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Novel monocyclic amide-linked phenol derivatives without mitochondrial toxicity have potent uric acid-lowering activity

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ABSTRACT

Although benzbromarone (BBR) is a conventional, highly potent uricosuric drug, it is not a standard medicine because it causes rare but fatal fulminant hepatitis. We transformed the bis-aryl ketone structure of BBR to generate novel monocyclic amide-linked phenol derivatives that should possess uric acid excretion activity without adverse properties associated with BBR. The derivatives were synthesized and tested for uric acid uptake inhibition (UUI) in two assays using either urate transporter 1-expressing cells or primary human renal proximal tubule epithelial cells. We also evaluated their inhibitory activity against mitochondrial respiration as a critical mitochondrial toxicity parameter. Some derivatives with UUI activity had no mitochondrial toxicity, including compound **3f**, which effectively lowered the plasma uric acid level in *Cebus apella*. Thus, **3f** is a promising candidate for further development as a uricosuric agent.

Increasing evidence indicates that hyperuricemia causes not only gout but is also associated with renal disease progression and a higher risk of cardiovascular events.[1,2] Thus, there is a critical unmet medical need to control hyperuricemia, which is caused by increased production and/or decreased excretion of uric acid (UA).

The two main classes of medicines for treating hyperuricemia are xanthine oxidase inhibitors (XOIs), which inhibit UA production from xanthine, and the uricosuric agents. Allopurinol is a traditional, representative XOI, whereas febuxostat and topiroxostat are newer medicines of the same class.[3] Allopurinol is metabolized to oxypurinol, which is mainly excreted via the kidney and is known to cause rare side effects, including skin disorders. This medicine often becomes a problem for patients with impaired renal function.[4] However, febuxostat and topiroxostat have a hepatic excretion route, which differentiates them from allopurinol.

The uricosuric agents used for hyperuricemia treatment include probenecid, benzbromarone (BBR), and lesinurad.[5] However, probenecid has low transporter selectivity, and its use is problematic due to critical drug-drug interactions.[6] BBR is known to cause rarely fatal fulminant hepatitis. It has been withdrawn from the market in the EU, and a warning document has been issued by regulatory authorities in Japan.[7] Furthermore, the use of lesinurad, which was more recently approved in the US and EU, is limited to combination therapy with XOI, based on clinical trial results.[8] In addition, both BBR and lesinurad are metabolized by CYP2C9, but they also inhibit this enzyme.[9] Due to the CYP2C9 polymorphism, patients with poor CYP2C9 activity are also poor drug metabolizers, and patients with reduced CYP2C9 activity are intermediate metabolizers. Thus, individual differences and drug interactions affect the efficacy and safety of these medicines.[10] Because of the disadvantages associated with each medicine, there is still no standard uricosuric agent recommended for clinical use. Despite the problems associated with BBR, it is a useful hyperuricemia medicine because of its potent uricosuric activity and high substrate selectivity.

The exact cause of BBR-induced hepatotoxicity is still unclear, despite the many studies that have been performed to clarify the involved mechanisms, including metabolic processes, metabolites, and mitochondrial toxicity.[11–15] Mitochondrial toxicity-induced hepatic injury is considered a likely mechanism because similar underlying processes have been associated with other drugs.[13–19]

We recently reported an approach aimed at finding a new medicine with potent uricosuric activity while reducing mitochondrial toxicity.[20] In this earlier research, we identified some excellent bicyclic derivatives,

Abbreviations: ABCG2, ATP-binding cassette sub-family G member 2; BBR, benzbromarone; GLUT9, glucose transporter 9; MIA, mitochondrial inhibitory activity; MRP4, multidrug resistance protein 4; OAT1, organic anion transporter 1; PK, pharmacokinetics; RPTECs, renal proximal tubule epithelial cells; UA, uric acid; URAT1, urate transporter 1; UUI, uric acid uptake inhibition; XOI, xanthine oxidase inhibitor.

