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Discovery, oral pharmacokinetics and in vivo efficacy of velusetrag, a highly selective 5-HT$_4$ receptor agonist that has achieved proof-of-concept in patients with chronic idiopathic constipation

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ABSTRACT

Utilization of Theravance's multivalent approach to drug discovery towards 5-HT$_4$ receptor agonists with a focus on identification of neutral (non-charged at physiological pH) secondary binding groups is described. Optimization of a quinolone-tropane primary binding group with a chiral 2-propanol linker to a range of neutral secondary binding group motifs, for binding affinity and functional potency at the 5-HT$_4$ receptor, selectivity over the 5-HT$_3$ receptor, oral pharmacokinetics, and in vivo efficacy in models of GI motility, afforded velusetrag (TD-5108). Velusetrag has achieved proof-of-concept in patients with chronic idiopathic constipation.

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Drug discovery efforts to identify novel selective 5-HT$_4$ receptor agonists have intensified in recent years following the approval and subsequent marketing suspension of cisapride (Propulsid®) (**1**) and tegaserod (Zelnorm®) (**2**), Figure 1. More recently prucalopride (Resolor®) (**3**) was approved in Europe for the treatment of women with chronic idiopathic constipation who have not responded adequately to laxatives. In contrast to cisapride and tegaserod, prucalopride has a high degree of selectivity for the 5-HT$_4$ receptor over other 5-HT or non-5-HT receptors.[1] All three of these agents have been prescribed to patients for the treatment of GI functional disorders. In addition, preclinical evidence that 5-HT$_4$ receptor agonists may be of benefit for both the symptomatic and disease-modifying treatment of cognitive disorders is substantial[2] and clinical benefit in a small Phase 2 study in Alzheimer's disease patients was reported with the selective 5-HT$_4$ receptor partial agonist, PRX-03140.[3]

In our earlier paper[4] we described the further application of Theravance's multivalent approach to drug discovery[5] directed to 5-HT$_4$ receptor agonists, through the elaboration of an indazole–tropane primary binding group, resulting in the identification of clinical compound TD-2749 (**4**). The key element of the approach was the optimization of both an amine-based secondary binding group and the linker motif according to the 5-HT$_4$ receptor agonist pharmacophore in Figure 2. Ultimately it was found that in the indazole–tropane series, short linkers (≤3 linear atoms) provided the best balance of high affinity 5-HT$_4$ receptor agonism, and good selectivity over the 5-HT$_3$ receptor. In addition, modulation of the pK_a of the secondary binding group was investigated to maximize rat in vivo oral pharmacokinetic properties. Since it was determined that lowering the pK_a correlated with a favorable overall profile of the 5-HT$_4$ receptor agonist compounds, we decided to revisit the concept of a neutral secondary binding group that would not be charged at physiological pH. In our original paper detailing the discovery of THRX-194556 (**5**) we reported that in the quinolone–tropane series, neutral-alkyl, hydroxyl and phthalimide secondary binding groups were generally not as high binding affinity or as potent compared with corresponding amine-based secondary binding groups such as the piperazine–sulfonamide of THRX-194556 (**5**), over a range of linker lengths.[6] Regardless, we wanted to investigate whether we could optimize a neutral secondary binding group using the short linker SAR we had subsequently determined, combined with key interactions that likely contribute to some of the more potent amine-based secondary binding groups. We herein describe application of this approach to the quinolone–tropane primary binding group to afford the clinical compound velusetrag (**15**).

