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# Pyrrolinone derivatives as a new class of P2X3 receptor antagonists. Part 3: Structure-activity relationships of pyrropyrazolone derivatives

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ABSTRACT

The P2X3 receptor is an attractive target for the treatment of pain and chronic coughing, and thus P2X3 antagonists have been developed as new therapeutic drugs. We previously reported selective P2X3 receptor antagonists by derivatization of hit compound **1**. As a result, we identified hit compound **3**, the structure of which was similar to hit compound **1**. On the basis of SAR studies of hit compound **1**, we modified hit compound **3** and compound **42** was identified as having analgesic efficacy by oral administration.

Adenosine triphosphate (ATP) is created from high-energy phosphate bonds and consumed as a source of energy by all animals and plants. Intracellular ATP is involved various processes including the synthesis of biomolecules as well as the active transport of chemical substances and bioluminescence. Extracellular ATP acts as a neurotransmitter by binding to purinergic P2 receptors. Two types of P2 receptors are known, P2X is a ligand-gated ion channel and P2Y is a G protein-coupled receptor. P2X receptors are classified into seven subtypes, from P2X1 to P2X7, and each subtype constitutes a homotrimer or heterotrimer[1]. P2X receptors are widely expressed in living organisms and are known to be involved in a variety of physiological phenomena, including neurotransmission[2], muscle contraction[3], pain[4], taste[5], and inflammatory responses[6]. Therefore, P2X receptors are regarded as promising targets for novel therapeutic drugs targeted toward neurological, cardiovascular and inflammatory diseases. P2X3 receptors are primarily expressed in the peripheral sensory nerves and are involved in neurotransmission for pain[7,8]. Therefore, many reported P2X3 receptor antagonists may have applications as analgesics. Among them, gefapixant showed improvement of interstitial cystitis/bladder pain syndrome (IC/BPS) in a Phase 2 clinical trial. Gefapixant also showed improvement of refractory chronic cough in a Phase 3 clinical trial. Therefore, P2X3 receptor antagonists have the potential to be useful for the treatment of various diseases[9].

We previously reported that the exploration of hit compound **1** led to the discovery of compound **2** as an orally available selective P2X3 antagonist[10]. The hit compound **3**, a pyrrolopyrazolone derivative, was also identified but its activity was less potent than hit compound **1**. Because of the high structural similarity between **1** and **3**, a SAR study was undertaken starting from hit compound **3** and with reference to the historical results from the hit to lead SAR studies of hit compound **1**. Additionally, a docking study using a constructed P2X3 homology model was applied to SAR studies of the pyrrolopyrazolone derivatives. In this paper, we report the discovery of an orally available compound from structure activity studies of pyrrolopyrazolone derivatives in conjunction with docking studies (see Fig. 1).

Pyrrolopyrazolone derivatives were synthesized according to a previously reported method (Scheme 1). Condensation of three components under acidic conditions gave pyrrolinone intermediates, which were cyclized with hydrazine hydrate to give the pyrropyrazolone derivatives[11]. *N*-Me compounds were also prepared by cyclization with

