Potential Radioprotective Agents. 1. Homologs of Melatonin

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Abstract □ Homologs of melatonin were prepared by acylation of 5-methoxytryptamine with the appropriate acid chloride or anhydride. The products were administered as solutions or suspensions in soybean oil by ip injection to mice 30 min prior to irradiation with 950 cGy of 6 mV photons. Protection was achieved with all compounds, survival rate being maximal for mice treated with the hexanoic amide **5** and the octanoic amide **6**.

The ever-present possibility of nuclear accidents such as those at Three Mile Island, Chernobyl, and Goiania[1] points up the necessity of developing effective drugs to protect humans against radiation damage. A further application of such a radioprotective compound could be in conjunction with treatment of cancer patients by radiation; *N*-acyldehydroalanines have been tested for this purpose in mice.[2] As reviewed by Foye,[3] various classes of compound have demonstrated radioprotective activity including mercaptans, di- and trisulfides, phosphorothioates, alcohols, acid hydrazides, imidazoles, benzofurans, amine oxides, and thiazolidines. The need still exists, however, for compounds that are more effective in response to both military and emergency needs.[4] Homologs of melatonin (*N*-acetyl-5-methoxytryptamine) comprise one of several classes of organic compound currently under study in our laboratory.

Serotonin (5-hydroxytryptamine)[5-9] and its creatinine sulfate salt,[10] either alone or in conjunction with other radioprotective agents, as well as indole analogs[11] and alkoxytryptamines,[12] have been found to exhibit radioprotective activity when administered to mice by ip injection. Serotonin was observed to provide 20% survival,[13] while melatonin gave 75% survival.[14] It seemed reasonable to us that other amides of 5-methoxytryptamine might be as active or more active than melatonin; consequently, we have synthesized and assayed an homologous series of amides of 5-methoxytryptamine.

Experimental Section

General—All chemicals (reagent grade) were purchased from Aldrich Chemical Co., Milwaukee, WI; Fluka Chemical Corp., Ronkonkoma, NY; Fisher Scientific, Itasca, IL; or J. T. Baker Chemical Co., Glen Ellyn, IL. ^{1}H and ^{13}C NMR spectra were measured on a General Electric QE-300 instrument at 300 and 75 MHz, respectively, using chloroform-D as the solvent and internal reference. The IR spectra were recorded on a Perkin-Elmer Model 283 spectrophotometer. Analytical vapor-phase chromatography (VPC) analyses were performed on a Varian GC Model 3700 instrument with an OV17 capillary column (25 m, 0.24 mm, nitrogen carrier gas) and a Hewlett-Packard 3390A integrator. Analytical thin-layer chromatography was performed on Macherey-Nagel Polygram Sil G/UV$_{254}$ plastic sheets at 0.25 mm thickness with a mobile phase of EtOAc–CH_2Cl_2 1:1, and the compounds were visualized by vanilin–H_2SO_4 and UV light detection (254 nm). Flash column chromatography was carried using an E. Merck AG silica gel 60 (230–400 mesh) column. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Microanalysis samples were prepared by drying over Drierite under a vacuum at 65 °C for 10 h. Chemical analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Radiation experiments were carried out with a Seimens Mevtron KD linear accelerator with a 6 mV photon beam with an output of 200 cGy/min.

Synthesis of Amides—The amides were prepared by acylation of 5-methoxytryptamine with either the requisite anhydride in pyridine (procedure A) or the acid chloride in toluene (procedure B), depending on availability of the acylating agent.

Procedure A—The required amount of 5-methoxytryptamine was charged into a 25-mL round-bottom flask and dissolved in 5 mL of pyridine. To this stirred solution was added the anhydride (1.2–1.3 equiv) neat, dropwise *via* a syringe, over a 2-min period. After 2 h at room temperature, the reaction mixture was poured into a separatory funnel; ether and aqueous $NaHCO_3$ were added, and the mixture was shaken. The ether layer was washed with brine and dried over MgSO4, and the solvent was evaporated to give the crude reaction mixture.

Procedure B—The required amount of 5-methoxytryptamine was charged into a 25-mL round-bottom flask and suspended in 2 mL of toluene by vigorous stirring, after which the suspension was cooled in an ice bath. The requisite acid chloride (1.3 equiv) in 2.5 mL of toluene was added dropwise to the amine suspension *via* a syringe pump over a 30-min period. Stirring was continued for 1 h at room temperature, after which the suspension was poured into a separatory funnel and extracted with ether. The organic layer was washed twice with brine and dried over $MgSO_4$, and the solvent was removed to give the crude reaction mixture.

