uneven substrate specificity of the individual enantiomers to folylpolyglutamate synthetase (FPGS). These enantiomers differ by a factor of 3 in their ability to inhibit DHFR derived from L1210 cells.[27]

The folate requiring microorganisms *L. casei* (ATCC 7469) and *Streptococcus faecium* (ATCC 8043) and two folate-dependent enzymes, dihydrofolate reductase (DHFR) and thymidylate synthase (TS) derived from *L. casei*, were used in the biological evaluations. The results in Table I show the effects of polyglutamylation on the growth inhibitory potency of MTX, 10-DAAM, and 10-EDAAM against *L. casei*. With MTX and 10-DAAM, inhibition diminishes progressively with increasing glutamylation, the hexaglutamate forms being 0.1% as active as the respective monoglutamate forms. These results are similar to those obtained for the transport of folylpolyglutamates by *L. casei*.[25] It is likely, therefore, that the diminished inhibitory potency of MTX and 10-DAAM with increasing glutamate chain length is due to diminished transport. The 10-EDAAM series contains a striking exception to the pattern obtained with MTX and 10-DAAM in that the derivative with two glutamate residues is the most potent inhibitor. Similar exceptional behavior has been observed with polyglutamyl derivatives of 5,8-dideaza-10-propargylfolate where the derivative with two glutamate residues was again the most inhibitory compound of the series.[12] A likely explanation for the exceptional growth inhibitory potency of the diglutamate forms in the two series mentioned is that, although they are probably transported more poorly than the monoglutamate forms, this effect is offset by their enhanced inhibitory potential toward TS.

Polyglutamylation generally decreased the inhibitory potency of MTX, 10-DAAM, and 10-EDAAM for the growth of *S. faecium* (Table I). However, the 10-DAAM derivatives having a total of four and five glutamate residues are almost equipotent, and in the MTX series, the corresponding pentaglutamate derivative is actually more potent than the tetraglutamate derivative.

The polyglutamyl derivatives of MTX, 10-DAAM, and 10-EDAAM listed in Table I were also tested for their ability to inhibit the growth of an MTX-resistant strain of *L. casei* (IC_{50} for MTX >1 mM). The only compound showing inhibitory activity was the derivative of 10-DAAM having two glutamate residues. It had an IC_{50} of 2 μM. All of the other compounds had IC_{50} values greater than 6 μM.[26]

The inhibitory activity of the polyglutamyl derivatives of MTX, 10-DAAM, and 10-EDAAM for *L. casei* DHFR is shown in Table II. The IC_{50} values range from 9 to 34 nM. The greatest differential in inhibitory potency is seen in the 10-EDAAM series where the derivatives having two and three glutamate residues are more than three times as potent as the derivatives having four and five glutamate residues. These results show that the polyglutamate chain length can influence the ability of antifolates to inhibit DHFR. This has also been reported to be the case for mammalian DHFR.[21]

The inhibitory activity of the polyglutamyl derivatives of MTX, 10-DAAM, and 10-EDAAM for *L. casei* TS is shown in Table II. As shown earlier for MTX polyglutamates,[8] polyglutamylation enhances inhibitory potency. The relative increments in potency caused by polyglutamylation are similar for all three antifolates. For example, the derivatives with five glutamate residues are about 25 times more potent than the derivatives with two glutamate residues in each case. MTX derivatives are 10–30 times more inhibitory than the corresponding 10-DAAM derivatives and 25–78 times more inhibitory than the corresponding 10-EDAAM derivatives. Similar results were obtained with TS derived from human acute myeloblastic leukemia cells[20] where 10-DAAM derivatives were 10–20-fold more potent than the corresponding 10-EDAAM derivatives.