Schemes 1–3 detail the preparation of the compounds described in this communication. We initially chose to retain both the quinolone–tropane primary binding group[6] and 2-propanol

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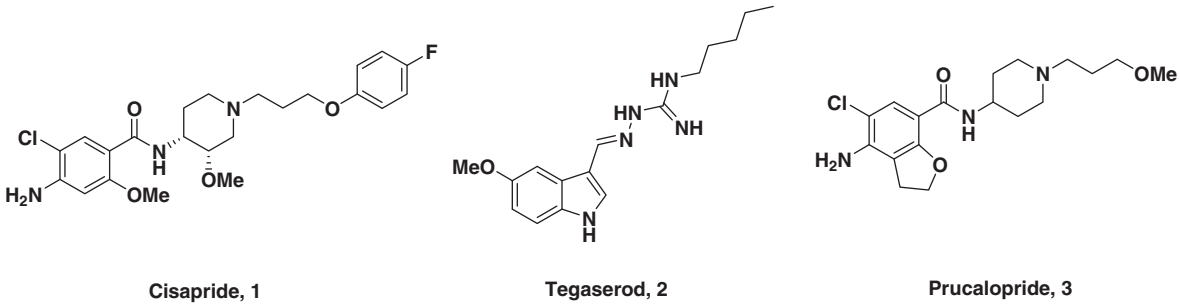


Figure 1. 5-HT_4 receptor agonists to have reached the market.

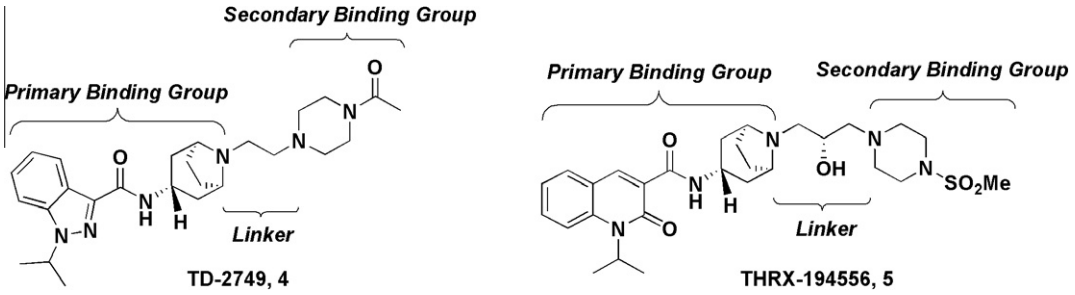
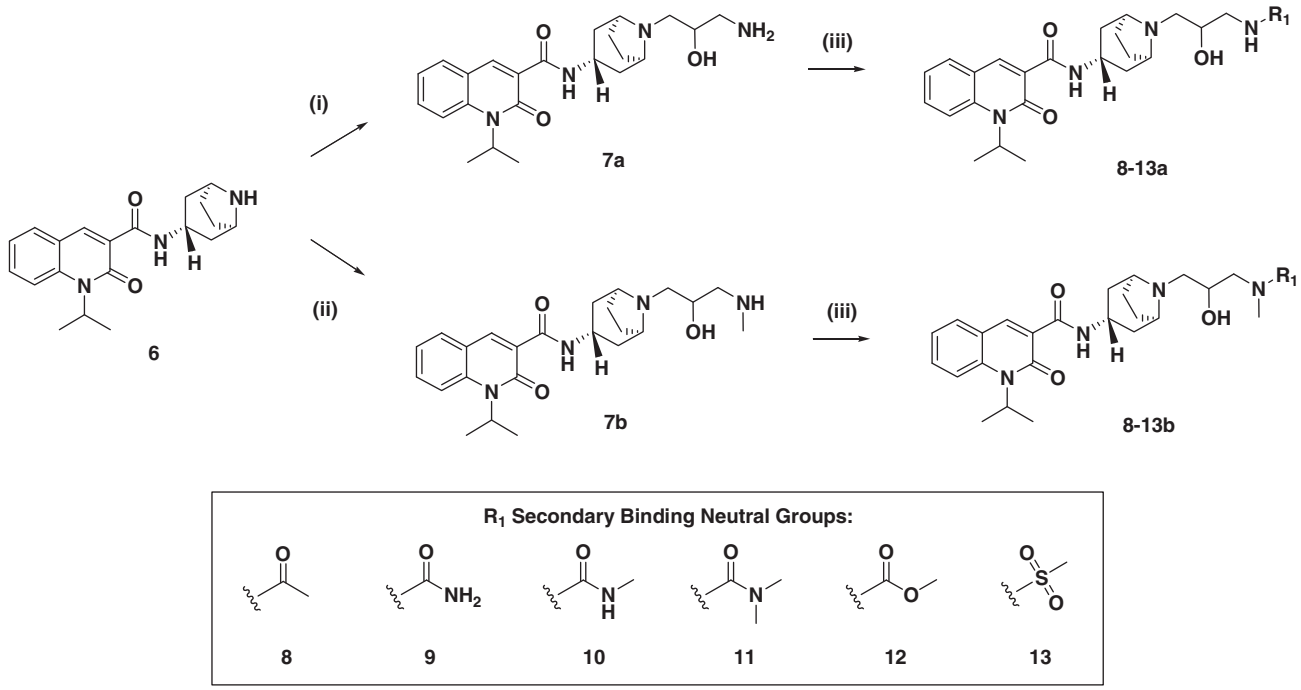


