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5-(2,6-Difluorobenzyl)oxymethyl-5-methyl-3-(3-methylthiophen-2-yl)-1,2-isoxazoline as a Useful Rice Herbicide

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5-(2,6-Difluorobenzyl)oxymethyl-5-methyl-3-(3-methylthiophen-2-yl)-1,2-isoxazoline derivative was synthesized, and its herbicidal activity was assessed under glasshouse and flooded paddy conditions. 5-(2,6-Difluorobenzyl)oxymethyl-5-methyl-3-(3-methylthiophen-2-yl)-1,2-isoxazoline demonstrated good rice selectivity and potent herbicidal activity against annual weeds at 125 g of a.i. ha^{-1} under greenhouse conditions. Soil application of this compound showed complete control of barnyardgrass to the fourth leaf stage at 250 g of a.i. ha^{-1}. Field trials indicated that this compound controlled annual weeds rapidly with a good tolerance on transplanted rice seedlings by postemergence and soil application. This compound showed a low mammalian and environmental toxicity in various toxicological tests.

KEYWORDS: Annual weeds; barnyardgrass; isoxazoline; sulfonylurea; toxicity

INTRODUCTION

Throughout the world, rice is considered to be a major food crop, especially in southeast Asia. The yield of rice is considered to be significantly reduced when weeds are not controlled. In a paddy, there are many weeds of various species such as annuals and perennials and broad leaves and sedges, and the composition of weeds changes, depending upon the climate, area, and soil condition. Among various weeds, the barnyardgrass is noxious in both transplanted and direct-seeded rice cultivation because of its ecological similarity to rice. Many types of herbicides, including soil- or foliar-applied herbicides, have been developed and used to control barnyardgrass. Most of the herbicides can control barnyardgrass at younger than 2 leaf stages with soil application; however, older than 3 leaf stages of barnyardgrass is hardly controlled with soil-applied herbicides. Differences in ambient temperature in rice-growing areas may affect barnyardgrass germination and growth rates, enabling the weed to grow past the susceptible stage and escape control in some areas (*1*−*4*).

Rice growers have been waiting anxiously for the introduction of new potent herbicides that can selectively control annual and perennial weeds, especially including the late stage of barnyardgrass by a 1-time application. Recently, highly active ALS (acetolactate synthase or acetohydroxy acid synthase) inhibiting herbicides have been developed and used worldwide, and their formulations with a combination of various herbicides to control barnyardgrass showed the ability of controlling all weeds in 1 time, called "one-shot" herbicides. It is the reason that these ALS-inhibiting sulfonylurea herbicides are very effective in controlling various kinds of weeds, while some of them lack the ability to control gramineous weeds including barnyardgrass. Instead of a sequential application, a premixture, "one-shot" herbicide was quickly developed, which contained sulfonylurea (i.e., bensulfuron-methyl, pyrazosulfuron-ethyl, or imazosulfuron), dominant in rice-planted areas, today. Also, the request has been made for a new herbicide whose characteristics include low environmental pollution or harmful effects, high activity, low toxicity, high selectivity, and low persistence (*5*−*8*).

5-Benzyloxymethyl-5-methyl-3-aryl-1,2-isoxazolines derivatives were introduced in 1989 by BASF(Ref). These compounds are known to have the herbicidal activity and selectivity to rice with an unknown mechanism of action. A large number of analogues have been reported in which various substituents contain alkyl or benzene derivatives at the 3 position of isoxazoline ring and substitution at the 5 position with methyl or benzyloxymethyl groups. We focused on a new chemical group, 5-(2,6-difluorobenzyl)oxymethyl derivatives and evaluated the herbicidal performance of these isoxazoline derivatives in a greenhouse. The compounds studied here have a novel 2,6-difluorobenzyl oxymethyl group introduced at the 5 position of the isoxazoline moiety (**Figure 1**). 5-(2,6-Difluorobenzyl)oxymethyl-5-methyl-3-(3-methylthiophen-2-yl)-1,2-isoxazoline exhibits an excellent herbicidal activity on barnyardgrass with a wide application window from the pre-emergence up to the 4th leaf stage and good crop compatibility to transplanted rice (*9*−*12*).