N-[2-(5-Methoxy-1H-indol-3-yl)ethyl]propanamide (**2**)—5-Methoxytryptamine (0.299 g, 1.57 mmol) and 0.242 mL (1.89 mmol, 1.2 equiv) of propionic anhydride were employed using procedure A. The brown crude oil was purified by flash chromatography on silica gel using ethyl acetate–methylene chloride 1:1 to afford a light brown oil [0.290 g, 100%, VPC starting at 250 °C and increasing 10 °C/min to a final temperature of 300 °C (250 °C → 300 °C, 10 °C/min), 8.47 min, 100%]. The compound was crystallized from methylene chloride at −5 °C as chunky, brown crystals: mp 105–108 °C; 0.305 g, 79%; ^{1}H NMR δ 1.08 (t, *J* = 7.5 Hz, 3H, CH_2CH_3), 2.07–2.15 (q, *J* = 7.5 Hz, 2H, CH_2CH_3), 2.89 (t, *J* = 6 Hz, 2H, $=CCH_2CH_2N$), 3.50–3.56 (td, *J* = 6 Hz, 2H, CH_2CH_2N), 3.79 (s, 3H, CH_3O), 6.00 (br s, 1H, $CH_2NHC(O)$), 6.79–6.83 (dd, *J* = 9, 3 Hz, 1H, MeOC=CHCH), 6.92 (br s, 1H, C=CHNH), 7.00–7.01 (d, *J* = 3 Hz, 1H, MeOC=CHC), 7.19–7.21 (d, *J* = 9 Hz, 1H, CH=CHC), 8.96 (br s, 1H, C=CHNHC); ^{13}C NMR δ 13.94 (CH_2CH_3), 25.08 (CH_2CH_2N), 29.47 ($CH_2C=O$), 39.62 (CH_2N), 55.68 (OCH_3), 100.21 (NCH=C), 111.62 and 111.98 [$CH_3O(CH)_2$], 112.02 (NCH), 122.91 (CHCN), 127.48 ($CCCH_2$), 131.54 (CHCN), 153.57 (CH_3OC), 174.04 (C=O); IR (KBr pellet) ν 3245 s (N-H), 3095 s (N-H), 2920 w (C-H), 1614 m (C=O), 1565 m, 1218 m cm^{-1}. Anal. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.36; N, 11.37. Found: C, 68.41; H, 7.38; N, 11.21.

N-[2-(5-Methoxy-1H-indol-3-yl)ethyl]butanamide (**3**) was synthesized via procedure A with 0.342 g (1.79 mmol) of 5-methoxytryptamine and 0.353 mL (2.16 mmol, 1.2 equiv) of butyric anhydride. The compound was purified by flash column chromatography on silica gel using 50% ethyl acetate in methylene chloride to afford the product as a light brown oil [0.444 g, 95%, VPC (250 °C → 300 °C), 10 °C/min) 9.09 min, 100%]. It was crystallized from methylene chloride at −5 °C as white, fine needles [0.314 g, 67% (one crop)]: mp 121–123 °C; ^{1}H NMR δ 0.87 (t, *J* = 6 Hz, 3H, CH_2CH_3), 1.53–1.65 (m, 2H, $CH_2CH_2CH_3$), 2.06 (t, *J* = 7.5 Hz, 2H, C(O)CH2CH2), 2.91 (t, *J* = 6 Hz, 2H, $=CCH_2CH_2N$), 3.50–3.57 (td, *J* = 6, 6 Hz, 2H, CH_2CH_2NH), 3.79 (s, 3H, CH_3O), 5.97 (br s, 1H, $CH_2NHC(O)$), 6.80–6.83 (dd, *J* = 9, 3 Hz, 1H, MeOC=CHCH), 6.90–6 .91 (d, *J* = 3 Hz, 1H, C=CHNH), 7.00–7.01 (d, *J* = 3 Hz, 1H, MeOC=CHC), 7.18–7.21 (d, *J* = 9 Hz, 1H, CH=CHC), 8.92 (br s, 1H, C=CHNHC); ^{13}C NMR δ 13.54, 19.00, 25.16, 34.45, 39.59, 55.73, 100.27, 111.67, 111.97, 112.02, 122.96, 127.46, 131.57, 153.59, 173.56; IR (KBr pellet) ν 3235 s (N-H), 3090 w (N-H), 2922 m (C-H), 1609 s (C=O), 1550 s, 1430 s, 1212 m cm^{-1}. Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.41; H, 7.43; 10.76N. Found: C, 68.83; H, 7.75; N, 10.72.