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including indoline and 1,2-dihydro-3*H*-benzothiazole derivatives. As a result, we developed dotinurad as a new uricosuric medicine, which was recently approved in Japan (Fig. 1). In the article, we reported that a bis-aryl ketone structure, such as BBR, could cause mitochondrial toxicity. We hypothesized that this moiety might affect the mitochondrial electron transfer system because the structure could stabilize the radical that is associated with adverse effects.[21] Interestingly, other compounds with a bis-aryl ketone moiety, such as amiodarone,[13–16] tolcapone,[18] and fenofibrate,[19] are known to induce mitochondrial toxicity. Therefore, we converted the bis-aryl ketone structures into amide-linked bicyclic derivatives to prevent unwanted toxicity (Fig. 2). The new compounds had properties that differed from those of the bis-aryl ketone compounds.[20] Specifically, they had potent pharmacological effects and low mitochondrial inhibitory activity (MIA). Additionally, the higher hydrophobicity of the compounds in the novel series could exacerbate the MIA.

The development of new monocyclic core ring derivatives with uricosuric activity could be a promising approach to obtain alternative analogs of bicyclic compounds, such as dotinurad (Fig. 2). We postulated that these derivatives should have a similar pharmacological activity with a lower hydrophobicity, which could potentially diminish the MIA. In the present study, we designed and synthesized monocyclic ring derivatives as novel uricosuric agents to investigate their structure–activity relationships, including the association between hydrophobicity and MIA.

As previously reported,[20] uricosuric compounds mimic the planar shape of uric acid. In the present study, we developed a strategy for synthesizing 5-membered monocyclic amide-linked phenol derivatives that mimic the planar structure of uric acid but do not contain the bis-aryl ketone core (Fig. 2). To test the hypothesis about the relationship between structure and MIA, we initially synthesized 'phenyl vinyl ketone' derivatives **1** and evaluated their inhibitory activity against mitochondrial respiration as a representative parameter for MIA (Table 1).

These compounds were prepared by Fries rearrangement which is a typical method for phenol acylation. Thus, Fries rearrangement of 2,6-dichloro- or 2,6-dibromo-phenyl cyclopent-1-ene-1-carboxylate with acid catalyst (trifluoromethanesulfonic acid) afforded the desired products **1a** and **1b** (described in supplementary information). We found that **1a** and **1b** possessed high MIA despite having considerably lower LogP values than BBR (LogP: 4.95). Thus, the aryl vinyl ketone core in **1a** and **1b** appeared to maintain the properties of the bis-aryl ketone core. Specifically, it is possible that the unsaturated bonds in aryl vinyl ketones were still able to conjugate intramolecularly and stabilize the radical as in bis-aryl ketones.

Next, we synthesized and tested 'phenyl pyrrolyl ketone' **2** (benzoyl aromatic amine), 'benzoyl 3-pyrroline' **3** and 'benzoyl pyrrolidine' **4** (benzoyl aliphatic amine) containing the amide structure as an alternative to the bis-aryl ketone (Table 2). Pyrrole derivative **2a** had high MIA despite having a lower LogP than BBR. In contrast, the 3-pyrroline amide-derivatives **3a** and **3b,** along with pyrrolidine derivative **4a**, had considerably lower MIA than **2a**, although the LogP of **3b** and **4a** was similar to that of **2a**. Thus, **2a** displayed undesirable bis-aryl ketone-like properties, probably due to the aromatic pyrrole ring, whereas **3a**,**3b** and **4a** exhibited favorable characteristics. The same trend was

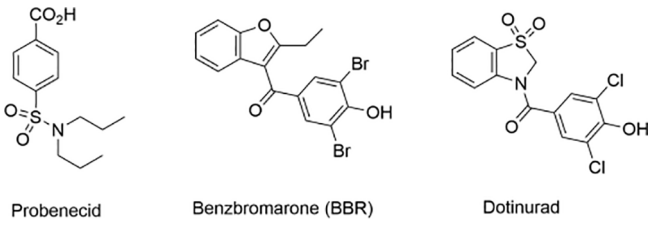


Fig. 1. Uricosuric agents.

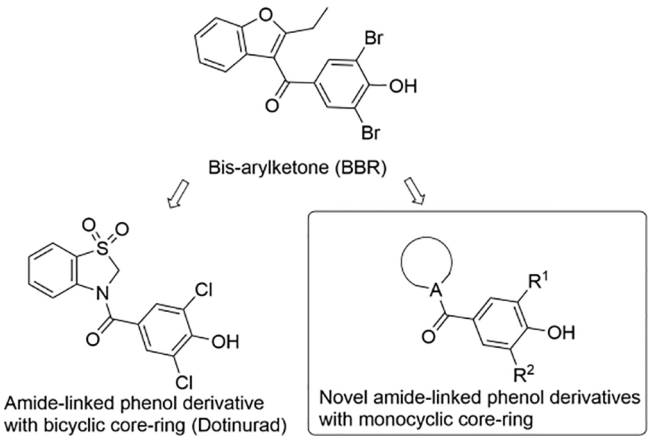


Fig. 2. Strategy for designing novel uricosuric compounds. A = carbon or nitrogen; R^1, R^2 = halogen, alkyl, CF_3, CN.

