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Replacing alkyl sulfonamide with aromatic sulfonamide in sulfonamide-type RXR agonists favors switch towards antagonist activity

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ABSTRACT

Retinoid X receptor (RXR) ligands are attractive candidates for clinical application because of their activity against tamoxifen-resistant breast cancer, taxol-resistant lung cancer, metabolic syndrome, and allergy. Though several RXR ligands, especially RXR antagonists, have been reported, the rational molecular design of such compounds is not well advanced. 4-[*N*-Methanesulfonyl-*N*-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)amino]nicotinic acid (**5a**) is a moderately RXRα-preferential agonist, and we examined the feasibility of replacing the methyl group on the sulfonamide with a longer alkyl chain or an aromatic ring as an approach to produce new RXR antagonists. Several of the resulting benzenesulfonanilide-type compounds showed RXR antagonist activity. This design strategy should be a useful approach for addressing the lack of structure diversity of RXR antagonists.

Retinoid X receptors (RXRs) are members of the nuclear receptor family of ligand-dependent transcription factors. RXRs work as homodimers or heterodimers with FXR, LXR, PPAR, RAR, etc., to control gene expression.[1–3] They are activated by 9-*cis* retinoic acid, an endogenous ligand.[4] This compound also activates retinoic acid receptors (RARs),[5] but several RXR-selective ligands have been developed (Fig. 1).[2,3,6–9] The first RXR-selective agonist, LGD1069, has been approved as a treatment for cutaneous T-cell lymphoma by the Food and Drug Administration (FDA) in the United States of America. In addition, RXR agonists are reported to be effective against tamoxifen-resistant breast cancer, taxol-resistant lung cancer and metabolic syndrome.[2,3,10,11]

Several RXR antagonists, **6**: LG100754[12], **7**: HX531[13], **8**: UVI3003[14], and PA452[15], have also been developed (Fig. 1) and some of them show anti-allergic activity via inhibition of Th2 differenciation[16] and anti-diabetic action via RXR-PPAR heterodimer modulation.[17] RXR antagonists are expected to be useful tools for studying the functions of RXR or RXR agonists. However, currently available RXR antagonists, except HX531 (**7**), are structurally rather similar, with a long alkyl chain on the tetramethyltetrahydronaphthyl hydrophobic domain of the corresponding RXR agonists (Fig. 1).

We were therefore interested in a new molecular design approach to RXR antagonists. For this purpose, we focused on the sulfonamide-type RXR agonist **5a**: 4-[*N*-methanesulfonyl-*N*-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)amino]nicotinic acid (Fig. 1).[6] The X-ray structure of **5a** is shown in Figure 2 and Table 1. Comparing the structure with those of existing RXR antagonists **7**: HX531[13] and **8**: UVI3003[14], we thought that replacement of the methyl group of the methanesulfonamide moiety of **5a** with a long alkyl chain or a steric bulky aromatic ring might produce RXR antagonist activity. This is because the longer the alkyl-chain on the tetramethyltetrahydronaphthyl group, the more likely compounds are to show RXR antagonistic activity, according to Nahoum et al.[14]

Sulfonamide compounds were synthesized according to Scheme 1. Amine **9** was prepared according to reference[18] and coupled with methyl 6-chloronicotinate under acidic conditions to give intermediate **10**. Introduction of a sulfonamide group into **10** was performed by with sulfonyl chloride after treatment of **10** with sodium hydride in DMF. Deprotection of the methyl ester group was performed under alkaline conditions to afford the desired compounds **5b**–**5j**. The RXR agonistic activity of these compounds

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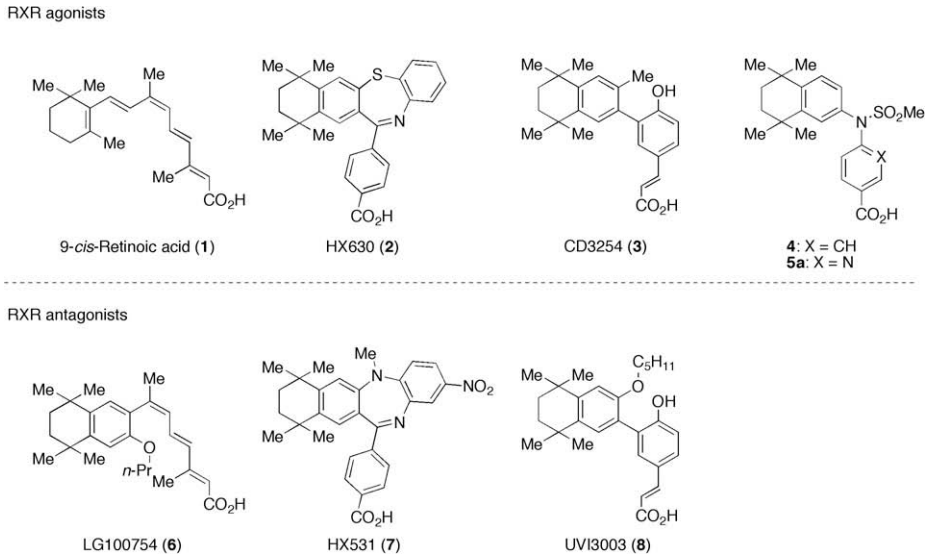


