ALS阻害型除草剤KIH-2023のラットにおける代謝

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Original Article

Metabolism of ALS Inhibitory Herbicide Bispyribac-sodium [KIH-2023] in Rats

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Absorption, distribution and metabolism of Bispyribac-sodium [sodium 2,6-bis(4,6-dimethoxypyrimidin-2-yloxy)benzoate] or [KIH-2023] in rats orally dosed with ^{14}C-KIH-2023 were investigated. More than 90% of the dosed radioactivity was detected in the excreta within 96 hr after dosing. Level of the radioactivity in the blood of male and female rats reached maxima at 2 and 1 hr after dosing, respectively, and then decreased rapidly to about a half level of maxima ($C_{1/2}$). The radioactivity of tissues was lower at 96 hr after dosing than that at $C_{1/2}$-time. Most of the radioactivity in the urine, feces, liver and plasma was detected as unchanged KIH-2023. The major radioactive compounds excreted into the bile were KIH-2023 and its glucuronide. Repeated oral administration of KIH-2023 for 15 days gave similar results from the single oral one in the excretion, tissue distribution and metabolism of ^{14}C-KIH-2023.

INTRODUCTION

Bispyribac-sodium [sodium 2,6-bis(4,6-dimethoxypyrimidin-2-yloxy) benzoate] or [KIH-2023] is a new herbicide, found and being developed by Kumiai Chemical Industry Co., Ltd.[1] KIH-2023 is effective for wide species of weeds, especially for barnyard grass, broadleaf signal grass, smart weed, cocklebur and day flower through the inhibition of acetolactate synthase (ALS) of these weeds, while not for rice and wheat.[2] The LD_{50} value to rats when orally administered was estimated to be 4111 mg/kg body weight in male rat and 2635 mg/kg body weight in female rat. These data suggest that KIH-2023 may be useful as a practical herbicide if it has little problem in mammalian toxicity. This report describes the excretion, tissue distribution and metabolic fate of KIH-2023 after oral administration of ^{14}C-KIH-2023 in rats.

MATERIALS AND METHODS

1. *Chemicals*

The authentic compounds used and their abbreviations are shown in Table 1. Structures of the compounds were confirmed by MS, NMR and IR spectrum analyses. Py-^{14}C-KIH-2023 [sodium 2,6-bis(4,6-dimethoxy[2-^{14}C]pyrimidin-2-yloxy)benzoate] and Bn-^{14}C-KIH-2023 [sodium 2,6-bis(4,6-dimethoxypyrimidin-2-yloxy) [U-^{14}C]benzoate] were obtained from Daiichi Pure Chemicals Co., Ltd.; their structures and labeled positions are shown in Fig. 1. The specific activities of the two compounds are 1.55 GBq/mmol and 0.807 GBq/mmol, respectively, and the radiochemical purity was higher than 97%, based on TLC and HPLC analyses.

2. *Treatment of Animals*

Fischer F344/NSlc male and female rats (7

Table 1 Authentic compounds used and their *Rf* values on TLC.

Authentic compound	[Abbreviation]	*Rf* values	
		A[a]	B[a]
2,6-Bis(4,6-dimethoxypyrimidin-2-yloxy)-benzoic acid[b]	[KIH-2023]	0.56	0.82
2-(5-Hydroxy-4,6-dimethoxypyrimidin-2-yloxy)-6-(4,6-dimethoxypyrimidin-2-yloxy)benzoic acid	[5-OH-2023]	0.56	0.77
2-Hydroxy-6-(4,6-dimethoxypyrimidin-2-yloxy)-benzoic acid	[BX-180]	0.56	0.73
2-(4-Hydroxy-6-methoxypyrimidin-2-yloxy)-6-(4,6-dimethoxypyrimidin-2-yloxy)benzoic acid[b]	[DesMe-2023]	0.39	0.60
2-Hydroxy-6-(4-hydroxy-6-methoxypyrimidin-2-yloxy)benzoic acid	[DesMe-180]	0.37	0.43
2-Hydroxy-4,6-dimethoxypyrimidine	[Me_2BA]	0.60	0.41
2,4-Dihydroxy-6-methoxypyrimidine	[MeBA]	0.52	0.36

[a] Solvent systems, A, chloroform: methanol: water=26: 14: 1; B, ethyl acetate: formic acid: water=28: 1: 1.

