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Discovery of a Muscarinic M_3 Receptor Antagonist with High Selectivity for M_3 Over M_2 Receptors Among 2-[(1*S*,3*S*)-3-Sulfonylaminocyclopentyl]phenylacetamide Derivatives

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Abstract—In the course of developing a metabolically stable M_3 receptor antagonist from the prototype antagonist, J-104129 (**1**), introduction of certain substituents into the cyclopentane ring of **1** was found to be effective not only in improving metabolic stability but also in greatly enhancing the subtype selectivity. Among the cyclopentane analogues, sulfonamide derivatives (**10f**) and (**10g**) displayed 160- and 310-fold selectivity for M_3 over M_2 receptors, and both were significantly more selective than the prototype antagonist (120-fold). Subsequent derivatization of the sulfonamide series led to the highly selective M_3 receptor antagonists (**10h**, **10i** and **10j**) with >490-fold selectivity for M_3 over M_2 receptors. Among them, *p*-nitrophenylsulfonamide (J-107320, **10h**) exhibited 1100-fold selectivity for M_3 receptors ($K_i = 2.5$ nM) over M_2 receptors ($K_i = 2800$ nM) in the human muscarinic receptor binding assay using [^{3}H]-NMS as a radio ligand.

Introduction

In the muscarinic field, five receptor subtypes have been identified and cloned.[1–5] These are classified as m1, m2, m3, m4 and m5 with distinct but homologous gene sequence. Structural and pharmacological criteria have suggested the presence of at least four subtypes, denoted M_1, M_2, M_3 and M_4 whilst a physiological role for M_5 gene product remains to be identified.[6,7] M_1 receptors are found in parasympathetic ganglia and in parts of central nervous system and facilitate neurotransmission. M_2 receptors are localized to the post ganglionic cholinergic nerve terminals and provide a functional negative feedback modulation of acetylcholine (ACh) release. M_3 receptors localized in smooth muscle and mucosal glands mediate contraction and mucus secretion, respectively. Subtype selective ligands that recognize the different localizations and functions of these receptor subtypes provide the possibility of developing more ideal drugs since they would avoid the occurrence of adverse effects. Therefore, it has been hypothesized that selective blockade of muscarinic M_3 receptors may be therapeutically useful in the treatment of respiratory disorders such as chronic obstructive pulmonary disease (COPD), gastrointestinal disorders such as irritable bowel syndrome (IBS) and urinary tract disorders such as urinary incontinence (UI).[8] Thus, pharmaceutical research into therapeutic agents selective for muscarinic receptor subtypes has been recently focused on exploration of M_3 selective antagonist for the above disorders.

In a previous paper, we reported the identification of J-104129 (**1**), a prototype muscarinic M_3 receptor antagonist with 120-fold greater selectivity for M_3 over M_2 receptors in a series of 4-acetamidopiperidine derivatives (Fig. 1).[9] J-104129 (**1**) is a potent bronchodilator in rats, guinea pigs and dogs.[10] In rats, oral administration of J-104129 (**1**) showed durable bronchodilatory action lasting over 10 h with 10 mg/kg. However, a recent pharmacokinetic study in the same species revealed its relatively short half life ($T_{1/2} = 2$ h). The discrepancy prompted us to explore active metabolite(s) in rats. As a result, we identified an active metabolite (**5b**)

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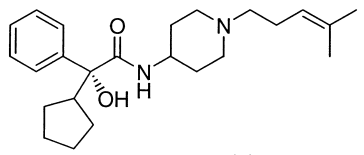


J-104129 (1)

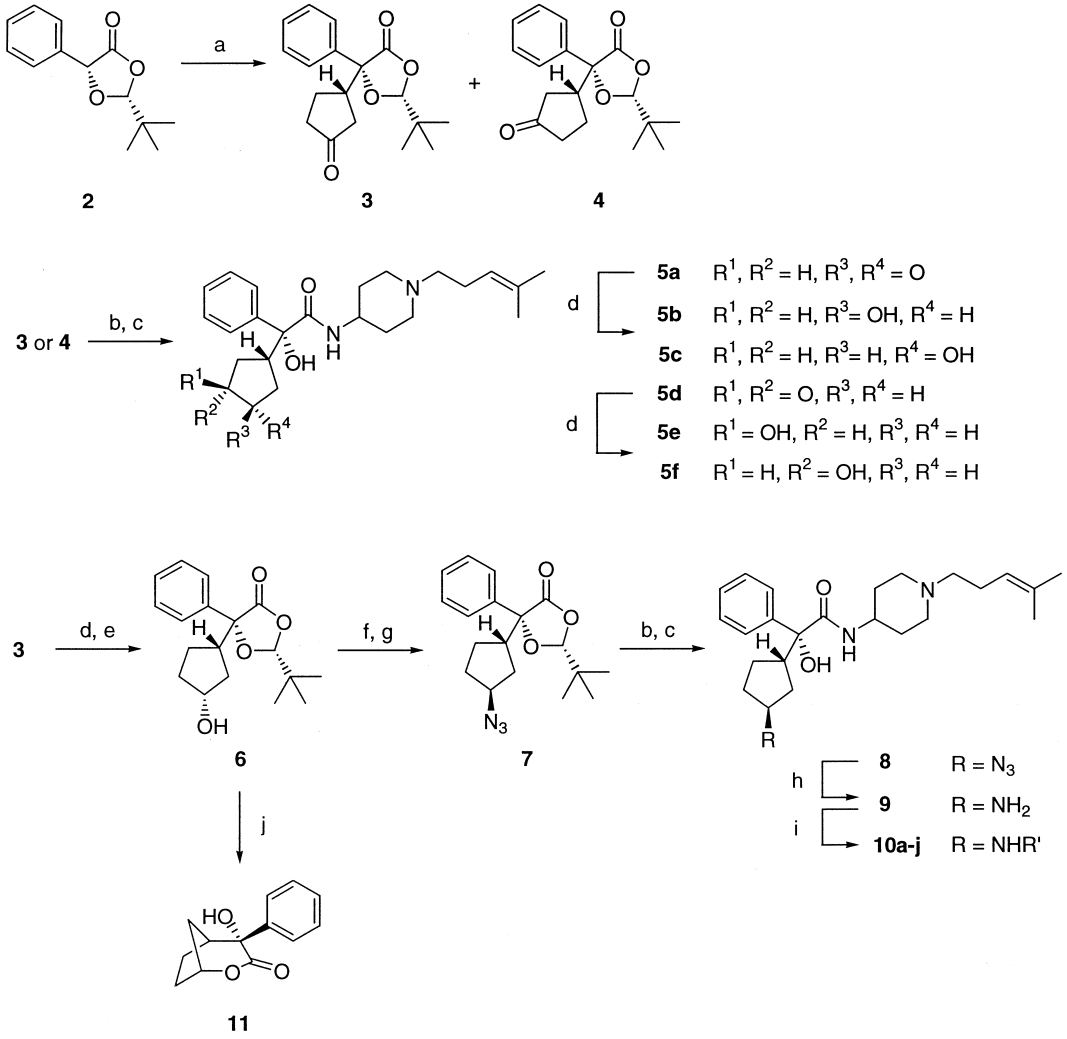
Figure 1.

