Bioorganic & Medicinal Chemistry Letters 26 (2016) 1817–1820

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Altered activity profile of a tertiary silanol analog of multi-targeting nuclear receptor modulator T0901317

Hirozumi Toyama [a], Shoko Sato [b], Hitoshi Shirakawa [c], Michio Komai [c], Yuichi Hashimoto [a], Shinya Fujii [a,*]

[a] Institute of Molecular and Cellular Biosciences, The University of Tokyo, 1-1-1 Yayoi, Bunkyo-ku, 113-0032 Tokyo, Japan
[b] Department of Biological Science and Technology, Tokyo University of Science, 6-3-1 Niijuku, Katsushika-ku, Tokyo 125-8585, Japan
[c] Graduate School of Agricultural Science, Tohoku University, 1-1 Tsutsumidori-Amamiyamachi, Aoba-ku, Sendai 981-8555, Japan

ARTICLE INFO

Article history:
Received 22 January 2016
Revised 9 February 2016
Accepted 12 February 2016
Available online 12 February 2016

Keywords:
Silanol
Sila-substitution
Nuclear receptor
Pregnane X receptor (PXR)
Retinoic acid receptor-related orphan receptor (ROR)
T0901317

ABSTRACT

We report the design, synthesis, and physicochemical/biological evaluation of novel silanol derivative **6** (sila-T) as a silanol analog of multi-target nuclear receptor modulator T0901317 (**5**). Compound **6** showed intermediate hydrophobicity between the corresponding alcohol **13** and perfluoroalcohol **5**. While **5** exhibited potent activities toward liver X receptor α and β, farnesoid X receptor, pregnane X receptor (PXR) and retinoic acid receptor-related orphan receptor (ROR)γ, silanol **6** exhibited activity only toward PXR and RORs. Incorporation of silanol instead of perfluoroalcohol is a promising option for developing novel target-selective, biologically active compounds.

The alcoholic hydroxy group is one of the most important functional groups in biologically active compounds.[1] It can be involved in hydrogen bonding and other polar contacts, functions as a nucleophilic reactive species, and markedly influences the absorption, distribution, metabolism, excretion, and toxicity (ADMET) profiles of compounds. Physicochemical properties such as the acidity of the hydroxy group and the hydrophobicity of a neighboring group also affect the biological activity. For example, in nuclear receptor ligands such as vitamin D receptor (VDR) ligands,[2,3] liver X receptor (LXR) ligands and pregnane X receptor (PXR) ligands,[4] modification of the acidity or hydrophobicity of the tertiary alcohol therein significantly affects the biological activities. Therefore, the use of novel substitutes for the alcoholic hydroxy group is a promising approach for structural development of drug candidates.

One possible approach for exploiting novel isosteric structures of alcoholic hydroxy groups is utilization of heteroatom functionalities. In the case of acidic carboxy groups, application of several heteroatom-hydroxy functionalities, such as sulfonic acid, phosphonic acid, hydroxamic acid and boronic acid, has been intensively investigated in the field of medicinal chemistry.[1,5] Regarding development of alternatives to the alcoholic hydroxy group, incorporation of heteroatoms is also useful, and silanol has potential as an isosteric substructure of alcoholic hydroxy groups.[6–8] The silicon atom is isoelectronic with carbon, and therefore various silicon/carbon exchanges (sila-substitutions) of biologically active compounds have been investigated, particularly for optimization of hydrophobic moieties.[9–16] There have also been some studies on the use of silanol as a hydrophilic structure. A representative example is a series of silanediol-based protease inhibitors, such as **1** and **2**.[17–19] Silanediols in these compounds function as mimics of the transition state in substrate hydrolysis. Another example is provided by cyclic silanol derivatives including sila-venlafaxine (**3**) and sila-haloperidol (**4**) (Fig. 1).[20–22] In the case

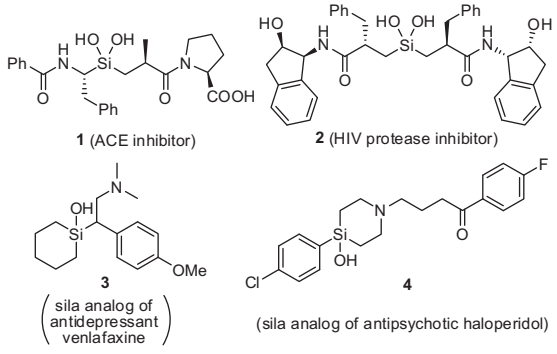


Figure 1. Examples of silanol-based biologically active compounds.

