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Discovery of XEN907, a spirooxindole blocker of $Na_V1.7$ for the treatment of pain

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ABSTRACT

Starting from the oxindole **2a** identified through a high-throughput screening campaign, a series of $Na_V1.7$ blockers were developed. Following the elimination of undesirable structural features, preliminary optimization of the oxindole C-3 and N-1 substituents afforded the simplified analogue **9b**, which demonstrated a 10-fold increase in target potency versus the original HTS hit. A scaffold rigidification strategy then led to the discovery of XEN907, a novel spirooxindole $Na_V1.7$ blocker. This lead compound, which in turn showed a further 10-fold increase in potency, represents a promising structure for further optimization efforts.

Voltage-gated sodium channels have been implicated in a number of neurological pathologies, including epilepsy, migraine, multiple sclerosis, neurodegenerative diseases and neuropathic pain.[1] In particular, the $Na_V1.7$ subtype (encoded by the *SCN9A* gene), primarily expressed in the peripheral nervous system, has elicited significant attention as a drug target for the treatment of chronic pain. Loss-of-function mutations in *SCN9A* have been linked to a condition known as congenital indifference to pain.[2] Individuals with such mutations are completely unable to experience pain but otherwise display normal neurological function. On the other hand, corresponding gain-of-function mutations correlate to two distinct pain syndromes: paroxysmal extreme pain disorder and hereditary erythromelalgia.[3]

In light of this genetic validation of $Na_V1.7$ as a target for the treatment of chronic pain, a high-throughput screening campaign, predicated on a previously described [^{14}C]guanidinium influx assay adapted for use in HEK-293 cells expressing human $Na_V1.7$, was undertaken.[4,5] From this effort, the 3-hydroxyoxindole analogue **2a** (Scheme 1) was identified as a promising candidate for hit-to-lead activities. The 3-hydroxy-2-oxindole framework is featured in a number of natural products with a broad range of biological activities.[6] Initial efforts were focused on replacing the β-hydroxyketone motif present in **2a** in order to obviate potential α,β-unsaturated ketone formation as well as on identifying a suitable surrogate for the metabolically labile furyl moiety.[7] Initial substitution of the furyl moiety with a thienyl ring was tolerated (Table 1). Geminal demethylation α to the ketone moiety led to a sharp reduction in potency observed in analogue **4**, whereas truncation of the methylene spacer to afford derivative **7** also led to reduced activity. However, upon further shortening of the spacer to obtain the 3-aryl-3-hydroxyoxindole **3f** (Table 2), modest potency was restored.

The SAR around the 3-aryl substituent was then explored (Table 2). Addition of aryl Grignard reagents or aryllithium species to the N-substituted isatin **1** allowed for the rapid generation of a series of analogues. The 3,4-methylenedioxyphenyl analogue **3a** showed the greatest target potency (equipotent with the original HTS hit **2a**). The corresponding 3,4-ethylenedioxyphenyl and 3,4-propylenedioxyphenyl analogues **3c** and **3f** demonstrated a decrease in potency with increasing ring size. The methoxypyridine analogue **3b** and 3-methoxyphenyl derivative **3d** were both potent, suggesting a preference for a H-bond acceptor at the aryl ring's 3-position. In contrast, both the 2-methoxyphenyl and the 4-methoxyphenyl analogues **3h** and **3j** were significantly less potent. The replacement of the 3,4-methylenedioxyphenyl moiety in **3a** with the corresponding monocyclic 3,4-dimethoxyphenyl ring in **3i** was poorly tolerated. Geminal difluorination of the dioxolane carbon in **3a** also led to a reduction in potency (**3k**).