with a hydroxyl group on the cyclopentane ring of J-104129 (**1**). Interestingly, **5b** showed not only improved metabolic stability, but also subtype selectivity as high as that of the parent compound (**1**). It should be noted that **5b** was the first example indicating that substitution on the cyclopentyl moiety might effectively improve both the metabolic stability and subtype selectivity. Thus, we tried to introduce various substituents into the cyclopentane ring based on the structure of the metabolite (**5b**) to further investigate the structure–activity relationships (SAR) on subtype selectivity and metabolic stability of the 2-(3-substituted cyclopentyl)-phenylacetamide series. In this paper, we describe the identification of the active metabolites of J-104129 (**1**) and the SAR of the substituted cyclopentyl derivatives.

Results and Discussion

Chemistry

General synthetic methods of derivatives (**5** and **10**) are highlighted in Scheme 1. Michael addition of an enolate of dioxolane (**2**),[11] derived from (*R*)-mandelic acid, with cyclopentenone gave ketones (**3**) and (**4**) in 31 and 34% yields, respectively, after separation by silica gel column chromatography.[12] These compounds were used as key intermediates in the following derivatization. Alkaline hydrolysis of **3** followed by coupling with 4-aminopiperidine produced an amide (**5a**) in 52% yield. Reduction of **5a** and the subsequent separation of the diastereomers on the resulting secondary alcohol moiety afforded the derivatives (**5b**) and (**5c**) in 25 and 35% yields, respectively. Other congeners (**5d**), (**5e**) and (**5f**)



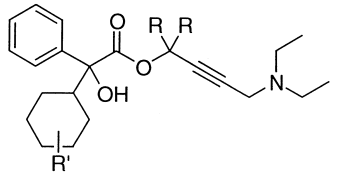
Scheme 1. Preparation of **5a–f** and **10a–j**. Conditions: (a) LDA, THF then 2-cyclopenten-1-one; (b) NaOH, H_2O-MeOH; (c) 1-(4-methyl-3-pentenyl)-4-aminopiperidine, WSC·HCl, HOBt, $CHCl_3$; (d) $NaBH_4$, MeOH; (e) recrystallization from hexane:AcOEt; (f) MsCl, Et_3N, AcOEt; (g) NaN_3, DMF; (h) Ph_3P, H_2O, THF; (i) acid chloride, Et_3N, $CHCl_3$; (j) NaH, THF.

were prepared from **4** in 75, 33 and 36% yields, respectively, by the method described above.

Preparation of derivatives (**10**) was initiated from **6**. Fractional recrystallization of the diastereomeric mixture, obtained by reduction of **3** with sodium borohydride gave the alcohol (**6**) in 33% yield. The stereochemical structure of the cyclopentane moeity in **6** was determined by conversion to **11**. Mesylation of **6** and subsequent nucleophilic substitution with sodium azide gave cyclopentylazide (**7**) in 82% yield. The cyclopentylazide (**7**) was converted to an amide (**8**) in 92% yield in a manner similar to that described for the preparation of **5a**. The amide (**8**) was reduced with triphenylphosphine and subsequently treated with various acid chloride analogues to produce derivatives (**10a**–**10j**) in 48∼94% yields.

Biological properties

First, J-104129 (**1**) was incubated in rat hepatic microsomes for the identification of its active metabolites. Oxidation of the cyclopentane moiety of **1** was predicted since oxybutynin (**12**) or its dimethyl analogue (**13**) was reported to be metabolized on 3- and 4-position of cyclohexyl group to produce metabolites (**14**) and (**15**)[13,14] (Fig. 2). Therefore, we synthesized the compounds (**5b**), (**5c**), (**5e**) and (**5f**) and compared their retention times and molecular weights by LC/MS with those of the metabolites in rats for unambiguous determination of their structures. Simultaneously, the binding affinities of these compounds were determined by inhibition of specific binding of [^{3}H]-NMS using membranes from CHO cells expressing cloned human m1–m3 receptors[9] (see Table 1). As expected, the hydroxylated compounds (**5b**), (**5c**), (**5e**) and (**5f**) were identified as the metabolites of **1**. Among them, **5b** with (1*S*,3*S*)-configuration on the cyclopentane moiety was the most active metabolite, showing improved metabolic stability and potent M_3 binding affinity ($K_i = 18$ nM) while maintaining M_3 selectivity (130-fold) over M_2 receptors. Moreover, oral administration of **5b** inhibited ACh-induced bronchoconstriction in anesthetized rats[9] with an ED_{50} value of 0.33 mg/kg. This interesting result indicated that the derivatization of J-104129 (**1**) by introducing certain substituents into the cyclopentane ring may improve the M_3 selectivity and metabolic stability. This new type of derivatization further intrigued us in that modification in the mandelic acid series involving **1** had so far been performed only by introducing simple substituents such as a halogen and alkyl moiety into the benzene ring or by replacing the cyclopentane ring with other ring-sized cycloalkanes.



12 R = H R' = H oxybutynin

13 R = Me R' = H

14 R = H R' = OH

15 R = Me R' = OH

Figure 2.

With the regio- and stereochemical structures of substituents on the cyclopentane ring being fixed in the (1*S*,3*S*)-configuration identical to that in **5b**, derivatives (**10a**–**10j**) were prepared and evaluated in the human muscarinic binding assay, and metabolic stability was examined in human microsomes (Table 2).

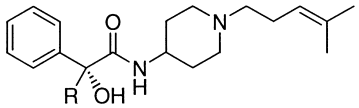
Conversion of the hydroxyl group in **5b** to an acetamide (**10a**) or methyl carbamate (**10d**) resulted in considerably decreased M_3 selectivity, but improved metabolic stability. Although the corresponding phenyl derivatives (**10b**) and (**10e**) also showed low M_3 selectivity, these exhibited some degree of improved binding affinity.