Table 1
Structure-MIA relationships associated with the core ring of cyclopentenyl derivatives.

Compound	LogP[a]	MIA[b], IC_{50} (μM)
1a	3.39	10
1b	3.93	6.6
BBR	4.95	3.1

[a] LogP was calculated using ChemDraw v19, [b] MIA: mitochondrial respiratory control ratio (RCR), IC_{50} (μM).

Table 2
Structure-MIA relationships associated with the core ring of compounds **2**, **3**, and **4**.

Compound	LogP[a]	MIA[b] IC_{50} (μM) or %
2a	2.92	6.7
3a	2.22	> 100 (17%)
3b	2.95	> 100 (22%)
4a	3.08	> 100 (22%)

[a] LogP was calculated using ChemDrawv19, [b] MIA: mitochondrial respiratory control ratio (RCR), IC_{50} (μM) or inhibition (%) at 100 μM.

previously reported for the bicyclic derivatives containing indoline and indole.[20] Therefore, these findings are in line with our hypothesis, indicating that the derivatives of compounds **3** and **4** represented a new class of potent uricosuric agents.

Two assays were performed to investigate uric acid uptake inhibition (UUI) by the monocyclic derivatives. Urate transporter 1 (URAT1)-expressing cells are used as the test system in the URAT1 assay, and primary human renal proximal tubule epithelial cells (RPTECs) are used in the RPTEC assay. RPTECs are critical for urate excretion and reabsorption in humans. Specifically, they can express various transporters, including URAT1, organic anion transporter 1 (OAT1), OAT3, multidrug resistance protein 4 (MRP4), ATP-binding cassette sub-family G member 2 (ABCG2), and glucose transporter 9 (GLUT9), which are all involved in urate transport.[22–24]

A correlation between the RPTEC and URAT1 assay has been observed for several compounds, including BBR, a well-studied hURAT1-specific inhibitor,[25] and dotinurad, as previously described.[20] Based on this correlation, we hypothesized that urate uptake into RPTECs was mainly due to URAT1, but results from the RPTEC assay could be affected by other endogenous transporters. Thus, the RPTEC assay more closely resembled an *in vivo* system.

Compounds **2a** (core ring; pyrrole), **3a** (core ring; 3-pyrroline) and **4a** (core ring; pyrrolidine), along with BBR, were tested in the UUI

assays (Table 3). These test compounds inhibited URAT1-mediated transport of uric acid but had almost no inhibitory effect on uric acid uptake by RPTECs. Thus, our results did not show a correlation between the URAT1 and RPTEC assays, and these new compounds were not potent enough to inhibit uptake in the RPTEC assay.

3-Pyrroline derivative **3a** and pyrrolidine **4a** had moderate URAT1 inhibitory activity, but almost no MIA. Therefore, the aliphatic monocyclic amide-linked structure removed the MIA toxicity of the bis-aryl ketone structure while maintaining UUI activity. We hypothesized that the UUI activity in the URAT1 and the RPTEC assay could be enhanced by structural optimization. We synthesized additional 3-pyrroline and pyrrolidine derivatives by replacing substituents on the phenyl ring in compounds **3** and **4**.

The synthetic pathway for **2a, 3** and **4** is shown in Scheme 1. These amide-linked phenol derivatives were prepared by acylation of 5-membered amines and following deprotection. Substituted benzoic acids as intermediates have been prepared earlier,[20] and we have described some new substituted benzoic acids in the supplementary information. The acylation of 3-pyrroline and pyrrolidine was accomplished with 3,5-disubstituted 4-methoxy or 4-methoxymethoxy -benzoic acid and 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (EDC), or acid chloride and triethylamine. The *N*-acylation of pyrrole was accomplished with acid chloride and sodium hydride as a base. Subsequent deprotection of the hydroxyl group on the phenyl ring yielded the desired analogs **2a**, **3** and **4**.

