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Generation of 3,8-substituted 1,2,4-triazolopyridines as potent inhibitors of human 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD-1)

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ABSTRACT

A series of pyridyl amide/sulfonamide inhibitors of 11β-HSD-1 were modified to incorporate a novel 1,2,4-triazolopyridine scaffold. Optimization of substituents at the 3 and 8 position of the TZP core, with a special focus on enhancing metabolic stability, resulted in the identification of compound **38** as a potent and metabolically stable inhibitor of the enzyme.

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A primary pathophysiological defect in type 2 diabetes is resistance to the action of insulin in the liver, adipose tissue and skeletal muscle. Glucocorticoids play an important role in the regulation of these processes. In the liver, glucocorticoids directly upregulate the rate limiting enzymes in both the glycogenolysis and gluconeogenesis pathways thereby providing a mechanism for increased hepatic glucose output. In the adipose tissue, glucocorticoids dampen insulin signaling thereby reducing the ability of insulin to stimulate glucose uptake. Excess glucocorticoid tone in these tissues represents an assault on glucose homeostasis, leading to hyperglycemia and eventually type 2 diabetes, a major risk factor for cardiovascular disease.[1] For example, it is well known that an excess of glucocorticoid tone via secretion from the adrenal gland, such as that observed in Cushing's Disease, leads to major perturbations in glucose and lipid metabolism including hyperglycemia, type 2 diabetes and accelerated cardiovascular disease. This has led to the hypothesis that lowering the glucocorticoid tone in patients afflicted with type 2 diabetes could be an efficacious therapeutic strategy that is relevant to the underlying pathophysiology of this disease.

11β-Hydroxysteroid dehydrogenase- type 1 (11β-HSD-1) is an enzyme that catalyzes the conversion of inert cortisone to the active glucocorticoid hormone cortisol and is expressed at high levels in the liver and adipose tissue, two tissues of primary importance to metabolic diseases.[2] As such, 11β-HSD-1-mediated in situ production of cortisol represents a pathway by which glucocorticoid tone may be modulated in tissues. As a result, numerous groups have reported generating highly potent and selective 11β-HSD-1 inhibitors,[3] with several compounds having been advanced to clinical trials.[4]

Recently we published our efforts on the exploration and optimization of a series of pyridyl amides[5] and sulfonamides[6] which afforded highly potent and selective inhibitors of human 11β-HSD-1 (represented by structure **1**, Fig. 1). Compound **2** proved to be one of the most potent analogs in this series, affording single-digit nanomolar activity versus the enzyme. From X-ray crystallographic structures of these inhibitors bound to human 11β-HSD-1, it was determined that the amide carbonyl served as the critical hydrogen bonding pharmacophore to the Ser170 and Tyr183 residues within the enzyme's active site. In an extension of this work, we focused our attention on finding novel and proprietary core structures which may serve as suitable hydrogen bonding surrogates for the amide carbonyl pharmacophore. Incorporation of various heterocyclic replacements led to the identification of the 1,2,4-triazolopyridine (TZP) core (as depicted in structure **3**) as a highly suitable replacement.[7] While potent in vitro, compound **3** suffered from extensive metabolic degradation in liver microsomal preparations, in part via oxidation of the benzylic and sulfide moieties. Replacement of the sulfur atom with oxygen (compound **4**) incrementally enhanced oxidative stability but attenuated potency. Gratifyingly, replacement of the cyclohexyl group in **4** with cycloheptyl (affording **5**) restored in vitro potency. Based on the potential of this lead, a more extensive structure–activity relationship (SAR) study was undertaken in this

