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Potential Radioprotective Agents—VI. Chalcones, Benzophenones, Acid Hydrazides, Nitro Amines and Chloro Compounds. Radioprotection of Murine Intestinal Stem Cells

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Abstract—There is an interest and need for new compounds that protect tissues from radiation injury. In cancer therapy, the protection of normal tissue without protecting tumors is one way to increase the therapeutic gain. Thiol compounds are currently in clinical trials, but are limited to some extent by their human toxicities including hypotension, nausea, and emesis. Several new aminochalcones and aminobenzophenones were synthesized and tested for radioprotective activity in mice. All were less active than *p*-aminobenzophenone itself. Several acid hydrazides were synthesized and tested similarly, but none exhibited significant activity. The high radioprotective activity of 4-nitroaniline was confirmed, but other nitro amines were substantially less active. 4-Chloro-*N*-methylaniline is as active as 4-chloroaniline, but other chloro aromatics are devoid of significant activity. When compared with the phosphorothioate amyfostine (WR-2721) using the intestinal clonogenic cell survival assay, 1-(*p*-aminophenyl)-1-propanol (**15**), *p*-aminopropiophenone (**16**), its ethylene ketal (**14**), and a mixture of the two (**17**) protected to a great extent, though slightly less than WR-2721. These results suggest that there is direct cellular radioprotection by these non-thiol compounds. The studies further suggest that preclinical toxicity testing of the most protective agents is warranted.

Introduction

We have earlier reported on the radioprotective activity of melatonin homologs,[1] substituted anilines,[2] ketals and thioketals,[3] Schiff bases,[4] and melatonin analogs[5] from a dose of photon radiation leading to death from the bone marrow syndrome. Significant protective activity was found using *p*-aminobenzophenone,[2,3] thus, it seemed appropriate to extend our studies to other aminoketones. We report here our results of radioprotection from marrow lethal photon doses with chalcones and substituted benzophenones, a series of hydrazides, nitro amines, and chloro compounds, as well as radioprotection of intestinal clonogenic stem cells using the most protective compounds.

Results and Discussion

Chalcone has been prepared by the base-catalyzed condensation of benzaldehyde and acetophenone.[6] Under comparable conditions, we condensed *p*-amino-acetophenone with benzaldehyde, *p*-cyanobenzaldehyde, *p*-nitrobenzaldehyde, and ferrocenecarboxaldehyde to give the chalcone analogs **1**, **3**, **4** and **5**, respectively (Fig. 1). The Schiff base **2** of benzaldehyde and chalcone **1** can also be isolated in the first synthesis, depending on the method of purification.

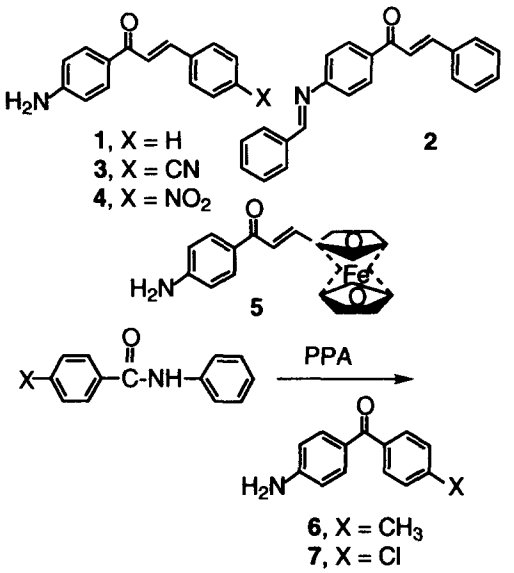


Figure 1. Chalcones and benzophenones.

Staskun prepared 4-amino-4'-methylbenzophenone (**6**) by rearrangement of 4-methylbenzanilide.[7] A similar rearrangement with 4-chlorobenzanilide gave 4-amino-4'-chlorobenzophenone (**7**). The conversion of amide to aminoketone is accompanied by replacement of the 3350 cm^{-1} NH peak in the infrared spectra of the former with a 3410–3420, 3325–3330, 3210–3220 cm^{-1} pattern characteristic of the latter.