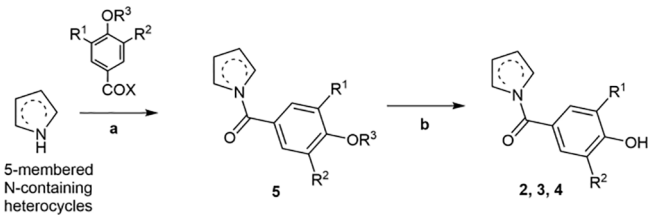
Compounds **3** and **4** were assessed in the *in vitro* uptake assays (Table 4). Although almost all derivatives inhibited URAT1-mediated transport of uric acid, they had almost no inhibitory activity against uric acid uptake by RPTECs, with a few exceptions. Compound **3k** showed potent URAT1 inhibitory activity and moderate inhibition in the RPTEC assay while having considerably weak MIA. Moreover, although **3f** exhibited lower potency than **3k** in the URAT1 and RPTEC assays, it is a promising lead compound due to the absence of MIA.

Next, we focused on the core ring structure. Compounds **6** derivatives with various core ring moieties, including azetidine, 3-methyl-3-pyrroline, thiazolidine and dioxo-thiazolidine were synthesized according to the same pathway as compounds **3** and **4** presented in Scheme 1, using 4- or 5-membered ring amines as the starting material. Dioxo-thiazolidine derivative **6i** was prepared by oxidation of thiazolidine type intermediate **7** using meta-chloroperoxybenzoic acid (m-CPBA) and following deprotection of phenol (Scheme 2). The UUI activities of the derivatives were investigated in the URAT1 and RPTEC assays (Table 5).

We found that almost all compounds had URAT1 inhibitory activities. However, in the RPTEC assay, some thiazolidine and 3-methyl-3-pyrroline derivatives, especially **6c**, **6d**, **6f**, and **6g**, showed moderate activity, whereas azetidine derivatives showed no activity. The *tert*-Bu derivative **6g** had the highest URAT1 inhibitory activity among those four compounds, but it also had the highest MIA. Thus, we found that the compounds with higher LogP values tended to have higher UUI and MIA values, which was the same tendency that we observed among the bicyclic derivatives, such as the indoline analogs, as previously described.[20] Although compounds **6c**, **6d**, and **6f** showed weaker UUI activity than BBR or dotinurad, they exhibited almost no MIA. Thus, these derivatives exhibited a clear divergence between two crucial parameters for uricosuric agents (UUI and MIA). Therefore, if they have appropriate pharmacokinetics (PK) profiles, sufficient activity might be observed in humans.

Next, we investigated the PK profiles of the four most promising compounds from our inhibition analysis, **3f**, **6c**, **6d**, and **6f**. According to our hypothesis, the presence of active compounds in the urine is essential for the pharmacological effects because URAT1 is located on the luminal side of epithelial cells of the renal tubule.[20] BBR is considered to produce its activity, at least in part, by the active metabolite 6-OH-BBR. This BBR metabolite appears to be involved in the inhibition of uric acid reabsorption from the luminal side of epithelial cells of the renal tubule where the urine is present.[26–28] Unlike BBR, the compounds in this study do not require the conversion to active metabolites avoidimg the involvement of metabolizing enzymes, such as CYP2C9. Therefore, the presence of the parent compounds in the urine (Exc. % of the dose) was a potential indication of activity in humans.

The PK profiles of **3f**, **6c**, **6d**, and **6f** are shown in Table 6. Compound **3f** exhibited the highest excretion in the urine and weak CYP2C9



Scheme 1. Synthetic pathway for 5-membered ring derivatives **2, 3** and **4**. Reagents and conditions: 5-membered ring = 3-pyrroline, pyrrolidine ; (a) X = OH; EDC, HOBt in DMF and CH_2Cl_2, or X = Cl; NEt_3, CH_2Cl_2: 5-membered ring = pyrrole; (a) X = Cl; NaH, THF: (b) R^3 = MOM; HCl, AcOEt, R^3 = Me; LiCl, DMF, 21–96% yield over two steps.

Table 3
UUI (URAT1 and RPTEC assays) and MIA of **2a**, **3a** and **4a**.