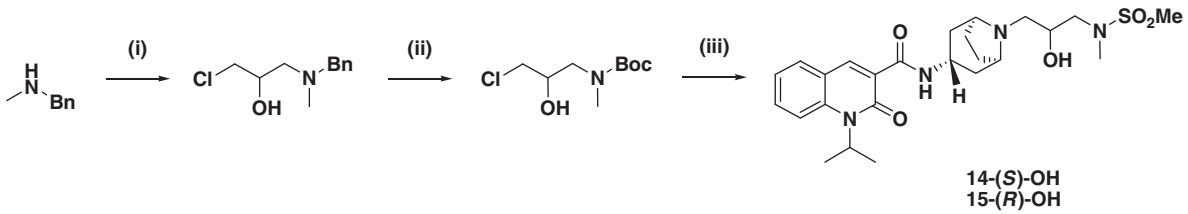
Figure 2. Theravance 5-HT_4 receptor agonists.



Scheme 1. Reagents and conditions: (i) (a) *N*-(2,3-epoxypropyl)-2-phthalimide, DIPEA, EtOH, 80 °C, (b) hydrazine, EtOH, 80 °C; (ii) (a) *rac*-epibromohydrin, EtOH, 80 °C, (b) $MeNH_2$ (41% in H_2O), EtOH, 80 °C; (iii) **8a**: AcOH, PyBOP, DIPEA, DMF; **8b**: AcCl, DIPEA, DMF; **9a,b**: $(CH_3)_3SiNCO$, DIPEA, DMF; **10a,b**: CH_3NCO, DIPEA, DMF; **11a,b**: $(CH_3)_2NCOCl$, DIPEA, DMF; **12a,b**: CH_3OCOCl, DIPEA, DMF; **13a,b**: MsCl, DBU, DCM.

linker (initially exploring the racemic form) of THRX-194556 (**5**) and investigated functionalization of both a terminal primary amine precursor **7a** and a terminal secondary *N*-methyl amine precursor **7b** to afford compounds **8–13a** (NH series) and **8–13b** (NMe series), respectively. Simple amide, carbamate, urea and sulfonamide neutral secondary binding group compounds were prepared, Table 1, Scheme 1.

Encouragingly a number of compounds from both the NH (**8a**, **9a**, **10a**, **13a**) and NMe (**8b**, **12b**, **13b**) series exhibited acceptable binding affinity (pK_i >7.4) and functional potency (pEC_{50} >7.9) along with high intrinsic activity (IA >82% of the maximum response achieved by 5-HT in a cAMP accumulation assay) at the human recombinant 5-HT_4 receptor. In addition, these same compounds were highly selective (>700-fold) over the 5-HT_3 receptor. The



Scheme 2. Reagents and conditions: (i) For **14**: (a) (*R*)-epichlorohydrin, hexane; For **15**: (a) (*S*)-epichlorohydrin, EtOH, (b) NaOH, THF, H_2O, 0 °C; (ii) H_2, $Pd(OH)_2$, Boc_2O, EtOAc, 60 psi; (iii) (a) **6**, DIPEA, MeOH, 80 °C, (b) TFA, DCM, (c) MsCl, DBU, DCM, 0 °C.