[b] Sodium salt was used.

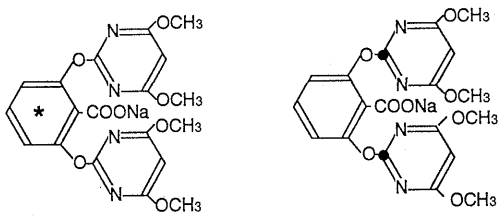


Fig. 1 Chemical structures and ^{14}C-labeled positions (* and ●) of ^{14}C-KIH-2023.

weeks old) were purchased from Japan Slc, Inc. and acclimated for a week at 25±1°C and fasted for 16 hr before the dosing. Every four male or female rats were accepted single oral administration of Py- or Bn-^{14}C-KIH-2023 at 5 or 100 mg/kg which was dissolved in distilled water. They were housed individually in all-glass fine metabolic cages (Metabolica-CO_2, Sugiyamagen Iriki Co., Ltd., Japan) to collect the urine, feces and expired radioactive carbon dioxide individually at every 24 hr after dosing. At $C_{1/2}$-time or 96 hr post dose, rats were sacrificed under ether anesthesia, withdrawing the blood from descending *vena cava*, and extirpated for various tissues and organs. To trace the level of the radioactivity after dosing, the blood was collected from the tail vein and combusted by 307 sample oxidizer (Packard, U.S.A.). The bile was collected through cannula inserted to the bile duct by anatomy. For the experiment of repeated administration, two male and female rats were orally administered with 5 mg/kg/day of unlabeled KIH-2023 once a day for 15 days. On day 16, the rats were orally administered with 5 mg/kg of Py-^{14}C-KIH-2023. The radiochemical purity of ^{14}C-KIH-2023 solution administered to rats was confirmed by TLC analysis.

3. *Analysis of Metabolites in Excreta, Liver and Plasma*

The feces collected for 0–24 and 24–48 hr after dosing was added with an equal volume of distilled water and homogenized well. The feces homogenate was extracted with a 60-fold volume of a solvent mixture (acetonitrile: water=2: 1) by sonication (29 kHz, 200 W, 15 min), and then centrifuged (1000 rpm, 1 min). The supernatant of the extract was filtered and concentrated *in vacuo*. Aliquot of the concentrate of feces extract or the original urine was applied to TLC analysis for the assay of radioactive metabolites.

For the assay of radioactive conjugates, the bile was incubated with β-glucuronidase (Sigma Chemical Co., U.S.A., EC 3.2.1.31) in

an acetate buffer solution (pH 5.0, 0.1 M) at 37°C for 6 hr. After incubation, the ^{14}C-compounds in the solution were extracted by ethyl acetate at pH 3.5 and dehydrated with Na_2SO_4. The ethyl acetate layer was applied to TLC analysis after the concentration *in vacuo*.

The liver was homogenized in an 80-fold volume of a solvent mixture (acetonitrile: water=1: 1), and supernatant (2000 rpm, 10 min) of the homogenate was concentrated *in vacuo* and extracted by ethyl acetate at pH 3.5. The ethyl acetate extract was dehydrated with Na_2SO_4, concentrated *in vacuo* and then applied to TLC analysis.

The blood sample was centrifuged (3000 rpm, 10 min) to separate plasma and blood-cells in a heparinized test tube. To an aliquot of the plasma, a 60-fold volume of acetone-acetonitrile (2: 1) was added, and the mixture was sonicated (29 kHz, 200 W, 5 min) and centrifuged (2000 rpm, 10 min). The supernatant was filtrated and concentrated *in vacuo* to apply to TLC-autoradiography (ARG) analysis.

4. TLC Analysis

For TLC analysis, pre-coated silica gel 60F254 chromatoplates (20×20 cm, 0.25 mm layer thickness, E. Merck, Germany) were used. The original urine or bile was spotted directly on a TLC plate together with the authentic compounds shown in Table 1. The extracts from the feces, liver, plasma or the enzymatic hydrolysate from the bile was spotted on a TLC-plate together with the authentic compounds and developed two-dimensionally by the solvent systems shown in Table 1. The authentic compounds were detected under UV lamp (Manaslu, Japan) and the radioactive metabolites by autoradiography (ARG) using medical X-ray film (Fuji photo film Co., Ltd., Japan). *Rf* values of the authentic compounds are shown in Table 1.