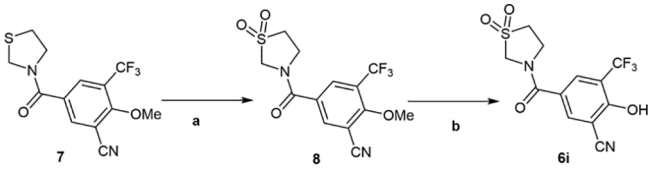
Compound	UUI[a]		MIA[b] IC_{50} (μM) or %
	URAT1 % inhibition at 3 μM	RPTEC IC_{50} (μM)	
2a	83%	> 1,000	6.7
3a	54%	> 1,000	> 100 (17%)
4a	84%	> 1,000	> 100 (22%)
BBR	91%	6.8	3.1

[a] UUI: inhibition of urate uptake via URAT1 or by RPTECs.
[b] MIA: mitochondrial respiratory control ratio (RCR), IC_{50} (μM) or inhibition (%) at 100 μM.

Table 4
UUI and MIA of compounds **3** and **4**.

Compound	R^1, R^2	UUI[a]		MIA[b] IC_{50} (μM) or %
		URAT1 % inhibition at 3 μM	RPTEC IC_{50} (μM)	
3c	I, CN	79%	> 1000	8%
3d	CN, SMe	58%	> 1000	6%
3e	*n*-Pr, CF_3	49%	903	47%
3f	CF_3, CN	83%	818	−1%
3g	Cl, CN	66%	> 1000	5%
3h	Me, CN	25%	> 1000	−10%
3i	Br, CN	69%	747	0%
3j	*n*-Pr, CN	70%	> 1000	7%
3k	*tert*-Bu, CN	92%	311	60% (64 μM)
3l	cyclopropyl, CN	69%	> 1000	−7%
4b	CF_3, CN	66%	> 1000	18%

[a] UUI: inhibition of urate uptake via URAT1 or by RPTECs.
[b] MIA: mitochondrial respiratory control ratio (RCR), IC_{50} (μM) or inhibition (%) at 100 μM.



Scheme 2. Synthetic pathway for **6i**. Reagents and conditions: (a) m-CPBA, CH_2Cl_2, 98.8% yield, (b) LiCl, DMF, 83.5% yield.

Table 5
UUI and MIA of compound **6** derivatives.

Compound	A	R^1, R^2	UUI[a]		MIA[b] IC_{50} (μM) or %
			URAT1 % inhibition at 3 μM	RPTEC IC_{50} (μM)	
6a	Azetidine	CN, CF_3	75%	> 1000	17%
6b	Azetidine	CN, *tert*-Bu	71%	> 1000	41%
6c	3-Methyl-3-pyrroline	CN, CF_3	88%	137	9%
6d	Thiazolidine	CN, CF_3	84%	202	29%
6e	Thiazolidine	CN, Br	72%	401	23%
6f	Thiazolidine	CN, Et	67%	124	25%
6g	Thiazolidine	CN, *tert*-Bu	92%	257	77% (27 μM)
6h	Thiazolidine	CN, CN	62%	614	23%
6i	1,1-Dioxo-thiazolidine	CN, CF_3	55%	272	−3%

[a] UUI: inhibition of urate uptake via URAT1 or by RPTECs; [b] MIA: mitochondrial respiratory control ratio (RCR), IC_{50} (μM) or inhibition (%) at 100 μM.

Table 6
PK profiles of **3f**, **6c**, **6d**, and **6f** in rats.

Compound	C_{max}[a] (μg/mL)	Exc.[b] (%)	CYP2C9 IC_{50} (μM)
3f	2.61	23	52
6c	2.22	10	94
6d	3.70	9.0	> 100
6f	–	9.5	–
dotinurad	9.14	1.1	5.7
BBR	4.42	0	0.041

[a] Maximum concentration (C_{max}); [b] Excretion rate in urine (%, 0–4 h) after oral administration of 3 mg/kg to rats.

inhibition. Although **3f** had an approximately 100-fold lower UUI activity than dotinurad (UUI in RPTEC assay: IC_{50} = 6.8 μM)[20], its urinary excretion was several tens of times higher than that of the control agent. These results suggested that **3f** was present as a parent compound in urine at a larger ratio and may possess true uricosuric activity. Therefore, we decided to investigate the activity of **3f** in *Cebus apella*, whose uricosuric mechanisms can be extrapolated to humans (Fig. 3). In this experiment, **3f** treatment decreased plasma urate concentrations, associated with an excretion rate of 9.0% of the compound dose in 24 h urine. Our observations indicated that the large proportion of parent compound **3f** in the urine might enhance the compound's effect and overcome its moderate intrinsic activity. Thus, these data supported our hypothesis that active compounds in the urine could contribute to the pharmacological effect.