Scheme 3. Reagents and conditions: (i) 50% NaOH in H_2O then (*S*)-epichlorohydrin, 4 °C; (ii) **6** (TFA salt), EtOH, 50% NaOH in H_2O, reflux; (iii) HCl, EtOH.

Table 1

Compound	Series (stereochem.)	5-HT_4 pK_i[a]	Selectivity versus 5-HT_3[b]	5-HT_4 pEC_{50}[c]	5-HT_4 IA[d]	RLM $t_{1/2}$ (min)	Caco-2 K_p (1×10^{-6} cm/s)	hERG inhibition[e] (%)
Cisapride	—	7.0	20	7.1	71	47	—	100
Tegaserod	—	8.4	580	8.6	92	>90	11	33
4	—	8.0	980	8.0	53	>90	31	9
5	(*S*)	7.9	7400	8.7	114	>90	14	4
8a	NH (*rac*)	7.5	2200	8.2	96	>90	6	—
8b	NMe (*rac*)	7.4	1500	7.9	95	>90	16	11
9a	NH (*rac*)	7.8	3300	8.3	82	>90	0	—
9b	NMe (*rac*)	7.3	1800	7.7	95	>90	1	—
10a	NH (*rac*)	7.6	2400	7.9	82	>90	0	—
10b	NMe (*rac*)	7.0	870	7.5	95	—	—	—
11a	NH (*rac*)	7.0	860	—	—	>90	3	—
11b	NMe (*rac*)	7.3	260	7.7	87	>90	33	64
12a	NH (*rac*)	7.3	1600	—	—	>90	35	74
12b	NMe (*rac*)	7.4	710	8.0	84	>90	35	40
13a	NH (*rac*)	7.7	1200	8.1	107	—	—	10
13b	NMe (*rac*)	7.7	1400	8.0	96	>90	31	16
14	NMe (*S*)	7.3	110	7.6	97	>90	19	9
15	NMe (*R*)	7.7	3300	8.3	95	>90	25	13

[a] 5-HT_4 receptor binding pK_i values were determined using a [^{3}H]-GR113808 radioligand binding assay with membranes prepared from HEK-293 cells stably-transfected with human recombinant 5-$HT_{4(c)}$ receptor splice variant.

[b] 5-HT_3 receptor binding pK_i values were determined with a [^{3}H]-GR65630 radioligand binding assay with membranes prepared from HEK-293 cells stably-transfected with human 5-HT_{3A} receptor and selectivity for the 5-HT_4 receptor type with respect to the 5-HT_3 receptor type was calculated as the ratio K_i(5-HT_{3A})/K_i(5-$HT_{4(c)}$).

[c] pEC_{50} values were determined using whole-cell cAMP accumulation studies in HEK-293 cells stably-transfected with the human recombinant 5-$HT_{4(c)}$ receptor splice variant.

[d] Maximum compound-evoked response (minus basal) expressed as a percentage of the maximum response evoked by 5-HT.

[e] Inhibition of hERG potassium ion currents was determined at a concentration of 3 μM using Chinese Hamster Ovary (CHO) cells stably-expressing hERG potassium channels.

difference in pK_i for a given neutral secondary binding group between the NH and NMe analogues was in general minimal (ΔpK_i <0.3 log) and was only significant for the urea compounds **9a,b** and **10a,b** ($\Delta pK_i \geq 0.5$ log); the NH **9a**, **10a** compounds displaying the higher affinity value. Stability in the rat liver microsome (RLM) assay was high ($t_{1/2}$ >90 min) for all the compounds **8–13a,b** tested. The permeability (as measured by the Caco-2 assay) was low for all the NH series compounds tested **8–13a**, ($K_p \leq 6$) with the surprising exception of the carbamate analogue **12a** ($K_p = 35$). In contrast the permeability of the NMe series compounds **8–13b** was in general much improved ($K_p \geq 16$) with the exception of primary urea analogue **9b** ($K_p = 1$) which was poorly permeable in both series. We previously postulated that the H-bond donating character of functionalized secondary binding groups of 5-HT_4 receptor agonists may contribute to low permeability and these results are in general consistent.[4] The NMe carbamate **12b** retained the good permeability ($K_p = 35$) of its NH analogue **12a** but unfortunately both compounds demonstrated potent inhibition of the hERG potassium ion current (40% and 74% inhibition of the channel at 3 μM, respectively). The fully substituted urea **11b** with no H-bond donating character also displayed potent hERG inhibition (64%). However, the NH sulfonamide compound **13a**, its NMe analogue **13b** and the NMe amide **8b** showed encouragingly weak inhibition (10%, 16% and 11%, respectively).

