Discovery of SHR1653, a Highly Potent and Selective OTR Antagonist with Improved Blood–Brain Barrier Penetration

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Supporting Information

ABSTRACT: The oxytocin receptor (OTR) plays a major role in the control of male sexual responses. Antagonists of the OTR have been reported to inhibit ejaculation in animal models and serve as a potential treatment for premature ejaculation (PE). Herein, we describe a novel scaffold featuring an aryl substituted 3-azabicyclo [3.1.0] hexane structure. The lead compound, SHR1653, was shown to be a highly potent OTR antagonist, which exhibited excellent selectivity over V_{1A}R, V_{1B}R, and V₂R. This novel molecule was shown to have a favorable pharmacokinetic profile across species, as well as robust *in vivo* efficacy in a rat uterine contraction model. Interestingly, SHR1653 exhibited excellent blood–brain barrier penetration, which might be beneficial for the treatment of CNS-related PE.

SHR1653

hOTR IC₅₀: 15 nM
hV_{1A}R/hV_{1B}R/hV₂R IC₅₀: 2885/37562/32604 nM
Cl(mL/min/kg): 16.1 (rat), 7.2 (dog)
Efficacious dose @ 30 mpk in uterine contraction model
K_{pu,u}: 0.188

KEYWORDS: Oxytocin receptor, antagonist, premature ejaculation, BBB penetration, SHR1653

The oxytocin receptor (OTR) is a member of the seven-transmembrane G-protein coupled receptors. The OTR has no subtypes but is structurally similar to three vasopressin receptors (V_{1A}, V_{1B}, and V₂).^{1,2} OTR antagonists have been reported to have therapeutic potential in a number of areas, including preterm labor,^{3,4} IVF-ET,^{5,6} and sexual dysfunction.⁷

Ejaculatory dysfunction, especially premature ejaculation (PE), is the most common type of male sexual disorder. Despite the high prevalence and detrimental impact on the quality of life for patients and their partners, there is neither a universally accepted definition nor a medication approved by the Food and Drug Administration (FDA).⁸ The involvement of oxytocin in sexual function and behavior has been thoroughly investigated in various animal models.⁹ The systemic administration of oxytocin reduces the latency time to ejaculation and also increases the number of sperm per ejaculate in rabbits.⁹ Both preclinical and clinical data indicate that oxytocin may play a unifying role in establishing ejaculatory latency through central and peripheral mechanisms.¹⁰ Further evidence has suggested that blockade of the brain OTR is an effective way to treat PE.^{11,12}

There has been considerable interest in developing an orally potent OTR antagonist with high selectivity.^{13–16} To date, two compounds have been advanced to human clinical trials for the treatment of PE, as shown in Figure 1. The proof of concept has been shown by IX-01,¹² while GSK-557296 failed in phase II trials likely due to the limited brain exposure.¹¹

GSK-557296

PSA: 91.8
hOTR IC₅₀: 9.2 nM

IX-01

PSA: 74.5
hOTR IC₅₀: 23.2 nM

Figure 1. Clinical compounds as OTR antagonists.

Based on the reported information, our program focused on the development of compounds with favorable brain exposure. Herein, a novel scaffold featuring an aryl substituted 3-azabicyclo [3.1.0] hexane structure was established. The lead compound, SHR1653, is a highly potent and selective OTR antagonist with improved BBB penetration compared to IX-01.

To obtain a favorable pharmacokinetic (PK) profile, the initial plan was to replace the flexible oxyazetidene ether of IX-01 and to maintain a low PSA value. One of the approaches was to decrease the number of rotatable bonds and introduce rigid ring systems. Thus, different linkages between the phenyl and triazole groups were synthesized (Table 1 [compounds 1–

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Table 1. SAR of LHS Chain of Aryl Group

R	Cmpd	PSA	hOTR IC ₅₀ (nM) ^a
1	74.5	6759
2	74.5	401
3	68.5	1379
4	68.5	1227
5	74.5	850
6	74.5	121
7	65.3	2794
8	68.5	910
9	65.3	10
10	65.3	27
11	65.3	23
12	65.3	624
13	65.3	15
14	74.5	2561

^aAll data are the mean values of at least three independent measurements.

