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Synthesis of Oxazolo[4,5-*c*]quinoline TRPV1 Antagonists

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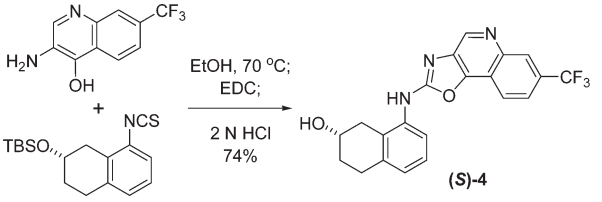

An efficient synthesis of 2-amino-oxazolo[4,5-*c*]quinoline TRPV1 antagonists is described via a thiourea formation/carbodiimide cyclization sequence. Synthetic route optimization eliminates intermediate isolations and facilitates the rapid preparation of a series of novel pentacyclic TRPV1 antagonists. From this series, compound (***S***)**-4** was identified as a potent and selective ligand for the TRPV1 ion channel.

Among the collection of ion channel targets believed to be involved in pain transmission, the transient receptor potential vanilloid-1 (TRPV1) receptor has been the subject of an outstanding quantity of pain-related research since its discovery.[1] A polymodal receptor, noxious stimuli (acid and heat), endogenous ligands involved in pain (e.g., anandamide, *N*-arachidonoyl-dopamine),[2] and pain-producing exogenous agonists (e.g., capsaicin from chili peppers) all activate TRPV1. In preclinical models of inflammatory and neuropathic pain, TRPV1 antagonists have shown promising analgesic efficacy; however, clinical proof-of-concept remains a challenge for the field.[3]

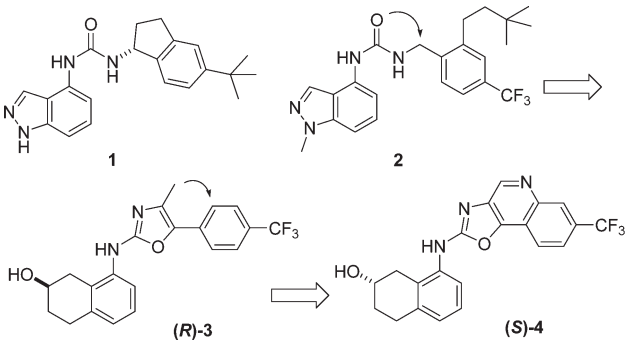

FIGURE 1. Abbott TRPV1 clinical candidates; structural modifications of TRPV1 antagonists.

Our TRPV1 antagonist medicinal chemistry efforts have resulted in the identification of clinical candidates ABT-102 (**1**)[4] and ABT-116 (**2**)[5] (Figure 1), both indazole ureas. In the course of our efforts to identify a structurally distinct TRPV1 antagonist with good brain penetration and pharmacokinetic properties as a backup compound, the 2-amino-oxazole urea isostere was investigated, leading to the discovery of oxazole (***R***)**-3**.[6] Herein, we describe the synthesis of compounds with an additional ring fusion tolerated by the TRPV1 receptor, represented by oxazolo[4,5-*c*]quinoline (***S***)**-4**.

At the outset of this work, no known examples of 2-amino-oxazolo[4,5-*c*]quinoline preparation had appeared,[7] although there were several reports of biologically active compounds with various five- and six-membered ring heterocycles fused to quinoline.[8] A route via cyclodesulfurization of thioureas was well precedented for the preparation of benzoxazoles.[9] We anticipated the application of this strategy to the synthesis of oxazoloquinolines **5**, which would require thioureas **6** as precursors (Figure 2). Initially, it was unknown which enantiomer of **5** would be preferred for TRPV1 activity, so both

(1) For recent reviews, see: (a) Szallasi, A.; Cortright, D. N.; Blum, C. A.; Eid, S. R. *Nat. Rev. Drug Discovery* **2007**, *6*, 357–372. (b) Broad, L. M.; Keding, S. J.; Blanco, M. J. *Curr. Top. Med. Chem.* **2008**, *8*, 1431–1441. (c) *Vanilloid Receptor TRPV1 in Drug Discovery: Targeting Pain and Other Pathological Disorders*; Gomtsyan, A., Faltynek, C. R., Eds.; John Wiley & Sons, Inc.: Hoboken, NJ, 2010.