Due to the good overall balance of high potency, high in vitro permeability and weak hERG inhibition observed with compound

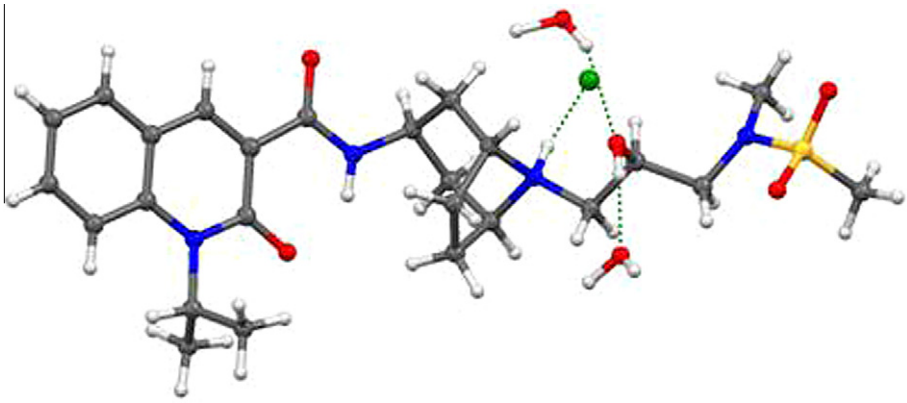


Figure 3. X-ray crystal structure of the hydrochloride salt of compound **15**.

13b its single enantiomers **14** and **15** were synthesized and profiled, Table 1, Scheme 2. Following the same trend as observed with THRX-194556 (**5**) and single enantiomer indazole–tropane analogues previously reported,[4] the (*R*)-enantiomer **15** was found to be preferable.[7] (*R*)-Enantiomer **15** exhibited weak hERG inhibition and had significantly higher 5-HT_4 receptor affinity and functional potency, and selectivity over the 5-HT_3 receptor, relative to the (*S*)-enantiomer **14**. The designation of (*R*)-stereochemistry of the hydroxyl was unambiguously assigned by a crystal structure of the hydrochloride salt of compound **15**, Figure 3.

The oral pharmacokinetics (PK) in rats of the (*R*)-enantiomer **15** was determined and found to be improved, as reflected by increased C_{max} and AUC, relative to that of the previously identified THRX-194556 (**5**) and was comparable to TD-2749 (**4**) albeit with a reduced oral bioavailability, Table 2. Having achieved the goal of discovering a 5-HT_4 receptor agonist possessing a neutral secondary binding group with suitable potency, selectivity and oral pharmacokinetics, the NMe sulfonamide compound **15** was selected for further in vitro[8] and in vivo[9] evaluation. In parallel with these activities a medicinal chemistry program to optimize the sulfonamide moiety was pursued, principally exploring alternates to both methyl groups (N*Me* and SO_2*Me*) and this will be the subject of a future article.

With respect to selectivity over other 5-HT receptors, compound **15** displayed less than 50% inhibition of 5-$HT_{1A,B,D}$, 5-$HT_{2A,B,C}$, 5-HT_{3A}, 5-HT_{5A}, 5-HT_6 and 5-HT_7 at a concentration of 10 μM. In contrast, tegaserod displays relatively high binding affinity (pK_i >7.0) at 5-HT_{1D}, 5-$HT_{2A,C}$ and 5-HT_7 receptors, and has particularly high binding affinity (pK_i >8.7) for the 5-HT_{2B} receptor. Cisapride is only 20-fold selective for the 5-HT_4 receptor relative to the 5-HT_3 receptor.