6]). The spiro-benzofuran [compound 1] was prepared to yield a much lower potency, while the spiro-benzopyran [compound 2] had a 10-fold higher potency. Then 3,6-diazabicyclo [3.2.0] heptane ring systems [compounds 3 and 4] were investigated to obtain moderate OTR activity. Fused

rings with an ether linker showed improved potency, especially for tropinol [compound 6] (the IC₅₀ was 121 nM). The longer ether linker did not favor potency [compound 5 vs 6]. The strategy to remove one heteroatom to reduce the PSA value was subsequently attempted. Accordingly, the N-linked triazole group was replaced by C-linked triazole to give piperidine [compound 7] with decreased potency (the IC₅₀ was approximately 3000 nM). Introducing one nitrogen atom next to triazole enabled piperazine [compound 8] to provide a 3-fold increment of potency compared with piperidine [compound 7]. Next, the methylene group was removed to reduce the rotatable bond and yield piperidine [compound 9] and pyrrolidine [compound 10], which exhibited very high OTR potency. Unfortunately, subsequent experiments showed that a single ring series [compounds 9 and 10] had less selectivity for vasopressin and unsatisfactory PK profiles in rats. Piperidine [compound 9] had high clearance and [compound 10] yielded low exposure and a short *t*_{1/2} (Table 2). To

Table 2. Selectivity and PK Data for Compounds 9 and 10

Cmpd	9	10
hV _{1A} R IC ₅₀ (nM) ^a	476	1018
hV _{1B} R IC ₅₀ (nM) ^a	9520	31661
hV ₂ R IC ₅₀ (nM) ^a	867	6727
C _{max} (ng/mL) ^b	96	204
AUC _{0–24h} (ng/mL·h) ^b	767	478
T _{1/2} (h) ^b	2.39	1.89
Cl (mL/min/kg) ^c	45	ND ^d

^aAll data are the mean values of at least three independent measurements. ^bRat P.O. @ 2 mg/kg. ^cRat i.v. @1 mg/kg. ^dND: not determined.

overcome these issues, more rigid ring systems and a different angle of the phenyl group were introduced thereafter. Finally, the racemic 3-azabicyclo [3.1.0] hexane template [compound 11] was obtained to afford the desirable high potency. Two isomers were synthesized, and it was shown that the *S,S*-configuration [compound 13] exhibited excellent potency (400-fold higher than the *R,R*-isomer [compound 12]). Alternatively, the pyrrolidine-fused furan skeleton was tested (compound 14), which had much lower potency (Table 1).

As the 3-azabicyclo [3.1.0] hexane structure was frequently used in CNS drugs and inspired by the promising data of compound 13, more effort in this series was undertaken to investigate the structure–activity relationship (SAR) between OTR potency and selectivity over vasopressin receptors. In these assays, compound 13 achieved 192-, 2504-, and 2174-fold selectivity over V_{1A}R, V_{1B}R, and V₂R, respectively (Table 3). The terminal methoxy group was replaced by ethoxy to deliver the same level of OTR potency, while V₂R selectivity decreased (Table 3 [compound 15]). Further addition of one fluorine atom resulted in decreased potency and lower V_{1A} selectivity (compound 16). The bulky terminal cyclic rings (compounds 17–19) did not favor OTR activity. Then, the short tail di-*F*-methyl was introduced, only yielding low V_{1A} selectivity. As shown in Table 3, the cyano and cyclopropane groups further decreased OTR potency (compounds 21 and 22). The 2,4-dihalo-substituted phenyl was replaced by 2,3-dihalo-disubstituted phenyl to give compound 23, which maintained the same level of potency and selectivity as compound 13. The 3,4-benzodioxole group was introduced to

Table 3. SAR of the Analogs of Compound 13

Structure	Cmpd	hOTR IC ₅₀ (nM) ^a	hV _{1A} R IC ₅₀ (nM) ^a	hV _{1B} R IC ₅₀ (nM) ^a	hV ₂ R IC ₅₀ (nM) ^a
link	13	15	2885	37562	32604
link	15	9.3	1757	27951	7320
link	16	44	819	24540	21450
link	17	826	4697	ND	ND
link	18	184	7520	56675	23047
link	19	223	1979	ND	ND
link	20	52	1867	ND	ND
link	21	235	769	44436	ND
link	22	433	10970	ND	ND

^aAll data are the mean values of at least three independent measurements.

Table 4. SAR for Compounds 23 and 24

Structure	Cmpd	hOTR IC ₅₀ (nM) ^a	hV _{1A} R IC ₅₀ (nM) ^a	hV _{1B} R IC ₅₀ (nM) ^a	hV ₂ R IC ₅₀ (nM) ^a
23	23	30	3811	59416	25665
24	24	132	810	ND	ND

^aAll data are the mean values of at least three independent measurements.

mimic methoxy pyridine, but resulted in decreased potency and selectivity (Table 4).