Table II. Inhibition of *Lactobacillus casei* Enzymes by Antifolyl Polyglutamates

total Glu residues	MTX	10-DAAM	10-EDAAM
	IC_{50}, nM		
	(A) dihydrofolate reductase		
1[a]	16.0	18.0	21.0
2	26.0	24.0	9.0
3	16.0	22.0	9.0
4	15.0	20.0	30.0
5	15.0	21.0	34.0
6	16.0	34.0	
	IC_{50}, μM		
	(B) Thymidylate synthase		
1[a]	100.00	>300	>300
2	6.00	88.0	170.0
3	1.10	11.0	28.0
4	0.18	5.5	14.0
5	0.28	3.5	7.4
6	0.28	2.3	

[a] Parent compound.

Experimental Section

All organic solvents were dried over type 3A molecular sieves before use. Isobutyl chloroformate was freshly distilled and stored over $CaCO_3$. Triethylamine and *N*-methylmorpholine were purchased from Aldrich and redistilled prior to use. Ultraviolet spectra were run on a Bausch and Lomb Spectronic Model 2000 spectrophotometer interfaced with a Commodore Superpet computer. Melting points were determined on a Fisher Model 355 digital melting point analyzer. Ion-exchange chromatography was carried out with DEAE-cellulose in the chloride form. The compounds were eluted from the column with a linear NaCl gradient in 0.005 M phosphate buffer at pH 7.0. All HPLC analyses were done on a Waters 6000 A instrument equipped with a Model 660 solvent programmer and U6K injector. Mass spectral analyses were carried out by Dr. Susan Weintraub, Department of Pathology, University of Texas.

Poly-γ-glutamyl Derivatives of 10-Deazaaminopterin and 10-Ethyl-10-deazaaminopterin. The 4-aminopteroic acid analogues **5** and **6** were available in this laboratory.[15] A series of resin-bound *N*-Boc-poly-γ-glutamic acid α-benzyl esters with the desired number of glutamate residues were prepared as described previously.[12] These intermediates are represented by the general structure 4 (Figure 1). The protected resin-bound polyglutamates (~3 g) were selectively deprotected at the α-amino group by treatment with a 25% solution of TFA in CH_2Cl_2 (60 mL) for 30 min. The deprotected resin-bound product was neutralized with a 10% solution of triethylamine in CH_2Cl_2 (30 mL) for 10 min and washed three times with 30-mL portions of CH_2Cl_2.

The mixed anhydrides of the pteroic acids **5** and **6** were made as follows: A solution of 1 mmol of either pteroic acid was made

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Table III

compound	% yield	t_R,[b] min	UV max,[a] nm	molecular ion $(MH)^+$
10-DAAM ($+G_1$)	27.2	12.15	369.2, 254.7	569
10-DAAM ($+G_2$)	25.8	10.18	369.8, 254.8	698
10-DAAm ($+G_3$)	24.7	9.30	371.0, 254.0	827
10-DAAM ($+G_4$)	23.0	8.25	372.0, 256.0	956
10-DAAM ($+G_5$)	22.0	7.00	372.2, 256.0	1085
10-EDAAM ($+G_1$)	31.0	18.00	370.3, 254.3	597
10-EDAAM ($+G_2$)	28.0	16.00	369.9, 254.4	726
10-EDAAM ($+G_3$)	26.0	14.00	367.8, 252.8	855
10-EDAAM ($+G_4$)	22.0	13.00	368.0, 253.2	984

[a] An ϵ value of 33 000 for 10-DAAM polyglutamates and 31 000 for 10-EDAAM polyglutamates at 254 nm (in 0.1 N NaOH) was used for the spectral quantitation of each product. [b] HPLC analyses were carried out on a Waters C18 μ Bondapak radially compressed cartridge. The compounds were injected as their ammonium salt in distilled water and eluted at 1 mL/min with a 20-min linear gradient from 5% to 25% acetonitrile in 0.1 M sodium acetate at pH 5.1.