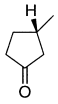
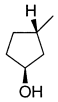
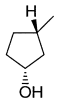
Next, we tried to introduce certain sulfonamides into the cyclopentane moiety. In contrast to the amide and carbamate derivatives, methanesulfonamide (**10f**) and benzenesufonamide (**10g**) displayed 160- and 300-fold selectivity for M_3 over M_2 receptors, although they also bound to M_1 receptors with high affinity. The significant improvement in M_3 selectivity especially over M_2 receptors as compared to that of the prototype J-104129 (**1**) prompted further modification of this sulfonamide series. Introduction of a methoxy moiety (**10i**) as a representative electron-donating group and a trifluoromethyl (**10j**), an electron-withdrawing group, into the *para*-position of the benzene ring further enhanced M_3 selectivity up to 640- and 490-fold, respectively. The best result was obtained by introducing a nitro group into the *para*-position. The resulting *p*-nitrophenylsulfonamide (**10h**) exhibited 1100-fold selectivity for M_3 receptors ($K_i = 2.5$ nM) over M_2 receptors ($K_i = 2800$ nM). These results indicated that substituted benzenesulfonamide on the cyclopentane ring played an important role in enhancing selectivity for M_3 over M_2 receptors. We are now investigating the role of the *p*-nitrophenylsulfonamide moiety for sparing M_2 receptors by computer modeling.

Conclusion

In the process of developing an M_3 receptor antagonist with improved metabolic stability over the prototype, J-104129 (**1**), we found that introduction of a substituent with the (1*S*,3*S*)-configuration into the 3-position of the cyclopentane group in **1** effectively improved both metabolic stability and selectivity for M_3 over M_2 receptors. In this series, the substituted benzenesulfonamide derivatives (**10g**, **10h**, **10i** and **10j**) showed more than 300-fold selectivity for M_3 over M_2 receptors. In particular, J-107320 (**10h**) displayed 1100-fold selectivity for M_3 receptors over M_2 receptors in the human muscarinic binding assay. The SAR on the subtype selectivity described here will be useful for designing an ideal M_3 selective antagonist.

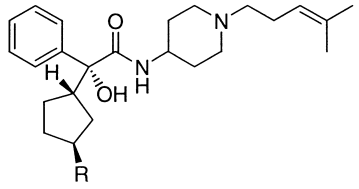
Table 1. Biological properties of **1** and **5a–f**



Compound	R	Binding affinity (K_i nM)[a]			Selectivity m2/m3	Metabolic stability[b] % remaining
		m3	m1	m2		
5a		71	260	9200	130	NT[c]
5b		18	88	2300	130	Rat75 Dog 75 Human 76
5c		480	1100	23,000	48	NT
5d		360	1300	29,000	81	NT
5e		140	640	12,000	86	NT
5f		770	2200	30,000	39	NT
J-104129 (**1**)		4.2	19	490	120	Rat 10 Dog 31 Human 54

[a]Values are the mean of two or more independent assays.
[b]% Remaining after 30 min incubation in hepatic microsomes ($n = 3$).
[c]Not tested (for compounds **5c**, **5d**, **5e**, and **5f**).

Table 2. Biological properties of **10a–j**



Compound	R	Binding affinity (K_i nM)[a]			Selectivity m2/m3	Metabolic stability[b] % remaining
		m3	m1	m2		
10a	CH_3CONH	30	60	1200	40	85
10b	$PhCH_2CONH$	13	47	350	27	11
10c	PhCOCONH	4.1	11	260	64	58
10d	CH_3OCONH	11	34	480	43	75
10e	$PhCH_2OCONH$	5.2	16	220	41	31
10f	CH_3SO_2NH	28	77	4500	160	95
10g	$PhSO_2NH$	6.0	3.3	1800	300	31
10h	4-NO_2-$PhSO_2NH$	2.5	4.6	2800	1100	38
10i	4-CH_3O-$PhSO_2NH$	9.0	5.6	5700	640	50
10j	4-CF_3-$PhSO_2NH$	6.6	11	3200	490	19
5b	OH	18	88	2300	130	76

[a]Values are the mean of two or more independent assays.
[b]% Remaining after 30 min incubation in human microsomes ($n > 2$).

Experimental

Melting points (mp) were determined with a Yanaco MP micromelting point apparatus and were not corrected. Proton NMR spectra were obtained on a Varian Gemini-300 with tetramethylsilane as an internal standard. Mass spectrometry were performed with JEOL JMS-SX 102A. IR spectra were recorded with Horiba FT-200 spectrometer. Optical rotations were measured with Jasco DIP-370 polarimeter. TLC were done with Merck Kieselgel F_{254} pre-coated plates. Silica gel (SiO_2) column chromatography was carried out on Wako gel C-300.

(2*R*,5*R*)-2-*tert*-Butyl-5-[(1*S*)-3-oxocyclopentyl]-5-phenyl-1,3-dioxolan-4-one (3) and (2*R*,5*R*)-2-*tert*-butyl-5-[(1*R*)-3-oxocyclopentyl]-5-phenyl-1,3-dioxolan-4-one (4). To a suspension of (2*R*,5*R*)-2-*tert*-butyl-5-phenyl-1,3-dioxolan-4-one[11] (**2**) (3.00 g, 13.6 mmol) in THF (120 mL) was added a 1.5 M solution of lithium diisopropylamide mono(tetrahydrofuran) in cyclohexane (10.0 mL, 15.0 mmol) dropwise at −78 °C, and the mixture was stirred for 30 min at the same temperature. A solution of 2-cyclopenten-1-one (1.25 g, 15.23 mmol) in THF (10 mL) was added for 10 min maintaining the temperature below −70 °C. After being stirred for additional 2 h, the reaction mixture was quenched by saturated aq NH_4Cl solution, and the mixture was allowed to warm to room temperature. The mixture was diluted with H_2O and extracted with AcOEt. The organic layer was washed with brine, dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexane:AcOEt = 12:1) to give less polar **3** (1.27 g, 31%) and polar **4** (1.48 g, 36%) as white crystals. The regiochemical structures of 3-oxocyclopentyl group were determined by NOE experiment. **3**: ^{1}H NMR ($CDCl_3$) δ 0.92 (9H, s), 1.74–1.84 (2H, m), 2.09 (1H, m), 2.20–2.46 (3H, m), 2.89 (1H, m), 5.39 (1H, s), 7.30–7.46 (3H, m), 7.67–7.73 (2H, m); MS *m*/*z* 303 $(M+H)^+$; mp 86–87 °C (hexane/AcOEt); anal. calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.56; H, 7.41; $[\alpha]_D^{20}$ −16.2 (*c* = 1.0, $CHCl_3$). **4**: ^{1}H NMR ($CDCl_3$) δ 0.93 (9H, s), 1.82–2.00 (2H, m), 2.10–2.28 (3H, m), 2.34 (1H, m), 2.89 (1H, m), 5.44 (1H, s), 7.26–7.40 (3H, m), 7.62–7.79 (2H, m); MS *m*/*z* 303 $(M+H)^+$; mp 104–105 °C (hexane/AcOEt); anal. calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.50; H, 7.27; $[\alpha]_D^{20}$ +82.8 (c = 1.0, $CHCl_3$).

