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Chroman and tetrahydroquinoline ureas as potent TRPV1 antagonists

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ABSTRACT

Novel chroman and tetrahydroquinoline ureas were synthesized and evaluated for their activity as TRPV1 antagonists. It was found that aryl substituents on the 7- or 8-position of both bicyclic scaffolds imparted the best in vitro potency at TRPV1. The most potent chroman ureas were assessed in chronic and acute pain models, and compounds with the ability to cross the blood–brain barrier were shown to be highly efficacious. The tetrahydroquinoline ureas were found to be potent CYP3A4 inhibitors, but replacement of bulky substituents at the nitrogen atom of the tetrahydroisoquinoline moiety with small groups such as methyl can minimize the inhibition.

Transient receptor potential vanilloid 1 (TRPV1) is the best characterized member of the TRP superfamily of ion channels. TRPV1 can be activated by a range of stimuli, including exogenous capsaicin as well as chemical (acid) and physical (heat) stimuli among others.[1] Its key role in nociceptive signal transduction pathways has been extensively discussed.[2,3] In the last decade significant efforts have been devoted to the design and synthesis of TRPV1 antagonists as analgesic agents.[4] Several TRPV1 antagonists have entered to human clinical trials in recent years. Some reports from these studies described signals of efficacy in dental pain trials, but also unwanted temperature effects for TRPV1 antagonists.[5–7] In the meantime the search for TRPV1 antagonists with suitable ADME, pharmacological, physico-chemical and toxicological profile continues.

The early lead compound **1** (Fig. 1) from Abbott urea class of TRPV1 antagonists was characterized by good potency at the target, modest efficacy in animal pain models, and less than desirable pharmacokinetic profile.[8–10] A series of structural modifications, including rigidification of the benzylic fragment in **3**, led to the indan urea **4** characterized by good potency and significantly optimized pharmacokinetic profile.[11] Conformational restriction of the benzylic group can also be achieved by generating the chroman and tetrahydroquinoline bicyclic scaffolds, which generally contribute to a higher solubility of the resulting ureas compared with analogous indan ureas. This paper describes the SAR studies of the chroman and tetrahydroquinoline TRPV1 antagonists of type **5** and **6**, as well as the pharmacokinetic properties and in vivo characterization of these compounds in animal pain models.

Synthesis of the target chroman and tetrahydroquinoline ureas was accomplished by reacting activated carbamate **7** with the appropriately substituted chromanyl amine **8** or tetrahydroquinolinyl amine **9** as shown in Scheme 1.

Scheme 2 illustrates the general protocol for the synthesis of the chromanyl amines **8**. Alkylation of the functionalized phenol **12** with propargyl bromide generated ether **13**, chlorination of which at the terminal site of the propargyl aryl ether with *N*-chloro-succinimide and silver acetate afforded **14**.[12] Reaction conditions for rearrangement of **14** to the chromanone **15** depended on the nature of the substituent: aryl ethers with electron donating substituents such as the *tert*-butyl group cyclized in refluxing ethylene glycol, while aryl ethers with electron withdrawing substituents such as the trifluoromethyl group cyclized in concentrated sulfuric acid. Chromamone **15** was converted to the methyl oxime **16**, which was then reduced by hydrogenation to the chromanyl amine **8**.

Synthesis of the piperidinyl–chromanyl amine **8n** started with chromanone **17** as shown in Scheme 3. Bromination of **17** with *N*-bromosuccinimide in concentrated sulfuric acid proceeded regioselectively to generate **18**. After converting the latter to a methyl oxime **19**, a Buchwald amination[13] was performed in the presence of piperidine in a microwave reactor to yield **20**. Finally, dechlorination and reduction of the oxime in a one-pot hydrogenation procedure afforded the desired chromanyl amine **8n**.

In vitro SAR of the chroman ureas is presented in Table 1. A variety of substituents such as the small lipophilic trifluoromethyl group, bulky *tert*-butyl group, even the basic piperidine ring are