The chalcone analogs were tested in mice by ip injection of solutions or suspensions of the compounds in soybean oil 30 min prior to irradiation with 950 cGy of 6 mV photons produced by a linear accelerator, and the results are shown in Table 1. 4-Aminochalcone (**1**) is highly toxic at this dose level; ten out of twenty-one mice died in the first 24 h period (control mice, which have been injected with soybean oil and irradiated, begin dying on day 5). Of the remaining eleven mice, ten survived to day thirty. The toxicity of chalcone **1** was greatly reduced by conversion to its Schiff base **2**, as all of the mice administered **2** survived to day 5; its radioprotective activity was 71%. We have found Schiff bases generally to be less toxic than their precursor amines.[4] Little or no radioprotective activity was observed with chalcones **3–5**.

Inasmuch as *p*-aminobenzophenone has been shown to be highly protective,[2,3] it was of interest to determine the effects of substituents in the 'second' ring. As shown in Table 2, 4'-methyl (in **6**), 4'-chloro (in **7**), and 4'-amino groups all decreased radioprotective activity.

In the light of reported[8] radioprotective activity for *p*-amino- and for 3,4-dichlorobenzoic acid hydrazide (**10**), we tested the hydrazides listed in Table 3, along with the acyl hydrazone **8**. Hydrazides **10–13** were prepared by the action of hydrazine on the corresponding methyl or ethyl ester,[9] while the diacyl compound **9** was prepared with 3,4-dichlorobenzoyl chloride. No major radioprotective activity was observed; the most active compound in the series was the hydrazone **9**, while the cyclic hydrazide antipyrine and the other hydrazides exhibited little or no activity.

The observation[2] that 4-nitroaniline exhibits a high level of radioprotective activity was confirmed (Table 4). β-(4-Nitrophenyl)ethyl amine exhibited moderate

Table 1. Radioprotective activity of chalcones[1]

Compound	Dosage mg kg^{-1}	Survivors
1 4-Aminochalcone	174	10/11, 91%[2]
2 Schiff base of 4-aminochalcone and benzaldehyde	243	15/21, 71%
3 4-Amino-4'-cyanochalcone	194	8/20, 40%
4 4-Amino-4'-nitrochalcone	209	6/20, 30%
5 1-(p-Aminophenyl)-3-ferrocenyl-2-propen-1-one	258	1/20, 5%
Control, soybean oil only		3/61, 5%

[1]Male, Swiss Webster mice were injected ip with solutions or suspensions of 0.78 mequiv. kg^{-1} of the test compounds in soybean oil 30 min before irradiation with 950 cGy of 6 mV photons. Thirty-day survivals are shown. [2]See discussion.

Table 2. Radioprotective activity of substituted benzophenones[1]

Compound	Dosage, mg kg^{-1}	Survivors
4-Aminobenzophenone	154	39/40, 97%
6 4-Amino-4'-methylbenzophenone	165	8/20, 40%
7 4-Amino-4'-chlorobenzophenone	181	5/20, 25%
4,4'-Diaminobenzophenone	166	3/21, 14%
Control, soybean oil only		5/80, 6%

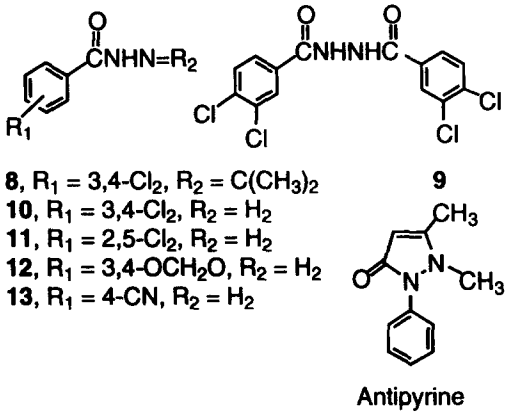
[1]Male, Swiss Webster mice were injected ip with solutions or suspensions of 0.78 mequiv. kg^{-1} of the test compounds in soybean oil 30 min before irradiation with 950 cGy of 6 mV photons. Thirty-day survivals are shown.