(2*R*)-*N*-[1-(4-Methyl-3-pentenyl)piperidin-4-yl]-2-[(1*S*)-3-oxocyclopentyl]-2-hydroxy-2-phenylacetamide (5a). To a solution of **3** (110 mg, 0.36 mmol) in MeOH (1.5 mL) was added 3 N NaOH (300 μL, 0.90 mmol) at room temperature. After being stirred for 5 h, the mixture was diluted with H_2O and washed with Et_2O. The aqueous layer was acidified with 1 N HCl and extracted three times with $CHCl_3$. The combined organic layer was dried over $MgSO_4$ and concentrated in vacuo. To a solution of the residual oil (90 mg) and 1-(4-methyl-3-pentenyl)-4-aminopiperidine[9] (84 mg, 0.47 mmol) in $CHCl_3$ (4 mL) were added HOBt (105 mg, 0.79 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (WSC·HCl, 118 mg, 0.62 mmol) at room temperature. After being stirred for 15 h, the mixture was concentrated in vacuo. The residue was partitioned between Et_2O and saturated aq $NaHCO_3$. The organic layer was separated, washed with H_2O and brine and dried over $MgSO_4$. Removal of the solvent in vacuo gave the crude residue which was purified by preparative TLC ($CHCl_3$:MeOH = 9:1) to yield **5a** (95 mg, 52%) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.28–2.40 (16H, m), 1.60 (3H, s), 1.68 (3H, s), 2.71–2.89 (2H, m), 3.29 (1H, m), 3.53–3.79 (2H, m, containing OH), 5.06 (1H, m), 6.24 (1H, m), 7.28–7.46 (3H, m), 7.59 (2H, brd, *J* = 8.1 Hz); HRMS calcd for $C_{24}H_{35}N_2O_3$ $(M+H)^+$: 399.2648, found 399.2654; $[\alpha]_D^{20}$ −52.2 (c = 1.0, $CHCl_3$).

(2*R*)-*N*-[1-(4-Methyl-3-pentenyl)piperidin-4-yl]-2-[(1*S*,3*S*)-3-hydroxycyclopentyl]-2-hydroxy-2-phenylacetamide (5b) and (2*R*)-*N*-[1-(4-methyl-3-pentenyl)piperidin-4-yl]-2-[(1*S*,3*R*)-3-hydroxycyclopentyl]-2-hydroxy-2-phenylacetamide (5c). To a solution of **5a** (63 mg, 0.16 mmol) in MeOH (3 mL) was added $NaBH_4$ (40 mg, 1.1 mmol) at 0 °C. After 1 h, the mixture was diluted with H_2O and extracted twice with $CHCl_3$. The combined organic layer was dried over $MgSO_4$ and concentrated in vacuo to give the crude residue which was purified by preparative TLC ($CHCl_3$:MeOH = 9:1) to yield **5b** (15 mg, 25%) and **5c** (22 mg, 35%) as oils. The stereochemical structure of **5c** was determined by conversion of **6** to **5c** in a similar method described for **5a** (70%). **5b**: ^{1}H NMR ($CDCl_3$) δ 1.20–1.95 (10H, m), 1.61 (3H, s), 1.69 (3H, s), 2.00–2.21 (4H, m), 2.26–2.39 (2H, m), 2.69–2.88 (2H, m), 3.31 (1H, m), 3.70 (1H, m), 3.75 (1H, brs, OH), 4.43 (1H, m), 5.08 (1H, m), 6.07 (1H, brd, *J* = 7.8 Hz), 7.21–7.42 (3H, m), 7.59 (2H, brd, *J* = 7.2 Hz); MS *m*/*z* 401 $(M+H)^+$; $[\alpha]_D^{20}$ −20.0 (*c* = 1.0, $CHCl_3$); **5b** fumarate mp 161–162 °C (*i*-Pr_2O/EtOH); anal. calcd for $C_{24}H_{36}N_2O_3$ $C_4H_4O_4$ $0.25H_2O$: C, 64.53; H, 7.83; N, 5.38. Found: C, 64.47; H, 7.86; N, 5.40. **5c**: ^{1}H NMR ($CDCl_3$) δ 1.35–1.80 (8H, m), 1.60 (3H, s), 1.68 (3H, s), 1.87–2.20 (6H, m), 2.25–2.36 (2H, m), 2.75–2.95 (2H, m), 3.58 (1H, m), 3.73 (1H, m), 4.35 (1H, m), 5.05 (1H, m), 5.78 (1H, m), 7.19–7.38 (3H, m), 7.74 (2H, brd, *J* = 8.3 Hz); MS *m*/*z* 401 $(M+H)^+$; $[\alpha]_D^{20}$ +37.6 (*c* = 1.0, $CHCl_3$); **5c** oxalate mp 200–201 °C (*i*-Pr_2O:EtOH); anal. calcd for $C_{24}H_{36}N_2O_3 \cdot C_2H_2O_4$: C, 63.65; H, 7.81; N, 5.71. Found: C, 63.86; H, 7.83; N, 5.57.