* Corresponding author.

http://dx.doi.org/10.1016/j.bmcl.2016.02.031
0960-894X/

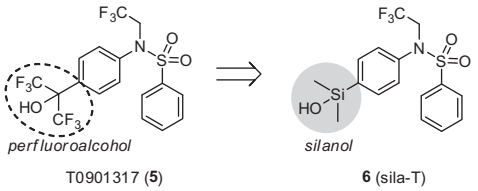


Figure 2. Design scheme of the silanol analog of T0901317 (sila-T; **6**).

Table 1
Determined and calculated physicochemical properties of compounds **5**, **6** and **13**

	5	6	13
Log$P_{o/w}$[a]	5.38	4.23	3.70
Partial volume ($PhXR_2OH$) (Å^3)[b]	170.7	154.4	141.3
pK_a[c]	7.5	12.5	14.6

[a] Determined by HPLC method.[30]
[b] Calculated by MOPAC software (methods: PM3 EF).[31]
[c] Estimated by ACD/Chemsketch software.[32]

of sila-haloperidol, dehydration to afford the toxic pyridinium metabolite is blocked, because the Si=C double bond is intrinsically thermodynamically instable.[21] Although other examples have also been reported, utilization of silanol in medicinal chemistry is still quite limited compared to other hydrophobic substructures.

To expand the utility of silanols, we focused on the similarity between silanol and perfluoroalcohol. Perfluoroalcohols show higher acidity and hydrophobicity than the corresponding hydrocarbon-based alcohols, owing to the differences of electronegativity and molecular volume between alkyl groups and the corresponding perfluoroalkyl groups. Silanols also show somewhat higher acidity and hydrophobicity than the corresponding alcohols because of the differences of electronic properties and molecular volume between silanols and the corresponding alcohols.[23] The 1,1,1,3,3,3-hexafluoro-2-hydroxypropyl group, one of the perfluoroalcoholic functionalities, is a key structural motif of T0901317 (**5**), which is a benzenesulfonamide-based compound that exhibits agonistic activity toward multiple nuclear receptors, including LXRα and LXRβ,[24] PXR (also SXR; steroid and xenobiotic receptor),[4,25] farnesoid X receptor (FXR),[26] and inverse agonistic activity toward retinoic acid receptor-related orphan receptors (RORs).[27] Previous researches revealed that the substituents around the hydroxy group have a significant influence on the activity and selectivity.[4,28] So, we planned to investigate the activity profile of silanol **6** (named sila-T), a silanol analog of perfluoroalcohol-based T0901317 (**5**) (Fig. 2).

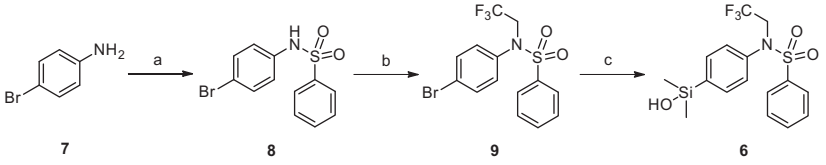
Scheme 1 shows the synthesis of the designed silanol derivative **6**. Sulfonamide formation using 4-bromoaniline (**7**) and benzenesulfonyl chloride gave sulfonamide **8**, and then N-alkylation with 2,2,2-trifluoroethyl triflate afforded compound **9**. The bromo group of **9** was converted to dimethylsilanol using Denmark's conditions;[29] namely, in the presence of $PdCl_2$ and 2-(di-*tert*-butylphosphino) biphenyl (BPTBP), compound **9** reacted with 1,2-diethoxy-1,1,2,2-tetramethyldisilane to afford a ethoxydimethylsilyl derivative as an intermediate, and then removal of the ethyl group gave the desired silanol **6** (Scheme 1).

In order to investigate the structure-activity relationship, the corresponding alcohol derivative **13** was also synthesized as shown in Scheme 2. Reaction with ethyl 4-aminobenzoate (**10**) and benzenesulfonyl chloride gave sulfonamide **11**, which was *N*-alkylated to afford compound **12**. Treatment of compound **12** with methylmagnesium bromide gave the desired alcohol **13** (Scheme 2).