Table 3. Radioprotective activity of hydrazides and an acyl hydrazone[1]

Compound	Dosage mg kg^{-1}	Survivors
8 Acetone 3,4-dichlorobenzoyl hydrazone	119.5	6/21, 29%
9 N,N'-Bis-(3,4-dichlorobenzoyl)hydrazine	184.6	5/20, 25%
Antipyrine	147.3	3/20, 15%
4-Chlorobenzoic acid hydrazide	83.3	3/20, 15%
10 3,4-Dichlorobenzoic acid hydrazide	100	3/21, 14%
11 2,5-Dichlorobenzoic acid hydrazide	100	1/20, 5%
12 Piperonylic acid hydrazide	86.7	1/20, 5%
13 4-Cyanobenzoic acid hydrazide	78.5	0/20
4-Bromobenzoic acid hydrazide	105	0/20
Control, soyean oil only		0/20

[1]Male, Swiss Webster mice were injected ip with solutions or suspensions of the test compounds in soybean oil 30 min before irradiation with 950 cGy of 6 mV photons. Thirty-day survivals are shown.

activity, and other nitroaryl amines, as well as 4-nitrobenzyl amine, exhibited little activity. Thus, adding a second nitro group, adding a 2-cyano group, or moving the nitro group from the 4- to the 3-position effectively destroyed the activity of 4-nitroaniline.



8, $R_1 = 3,4\text{-}Cl_2$, $R_2 = C(CH_3)_2$ **9**
10, $R_1 = 3,4\text{-}Cl_2$, $R_2 = H_2$
11, $R_1 = 2,5\text{-}Cl_2$, $R_2 = H_2$
12, $R_1 = 3,4\text{-}OCH_2O$, $R_2 = H_2$
13, $R_1 = 4\text{-}CN$, $R_2 = H_2$

Antipyrine

Figure 2. Hydrazides and an acyl hydrazone.

The substantial radioprotective activity of 4-chloroaniline[2] was retained by substitution of a methyl group on the nitrogen atom (Table 5), but other chloro compounds exhibited little or no activity.

In order to obtain confirmation of protective activity in a second test system, *p*-aminobenzophenone and other protective compounds were compared with WR-2721 (the phosphorothioate developed by the U.S. Army Medical Research and Development Command)[10] using the intestinal microcolony assay;[11] the results are shown in Table 6. The number of surviving intestinal stem cells in control mice (15 Gy only) was about 10 per jejunal circumference. The soybean oil vehicle did not influence cell survival following irradiation. WR-2721 provided the greatest degree of protection, and the observed value was consistent with previous studies.[12] 1-(*p*-Aminophenyl)-1-propanol (**15**), *p*-aminopropiophenone (**16**), its ethylene ketal (**14**), and a mixture of the two (**17**) also demonstrated high degrees of protection, while *p*-aminobenzophenone and *p*-aminobenzonitrile (**18**) were only slightly less active. 5-Amino-2-chloropyridine (**19**), the Schiff base (**2**) of *p*-

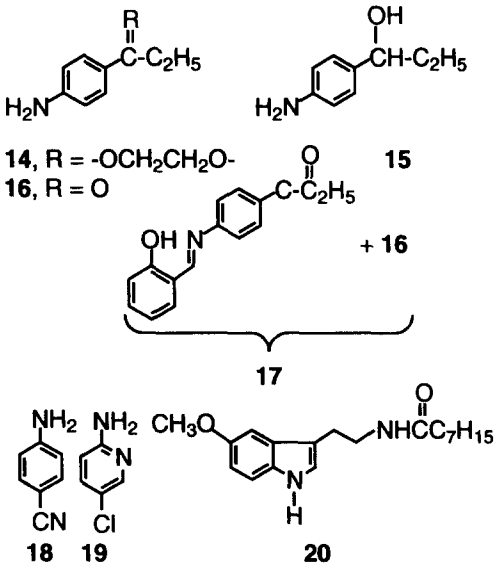


Figure 3. Compounds tested in the clonogenic stem cell assay.

Table 4. Radioprotective activity of nitro amines[1]

Compound	Dosage mg kg^{-1}	Survival
4-Nitroaniline	108	35/42, 83%
β-(4-Nitrophenyl)ethyl amine	130	9/21, 43%
3,5-Dinitroaniline	143	12/41, 29%
2-Cyano-4-nitroaniline	128	4/21, 19%
3-Nitroaniline	108	2/21, 10%
4-Nitrobenzyl amine	119	1/21, 5%
Control, soybean oil only		4/61, 6.6%

[1]Male, Swiss Webster mice were injected ip with solutions or suspensions of 0.78 mmol kg^{-1} of the test compounds in soybean oil 30 minutes before irradiation with 950 cGy of 6 mV photons. Thirty-day survivals are shown.