The potency and intrinsic activity of compound **15** in the functional cAMP accumulation assay were determined to be high (pEC_{50} = 8.3; IA = 95%) using a cell line expressing the 5-$HT_{4(c)}$ receptor at 10-fold physiological levels (B_{max} 500–800 fmol/mg protein).[8] When a cell line expressing the 5-$HT_{4(c)}$ receptor at 100-fold physiological levels was used the potency (pEC_{50} = 9.2) was higher and compound **15** elicited a full agonist (IA = 110%) response. These results are consistent with the full agonist properties of THRX-194556 (**5**) but in contrast to the partial agonist profile of TD-2749 (**4**).

Compound **15** produced a concentration-dependent contraction of the guinea pig isolated colonic longitudinal muscle/myenteric plexus preparation. The potency of **15** (pEC_{50} = 7.9) was similar to that of 5-HT and tegaserod (**2**) (pEC_{50} = 8.0 and 8.2, respectively). However, **15** had an intrinsic activity greater than that of tegaserod (83% vs 65% of the 5-HT maximum, respectively). Considering the wealth of literature demonstrating that 5-HT_4 receptor activation results in contraction of this smooth muscle preparation,[10,11] and the presence of antagonists of 5-HT_1, 5-HT_2 and 5-HT_3 receptors in these isolated tissue experiments, the observed activity of **15** was concluded to represent 5-HT_4 receptor activation.

To characterize the in vivo activity of **15**, digital sonomicrometry was used to monitor 5-HT_4 receptor-mediated esophageal relaxation in the anesthetized rat.[12] This method provided a novel and sensitive means to demonstrate 5-HT_4 receptor agonist-mediated changes in endogenous esophageal tone. Compound **15** produced a dose-dependent, 5-HT_4 receptor-mediated relaxation of the esophagus, following intravenous administration, Figure 4. The mean ED_{50} values for the relaxation response mediated by intravenous tegaserod, **15** and cisapride were 11, 25 and 142 μg/kg, respectively. However, following intraduodenal dosing in the rat, **15** was approximately fivefold more potent than tegaserod (data not shown).

In the guinea pig colonic transit model, **15** (0.3 mg/kg sc) produced a statistically significant decrease in the colonic transit time

Table 2

Compound	C_{max}[a] (μg/mL)	$AUC_{(0\text{-}t)}$ (μg h/mL)	$t_{1/2}$ (h)	F[b] (%)
4	0.254	0.73	3.2	>100
5	0.031	0.20	5.2	20
15	0.160	0.46	1.9	19

[a] Pharmacokinetic properties were evaluated in male Sprague–Dawley rats dosed with test compounds via oral gavage (PO) at a dose of 5 mg/kg, n = 3.
[b] F = oral bioavailability.

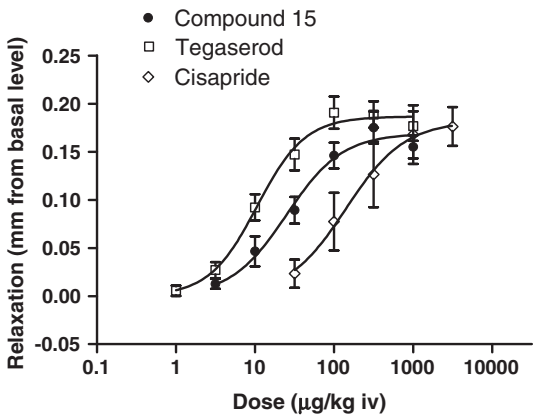


Figure 4. Relaxation of rat esophagus following intravenous dosing of compound **15**.

