RADIOCHEMISTRY AND RADIOPHARMACEUTICALS

1-Aminocyclobutane[^{11}C]carboxylic Acid, a Potential Tumor-Seeking Agent

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1-Aminocyclobutane[^{14}C]carboxylic acid [(C-14) ACBC] was incorporated preferentially by several tumor types in rats and hamsters. The agent was cleared rapidly from rat blood, attaining its maximum tissue concentrations within 30 min after i.v. injection. Carrier ACBC had little effect on the tissue distribution of (C-14) ACBC. This agent showed no affinity for a *Staphylococcus aureus* abscess in rats. The total excretion was low, 3.6% in 2 hr.

(C-11) ACBC was synthesized in amounts up to 415 mCi (55% chemical yield) using our modified Bücherer–Strecker technique. Forty minutes were required for the two-step synthesis and chromatographic purification. ACBC was found to be nontoxic in three animal species. The radiation dose from (C-11) ACBC should be minimal. (C-11) ACBC thus appears to have good potential as a tumor-seeking agent, particularly when used with a positron emission computed tomograph.

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The unnatural, alicyclic α-amino acid, 1-aminocyclopentanecarboxylic acid (ACPC), has been shown to inhibit tumor growth in animals (*1,2*) and has been tested as an anticancer agent in man (*3*). Autoradiographic studies with the carboxyl-labeled compound, (C-14) ACPC, showed that it concentrates selectively in tumor tissue (*4*). We have previously reported the production of multimillicurie amounts of the C-11 analog, (C-11) ACPC, along with animal studies that showed the potential of this agent for tumor scanning (*5*). Preliminary clinical results with single-photon imaging supported these observations and suggested that the diagnostic value of (C-11) ACPC might be improved through use with a positron tomograph (*6*).

We studied the tissue distribution of a series of analogs of ACPC in Buffalo rats bearing Morris 5123C hepatomas in order to determine the effect of structure on the tumor specificity of alicyclic α-amino acids (*7*). 1-Aminocyclobutane[^{14}C]carboxylic acid [(C-14) ACBC] generally gave higher tumor-to-nontumor concentration ratios than (C-14) ACPC. These differences were significant for muscle, kidney, and testis, and marginally so for blood. This led us to postulate that (C-11) ACBC might be superior to (C-11) ACPC as a tumor-scanning agent (*7*) and to undertake a more detailed preclinical investigation of this agent, which we report here.

MATERIALS AND METHODS

(C-11) ACBC was synthesized in a hot cell at Oak Ridge National Laboratory's 86-inch cyclotron complex using our rapid, high-temperature, high-pressure modification of the Bücherer–Strecker amino acid synthesis (*8*). Purification was done by anion-exchange followed by cation-exchange chromatography (*5,8*). (C-14) ACBC was prepared by the same method, using K^{14}CN* as a precursor. Stable ACBC for toxicity studies was synthesized and purified as previously described (*9*).

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The purity of the products was assessed by thin layer chromatography using silica-gel chromatogram sheets† developed in butanol:water:acetic acid (100:10:5 by volume). Chromatographic patterns were viewed either by ninhydrin development or, when $K^{14}CN$ had been added to the original reaction mixture, by use of a spark chamber‡. Elemental analysis for carbon, hydrogen, and nitrogen‖ was also performed on the stable ACBC.

The tissue distribution of (C-14) ACBC was studied in several transplanted rat and hamster tumors, obtained as follows. Morris rat hepatomas 5123C and 7777 (used at 52–59 days and ~35 days after implantation, respectively) were obtained originally from Dr. Fred Synder of Oak Ridge Associated Universities. Dr. Francis T. Kenney of Oak Ridge National Laboratory supplied cell cultures of the Reuber H-35 hepatoma, which we subsequently transformed into solid, transplantable tumors and used at ~55 days after implantation. When used, these rat hepatomas weighed 15–20 g (5–8% of the total body weight). Hamster tumors—pancreatic islet-cell adenocarcinoma 2309V and pancreatic duct adenocarcinoma 46710—were obtained from Drs. H. D. Burns and V. R. Risch of Hahnemann Medical College and Hospital of Philadelphia, and were used at 66 and 36 days after implantation, respectively. The 2309V adenocarcinoma weighed 5–7 g (3–4% of the total body weight), and the 46710 adenocarcinoma weighed ~20 g (~11% of the total body weight), of which only ~5 g (~3%) was viable tissue. The tissue distribution of (C-14) ACBC was also assessed in normal male and female Fischer 344 rats, and in male Fischer 344 rats bearing *S. aureus* abscesses (*S. aureus* No. 6339, American Type Culture Collection), which were studied at 5 days after implantation. Viable and necrotic tissues were visually distinguished for both the tumors and the abscess. Only viable tumor tissue was taken for radioassay, whereas viable and necrotic abscess tissues were assayed separately.