Table 5. Radioprotective activity of chloro compounds[1]

Compound	Dosage mg kg^{-1}	Survivals
4-Chloro-*N*-methylaniline	110	15/21, 71%
N-(4-Chlorophenyl)-*N'*,*N'*-dimethylurea	155	4/20, 20%
2,4,5-Trichlorobenzenesulfonyl hydrazide	215	4/20, 20%
N-(3,4-Dichlorophenyl)-thiourea	172	0/20
3,4-Dichloropropiophenone	158	0/20
N-(4-Chlorophenyl)-*o*-phenylene diamine	171	0/20
Control, soybean oil only		0/20

[1]Male, Swiss Webster mice were injected ip with solutions or suspensions of 0.78 mmol kg^{-1} of the test compounds in soybean oil 30 min before irradiation with 950 cGy of 6 mV photons. Thirty-day survivals are shown.

Table 6. Protection of murine intestinal clonogenic stem cells[1]

Compound	Dosage mg kg^{-1}	Microcolonies per Intestinal Circumference	S.D. $n = 4$	SEM
Control		9.7	1.1	0.5
soybean oil		9.0	0.9	0.4
WR-2721	228.6	78.4	5.9	3.0
p-Aminobenzonitrile, **18**	92	53.1	5.0	2.5
5-Amino-2-chloropyridine, **19**	128.6	35.9	9.2	4.6
1-(*p*-Aminophenyl)-1-propanol, **15**	118	64.2	5.0	2.5
p-Aminobenzophenone	153.7	51.3	5.0	2.5
p-Aminopropiophenone, **16**	86	63.8	8.8	4.4
Mixture of **16** and Schiff base	198	61.9	6.8	3.4
p-Aminopropiophenone ethylene ketal, **14**	151	64.5	7.5	3.7
Schiff base **2** of *p*-aminochalcone and benzaldehyde	243	20.9	6.5	3.3
5-Methoxytryptamine octanoic amide, **20**	340	24.6	3.0	1.5

[1]Male $B_6D_2F_1$ mice were injected ip with solutions or suspensions of compounds in soybean oil (except for WR-2721 in water) 30 min before irradiation with 15 Gy ^{137}Cs. Four days later the mice were sacrificed and 9 jejunum cross sections from each of four mice in each group were taken.

aminochalcone and benzaldehyde, and 5-methoxytryptamine octanoic amide (**20**) exhibited modest activity. These results provide stimulus for continued study of the more active of these examples.

Experimental

General

Chemicals were purchased from Aldrich Chemical Co., Milwaukee. ^1H NMR spectra were obtained on a Varian EM 390 spectrophotometer. IR spectra were obtained on a Perkin–Elmer 237 spectrophotometer. Melting points were taken on a Thomas–Hoover capillary melting point apparatus and are uncorrected. Chemical analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN, and agreed to within 0.4% of theoretical for the elements listed.

Synthesis

4-Aminochalcone (1). Benzaldehyde (456 mg, 4.3 mmol) was added dropwise to a stirred suspension of 580 mg (4.3 mmol) of *p*-aminoacetophenone in 3.2 mL of a solution of 3.08 g of KOH in 20 mL of H_2O and 12 mL of ethanol. The mixture was stirred at room temperature for 95 min, during which time a gum separated. Its solution in CH_2Cl_2 was washed with H_2O, dried over Na_2SO_4, and evaporated to leave 840 mg of viscous oil. It was dissolved in CH_2Cl_2 and chromatographed on 37 g of silica gel. The portion eluted by 7% ethanol in CH_2Cl_2, 820 mg, crystallized twice from ethanol–water to give 4-aminochalcone (**1**), yellow crystals, mp 84–86 °C; IR 3450, 3335, 3200, 1630, 1600, 1575, 1540 cm^{-1}; ^1H NMR ($CDCl_3$) 4.19 (*s*, 2H, NH_2), 6.6–7.9 (*m*, 11H, aromatic and vinylic); anal. $C_{15}H_{13}NO$ (H, N).