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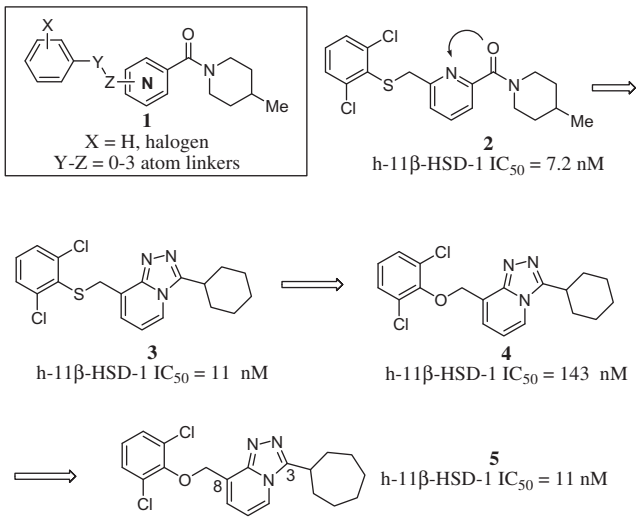


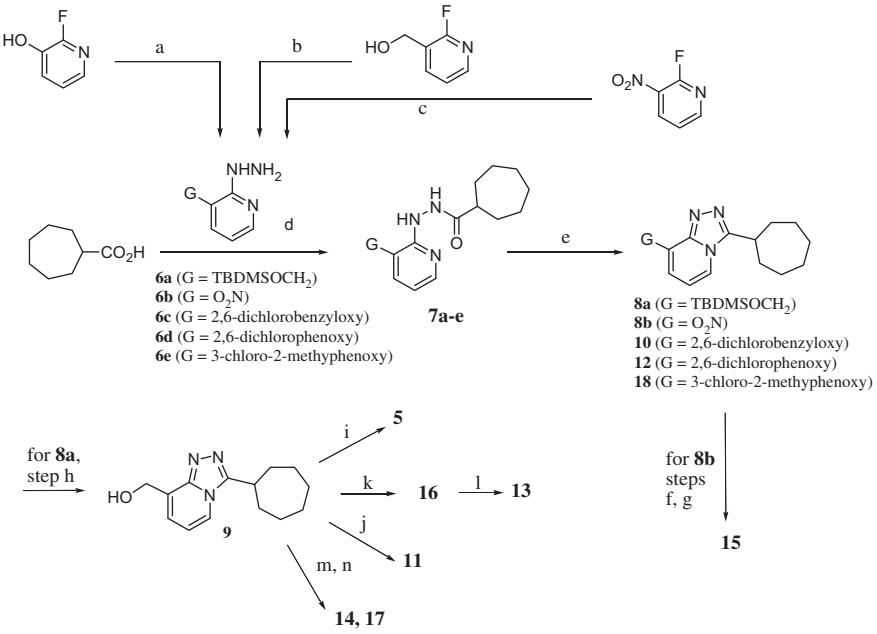
Figure 1. Generation of 1,2,4-trizolopyridine 11β-HSD-1 inhibitors based on pyridyl amide chemotype **1**.

series to enhance in vitro potency while attenuating potential development liabilities (e.g. metabolic stability, solubility, PXR induction, etc.). Using compound **5** as a starting point, studies were undertaken to independently vary the substituents at both the C-3 (i.e., cycloheptyl) and C-8 (i.e., aryl-linker) position of the TZP core.

Initial work was focused on the effect of linker variation between the TZP core and the distal aromatic group. The synthesis of these compounds is depicted in Scheme 1. The requisite pyridyl hydrazines **6a–e** were generated from the commercially available chlorides or fluorides shown below. Cycloheptane carboxylic acid was coupled with various 3-substituted 2-pyridyl hydrazines to afford the corresponding acyl hydrazides **7a–e** in typically high yields. A variety of methods were employed to effect cyclization of **7a–e** to the corresponding TZP intermediates/final products, the most effective of which was treatment with PPh_3Cl_2 and *i*-Pr_2NEt or Et_3N in methylene chloride. Reduction of **8b** was effected via catalytic hydrogenation and the intermediate amine subject to sulfonylation to afford **15**. Desilylation of **8a** afforded the versatile intermediate **9** which could then be further functionalized according to the methods in Scheme 1, affording the inhibitors listed in Table 1.