in 30 mL of Me_2SO. An equal volume of dry THF was added to the pteroic acid solution, and the mixture was placed in an ice bath. After 15 min, 0.14 mL (1.25 mmol) of *N*-methylmorpholine followed by 0.13 mL (1.0 mmol) of isobutyl chloroformate was added, mixed, and kept at 25 °C for 30 min to complete the reaction. The mixed anhydride solution thus obtained was allowed to react with the deprotected resin-bound polyglutamates 4 (n = 0–4) for 18 h at room temperature and filtered. The resin was washed successively with Me_2SO, DMF, ethanol, and water (30 mL each), and the product was cleaved from the resin by shaking with a 1:1 mixture of 2 N NaOH and *p*-dioxane (20 mL) for 1.25 h. The product was filtered, and the filtrate was immediately diluted to 200 mL with distilled water. The pH of the solution was lowered to 7.3 with 1 N HCl, and the resultant solution was applied on a DEAE-cellulose column and eluted with a linear NaCl gradient from 0 to 0.45 M in 0.005 M phosphate buffer at pH 7.0. A major UV-absorbing peak corresponding to the desired poly-γ-glutamate was obtained in each case. The column effluents corresponding to the major peak were pooled, diluted 10-fold with distilled water, and reapplied on another DEAE-cellulose column (3 × 28 cm). After application of the sample, the column was washed with distilled water and the product eluted with a 10% solution of NH_4OH. The NH_4OH eluate was evaporated to a small volume at reduced pressure, and each product was quantitated spectrophotometrically.

The polyglutamyl derivatives of both 10-DAAM and 10-EDAAM were separated as expected on a DEAE-cellulose column, and the NaCl concentration at which each compound was eluted was dependent on the number of glutamate residues. On HPLC analyses, all of these synthetic metabolites exhibited a purity of >95%. The polyglutamates were stored frozen as their respective ammonium salts. The percentage yield of the various products based on the pteroic acid used, the retention time of each metabolite on the C18 μ Bondapak cartridge used for HPLC analyses, the ultraviolet spectral data of all polyglutamyl derivatives, and the molecular weight of each metabolite determined by FAB mass spectrometry are summarized in Table III.

Isolation and Characterization of the Polyglutamyl Metabolites of 10-DAAM and 10-EDAAM. A group of six adult B6D2F1 female mice (20 + 2 g) were injected intraperitoneally each with a single dose of 10 μCi of 10-DAAM, and after 4 days another similar injection was given. At 24 h after the final injection, the animals were anesthetized with ether, and the liver, spleen, kidneys, and small intestine were removed. The small intestine was cleaned, all tissues were washed in an ice-cold isotonic saline and blotted dry, and their combined weight was rapidly determined (25 g). They were next added to a mixture of 125 mL of 6 M urea and 625 mL of chloroform and homogenized in a 4-L Waring blender for about 5 min. The homogenate was then centrifuged (20 000*g*) for 45 min at room temperature. The middle layer of gelled protein was removed with a spatula, and the mixture of urea and $CHCl_3$ layers was transferred to a 1-L separatory funnel. The $CHCl_3$ layer was drawn off and did not contain any appreciable radioactivity. This layer was discarded. The urea extract, which contained almost all the radioactivity, was diluted to 4 times its volume with distilled water (500 mL) and applied on a DEAE-cellulose column. The column was washed with 100 mL of distilled water and eluted with 100 mL of 15% of NH_4OH. All the radioactivity was eluted in the NH_4OH fraction. The