In a separate preparation in which the crude product was not chromatographed, three recrystallizations in ethanol gave the Schiff base (**2**) of benzaldehyde and 4-aminochalcone, mp 143–145 °C; ^1H NMR ($CDCl_3$) 7.0–8.0 (*m*, 16H, aromatic and vinylic), 8.32 (*s*, 1H, N=CH); anal. $C_{22}H_{17}NO$ (C, H, N).

4-Amino-4'-cyanochalcone (3). A similar condensation with 262 mg (2.0 mmol) of *p*-cyanobenzaldehyde and 270 mg (2.0 mmol) of *p*-aminoacetophenone gave 371 mg of crude product, yellow crystals, mp 204–206 °C. Recrystallization in acetone–water gave 4-amino-4'-cyanochalcone (**3**), mp 211–213 °C; IR 3460, 3360, 3220, 1625, 1580 cm^{-1}; anal. $C_{16}H_{12}N_2O \cdot 2/3H_2O$ (C, H, N).

4-Amino-4'-nitrochalcone (4). A similar condensation with 302 mg (2.0 mmol) of *p*-nitrobenzaldehyde and 270 mg (2.0 mmol) of *p*-aminoacetophenone gave 354 mg of crude product, orange crystals, mp 195–200 °C. Recrystallization in ethanol–water gave 4-amino-4'-nitrochalcone (**4**), mp 212–215 °C; IR 3455, 3330, 3200 (w), 1630, 1600, 1580, 1550 cm^{-1}; anal. $C_{15}H_{12}N_2O_3$ (C, H, N).

1-(p-Aminophenyl)-3-ferrocenyl-2-propen-1-one (5). A similar condensation with 535 mg (2.5 mmol) of ferrocenecarboxaldehyde and 337 mg (2.5 mmol) of *p*-aminoacetophenone gave 407 mg of crude product, red crystals, mp 202–204 °C. Two recrystallizations in ethanol–water gave 1-(*p*-aminophenyl)-3-ferrocenyl-2-propen-1-one (**5**), mp 210–213 °C, IR 3425, 3300, 3170, 1640, 1620, 1599 cm^{-1}; anal. $C_{19}H_{17}NOFe \cdot 1/2H_2O$ (H, N).

4-Amino-4'-methylbenzophenone (6). 4-Methylbenzanilide was prepared by acylation of aniline with *p*-toluoyl chloride, mp 140–142 °C; IR 3350, 1648, 1599 cm^{-1}; ^1H NMR (DMSO-d_6) 2.10 (*s*, 3H, CH_3), 6.8–7.7 (*m*, 10H, aromatic and NH). A solution of 2.0 g of the anilide in 22.8 g of polyphosphoric acid was stirred and heated at 165–170 °C for 1 h. It was cooled to 100 °C, water (5 mL) was added, the mixture was stirred under

reflux 30 min and then cooled to room temperature. Water (50 mL) and 10% HCl (10 mL) were added, a small, black ppt. was filtered, and the filtrate was adjusted to pH 5.5 with NH_4OH. The brown ppt. was filtered, washed with water and vacuum dried: 1.152 g of crude product, mp 132–135 °C. Two recrystallizations in ethanol–water gave 4-amino-4'-methylbenzophenone (**6**), mp 167–169 °C (lit.[7] mp 184–185 °C); IR 3420, 3330, 3200, 1620, 1575 cm^{-1}; ^1H NMR (DMSO-d_6) 2.09 (*s*, 3H, $C\underline{H}_3$), 5.78 (*s*, 2H, $N\underline{H}_2$), 6.2–7.2 (*m*, 8H, aromatic); anal. $C_{14}H_{13}NO$ (H, N).

4-Amino-4'-chlorobenzophenone(7). A similar rearrangement was carried out with 2.0 g of 4-chlorobenzanilide (mp 188–190 °C; IR 3350, 1650, 1600 cm^{-1}) in 17.1 g of polyphosphoric acid at 190 °C for 30 min. A crude product, 1.784 g, was filtered from the acid solution, another 414 mg after treatment with NH_4OH. Recrystallization of the major product in ethanol gave a fraction, 510 mg, mp 180–190 °C, which appears to be the hydrochloride salt of the desired product. From its filtrate a second crop (similar to that obtained from NH_4OH neutralization, above) of 647 mg was obtained. Two recrystallizations of it in ethanol–water gave 4-amino-4'-chlorobenzophenone (**7**), mp 150–153 °C; IR 3410, 3325, 3210, 1615, 1575 cm^{-1}; anal. $C_{13}H_{10}ClNO \cdot 1/8HCl$ (C, H, N).