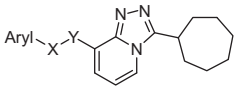
Table 1 predominantly focuses on the effect of the linker (X–Y) on human 11β-HSD-1 inhibitory activity. Overall, the SAR appears to be more empirical than predictable. Highest potency was achieved when X–Y is OCH_2 (**5**) or SCH_2 (**16**). Interestingly, simple transposition of the OCH_2 linker in **5** to give the CH_2O linked **10** resulted in a significant attenuation in potency, while the longer (**11**) and shorter (**12** and **18**) oxygen linked analogs still retained reasonable activity. Surprisingly, although the 'three atom linker' sulfonamide **14** was very potent versus the enzyme, the related 'two atom' sulfone (**13**) and sulfonamide (**15**) were weakly active. The significant variation in activity with respect to linker identity suggests strict structural requirements at this position of the molecule. Of high interest in this data set were the direct oxygen linkers (X–Y = O, compounds **12** and **18**). While not the most potent in the series, they presented more favorable metabolic stability profiles due to the absence of benzylic methylene groups and therefore represented preferable appendages for additional exploration in the series (see Table 2 for microsomal stability of **18**).

Extending the findings above, we embarked on a detailed exploration of replacements for the cycloheptyl appendage found in compound **18**. The synthesis of these derivatives is depicted generically in Scheme 2. A variety of commercially available or readily synthesized carboxylic acids **19** were coupled with hydrazine **6e** to afford hydrazide **20** in generally good yields (31–99%). Cyclization using one of the three methods (d, e or f) yielded the desired inhibitors **18**–**23**, **25**, **26**, **28**, **29**, **31**, **32**, **35** and **36**. Compounds **24**,



Scheme 1. Reagents and conditions: (a) For compounds **6d** and **6e**: substituted phenylboronic acid, $Cu(OAc)_2$, pyridine, 4A mol. sieves, CH_2Cl_2, rt, 14 h (6% for **6d**, 77% for **6e**), then excess anhydrous H_2NNH_2, dioxane, reflux (~100%); For compound **6c**: 2,6-dichlorobenzyl bromide, K_2CO_3, acetone, rt (~100%), then 10 equiv. anhydrous H_2NNH_2, dioxane, reflux (96%); (b) For compound **6a**: TBDMSCl, imidazole, CH_2Cl_2 (~100%), then 10 equiv anhydrous H_2NNH_2, dioxane, reflux (32%); (c) For compound **6b**: 5 equiv anhydrous H_2NNH_2, EtOH, rt, ~100%; (d) *N*-methyl morpholine, *i*-BuOCOCl, 0 °C, then **6a**–**e**, 31–94%; (e) PPh_3Cl_2, *i*-Pr_2NEt or Et_3N, 54–92%; (f) 15 psi H_2/Pd–C, 45%; (g) 2,6-dichlorophenylsulfonyl chloride, polyvinyl pyridine, 13%; (h) (*n*-Bu)$_4$NF, THF, rt, 95%; (i) 2,6-dichlorophenol, Ph_3P, DIAD, 89%; (j) NaH, 2,6-dichlorobenzyl bromide, 56%; (k), $SOCl_2$, then 2,6-dichlorothiophenol, *i*-Pr_2NEt, 91%; (l) *m*-$ClPhCO_3H$, CH_2Cl_2, rt, 48%; (m) (i) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 °C to rt; (ii) NaN_3, DMF, 50 °C; (iii) polymer bound PPh_3, THF, 50 °C, 80% for three steps; (n) 2,6-dichlorophenylsulfonyl chloride or 2-chloro-3-methylphenylsulfonyl chloride, Et_3N, 35–41%.