(2) Starowicz, K.; Nigam, S.; DiMarzo, V. *Pharmacol. Ther.* **2007**, *114*, 13–33.

(3) For a clinical development review, see: Gunthorpe, M. J.; Chizh, B. A. *Drug Discovery Today* **2009**, *14*, 56–67.

(4) Gomtsyan, A.; Bayburt, E. K.; Schmidt, R. G.; Surowy, C. S.; Honore, P.; Marsh, K. C.; Hannick, S. M.; McDonald, H. A.; Wetter, J. M.; Sullivan, J. P.; Jarvis, M. F.; Faltynek, C. R.; Lee, C.-H. *J. Med. Chem.* **2008**, *51*, 392–395.

(5) Brown, B. S.; Keddy, R.; Perner, R. J.; DiDomenico, S.; Koenig, J. R.; Jinkerson, T. K.; Hannick, S. M.; McDonald, H. A.; Bianchi, B. R.; Honore, P.; Puttfarcken, P. S.; Moreland, R. B.; Marsh, K. C.; Faltynek, C. R.; Lee, C.-H. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3291–3294.

(6) Perner, R. J.; Koenig, J. R.; DiDomenico, S.; Gomtsyan, A.; Schmidt, R. G.; Lee, C.-H.; Hsu, M. C.; McDonald, H. A.; Gauvin, D. M.; Joshi, S.; Turner, T. M.; Reilly, R. M.; Kym, P. R.; Kort, M. E. *Bioorg. Med. Chem.* **2010**, *18*, 4821–4829.

(7) During the preparation of this manuscript, an example of 4-aryl-2-amino-oxazolo[4,5-*c*]quinolines as antibacterial and antituberculosis compounds appeared: Eswaran, S.; Adhikari, A. V.; Kumar, R. A. *Eur. J. Med. Chem.* **2010**, *45*, 957–966.

(8) For example, see: (a) Colotta, V.; Capelli, F.; Lenzi, O.; Catarzi, D.; Varano, F.; Poli, D.; Vincenzi, F.; Varani, K.; Borea, P. A.; Ben, D. D.; Volpini, R.; Cristalli, G.; Filacchioni, G. *Bioorg. Med. Chem.* **2009**, *17*, 401–410. (b) Gerster, J. F.; Lindstrom, K. J.; Miller, R. L.; Tomai, M. A.; Birmachu, W.; Bomersine, S. N.; Gibson, S. J.; Imbertson, L. M.; Jacobsen, J. R.; Knafla, R. T.; Maye, P. V.; Nikolaides, N.; Oneyemi, F. Y.; Parkhurst, G. J.; Pecore, S. E.; Reiter, M. J.; Scribner, L. S.; Testerman, T. L.; Thompson, N. J.; Wagner, T. L.; Weeks, C. E.; Andre, J. D.; Lagain, D.; Bastard, Y.; Lupu, M. *J. Med. Chem.* **2005**, *48*, 3481–3491. (c) Dinakaran, M.; Senthilkumar, P.; Yogeeswari, P.; China, A.; Nagaraja, V.; Sriram, D. *Bioorg. Med. Chem.* **2008**, *16*, 3408–3418. (d) Marco, A.; Loza-Mejía; Olvera-Vázquez, S.; Maldonado-Hernández, K.; Salgado, T. G.; González-Sánchez, I.; Rodríguez-Hernández, F.; Solano, J. D.; Rodríguez-Sotres, R.; Rocha, A. L. *Bioorg. Med. Chem.* **2009**, *17*, 3266–3277. (e) Izumi, T.; Sakaguchi, J.; Takeshita, M.; Tawara, H.; Kato, K.; Dose, H.; Tsujino, T.; Watanabe, Y.; Kato, H. *Bioorg. Med. Chem.* **2003**, *11*, 2541–2550.

(9) For example, see: Tian, Z.; Plata, D. J.; Wittenberger, S. J.; Bhatia, A. V. *Tetrahedron Lett.* **2005**, *46*, 8341–8343. and references cited therein.