The next phase of optimization involved variation of the oxindole N-substituent while preserving the 3-(3,4-methylenedioxyphenyl) moiety present in **3a** (Scheme 2, Table 3). While the N-unsubstituted compound **9r** was poorly active, a wide variety

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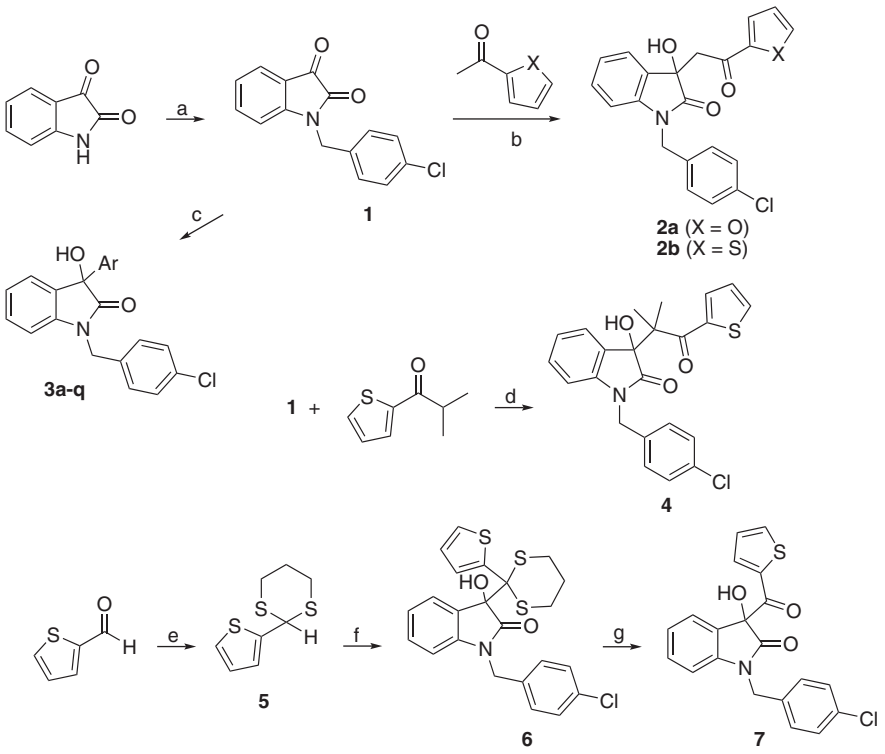
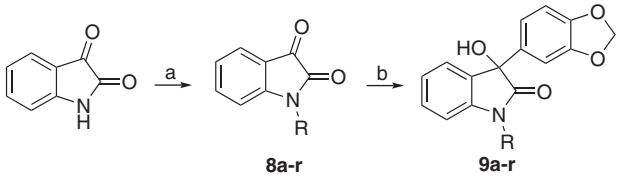


Scheme 1. Reagents and conditions: (a) *p*-chlorobenzyl chloride, NaH, DMF, 1 h; (b) *i*Pr_2NH (cat.), EtOH, reflux, 1 h; (c) ArMgX, 0 °C to rt or ArLi, −78 °C to rt, THF, 2–16 h; (d) (i) *N*-methylaniline, EtMgBr, PhH, rt, 1 h; (ii) **1**, THF, −15 °C to rt, 3 h; (e) $HS(CH_2)_3SH$, $BF_3{\cdot}Et_2O$ (cat.), CH_2Cl_2, rt, 24 h; (f) ^{n}BuLi, THF, −78 °C then **1**, −78 °C to rt, 16 h; (g) $PhI(OCOCF_3)_2$, $MeCN/H_2O$, 0 °C to rt, 2.5 h.

Table 1
Guanidinium influx assay potencies of initial 3-hydroxyoxindole analogues and reference compounds

Compound	$hNa_V1.7$ IC_{50} (μM)	*c* log *P*
2a	0.30	2.50
2b	0.20	3.87
4	6.08	5.14
7	>10	3.92
Tetrodotoxin	0.006	<−1
Tetracaine	7.51	0.41



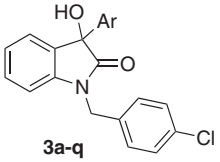
Scheme 2. Reagents and conditions: (a) RX, NaH, DMF, rt, 1–16 h; (b) 3,4-methylenedioxyphenylmagnesium bromide, THF, 0 °C to rt, 16 h.

of substituted alkyl and benzyl moieties were well tolerated at that position. Of note, potency was invariant with respect to the electronic nature of the benzyl substituent (c.f. compounds **9d**, **9e** and **9o**). Amongst the *N*-alkyl derivatives, branching (e.g., **9c** and **9i**) as well as the inclusion of saturated carbocycles (e.g., **9a**, **9j**, **9m**, and **9n**) were also tolerated. When compared to the starting *p*-chlorobenzyl compound **3a**, several analogues demonstrated improved activity along with reduced lipophilicity. The simple *n*-pentyl derivative **9b** was selected over the equipotent but somewhat less soluble and permeable (2-cyclopropyl)ethyl analogue **9a** as the starting point for investigations aimed at further improvements by replacement of the potentially labile tertiary alcohol.