(2*R*)-*N*-[1-(4-Methyl-3-pentenyl)piperidin-4-yl]-2-[(1*R*)-3-oxocyclopentyl]-2-hydroxy-2-phenylacetamide (5d). Compound **5d** was obtained as an oil from **4** in a similar method described for **5a** (75%): ^{1}H NMR ($CDCl_3$) δ 1.30–2.48 (16H, m), 1.60 (3H, s), 1.68 (3H, s), 2.68–2.90 (2H, m), 3.29 (1H, m), 3.63 (1H, brs, OH), 3.73 (1H, m), 5.07 (1H, m), 6.24 (1H, m), 7.24–7.42 (3H, m), 7.54 (2H, brd, *J* = 8.4 Hz); HRMS calcd for $C_{24}H_{35}N_2O_3$ $(M+H)^+$: 399.2648, found 399.2638; $[\alpha]_D^{20}$ +30.2 (*c* = 1.0, $CHCl_3$).

(2*R*)-*N*-[1-(4-Methyl-3-pentenyl)piperidin-4-yl]-2-[(1*R*,3*R*)-3-hydroxycyclopentyl]-2-hydroxy-2-phenylacetamide (5e) and (2*R*)-*N*-[1-(4-methyl-3-pentenyl)piperidin-4-yl]-2-[(1*R*,3*S*)-3-hydroxycyclopentyl]-2-hydroxy-2-phenylacetamide (5f). Compound **5e** (33%) and **5f** (36%) were obtained as a white crystal and a foam from **5d** in a similar method described for **5b** and **5c**. The stereochemical

structure of the cyclopentane moeity in **5f** was determined by NOE experiment. **5e**: ^{1}H NMR ($CDCl_3$) δ 1.20–220 (14H, m), 1.60 (3H, s), 1.68 (3H, s), 2.26–2.36 (2H, m), 2.68–2.88 (2H, m), 3.30 (1H, m), 3.70 (1H, m), 3.74 (1H, brs, OH), 4.34 (1H, m), 5.06 (1H, m), 6.08 (1H, brd, J = 8.4 Hz), 7.23–7.40 (3H, m), 7.57 (2H, brd, J = 7.2 Hz); MS m/z 401 $(M+H)^+$; $[\alpha]_D^{20}$ −11.6 (c = 1.0, $CHCl_3$); mp 181–182 °C (hexane:$CHCl_3$); anal. calcd for $C_{24}H_{36}$ N_2O_3 $0.25H_2O$: C, 71.17; H, 9.08; N, 6.92. Found: C, 71.11; H, 9.03; N, 6.92. **5f**: ^{1}H NMR ($CDCl_3$) δ 1.22–2.20 (14H, m), 1.59 (3H, s), 1.67 (3H, s), 2.22–2.39 (2H, m), 2.79–2.95 (2H, m), 3.52 (1H, m), 3.76 (1H, m), 4.22 (1H, m), 5.03 (1H, m), 6.10 (1H, m), 7.19–7.37 (3H, m), 7.75 (2H, brd, J = 7.2 Hz); MS m/z 401 $(M+H)^+$; $[\alpha]_D^{20}$ +5.8 (c = 1.0, $CHCl_3$); anal. calcd for $C_{24}H_{36}N_2$ $O_3 \cdot 0.5H_2O$: C, 70.38; H, 9.11; N, 6.84. Found: C, 70.59; H, 9.38; N, 6.69.

(2*R*,5*R*)-2-*tert*-Butyl-5-[(1*S*,3*R*)-3-hydroxycyclopentyl]-5-phenyl-1,3-dioxolan-4-one (6). To a solution of **3** (1.1 g, 3.5 mmol) in MeOH (50 mL) was added $NaBH_4$ (700 mg, 19 mmol) at 78 °C in several portions. The mixture was allowed to warm to 0 °C over 1 h and concentrated to a small volume. After addition of H_2O, the mixture was extracted twice with $CHCl_3$. The combined organic layer was dried over $MgSO_4$ and concentrated in vacuo to give a mixture of diastereomers (ca. 3.5:1). This was recystallized twice from hexane:AcOEt to obtain **6** (350 mg, 33%) as a white crystal. The stereochemical structure of **6** was determined by conversion to **11**. **6**: ^{1}H NMR ($CDCl_3$) δ 0.92 (9H, s), 1.34 (1H, m), 1.50–1.79 (3H, m), 1.86 (1H, m), 2.11 (1H, m), 2.67 (1H, m), 4.29 (1H, m), 5.51 (1H, s), 7.23–7.41 (3H, m), 7.67 (2H, brd, J = 7.2 Hz); MS m/z 305 $(M+H)^+$; mp 123–125 °C (hexane/AcOEt); anal. calcd for $C_{18}H_{24}O_4$: C, 71.03; H, 7.95. Found: C, 71.13; H, 8.07; $[\alpha]_D^{20}$ +25.8 (c = 1.0, $CHCl_3$).

(1*R*,4*R*,5*R*)-4-Hydroxy-4-phenyl-2-oxabicyclo[3,2,1]octan-3-one (11). To a solution of **6** (160 mg, 0.53 mmol) in THF (8.0 mL) was added NaH (60% in oil, 30 mg, 0.75 mmol) at 0 °C. The mixture was stirred for 1 h at the same temperature. After addition of saturated aq NH_4Cl, the mixture was extracted with AcOEt. The organic layer was washed with H_2O and brine and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by preparative TLC (hexane: AcOEt = 4:1) to yield **11** (70 mg, 61%) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.55 (1H, m), 1.81–2.01 (2H, m), 2.06–2.24 (2H, m), 2.49 (1H, m), 2.75 (1H, m), 3.38 (1H, s, OH), 4.93 (1H, m), 7.25–7.41 (5H, m); HRMS calcd for $C_{13}H_{14}O_3Na$ $(M+Na)^+$: 241.0841, found 241.0827; $[\alpha]_D^{20}$ −50.0 (c = 1.0, $CHCl_3$).