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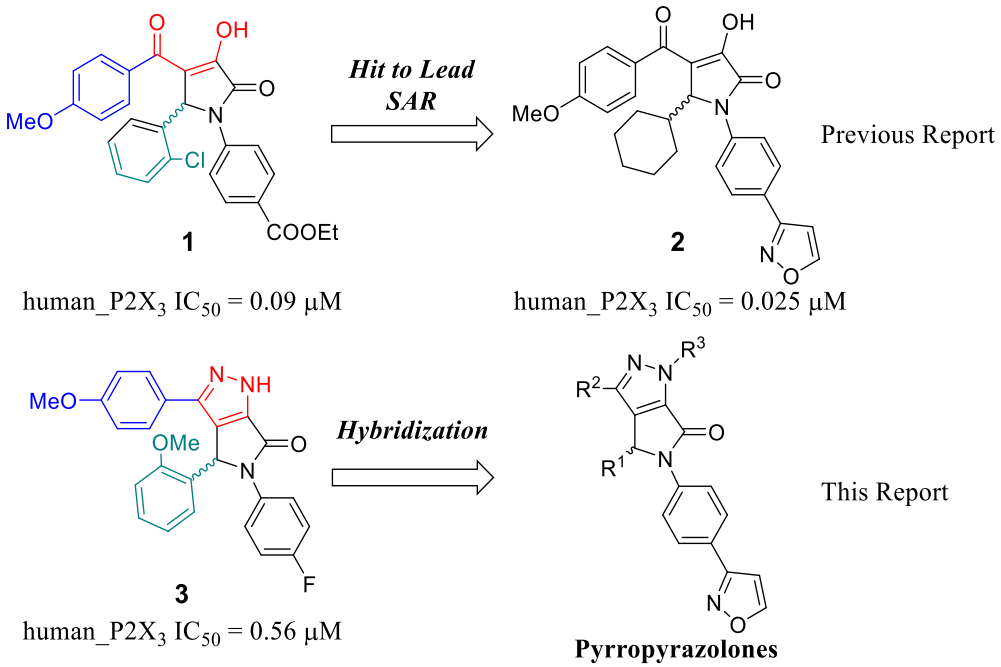
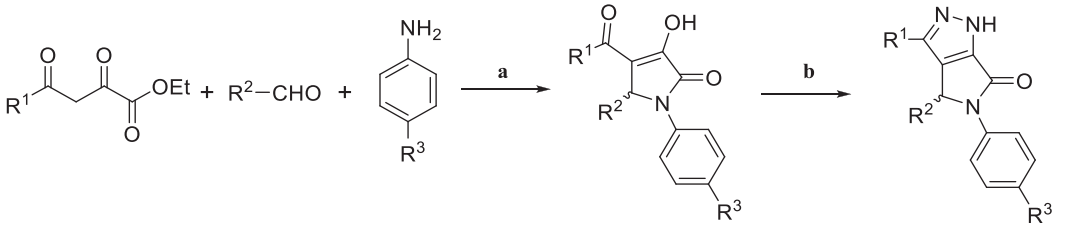
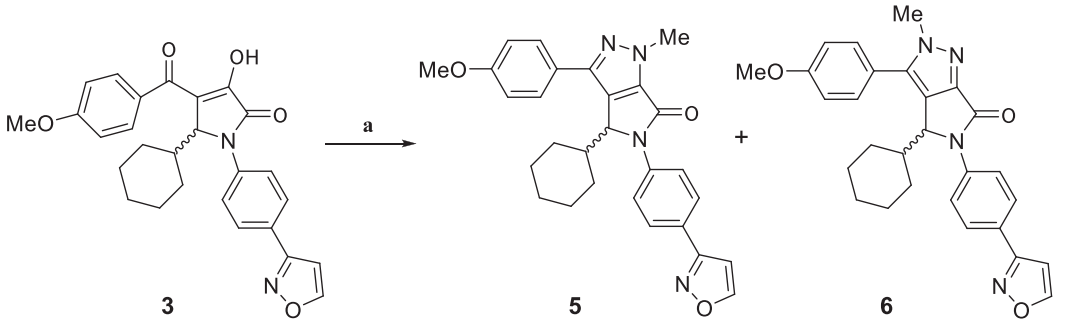



**Fig. 1.** The structural similarity of hit compounds **1** and **3**.



**Scheme 1.** Reagents and conditions for synthesis of the pyrrolopyrazolone skeletons: (a) AcOH, dioxane, and reflux; (b) hydrazine hydrate, AcOH, 95 °C.



**Scheme 2.** Reagents and conditions for synthesis of *N*-methylated pyrrolopyrazolone: (a) methylhydrazine, AcOH, 95 °C, **5** (44%), **6** (11%).