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N-[2-(5-Methoxy-1*H*-indol-3-yl)ethyl]pentanamide (**4**) was synthesized via procedure B with 0.349 g (1.83 mmol) of 5-methoxytryptamine and 0.283 mL (2.38 mmol, 1.3 equiv) of valeryl chloride in 2.5 mL of toluene. The crude product was purified by flash column chromatography on silica gel using 40% ethyl acetate in methylene chloride to afford amide **4** as a yellow oil [0.484 g, 96%, VPC (250 °C → 300 °C, 10 °C/min), 10.27 min, 100%]: ^{1}H NMR δ 0.87 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 1.23–1.34 (tt, *J* = 7.5, 7.5 Hz, 2H, $CH_2CH_2CH_2CH_3$), 1.52–1.62 (tq, *J* = 7.5, 7.2, 2H, $CH_2CH_2CH_3$), 2.10 (t, *J* = 7.5 Hz, 2H, $C(O)CH_2CH_2$), 2.91 (t, *J* = 6. 6 Hz, 2H, $=CCH_2CH_2N$), 3.53–3.59 (td, *J* = 6.6, 6.3 Hz, 2H, CH_2CH_2NH), 3.82 (s, 3H, CH_3O), 5.95 (br t, *J* = 6.3 Hz, 1H, $CH_2NHC(O)$), 6.82–6.86 (dd, *J* = 8.7, 2.4 Hz, 1H, MeOC=CHCH), 6.93–6.94 (d, *J* = 2.1 Hz, 1H, C=CHNH), 7.02–7.03 (d, *J* = 2.4 Hz, 1H, MeOC=CHC), 7.21–7.24 (d, *J* = 8.7 Hz, 1H, CH=CHC), 8.93 (br s, 1H, C=CHNHC); ^{13}C NMR δ 13.59, 22.18, 25.17, 27.69, 36.32, 39.58, 55.70, 100.25, 111.87, 111.99, 112.03, 122.90, 127.51, 131.57, 153.63, 173.36; IR (NaCl, neat) ν 3300 s (N-H), 3290 s (N-H), 2930 s (C-H), 1640 s (C=O), 1550 s, 1215 m, 793 m cm^{-1}. Anal. Calcd for $C_{16}H_{22}N_2O_2$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.53; H, 8.26; N, 9.30.

N-[2-(5-Methoxy-1*H*-indol-3-yl)ethyl]hexanamide (**5**) was synthesized via procedure A with 0.373 g (1.96 mmol) of 5-methoxytryptamine and 0.590 mL (2.55 mmol, 1.3 equiv) of hexanoic anhydride. The crude amide was purified by flash column chromatography on silica gel using 40% ethyl acetate in methylene chloride to afford **5** as a yellow oil [0.513 g, 70%, VPC (250 °C → 300 °C, 10 °C/min), 10.12 min, 100%]: ^{1}H NMR δ 0.84 (t, *J* = 6.9 Hz, 3H, CH_2CH_3), 1.19–1.32 (m, 4H, $CH_2CH_2CH_2CH_2$), 1.52–1.62 (tq, *J* = 7.5, 6.9 Hz, 2H, $CH_2CH_2CH_3$), 2.08 (t, *J* = 7.5 Hz, 2H, $C(O)CH_2CH_2$), 2.89 (t, *J* = 9 Hz, 2H, $=CCH\ 2CH_2N$), 3.51–3.57 (td, *J* = 6.9, 5.4 Hz, 2H, CH_2CH_2NH), 3.79 (s, 3H, CH_3O), 6.09 (br t, *J* = 5.4 Hz, 1H, $CH_2NHC(O)$), 6.79–6.84 (dd, *J* = 8.7, 2.4 Hz, 1H, MeOC=CHCH), 6.89–6.91 (d, *J* = 2.1 Hz, 1H, C=CHNH), 7.01–7.02 (d, *J* = 2.4 Hz, 1H, MeOC=CHC), 7.18–7.22 (d, *J* = 8.7 Hz, 1H, CH=CHC), 8.96 (br s, 1H, C=CHNHC); ^{13}C NMR δ 13.75, 22.16, 25.11, 25.29, 31.19, 36.50, 39.63, 55.70, 100.19, 111.75, 111.84, 112.03, 122.98, 127.46, 131.56, 153.59, 173.54; IR (NaCl, neat) ν 3290 s (N-H), 2920 s (C-H), 1635 s (C=O), 1520 s, 1450 s, 1209 s, 1030 m, 793 m cm^{-1}. Anal. Calcd for $C_{17}H_{24}N_2O_2$: C, 70.80; H, 8.39; N, 9.71. Found: C, 70.27; H, 8.37; N, 9.95.