Figure 1. Chemical structures of known RXR agonists and antagonists.

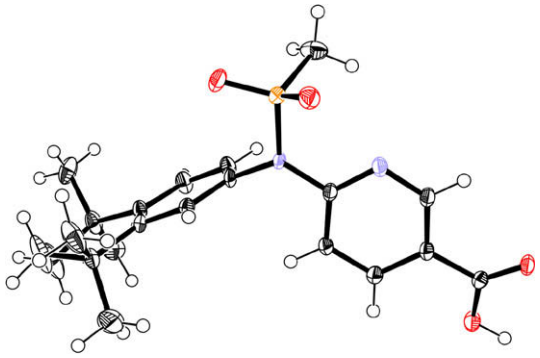


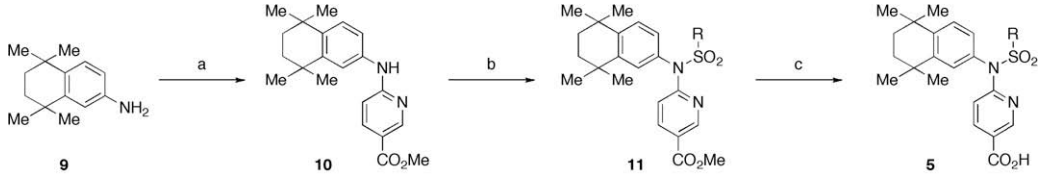
Figure 2. ORTEP drawing of compound **5a**.

Table 1
Crystallographic data for compound **5a**

Formula	$C_{21}H_{26}N_2O_4S$
Crystal system	Triclinic
Space group	P-1
Temperature	90 K
a (Å)	8.8310(13)
b (Å)	10.8501(16)
c (Å)	11.9915(18)
α (°)	75.853(2)
β (°)	71.405(2)
γ (°)	69.786(2)
v (Å^3)	1010.2(3)
Z	2
D (g/cm^3)	1.323
No. of obsd. reflns.	6218
*R*1; *wR*2	0.0680; 0.1975

was evaluated by means of luciferase-reporter gene assay in COS-1 cells using 1 μM LGD1069 (RXR-pan-agonist) as a reference. As shown in Figure 3, the longer the alkyl chain on the sulfonamide group, the weaker the RXR agonistic activity. Compounds **5e**–**5j** bearing an aromatic sulfonamide group also did not show RXR agonistic activity. We judged that the decreasing RXR agonistic activity represented a shift from agonist to antagonist activity, and therefore evaluated the RXR antagonistic activity.

RXR antagonistic activity of the compounds was evaluated in terms of inhibition of the agonistic activity of LGD1069 at 10 nM (see Table 2). Whereas the alkyl-sulfonamide derivatives did not show RXR antagonistic activity below 10 μM, some benzenesulfo-



Compound	R
b	Et
c	*n*-Pr
d	*n*-Bu
e	Ph
f	*p*-MePh
g	*p*-MeOPh
h	*p*-ClPh
i	*p*-CF_3Ph
j	*p*-NO_2Ph

Scheme 1. Reagents and conditions: (a) i—6-chloronicotinic acid, MsOH, dioxane; ii—MeOH, H_2SO_4; (b) RSO_2Cl, NaH, DMF; (c) NaOH, MeOH, then HCl.