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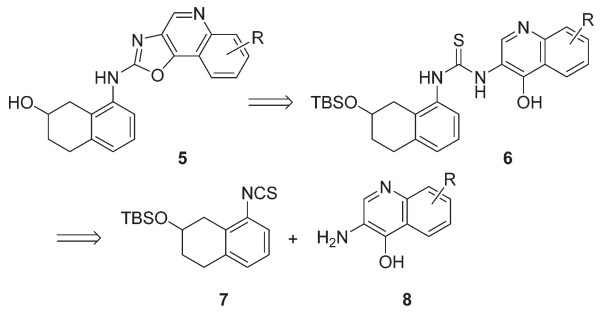
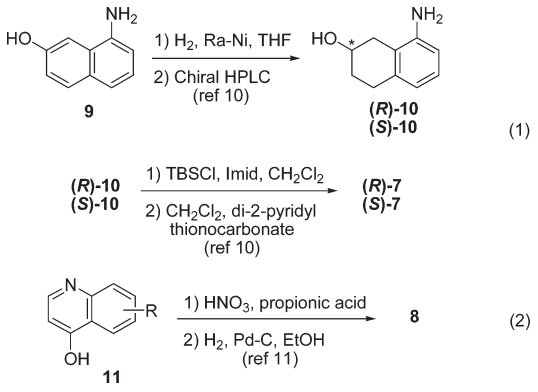


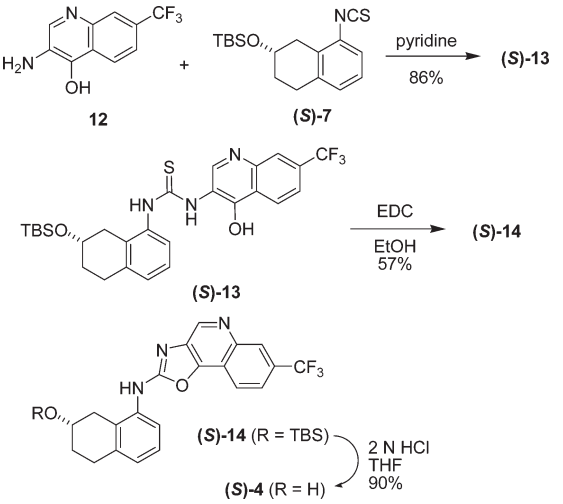
FIGURE 2. Retrosynthetic analysis of oxazoloquinoline TRPV1 antagonists **5**.

antipodes were targeted. The route in Figure 2 was particularly attractive since chiral isothiocyanates (***R***)-**7** and (***S***)-**7** were readily available in four steps (including a chiral HPLC separation) from 1-amino-7-hydroxynapthalene (eq 1),[10] and 3-amino-4-hydroxyquinolines **8** were either commercially available or prepared via nitration of 4-hydroxyquinolines **11** followed by hydrogenation (eq 2).[11]

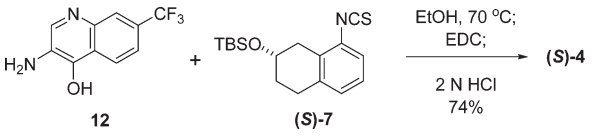


Starting from 7-trifluoromethylquinoline derivative **12**,[11] reaction with isothiocyanate (***S***)-**7** in pyridine gave thiourea (***S***)-**13** (Scheme 1). Initially, a stoichiometric mercury(II) oxide cyclodesulfurization was used to convert (***S***)-**13** to oxazoloquinoline (***S***)-**14**. However, low yields and the use of an undesirable mercury reagent motivated efforts to find alternative conditions. Oxidative cyclodesulfurization conditions (LiOH, H_2O_2) were reported to work well for benzoxazole preparation.[9] For quinoline substrates, these conditions led to conversion of the thiourea to urea after prolonged heating. This was presumably due to the lower nucleophilicity of the 4-hydroxyquinoline oxygen atom. Cyclization with EDC in EtOH proceeded readily,[12] providing oxazoloquinoline (***S***)-**14** in 57% yield. A final TBS group removal

SCHEME 1. Stepwise Preparation of Oxazoloquinoline (*S*)-4



SCHEME 2. One-Pot Preparation of Oxazoloquinoline (*S*)-4



was accomplished with 2 N HCl in THF, giving the desired oxazoloquinoline (***S***)-**4**. Preparation of (***R***)-**4** from (***R***)-**7** by the same three-step route demonstrated that the (*S*) stereochemistry was preferred for affinity to the TRPV1 receptor;[13] thus, the (*S*)-hydroxytetralin stereochemistry was maintained for all additional oxazoloquinolines.