For tissue distribution studies, rats and hamsters were injected via the tail vein and femoral vein, respectively, with 10 μCi (C-14) ACBC/kg. All tumor-bearing animals in each comparative study were from the same transplantation group, and abscess-bearing rats were likewise from the same implantation group. For studies of the effect of carrier ACBC on tissue distribution, the appropriate amount of stable ACBC was added to the injection solution. At the desired time intervals, the animals were killed by exsanguination under light ether anesthesia. Tissue samples were weighed, dissolved in NCS tissue solubilizer§, and assayed by liquid-scintillation counting.

Rectilinear scanning of rats bearing Morris 7777 and 5123C and Reuber H-35 hepatomas was begun 30 min after i.v. administration of 1 mCi of (C-11) ACBC to each rat. An 88-hole, 5.5-in. diameter, focusing collimator with a focal length of 4 in. was used. No correction was made for radionuclide decay during the approximately 20-min scanning period.

Blood clearance and whole-body retention studies were carried out in male Fischer 344 rats injected via the tail vein with (C-14) ACBC and (C-11) ACBC, respectively. The methods used have been reported previously (*10*).

The toxicity of ACBC was studied in 6-week-old male HA/ICR mice, in adult male and female laboratory-grade beagle dogs, and in a male *Saguinus fuscicollis leucogenys* marmoset (from the marmoset colony of Oak Ridge Associated Universities). Ten mice were administered i.v. doses of 2.0 g ACBC/kg, and doses of 2.9 and 4.0 g ACBC/kg were given to one mouse each. Four dogs and one marmoset were administered 200 mg ACBC/kg. In the dog study, two baseline blood-cell studies (hemoglobin; hematocrit; platelets; RBC; total WBC; differential WBC, with RBC and WBC cytology) were made during the week before ACBC administration, along with biochemical determinations (BUN, prothrombin, SGOT, SGPT, LDH, and bilirubin). Similar studies were made on Days 1, 7, 14, and 28 after administration. In the marmoset study, one complete baseline blood-cell study was done 7 days before administration of ACBC, with repeats on Days 1, 14, 28, and 42 after administration.

RESULTS AND DISCUSSION

(C-11) ACBC was produced in amounts as great as 415 mCi using the rapid Bücherer–Strecker reaction. The chemical yield averaged 55% for the two-step synthesis and chromatographic purification, which required approximately 40 min. The specific activity of (C-11) ACBC at the completion of chromatographic purification was 2–4 Ci/mmole.

Synthesis of stable ACBC by previously reported techniques (*9*) gave white crystals having a decomposition point of 279–280°C (uncorrected). According to the literature (*9*), the decomposition point is 290 °C. Elemental analysis for carbon, hydrogen, and nitrogen gave the following results: calculated for $C_5H_9NO_2$: C, 52.16%; H, 7.88%; N, 12.17%; found: C, 52.29%; H, 7.92%; N, 12.20%.

Thin-layer chromatograms of (C-11) and (C-14) ACBC, prepared by the modified Bücherer–Strecker route, were identical to those of stable ACBC prepared by standard procedures. Single spots of identical R_f (0.17) were obtained by treatment of chromatograms of the three preparations with ninhydrin. A single spot of the same R_f value was visualized for (C-14) ACBC through use of spark chamber. No radiolytic decomposition of (C-11) ACBC has been observed.