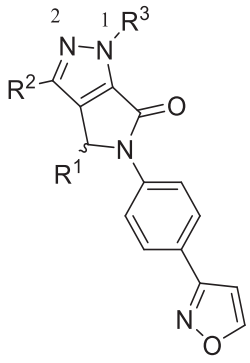
methylhydrazine to give **5** as a major product and **6** as a minor product (Scheme 2)[12].

Table 1 shows the effects of substitutions at various positions around the pyrropyrazolone ring structure on the antagonistic activity. Compound **4** showed higher potency than hit compound **1**. However, the potency of **4** decreased compared with pyrrolinone derivatives **1** and **3**. The *N*-methylated compounds (**5**, **6**) showed large decreases in potencies, which may indicate that the proton of the pyrazole ring plays an important role in the antagonistic activity.

To reduce the number of ring structures, a 4-methoxyphenyl moiety at position-3 on the pyrrolopyrazolone was converted into a *tert*-butyl group and the effects of substituents at $R^1$ were investigated. The 2-methoxyphenyl derivative (**9**) showed a large increase in activity, while the cyclohexyl version (**8**) showed a decrease in activity. Compounds with other substituents at $R^1$, including non-substituted (**10**), 3-methoxy (**11**) and 4-methoxy (**12**), all showed reductions in activity. Also, the chlorine substituted compounds (**13–15**) showed reductions in activity. As a result of further exploration of the 2-substituted phenyl compounds at $R^1$, the ethoxy derivative (**17**) maintained similar activity as compound **4**, and the dimethylamino derivative (**18**) showed slightly less activity. Introduction of a methoxy substituent to compound **9** at position-3 or position-6 on the phenyl ring (**19**, **20**) decreased the activity. These results suggest that electron donating groups in the ortho position of the phenyl ring are important for high antagonistic activity.

We explored the effects of varying the $R^2$ substituent at position-3 of the pyrrolopyrazolone derivatives (**21–26**). The *n*-butyl derivative (**22**) showed almost the same activity as the *tert*-butyl derivative (**9**), but the other smaller substituents (**23**: *i*-Pr, **24**: Me) or larger substituents (**21**:

**Table 1**
Initial structure activity relationship studies of the pyrrolopyrazolone derivatives.



| Compound | $R^1$ | $R^2$ | $R^3$ | $IC_{50}$ (μM) |
|---|---|---|---|---|
| **4** | *c*-Hexyl | 4-MeO-Ph | H | 0.211 |
| **5** | *c*-Hexyl | 4-MeO-Ph | 1-Me | 1.56 |
| **6** | *c*-Hexyl | 4-MeO-Ph | 2-Me | > 10 |
| **7** | 2-MeO-Ph | 4-MeO-Ph | H | 0.376 |
| **8** | *c*-Hexyl | *t*-Bu | H | 0.916 |
| **9** | 2-MeO-Ph | *t*-Bu | H | 0.025 |
| **10** | Ph | *t*-Bu | H | 0.304 |
| **11** | 3-MeO-Ph | *t*-Bu | H | 0.69 |
| **12** | 4-MeO-Ph | *t*-Bu | H | 1.59 |
| **13** | 2-Cl-Ph | *t*-Bu | H | 0.466 |
| **14** | 3-Cl-Ph | *t*-Bu | H | 1.68 |
| **15** | 4-Cl-Ph | *t*-Bu | H | 0.633 |
| **16** | 2-Et-Ph | *t*-Bu | H | 0.226 |
| **17** | 2-EtO-Ph | *t*-Bu | H | 0.27 |
| **18** | 2-$Me_2$N-Ph | *t*-Bu | H | 0.137 |
| **19** | 2,3-$(MeO)_2$-Ph | *t*-Bu | H | 1.69 |
| **20** | 2,6-$(MeO)_2$-Ph | *t*-Bu | H | 0.538 |
| **21** | 2-MeO-Ph | *t*-$BuCH_2$ | H | 0.105 |
| **22** | 2-MeO-Ph | *n*-Bu | H | 0.021 |
| **23** | 2-MeO-Ph | *i*-Pr | H | 0.112 |
| **24** | 2-MeO-Ph | Me | H | 1.633 |
| **25** | 2-MeO-Ph | 2-Furanyl | H | 0.36 |
| **26** | 2-MeO-Ph | 3-Pyridyl | H | 0.665 |

neopentyl, **25**: 2-furanyl, **26**: 3-pyridyl) tended to decrease the activity. These results showed that substitution with an appropriate size group at $R^2$ was necessary for good activity.