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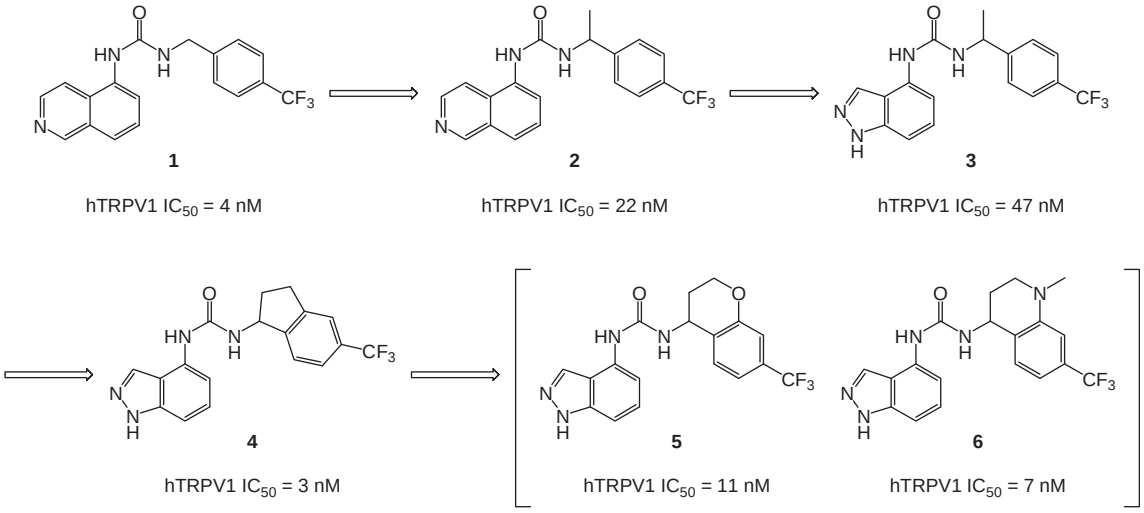
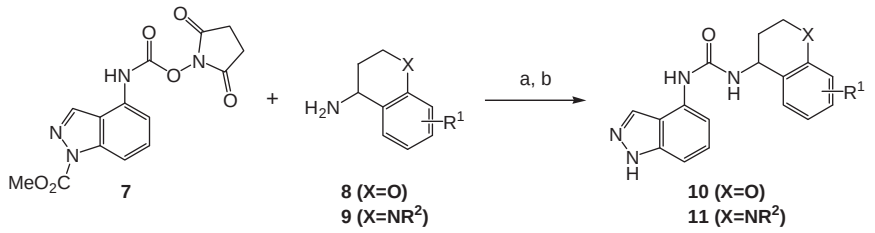
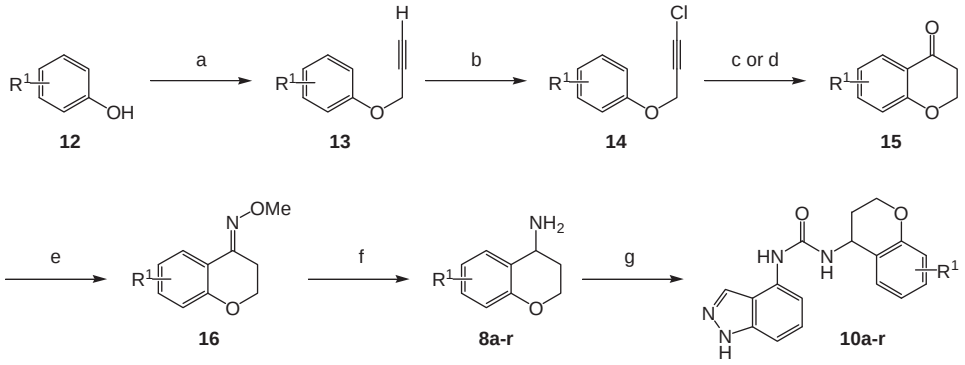


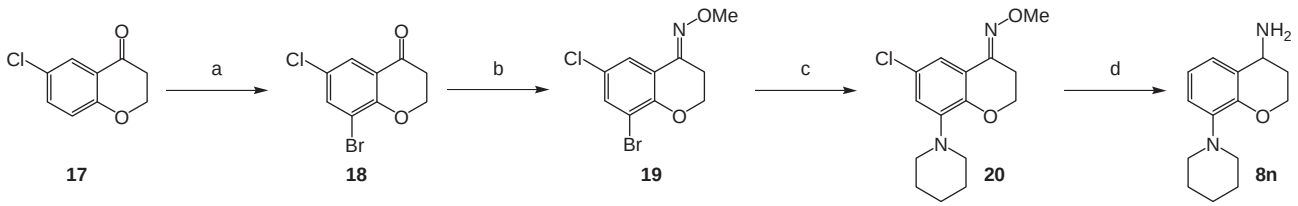
Figure 1.



Scheme 1. Reagents and conditions: (a) DIPEA, DMF, 30 min, rt; (b) MeOH, H_2O, TEA, 1 h, reflux, 70–90% for two steps.