Derivatization of the tertiary alcohol in **9b** to the corresponding methyl ether **12** was not tolerated (Scheme 3, Table 4). Triethylsilane-mediated dehydroxylation of **9b** afforded the key intermediate **10**.[8] Treatment of **10** with sodium hydride, followed by alkylation with iodomethane furnished the modestly active 3-methyl analogue **13**. A lanthanide triflate-catalyzed aldol condensation between *p*-formaldehyde and oxindole **10** yielded the hydroxymethylene compound **11**, which was ca. 20-fold less potent than **9b**.[9] Deprotonation of the intermediate **10**, followed by treatment with methyl cyanoformate led to the carboxylic ester **14**, which was subsequently elaborated to the carboxamide derivatives **15** and **16** with loss of target potency. However, conversion of the ester **14** to the corresponding acyl hydrazide, followed by oxidation and Curtius rearrangement, provided the highly potent 3-amino-3-aryloxindole **17**.[10] Finally, alkylation of intermediate **10** with either methyl 3-bromopropionate or methyl bromoacetate led to a series of inactive homologated esters, acid and amides (**18**–**23**).

In light of the results obtained with the 3-methyl derivative **13**, which suggested that substitution of the oxindole 3-position with an aliphatic moiety allowed for some target potency to be retained, a rigidification strategy involving the preparation of a number of spirooxindole derivatives was then explored (Scheme 4). Addition of the Grignard reagent obtained from treating sesamol (3,4-methylenedioxyphenol) with isopropylmagnesium chloride to the substituted isatin **8b** afforded the diol **24**.[11] Triethylsilane-mediated dehydroxylation to the phenol derivative **25**, followed by aldol condensation and intramolecular cyclization under Mitsunobu conditions afforded spiroether **29** (XEN907).[12,13] This analogue was 10-fold more active than the most potent acyclic oxindole analogue **9b** (Table 5). The estimated lipophilicity of XEN907 (*c* log *P* 3.97) is comparable to or less than those of some reported sodium channel blockers under investigation for the

Table 2
SAR of 1-(4′-Chlorobenzyl)-3-aryl-3-hydroxyoxindoles



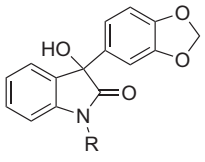
3a-q

Compound	Ar	hNa$_V$1.7 IC$_{50}$ (μM)	*c* log *P*	Solubility[a] (μg/mL)	Permeability[b] (×10^{-6} cm/s)
3a	3,4-Methylenedioxyphenyl	0.20	4.19	<5	9.0/10.9
3b	(2-Methoxypyridin)-5-yl	0.27	4.08	<5	ND[c]
3c	3,4-Ethylenedioxphenyl	0.48	3.91	9	1.9/3.5
3d	3-Methoxyphenyl	1.19	4.28	6	ND
3e	Phenyl	1.58	4.41	5	13.1/12.5
3f	3,4-Propylenedioxyphenyl	3.21	4.02	<5	ND
3g	3-Furyl	4.17	3.02	11	ND
3h	2-Methoxyphenyl	6.08	4.28	<5	ND
3i	3,4-Dimethoxyphenyl	6.14	4.15	26	ND
3j	4-Methoxyphenyl	7.37	4.28	<5	ND
3k	2,2′-Difluoromethylenedioxyphenyl	>5	5.59	<5	ND
3l	(Benzo[*b*]furan)-6-yl	>5	4.02	<5	ND

[a] Solubility at pH 7.4 in phosphate-buffered saline.
[b] Permeability (a→b/b→a) determined in CaCo-2 cells.
[c] ND = not determined.