Table 2 shows the effects of substituents at $R^4$ on the pyrropyrazolone ring structure on antagonistic activity. We explored the isoxazole moiety by fixing a *tert*-butyl group at position-3 and 2-methoxyphenyl at position-4 of the pyrrolopyrazolone ring (**27**–**37**). The ethoxycarbonyl derivative (**28**) showed good activity, but the fluoro (**27**) and amide (**28**, **29**) derivatives showed decreased activity. In case of the other 5-menbered hetero aromatic compounds, almost all compounds showed good activity ($IC_{50}$ < 0.1 μM) except for the 1,3,4-oxadiazole derivative (**35**). In particular, the 1,2,4-oxazole-3-yl (**33**), thiazole-2-yl (**36**) and thiophene-3-yl (**37**) derivatives showed high activity, which was a similar pattern those observed for previously reported SAR studies of pyrrolinone derivatives[10]. The solubility at pH 6.8 of compound **9** was poor, but these compounds showed good PK profiles in rat pharmacokinetics.

**Al**though the isoxazole compound **9** showed weak inhibition of cytochrome P450 2C9, it was selected for further evaluation (Table 3). We tested compound **9** for its analgesic effects against hyperalgesia in a partial sciatic nerve ligation model for neuropathic pain in rats[13,14]. Compound **9** showed analgesic effects by oral administration of a 100 mg/kg/dose in rats, and its efficacy was almost the same as a clinical dose of pregabalin (10 mg/kg/dose: 30% reversal). To further understand its efficacy *in vivo*, the pharmacokinetics of compound **9** was tested in rats by oral administration at a 100 mg/kg/dose. The plasma concentration of compound **9** was lower than the estimated concentration from a low dose test, thus, its oral bioavailability was greatly decreased. This suggested that the low oral bioavailability of compound **9** was caused by its low solubility at pH 6.8. Therefore, the introduction of hydrophilic substituents on the pyrrolopyrazolone ring structure was needed to improve the solubility.

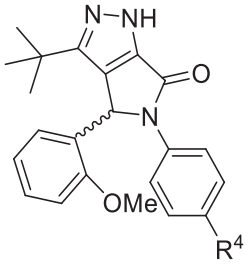
Before the introduction of a hydrophilic substituent to the pyrrolopyrazolone derivatives, we speculated which positions were amenable to substitution by using a P2X3 homology model. We previously reported the SAR studies of pyrrolinone derivatives examined by a docking study with a P2X3 homology model that was constructed as a template for the zebrafish P2X4 receptor[15]. We also studied the SAR of pyrrolopyrazolone derivatives using a docking study based on the same P2X3 homology model[16]. As a result, the docking study using the P2X3 homology model agreed well with the SAR of the pyrrolopyrazolone derivatives as well as the pyrrolinone derivatives. In this study, solvent accessible regions were observed around the ortho methoxy substituent on the phenyl ring at position-4 and the *tert*-butyl at position-3 (Fig. 2). Therefore, we decided to introduce hydrophilic substituents at position-4 and position-3.