Intravenously administered (C-14) ACBC was cleared very rapidly from rat blood (Fig. 1). (It was assumed that the blood pool comprises 7% of the total body

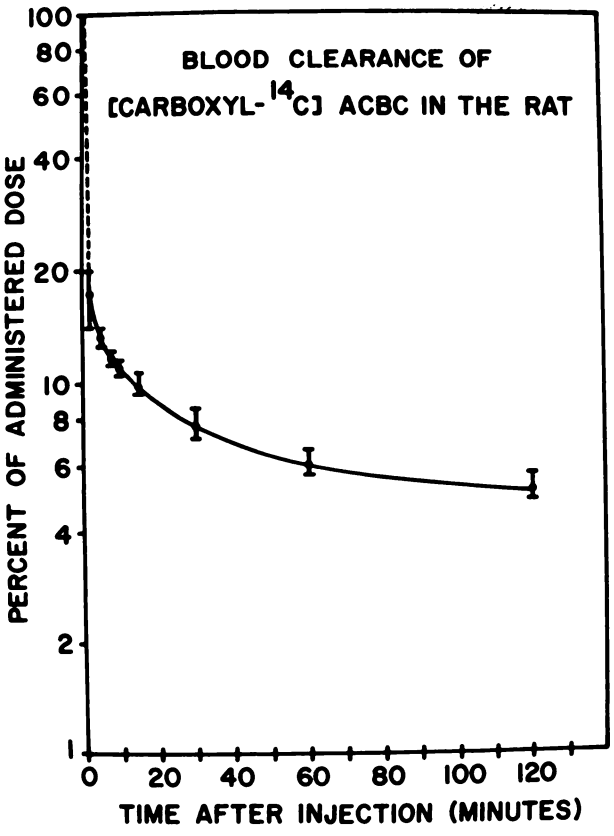

FIG. 1. Average blood clearance of intravenously administered (C-14) ACBC (containing 0.09 mg stable ACBC/kg) in four male Fischer 344 rats.

weight.) Only 10% of the administered dose remained in the blood at 15 min after injection.

The uptake by rat tissues was likewise rapid (Table 1). Both the absolute tumor concentration and the tumor-to-tissue concentration ratios were higher at 30 min than at 15 min after injection, but there were no significant differences between the 30- and 60-min values. (The significance of differences was determined using the Student's t test for small samples.) Therefore, based on the rat data, tumor scanning with (C-11) ACBC should be started at approximately 30 min after injection, which is compatible with the 20.4-min half-life of C-11.

The high pancreatic uptake of (C-14) ACBC may be largely rodent-specific, arguing from its structural similarity to (C-14) ACPC. The latter agent was incorporated quite selectively by the pancreas in rats and mice, but not in rabbits, dogs, and Rhesus monkeys (*11,12*).

The total excretion (urinary excretion plus loss by decarboxylation) for (C-11) ACBC was very low in the rat. An average of only 3.6% (2.1–5.1%) of the administered dose was excreted by 120 min after injection. This suggests that ACBC, like ACPC (*13*), may not be metabolized or incorporated appreciably into proteins, but rather taken up and retained by the tissues, then very slowly excreted in the original form.

The presence of carrier ACBC up to 5 mg/kg had little effect on the tissue distribution of (C-14) ACBC in tumor-bearing rats (Table 2). Three carrier levels were tested: 0.09, 1.0, and 5.0 mg/kg. In comparing the 0.09- and 1.0-mg/kg levels, the only significant differences observed were slight differences ($0.02 < p < 0.05$) in the absolute tumor concentrations and in the tumor-to-marrow ratios. Significant differences ($0.10 < p < 0.05$) between the 0.09- and 5.0-mg/kg levels were found for the tumor-to-marrow and tumor-to-small intestine ra-

TABLE 1. EFFECT OF TIME ON TISSUE DISTRIBUTION OF (C-14) ACBC* IN MALE BUFFALO RATS BEARING MORRIS 5123C HEPATOMAS

Tissue	15 min	30 min	60 min
	% dose/g†,‡		
Tumor	3.0 (2.4–3.6)	4.5 (3.2–5.8)	4.4 (3.9–5.0)
	Tumor-to-tissue concentration ratio†		
Liver	5.4 (3.3–6.9)	9.6 (6.7–11.1)	9.8 (5.3–12.7)
Spleen	3.4 (2.3–4.0)	7.6 (6.0–9.0)	6.9 (4.7–9.4)
Kidney	3.8 (2.6–4.4)	6.8 (6.5–7.1)	7.8 (5.6–10.1)
Lung	4.1 (2.7–5.1)	8.0 (7.5–8.6)	8.5 (6.1–12.0)
Muscle	10.4 (8.3–12.7)	16.3 (15.1–19.3)	14.5 (11.1–21.0)
Marrow	2.5 (1.8–2.9)	7.3 (5.5–8.2)	5.1 (3.1–6.7)
Blood	7.9 (7.7–8.2)	15.1 (11.9–17.9)	—
Small intestine	2.1 (1.3–2.5)	4.3 (3.9–5.0)	4.9 (4.1–6.2)
Pancreas	0.6 (0.4–0.8)	1.3 (1.1–1.4)	1.5 (1.1–2.2)

* Containing 0.09 mg stable ACBC/kg.
† Mean of four animals and range.
‡ Normalized to body weight of 250 g.