Acetone 3,4-dichlorobenzoyl hydrazone (8). A solution of 225 mg of 3,4-dichlorobenzoic acid hydrazide (**10**) in 12 mL of acetone was heated at reflux overnight. Evaporation left a residue that was recrystallized twice out of acetone to give the analytical sample, mp 136–139 °C; IR 3220, 1650, 1540 cm^{-1}; ^1H NMR ($CDCl_3$) 1.92 (*s*, 3H, $N{=}CC\underline{H}_3$), 2.02 (*s*, 3H, $N{=}CC\underline{H}_3$), 7.4, 7.5, 7.85 (*m*, 3H, aromatic $\underline{H}$), 9.08 (broad *s*, 1H, $O{=}CN\underline{H}$); anal. $C_{10}H_{10}N_2OCl_2 \cdot 1/2H_2O$ (C, H, N, Cl).

N,N'-Bis-(3,4-dichlorobenzoyl)hydrazine (9). The reaction of 2.095 g of 3,4-dichlorobenzoyl chloride with 10 mL of hydrazine at room temperature for 1 h, followed by addition of water gave 1.934 g of crude product. Recrystallization in methanol–DMF gave the analytical sample, mp 278–279 °C; IR broad 3400–3200, 1645, 1310, 1270, 1075, 910, 780 cm^{-1}; anal. $C_{14}H_8Cl_4N_2O_2$ (C, H, N).

3,4-Dichlorobenzoic acid hydrazide (10). A solution of 3,4-dichlorobenzoyl chloride in pyridine was treated with ethanol at room temperature; worked up in the usual way, it gave ethyl 3,4-dichlorobenzoate, mp 35–37 °C; IR ester C=O at 1730 cm^{-1}. It reacted with warm hydrazine (85%) to give the acid hydrazide, recrystallized in ethanol, mp 154–166 °C (lit.[9] mp 167–168 °C); IR 3280, 3180, 1600 cm^{-1}.

2,5-Dichlorobenzoic acid hydrazide (11). A similar reaction between methyl 2,5-dichlorobenzoate and hydrazine gave the hydrazide, mp 152–157 °C. Recrystallization in ethanol gave the analytical sample, mp 168–170 °C; anal. $C_7H_6N_2Cl_2O \cdot 1/6C_2H_5OH$ (C, H, N, Cl).

Piperonylic acid hydrazide (12). Methyl piperonylate and hydrazine gave the hydrazide, mp 171–173 °C, out of ethanol; anal. $C_8H_8N_2O_3$ (C, H, N).

4-Cyanobenzoic acid hydrazide (13). Ethyl 4-cyanobenzoate and hydrazine gave the hydrazide, mp 188–190 °C, out of ethanol; anal. $C_8H_7N_3O$ (C, H, N).

Radiation-protective evaluation

Male, Swiss Webster ND4 mice were obtained from Harlan Industries, Indianapolis, weighing 21–24 g, and housed five to a cage. Compounds that were soluble in soybean oil were dissolved; those that did not dissolve were suspended by rapid stirring. The mice were injected ip, and 30 min 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 Siemens Mevatron KD linear accelerator. Mice in the control group were injected with 0.2 mL of soybean oil and irradiated similarly.

Microcolony assay

Male, $B_6D_2F_1$ mice, 15–19 weeks of age, were injected ip with solutions or suspensions of test compounds in soybean oil 30 min before irradiation with 15 Gy ^{137}Cs delivered in a dual head Gamma Cell-40 instrument (Nordian, Inc.). Doses of the compounds are presented in Table 6. WR-2721 was dissolved in phosphate buffer (pH 6.8) and given ip 30 min before irradiation (8 mg/average 30 g mouse). Four days later, the mice were sacrificed by cervical fracture, and the portion of the jejunum from 1 to 6 cm distal to the ligament of Treiez was removed and fixed for histology. At least 9 cross sections of 5-micron thickness were prepared from each of 4 mice in each group. The number of regenerating foci in intestinal epithelial stem cells in the jejunal mucosa was counted in each group (N = 4).[11]

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