Table 1
SAR of cycloheptyl substituted TZP analogs **5** and **10–18**



Compd	Aryl	X–Y	IC_{50}[a] (nM)
5	2,6-diClPh	OCH_2	11
10	2,6-diClPh	CH_2O	578
11	2,6-diClPh	CH_2OCH_2	34
12	2,6-diClPh	O	36
13	2,6-diClPh	SO_2CH_2	2962
14	2,6-diClPh	SO_2NHCH_2	17
15	2,6-diClPh	SO_2NH	8778
16	2,6-diClPh	SCH_2	2.8
17	2-Me,3-ClPh	SO_2NHCH_2	12
18	2-Me,3-ClPh	O	23

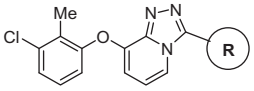
[a] IC_{50}'s refer to biochemical human 11β-HSD-1 assay data[8].

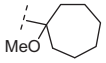
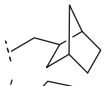
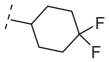
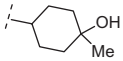
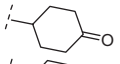
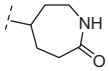
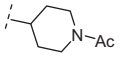
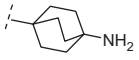
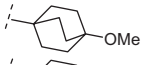
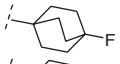
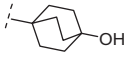
27, **30**, **33**, **34**, **37** and **38** were prepared through subsequent transformations of the initially formed cyclization products.[9]

As mentioned previously, the majority of the derivatives suffered from poor microsomal stability and thus was anticipated to exhibit little/modest exposure in our in vivo models upon oral dosing. Metabolic identification studies on compound **18** clearly indicated that the cycloheptyl ring (and not the disubstituted aryl ether) was highly subject to oxidative metabolism in human and mouse liver microsomes. As a result, we sought to simultaneously maintain/enhance in vitro potency while modulating metabolism at this position by either blocking the sites of metabolism or incorporating polar substitutents, making the compounds poorer substrates for the metabolizing enzymes. Susceptibility to oxidative metabolism was measured via incubation of compound in liver microsomes and the percent compound remaining was determined. Listed in Table 2 is a limited but representative set of compounds generated in this assessment.

As compared to lead **18**, increasing lipophilicity, especially with quaternary substitution at the carbon directly attached to the TZP core, had a positive impact on in vitro potency (compare compound **18** vs **21**–**24**). Though both **21** and **25** contain relatively large lipophilic groups, the sub-optimal methylene spacer present in **25** likely contributed to the >40-fold reduction in the IC_{50} versus **21**. The highly lipophilic nature of these groups likely contributes to the generally poor metabolic stability of these compounds. Though quite stable metabolically, presumably due to blocking of metabolism by the fluorine groups, compound **26** exhibited poor activity as a result of minimal hydrophobic space-filling in the enzyme binding pocket. Introduction of polar functionalities (i.e., examples **27**–**31**) had a dramatic effect on enhancing metabolic stability towards human and mouse microsomes but the modifications were poorly tolerated by 11β-HSD-1. Not surprisingly, incorporation of a protonatable amine group (examples **32** and **33**) resulted in poor enzyme activity but excellent metabolic stability. A nearly direct comparison of **21** versus the related amino-substituted derivative **32** illustrates the magnitude of the effect. With these observations in mind, we turned our attention to incorporation of substituted bi- and polycyclic groups at R. Hydroxy-substituted cycloheptyl **34** and adamantyl **35** analogs showed marginally better metabolic stability (human) but at the expense of in vitro potency. In contrast, introduction of the 2,2,2-bicyclooctane moiety proved to be a superior scaffold for compound optimization. While the methoxy-substituted analog **36** was sub-optimal with respect to potency (and incidentally subject to bioconversion to **38** via oxidation of the methoxy group), the corresponding fluoro-derivative **37** afforded superior potency. Finally, introduction of hydroxyl at the bridgehead position (**38**) proved to be an ideal combination of potency and in vitro metabolic stability in this set of compounds.