(2*R*,5*R*)-2-*tert*-Butyl-5-[(1*S*,3*S*)-3-azidocyclopentyl]-5-phenyl-1,3-dioxolan-4-one (7). To a solution of **6** (10.5 g, 34.5 mmol) and Et_3N (7.20 mL, 51.7 mmol) in AcOEt (350 mL) was added MsCl (3.00 mL, 38.8 mmol) at 0 °C and the mixture was stirred for 1 h. After addition of saturated aq $NaHCO_3$, the organic layer was separated, washed with H_2O and brine and dried over $MgSO_4$. The solvent was evaporated to dryness and the resulting mesylate (13.5 g) was used in the next step without further purification. To a solution of the mesylate in DMF (200 mL) was added NaN_3 (2.70 g, 41.5 mmol) at room temperature, and the mixture was heated at 90 °C for 1 h. The mixture was diluted with H_2O and extracted with AcOEt. The organic layer was washed with H_2O and brine and dried over $MgSO_4$. The solvent was evaporated to give the crude material which was purified by SiO_2 column chromatography (hexane: AcOEt = 10:1) to yield **7** (9.55 g, 82%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 0.92 (9H, s), 1.49–1.70 (3H, m), 1.77–1.89 (2H, m), 1.96 (1H, m), 2.82 (1H, m), 4.01 (1H, m), 5.42 (1H, s), 7.26–7.43 (3H, m), 7.67 (2H, brd, J = 8.2 Hz); MS m/z 330 $(M+H)^+$; mp 62–64 °C (hexane at −20 °C); anal. calcd for $C_{18}H_{23}N_3O_4$: C, 65.63; H, 7.04; N, 12.76. Found: C, 65.48; H, 7.02; N, 12.81; $[\alpha]_D^{20}$ +3.2 (c = 1.0, $CHCl_3$).

(2*R*)-*N*-[1-(4-Methyl-3-pentenyl)piperidin-4-yl]-2-[(1*S*,3*S*)-3-azidocyclopentyl]-2-hydroxy-2-phenylacetamide (8). To a solution of **7** (730 mg, 2.2 mmol) in MeOH (10 mL) was added 3 N NaOH (2 mL, 6.0 mmol), and the mixture was stirred for 14 h at room temperature. After addition of H_2O, the mixture was concentrated in vacuo to remove MeOH and washed with Et_2O. The aqueous layer was acidified with 1 N HCl and extracted three times with $CHCl_3$. The combined organic layer was dried over $MgSO_4$ and concentrated in vacuo. To a solution of the residual oil (620 mg) and 1-(4-methyl-3-pentenyl)-4-aminopiperidine[9] (470 mg, 2.6 mmol) in $CHCl_3$ (30 mL) were added HOBt (460 mg, 3.4 mmol) and WSC·HCl (560 mg, 2.9 mmol) at room temperature. After being stirred for 18 h, the mixture was concentrated in vacuo. The residue was partitioned between Et_2O and saturated aq $NaHCO_3$. The organic layer was separated, washed with brine and dried over $MgSO_4$. Evaporation of the solvent in vacuo gave the residue which was purified by SiO_2 column chromatography ($CHCl_3$:MeOH = 100:1) to yield **8** (920 mg, 92%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 1.28–1.97 (10H, m), 1.62 (3H, s), 1.69 (3H, s), 2.04–2.23 (4H, m), 2.27–2.39 (2H, m), 2.70–2.90 (2H, m), 3.20 (1H, m), 3.71 (1H, m), 3.85 (1H, brs, OH), 5.08 (1H, m), 5.99 (1H, m), 7.27–7.43 (3H, m), 7.55 (2H, brd, J = 7.2 Hz); MS m/z 426 $(M+H)^+$; mp 137–139 °C (hexane:AcOEt); anal. calcd for $C_{24}H_{35}N_5O_2$: C, 67.73; H, 8.29; N, 16.46. Found: C, 67.82; H, 8.42; N, 16.36; $[\alpha]_D^{20}$ −29.2 (c = 1.0, $CHCl_3$).

(2*R*)-*N*-[1-(4-Methyl-3-pentenyl)piperidin-4-yl]-2-[(1*S*,3*S*)-3-aminocyclopentyl]-2-hydroxy-2-phenylacetamide (9). To a solution of **8** (330 mg, 0.78 mmol) in THF (6 mL) were added H_2O (1 mL) and Ph_3P (260 mg, 0.99 mmol), and the mixture was heated at 75 °C for 6 h. After evaporation of THF, the mixture was acidified with 1 N HCl and washed with $CHCl_3$. The aqueous layer was basified with 1 N NaOH and extracted three times with $CHCl_3$. The combined extract was dried over $MgSO_4$ and concentrated in vacuo to produce the crude amine (290 mg), which was used in the next step without further purification: ^{1}H NMR ($CDCl_3$) δ 1.27–2.23 (14H, m), 1.61 (3H, s), 1.69 (3H, s), 2.26–2.38 (2H, m), 2.70–2.90 (2H, m), 3.28 (1H, m), 3.69 (1H, m), 5.08 (1H, m), 7.25–7.40 (3H, m), 7.53–7.63 (2H, m); MS m/z 426 $(M+H)^+$.

(2*R*)-*N*-[1-(4-Methyl-3-pentenyl)piperidin-4-yl]-2-[(1*S*,3*S*)-3-acetylaminocyclopentyl]-2-hydroxy-2-phenylacetamide (10a). To a solution of **9** (40 mg, 0.10 mmol) and Et_3N (30 μL, 0.22mmol) in $CHCl_3$ (2 mL) was added acetyl chloride (15 μL, 0.21 mmol) at 0 °C, and the mixture was stirred at the same temperature for 2 h. The excess amount of acetyl chloride was quenched with 3 N NaOH. The organic layer was separated, washed with brine and dried over $MgSO_4$. Removal of the solvent in vacuo gave the crude residue, which was purified by preparative TLC ($CHCl_3$:MeOH = 9:1) to yield **10a** (27 mg, 61%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 1.18–2.20 (14H, m), 1.60 (3H, s), 1.68 (3H, s), 1.96 (3H, s), 2.28–2.39 (2H, m), 2.72–2.90 (2H, m), 3.29 (1H, m), 3.37 (1H, brs, OH), 3.69 (1H, m), 4.28 (1H, m), 5.07 (1H, m), 5.54 (1H, brd, J = 7.5 Hz), 6.58 (1H, brd, J = 8.4 Hz), 7.22–7.40 (3H, m), 7.58 (2H, brd, J = 8.4 Hz); MS m/z 442 $(M+H)^+$; mp 139.5–141 °C (hexane:AcOEt); anal. calcd for $C_{26}H_{39}N_3O_3$: C, 70.71; H, 8.90; N, 9.52. Found: C, 70.54; H, 9.03; N, 9.50; $[\alpha]_D^{20}$ +5.0 (c = 1.0, $CHCl_3$). The following compounds (**10b–j**) were prepared from **9** and the appropriate acid chlorides in a similar method described for **10a**.