The synthesis of a new isoxazoline derivative, its herbicidal activity under greenhouse conditions, field trial for "one-shot" herbicide, and its toxicological evaluation results are described in this paper.

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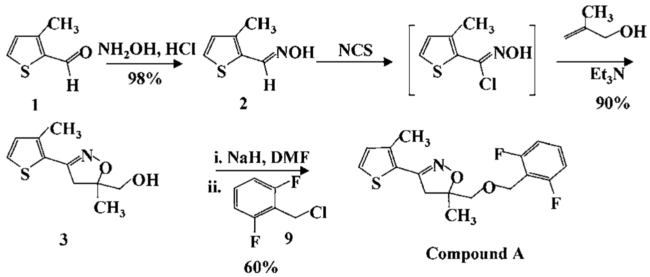

Figure 1. Organic synthesis and chemical structures.

MATERIALS AND METHODS

Synthesis. Isoxazoline derivatives were synthesized as described in our patent (*12*). **Figure 1** described the final steps of the synthesis from 3-methyl-2-thiophene carboxaldoxime to 5-(2,6-difluorobenzyl)oxymethyl-5-methyl-3-(3-methylthiophen-2-yl)-1,2-isoxazoline (compound A).

3-Methyl-2-thiophenecarboxaldoxime. Freshly distilled 3-methyl-2-thiophenecarboxaldehyde (126.0 g, 1.0 mol) was dissolved in ethanol/water solution (200 mL/150 mL), and hydroxylamine hydrochloride (76.5 g, 1.1 mol) was added during 15 min at 10−15 °C with good stirring. A solution of NaOH (44.0 g, 1.1 mol) in water (50 mL) was added dropwise to the reaction mixture, and it was stirred for an additional 15 min at room temperature. The reaction mixture was concentrated by rotary evaporation to precipitate white crystalline solids. The precipitates were filtered and dried under vacuum to afford 3-methyl-2-thiophenecarboxaldoxime (139.0 g, 98.5%).

5-Hydroxymethyl-5-methyl-[3-(3-methylthiophen-2-yl)]-1,2-isoxazoline. To a solution of 3-methyl-2-thiophenecarboxaldoxime (139.0 g, 0.98 mol) in DMF (300 mL) was added *N*-chlorosuccinimde (152.2 g, 1.14 mol) by potions for 45 min at 30−40 °C. After the reaction mixture was stirred for an additional 1 h, it was poured into methylene chloride (1000 mL). The solution was washed with aqueous 1 N HCl solution (200 mL × 2) and brine (300 mL × 2), dried over $MgSO_4$, and filtered. The filtrate was placed in a 2-L round-bottomed flask, and a mixture of 2-methylpropen-1-ol (86.6 g, 1.2 mol) and triethylamine (118.0 g, 1.2 mol) was added to the mixture by dropping in a funnel for 30 min at 5 °C. The reaction mixture was washed with brine (200 mL × 2), dried over $MgSO_4$, and concentrated by rotary evaporation to give a pale yellow solid. A total of 50 mL of ethyl acetate and 250 mL of hexane were added to the solids with good shaking, and then, the suspension was cooled in an ice bath. The solid precipitates were filtered and washed with hexane to give 5-hydroxymethyl-5-methyl-3-(3-methylthiophen-2-yl)-1,2-isoxazoline as an ivory solid (186.0 g, 90%).