treatment of pain, such as PPPA[14] (*c* log *P* 4.25) or BZP[15] (*c* log *P* 5.95). The corresponding five- and six-membered carbocyclic derivatives were prepared from the 3-aryloxindole derivative **10** by treatment with an excess of sodium hydride, followed by alkylation with a suitable bromoester. Following saponification and acyl halide formation, the poorly active ketones **27** and **28** were obtained via tin (IV) chloride-promoted internal Friedel–Crafts acylation.[16] Reduction of the benzylic ketone with triethylsilane

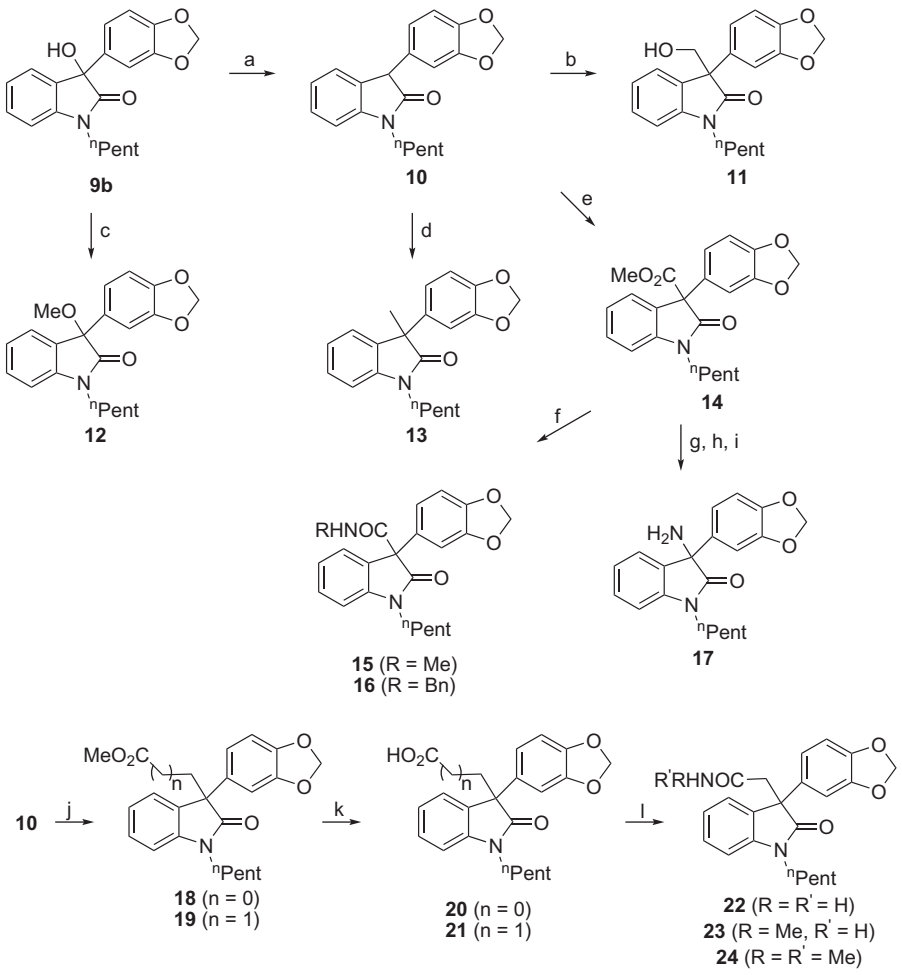
Table 3
SAR of 1-substituted-3-(3,4-methylenedioxyphenyl)-3-hydroxyoxindoles