(2*R*)-*N*-[1-(4-Methyl-3-pentenyl)piperidin-4-yl]-2-[(1*S*,3*S*)-3-phenylacetylaminocyclopentyl]-2-hydroxy-2-phenylacetamide (10b). Compound **10b** was obtained as an oil from **9** and phenylacetylchloride (70%): ^{1}H NMR ($CDCl_3$) δ 1.16–2.20 (14H, m), 1.60 (3H, s), 1.68 (3H, s), 2.24–2.39 (2H, m), 2.70–2.90 (2H, m), 3.23 (1H, m), 3.53 (2H, s), 3.69 (1H, m), 4.24 (1H, m), 5.07 (1H, m), 5.56 (1H, brd, J = 7.6 Hz), 6.58 (1H, brd, J = 8.2 Hz), 7.20–7.41 (8H, m), 7.55 (2H, brd, J = 7.2 Hz); HRMS calcd for $C_{32}H_{44}N_3O_3$ $(M+H)^+$: 518.3383, found 518.3383; $[\alpha]_D^{20}$ +13.4 (c = 1.0, $CHCl_3$).

(2*R*)-*N*-[1-(4-Methyl-3-pentenyl)piperidin-4-yl]-2-[(1*S*,3*S*)-3-phenylglyoxylaminocyclopentyl]-2-hydroxy-2-phenylacetamide (10c). Compound **10c** was obtained as an oil from **9** and phenylglyoxyl chloride (94%): ^{1}H NMR ($CDCl_3$) δ 1.30–1.92 (8H, m), 1.60 (3H, s), 1.68 (3H, s), 2.03–2.21 (6H, m), 2.28–2.40 (2H, m), 2.72–2.91 (2H, m), 3.32 (1H, m), 3.70 (1H, m), 4.38 (1H, m), 5.06 (1H, m), 6.38 (1H, m), 7.11 (1H, m), 7.25–7.41 (3H, m), 7.43–7.69 (5H, m), 8.33 (2H, brd, J = 7.1 Hz); HRMS calcd for $C_{32}H_{42}N_3O_4$ $(M+H)^+$: 532.3175, found 532.3161; $[\alpha]_D^{20}$ −6.6 (c = 1.0, $CHCl_3$).

(2*R*)-*N*-[1-(4-Methyl-3-pentenyl)piperidin-4-yl]-2-[(1*S*,3*S*)-3-methoxycarbonylaminocyclopentyl]-2-hydroxy-2-phenylacetamide (10d). Compound **10d** was obtained as an oil from **9** and methoxycarbonyl chloride (57%): ^{1}H NMR ($CDCl_3$) δ 1.20–2.20 (14H, m), 1.60 (3H, s), 1.68 (3H, s), 2.26–2.38 (2H, m), 2.71–2.90 (2H, m), 3.25 (1H, m), 3.65 (3H, s), 3.68 (1H, m), 4.03 (1H, m), 4.72 (1H, m), 5.07 (1H, m), 6.44 (1H, m), 7.21–7.40 (3H, m), 7.56 (2H, brd, J = 7.2 Hz); HRMS calcd for $C_{26}H_{40}N_3O_4$ $(M+H)^+$: 458.3019, found 458.2996; $[\alpha]_D^{20}$ −13.4 (c = 1.0, $CHCl_3$).

(2*R*)-*N*-[1-(4-Methyl-3-pentenyl)piperidin-4-yl]-2-[(1*S*,3*S*)-3-benzyloxylcarbonylaminocyclopentyl]-2-hydroxy-2-phenylacetamide (10e). Compound **10e** was obtained as an oil from **9** and benzyloxycarbonyl chloride (72%): ^{1}H NMR ($CDCl_3$) δ 1.19–2.20 (14H, m), 1.60 (3H, s), 1.68 (3H, s), 2.25–2.40 (2H, m), 2.72–2.90 (2H, m), 3.26 (1H, m), 3.69 (1H, m), 4.06 (1H, m), 4.87 (1H, m), 5.06–5.17 (3H, m$^+$s), 6.49 (1H, m), 7.21–7.41 (8H, m), 7.56 (2H, brd, J = 7.2 Hz); HRMS calcd for $C_{32}H_{44}N_3O_4$ $(M+H)^+$: 534.3332, found 534.3312; $[\alpha]_D^{20}$ −9.4 (c = 1.0, $CHCl_3$).

(2*R*)-*N*-[1-(4-Methyl-3-pentenyl)piperidin-4-yl]-2-[(1*S*,3*S*)-3-methanesulfonylaminocyclopentyl]-2-hydroxy-2-phenylacetamide (10f). Compound **10f** was obtained from **9** and methanesulfonyl chloride (48%): ^{1}H NMR ($CDCl_3$) δ 1.25–1.88 (8H, m), 1.60 (3H, s), 1.68 (3H, s), 1.95–2.19 (6H, m), 2.25–2.34 (2H, m), 2.70–2.93 (2H, m), 2.98 (3H, s), 3.25 (1H, m), 3.52 (1H, brs, OH), 3.68 (1H, m), 3.90 (1H, m), 4.49 (1H,m), 5.06 (1H, m), 6.58 (1H, brd, J = 8.1 Hz), 7.23–7.40 (3H, m), 7.54 (2H, brd, J = 7.5 Hz); MS m/z 478 $(M+H)^+$; mp 211–212 °C (AcOEt); anal. calcd for $C_{25}H_{39}N_3O_4S$: C, 62.86; H, 8.23; N, 8.80; S, 6.71. Found: C, 62.89; H, 8.55; N, 8.79; S, 6.92; $[\alpha]_D^{20}$ −14.4 (c = 1.0, $CHCl_3$).

(2*R*)-*N*-[1-(4-Methyl-3-pentenyl)piperidin-4-yl]-2-[(1*S*,3*S*)-3-phenylsulfonylaminocyclopentyl]-2-hydroxy-2-phenylacetamide (10g). Compound **10g** was obtained from **9** and phenylsulfonyl chloride (63%): ^{1}H NMR ($CDCl_3$) δ 1.17–1.88 (10H, m), 1.60 (3H, s), 1.68 (3H, s), 2.03–2.21 (4H, m), 2.29–2.40 (2H, m), 2.76–2.93 (2H, m), 3.22 (1H, m), 3.58–3.68 (2H, m), 5.06 (1H, m), 5.41 (1H, m), 6.38 (1H, brd, J = 8.2 Hz), 7.20–7.36 (3H, m), 7.46–7.60 (5H, m), 7.87–7.95 (2H, m); MS m/z 540 $(M+H)^+$; mp 197.5–198.5 °C (hexane:AcOEt); anal. calcd for $C_{30}H_{41}N_3O_4S$: C, 66.76; H, 7.66; N, 7.79; S, 5.94. Found: C, 66.65; H, 7.95; N, 7.74; S, 6.11; $[\alpha]_D^{20}$ −19.2 (c = 1.0, $CHCl_3$).