5-(2,6-Difluorobenzyl)oxymethyl-5-methyl-3-(3-methylthiophen-2-yl)-1,2-isoxazoline. To a solution of 5-hydroxymethyl-5-methyl-3-(3-methylthiophen-2-yl)-4,5-dihydroisoxazole (105.5 g, 0.5 mol) in DMF (400 mL) was added NaH (60% in mineral oil, 24.0 g, 0.6 mol) during 15 min at 40 °C, and the mixture was stirred for 15 min at that temperature. A solution of 2,6-difluorobenzyl bromide (124.0 g, 0.6 mol) in DMF (60 mL) was added to the reaction mixture during 15 min, and the reaction temperature increased to 60−70 °C. The reaction mixture was stirred for an additional 1 h at that temperature and poured into ice water (500 mL). The solution was extracted with ethyl acetate (500 mL × 2), and the organic layer was washed with 1 N HCl solution (200 mL × 2) and brine (200 mL × 2). The organic layer was dried over $MgSO_4$ and concentrated to form as oil. The oil was purified by silica gel column chromatography (300 g, 1:20 ethyl acetate/hexane), and the crude product was recrystallized in hexane to give 5-(2,6-difluorobenzyl)oxymethyl-5-methyl-3-(3-methylthiophen-2-yl)-1,2-isoxazoline as a white crystalline solid (100.0 g, 60%). mp: 45−46 °C. ^1H NMR ($CDCl_3$) δ: 1.42 (s, 3H), 2.41 (s, 3H), 2.95 (d, 1H, J = 16.5 Hz), 3.41 (d, 1H, J = 16.5 Hz), 3.53 (dd, 2H, J = 10.0, 15.9 Hz), 4.68 (s, 2H), 6.82−6.89 (m, 3H), 7.20−7.25 (m, 2H). MS *m/z* (relative intensity): 338 (17.8), 337 (42.5), 180 (87.3), 137 (100), 127 (53.6). IR (KBr, cm^{-1}): 3104.0, 2973.2, 2928.2, 2882.7, 1626.8, 1594.1, 1471.0, 1234.7, 1097.5, 1056.6, 786.0. Anal. Calcd for $C_{17}H_{17}F_2NO_2S$: C, 60.52; H, 5.08; N, 4.15; S, 9.50. Found: C, 60.53; H, 5.20; N, 4.14; S, 9.43. UV λ_{max}: 279.5 cm^{-1}

Screening under Greenhouse Conditions. Three rice seedlings (cv. Dongin) at 2.5 leaf stages were transplanted at a 2-cm depth in a pot (surface area, 140 cm^2) filled with muddy loam soil (clay, 14%; total carbon, 1.5%; pH 5.6). Eight annual weed seeds were sown at 0.5∼1.0-cm depths in the same pot. The pots were maintained under flooded conditions at a 3-cm depth of water at 28−33 °C (day) and 20−26 °C (night) in a greenhouse. The stock solution of test compounds in acetone and water (50/50 by volume) was gently added to the water surface at a prescribed rate of 5 days after transplanting. A total of 3 weeks after the application, the herbicidal efficacy and rice injury was evaluated on a visual scale of 0 (inactive or no damage) to 100 (complete kill of weed or crop). Final results were presented as the average of triplicates.

Combination Experiment. Three rice seedlings (cv. Dongin) of 2.5 leaf stages were transplanted at a 3-cm depth in a pot (surface area, 500 cm^2). A total of 10 annual and perennial weed species were sown at 0.5∼1.0-cm depths in the same pot. The test compound and several sulfonylurea in acetone were mixed and applied to the water surface at 13 days after seeding (DAS). A total of 3 weeks after the application, the herbicidal activity was evaluated on a visual rating scale as described above.

Field Trial. Field experiments were conducted in the year 2002 at the experimental field in the Korean Research Institute of Chemical Technology, Taejon, Korea. The soil was a silty to sandy loam soil with a composition of 51% sand, 39% silt, and 10% clay. The content of organic matter was 1.2%, and the pH of the soil was 5.9. The field was rotavated and leveled in submerged conditions, and rice seedlings (3 leaf stages, cv. Donjin) were transplanted with a transplanting machine to an approximately 3-cm depth with 30-cm row spacing on May 10th. To evaluate the herbicidal activity, the pregerminated seed of annual weed species and rhizomes of perennial weeds were additionally sown within each plot (2 × 3 m^2). The test compounds were formulated as granules (2/0.7% G, 600/21 g of a.i. ha^{-1}) of the following composition: test compound, 2.0/0.7 g; sodium tripolyphosphate, 2 g; sodium dodecylbenzene sulfonate, 0.1 g; talc, 30 g; and bentonite, 65.2 g. The granule was dropped uniformly on the water surface of the plot at a prescribed rate 15 days after transplanting the rice seedlings. Rice injury was estimated by visual rating on a 0∼100 scale. Weed control at 45 days after application was determined as the average of triplicates by the comparison of each weed species remaining in the quadrat (0.5 × 0.5 m^2) with those in the untreated.