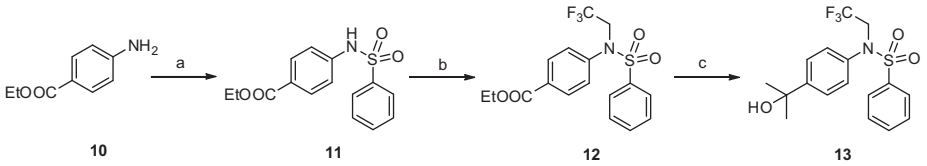
We next investigated the physicochemical properties of the synthesized compounds and parent T0901317 (**5**). Hydrophobicity was determined in terms of the octanol–water partition coefficient ($P_{o/w}$), using an HPLC method.[30] Silanol **6** exhibited a log$P_{o/w}$ value of 4.23, which is larger than that of corresponding alcohol **13** (log$P_{o/w}$; 3.70). Previous results indicated that C/Si-exchange of alkylsilanes increases the hydrophobicity of the compounds by 0.5–0.7 in log$P_{o/w}$ value,[16] and the present result suggests that this is also the case with silanols. Compound **5** exhibited a log$P_{o/w}$ value of 5.38, significantly larger than that of corresponding alcohol **13**, and the hydrophobicity of silanol is intermediate between those of the alcohol and perfluoroalcohol. The difference of hydrophobicity can be mainly attributed to the difference of molecular volume, and the calculated values of partial volume of the compounds ($PhXR_2OH$) are consistent with the order of hydrophobicity. The acidity of the compounds was also calculated. The estimated pK_a value of compound **6** (12.5) is smaller than that of alcohol **13** (14.6), while both values are considerably larger than that of compound **5** (7.5). Though the acidity of silanols may be larger than that of corresponding alcohols, it is considerably smaller than that of perfluoroalcohols (Table 1).

Next, the ligand potencies of the compounds toward hLXRα, hLXRβ, hFXR, hPXR (SXR), and hRORα, β and γ were evaluated by means of luciferase reporter gene assay in HEK293 cells. Compound **5** exhibited significant agonistic activity toward LXRα and β, FXR and PXR, and inverse agonistic activity toward RORγ.[33] On the other hand, compound **13** bearing a hydrocarbon-based alcohol instead of the perfluoroalcohol moiety of **5** exhibited no significant activity toward any of these nuclear receptors. These results indicate that high hydrophobicity and/or potent acidity of compound **5** is essential for biological activity toward these nuclear receptors. As for the silanol derivative **6**, it exhibited neither agonistic nor antagonistic activity toward LXRs, and showed only modest partial agonistic activity toward FXR. In contrast to the case of LXRs and FXR, compound **6** exhibited inverse agonistic activity toward RORs. In addition, silanol **6** exhibited significant agonistic activity toward PXR. The PXR agonistic activity of silanol **6** is comparable to that of representative PXR agonist rifampicin (EC_{50} value for PXR; 1.1 μM, maximum efficacy is 75% compared to **5** in the same assay system). This result suggests that the silanol group could function as an isoster of the perfluoroalkyl group in the case of PXR ligands. The silanol functionality may be a useful option for development of other target-selective bioactive compounds (Table 2).

X-Ray crystal structures of compound **5** complexed with hLXRα,[34] hLXRβ,[35] hPXR[4] and hRORγ[28] have been reported, and we conducted docking simulations using the crystal structures.[36] In the co-crystal structures with RORγ, the hexafluorohydroxypropyl group of compound **5** does not form a hydrogen bond to



Scheme 1. Synthesis of silanol derivative **6** (sila-T). Reagents and conditions: (a) benzenesulfonyl chloride, pyridine, THF, rt, 93%; (b) NaH, CF_3CH_2OTf, DMF, 80 °C, 68%; (c) (i) $PdCl_2$, BPTBP, *i*-Pr_2EtN, $(Me_2SiOEt)_2$, NMP, 60 °C; (ii) AcOH, MeCN, $Me_2N(CH_2)_2SH$–HCl, 26%.



Scheme 2. Synthesis of alcohol derivative **13**. Reagents and conditions: (a) benzenesulfonyl chloride, pyridine, THF, rt; (b) NaH, CF_3CH_2OTf, DMF, 80 °C, 33% from **10**; (c) MeMgBr, THF, 0 °C, 77%.

Table 2
Biological activities of compounds toward nuclear receptors

Compd	hLXRα		hLXRβ		hFXR	hPXR	hRORα	hRORβ	hRORγ
	EC_{50} (μM)	IC_{50}[a] (μM)	EC_{50} (μM)	IC_{50}[b] (μM)	EC_{50} (μM)	EC_{50} (μM)	IC_{50} (μM)	IC_{50} (μM)	IC_{50} (μM)
5	0.40	–	0.23	–	3.4	0.27	N.A.	N.A.	3.0
6	N.A.	N.A.	N.A.	N.A.	11 (23%)[c]	0.88 (61%)[d]	53	60	43
13	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.