Based on potency and selectivity, compounds **13**, **15**, and **23** were selected for further PK studies. As shown in Table 5, ethoxy [compound **15**] exhibited lower exposure and C_{max} concentration than compound **13** in rats. Surprisingly, compound **23** had a minor shift of fluorine compared to compound **13**, and unexpectedly had significantly lower exposure in rats. Additionally, based on the hERG experiment, compound **13** displayed less inhibition (IC₅₀ = 16 μM) than compound **15** (IC₅₀ = 6.1 μM), which suggested a relatively better hERG safety window. Taken together, compound **13**

Table 5. Rat PK of Compounds 13, 15, and 23

P.O. @ 2 mg/kg	13	15	23
C _{max} (ng/mL)	350	135	15
AUC _{0–24h} (ng/mL·h)	1683	1020	34
T _{1/2} (h)	3.98	3.48	3.15
Cl (mL/min/kg) ^a	16.1	17.8	ND

^aCl data was tested @ 1 mg/kg i.v.

(hereafter named SHR1653) was chosen for further investigations.

As shown in Table 6, SHR1653 was stable in liver microsomes across species, such as rats, dogs, and humans,

Table 6. *In Vitro* ADME Properties of SHR1653

Cl _{hepa} (mL/min/kg) ^a	14.8 (h)	20.3 (d)	54.9 (r)	77.4 (m)
P _{app} × 10 ⁶ (cm·s ⁻¹)	24.34 (A-B), 15.61 (B-A)			
P _{app} (B-A)/P _{app} (A-B)	0.64 (efflux ratio)			
solubility (μM) (amorphous)	419.52 (PBS 7.4), 107.54 (FassIF 6.5)			
logD _{7.4}	2.86			
human PPB%	96.48			

^ah = humans, d = dogs, r = rats, m = mice.

which correlated well with the *in vivo* PK results (Table 7). Based on these data, we predicted that SHR1653 might have a

Table 7. *In Vivo* PK Profiles of SHR1653 Across Species

species	mouse	rat	dog	
t _{max} (h)	0.5	0.63	0.67	0.75
P.O. dosage (mg/kg)	4	30	150	2
C _{max} (ng/mL)	330	3305	14047	930
AUC _{0-24h} (ng/mL·h)	548	16076	57244	3833
t _{1/2} (h)	1.9	2.23	3.24	4.64
Cl (mL/min/kg) @1 mg/kg, i.v.	31.3	16.1	7.2	

favorable PK profile in humans with a low clearance of 4.3 mL/min/kg by allometric scaling.¹⁷ In addition, SHR1653 displayed desirable physicochemical properties, including high solubility in PBS at pH 7.4 and FassIF solutions, as well as high passive permeability. Furthermore, the logD value and human PPB% data were collected (Table 6).

Table 7 summarizes the pharmacokinetic data of SHR1653 across species, which consistently exhibited low clearances in rats and dogs. More importantly, this compound showed a linear exposure escalation effect from 30 to 150 mg/kg in rats and from 2 to 20 mg/kg in dogs. Overall, SHR1653 demonstrated favorable PK profiles in rodents and nonrodents.

The anesthetized rat uterine contraction model is widely used to evaluate the efficacy of OTR antagonists.¹⁸ As shown in Figure 2, both IX-01 and SHR1653 exhibited significant inhibition of rat uterine contractions. A clear dose-dependent effect was observed from 10 to 100 mg/kg for SHR1653. It should be noted that IX-01 exhibited slightly higher exposure

Figure 2. *In vivo* efficacy of IX-01 and SHR1653 in an anesthetized rat uterine contraction model. **p* < 0.05, vs vehicle, one-way ANOVA, Dunnett's posthoc test; *n* = 10, except vehicle, *n* = 17. The contractile response was calculated by the ratio of AUC changes in the intraluminal uterine pressure to the baseline AUC₀. The baseline AUC₀ was the 5 min area under the curve pressure prior to oxytocin dosing. The AUC_T was the 5 min area under the curve pressure after oxytocin dosing. The changes in the baseline AUC ratio (ΔAUC ratio) were calculated ΔAUC ratio = (AUC_T - AUC₀)/AUC₀.

than SHR1653 in a separate anesthetized female rat PK study @ 30 mg/kg (AUC_{0-24h} = 39529 vs 28328 ng/mL·h). This finding might be the reason why IX-01 exhibited lower reduction of uterine contractions during the *in vivo* study (76.51% vs 65.05%; Figure 2).