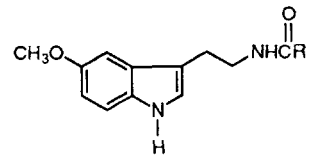
N-[2-(5-Methoxy-1*H*-indol-3-yl)ethyl]octanamide (**6**) was synthesized via procedure B with 0.395 g (2.08 mmol) of 5-methoxytryptamine and 0.461 mL (2.70 mmol, 1.3 equiv) of octanoyl chloride in 2.5 mL of toluene. The crude amide was purified by flash column chromatography on silica gel using 30% ethyl acetate in methylene chloride to afford **6** as a colorless oil [VPC (250 °C → 300 °C, 10 °C/min), 12.79 min, 100%]. This oil was crystallized from toluene at −5 °C as a white solid (0.511 g, 78%, mp 70–73 °C): ^{1}H NMR δ 0.87 (t, *J* = 6.9 Hz, 3H, CH_2CH_3), 1.25 (br s, 8H, $CH_2(CH_2)_4CH_2CH_3$), 1.55–1.61 (m, 2H, $CH_2CH_2CH_2CH_3$), 2.10 (t, *J* = 7.6 Hz, 2H, $C(O)CH_2CH_2$), 2.94 (t, *J* = 6.6 Hz, 2H, $=CCH_2CH_2N$), 3.56–3.63 (td, *J* = 6.6, 6.0 Hz, 2H, CH_2CH_2NH), 3.86 (s, 3H, CH_3O), 5.54 (br s, 1H, $CH_2NHC(O)$), 6.85–6.89 (dd, *J* = 9.0, 2.1 Hz , 1H, MeOC=CHCH), 6.99 (d, *J* = 2.1 Hz, 1H, C=CHNH), 7.03–7.04 (d, *J* = 2.1 Hz, 1H, MeOC=CHC), 7.25–7.28 (d, *J* = 9.0 Hz, 1H, CH=CHC), 8.13 (br s, 1H, C=CHNHC); ^{13}C NMR δ 13.99, 22.55, 25.39, 25.74, 28.97, 29.23, 31.66, 36.92, 39.56, 55.97, 100.65, 111.96, 112.42, 112.79, 122.76, 127.80, 131.62, 154.14, 173.11; IR (KBr pellet) ν 3380 s (N-H), 3309 s (N-H), 2910 s (C-H), 1634 s (C=O), 1555 m, 1220 m cm^{-1}. Anal. Calcd for $C_{19}H_{28}N_2O_2$: C, 72.12; H, 8.92; N, 8.85. Found: C, 72.10; H, 8.90; N, 8.78.

N-[2-(5-Methoxy-1*H*-indol-3-yl)ethyl]decanamide (**7**) was synthesized via procedure B with 0.401 g (2.11 mmol) of 5-methoxytryptamine and 0.569 mL (2.74 mmol, 1.3 equiv) of decanoyl chloride in 3 mL of toluene. The crude product was purified by flash column chromatography on silica gel using 30% ethyl acetate in methylene chloride to afford **7** as a colorless oil [VPC (250 °C → 300 °C, 10 °C/min), 16.85 min, 100%]. The crude product crystallized from toluene at −5 °C as a white solid [0.536 g, 74% (first crop only), mp 83–85 °C]: ^{1}H NMR δ 0.88 (t, *J* = 6.9 Hz, 3H, CH_2CH_3), 1.24 (br s, 12H, $CH_2(CH_2)_6CH_2CH_3$), 1.55–1.61 (m, 2H, $CH_2CH_2CH_3$), 2.10 (t, *J* = 7.5 Hz, 2H, $C(O)CH_2CH_2$), 2.93 (t, *J* = 6.6 Hz, 2H, $=CCH_2CH_2N$), 3.56–3.63 (td, *J* = 6.6, 6.3 Hz, 2H, CH_2CH_2NH), 3.85 (s, 3H, CH_3O), 5.56 (br s, 1H, $CH_2NHC(O)$), 6.85–6.88 (dd, *J* = 8.7, 2.4 Hz, 1H, MeOC=CHCH), 6.99 (d, *J* = 1.5 Hz, 1H, C=CHNH), 7.03–7.04 (d, *J* = 2.4 Hz, 1H, MeOC=CHC), 7.24–7.27 (d, *J* = 8.7 Hz, 1H, CH=CHC), 8.19 (br s, 1H, C=CHNHC); ^{13}C NMR δ 14.03, 22.62, 25.39, 25.39, 25.74, 29.23, 29.31, 29.39, 30.82, 31.82, 36.91, 39.58, 55.97, 100.65, 111.97, 112.39, 112.74, 122.79, 127.79, 131.66, 154.11, 173.14; IR (KBr pellet) ν 3388 s (N-H), 3300 s (N-H), 2910 s (C-H), 1634 s (C=O), 1551 m, 1218 s cm^{-1}. Anal. Calcd for $C_{21}H_{32}N_2O_2$: C, 73.22; H, 9.36; N, 8.13. Found: C, 73.44; H, 9.24; N, 8.16.