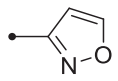
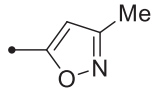
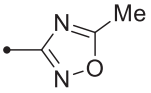
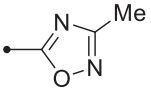
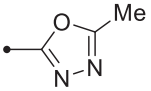
Table 4 shows the optimization of compound **9**. To improve its solubility and PK profiles, hydrophilic substituents were introduced at $R^2$ and $R^5$ (**38**–**43**). The conversion of the hydrophilic $R^5$ group was carried out while $R^2$ was fixed as a *tert*-butyl group. The resulting compounds showed good activity (**38**–**40**). In particular, compounds **39** and **40** showed great improvements in their solubilities and inhibition of cytochrome P450. However, these compounds were excreted rapidly, resulting in low oral bioavailability in rat. The conversion of the hydrophilic $R^2$ from a *tert*-butyl moiety was also carried out (**41**–**43**). Compound **42**, synthesized by introducing a hydroxyl group into the *tert*-butyl moiety, maintained high activity and had improved solubility. Additionally, compound **42** had a similar PK profile as compound **9**, and improved inhibition of cytochrome P450 2C9. Unlike compound **42**, the hydroxyethyl (**41**) and diol derivatives (**43**) showed decreased activities. It was speculated that the activity decrease observed for **41** was caused by reducing the bulkiness at $R^2$ and the activity decrease observed for **43** resulted from substituting a more hydrophilic moiety at the $R^2$ site. The introduction of hydrophilic groups at the $R^2$ site did not decrease the activity and agreed well with the prediction from the docking study of the homology model.

From the above SAR investigation, compound **42** was selected for further evaluation (Table 5). The oral bioavailability of **42** was not decreased by oral administration of a 30 mg/kg/dose, and the plasma concentration of **42** was sufficient to test its efficacy *in vivo*. The results suggested that the improvement of solubility of compound **42** led to a good PK profile in rats. Compound **42** showed higher analgesic effects by oral administration of a 30 mg/kg/dose than those observed for the 100 mg/kg/dose of compound **9**. It should be noted that the analgesic effect of compound **42** at 30/mg/kg/dose was higher than that of the clinical dose of pregabalin.

To confirm the predictions from the docking study using the homology model, both the enantiomers of compound **42** were synthesized (Scheme 3)[17]. The β-hydroxyester (**44**) as the starting material was protected by THP and reacted with methyl magnesium bromide in the presence of triethylamine to give the ketone (**45**). The ketone compound was reacted with diethyl oxalate under basic conditions to give the α, γ-ketoester (**46**). The condensation of three components shown in Scheme 1 gave the pyrrolinone (**47**). The Mitsunobu reaction with (*S*)-methyl mandelate led to the ether (**48**), and then deprotection of THP under acidic conditions gave a separable mixture of the diastereomers (**49**). After separation of the each diastereomer, removal of (*S*)-methyl mandelate with hydrogenation and cyclization with hydrazine hydrate gave both enantiomers, (*S*)-**42** and (*R*)-**42**. The absolute stereochemistry was determined by X-ray crystal structure analysis

**Table 2**
Structure activity relationship studies on substituents at $R^4$.




| Compound | $R^4$ | $IC_{50}$ (μM) | Solubility [a] (μM) | CYP $IC_{50}$ (μM) 1A2 | 2C9 | 3A4 | CLt [b] (ml/min/kg) | $t_{1/2}$ [b] (hr) | BA [b] (%) |
|---|---|---|---|---|---|---|---|---|---|
| **9** |  | 0.025 | ND | > 20 | 10 | > 20 | 16.6 | 2.1 | 33.8 |
| **27** | F | 9.3 | 20.4 | > 20 | 7 | 18 | NT | NT | NT |
| **28** | COOEt | 0.017 | 0.2 | > 20 | 4 | 5 | NT | NT | NT |
| **29** | CONHMe | 1.336 | 3.5 | NT | | | NT | NT | NT |
| **30** | $CONMe_2$ | 1.26 | > 50 | > 20 | > 20 | > 20 | NT | NT | NT |
| **31** |  | 0.072 | ND | > 20 | 1 | 2 | NT | NT | NT |
| **32** |  | 0.087 | 0.9 | > 20 | 4 | 8 | 16.9 | 1.9 | 20 |
| **33** |  | 0.026 | ND | > 20 | 1 | 13 | 3.79 | 8.2 | 20.8 |
| **34** |  | 0.095 | ND | > 20 | 2 | 2 | NT | NT | NT |
| **35** |  | 0.417 | 2.6 | > 20 | 5 | 8 | NT | NT | NT |
| **36** |  | 0.025 | ND | 10 | 2 | 13 | 19.3 | 2.2 | 26.5 |
| **37** |  | 0.017 | ND | > 20 | 6 | 10 | 15.4 | 3.1 | 36.8 |