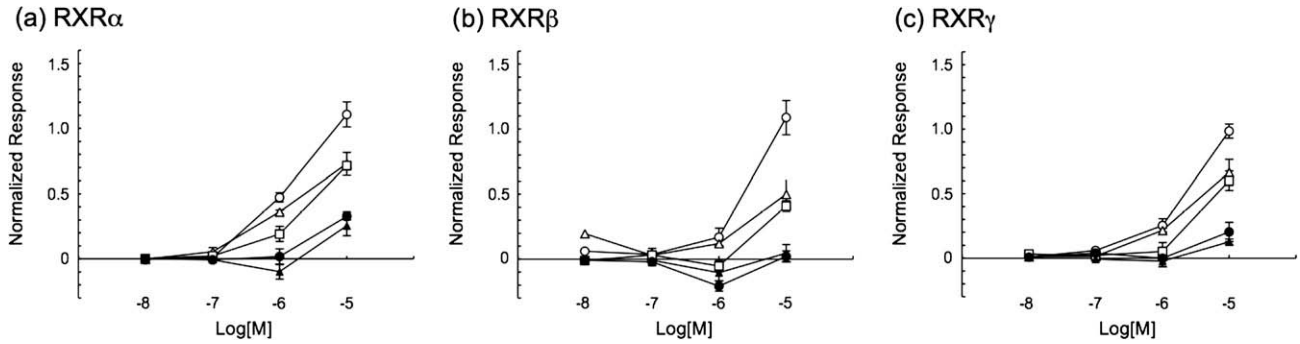
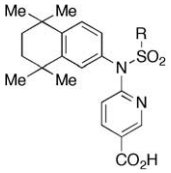


Figure 3. Dose-dependent RXR agonistic activities of compounds **5a**–**5d** against RXRα, RXRβ, and RXRγ. Open circles, open triangles, open squares, closed circles and closed triangles indicate compounds **5a**, **5b**, **5c**, **5d**, and **5e**, respectively. Luciferase activity of LGD1069 at 1 μM was defined as 1.0.

Table 2
RXR antagonistic activities of compounds **5d**–**5j** and HX531 (**7**) against 10 nM LGD1069 (RXR pan-agonist)[a]



Compound	R	RXRα IC_{50}[b] (μM)	RXRβ IC_{50}[b] (μM)	RXRγ IC_{50}[b] (μM)
5d	*n*-Bu	>10	>10	>10
5e	Ph	>10	>10	>10
5f	*p*-MePh	5.2 ± 1.4	3.0 ± 1.4	3.8 ± 0.2
5g	*p*-MeOPh	2.7 ± 0.4	3.9 ± 2.0	6.6 ± 0.8
5h	*p*-ClPh	4.1 ± 1.1	0.87 ± 0.36	4.5 ± 1.3
5i	*p*-CF_3Ph	3.2 ± 1.1	0.75 ± 0.46	2.7 ± 0.9
5j	*p*-NO_2Ph	>10	>10	>10
7: HX531	—	0.29 ± 0.04	0.044 ± 0.002	0.38 ± 0.14

[a] All values represent the standard error of the mean value of at least two separate experiments with triplicate determinations.
[b] IC_{50} values were determined from full dose–response curves ranging from 10^{-7} to 10^{-5} M in COS-1 cells.

nanilide derivatives were found to show RXR antagonistic activity at single digit micromolar concentrations. Among them, compounds bearing a chloro substituent **5h** or trifluoromethyl group **5i** at the *para*-position on the benzenesulfonyl group showed moderate RXR antagonistic activity against RXRβ.

In conclusion, we found that introduction of a bulky substituent on the sulfonamide group that links the hydrophobic aromatic group and aromatic carboxylic group of RXR ligands can generate RXR antagonistic activity. Although the RXR antagonistic activity of the compounds **5h** and **5i** prepared in this study is slightly weaker than that of **7**: HX531, this molecular design strategy should be a useful approach for addressing the lack of structure diversity of RXR antagonists.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2008.11.086.