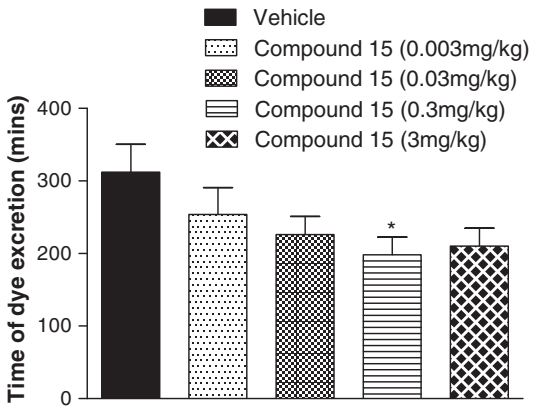


Figure 5. Guinea pig colonic transit following subcutaneous dosing of compound **15**.

of carmine red dye relative to vehicle treated animals. Following subcutaneous administration, prokinetic activity was evident when the distance traveled by the dye was measured 60 min later (data not shown), or when the time for excretion of the first fecal pellet containing the marker was recorded, Figure 5. In this assay, **15** appeared to have superior potency to tegaserod, although tegaserod did not achieve a statistically significant increase in colonic transit at the doses tested.

Additional profiling of **15** included demonstration of good oral bioavailability and GI motility in dogs.[9,13] The effects of **15** on secretion of soluble amyloid precursor protein alpha (sAPPα from HEK293 cells-stably transfected with human 5-$HT_{4(d)}$ receptor and human APP_{695} in an in vivo model of cognition (rat Morris water maze) were also examined.[2] The results obtained support a potential role for potent and efficacious 5-HT_4 receptor agonists in providing symptomatic and disease-modifying benefit in the treatment of Alzheimer's disease.

Subsequently compound **15** was nominated as a development candidate, velusetrag (TD-5108) and advanced to human clinical trials. Accordingly an alternate, optimized synthesis of velusetrag was devised to support IND-enabling studies and clinical manufacture, Scheme 3.[14] The key chiral NMe-sulfonamide substituted epoxide **17** was prepared in a single step by reaction of $MeNHSO_2Me$ **16** with (*S*)-epichlorohydrin under basic aqueous conditions. It is believed that opening of the epoxide occurs first with subsequent base mediated closure of the hydroxy chloro intermediate to yield **17**. Reaction of this functionalized epoxide **17** with the quinolone tropane **6** and subsequent freebasing and crystallization as the hydrochloride salt afforded velusetrag.

In healthy human subjects, dose-related prokinetic activity, including increases in stool production, were observed with single doses of velusetrag up to 70 mg and repeated daily doses of up to 50 mg for 14 days.[15] The pharmacokinetics of velusetrag over the single dose-range demonstrated dose-dependent increases in systemic exposure and was supportive of once daily dosing (elimination half-life of 12–14 h). These pharmacokinetic findings were similar in patients with chronic constipation from a separate study in which velusetrag was shown to increase gastric emptying as well as intestinal and colonic transit in healthy volunteers, suggesting utility in both upper and lower GI disorders.[16] In a large (n = 401), proof-of-concept, Phase 2 trial (ACCORD) in patients with chronic idiopathic constipation velusetrag showed statistically and clinically significant increases relative to placebo in both weekly spontaneous bowel movement frequency and the weekly frequency of complete SBM at all three doses tested (15 mg, 30 mg and 50 mg, qd).[17] Velusetrag also improved stool consistency, and reduced both straining and the use of laxatives. In both the Phase 1 and Phase 2 studies velusetrag was well tolerated.

Following on from our previous efforts utilizing our multivalent approach to drug discovery towards 5-HT_4 receptor agonists we focused on identification of neutral secondary binding groups. Combination of a quinolone–tropane primary binding group with a chiral 2-propanol linker to a neutral *N*-methyl-methylsulfonamide secondary binding group afforded velusetrag (TD-5108), which was selected as a development candidate. Velusetrag is a potent and highly selective 5-HT_4 receptor agonist in vitro with robust in vivo GI activity and an attractive oral pharmacokinetic profile. In human subjects, velusetrag has achieved proof-of-concept in patients with chronic idiopathic constipation and shown clinical evidence for potential utility in the treatment of both upper and lower GI disorders. Velusetrag has been well tolerated in all clinical trials to date and is currently under active development.

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