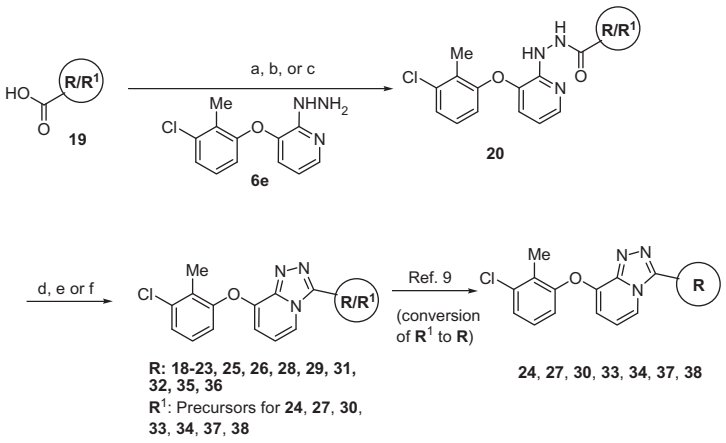
Table 2
Structure–activity relationship regarding variation of the R substituent of the 1,2,4-trizolopyridine ring



Compd	R	IC_{50}[a] (nM)		% Remaining[b]	
		Hu	Mu	Hu	Mu
18		23	4105	64	53
21		3.7	167	69	57
22		5.5	327	<1	<1
23		5.6	1214	19	13
24		8.2	4313	25	21
25		163	>10,000	53	13
26		939	>10,000	100	87
27		367	>10,000	99	97
28		7804	NT[c]	NT	NT
29		544	>10,000	100	100
30		14,030	>10,000	95	99
31		48,240	>10,000	87	90
32		16,060	NT	100	96
33		1298	21,130	NT	NT
34		197	>10,000	81	43
35		64	NT	69	53
36		72	6851	87	70
37		8.5	4155	76	62
38		12	1026	100	96

[a] IC_{50}'s refer to biochemical human (Hu) or mouse (Mu) 11β-HSD-1 assay data.
[b] Represents % compound remaining in human or mouse liver microsomes after a 10 min incubation.
[c] Not tested.

Compound **38** also proved to be superior for other aspects of profiling as well. Pregnane-X receptor (PXR) transactivation has been observed for many compounds in this chemotype, as well as for compounds from other laboratories targeting this enzyme.[10]



Scheme 2. Reagents and conditions: (a) *N*-methyl morpholine, *i*-BuOCOCl, 0 °C; (b) $(COCl)_2$; (c) HOBT, EDAC, rt, 31–99%; (d) PPh_3Cl_2, *i*-Pr_2NEt, CH_2Cl_2, rt; (e) HOAc, EtOH, reflux; (f) HOAc, trifluorotoluene, μW, 180 °C, 71–95%.

Indeed, this liability seemed to be evident with most, if not all, of the chemotypes explored in our chemical program. Since activation of PXR in vivo is a liability risk for CYP450 induction and increased potential for drug–drug interactions, removing this off-target activity was a constant focus of the program. Compounds containing non-polar highly lipophilic 'R' groups such as **18**, **21**–**25**, and **37** exhibited partial to full activation of PXR with EC_{50}'s in the 0.15–3 μM range. In contrast, compound **38** exhibited weak activation of this receptor (EC_{50} >50 μM), suggesting that critical placement of the polar hydroxyl group significantly attenuated activity against PXR. Beneficially, compound **38** also exhibited marginal but enhanced solubility (~11 μg/mL, pH 7.4) as compared to lipophilic analogs such as **21** and **37** (~1 μg/mL, pH 7.4). Other in vitro development properties (CYP inhibition, ion channel activity, cytotoxicity, etc.) were also favorable for **38**.