5. Mass Spectrometry

An HPLC-MS system (Hitachi Ltd., Japan) was used in the atmospheric pressure ionization (API) positive mode to determine glucuronide. The system consisted of a Hitachi M-2000A mass spectrometer (API drift voltage=650 V, aperture temperature=360°C), a Hitachi L-6200 intelligent pump (mobile phase; acetonitrile: water=60: 40, 1.0 ml/min), a Capcel PAK C18 SG type HPLC column (Shiseido Co., Ltd., Japan; i.d.=4.6 mm, length=250 mm) and a Hitachi M-003 data processing system.

6. Radioactivity Measurement

The radioactive carbon dioxide trapped in 2-aminoethanol was diluted with methanol. Aliquots of radioactive feces and plasma were solubilized by using Protosol (NEN Research Products, U.S.A.). Radioactive regions on the silica gel TLC plate were scraped off, dissolved in 1 ml of methanol, and added with toluene-scintillator containing 0.4% of DPO and 0.005% of POPOP. Aliquots of urine, bile or aqueous fraction after the ethyl acetate extraction was dissolved in Hionic-Fluor scintillator (Packard, U.S.A.). Organs, tissues, blood cells, plasma protein and unextractable residues of feces were combusted by the sample oxidizer. Radioactivity in the scintillation solutions was measured by a liquid scintillation spectrometer (ESCR method; Aloka LSC-3100).

RESULTS

1. ^{14}C-Excretion

Figure 2 shows the excretion pattern of ^{14}C-radioactivity in rats orally administered with Py-^{14}C-KIH-2023 at 100 mg/kg body weight. More than 90% of the dosed radioactivity was detected in the excreta within 96 hr. The excretion ratio into feces was higher than urine, especially in male rats. Although data are not shown, similar results were obtained from the assays using Bn-^{14}C-KIH-2023 at 100 mg/kg and also in the assays using Py-^{14}C-KIH-2023 at 5 mg/kg. On the other hand, no radioactivity was detected in the expiration within 48 hr. Moreover, the pattern was not significantly changed in rats orally administered Py-^{14}C-KIH-2023 at 5 mg/kg after oral administration of unlabeled KIH-2023 at 5 mg/kg/day for 15 days.

2. ^{14}C-Levels in Blood and Tissues

Levels of radioactivity in blood after single oral administration of Py-^{14}C-KIH-2023 at

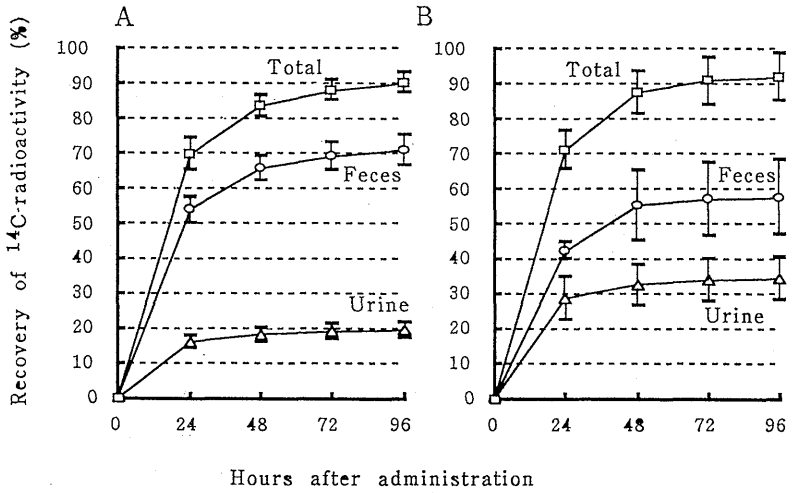


Fig. 2 Cumulative ^{14}C excretion after single oral administration of Py-^{14}C-KIH-2023 at 100 mg/kg in rats.

A: male, B: female (mean±S.D. for four rats).