Toxicology. Acute toxicity, genetic toxicity, and aquatic toxicity tests were performed according to the OECD standard procedure (*13*−*15*). LC_{50} data for compound A was obtained from a mouse for acute toxicity and *Oryzias latipes* and *Daphnia magna* for aquatic toxicity. For genetic toxicity test, stock solutions of these compounds were prepared by dissolving the compounds in dimethyl sulfoxide. Chinese hamster lung fibroblast (CHL) cells were maintained in minimum essential medium supplemented with 5% fetal bovine serum (GIBCO BRL, Grand Island, NY). Cells were harvested using 0.2% trypsin and seeded onto Ø 50-mm culture dishes. The cells were then allowed to grow at 37 °C in a 5% CO_2−95% air-humidified incubator.

RESULTS AND DISCUSSIONS

Synthesis. As mentioned above, 5-benzyloxymethyl-1,2-isoxazolines were described as herbicides and we discovered that when we substituted R groups with phenyl or aminocarbonyl groups (*12*). They showed good herbicidal activity against weeds including barnyardgrass in paddy fields. Also, we substituted various aromatic groups, furans, and thiophenes at the 3 position in 5-benzyloxymethyl-1,2-isoxazoline and evaluated their herbicidal effects under submerged paddy conditions (*12*). Among them, thiophene derivatives showed significant herbicidal activity under rice paddy conditions with good safety to the transplanted rice. Various 5-benzyloxymethyl-5-methyl-3-thiophenyl-1,2-isoxazolines were prepared from substituted thiophenocarboxyaldoxime by several steps described above. The modifications of substituents on the thiophene ring and

Table 1. Herbicidal Activity of Compound A on the Annual Paddy Weeds Treated at 5 DA(S)T[a]

		annual weed species							
rate (g/ha)	rice(TR)	ECHOR	SCPJU	MOOVA	LIDPY	ROTIN	ANEKE	CYPDI	LUDPR
1000	0	100	50	100	87	100	70	100	100
500	0	100	37	100	53	100	23	100	100
250	0	100	0	100	50	100	0	100	100
125	0	100	0	100	33	100	0	100	100
62.5	0	63	0	20	33	30	0	100	100

[a] DA(S)T, days after (seeding) transplanting; TR, transplanted rice; rice(TR), transplanting 2.5 leaf stages of rice seedlings; ECHOR, *Echinochloa oryzicola*; SCPJU, *Scirpus juncoides* ROXB.; MOOVA, *Monochoria vaginalis* PRESL.; LIDPY, *Lindernia pyxidaria* L.; ROTIN, *Rotala indica* KOEHE.; ANEKE, *Aneilema keisak* HASSK.; CYPDI, *Cyperus difformis* L.; LUDPR, *Ludwigia prostrata* ROXB. Results are evaluated 3 weeks after application by visual rating scales of 0–100.

5-benzyl ring were mainly performed. In general, isoxazolines attached at the 2 position of thiophene ring showed better herbicidal activity than those attached at the 3 position. In case of 3-(thiophen-2-yl)-isoxazolines, 3 substituents such as methyl and bromine in thiophene and the 5-(2,6-difluorobenzyl)-oxymethyl group increased the herbicidal activity along with the selectivity for rice (*12*).

Herbicidal Activity and Selectivity under Greenhouse Conditions. Compound A, 5-(2,6-difluorobenzyl)oxymethyl-5-methyl-3-(3-methylthiophen-2-yl)-1,2-isoxazoline, showed the best results in herbicidal activity against paddy weeds and safety to rice. This compound also showed good safety to transplanted rice at 1000 g of a.i. ha^{-1} and potent herbicidal activity on annual weeds, such as *Echinochloa oryzicola*, *Monochoria vaginalis*, *Rotala indica*, *Cyperus difformis*, and *Ludwigia prostrate*, at a rate of 62.5∼125 g of a.i. ha^{-1} when applied at 5 days after transplanting (DAT). Even at the rate of 62.5 g of a.i. ha^{-1}, this compound showed complete control of *Cyperus difformis* and *Ludwigia prostrata* tested. However, *Scirpus juncoides*, *Lindernia pyxidaria*, and *Aneilema keisak* were not controlled by this compound even at the rate of 1000 g of a.i. ha^{-1} (**Table 1**).