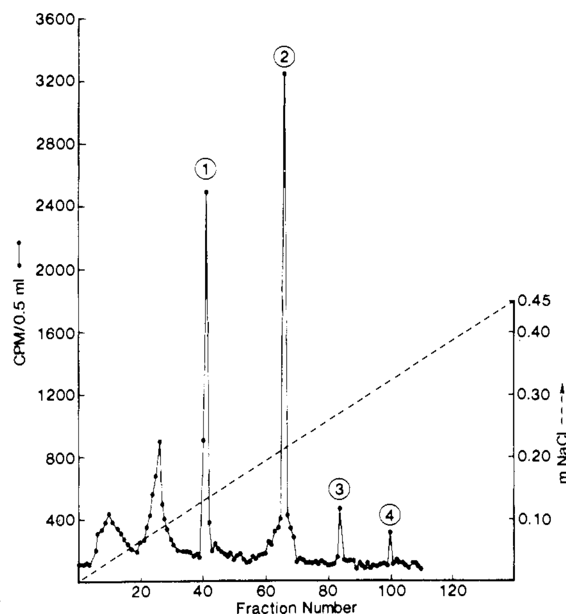

Figure 2. Elution pattern from DEAE-cellulose column of radioactive poly-γ-glutamyl derivatives of 10-DAAM. Chromatography was carried out on DEAE-cellulose in the chloride form with 1.2 × 22 cm packing. A linear gradient of 0–0.45 M NaCl in 0.005 M phosphate buffer at pH 7.0 was used to elute the column. The volume of each fraction was 14.3 mL.

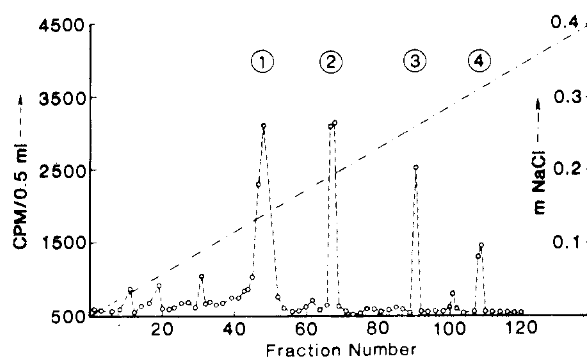

Figure 3. Total distribution of ^{14}C-10-EDAAM metabolites in the biological sample after denaturization with TCA. Chromatography was carried out as described in Figure 2, except that the gradient used was from 0 to 0.4 M NaCl. Circled members corresponding to each radioactive peak represent the number of glutamyl residues on 4-amino-4-deoxy-10-ethyl-10-deazapteroic acid (e.g., peak 1 is 10-EDAAM).

NH_4OH solution was evaporated to dryness under reduced pressure, and the residue was dissolved in 24 mL of 2% TCA. After 1 h, the turbid solution was centrifuged, and the supernatant was adjusted to pH 7.3 with 1 N NaOH. This solution was divided into two parts. One part was chromatographed on a DEAE-cellulose column with a linear NaCl gradient. The results are

shown in Figure 2. On cochromatography with authentic samples, the radioactive metabolites were characterized as 2,4-diamino-10-deazapteroyl glutamate (peak 1), (2,4-diamino-10-deazapteroyl)glutamyl-γ-glutamate (peak 2), (2,4-diamino-10-deazapteroyl)glutamyl-γ-glutamyl-γ-glutamate (peak 3), and (2,4-diamino-10-deazapteroyl)-γ-glutamyl-γ-glutamyl-γ-glutamyl-γ-glutamate (peak 4). This experiment was repeated with radiolabeled 10-EDAAM under identical conditions. The results are shown in Figure 3.

Hydrolysis of Polyglutamyl Metabolites with Human Plasma Conjugase. The plasma used in this experiment was obtained from one of the investigators (N.T.N.). The second part of the homogenate containing the radioactive metabolites of either 10-DAAM or 10-EDAAM was diluted 10 times (120 mL) with distilled water and applied on a DEAE column. The column was washed with water (200 mL). The water washings were devoid of radioactivity. The column was eluted with 50 mL of 15% NH_4OH. More than 90% of the radioactivity that was present in the original sample was eluted in this fraction. The NH_4OH eluent was evaporated to dryness in vacuum, and the residue was dissolved in 1 mL of distilled water. To this sample was added 0.05 mL of 0.1 M sodium acetate buffer (pH 4.5), and the mixture was kept at 37 °C in a water bath. After 20 min, 0.05 mL of a preparation of plasma FPGH was added, and the mixture was diluted with 0.05 mL of distilled H_2O. The mixture was incubated for 24 h at 37 °C, and 0.05 mL of 10% TCA was added to precipitate the proteins. The mixture was then diluted with 10 mL of distilled water and centrifuged for 90 min. The supernatant was decanted and diluted with 50 mL of H_2O, the pH was adjusted to 7.3 with 0.1 N NaOH, and the resultant mixture was chromatographed on a DEAE-cellulose column. More than 95% of the radioactivity was found in a single fraction, which was identified to be either [^{14}C]-10-DAAM or [^{14}C]-10-EDAAM by comparison with authentic samples.