3a, 9a-r

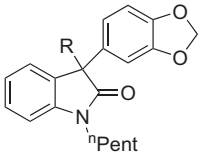
Compound	R	hNa$_V$1.7 IC$_{50}$ (μM)	*c* log *P*	Solubility[a] (μg/mL)	Permeability[b] (a→b/b→a) (×10^{-6} cm/s)
9a	(2-Cyclopropyl)ethyl	0.02	2.97	11	19.9/19.8
9b	*n*-Pentyl	0.03	3.56	37	28.9/25.4
9c	3-Methylpentyl	0.04	3.89	14	10.5/11.5
9d	4-Methoxybenzyl	0.04	3.50	6	6.5/11.9
9e	Benzyl	0.06	3.63	<5	9.3/13.6
9f	(5-Chloro-2-thienyl)methyl	0.06	3.98	<5	ND[c]
9g	3,4-Methylenedioxybenzyl	0.06	3.41	14	7.7/12.1
9h	4,4,4-Trifluorobutyl	0.07	3.43	9	ND
9i	Isopentyl	0.07	3.47	<5	ND
9j	(Cyclopropyl)methyl	0.08	2.62	22	ND
9k	*n*-Hexyl	0.09	3.97	10	ND
9l	4-Fluorobenzyl	0.09	3.79	<5	ND
9m	(Cyclohexyl)methyl	0.11	3.87	<5	ND
9n	(Cyclobutyl)methyl	0.13	3.04	38	21.7/21.1
9o	3,4-Difluorobenzyl	0.14	3.95	<5	ND
3a	4-Chlorobenzyl	0.20	4.19	<5	9.0/10.9
9p	4-(Trifluoromethyl)benzyl	0.22	4.55	<5	5.4/7.9
9q	(1-Napthyl)methyl	2.14	4.63	<5	ND
9r	H	>5	1.66	56	ND

[a] Solubility at pH 7.4 in phosphate-buffered saline.
[b] Permeability (a→b/b→a) determined in CaCo-2 cells.
[c] ND = not determined.



Scheme 3. Reagents and conditions: (a) Et_3SiH, TFA, DCM, rt, 6 h; (b) (i) TMSCl, NEt_3, CH_2Cl_2, 0 °C, 2 h; (ii) $(CH_2O)_n$, $Yb(OTf)_3$ (cat.), THF, rt, 48 h; (c) MeI, NaOMe, THF, 0 °C to rt, 16 h; (d) MeI, NaH, THF, 0 °C, 1 h; (e) NaH, $NCCO_2Me$, THF, 0 °C to rt, 2 h; (f) $MeNH_2$ or $BnNH_2$, MeOH, sealed tube, 70–100 °C, 16 h; (g) hydrazine monohydrate, *n*-PrOH, 100 °C, 2 h; (h) $NaNO_2$, AcOH, 10 °C, 1 h; (i) *t*-BuOH, PhMe, reflux, 1 h then HBr, HOAc, rt, 1 h; (j) (c) NaH, THF, 0 °C, 0.5 h, then methyl 3-bromoproionate or methyl bromoacetate, rt; (k) LiOH, THF/H_2O, rt, 16 h; (l) (i) $(COCl)_2$, DMF (cat.), PhMe, rt, 4 h; (ii) amine, $NaHCO_3$, CH_2Cl_2, rt, 16 h.