CLt: total clearance; BA: oral bioavailability; fu: fraction unbound in rat serum; ND: not detected; NT: not tested.
a. Solubilities were measured in sodium phosphate buffer (pH 6.8, 10 mmol) containing 1% DMSO.
b. All compounds were administered at 0.5 mg/kg iv and 1.0 mg/kg po.
Compounds were administered as a mixture of three to five compounds.

**Table 3**
Biological test results of selected compounds.

| Compound | Analgesic test[a] | | Rat pharmacokinetics | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | dose, po (mg/kg) | efficacy (% reversal) | dose, iv (mg/kg) | $t_{1/2}$ (hr) | CLt (ml/min/kg) | dose, po (mg/kg) | Cmax (ng/ml) | AUC (μg·hr/ml) | BA (%) |
| **9** | 100 | 30.5 | 10 | 3.2 | 12.6 | 100 | 450 | 6.48 | 4.9 |
| Pregabalin | 10 | 20–30 | | | | | | | |

a. Rat Seltzer model: Hyperalgesia (paw pressure test).

using similar compounds[15]. From the activity assessment, it was confirmed that (*S*)-**42** showed higher activity compared with (*R*)-**42**. The differences in potency between (*S*)-**42** and (*R*)-**42** agreed well with the predictions from the docking study.

In conclusion, the SAR studies of a hit compound containing a pyrrolopyrazolone skeleton identified from an in-house compound library led to the discovery of lead compound **9**. A human P2X3 homology model was constructed as a template for the zebrafish P2X4 receptor, and then a docking study of the pyrrolopyrazolone derivatives was carried out. The compounds predicted to bind to the receptor from the docking study using the P2X3 homology model agreed well with the experimental efficacy results of the compounds generated from the SAR study. After further compound optimization based on the above results, we discovered the selective P2X3 antagonist **42**, which showed a good

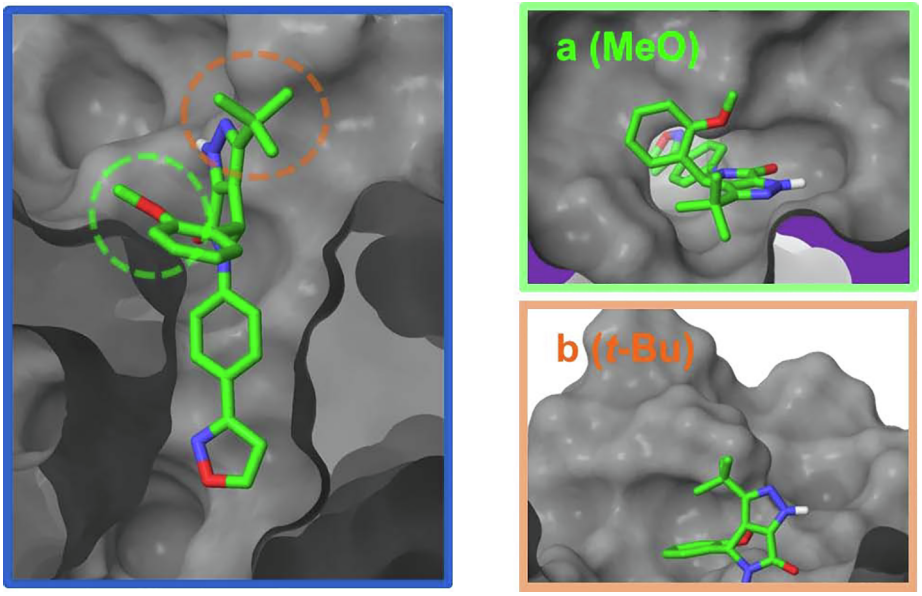
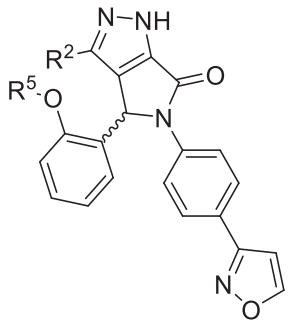



