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Optimization of 1,2,4-Triazolopyridines as Inhibitors of Human 11β-Hydroxysteroid Dehydrogenase Type 1 (11β-HSD-1)

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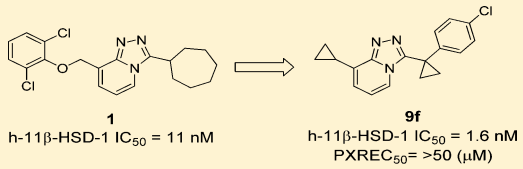
Supporting Information

ABSTRACT: Small alkyl groups and spirocyclic-aromatic rings directly attached to the left side and right side of the 1,2,4-triazolopyridines (TZP), respectively, were found to be potent and selective inhibitors of human 11β-hydroxysteroid dehydrogenase-type 1 (11β-HSD-1) enzyme. 3-(1-(4-Chlorophenyl)cyclopropyl)-8-cyclopropyl-[1,2,4]triazolo[4,3-*a*]pyridine (**9f**) was identified as a potent inhibitor of the 11β-HSD-1 enzyme with reduced Pregnane-X receptor (PXR) transactivation activity. The binding orientation of this TZP series was revealed by X-ray crystallography structure studies.



KEYWORDS: *Enzyme inhibitors, human 11β-hydroxysteroid dehydrogenase-type 1, triazolopyridines*

Glucocorticoids such as cortisol are stress hormones that play an important role in regulating carbohydrate, protein, and lipid metabolism, as well as modulating inflammatory and immune responses. Glucocorticoids are present in two forms in humans: the active cortisol (corticosterone in rodents) and the inactive cortisone (11-dehydrocorticosterone in rodents). Excess cortisol expression in humans, as typified in patients with Cushing's syndrome, can cause a variety of abnormalities including obesity, insulin resistance, hyperglycemia, dyslipidemia, and hypertension. These symptoms are also typically found in patients with metabolic syndrome or related diabetes/obesity diseases.[1−3] A good correlation of salivary cortisol levels with components of the metabolic syndrome have been reported.[4] Largely expressed in liver and adipose tissue, 11β-HSD-1 is an enzyme that catalyzes the conversion of inactive cortisone to the active glucocorticoid hormone cortisol.[5] Transgenic mice that overexpress 11β-HSD-1 in the adipose develop many of the features of metabolic syndrome, including glucose intolerance, insulin resistance, dyslipidemia, hypertension, and obesity.[6,7] In contrast, whole-body genetic knockout of 11β-HSD-1 expression in mice placed on a high fat diet has been shown to improve glucose tolerance and reduce triglyceride level relative to wild-type controls on a similar diet.[8] These preclinical results suggest that inhibition of 11β-HSD-1 activity in humans may provide a beneficial impact for the treatment of metabolic syndrome. As a result, significant attention has been given to modulation of this enzyme from both academia and industry,[9−11] and numerous selective inhibitors have been reported as a potential treatment for diabetes, metabolic syndrome, and related disorders.[12−21]

Our laboratory has recently reported novel inhibitors of 11β-HSD-1 based on a 1,2,4-triazolopyridine (TZP) framework, represented by compound **1** (Figure 1), which showed reasonable good potency but with liabilities, such as PXR activity (EC_{50} = 1.2 μM). Structure−activity relationship (SAR) optimization of substituents at the C-3 and C-8 positions of the TZP core resulted in the identification of compound **2a** as a reasonable potent and metabolically stable inhibitor of the

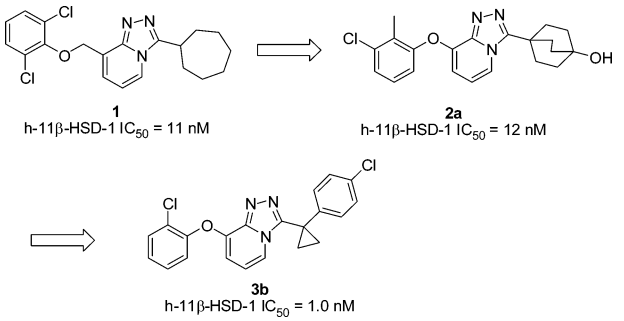


Figure 1. Generation of lead 1,2,4-trizolopyridine (TZP) 11β-HSD-1 inhibitor **3b** based on previous leads **1** and **2a**.