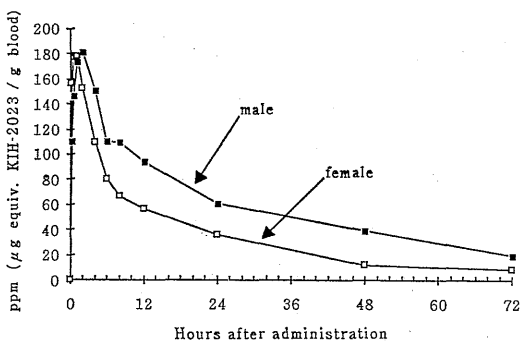


Fig. 3 Level of ^{14}C-radioactivity in the blood of rats orally dosed with Py-^{14}C-KIH-2023 at 100 mg/kg (mean for two rats).

100 mg/kg are shown in Fig. 3. The ^{14}C-radioactivity in blood reached peak (C_{max}: *ca.* 180 ppm) at 1 hr after dosing in female and 2 hr in male rats and then decreased. The $C_{1/2}$-time was estimated to be approximately 5 and 7 hr in female and male rats, respectively. The area under the curve (AUC) of male rats exceeded that of female.

Tissue distribution of ^{14}C-radioactivity in the rats dosed with Py- and Bn-^{14}C-KIH-2023 at 100 mg/kg is shown in Table 2. In any tissues, ^{14}C-concentration at 96 hr post dose is 10 or more times lower than that at $C_{1/2}$-time. The liver and blood contained higher concentration of ^{14}C-radioactivity than any other tissues. The two ^{14}C-labeled positions in KIH-2023 showed no difference in the tissue distribution of radioactivity.

Table 3 shows tissue distribution of ^{14}C-radioactivity in repeatedly-dosed or single-dosed rats with Py-^{14}C-KIH-2023 at 5 mg/kg. At 96 hr after dosing, the level in tissues of the repeatedly dosed male rats was slightly lower than that in the single-dosed ones. In general, the level of ^{14}C-radioactivity in the female rats showed lower level than that of male rats.

3. *Metabolites in Excreta, Liver and Plasma*

The amounts of metabolites in the excreta of male and female rats dosed at 100 mg/kg are shown in Table 4. At the period of 0–24 hr after dosing, most of the ^{14}C-compounds excreted in the urine and feces was identified to be unchanged KIH-2023 (61–65% of dosed-^{14}C). The principal metabolites was DesMe-2023 (6–9%). BX-180, 5-OH-2023, DesMe-180, Me_2BA and MeBA were also detected (0.2–3.1%) together with unidentified metabolites (0.7–1.9%). Excreta from 24–48 hr also contained KIH-2023 as the major radioactive compound and the metabolic pattern was similar to the excreta from 0–24 hr.

Table 5 shows the amount of ^{14}C-compounds detected in the liver of rats dosed with Py- or

Table 2 Distribution of ^{14}C-radioactivity in blood and tissues of rats orally dosed with Py- or Bn-^{14}C-KIH-2023 at 100 mg/kg.

Tissues	ppm (μg equiv. to KIH-2023/g tissue)[a]					
	Male			Female		
	7 hr	96 hr		5 hr	96 hr	
	Py[b]	Py[b]	Bn[b]	Py[b]	Py[b]	Bn[b]
Blood	99.5	4.6	3.3	78.6	3.0	1.3
Liver	100.6	5.8	5.2	90.6	2.7	1.3
Pancreas	22.4	0.6	0.7	11.1	0.4	0.2
Spleen	13.8	0.6	0.6	10.6	0.7	0.2
Kidney	43.3	1.6	1.7	38.9	1.4	0.6
Lung	36.8	1.7	1.4	27.6	1.2	0.6
Heart	28.1	1.2	1.0	22.0	1.0	0.4
Brain	2.9	0.1	0.2	2.6	0.2	N.D.
Testis	23.1	0.9	0.9	—	—	—
Ovary	—	—	—	29.1	1.1	0.5
Uterus	—	—	—	34.0	1.2	0.6
Bladder	—	—	1.1	—	—	—
Fat	17.3	—	0.4	8.3	—	0.1
Muscle	10.5	—	0.5	7.4	—	0.2

[a] Data present mean values for two rats.
[b] Py: Py-^{14}C-KIH-2023 was dosed. Bn: Bn-^{14}C-KIH-2023 was dosed.
N.D.: not detected (<0.1 ppm), —: not determined.