[a] Compounds were treated with 0.30 μM T0901317 (**5**).
[b] Compounds were treated with 0.10 μM T0901317 (**5**).
[c] Percentage with respect to the response to 10 μM T0901317 (**5**).
[d] Percentage with respect to the response to 1.0 μM T0901317 (**5**). N.A.: No significant activity.

any amino acid residue of the receptor. In the docked structure with RORγ, the hydroxy group of silanol **6** also shows no notable hydrogen bonding (Fig. 3). These results suggest that hydrophobic interaction around the hydroxy moiety of the compound and the receptor surface of RORγ is rather more important than polar interaction for the activity. It is possible that silanol **6** exhibited inverse agonistic activity toward RORs due to its relatively high hydrophobicity compared with that of the corresponding alcohol **13**.

In the cases of LXRα, LXRβ and PXR, the hexafluorohydroxypropyl group of compound **5** forms a key hydrogen bond to a His residue of the receptor (His 421, His435 and His407, respectively). In the docked structure with PXR, the hydroxy group of silanol **6** also forms a hydrogen bond to His407. Structure–activity relationship study of T0901317 derivatives indicates that introduction of bulky hydrophobic substituents, as well as perfluoroalkyl groups, at the tertiary alcohol moiety is effective for potent PXR agonistic activity, whereas LXR agonistic activity strictly requires perfluoroalkyl substituents. We speculate that high hydrophobicity around the hydroxy moiety is important for PXR agonistic activity, whereas both hydrophobicity and high polarization of the hydroxy moiety may be essential for LXR agonistic activity. It is possible that silanol **6** exhibited PXR agonistic activity due to its relatively high hydrophobicity, but did not exhibit LXR ligand potency because of its lower polarization compared to compound **5**, and therefore shows selectivity for PXR over LXRs. Although the reason of the inactivity of compound **6** toward LXRs is unclear, alcohol/silanol exchange appears to be a promising option for modifying the activity profile of bioactive compounds.

In summary, in order to expand the utility of silanols in medicinal chemistry, we designed and synthesized silanol **6** (sila-T), a novel silanol derivative of T0901317 (**5**), focusing on the silanol functionality as an isosteric structure of perfluoroalcohol, and we compared the physicochemical properties and biological activities of **5** and **6**. In contrast to the parent compound **5**, which exhibited potent activities toward LXRα and β, FXR, PXR and RORγ, the synthesized silanol **6** exhibited only agonistic activity toward PXR and inverse agonistic activity toward RORs. The difference in activity could be attributed to the similarity of hydrophobicity and the difference of polarization between silanol and perfluoroalcohol. Silanol appears to be promising option for development of novel,