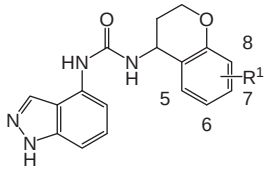
Scheme 2. Reagents and conditions: (a) propargyl bromide, K_2CO_3, MeCN, 96 h, rt, 80–99%; (b) NCS, AgOAc, acetone, 4 h, reflux; (c) when $R^1 = CF_3$, concd H_2SO_4, 30 min, rt, 15–85%; (d) when $R^1 = t$Bu, ethylene glycol, 4 h, reflux, 20–65%; (e) $MeONH_2$·HCl, Py, 24 h, rt, 80–99%; (f) H_2, 60 psi, 10% Pd/C, NH_3–MeOH, 1 h, rt, 80–99%; (g) see Scheme 1.



Scheme 3. Reagents and conditions: (a) concd H_2SO_4, NBS, 3 h, rt, 99%; (b) $MeONH_2$·HCl, Py, 24 h, rt, 82%; (c) piperidine, NaO*t*Bu, $Pd_2(dba)_3$, BINAP, dioxane, 30 min, 170 °C, μw, 20%; (d) H_2, 60 psi, 10% Pd/C, NH_3–MeOH, 18 h, 50 °C, 37%.

well tolerated. The site of the functional group placement appears to be the key to in vitro potency. Thus, substitutions at 7- and 8-positions afforded the most potent compounds, whereas substitutions at the 6-position led to a dramatic drop in activity. Chirality also has an effect on in vitro activity. For example, the (*R*)-enantiomer **10f** exhibits greater potency than the (*S*)-enantiomer **10g**. The

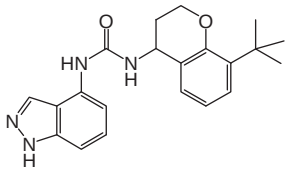
Table 1
In vitro functional potencies of selected chroman TRPV1 antagonists in human TRPV1 Ca^{2+} influx assay



Compd	R^1	hTRPV1 IC_{50}[a] (nM)
10a	7-CF_3	11
10b	7-CF_3-*R*	4
10c	7-CF_3-*S*	43
10d	7-OCF_3	8
10e	7-*t*Bu	43
10f	7-*t*Bu-*R*	31
10g	7-*t*Bu-*S*	1200
10h	8-CF_3	5
10i	8-OCF_3	5
10j	8-*t*Bu	5
10k	8-*t*Bu-*R*	3
10l	8-*t*Bu-*S*	19
10m	8-Cyclohexyl	15
10n	8-Piperidino	16
10o	8-Morpholino	110
10p	6-Me	933
10q	6-F	718
10r	H	234

[a] All values are means ± SEM of at least three separate experiments.

Table 2
Analgesic effects of **10j**[a]



Rat models of pain	
Capsaicin-induced acute pain	89%[b]
Carrageenan-induced thermal hyperalgesia	10[c]
CFA-induced thermal hyperalgesia	15[c]
MIA-induced osteoarthritis pain (grip force)	56%[b]

[a] Positive controls are A-784168[14] (Capsaicin model), diclofenac (Carrageenan and CFA-models), celecoxib (MIA model).
[b] % inhibition at 30 μmol/kg po.
[c] ED_{50} (μmol/kg) po.

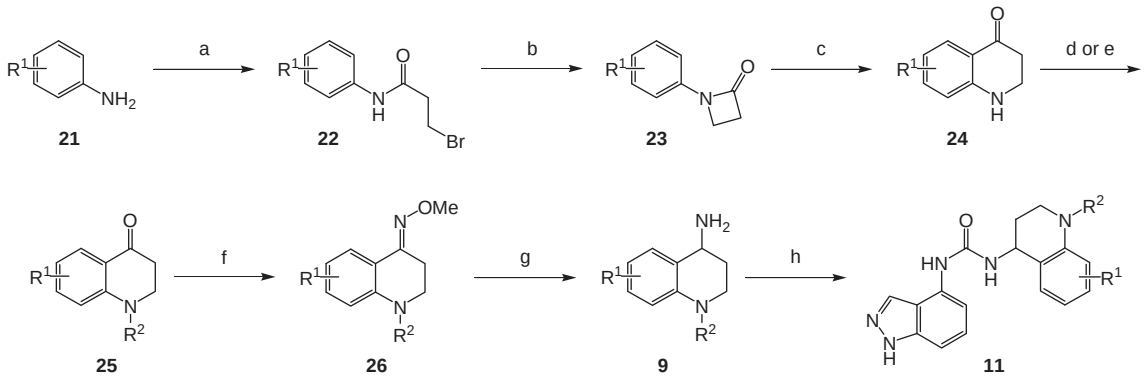
in vitro SAR of the chroman ureas strongly correlates with the SAR of the indane ureas.[11]