Table 3 Distribution of ^{14}C-radioactivity in blood and tissues of rats orally dosed with Py-^{14}C-KIH-2023 at 5 mg/kg.

Tissues	ppm (μg equiv. to KIH-2023/g tissues)[a]				
	Male			Female	
	Repeated[b]		Single	Repeated[b]	
	7 hr	96 hr	96 hr	5 hr	96 hr
Blood	6.19	0.74	1.22	5.13	0.34
Liver	18.87	0.94	1.68	19.39	0.24
Pancreas	0.74	0.12	0.19	1.23	0.06
Spleen	0.88	0.11	0.16	0.81	0.06
Kidney	2.54	0.27	0.41	3.67	0.12
Lung	3.59	0.31	0.44	2.71	0.18
Heart	1.91	0.22	0.33	1.68	0.10
Brain	0.25	0.03	0.04	0.18	0.02
Testis	1.38	0.19	0.21	—	—
Ovary	—	—	—	2.36	0.11
Uterus	—	—	—	2.66	0.14
Fat	0.63	0.09	—	1.07	0.04
Muscle	0.47	0.07	—	0.56	0.04

[a] Data represent mean values for two rats.
[b] Unlabeled KIH-2023 was repeatedly dosed for 15 days at 5 mg/kg/day before the administration of ^{14}C-KIH-2023 at 5 mg/kg.
—: not determined.

Bn-^{14}C-KIH-2023 at $C_{1/2}$-time. About 90% of the radioactive compounds was identified as KIH-2023. The metabolic pattern was not remarkably different between Py- and Bn-labeling, between male and female, and between single administration (at 100 mg/kg) and repeated administration (at 5 mg/kg).

Table 6 shows the distribution of ^{14}C in the blood of rats dosed with Bn-^{14}C-KIH-2023 at 100 mg/kg at $C_{1/2}$-time. Most of the radioactivity was found in plasma, particularly in its extract fraction, mainly as unchanged KIH-2023. Its metabolites, *i.e.*, 5-OH-2023, BX-180, DesMe-2023, and DesMe-180, were detected at low level.

4. Biliary Excretion

Three male rats dosed with Py-^{14}C-KIH-2023 at 100 mg/kg excreted 20 to 45% dose of radioactivity into the bile at 0–48 hr. The metabolites recovered from the bile are shown in Table 7. One of the major ^{14}C-compounds was unchanged KIH-2023 and the other was its β-glucuronic acid conjugate. The aglycone of the latter was characterized as ^{14}C-KIH-2023 after β-glucuronidase treatment. Figure 4

Table 4 Amounts of metabolites in the excreta of rats orally dosed with Bn- or Py-^{14}C-KIH-2023 at 100 mg/kg.

Dose (sample duration) compound	% dose of ^{14}C-radioactivity[a]					
	Male			Female		
	Urine	Feces	Total	Urine	Feces	Total
Bn-^{14}C-KIH2023 (0–24 hr)						
KIH-2023	11.2	54.0	65.2	19.5	44.4	63.8
5-OH-2023	0.1	0.6	0.7	ND	0.6	0.6
BX-180	0.4	1.6	2.0	2.2	0.9	3.1
DesMe-2023	0.9	4.8	5.7	3.8	4.0	7.8
DesMe-180	0.2	0.4	0.6	1.3	0.2	1.5
Others	0.1	1.4	1.5	ND	1.1	1.1
Unextractable		3.5	3.5		3.8	3.8
Total	12.9	66.3	79.2	26.8	55.0	81.7
Bn-^{14}C-KIH-2023 (24–48 hr)						
KIH-2023	1.4	6.0	7.4	1.1	4.1	5.2
5-OH-2023	ND	ND	ND	ND	ND	ND
BX-180	0.1	0.7	0.8	0.2	0.3	0.5
DesMe-2023	0.4	0.4	0.8	0.6	0.2	0.8
DesMe-180	0.1	0.2	0.3	0.1	0.1	0.2
Others	ND	1.4	1.4	0.1	0.3	0.4
Unextractable		0.7	0.7		0.6	0.6
Total	2.0	9.4	11.4	2.1	5.6	7.7
Py-^{14}C-KIH-2023 (0–24 hr)						
KIH-2023	13.1	48.0	61.1	23.8	37.9	61.7
5-OH-2023	0.1	1.0	1.1	0.5	0.7	1.2
BX-180	0.4	1.1	1.5	0.5	0.4	1.0
DesMe-2023	1.8	7.4	9.2	1.4	5.5	6.9
Me_2BA	0.1	0.4	0.5	0.6	0.2	0.8
MeBA	0.5	0.3	0.8	0.3	0.1	0.4
Others	1.0	0.9	1.9	0.5	0.2	0.7
Unextractable		<0.1			<0.1	
Total	17.9	59.4	76.1	27.6	45.0	72.7