Since the EDC cyclization was carried out in EtOH, a one-pot synthesis was anticipated if the thiourea formation and deprotection could be carried out in the same solvent (Scheme 2). Therefore, 3-amino-4-hydroxyquinoline **12** and isothiocyanate (***S***)-**7** were heated at 70 °C in EtOH. After completion of thiourea formation, EDC was added, and the cyclodesulfurization occurred rapidly (10 min) at the same temperature. An aqueous 2 N HCl solution was then added, and TBS deprotection to oxazoloquinoline (***S***)-**4** was complete in 15 min. The resulting yellow slurry was cooled to room temperature and filtered, giving pure oxazoloquinoline (***S***)-**4** as an HCl salt monohydrate in 74% yield.[14] Recrystallization of (***S***)-**4** from MeOH gave X-ray quality methanol solvate crystals, allowing confirmation of the structure via X-ray crystallography.

With an efficient method in hand to prepare oxazoloquinoline TRPV1 antagonists, the scope of the reaction with respect to quinoline substitution was explored (Table 1). In all cases, 3-amino-4-hydroxyquinolines **15**−**20** were converted to oxazoloquinolines **21**−**26** in good yield (61−79%) using the general procedure in Scheme 2. Unsubstituted (entry 1), halogen-substituted (entries 2−4), and trifluoromethyl-substituted (entries 5−6) substrates were all tolerated, providing efficient access to 6-, 7-, and 8-substituted oxazoloquinolines. No intermediate purification or chromatography was required,

(10) For the preparation of (***R***)-**7** and (***S***)-**7**, see ref 6 and: Gomtsyan, A. R.; Voight, E. A.; Bayburt, E. K.; Chen, J.; Daanen, J. F.; Didomenico, S. J.; Kort, M. E.; Kym, P. R.; McDonald, H. A.; Perner, R. J.; Schmidt, R. G. PCT Int. Appl. WO/2010/045402, 2010.

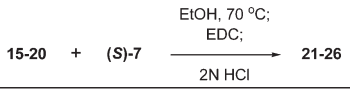
(11) For the preparation of 7-trifluoromethylquinoline **12**, see: Gerster, J. F.; Lindstrom, K. J.; Marszalek, G. J.; Merrill, B. A.; Mickelson, J. W.; Rice, M. J. PCT Int. Appl. WO/2000/006577, 2000. Other 3-amino-4-hydroxyquinolines which were not commercially available were prepared analogously.

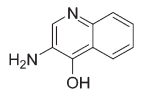
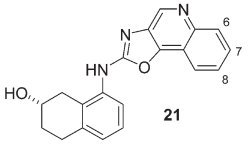
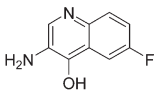
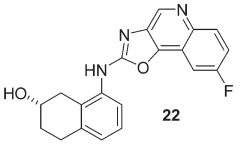
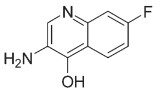
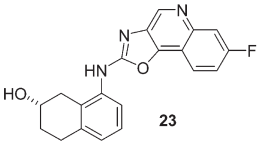
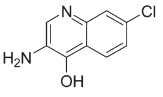
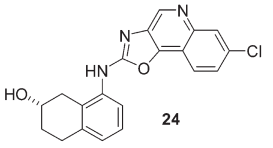
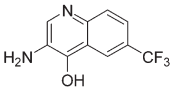
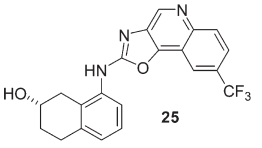
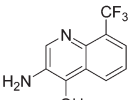
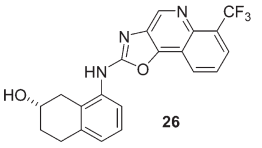
(12) These conditions have been employed for 2-aminobenzoxazole preparation: Smith, R.; Campbell, A.-M.; Coish, P.; Dai, M.; Jenkins, S.; Lowe, D.; O'Connor, S.; Su, N.; Wang, G.; Zhang, M.; Zhu, L. U.S. Pat. Appl. Publ. U.S. 2004/224997, 2004. The EDC HCl salt worked for this transformation, but the reaction was sluggish (2−3 days).