(2*R*)-*N*-[1-(4-Methyl-3-pentenyl)piperidin-4-yl]-2-[(1*S*,3*S*)-3-(4-nitrophenyl)sulfonylaminocyclopentyl]-2-hydroxy-2-phenylacetamide (10h). 10h was obtained from **9** and 4-nitrophenylsulfonyl chloride (61%): ^{1}H NMR ($CDCl_3$) δ 1.18–2.28 (14H, m), 1.62 (3H, s), 1.69 (3H, s), 2.35–2.48 (2H, m), 2.80–3.00 (2H, m), 3.22 (1H, m), 3.50–3.87 (3H, m), 5.06 (1H, m), 6.39 (1H, m), 7.20–7.39 (3H, m), 7.50 (2H, brd, J = 8.3 Hz) 8.10 (2H, brd, J = 9.0 Hz) 8.36 (2H, brd, J = 9.0 Hz); MS m/z 585 $(M+H)^+$; IR (KBr) 3250, 1650, 1543, 1525, 1352, 1336, 1157 cm^{-1}; mp 208–210 °C (hexane:AcOEt); anal. calcd for $C_{30}H_{40}N_4O_6S{\cdot}0.25H_2O$: C, 61.15; H, 6.93; N, 9.51; S, 5.44. Found: C, 61.25; H, 7.03; N, 9.44; S, 5.04; $[\alpha]_D^{20}$ −13.4 (c = 1.0, $CHCl_3$).

(2*R*)-*N*-[1-(4-Methyl-3-pentenyl)piperidin-4-yl]-2-[(1*S*,3*S*)-3-(4-methoxyphenyl)sulfonylaminocyclopentyl]-2-hydroxy-2-phenylacetamide (10i). 10i was obtained as an oil from **9** and 4-methoxyphenylsulfonyl chloride (84%): ^{1}H NMR ($CDCl_3$) δ 1.19–2.24 (14H, m), 1.61 (3H, s), 1.69 (3H, s), 2.28–2.41 (2H, m), 2.71–2.92 (2H, m), 3.20 (1H, m), 3.58–3.82 (3H, m), 3.87 (3H, s), 4.91 (1H, m, NH), 5.06 (1H, m), 6.25 (1H, brd, J = 8.1), 6.98 (2H, d, J = 9.0), 7.20–7.38 (3H, m), 7.51 (2H, brd, J = 7.2 Hz) 7.82 (2H, d, J = 9.0 Hz); HRMS calcd for $C_{31}H_{44}N_3O_5S$ $(M+H)^+$: 570.3002, found 570.3012; $[\alpha]_D^{20}$ −20.8 (c = 1.0, $CHCl_3$).

(2*R*)-*N*-[1-(4-Methyl-3-pentenyl)piperidin-4-yl]-2-[(1*S*,3*S*)-3-(4-trifluoromethylphenyl)sulfonylaminocyclopentyl]-2-

hydroxy-2-phenylacetamide (10j). Compound **10j** was obtained as an oil from **9** and 4-trifluorophenylsulfonyl chloride (68%): ^{1}H NMR ($CDCl_3$) δ 1.18–2.29 (14H, m), 1.60 (3H, s), 1.68 (3H, s), 2.33–2.45 (2H, m), 2.80–3.00 (2H, m), 3.22 (1H, m), 3.58–3.85 (3H, m), 5.05 (1H, m), 6.40 (1H, brd, J = 8.4), 7.20–7.39 (3H, m), 7.50 (2H, brd, J = 7.0 Hz) 7.78 (2H, d, J = 8.5 Hz) 8.03 (2H, d, J = 8.5 Hz); HRMS calcd for $C_{31}H_{41}N_3O_4F_3S$ $(M+H)^+$: 608.2770, found 608.2751; $[\alpha]_D^{20}$ −13.0 (c = 1.0, $CHCl_3$).

Binding assay. According to the reported method,[9] the binding affinities were determined by inhibition of specific binding of [^{3}H]-NMS using membranes from CHO cells expressing cloned human m1–m3 receptors.

Metabolic stability in hepatic microsomes. Hepatic microsomes were prepared from liver samples of male rats and female dogs. Human liver microsomes were obtained from Pennsylvania Regional Tissue Bank via KAC. The test compound (10 μM) was incubated at 37 °C for 30 min with the hepatic microsomes (1 mg protein/mL) in the presence of an NADPH-generating system. The reaction was terminated by mixing 4 volumes of EtOH to the medium. After centrifugation, the supernatant was analyzed for concentration of the test compound by HPLC (GL-Science Inertsil ODS-3.5 μm, 1.5×150 mm, eluent CH_3CN:H_2O (55:45) containing 10 mM $AcONH_4$, flow rate = 0.1 mL/min, oven temperature 40 °C, electrochemical detection 950 mV).

Identification of the metabolites of 1 in rat microsomes. Compound **1** (100 μM) was incubated at 37 °C for 2 h with rat hepatic microsomes (3 mg protein/mL) in the presence of an NADPH-generating system. The reaction was terminated by adding 4 volumes of EtOH. The supernatant was obtained after the centrifugation of the mixture and concentrated to dryness under N_2-flow. The residue was dissolved in a small volume of CH_3CN:H_2O (55:45) containing 10 mM $AcONH_4$ and filtered. The filtrate was analyzed by LC/MS/MS (GL-Science Inertsil ODS-3.5 μm, 1.5×150 mm, eluent CH_3CN:H_2O (20:80–70:30) containing 10 mM $AcONH_4$, flow rate = 0.1 mL/min, oven temperature 40 °C, tandem mass Quattro 2 Micromass, ES+). Hydroxylated compounds (m/z 401 $(M+H)^+$) were detected. Among these, **5b**, **5c**, **5e** and **5f** were identified by comparison of their retention times with those of the synthesized standard samples (t_R: **5b** 11.5 min, **5c** 14.7 min, **5e** 11.2 min, **5f** 14.2 min; Capcell pak C18 UG-120 4.6×250 mm, eluent CH_3CN:H_2O:100 mM $AcONH_4$ (25:65:10–55:35:10 for 20 min), flow rate = 0.5 mL/min, oven temperature 40 °C, UV detection 220 nm).

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