[a] Data represent mean values for two rats.
ND: not detected.

shows the result of MS fragmentation analysis of the metabolite from the bile of a male rat orally dosed with unlabeled KIH-2023 at 350 mg/kg. The peaks at m/z 607 and 431 is estimated to be the quasi-molecular ion of the glucuronic acid conjugate and its aglycone-moiety, and the m/z 157 to be its pyrimidine-moiety.

DISCUSSION

Although sex difference was not found in C_{max} (180 ppm), AUC and the tissue distribution of male rats were larger than those of female. This may depend on the superiority of the urinary excretion in female rats.

After 15 days administration of unlabeled KIH-2023 at 5 mg/kg/day, Py-^{14}C-KIH-2023 dosed rats excreted more than 90% of dosed-^{14}C within 96 hr, similarly to the case of single-dosed rats. The tissue distribution and ^{14}C-compounds in the liver at $C_{1/2}$-time were similar between the single-dosed and the repeatedly-dosed rats. These results suggested that habitual intake of KIH-2023 did not in-

Table 5 Metabolites in the liver of rats orally dosed with Py- or Bn-^{14}C-KIH-2023 at $C_{1/2}$-time.

Compound	% of ^{14}C-radioactivity in liver[a]					
	Male (7 hr)			Female (5 hr)		
	Py-^{14}C		Bn-^{14}C	Py-^{14}C		Bn-^{14}C
	Single[b]	Repeated[c]	Single[b]	Single[b]	Repeated[c]	Single[b]
KIH-2023	91.2	93.7	87.0	91.5	93.6	88.6
5-OH-2023	N.D.	N.D.	1.0	N.D.	N.D.	0.9
BX-180	0.3	0.2	2.1	0.2	0.6	1.6
DesMe-2023	1.7	1.7	0.4	1.1	0.9	0.5
DesMe-180	N.D.	N.D.	0.2	N.D.	N.D.	0.2
Unknowns	1.1	1.3	4.9	0.7	1.4	5.4
Unextracted	5.7	3.1	4.4	6.5	3.5	2.8

[a] Data represent mean values for two rats.
[b] ^{14}C-KIH-2023 was administered at 100 mg/kg.
[c] Unlabeled KIH-2023 was dosed repeatedly for 15 days at 5 mg/kg/day before the administration of Py-^{14}C-KIH-2023 at 5 mg/kg.
ND: not detected (<0.2%).

Table 6 Distribution of ^{14}C at $C_{1/2}$-time in blood and metabolites in the plasma extract of rats orally dosed with Bn-^{14}C-KIH-2023 at 100 mg/kg.

Fraction or compound	% of ^{14}C-radioactivity in blood[a]	
	Male (7 hr)	Female (5 hr)
Blood-cells	4.8	6.0
Plasma protein	17.2	16.7
Plasma extract	78.0	77.3
KIH-2023	74.0	74.7
5-OH-2023	1.8	0.9
BX-180	0.9	0.5
DesMe-2023	0.9	0.9
DesMe-180	0.4	0.3

[a] Data represent mean values for two rats.

Table 7 Amounts of metabolites in bile of a male rat orally dosed with Py-^{14}C-KIH-2023 at 100 mg/kg.

Compound	% dose of ^{14}C-radioactivity		
	Hours after administration		
	0–6	6–12	12–24
KIH-2023	3.50	2.75	2.30
DesMe-2023	0.64	0.63	0.73
KIH-2023-Gluc.[a]	5.03	2.95	2.07
Me_2BA	0.13	0.07	<0.01

[a] Glucuronic acid conjugate of KIH-2023.