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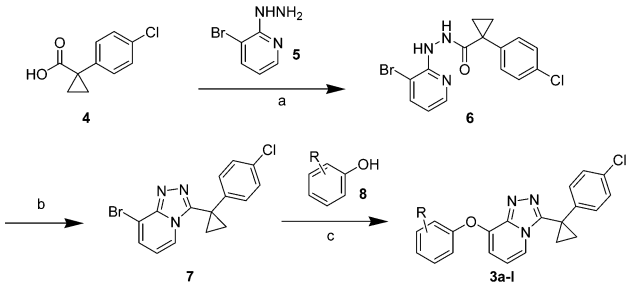
enzyme without Pregnane-X receptor (PXR) activity.[22] While certain aliphatic bicyclic rings (such as the bicyclo[2.2.2]octan-1-ol in compound **2a**) served well to address potency and metabolic stability issues for this chemotype, the rigidity and limited synthetic accessibility of these bridged structures made further modification to this moiety very challenging. Looking to incorporate simpler replacements for the bicyclic ring system, we turned our attention to incorporation of a 3-(1-phenyl)-cyclopropyl functionality, which was previously identified as a potent binding pharmacophore in a related series of substituted triazoles.[15,23] Indeed, replacement of the bicyclo[2.2.2]octan-1-ol moiety in **2a** with 4-chlorophenyl-cyclopropyl group resulted in **3b**, a compound that possessed excellent inhibitory activity toward human 11β-HSD-1 (IC_{50} = 1.0 nM) while retaining good metabolic stability. Unfortunately the modification also resulted in a significantly increased liability for PXR transactivation, an off-target liability that was also observed in a series of related triazoles from Merck.[15,16] As such we initiated a systematic SAR study to determine if a robust separation of PXR transactivation from dehydrogenase activity was possible in this series.

Our initial SAR approach focused on modification of the left-hand portion of the molecule. A convenient synthesis of these derivatives is given in Scheme 1. The commercially available 1-

Scheme 1[a]

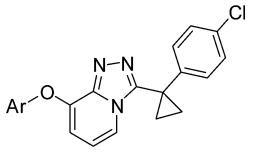


[a]Reagents and conditions: (a) *N*-methylmorpholine, *i*-BuOCOCl, 0 °C, (90%); (b) PPh_3Cl_2, *N,N*-diisopropylethylamine, CH_2Cl_2, rt, (75%); (c) Cs_2CO_3, DMF or neat, 120 °C.

(4-chlorophenyl) cyclopropane-1-carboxylic acid (**4**) was coupled with hydrazine **5** to afford acyl hydrazide **6** in good yield (90%). Mild cyclodehydration of **6** using PPh_3Cl_2 produced bromo-triazolopyridine **7** in 75% yield. Coupling of **7** with various phenols **8** under modified literature conditions (i.e., Cs_2CO_3 under concentrated or neat reaction conditions) typically resulted in acceptable yields (>50%) of final products. Analogues **3a**–**l** were synthesized via this route as well as analogues **9a**–**d** with lower yield (5–20%).

As outlined in Table 1, the presence of the *ortho*-Cl substituent **3b** only marginally enhanced potency as compared to the unsubstituted phenyl analogue **3a**. A chlorine was employed to study the positional effect of phenyl substitution. Compared with ortho-substituted phenyl analogue **3b**, chlorine at the meta- and para-positions of the phenyl ring (**3c** and **3d**, respectively) resulted in a significant loss of potency. This finding suggested that the ortho-position may be a favorable site to explore additional substituent effects on the phenyl ring. For this purpose, several functional groups with varied steric and electronic properties were introduced. Groups such as fluoro (**3e**), an electron-donating *N*-morpholinyl (**3f**), and the large hydrophobic trifluoromethoxy (**3g**, ClogP, 6.07) afforded

Table 1. SAR of 3-[1-(4-Chlorophenyl)cyclopropyl]-8-aryloxy-TZP Analogues 3a–3l[a]