References and notes

1. Mangelsdorf, D. J.; Thummel, C.; Beato, M.; Herrlich, P.; Schultz, G.; Umesono, K.; Blumberg, B.; Kastner, P.; Mark, M.; Chambon, P.; Evans, R. M. *Cell* **1995**, *83*, 835.
2. de Lera, A. R.; Bourguet, W.; Altucci, L.; Gronemeyer, H. *Nat. Rev. Drug Discov.* **2007**, *6*, 811.
3. Altucci, L.; Leibowitz, M. D.; Ogilvie, K. M.; Lera, A. R. D.; Gronemeyer, H. *Nat. Rev. Drug Discov.* **2007**, *6*, 793.
4. Heyman, R. A.; Mangelsdorf, D. J.; Dyck, J. A.; Stein, R. B.; Eichele, G.; Evans, R. M.; Thaller, C. *Cell* **1992**, *68*, 397.
5. Germain, P.; Chambon, P.; Eichele, G.; Evans, R. M.; Lazar, M. A.; Leid, M.; Lera, A. R. D.; Lotan, R.; Mangelsdorf, D. J.; Gronemeyer, H. *Pharmacol. Rev.* **2006**, *58*, 760.
6. Takamatsu, K.; Takano, A.; Yakushiji, N.; Morishita, K.; Matsuura, N.; Makishima, M.; Ali, H. I.; Akaho, E.; Tai, A.; Sasaki, K.; Kakuta, H. *ChemMedChem* **2008**, *3*, 454.
7. Takamatsu, K.; Takano, A.; Yakushiji, N.; Morohashi, K.; Morishita, K.; Matsuura, N.; Makishima, M.; Tai, A.; Sasaki, K.; Kakuta, H. *ChemMedChem* **2008**, *3*, 780.
8. Muccio, D. D.; Brouillette, W. J.; Breitman, T. R.; Taimi, M.; Emanuel, P. D.; Zhang, X.-K.; Chen, G.-Q.; Sani, B. P.; Venepally, P.; Reddy, L.; Alam, M.; Herren, L. S.; Hill, D. L. *J. Med. Chem.* **1998**, *41*, 1679.
9. Umemiya, H.; Fukasawa, H.; Ebisawa, M.; Eyrolles, L.; Kawachi, E.; Eisenmann, G.; Gronemeyer, H.; Hashimoto, Y.; Shudo, K.; Kagechika, H. *J. Med. Chem.* **1997**, *45*, 3327.
10. Grubbs, C. J.; Hill, D. L.; Bland, K. I.; Beenken, S. W.; Lin, T. H.; Eto, I.; Atigadda, V. R.; Vines, K. K.; Brouillette, W. J.; Muccio, D. D. *Cancer Lett.* **2003**, *201*, 17.
11. Yen, W.-C.; Corpuz, M. R.; Prudente, R. Y.; Cooke, T. A.; Bissonnette, R. P.; Negro-Vilar, A.; Lamph, W. W. *Clin. Cancer Res.* **2004**, *10*, 8656.
12. Koch, S. S. C.; Dardashti, L. J.; Hebert, J. J.; White, S. K.; Croston, G. E.; Flatten, K. S.; Heyman, R. A.; Nadzan, A. M. *J. Med. Chem.* **1996**, *39*, 3229.
13. Ebisawa, M.; Umemiya, H.; Ohta, K.; Fukasawa, H.; Kawachi, E.; Christoffel, G.; Gronemeyer, H.; Tsuji, M.; Hashimoto, Y.; Shudo, K.; Kagechika, H. *Chem. Pharm. Bull.* **1999**, *47*, 1778.
14. Nahoum, V.; Pérez, E.; Germain, P.; Rodríguez-Barrios, F.; Manzo, F.; Kammerer, S.; Lemaire, G.; Hirsch, O.; Royer, C. A.; Gronemeyer, H.; de Lera, A. R.; Bourguet, W. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 17323.
15. Takahashi, B.; Ohta, K.; Kawachi, E.; Fukasawa, H.; Hashimoto, Y.; Kagechika, H. *J. Med. Chem. Lett.* **2002**, *45*, 3327.
16. Grenningloh, R.; Gho, A.; di Lucia, P.; Klaus, M.; Bollag, W.; Ho, I.-C.; Sinigaglia, F.; Bordignon, P. P. *J. Immunol.* **2006**, *176*, 5161.
17. Yamauchi, T.; Waki, H.; Kamon, J.; Murakami, K.; Motojima, K.; Komeda, K.; Miki, H.; Kubota, N.; Terauchi, Y.; Tsuchida, A.; Tsuboyama-Kasaoka, N.; Yamauchi, N.; Ide, T.; Hori, W.; Kato, S.; Fukayama, M.; Akanuma, Y.; Ezaki, O.; Itai, A.; Nagai, R.; Kimura, S.; Tobe, K.; Kagechika, H.; Shudo, K.; Kadowaki, T. *J. Clin. Invest.* **2001**, *108*, 1001.
18. Kagechika, H.; Kawachi, E.; Hashimoto, Y.; Himi, T.; Shudo, K. *J. Med. Chem.* **1988**, *31*, 2182.