TABLE 2. EFFECT OF CARRIER ACBC ON 30-MIN TISSUE DISTRIBUTION OF (C-14) ACBC IN MALE BUFFALO RATS BEARING MORRIS 5123C HEPATOMAS

Carrier:	0.09 mg/kg	1.0 mg/kg	5.0 mg/kg
Tissue	% dose/g*,†		
Tumor	3.7 (3.0–4.0)	4.7 (4.3–5.7)	4.1 (3.6–4.5)
	Tumor-to-tissue concentration ratio*		
Liver	9.5 (8.9–10.9)	8.9 (5.6–11.0)	10.8 (8.3–14.7)
Spleen	5.8 (5.6–6.3)	6.4 (4.3–7.7)	7.3 (6.1–9.8)
Kidney	6.2 (5.8–6.4)	6.5 (4.7–7.4)	7.5 (6.0–9.8)
Lung	5.4 (3.6–6.9)	6.9 (4.3–8.9)	5.4 (3.4–7.8)
Muscle	12.7 (12.3–12.9)	17.5 (11.2–22.4)	16.6 (13.4–23.1)
Marrow	4.7 (4.5–5.1)	5.5 (4.8–6.0)	5.7 (5.2–6.7)
Blood	13.2 (12.6–14.1)	13.3 (8.3–16.1)	15.4 (12.0–21.5)
Small intestine	3.9 (3.6–4.4)	4.0 (3.1–4.9)	4.8 (4.2–5.2)
Pancreas	1.3 (1.2–1.4)	1.3 (0.9–1.6)	1.4 (1.1–2.0)

* Mean of four animals and range.
† Normalized to body weight of 250 g.

tios. There were no differences between the 1.0- and 5.0-mg/kg levels.

(C-14) ACBC was taken up preferentially by a variety of tumor types (Table 3). Of the five tumors studied, the agent was most selectively incorporated by the Morris 5123C hepatoma, followed closely by the Reuber H-35 hepatoma. The Morris 7777 hepatoma, the pancreatic islet-cell adenocarcinoma 2309V, and the pancreatic duct adenocarcinoma 46710 showed less tumor specificity. The reason for such variable uptake of (C-14) ACBC by different tumor types is unknown. Although the uptake of (C-14) ACBC by the Morris 7777 hepatoma was lower than in the other hepatomas, it was much higher than that of the analogous agent, (C-14) ACPC. The Morris 7777 hepatoma was the only one of eight tumor types studied that gave no selective uptake of (C-14) ACPC (5).

Figure 2 shows rectilinear scans of rats bearing Morris 7777 and 5123C and Reuber H-35 hepatomas. Each was started 30 min after i.v. administration of (C-11) ACBC.