Table 4
SAR of 1-pentyl-3-(3,4-methylenedioxyphenyl)-3-substituted oxindoles



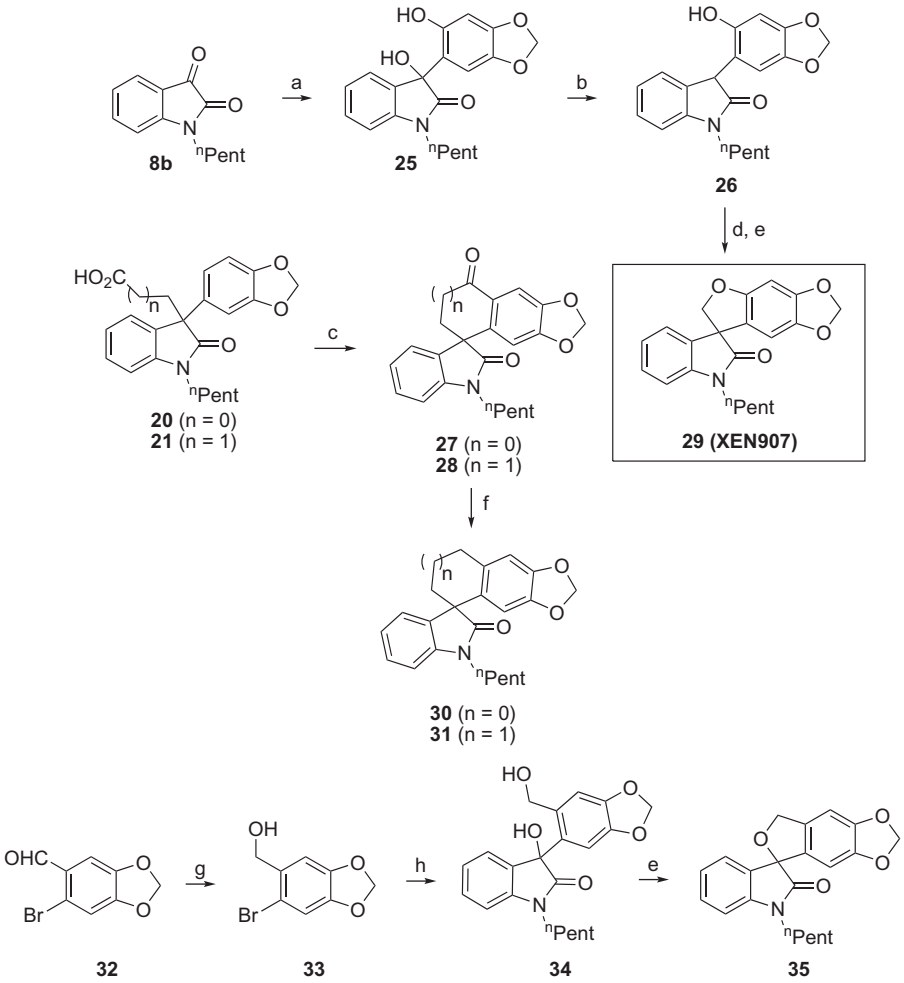
9b-24

Compound	R	$hNa_V1.7$ IC_{50} (μM)	*c* log *P*	Solubility[a] (μg/mL)	Permeability[b] ($\times10^{-6}$ cm/s)
9b	OH	0.03	3.17	37	28.9/25.4
10	H	1.74	4.18	6	ND[c]
11	CH_2OH	0.63	3.82	<5	ND
12	OMe	>5	3.92	<5	ND
13	Me	1.63	4.89	<5	2.4/3.6
14	CO_2Me	1.90	4.22	<5	ND
15	CONHMe	>5	3.54	10	ND
16	CONHBn	1.10	5.27	<5	ND
17	NH_2	0.03	3.56	34	22.0/22.3
18	CH_2CO_2Me	>5	4.16	<5	ND
19	$(CH_2)_2CO_2Me$	>5	4.58	<5	ND
20	CH_2CO_2H	>5	3.90	73	ND
21	$(CH_2)_2CO_2H$	>5	4.32	35	ND
22	CH_2CONH_2	>5	3.25	35	ND
23	CH_2CONMe	>5	3.48	31	ND
24	CH_2CONMe_2	>5	3.72	<5	ND

[a] Solubility at pH 7.4 in phosphate-buffered saline.
[b] Permeability (a→b/b→a) determined in CaCo-2 cells.
[c] ND = not determined.

afforded the carbocycles **30** and **31**, which themselves were modestly active against $Na_V1.7$. Finally, the regioisomeric tetrahydrofuran spirocycle **35** was prepared from the bromoaldehyde **32** by means of a reduction/metal-halogen exchange/carbonyl addition sequence, followed by Mitsunobu cyclization. Notably, this analogue was ca. 400-fold less potent than its regioisomer XEN907.

XEN907 showed no significant activity at 10 μM against a broad panel of 63 receptors and transporters. Determination of the ADME properties of XEN907 (Table 6) revealed that the compound was not cytotoxic and had favourable hepatocyte metabolic stability for both human and dog, although inhibition of CYP3A4 was observed in a recombinant human enzyme assay.