This compound showed excellent control efficacy to 2 and 3 leaf stages (LS) of barnyardgrass at 62.5 g of a.i. ha^{-1}; however, 250 g of a.i. ha^{-1} was required to control 4 LS of barnyardgrass (**Figure 2**).

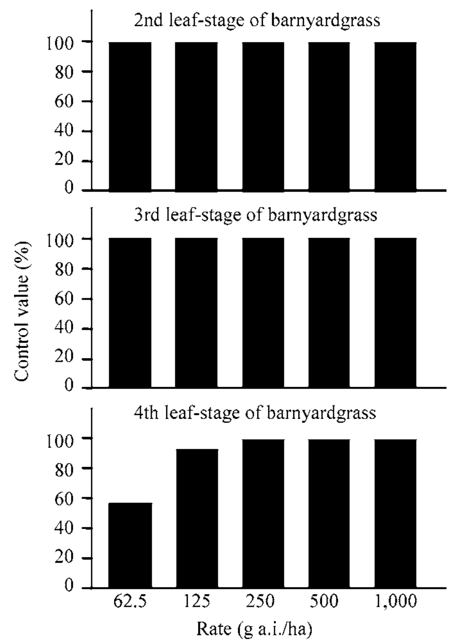

Figure 2. Control values of compound A against the leaf stages of barnyardgrass under greenhouse conditions.

Combination Activity. As shown in **Table 2**, a combination effect of compound A and five sulfonylurea herbicides was evaluated against six annual and four perennial weeds in a pot test under greenhouse conditions. All of these combinations were safe to the transplanting rice and showed excellent weed control activity to these weeds tested. A combination with bensulfuron, cyclosulfamuron, halosulfuron, and azimsulfuron showed the additive effect to the *Echinochloa oryzicola*. *Aeschynomene indica* was also effectively controlled in the combination of bensulfuron, but the combination of pyrazosulfuron showed an antagonistic interaction to *Scirpus juncoides*. These results showed that the 300 g of a.i. ha^{-1} of this compound was enough for the purpose of these combinations.

Field Trial. The combination of compound A and pyrazosulfuron (2/0.7%, 600/21 g of a.i. ha^{-1}) granules showed excellent weed control (≥98%) efficacy against annual and perennial weeds treated at 15 days after transplanting. The reference of molinate/pyrazosulfuron (5/0.7%, 1500/21 g of a.i. ha^{-1}) granules also showed low injury and herbicidal activity; however, the test compound showed better efficacy compared to the reference (**Table 3**). This mixture induced slight injury to the transplanting rices at 1200/42 g of a.i. ha^{-1}, twice the recommended rate.

Toxicity. Acute toxicity (LD_{50} data) of compound A to mice was over 5000 mg/kg. This compound showed low aquatic toxicity with an LC_{50} of 1.9 and 2.7 mg/L to *Oryzias latipes* and *Daphnia magna*, respectively. They did not show any harmful effects on the Chinese hamster lung fibroblast (CHL) cells, being negative in both mutation and chromosome aberration tests (**Table 4**). These results were sufficient toxicological data for pesticide registration in Korea.

In the recent year, many types of herbicides have been introduced for selective control of annual weeds, especially including the late stage of barnyardgrass and perennial weeds as "one-shot" herbicides in paddy rice fields. Most of the herbicides can control barnyardgrass at younger than 2 leaf stages with soil application; however, older than 3 leaf stages of barnyardgrass are hardly controlled with soil-applied herbicides (*1*−*3*). We focused on the new chemical group, 5-benzyloxymethyl-1,2-isoxazoline derivatives, and evaluated the herbicidal performance of these isoxazoline derivatives in a greenhouse and field trials. Among these compounds, 5-(2,6-difluorobenzyl)oxymethyl-5-methyl-3-(3-methylthiophen-2-yl)-1,2-isoxazoline was identified to have excellent efficacy on barnyardgrass, being in wide growth stages from the 2 leaf to 4 leaf stage, and good crop compatibility to transplanted rice. Also, we evaluated the herbicidal properties in soil and a combination effect of this compound with sulfonylurea herbicides as a one-shot herbicide. Furthermore, mammal toxicity was investigated as informal methods.