Because the treatment of PE relies largely on CNS exposure of the drug, SHR1653 was investigated in a rat BBB model using the *K*_{pu,u} value for evaluation of CNS penetration evaluation.^{19,20} As indicated in Figure 3 and Table 8, SHR1653

Figure 3. BBB penetration results of SHR1653 and IX-01.

Table 8. *In Vivo* Rat BBB Penetration Results

Cmpd	fu _{rat} plasma	fu _{brain} tissue	plasma (ng/mL)	brain tissue (ng/g)	<i>K</i> _{pu,u}
SHR1653	1.46%	1.66%	1379	229	0.188*
IX-01	6.64%	1.65%	699	179	0.064*

* *t* test (*P* = 0.007).

afforded favorable brain exposure and improved *K*_{pu,u} 3-fold higher than IX-01 (0.188 vs 0.064). Taken together with the *in vivo* uterine contraction model results, SHR1653 is expected to have advantages for the potential treatment of CNS-related PE indications.

Moreover, the cytochrome P450 inhibition of SHR1653 was investigated to assess the potential likelihood of drug–drug interactions (DDI) with major CYPs, including CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. As shown in Table 9, SHR1653 exhibited weak CYP450 inhibition with all IC₅₀ values >10 μM.

Table 9. CYP Inhibition Data of SHR9352

CYP450 isoform	1A2	2C9	2C19	2D6	3A4(m) ^a	3A4(t) ^b
IC ₅₀ (μM)	>30	>30	11	>30	>30	20

^am: midazolam. ^bt: testosterone (FDA recommended 3A4 substrates).

Finally, a non-GLP 7-day acute rat toxicity study was conducted using SHR1653 at dosages of 100, 300, and 900 mg/kg. All of the groups tolerated SHR1653 well, and no abnormal findings were observed with the exception of increased urinary output at the highest dosage (900 mg/kg). Based on the general toxicity studies, including body weight, hematologic and blood chemistry parameters, and clinical

observations, it was concluded that the NOAEL and MTD were 300 and >900 mg/kg, respectively. The estimated safety margin was 10-fold based on the efficacious dose of 30 mg/kg and the NOAEL at 300 mg/kg.

The synthesis of SHR1653 was straightforward, as shown in Scheme 1. The commercially available cyanide [compound 25]

Scheme 1. Synthetic Route of SHR1653

and chiral epoxy [compound 26] underwent a nucleophilic addition/cyclization reaction to afford hydroxyl [compound 27], which was reduced with LAH in quantitative yield. The key intermediate [compound 29] was prepared under SOCl_2 conditions, then coupled with the known isothiocyanate [compound 30]¹³ to finish thio-urea [compound 31]. Subsequently, the methylated product [compound 32] was prepared under KOtBu and TsOMe conditions. The overall yield for these five steps was approximately 32%. In the final step, the triazole group was established under TFA acid conditions to successfully obtain SHR1653.

In summary, SHR1653 was shown to be a highly potent OTR antagonist that exhibited excellent selectivity over $\text{V}_{1\text{A}}\text{R}$, $\text{V}_{1\text{B}}\text{R}$, and $\text{V}_{2\text{R}}$. This novel molecule displayed favorable PK profiles across species, as well as robust *in vivo* efficacy in a rat uterine contraction model. Notably, SHR1653 showed improved BBB penetration with a relatively higher $K_{\text{pu,u}}$ value than IX-01, which might be beneficial for the potential treatment of PE. Additional studies, including the rat PE model, will be investigated in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmchemlett.9b00186.

Synthetic procedures, analytical data, *in vitro* assay protocols, *in vivo* pharmacokinetic studies, and *in vivo* efficacy model details (PDF)

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

OTR, oxytocin receptor; $\text{hV}_{1\text{A}}\text{R}$, human arginine vasopressin receptor 1A; $\text{hV}_{1\text{B}}\text{R}$, human arginine vasopressin receptor 1B; $\text{hV}_{2\text{R}}$, human arginine vasopressin receptor 2; PE, premature ejaculation; LHS, left-hand side; CNS, central nervous system; BBB, blood–brain barrier; hERG, human ether-a-go-go related gene; NOAEL, no observed adverse effect level; MTD, maximum tolerance dose; LAH, lithium aluminum hydride

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