**Fig. 2.** Docking studies of two pyrrolopyrazolone derivatives.

**Table 4**
Optimization of compound **9**.

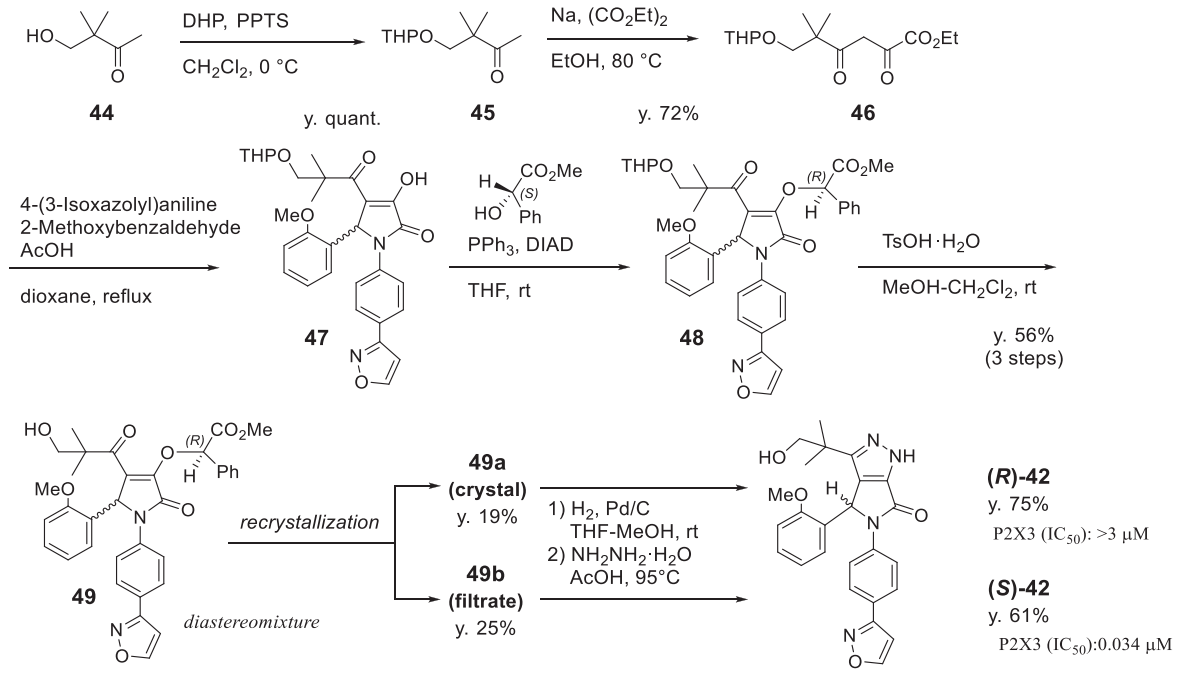


| Compound | $R^2$ | $R^4$ | $IC_{50}$ (μM) | Solubility [a] (μM) | CYP $IC_{50}$ (μM) 1A2 | 2C9 | 3A4 | CLt [b] (ml/min/kg) | $t_{1/2}$ [b] (hr) | BA [b] (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| **9** | *t*-Bu | Me | 0.025 | ND | > 20 | 10 | > 20 | 16.6 | 2.1 | 33.8 |
| **38** | *t*-Bu | $HO(CH_2)_2$ | 0.031 | 0.8 | > 20 | 11 | > 20 | 24.5 | 1.3 | NC |
| **39** | *t*-Bu | $MeSO_2(CH_2)_2$ | 0.101 | 40.5 | > 20 | > 20 | > 20 | 79.2 | 0.8 | NC |
| **40** | *t*-Bu | $HO(O)CCH_2$ | 0.09 | > 50 | > 20 | > 20 | > 20 | 94.9 | 0.1 | NC |
| **41** | $HO(CH_2)_2$ | Me | 0.66 | > 50 | > 20 | 15 | 16 | NT | NT | NT |
| **42** | $HOCH_2(CH_3)_2C$ | Me | 0.063 | > 50 | > 20 | 16 | > 20 | 18.6 | 1.5 | 27.2 |
| **43** | $(HOCH_2)_2(CH_3)C$ | Me | 0.304 | > 50 | > 20 | > 20 | > 20 | 33.7 | 1 | 1.7 |

**Table 5**
Characterization of compound **42**.

| Compound | Analgesic test[a] | | Rat pharmacokinetics | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | dose, po (mg/kg) | efficacy (% reversal) | dose, iv (mg/kg) | $t_{1/2}$ (hr) | CLt (ml/min/kg) | dose, po (mg/kg) | Cmax (ng/ml) | AUC (μg·hr/ml) | BA (%) |
| **9** | 100 | 30.5 | 10 | 3.2 | 12.6 | 100 | 450 | 6.48 | 4.9 |
| **42** | 30 | 41 | 10 | 1.8 | 14.9 | 30 | 1410 | 10.45 | 30.4 |
| Pregabalin | 10 | 20–30 | | | | | | | |

a. Rat Seltzer model: Hyperalgesia (paw pressure test).