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Molecular Structure of Fluoxetine Hydrochloride, a Highly Selective Serotonin-Uptake Inhibitor

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Fluoxetine, a selective inhibitor of serotonin uptake, is clinically useful in treating depression and may be useful for management of a variety of other psychiatric and metabolic derangements. Using X-ray crystallography, we have determined the three-dimensional structure of fluoxetine hydrochloride. A total of 2394 unique reflections were measured, and full-matrix least-squares refinement of all non-hydrogen coordinates and thermal parameters gave a final discrepancy index of 0.074 for 1759 observed reflections. In the solid state, the planes defined by the two aromatic rings are skewed, precluding the possibility of intramolecular ring–ring interactions. The methylene units of the methylpropanamine moiety adopt the anticipated conformational relationships to minimize torsional strain. An exact antiperiplanar relationship exists between N11 and C3; the N11–C1–C2–C3 dihedral angle is −180°. The C1–C2–C3–O4 dihedral angle is 60.6°, indicating that the propanamine side-chain folds toward the phenoxy moiety rather than adopting a fully extended conformation. This folded three-dimensional relationship may be necessary for high-affinity interaction with the serotonin-uptake carrier and confers considerable structural homology between this portion of fluoxetine and the phenylcyclohexylamine substructure of sertraline and EXP-561. However, the nature of substituents on the phenoxy portion of fluoxetine is also critical in determining potency and selectivity in this series of compounds.

Drugs that enhance serotonergic neurotransmission are useful or potentially useful in treating a variety of major psychiatric and metabolic derangements, including depression, eating disorders, alcoholism, pain, anxiety, and obsessive-compulsive behavior.[1] Serotonin released at synapses is actively removed from the synaptic cleft via a presynaptic serotonin transport carrier in an energy-dependent process, and this uptake is a rapid, efficient mechanism for physiological modulation of serotonin-mediated neurotransmission. Inhibitors of presynaptic reuptake augment physiological signals mediated by serotonin by increasing its availability in the synaptic cleft, thereby increasing postsynaptic receptor activation. The availability of a variety of compounds that selectively inhibit neuronal uptake of serotonin, without an effect on uptake of the catecholamines norepinephrine or dopamine, has been invaluable in elucidating the central role of serotonin in several physiological systems and pathophysiological states.[2]

One of the earliest selective inhibitors of serotonin uptake was fluoxetine (*N*-methyl-γ-[4-(trifluoromethyl)phenoxy]benzenepropanamine; Chart I).[3,4] Fluoxetine is a selective and competitive inhibitor of serotonin uptake both in vitro and ex vivo; the selectivity for the serotonin-uptake carrier vs other monoamine-uptake carriers appear to be greater than 50-fold.[3,4] Fluoxetine antagonizes the neurotoxic effects of *p*-chloroamphetamine, a com-

Table I. Crystal Data and Experimental Details for Analysis of Fluoxetine Hydrochloride

formula	$C_{17}H_{18}F_3NO{\cdot}HCl$
formula wt	345.8
space group	*Pcab*
a, Å	10.457 (2)
b, Å	10.387 (2)
c, Å	32.345 (6)
V, Å^3	3513.1 (1.4)
Z	8
d_{calcd}, g cm^{-3}	1.307
reflections measured	2394
observed reflections	1759
final *R*	0.074

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