TABLE 3. EFFECT OF TUMOR TYPE ON 30-MIN TISSUE DISTRIBUTION OF (C-14) ACBC*

Tissue	Morris 5123C hepatoma (rat)†	Reuber H-35 hepatoma (rat)†	Morris 7777 hepatoma (rat)‡	Pancreatic islet-cell adenocarcinoma 2309V (hamster)‡	Pancreatic duct adenocarcinoma 46710 (hamster)‡
	% dose/g‖				
Tumor	4.5 (3.2–5.8)	3.1 (2.7–3.3)	1.2 (1.2–1.4)	1.7 (1.6–1.9)	1.3 (1.3–1.4)
	Tumor-to-tissue concentration ratio				
Liver	9.6 (6.7–11.1)	6.3 (5.2–7.2)	1.7 (1.6–1.8)	2.2 (1.7–2.5)	1.7 (1.6–1.7)
Spleen	7.6 (6.0–9.0)	3.9 (3.4–4.2)	1.4 (1.2–1.6)	1.3 (1.1–1.3)	1.0 (0.8–1.1)
Kidney	6.8 (6.5–7.1)	5.1 (4.5–5.4)	1.5 (1.3–1.7)	1.0 (0.9–1.2)	0.8 (0.6–1.1)
Lung	8.0 (7.5–8.6)	5.8 (4.5–6.3)	1.5 (1.2–1.9)	1.5 (1.2–1.9)	1.4 (1.1–1.6)
Muscle	16.3 (15.1–19.3)	10.3 (9.0–11.3)	3.7 (3.5–3.9)	7.2 (5.9–8.0)	6.3 (6.0–7.0)
Marrow	7.3 (5.5–8.2)	4.2 (3.1–5.0)	1.2 (1.1–1.6)	1.3 (1.2–1.3)	0.7 (0.7–0.7)
Blood	15.1 (11.9–17.9)	11.4 (9.9–13.1)	2.6 (2.3–2.9)	2.8 (2.3–3.2)	3.0 (2.6–3.5)
Small intestine	4.3 (3.9–5.0)	3.9 (3.1–4.3)	0.9 (0.9–0.9)	2.1 (2.1–2.2)	1.5 (1.3–1.6)
Pancreas	1.3 (1.1–1.4)	0.8 (0.6–1.0)	0.3 (0.3–0.3)	0.3 (0.3–0.3)	0.3 (0.2–0.4)

* Containing 0.09 mg stable ACBC/kg.
† Mean of four animals and range.
‡ Mean of three animals and range.
‖ Normalized to body weight of 250 g.

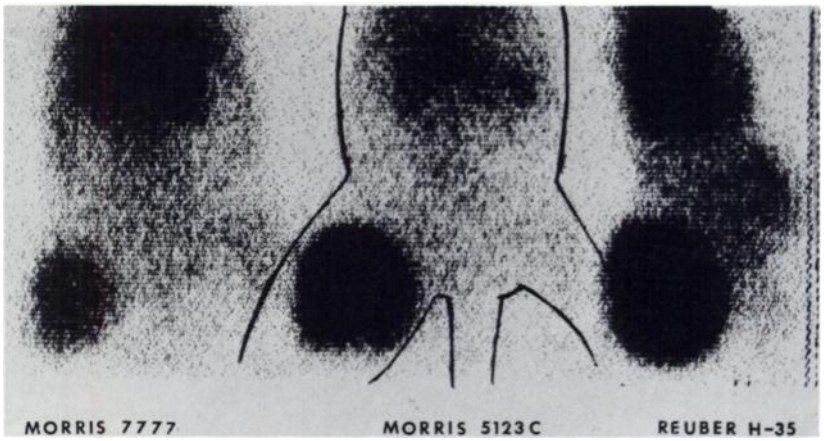

FIG. 2. Rectilinear scans of (C-11) ACBC in rats bearing (left to right) Morris 7777, Morris 5123C, and Reuber H-35 hepatomas. Doses contained ~0.3 mg stable ACBC/kg.

The clear visualization of all three tumors shows the potential of (C-11) ACBC as a tumor-seeking agent. The relative affinities of the amino acid for the three tumor types, determined by image appearance, were: Morris 5123C > Reuber H-35 > Morris 7777. This follows the same pattern seen with (C-14) ACBC.

Although we made no direct comparison of the biodistribution of (C-14) ACBC and Ga-67, the results of separate Ga-67 citrate experiments indicated that, for rats bearing Morris 5123C, Reuber H-35, and Morris 7777 hepatomas, the absolute tumor uptake of (C-14) ACBC at 30 min after injection was approximately one-half that of Ga-67 at 24 hr, and that the (C-14) ACBC tumor-to-nontumor ratios were on the average in the range of one-half to one-third those of Ga-67. In the pancreatic duct adenocarcinoma 46710, (C-14) ACBC was superior to Ga-67 citrate on both an absolute and relative basis, but neither of these agents had good specificity for this tumor. The pancreatic islet-cell adenocarcinoma 2309V was not studied with Ga-67 citrate. Although the tumor-to-nontumor ratios for (C-14) ACBC are lower than those for Ga-67 in three of the four tumor types in which both agents have been studied, good tumor visualization should be obtained when (C-11) ACBC is used in conjunction with positron emission computed tomography. Gallium-68 ($T_{1/2}$ = 68 min) is, of course, a positron emitter and readily available from a $^{68}Ge/^{68}Ga$ generator, but the short half-life and the slow kinetics of Ga-68 distribution combine to prevent satisfactory tomographic imaging.