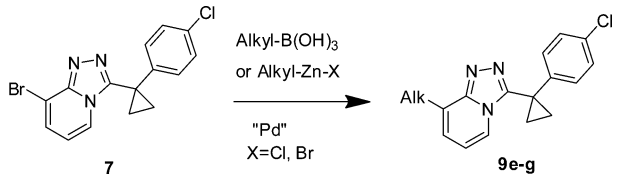
compd	aryl	IC_{50}[a] (nM)	PXR EC_{50} (μM)/Y_{max} (%)
3a	Ph	1.7	1.8/71
3b	2-Cl-Ph	1.0	0.97/100
3c	3-Cl-Ph	22	0.8/95
3d	4-Cl-Ph	21	1.2/85
3e	2-F-Ph	0.7	1.1/86
3f	2-(*N*-morpholinyl)-Ph	0.9	0.4/123
3g	2-CF_3O-Ph	0.5	0.3/123
3h	2-hydroxyl-Ph	1.4	2.6/50
3i	2-methylsulfonyl-Ph	8.1	0.7/105
3j	2-Ph-Ph	2.7	0.5/95
3k	2-naphthyl	20	0.8/75
3l	2-Me-pyridin-3-yl	5.5	2.8/63

[a]IC_{50} values refer to biochemical human 11β-HSD-1 assay data; average of at least two replicates.

similar human 11β-HSD-1 inhibition potencies. The more polar hydroxyl group (**3h**) was also well tolerated, but the methylsulfonyl group (**3i**) exhibited attenuated in vitro activity. A phenyl (**3j**) at the ortho-position exhibited good potency, but fused 2-naphthalene analogue (**3k**) was much less active. While the majority of these analogues showed high human 11β-HSD-1 inhibitory activity, all possessed significant PXR activity (EC_{50} < 3 μM). The more lipophilic analogues (e.g., **3g** and **3f**) were among the most potent tranasactivators in this series. Incorporation of polar groups (e.g., **3h** and **3l**) only had a modest effect on attenuating PXR transactivation.

We next directed our attention to the incorporation of smaller aliphatic rings at the C-8 position of the TZP core. Introduction of cycloalkyl substituents was achieved via reaction of bromo-TZP intermediate **7** with various alkyl boronic acids or alkyl zinc halides under Pd-catalysis (Scheme 2). This method was used to generate compounds **9e**–**g** in 40–75% yields. Compound **9h** was made directly from 2-hydrazinyl-3-methylpyridine as shown in Scheme 1.

Scheme 2. Synthesis of Alkyl-TZP Analogues[a]



[a]Reagents and conditions: alkyl-$B(OH)_2$ or alkyl-Zn-Br, 1,1′-bis-(diphenylphosphino)ferrocene palladium(II)dichloride dichloromethane complex, K_3PO_4 or K_2CO_3, 85 °C, DMF.

Among the first analogues examined (Table 2) was the cyclohexyloxy derivative **9a**, which was the aliphatic counterpart of compound **3a**. However, compound **9a** showed much weaker 11β-HSD-1 inhibition while retaining similar PXR activity. Attenuated potency was also observed for the cyclopropylmethoxy analogue **9c**. Although the 4-tetrahydropyranyloxy substituent **9b** (ClogP, 3.49) exhibited reduced 11β-

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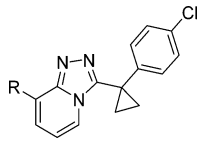
Table 2. SAR of 3-[1-(4-Chlorophenyl)cyclopropyl]-TZP 9a–h with (Cyclo)alkyloxy and Cycloalkyloxy or Alkyl Groups at C-8[a]



compd	R	IC_{50}[a] (nM)	PXR EC_{50} (μM)/Y_{max} (%)
9a	cyclohexyloxy	42	0.6/103
9b	4-tetrahydropyranyloxy	65	10/52
9c	c-$PrCH_2O$	51	not tested
9d	cyclobutoxy	4.2	1.5/60
9e	cyclobutyl	2.4	0.9/24
9f	cyclopropyl	1.6	50/14
9g	isopropyl	0.61	1.0/34
9h	methyl	17	8.8/22

[a]IC_{50} values refer to biochemical human 11β-HSD-1 assay data; average of at least two replicates.