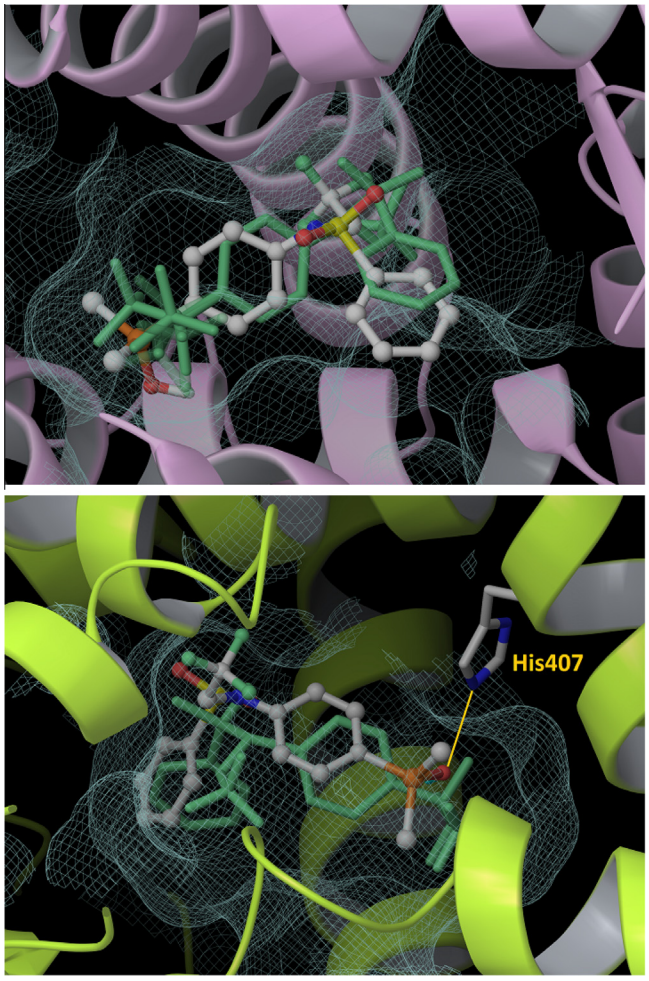


Figure 3. Docking simulations of compound **6** using the crystal structures of hRORγ (PDB-ID: 4NB6, upper) and hPXR (PDB-ID: 2O9I, bottom). The protein surface is indicated as a light-blue mesh. The native ligand T0901317 (**5**) in the crystal structures is shown in green.

target-selective, biologically active compounds. Further structural development and structure–activity relationship studies are in progress.

Acknowledgments

This work was partially supported by Platform for Drug Discovery, Informatics, and Structural Life Science, and Grants in-Aid for Scientific Research from The Ministry of Education, Culture, Sports, Science, and Technology, Japan, and the Japan Society for the Promotion of Science (KAKENHI Grant No. 26293025 (Y.H.), No. 25460146 (S.F.), Nos. 20380071 and 23380070 (H.S.)). We thank Dr. Shuichi Mori (Tokyo Medical and Dental University) for helpful discussions.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2016.02.031.