(C-14) ACBC was not selectively incorporated by either viable or necrotic *S. aureus* abscess tissue (Table 4). This suggests that (C-11) ACBC may be able to differentiate malignant from inflammatory lesions.

Toxicity studies were carried out to assess possible toxic effects of ACBC in amounts present in radiopharmaceutical doses of (C-11) ACBC, which will be approximately 0.1 mg ACBC/kg. Mice administered 2.0 or 2.9 g ACBC/kg (20,000 and 29,000 times the proposed radiopharmaceutical dose) tolerated the doses very well, with no deaths observed within 60 days. The one mouse to which 4.0 g ACBC/kg was administered (40,000 times the proposed dose) died immediately after the completion of injection, perhaps in part because of hypervolemia; the 27-g mouse was given 0.86 ml of a saturated solution of ACBC i.v.

Studies in four laboratory-grade beagle dogs and one marmoset—at i.v. dosage levels of 200 mg ACBC/kg (2000 times the proposed dose)—indicated a similar lack of toxicity. In the dog study, complete blood-cell and biochemical determinations were made, and in the marmoset study complete blood-cell profiles were again obtained. In neither study was there any significant change in any of the determinations, and both the dogs and the marmoset remained clinically normal throughout the test. These results suggest that ACBC is unusually nontoxic and that doses of 0.1 mg ACBC/kg, given

TABLE 4. TISSUE DISTRIBUTION (30-MIN) OF (C-14) ACBC* IN MALE FISCHER 344 RATS BEARING *S. AUREUS* ABSCESSES

Tissue	% dose/g†
Viable abscess	0.62 (0.52–0.74)
Necrotic abscess	0.18 (0.10–0.30)
Liver	0.72 (0.64–0.78)
Spleen	1.11 (0.89–1.44)
Kidney	0.94 (0.85–1.09)
Lung	0.70 (0.69–0.74)
Muscle	0.32 (0.30–0.38)
Marrow	1.10 (1.07–1.15)
Blood	0.34 (0.26–0.41)
Small intestine	1.64 (1.25–1.97)
Pancreas	3.65 (3.25–4.03)

* Containing 1 mg/kg of stable ACBC/kg.

† Mean of five animals and range; normalized to body weight of 250 g.

TABLE 5. ESTIMATED RADIATION DOSE TO REFERENCE MAN FROM INTRAVENOUSLY ADMINISTERED (C-11) ACBC

Tissue	Radiation dose (rads/mCi)*
Total body	0.011
Liver	0.015
Spleen	0.019
Kidney	0.019
Lung	0.016
Muscle	0.011
Marrow	0.020
Small intestine	0.022
Pancreas	0.078
Testis	0.009
Ovary	0.021

* Based on 30-min tissue distribution of intravenously administered (C-14) ACBC (containing 2.3 mg stable ACBC/kg) in male and female Fischer 344 rats, assuming immediate uptake by organs followed by complete decay in situ.

with (C-11) ACBC, should be innocuous, with a safety factor of 20,000-30,000.

Because of the short half-life of C-11, the radiation dose from intravenously administered (C-11) ACBC should be minimal (Table 5). Because the selective uptake of alicyclic amino acids by the pancreas appears to be rodent-specific (see above), the actual radiation dose to the human pancreas is expected to be much less than that calculated from rat data.

(C-11) ACBC appears to have good potential as a clinical tumor-seeking agent. Its use in conjunction with positron emission computed tomography may permit the visualization of deep-seated lesions that cannot be located using conventional techniques. Clinical studies with (C-11) ACBC are in progress under Investigational New Drug (IND) status from the U. S. Food and Drug Administration.

Future studies may also reveal the value of (C-11) ACBC for studies of amino acid transport. ACBC apparently behaves metabolically like ACPC, which has been used in the past as a nonmetabolizable model for amino acid transport studies in both normal and tumor systems (*14*). Like 2-[^{18}F]fluoro-2-deoxyglucose (*15*), (C-11) ACBC may have the ability to mimic natural substances and be influenced by the same transport processes. Investigations of the usefulness of (C-11) ACBC for such studies are planned.

FOOTNOTES

* New England Nuclear Corp., Boston, MA.
† Eastman No. 13179.
‡ Birchover Instruments, Bancroft, U.K.
‖ Galbraith Laboratories, Inc., Knoxville, TN.
§ Amersham/Searle, Arlington Heights, IL.

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