(13) For in vitro assay conditions, see ref 6.

(14) With the exception of compound **26**, elemental analyses of final products were consistent with HCl salts containing 0.4−1.3 equiv water. Yields were calculated assuming HCl salt monohydrates (except for compound **26**).

TABLE 1. Scope of One-Pot Oxazoloquinoline Synthesis



entry	Substrate	Product	Yield (%)[a]
1	 **15**	 **21**	79
2	 **16**	 **22**	76
3	 **17**	 **23**	78
4	 **18**	 **24**	61
5	 **19**	 **25**	77
6	 **20**	 **26**	68[b]

[a]Isolated yields of HCl salt monohydrates. [b]Isolated yield of free base oxazoloquinoline.

since filtration of HCl salt monohydrate products provided the target compounds with sufficient purity.[14]

In conclusion, a three-step, one-pot synthesis of pentacyclic (*S*)-hydroxytetralin oxazolo[4,5-*c*]quinolines was developed to facilitate structure−activity relationship studies in this new series of TRPV1 antagonists. Compound (***S*)-4** was identified as a potent and selective TRPV1 antagonist, with hTRPV1 IC_{50} = 5 nM and > 100-fold selectivity versus other TRP channels.[13] The unique structure of this compound among other TRPV1 ligands in the literature expands understanding of this important pain target at a structural level and may provide new directions for future studies.

Experimental Section

(*S*)-8-(7-(Trifluoromethyl)Oxazolo[4,5-c]quinolin-2-ylamino)-1,2,3,4-tetrahydronaphthalen-2-ol Hydrochloride Hydrate [(*S*)-4]. Typical Procedure for One-Pot Oxazoloquionline Preparation. A slurry of (***S*)-7** (560 mg, 1.75 mmol), EtOH (4 mL), and **12** (400 mg, 1.75 mmol) was heated to 70 °C. After 90 min, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (0.369 mL, 2.10 mmol) was added dropwise. After 20 min, 2 N HCl (4 mL) was added dropwise, keeping the internal temperature > 60 °C. After 15 min, the yellow slurry was cooled slowly to room temperature and filtered, washing with 1:1 EtOH/water (4 mL). The solid was dried in a vacuum oven at 50 °C, giving (***S*)-4** HCl salt monohydrate (587 mg, 1.29 mmol, 74%) as a light-yellow solid. Mp = 238−240 °C; $[\alpha]^{D}_{20}$ = −0.9 (*c* = 0.76, MeOH); IR (cm^{-1}): 3387, 3042, 2947, 2441, 2007, 1645, 1585, 1313, 1133, 1072. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.46−10.72 (br s, 1H), 9.47 (s, 1H), 8.70−8.71 (br s, 1H), 8.39 (d, *J* = 8.7 Hz, 1H), 8.10 (dd, *J* = 8.7, 1.7 Hz, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.25 (t, *J* = 7.7 Hz, 1H), 7.07 (d, *J* = 7.6 Hz, 1H), 3.96−4.03 (m, 1H), 3.07 (dd, *J* = 16.8, 4.9 Hz, 1H), 2.97 (dt, *J* = 16.7, 5.5 Hz, 1H), 2.74−2.90 (m, 1H), 2.64 (dd, *J* = 16.9, 7.6 Hz, 1H), 1.91−1.98 (m, 1H), 1.64−1.84 (m, 1H); ^{13}C NMR (101 MHz, DMSO) δ 161.8, 150.0, 140.5, 139.0, 138.7, 137.4, 135.5, 129.6, 128.6, 126.1, 125.8, 123.8, 123.74, 123.68, 121.9, 121.6, 116.4, 65.0, 33.8, 30.8, 26.9; HRMS (ESI+) *m*/*e* calcd for $[M + H]^+$ $C_{21}H_{16}N_3O_2F_3$ 399.11946, found 399.11947. Anal. Calcd for $C_{21}H_{16}N_3O_2F_3 \cdot HCl \cdot 1.3H_2O$: C, 54.92; H, 4.30; N, 9.15. Found: C, 54.85; H, 4.48; N, 9.21.

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Supporting Information Available: Experimental details, copies of ^{1}H and ^{13}C NMR spectra, and X-ray data for compound (***S*)-4**. This material is available free of charge via the Internet at http://pubs.acs.org.