References and notes

1. *The Practice of Medicinal Chemistry*; Wermuth, C. G., Aldous, D., Raboisson, P., Rognan, D., Eds., 4th ed.; Elsevier Academic Press, 2015.
2. *Vitamin D*; Feldman, D., Pike, J. W., Glorieux, F. H., Eds., 2nd ed.; Elsevier Academic Press, 2005.
3. Sai, H.; Takatsuto, S.; Hara, N.; Ikekawa, N. *Chem. Pharm. Bull.* **1985**, *33*, 878.
4. Xue, Y.; Chao, E.; Zuercher, W. J.; Willson, T. M.; Collins, J. L.; Redinbo, M. R. *Bioorg. Med. Chem.* **2007**, *15*, 2156.
5. Ballatore, C.; Huryn, D. M.; Smith, A. B., III *ChemMedChem* **2013**, *8*, 385.
6. Franz, A. K.; Wilson, S. O. *J. Med. Chem.* **2013**, *56*, 388.
7. Bains, W.; Tacke, R. *Curr. Opin. Drug Discovery Dev.* **2003**, *6*, 526.
8. Mills, J. S.; Showell, G. A. *Expert Opin. Invest. Drugs* **2004**, *13*, 1149.
9. Showell, G. A.; Mills, J. S. *Drug Discovery Today* **2003**, *8*, 551.
10. Gately, S.; West, R. *Drug Dev. Res.* **2007**, *68*, 156.
11. Yamakawa, T.; Kagechika, H.; Kawachi, E.; Hashimoto, Y.; Shudo, K. *J. Med. Chem.* **1990**, *33*, 1430.
12. Tacke, R.; Müller, V.; Büttner, M. W.; Lippert, W. P.; Bertermann, R.; Daiß, J. O.; Khanwalkar, H.; Furst, A.; Gaudon, C.; Gronemeyer, H. *ChemMedChem* **2009**, *4*, 1797.
13. Büttner, M. W.; Burschka, C.; Daiss, J. O.; Ivanova, D.; Rochel, N.; Kammerer, S.; Peluso-Iltis, C.; Bindler, A.; Gaudon, C.; Germain, P.; Moras, D.; Gronemeyer, H.; Tacke, R. *ChemBioChem* **2007**, *8*, 1688.
14. Daiss, J. O.; Burschka, C.; Mills, J. S.; Montana, J. G.; Showell, G. A.; Fleming, I.; Gaudon, C.; Ivanova, D.; Gronemeyer, H.; Tacke, R. *Organometallics* **2005**, *24*, 3192.
15. Lippert, W. P.; Burschka, C.; Götz, K.; Kaupp, M.; Ivanova, D.; Gaudon, C.; Sato, Y.; Antony, P.; Rochel, N.; Moras, D.; Gronemeyer, H.; Tacke, R. *ChemMedChem* **2009**, *4*, 1143.
16. Fujii, S.; Miyajima, Y.; Masuno, H.; Kagechika, H. *J. Med. Chem.* **2013**, *56*, 160.
17. Sieburth, S. McN.; Chen, C.-A. *Eur. J. Org. Chem.* **2006**, 311.
18. Sieburth, S. McN.; Nittoli, T.; Mutahi, A. M.; Guo, L. *Angew. Chem., Int. Ed.* **1998**, *37*, 812.
19. Chen, C.-A.; Sieburth, S. McN.; Glekas, A.; Hewitt, G. W.; Trainor, G. L.; Erickson-Viitanen, S.; Garber, S. S.; Cordova, B.; Jeffry, S.; Klabe, R. M. *Chem. Biol.* **2001**, *8*, 1161.
20. Tacke, R.; Heinrich, T.; Bertermann, R.; Burschka, C.; Hamacher, A.; Kassack, M. U. *Organometallics* **2004**, *23*, 4468.
21. Tacke, R.; Popp, F.; Mueller, B.; Theis, B.; Burschka, C.; Hamacher, A.; Kassack, M. U.; Schepmann, D.; Wuensch, B.; Jurva, U.; Wellner, E. *ChemMedChem* **2008**, *3*, 152.
22. Daiss, J. O.; Burschka, C.; Mills, J. S.; Montana, J. G.; Showell, G. A.; Warneck, J. B. H.; Tacke, R. *Organometallics* **2006**, *25*, 1188.
23. Brook, M. A. *Silicon in Organic, Organometallic, and Polymer Chemistry*; John Wiley & Sons: New York, 2000.
24. Schultz, J. R.; Tu, H.; Luk, A.; Repa, J. J.; Medina, J. C.; Li, L.; Schwendner, S.; Wang, S.; Thoolen, M.; Mangelsdorf, D. J.; Lustig, K. D.; Sham, B. *Genes Dev.* **2000**, *14*, 2831.
25. Mitro, N.; Vargas, L.; Romeo, R.; Koder, A.; Saez, E. *FEBS Lett.* **2007**, *581*, 1721.
26. Houck, K. A.; Borchert, K. M.; Hepler, C. D.; Thomas, J. S.; Bramlett, K. S.; Michael, L. F.; Burris, T. P. *Mol. Genet. Metab.* **2004**, *83*, 184.
27. Kumar, N.; Solt, L. A.; Conkright, J. J.; Wang, Y.; Istrate, M. A.; Busby, S. A.; Garcia-Ordonez, R. D.; Burris, T. P.; Griffin, P. R. *Mol. Pharmacol.* **2010**, *77*, 228.
28. Fauber, B. P.; de Leon Boenig, G.; Burton, B.; Eidenschenk, C.; Everett, C.; Gobbi, A.; Hymowitz, S. G.; Johnson, A. R.; Liimatta, M.; Lockey, P.; Norman, M.; Ouyang, W.; René, O.; Wong, H. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 6604.
29. Denmark, S. E.; Kallemeyn, J. M. *Org. Lett.* **2003**, *5*, 3483.
30. OECD Guideline for Testing of Chemicals 117, Partition Coefficient (n-octanol/water), High Performance Liquid Chromatography (HPLC) Method; March 1989.
31. http://openmopac.net/
32. ACD/chemsketch (Freeware) 2012, version 14.01, Advanced Chemistry Development Inc, Toronto, ON, Canada, www.acdlabs.com, 2015.
33. Activities toward LXRs, FXR and RORs were evaluated using NR-LBD-GAL4 and MH100-luc. Activity toward hPXR was evaluated using VP16-hPXR and MDR1-luc.
34. Svensson, S.; Oestberg, T.; Jacobsson, M.; Norstroem, C.; Stefansson, K.; Hallen, D.; Johansson, I. C.; Zachrisson, K.; Ogg, D.; Jendeberg, L. *EMBO J.* **2003**, *22*, 4625.
35. Hoerer, S.; Schmid, A.; Heckel, A.; Budzinski, R.-M.; Nar, H. *J. Mol. Biol.* **2003**, *334*, 853.
36. Molecular docking was performed using AutoDock 4.2. Morris, G. M.; Huey, R.; Lindstrom, W.; Sanner, M. F.; Belew, R. K.; Goodsell, D. S.; Olson, A. J. *J. Comput. Chem.* **2009**, *16*, 2785. AutoDock parameters for silicon atom Rii = 4.30 and εii = 0.402 were used.