Scheme 4. Reagents and conditions: (a) sesamol, *i*PrMgCl, THF, 0 °C to rt, 16 h; (b) Et_3SiH, TFA, CH_2Cl_2, rt, 6 h; (c) (i) $(COCl)_2$, DMF (cat.), PhMe, rt, 4 h; (ii) $SnCl_4$, CH_2Cl_2, 0 °C to rt, 16 h; (d) (i) TMSCl, NEt_3, CH_2Cl_2, 0 °C, 2 h; (ii) $(CH_2O)_n$, $Yb(OTf)_3$ (cat.), THF, rt, 48 h; (e) PPh_3, DEAD, THF, −10 °C to rt, 16 h; (f) Et_3SiH, TFA, rt, 16 h; (g) $NaBH_4$, THF, 0 °C to rt, 10 h; (h) ^{n}BuLi, THF, −78 °C, 0.5 h then isatin **8b**, −78 °C to rt, 16 h.

Table 5
SAR of spirocyclic analogues

Compound	$hNa_V1.7$ IC_{50} (μM)	*c* log *P*	Solubility[a] (μg/mL)	Permeability[b] (a→b/b→a) ($\times10^{-6}$ cm/s)
27	3.34	3.52	<5	ND[c]
28	1.81	3.94	<5	ND
29 (XEN907)	0.003	3.97	7.3	5.9/7.2
30	0.44	4.87	<5	1.1/1.6
31	1.48	5.29	<5	ND
35	1.18	3.62	<5	ND

[a] Solubility at pH 7.4 in phosphate-buffered saline.
[b] Permeability (a→b/b→a) determined in CaCo-2 cells.
[c] ND = not determined.

Table 6
Selected ADME properties of **29** (XEN907)

Property	Value for **29**
Plasma protein binding (rat)	97%
Cytotoxicity (HepG2, % viable after 16 h)	>99%
Hepatocyte stability, % remaining after 2 h (rat/human/dog)	21%/34%/46%

Pharmacokinetic analysis in rats of XEN907 (Table 7) demonstrated that, consistent with the compound's ADME parameters, the compound was modestly bioavailable. Following an initial rapid absorption phase (oral T_{max} = 20 min), XEN907 was extensively distributed (V_{ss} ~600-fold higher than the plasma volume in rats) and rapidly cleared.

Table 7
Mean pharmacokinetic parameters of **29** (XEN907) after administration to male lewis rats (*n* = 3/group)

Parameter	po (10 mg/kg)	iv (3 mg/kg)
C_{max} (ng/mL)	35 ± 26	953 ± 96
AUC_{last} (h ng/mL)	143 ± 61	320 ± 52
$t_{1/2}$ (h)	—	2.6 ± 0.1
T_{max} (h)	0.33	—
V_{ss} (L/kg)	—	35.0 ± 4.5
Cl (L/h/kg)	—	9.4 ± 1.7
F (%)	13	—

In summary, progressive elaboration of the HTS hit **2a** via structural simplification to the 3-aryl-3-hydroxyoxindole **9b**, preliminary optimization of the N1- and C3-substituents and rigidification to a spirooxindole framework led to the identification of the highly potent (IC_{50} = 3 nM) lead XEN907. Further optimization efforts in this structural class aimed at defining analogues with improved physico-chemical and ADME properties will be described in due course.

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13. All compounds described herein were characterized by ^{1}H NMR, ^{13}C NMR and ESI-MS and had purities $\geqslant$98% a/a by HPLC. Characterization data for **29** (XEN907): mp 89–90 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.29 (m, 1H), 7.19–7.15 (m, 1H), 7.07–7.01 (m, 1H), 6.92–6.87 (m, 1H), 6.51 (s, 1H), 6.12 (s, 1H), 5.88–5.84 (m, 2H), 4.91, 4.66 (ABq, J_{AB} = 8.9 Hz, 2H), 3.87–3.64 (m, 2H), 1.77–1.65 (m, 2H), 1.41–1.32 (m, 4H), 0.91 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.4, 156.0, 148.9, 142.5, 142.4, 132.6, 129.0, 124.0, 132.2, 119.7, 108.7, 103.1, 101.6, 93.7, 80.6, 58.3, 40.5, 29.1, 27.2, 22.5, 14.1; MS (ESI+) m/z 352.3 (M+1); purity (HPLC, UV at 254 nm) 99.2% a/a.
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