**Scheme 3.** Reagents and conditions for the synthesis of (*S*)-**42**.

analgesic effect by oral administration because of its improved potency and PK profile.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bmcl.2020.127636.

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12. Experimental procedure for preparation of compound 5 and 6: To a suspension of compound 3 (92 mg, 2 mmol) in AcOH (2 mL), methylhydrazine (0.032 mL, 6 mmol) was added and the mixture was stirred at 95 °C for 2 h. The reaction mixture was quenched with water, and extracted with EtOAc. The organic layer was washed with H2O and brine, dried over MgSO4, and concentrated under reduced pressure. The residue was purified by washing with EtOAc/n-hexane to give 5 (41 mg, yield 44%) as a yellow solid and 6 (10 mg, yield 11%) as a yellow solid. Compound 5; 1H-NMR (CDCl3) δ: 0.44–1.01 (6H, m), 1.26–1.53 (4H, m), 1.70–1.79 (2H, m), 3.93 (7H, s), 5.22 (1H, d, J = 3.0 Hz), 6.70 (1H, d, J = 1.8 Hz), 7.06 (2H, dt, J = 9.3, 2.4 Hz), 7.36 (2H, dt, J = 9.2, 2.4 Hz), 7.67–7.70 (2H, m), 7.89–7.93 (2H, m), 8.48 (1H, t, J = 1.4 Hz).; MS-ESI (m/z) = 469 [M + H] + .; Compound 6; 1H-NMR (CDCl3) δ: 0.52–1.05 (4H, m), 1.23–1.55 (6H, m), 1.86 (1H, d, J = 11.9 Hz), 3.89 (3H, s), 4.14 (3H, s), 5.38 (1H, d, J = 2.9 Hz), 6.72 (1H, d, J = 1.7 Hz), 6.98–7.00 (2H, m), 7.63–7.66 (4H, m), 7.93–7.96 (2H, m), 8.50 (1H, d, J = 1.5 Hz).; MS-ESI (m/z) = 469 [M + H] + .
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16. Docking study was carried out using the program Glide (Schrödinger, LLC, New York, NY, USA).
17. See the supplementary data.