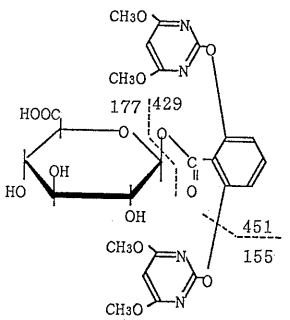
Structure	MS *m/z* (Relative intensity, %)
	607 (11) M+1 431 (10) aglycon-part+1 157 (100) Me_2BA+1

Fig. 4 MS fragmentation of a metabolite in the bile of a male rat orally dosed with KIH-2023 at 350 mg/kg given by the HPLC-MS(API)-system.

fluence the absorption, excretion and metabolic functions of KIH-2023 in rats.

The major ^{14}C-compound in the liver was unchanged KIH-2023 and that in the bile were also KIH-2023 and its glucuronide conjugate. As the conjugate was not detected in the liver, plasma and urine, most of the conjugated KIH-2023 was excreted into the bile, together with some amount of the unconjugated KIH-2023. The remainder of the unconjugated KIH-2023 seemed to be absorbed

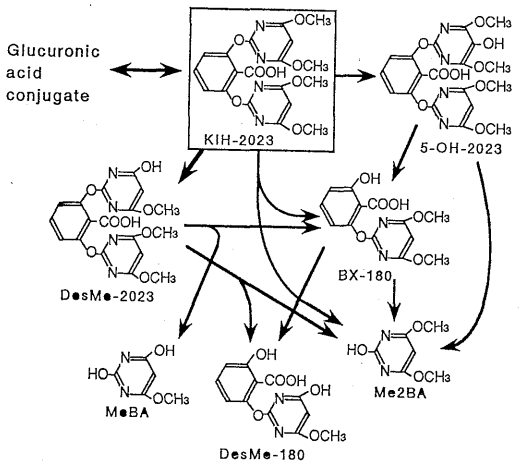


Fig. 5 Proposed metabolic pathways for Bispyribac-sodium [KIH-2023] in rats.

into the systemic circulation and gradually excreted into the urine.

Biliary excretion of foreign compounds in rats depends on their molecular weight (≧325 ±50) and their strongly polar anionic group.[3,4] That is the reason why KIH-2023 (*m.w.*=430) itself could be excreted in bile as well as its glucuronide.

The conjugated KIH-2023 could be hydrolyzed completely by intestinal microorganisms and re-absorbed or excreted into the feces. A number of investigations have shown that glucuronides were hydrolyzed by intestinal microorganisms of mammals and caused enterohepatic circulation.[5-9] In fact, the major ^{14}C-compound in the feces was also intact KIH-2023.

Figure 5 shows the proposed metabolic pathways of KIH-2023 in rats. In the urine, feces, bile and tissues, KIH-2023 was detected as major ^{14}C-compound. As the rats poorly metabolized the dosed KIH-2023, the ^{14}C-distribution and excretion pattern was little different between the Py-2- and Bn-U-^{14}C-KIH-2023, both at high and low dose.

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ALS 阻害型除草剤 KIH-2023 のラットにおける代謝

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KIH-2023 [Sodium 2,6-bis(4,6-dimethoxypyrimidin-2-yloxy)benzoate] の，ベンゼン環–U- またはピリミジン環–2-^{14}C 標識体を F_{344} ラットに 5 ないし 100 mg/kg 単回経口投与した．投与 ^{14}C–放射活性 (^{14}C) の 90% 以上が，投与 96 時間までに尿糞中に排泄された．投与後の血中 ^{14}C は雄で投与 2 時間後，雌で 1 時間後に最高値 (C_{max}) を示し，以後 $C_{1/2}$ 時点まで急速に減少した．$C_{1/2}$ 時点に比べ，投与 96 時間後の臓器・組織中の ^{14}C は低濃度に減衰した．胆汁中の ^{14}C の大部分は未変化の KIH-2023 とそのグルクロン酸抱合体であった．また，尿糞中 ^{14}C の大部分は未変化の KIH-2023 であった．非標識体を 15 日間反復投与後，^{14}C-KIH-2023 を 5 mg/kg 単回経口投与した結果，^{14}C の排泄，臓器・組織分布および代謝は単回投与の場合とほぼ同様の結果であった．