Although the monocyclic derivatives discussed here had a much lower UUI activity than the bicyclic compounds, the new derivatives also displayed a divergence between UUI and MIA, and representative compound **3f** showed moderate activity in *Cebus apella*. This characteristic is a promising property of potential uricosuric agents, which applied also to the bicyclic compounds.

In conclusion, we initially focused on designing compounds that do not exhibit MIA while retaining relevant uricosuric activity. We pursued this aim by synthesizing phenol derivatives with amide-linked monocyclic core rings to eliminate the adverse effects associated with bis-aryl ketone-containing compounds, such as BBR. This approach resulted in compounds with low hydrophobicity and no MIA. In addition, we demonstrated that bis-aryl ketones or aryl vinyl ketones could stabilize

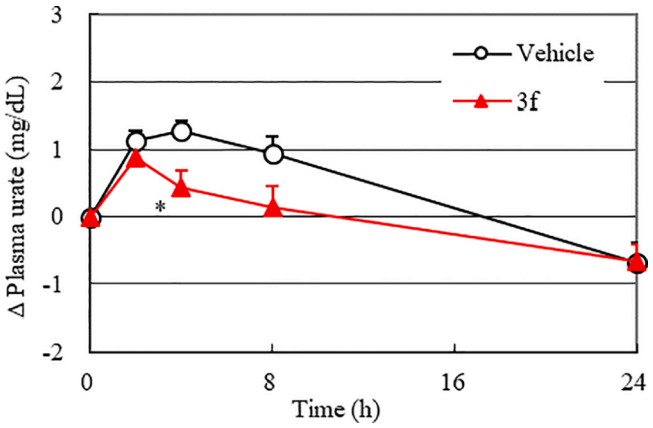
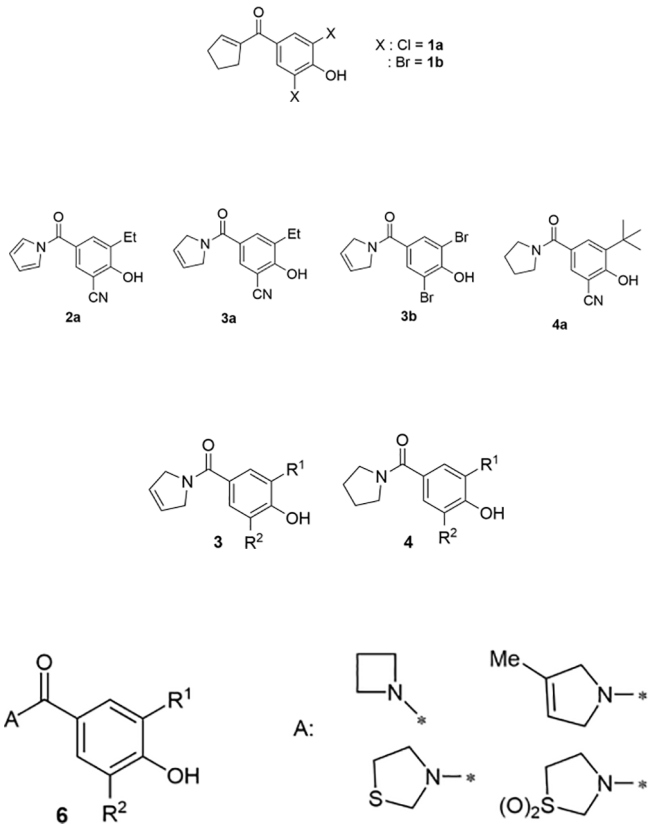


Fig. 3. Changes in plasma urate level compared with the baseline value in *Cebus apella* at 0–24 h after oral administration of 300 mg/kg **3f** or vehicle. Values are the means + S.D. of three animals. The baseline average value of the vehicle control group: 2.82 mg/dL. *P < 0.05, significantly different from control at each time point according to Dunnett's test.



the conjugated ketone radicals and that the lipophilicity of compounds affects MIA. However, the UUI activity, especially in RPTECs, tended to be reduced by lowering the lipophilicity of the test compounds.

This structural property may have contributed to the results seen in *Cebus apella*, in which **3f** caused a moderate decrease of plasma urate concentrations, compared to that of dotinurad, which had a significant pharmacological effect at > 5 mg/kg (p.o.), as reported previously.[20] Thus, we have identified new compounds with potency as real uricosuric agents without the negative consequences of MIA. The series could

further be improved by increasing the UUI activity.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bmcl.2021.127900.

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