Though favorable in many aspects, two significant properties proved difficult to address in this series. First, many of the compounds exhibited marginal selectivity against the human 11β-HSD-2 enzyme. Selectivity is a critical component in order to minimize the potential for deleterious side-effects associated with 11β-HSD-2 inhibition (e.g., hypertension and hypokalemia). While compound **38** exhibited ~200-fold selectivity for h-11β-HSD-1 versus h-11β-HSD-2 (IC_{50} = 2.52 μM), other compounds such as **22** and **37** were less so (~70-fold). This represented an area for further improvement. Additionally, and as a class, the TZP series exhibited routinely poor mouse in vitro activity. As seen in Table 2, none of the compounds exhibited robust potency for the mouse enzyme, precluding our ability to assess pharmacological inhibition in murine in vivo models.

In conclusion, replacement of an amide/sulfonamide pharmacophore in an early lead series with a triazolopyridine group afforded a novel platform for further SAR exploration. Variation of both the left and right-hand portions of the lead **5** resulted in a series of highly potent inhibitors of human 11β-HSD-1. In an attempt to overcome some of the historical liabilities (poor metabolic stability, PXR transactivation, etc.) associated with the drug optimization for this target, compound **38** was identified as a highly advanced lead. Future disclosures in this chemotype will focus on the further optimization of **38** with the goal to identify a candidate suitable for in vivo evaluation.