HSD-1 inhibitory potency, the dramatically reduced PXR activation profile (EC_{50} = 10 μM, Y_{max} = 52%) again suggested that reducing lipophilicity at this position of the molecule was desired. A significant advance was observed by removing "O" linker affording compounds **9e–9h**, which exhibited good to excellent 11β-HSD-1 potency while attenuating the full agonist profile (Y_{max} < 35%) for PXR. The "sweet-spot" in this SAR study is observed with compound **9f**, which exhibits a superior combination of high enzyme inhibitory activity and low PXR transactivation (EC_{50} > 50 μM).

Certain structure–activity and structure–liability relationships observed in this new TZP series (as exemplified by compounds **9b** and **9f**) appeared highly reminiscent with that observed in the lead TZP chemotype (as exemplified by compound **2a**). The original assumption that the 1-(4-chlorophenyl)cyclopropyl group in **3b** was a surrogate for the [2,2,2]-bicyclooctanol group in **2a** may now be better explained by an ~180° rotation of the TZP core so that the 1-(4-chlorophenyl)cyclopropyl group in **3b** (now spatially represented by **3b′**) is actually substituting for the 3-chloro-2-methylphenoxy group in **2** instead (see Figure 2).

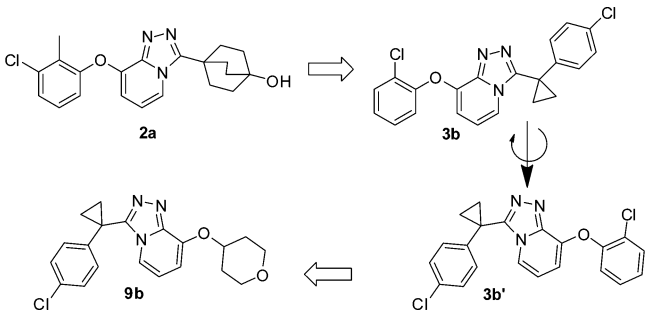


Figure 2. Reversal of core binding orientations for "original" TZP series **2a** versus "alternate" TZP series **9b**.

In order to visualize binding modes for compounds in the two TZP subseries, compounds **2a** and **3b** were docked into a crystal structure of 11β-HSD-1 complexed with NADPH and a ligand, 3-[1-(4-fluorophenyl)cyclopropyl]-4-(1-methylethyl)-5-[4-(trifluoromethoxy)phenyl]-4*H*-1,2,4-triazole (structure shown in Supporting Information), which contains a 1,2,4 triazole core and is the most closely resembled TZP core of interest (PDB code 3D5Q).[24,25] While complete flexibility of the ligands was assumed in the calculation, the receptor was treated rigidly during docking, and the docking site was assumed to be the pocket occupied by the ligand in the 11β-HSD-1 complex. As a post processing step, local energy minimization in the gas phase using the OPLS 2005 force field was carried out in order to relax the overall structure; this also allowed for partial flexibility of the receptor atoms surrounding the docked ligand. The favored poses from the docking calculations are shown in Figure 3 along with the residues in

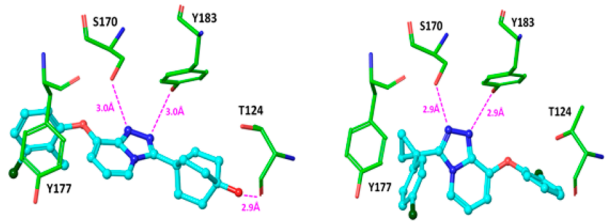


Figure 3. Preferred binding poses of compounds **2a** and **3b** using protein coordinates from 3D5Q, which has a 1,2,4-triazole ligand bound at the active site. The protein carbon atoms are shown in green and those of compound **2a** and **3b** in cyan; nitrogen atoms are shown in blue, oxygen atoms in red, and chlorine atoms in dark green. The interatomic distances (in Angstroms) between polar ligand atoms and protein residues that are indicative of hydrogen bonds are shown in magenta.

the binding pocket that contribute most significantly to the binding energy. The most striking observation is that the two compounds **2a** and **3b** bind to 11β-HSD-1 in opposite orientations, as inferred from our SAR studies. As with the triazole structure 3D5Q, both TZPs bind in an orientation in which the triazole ring is oriented toward the side chains of Ser170 and Tyr183 suggesting probable hydrogen bonds. The overall docking pose shows that the phenoxy substituent at the 8 position in the TZP scaffold lies on opposite sides of the binding pocket in compounds **2a** and **3b**. As seen in Figure 3A, the preferred tendency of **2a** to bind in an orientation opposite to **3b** may be caused by the tendency of the hydroxyl group on the bicyclo[2.2.2]octyl ring in the former to form a hydrogen bond with the backbone carbonyl oxygen on Thr124. The interaction energy of this hydrogen bond is estimated at about 1.5 kcal/mol from the docking result, favoring this pose over the 180-degree flipped pose (as for compound **3b**).