N-[2-(5-Methoxy-1*H*-indol-3-yl)ethyl]hexadecanamide (**8**) was synthesized via procedure B with 0.401 g (2.11 mmol) of 5-methoxytryptamine and 0.569 mL (2.74 mmol, 1.3 equiv) of palmitoyl chloride in 4 mL of toluene. After workup, the solvent was removed to afford a white solid. Material was purified by recrystallization from toluene at −5 °C as a gray powder [0.680 g, 73% (first crop only), mp 102–104 °C]. The product could not be eluted through the GC with nitrogen carrier gas: ^{1}H NMR δ 0.87 (t, *J* = 6.6 Hz, 3H, CH_2CH_3), 1.24–1.30 (br s, 24H, $CH_2(CH_2)_{12}CH_2CH3$), 1.55–1.59 (m, 2H, $CH_2CH_2CH_2CH_3$), 2.10 (t, *J* = 7.6 Hz, 2H, $C(O)CH_2CH_2$), 2.94 (t, *J* = 6.8 Hz, 2H, $=CCH_2CH_2N$), 3.57–3.63 (td, *J* = 6.8, 6.2 Hz, 2H, CH_2CH_2NH), 3.86 (s, 3H, CH_3O), 5.52 (br s, 1H, $CH_2NHC(O)$), 6.85–6.89 (dd, *J* = 8.7, 2.3 Hz, 1H, MeOC=CHCH), 7.00–7.01 (d, *J* = 2.1 Hz, 1H, C=CHNH), 7.03–7.04 (d, *J* = 2.3 Hz, 1H, MeOC=CHC), 7.25–7.28 (d, *J* = 8.7 Hz, 1H, CH=CHC), 8.03 (br s, 1H, C=CHNHC), ^{13}C NMR δ 14.07, 22.67, 25.40, 25.76, 29.33, 29.47, 29.66, 31.90, 36.94, 39.55, 55.99, 100.69, 111.95, 112.48, 112.90, 122.73, 127.83, 131.63, 154.19, 173.12. IR (KBr pellet) ν 3380 s (N-H), 3300 s (N-H), 2910 s (C-H), 1635 s (C=O), 1555 m, 1440 m, 1220 s, 790 w cm^{-1}. Anal. Calcd for $C_{27}H_{44}N_2O_2$: C, 75.65; H, 10.35; N, 6.54. Found: C, 76.00; H, 10.25; N, 6.54.

Radiation-Protective Evaluation—Male Swiss ND4 mice were obtained from Harlan Industries, Indianapolis, IN, and housed five to a cage. Compounds that were soluble in soybean oil (**3–8**) were dissolved; those that did not dissolve (**1** and **2**) were finely suspended by rapid stirring. The mice were injected ip at a dose level of 1.076 mmol/kg. Thirty minutes later they were placed in a cloth holder (in groups of 19–22 mice) which was taped to the treatment table of the instrument so that they were confined in a 20 cm^2 area 100 cm from the source; they were then irradiated over a period of approximately 5 min with 950 cGy of 6 mV photons produced by a linear accelerator.[15] Mice in the control group were each injected with 0.2 mL of soybean oil; all died by day 12 postinjection. The values reported in Table 1 represent 30-day survival.