References and notes

1. Morton, N. M. *Mol. Cell. Endocrinol.* **2010**, *316*, 154.
2. (a) Walker, B. R.; Andrew, R. *Ann. N.Y. Acad. Sci.* **2006**, *1083*, 165; (b) Oppermann, U. *Endo. Metabol. Immun. Disord.-Drug Targets* **2006**, *6*, 259.
3. For recent reviews on the design of inhibitors for this target, see: (a) Fotsch, C.; Wang, M. *J. Med. Chem.* **2008**, *51*, 4851; (b) Morgan, S. A.; Tomlinson, J. W. *Exp. Opin. Invest. Drugs* **2010**, *19*, 1067.
4. Several companies have advanced compounds into clinical trials: (a) for AMG-221 see: (a) Veniant, M. M.; Hale, C.; Hungate, R. W.; Gahm, K.; Emery, M. G.; Jona, J.; Joseph, S.; Adams, J.; Hague, A.; Moniz, G.; Zhang, J.; Bartberger, M. D.; Li, V.; Syed, R.; Jordan, S.; Komorowski, R.; Chen, M. M.; Cupples, R.; Kim, K. W.; St. Jean, D. J., Jr.; Johannsson, L.; Henriksson, M. A.; Williams, M.; Vallgarda, J.; Fotsch, C.; Wang, M. *J. Med. Chem.* **2010**, *53*, 4481; for PF-915275 see: (b) Siu, M.; Johnson, T. O.; Wang, Y.; Nair, S. K.; Taylor, W. D.; Cripps, S. J.; Matthews, J. J.; Edwards, M. P.; Pauly, T. A.; Ermolieff, J.; Castro, A.; Hosea, N. A.; LaPaglia, A.; Fanjul, A. N.; Vogel, J. E. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3493; for INCB13739 see: (c) Rosenstock, J.; Banarer, S.; Fonseca, V. A.; Inzucchi, S. E.; Sun, W.; Yao, W.; Hollis, G.; Flores, R.; Levy, R.; Williams, W.; Seckl, J. R.; Huber, R. *Diabetes Care* **2010**, *33*, 1516; for MK-0916 and MK-0736 see, (d) Shah, S.; Hermanowski-Vosatka, A.; Gibson, K.; Ruck, R. A.; Jia, G.; Zhang, J.; Hwang, P. M. T.; Ryan, N. W.; Langdon, R. B.; Feig, P. U. *J. Am. Soc. Hypertens.* **2011**, *5*, 166.
5. Wang, H.; Ruan, Z.; Li, J. L.; Simpkins, L. M.; Smirk, R. A.; Wu, S. C.; Hutchins, R. D.; Nirschl, D. S.; Van Kirk, K.; Cooper, C. B.; Sutton, J. C.; Ma, Z.; Golla, R.; Seethala, R.; Salyan, M. E. K.; Nayeem, A.; Krystek, S. R., Jr.; Sheriff, S.; Camac, D. M.; Morin, P. E.; Carpenter, B.; Robl, J. A.; Zahler, R.; Gordon, D. A.; Hamann, L. G. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3168.
6. Wang, H.; Li, J. L.; Simpkins, L. M.; Sutton, J. C.; Wu, S. C.; Smirk, R. A.; Yoon, D.; Ruan, Z.; Cooper, C. B.; Van Kirk, K.; Hutchins, R. D.; Li, C.; Ma, P.; Seethala, R.; Golla, R.; Nayeem, A.; Krystek, Jr., S. R.; Gordon, D. A.; Robl, J. A.; Hamann, L. G. *Abstract of Papers*, 233rd National Meeting of the American Chemical Society: Chicago, IL, March 2007; MEDI 377.
7. Li, J. J; Hamann, L. G.; Wang, H.: Ruan, Z.; Cooper, C. B.; Li, J.; Robl, J. A. WO2006/135995 A1, Dec 21, 2006.
8. 11β-HSD1 microsomes isolated from HEK 293 cells over-expressing human 11β-HSD1 were incubated with the substrate cortisone and cofactor NADPH at room temperature. The reactions were terminated with the addition of a nonspecific 11β-HSD1 inhibitor (18β-glycyrrhetinic acid). The product, cortisol was quantified in an immuno-competition SPA wherein the [^{3}H]-cortisol bound to anti-rabbit antibody yttrium silicate SPA beads coated with polyclonal anti-cortisol antibody was competed by cortisol produced in the reaction and the reaction mixture was read in a scintillation plate reader (TopCount). The IC_{50} was then determined by amount of cortisol formed from a cortisol standard curve.
9. Compound **24** was prepared by reduction of the corresponding ketone: $NaBH_4$, 78%; **27** was made from ketone **28**: MeMgBr, 62%; **30** was also obtained from ketone **28**: (1) $NH_2OH.HCl$, NaOAc, (2) $PhSO_2Cl$, NaOH, 31% for two steps; **33** was obtained from compound **36**: (1) HBr, Ac_2O, 3%, (2) NH_3/MeOH, μW, 5%; **34** was obtained from the corresponding TBDMS protected alcohol: TBAF, 92%; **37** was synthesized from compound **38**: DAST, 53%; **38** was obtained from compound **36**: HBr, Ac_2O, 79%.
10. Recent examples of chemotypes with PXR activities include: (a) Zhu, Y.; Olson, S. H.; Hermanowski-Vosatka, A.; Mundt, S.; Shah, K.; Springer, M.; Thieringer, R.; Wright, S.; Xiao, J.; Zokian, H.; Balkovec, J. M. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3412; (b) Fotsch, C.; Bartberger, M. D.; Bercot, E. A.; Chen, M.; Cupples, R.; Emery, M.; Fretland, J.; Guram, A.; Hale, C.; Han, N.; Hickman, D.; Hungate, R. W.; Hayashi, M.; Komorowski, R.; Liu, Q.; Matsumoto, G.; St Jean, D. J., Jr.; Ursu, S.; Veniant, M.; Xu, G.; Ye, Q.; Yuan, C.; Zhang, J.; Zhang, X.; Tu, H.; Wang, M. *J. Med. Chem.* **2008**, *51*, 7953; (c) Rew, Y.; McMinn, D. L.; Wang, Z.; He, X.; Hungate, R. W.; Jaen, J. C.; Sudom, A.; Sun, D.; Tu, H.; Ursu, S.; Villemure, E.; Walker, N. P. C.; Yan, X.; Ye, Q.; Powers, J. P. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1797.