The opposite binding orientations based on docking suggests that while analogues of compound **2a** (lead TZP series) will bind in the orientation shown for **2a**, analogues of compound **3b** (alternate TZP series), which besides the two hydrogen bond interactions shown in Figure 3B does not show any other polar interactions between ligand and protein, may often bind in an orientation similar to **2a** rather than **3b** depending on the nature of the substitutions in the two terminal phenyl rings. This is consistent with the observation that the SAR for C-3 and C-8 substitutions on the TZP core do not parallel for the lead and alternate series.

The observed SAR findings and docking calculation predictions prompted us to further examine the binding mode of these compounds to 11β-HSD-1 using X-ray crystallography to confirm the binding orientation. Although X-ray crystal structures are not available for a human 11β-HSD-

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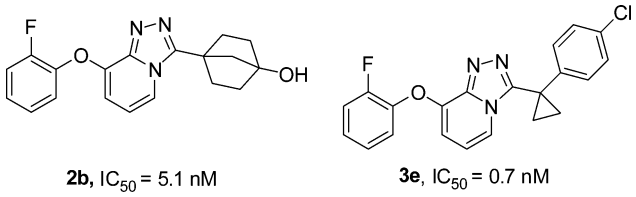
1 complex with either compound **2a** or **3b**, the complex structures of closely related analogues **2b** and **3e** (Figure 4)



2b, IC_{50} = 5.1 nM **3e**, IC_{50} = 0.7 nM

Figure 4. Structures and human 11β-HSD-1 activities of compounds **2b** and **3e**.

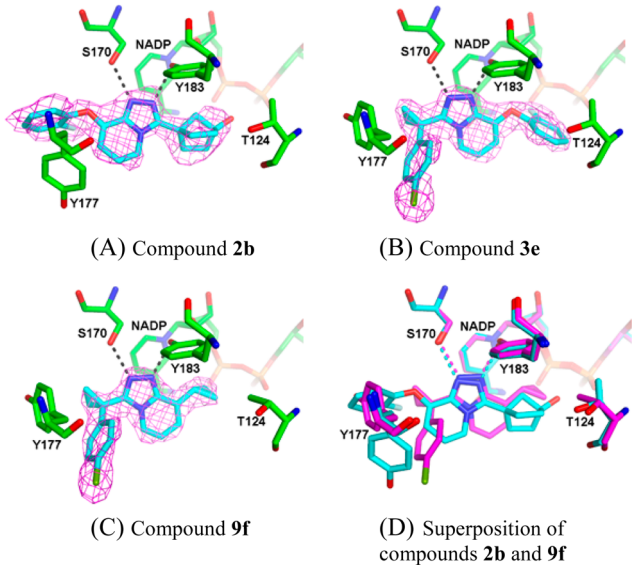


Figure 5. Binding of compounds to human 11β-HSD-1 as obtained through X-ray crystallographic analysis. Figures 5A (**2b**), B (**3e**), and C (**9f**) show the final coordinates with the initial (prior to placement) $2F_o - F_c$ electron density (magenta; contoured at 1 rmsd) and several surrounding residues. Carbon atoms of compounds are shown in green and those of 11β-HSD-1 in cyan. Nitrogen atoms are shown in blue, oxygen atoms in red, fluorine atoms in teal, and chlorine atoms in pea green. Hydrogen bonds are shown as a series of ellipsoids (black). In particular, note that the two exposed nitrogen atoms of the triazolyl moiety form hydrogen bonds to Ser 170 OH and Tyr 183 OH. Figure 5D depicts the superposition of compounds **2b** (cyan) and **9f** (magenta) and surrounding residues showing that the orientation of the core triazolopyridine flips ~180° about the vertical axis while maintaining the hydrogen bonds to Ser 170 OH and Tyr 183 OH. Note also that the *o*-fluorophenyl moiety of compound **2b** forces Tyr 177 side chain to flip out of the way.