Table 1—Radioprotective Activity of Amides of 5-Methoxytryptamine



Compound	R	Dose, mg/kg	Radiation survivors[a]	p^b	p^c
Control			0/20, 0%		
1, Melatonin[d]	CH_3	250	9/21, 43%		0.0045
2	C_2H_5	265	9/22, 41%	ns	0.0069
3	C_3H_7	280	6/19, 32%	ns	0.032
4	C_4H_9	295	15/20, 75%	0.036	<0.0001
5	C_5H_{11}	310	19/20, 95%	0.0004	<0.0001
6	C_7H_{15}	340	20/21, 95%	0.0004	<0.0001
7	C_9H_{19}	371	13/20, 65%	ns	<0.0001
8	$C_{15}H_{31}$	461	10/21, 48%	ns	0.0021

[a] Male Swiss mice were injected ip with solutions (**3–8**) or suspensions (**1** and **2**) of the test compound in soybean oil at a dose level of 1.076 mmol/kg 30 min before irradiation with 950 cGy of 6 mV photons. [b] Normal difference test[17] as compared with melatonin; ns = not significant. [c] Normal difference test as compared with the control. [d] Obtained from Aldrich Chem. Co., 97%.

Results and Discussion

Radioprotective activity, as evidenced by 32%–95% survival, was observed for all eight compounds studied (see columns 3 and 5 in Table 1). These values may be compared with our 50% survival data obtained with $H_2N(CH_2)_3NHC_2H_4SPO_3H_2$, WR 2721, at a dose level of 0.78 mmol/kg in an otherwise similar experiment.[16] The hexanoic (**5**) and octanoic (**6**) amides were

statistically significantly more radioprotective than melatonin (1), while the highest homolog tested (8) was comparable in activity to melatonin. Thus, under the radiation test conditions employed, maximal survival rate in our strain of mouse was achieved with homologs having acyl chain lengths of six or eight carbons, with homologs having shorter or longer acyl chain lengths being less effective. The factor(s) (lipophilicity, bioavailability, metabolism, solubility, and affinity for an as yet unidentified receptor) responsible for these results remain to be determined.

Conclusion

The finding that the level of radioprotective activity induced by melatonin could be doubled by the simple expedient of increasing the chain length of the *N*-acyl group to C_{6-8} raises the possibility that other modifications of structure might also improve activity; these are now being explored.

References and Notes

1. Roberts, L. *Science* **1987**, *238*, 1028–1031.
2. Buc-Calderon, P.; Defresne, M. P.; Barvais, C.; Roberfroid, M. *Carcinogenesis* **1989**, *10*, 1641–1644.
3. Foye, W. O. In *Burger's Medicinal Chemistry*, Wolff, M. E., Ed.; Wiley: New York, 1981; Part 3, Chapter 37.
4. Walker, R. I. *Pharmacol. Ther.* **1988**, *39*, 13–20.
5. Maisin, J. R. *Pharmacol. Ther.* **1988**, *39*, 189–193.
6. Baev, I., Benova, D. *Roentgenol. Radiol.* **1975**, *14*, 50–53.
7. van der Meer, C.; van Bekkum, D. W. *Int. J. Radiat. Biol.* **1961**, *4*, 105–110.
8. van den Brenk, A. S.; Elliott, K. *Nature* **1959**, *182*, 1506–1507.
9. Bacq, Z. M., Beaumariage, M. L., Radivojevic, D. *Bull. Acad. R. Med. Belg.* **1961**, *1*, 519–530.
10. Wang, R. I. H.; Davidson, D. E. *U.S. Army Med. Research Lab. Rept.*, **1961**, *No. 484*; *Chem. Abstr.* **1962**, *57*, 5082*g*.
11. Andrieu, L.; Fatome, M.; Granger, R.; Robbe, Y.; Terol, A. *Eur. J. Med. Chem.—Chim. Ther.*, **1974**, *9*, 453–457.
12. Krasnykh, I. G., Zherebchenko, P. G., Murashova, V. S., Suvorov, N. N., Sorokina, N. R., Shashkov, V. S. *Radiobologiya* **1962**, *2*, 156–160.
13. Bonner, J. F., Jr. *Progress Report to AEC*, 1966, Contract No. AT(11-1), p 1223.
14. Bonner, J. F., Jr. Personal communication.
15. This equipment is that which is most commonly used for therapeutic radiation, and one of our future research projects is to use a selective radioprotective agent in a clinical setting.
16. Unpublished observations.
17. Bahn, A. K. *Basic Medical Statistics*; Grune & Stratton: New York, 1972, pp 52–54.

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