Table 2. Combination Activity between Compound A and Several Sulfonylureas[a]

herbicide	rate (g/ha)	ORYSA (TR)	ECHOR	SCPJU	MOOVA	ANEKE	LUDRP	AESIN	SAGPY	ELOKU	SAGTR	CYPSE
com. A + PYR	0/21	10	100	100	100	100	90	70	70	95	90	100
	300/21	0	100	100	100	100	100	80	70	100	80	98
	600/21	0	100	50	80	100	90	100	70	100	80	98
com. A + BEN	0/51	0	60	50	90	60	90	30	50	90	80	95
	300/51	0	100	50	90	40	90	70	70	100	80	95
	600/51	0	100	60	90	40	90	100	60	100	80	95
com. A + CYC	0/60	0	60	60	90	100	80	100	70	90	90	100
	300/60	0	100	50	90	100	80	100	70	100	80	95
	600/60	10	100	50	90	100	80	100	60	100	60	90
com. A + HAL	0/54	20	90	50	80	60	100	100	60	100	80	100
	300/54	10	100	50	90	100	100	100	70	100	90	100
	600/54	10	100	50	90	100	80	100	70	100	90	100
com. A + HAL	0/15	0	95	70	90	100	100	90	60	95	80	100
	300/15	0	100	60	90	100	90	100	50	95	80	100
	600/15	0	100	60	80	100	90	100	60	100	80	100

[a] Herbicide was applied at 13 days after transplanting (TR). PYR, pyrazosulfuron; BEN, bensulfuron; CYC, cyclosulfamuron; HAL, halosulfuron; AZY, azimsulfuron. Results are evaluated 3 weeks after application by visual rating scales of 0–100.

Table 3. Herbicidal Activity and Rice Injury of Compound A in Combination with Pyrazosulfuron under a Submerged Paddy Field

treatment	application (g of a.i. ha^{-1})	rice injury[a]		control value (%)			
		R	D	ECHOR[b]	other annuals[c]	perennials[d]	total[e]
compound A/pyrazosulfuron (granule)	600/21	10	30	98.8	98.3	97.9	98.3
molinate/pyrazosulfuron (granule)	1500/21	10	20	95.9	94.5	96.5	95.6

[a] Rice injury, transplanted rice at three leaf stages of seedling; rice injury, where 0 indicates no visible effect and 100 indicates complete death of plants. R, recommended rate; D, double rate. [b] ECHOR, *Echinochloa oryzicola*. [c] Other annuals included *Scirpus juncoides*, *Monochoria vaginalis*, *Lindernia pyxidaria*, *Rotala indica*, *Aneilema keisak*, *Cyperus difformis*, and *Ludwigia prostrata*. [d] Perennials included *Cyperus serotinus*, *Sagittaria pygmaea*, *Eleocharis kuroguwai*, and *Sagittaria trifolia*. [e] Total means the average control values of ECHOR, other annuals, and perennials.

Table 4. Toxicological Data for Compound A

	acute toxicity	genetic toxicity		aquatic toxicity	
	mouse	mutation	chromosome aberration test	*Oryzas latipes*	*Daphnia magna*
compound A	>5000 mg/kg	negative	negative	1.9 mg/L	2.7 mg/L

In transplanting rice cultivations, herbicide application has been usually carried out around 10 days after transplanting. It is the reason for securing rice safety from herbicidal crop injury. However, many kinds of weeds might have occurred and grew up to 2 leaf stages of seedlings during these periods. This compound showed good safety to transplanted rice at 1000 g of a.i. ha^{-1} and herbicidal activity to the aged barnyardgrass. These advantages were more active and valuable to rice cultivation as a one-shot herbicide. It is the reason of sulfonylurea herbicides that is very effective in controlling various kinds of weeds other than gramineous weeds, including barnyardgrass. A combination effect with several sulfonylurea herbicides was safe to the transplanting rice and showed excellent weed control activity to annual and perennial weed species. It is suggested that these results might have a good possibility for developing a mixture with sulfonylurea herbicide as a one-shot herbicide for rice cultivation.

In conclusion, 5-(2,6-difluorobenzyl)oxymethyl-5-methyl-3-(3-methylthiophen-2-yl)-1,2-isoxazoline will be selected as the most useful herbicide in paddy rice from the results of the pot tests in a greenhouse. Its excellent herbicidal performance has also been confirmed in field trials and by investigation of its mammalian toxicity.

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