were obtained at 2.35 Å resolution (Figure 5).[26,27] The X-ray crystal structures confirmed our hypothesis: the orientation of the core TZP rings are indeed rotated ~180° about the vertical axis for the two compounds as shown in Figure 2 while maintaining productive hydrogen bonding interactions to the Ser 170 and Tyr 183 hydroxyl groups (compare Figure 5A,B). Furthermore, compound **9f** was also shown to exhibit the same orientation as that of **3e** (Figure 5C). It is worthy to point out that the phenylcyclopropyl group in the 3D5Q ligand is oriented toward T124, whereas in **3e** and **9f** it is oriented in the opposite direction, toward Y177, as determined by the preferred binding orientation. For direct comparison, the superposition of compounds **2b** and **9f** and surrounding residues are shown in Figure 5D. These findings are consistent with previously reported ~180° flips of inhibitors of 11β-HSD-1 derived from different chemical series by others,[28] and further revealed the flexibility of 11β-HSD-1 inhibitor of binding mode.

As compound **9f** seemed to afford a superior combination of potency, low PXR activity, and reasonable solubility (76 μg/mL, pH 7.4), it was selected for more extensive in vitro and in vivo evaluation. As observed with other analogues in this series, compound **9f** was essentially inactive versus 11β-HSD-2 (IC_{50} > 10 μM), an unwanted activity. With the exception of CYP2C19 (IC_{50} ≈ 2 μM), compound **9f** was not a significant inhibitor of other human CYP450 enzymes such as 1A2, 2C8, 2C9, 2D6, or 3A4 (IC_{50} > 20 μM). Ion channel activities including hERG were acceptable (hERG flux IC_{50} > 60 μM). Excellent in vitro metabolic stability in isolated microsomes was observed across all species tested (human, mouse, cyno, and rat: ~100% remaining after 30 min of incubation). When orally dosed to male Balb/C mice at 3.5 mpk (0.5% methocel/0.1% Tween-80 in water as the vehicle), oral absorption was rapid with a short t_{max} (1 h). The maximum plasma concentration c_{max} was 2.5 μM, and plasma exposure was acceptable with the AUC (0−8 h) reaching 5.6 μM·h. The compound was found to distribute extensively in adipose tissue as well, affording an adipose/plasma ratio of ~5 when measured 8 h postdosing.

Although compound **9f** demonstrated excellent human 11β-HSD-1 inhibition (IC_{50} = 1.6 nM), its activity was dramatically weaker for the murine enzyme (IC_{50} = 241 nM). A significant difference in potency with respect to species was also observed comparing activities in human (HEK IC_{50} = 13 nM) and mouse (3T3L1 IC_{50} = 293 nM) derived cellular assays. Indeed, attenuated activity for mouse and rat (versus human or cyno) 11β-HSD-1 was typically consistent across the chemotype and complicated in vivo testing of analogues with this series. As such, it was not surprising that compound **9f** failed to elicit a response in a standard DHC challenge assay in mice at doses up to 30 mpk.

In summary, a series of novel, potent, and selective inhibitors of human 11β-HSD-1 enzyme were revealed through structure−activity relationship studies of a 1,2,4-triazolopyridine (TZP) core, and representative lead compounds such as **9f** were identified. A disconnect in the SAR between analogues in this series (represented by compounds like **3e** and **9f**) and the lead TZP analogue **2a** suggested a "flipped" binding orientation within the catalytic site of 11β-HSD-1, which was confirmed by docking calculations and X-ray structure studies. This finding suggests that the TZP core might provide an ideal, flexible platform for future compound optimization. While these compounds proved to be challenging to evaluate due to their weak rodent activities, they served as excellent starting points for further modifications of this chemotype resulting from discovery of our clinical candidate, which will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Protocols or methods of in vitro and in vivo assays, analytical and spectroscopic data for compounds **3**−**9h**, and X-ray crystallographic data of compound **2b**, **3e**, and **9f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

ABBREVIATIONS USED

11β-HSD-1, 11β-hydroxysteroid dehydrogenase type 1; TZP, triazolopyridines; PXR, Pregnane-X receptor

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