Most of the chroman ureas were efficacious in the rat model of CFA-induced thermal hyperalgesia, but lacked efficacy in other pain models. The exception was compound **10j**, which was highly efficacious in multiple animal pain models (Table 2). This TRPV1 antagonist possessed a brain/plasma ratio of 0.42 in rats, which was higher than the brain penetration of the other chroman ureas evaluated. These data are consistent with the hypothesis that CNS penetration is a desirable characteristic for a broad-spectrum analgesic effects of a potent, selective TRPV1 antagonist.[14]

Complimenting the indane and chroman ureas were the tetrahydroquinoline ureas, another structural series with a rigid scaffold. Scheme 4 illustrates the general synthetic route of preparing the target molecules in this series. Acylation of the functionalized aniline **21** with bromopropionyl chloride afforded amide **22**, which was then cyclized to β-propiolactam **23**. Next, triflic acid was utilized to initiate a Fries rearrangement to yield dihydroquinolinone **24**.[15] *N*-Substitution of **24** by either reductive amination with aldehydes or alkylation with alkyl halides gave **25**. Finally, the methyl oxime **26** was prepared, and then reduced by hydrogenation to generate the tetrahydroquinoline amine **9**.

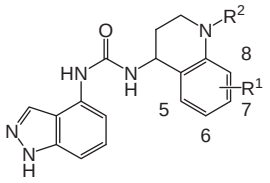
SAR of the tetrahydroquinoline ureas presented in Table 3 strongly correlates with the SAR of the chroman ureas. Placement of the aryl substituent is a key factor for in vitro potency as demonstrated with the shifting positions of the *tert*-butyl group in compounds **11d–f**. Once more, the 7- and 8-positions are the favorable sites for higher potency. A variety of substituents are well tolerated, both on the aryl ring and on the nitrogen. Evidently, better in vitro activity is obtained from large N-substituents such as the benzyl group. For instance, benzyl substituted **11j** is seven-fold more potent then its methyl analog **11f**. Unlike chromans, the tetrahydroquinoline ureas were found to be inhibitors of the CYP3A4 enzyme as shown in Table 3. Large bulky substituents such as the benzyl group generated compounds that were especially potent inhibitors. However, replacement of the benzyl moiety with a methyl group on the nitrogen has a major effect in decreasing the inhibition (**11k** vs **11g**). The best combination of potency and CYP inhibition was achieved with **11c**.

In summary, we have demonstrated that the chroman and tetrahydroquinoline ureas are potent TRPV1 antagonists. They share an in vitro SAR profile with the original rigid bicyclic scaffold, the indanes. The chroman ureas also exhibited a broad-spectrum analgesic profile when the compounds crossed the blood–brain barrier into the CNS. The tetrahydroquinolines were hampered by inhibition of the CYP3A4 enzyme, yet the correct selection of substituents can alleviate this liability and still provide potent TRPV1 antagonists.



Scheme 4. Reagents and conditions: (a) 3-bromopropionyl chloride, K_2CO_3, CH_2Cl_2, 3 h, rt, 80–99%; (b) NaO*t*Bu, DMF, 2 h, rt, 80–99%; (c) TfOH, DCE, 80–99%; (d) R^2CHO, DCE, cat AcOH, 30 min, rt, then $NaBH(OAc)_3$, 18 h, 55 °C, 80–99%; (e) R^2Br, DIPEA, MeCN, 30 min, 150 °C, μw, 80–99%; (f) $MeONH_2$·HCl, Py, 24 h, rt, 80–99%; (g) H_2, 60 psi, RaNi, NH_3–MeOH, 4 h, rt, 80–99%; (h) see Scheme 1.

Table 3
In vitro functional potencies of selected tetrahydroquinoline TRPV1 antagonists in human TRPV1 Ca^+ influx assay and their CYP3A4 inhibition



Compd	R^1	R^2	hTRPV1 IC_{50}[a] (nM)	CYP3A4 % inhibition[b]
11a	H	Methyl	215	65
11b	7-F	Methyl	34	66
11c	7-CF_3	Methyl	7	47
11d	8-*t*Bu	Methyl	6	
11e	7-*t*Bu	Methyl	115	
11f	6-*t*Bu	Methyl	853	
11g	6-OMe	Methyl	1380	59
11h	H	Benzyl	70	94
11i	6-F	Benzyl	66	
11j	6-*t*Bu	Benzyl	121	
11k	6-OMe	Benzyl	160	97
11l	6-OMe	Cyclohexylmethyl	196	93
11m	8-Cl	3-Methylbutyl	11	

[a] All values are means ± SEM of at least three separate experiments.
[b] At 10 μM.

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