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Discovery of 1-oxa-4,9-diazaspiro[5.5]undecane-based trisubstituted urea derivatives as highly potent soluble epoxide hydrolase inhibitors and orally active drug candidates for treating of chronic kidney diseases

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ABSTRACT

We identified 1-oxa-4,9-diazaspiro[5.5]undecane-based trisubstituted ureas as highly potent soluble epoxide hydrolase (sEH) inhibitors and orally active agents for treating chronic kidney diseases. Compound **19** exhibited excellent sEH inhibitory activity and bioavailability. When administered orally at 30 mg/kg, **19** lowered serum creatinine in a rat model of anti-glomerular basement membrane glomerulonephritis but 2,8-diazaspiro[4.5]decane-based trisubstituted ureas did not. These results suggest that **19** is an orally active drug candidate for treating chronic kidney diseases.

Soluble epoxide hydrolase (sEH) is an enzyme that catalyzes the conversion of epoxyeicosatrienoic acids (EETs) into dihydroxy eicosatrienoic acids (DHETs) (Fig. 1),[1] and is mainly expressed in liver, kidney, and vascular tissue.[2] EETs, which are synthesized by CYP2J- and CYP2C-mediated epoxidation of arachidonic acid, are associated with physiologically beneficial effects such as vasodilatation, vasoprotection, and anti-inflammation.[3] Inhibition of sEH produces effects expected from an increase in EET level.[4]

According to a recent report,[5] sEH in proximal tubular cells is upregulated in chronic proteinuric kidney diseases. According to that study, 1-(1-methylsulfonyl-piperidin-4-yl)-3-(4-trifluoromethoxy-phenyl)-urea reduces long-term elevated serum creatinine level, interstitial inflammation, fibrosis, and α-smooth muscle actin expression in adriamycin-induced nephropathic mice. These findings suggest that sEH inhibitors have potential use in treating chronic proteinuric kidney diseases.

We previously reported that 2,8-diazaspiro[4.5]decane-based trisubstituted ureas are highly potent sEH inhibitors and orally active drug candidates for treating hypertension (Fig. 2, **1**).[6] Contrary to our expectation, oral administration of these derivatives failed to reduce serum creatinine in a rat model of anti-glomerular basement membrane (GBM) glomerulonephritis.[7] We found that 2,8-diazaspiro[4.5]decane-based trisubstituted ureas had high sEH inhibitory activity and oral availability. The solubility and

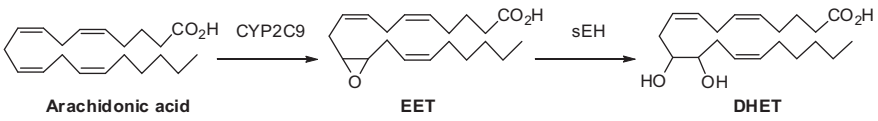

Figure 1. Role of sEH.

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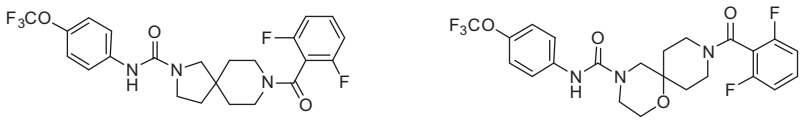


1 CLogP: 3.33 **2** CLogP: 2.84

Figure 2. Structure of **1** (previously reported) and **2** (newly designed).

microsomal stability of these compounds can be conveniently modified by changing the substituent on the amide group. On the basis of these findings, we hypothesized that spirocyclic diamine-based trisubstituted ureas could be developed as sEH inhibitors and we aimed to find other such ureas that inhibited sEH as strongly as 2,8-diazaspiro[4.5]decane-based trisubstituted ureas and had different pharmacokinetic profiles. Here we report that 1-oxa-4,9-diazaspiro[5.5]undecane-based trisubstituted ureas are highly potent sEH inhibitors and are available for oral administration in a rat model of anti-GBM glomerulonephritis.

The hydrolase catalytic pocket of sEH consists of Tyr381, Tyr465, and Asp333, which are responsible for its enzymatic activity. Amide or urea derivatives bind to the pocket via hydrogen bonds between the carbonyl oxygen of the amide or urea moiety and the hydroxyl group of Tyr381 or Tyr465, and between the NH of the amide or urea moiety and the carboxylate of Asp333.[8] We previously reported that **1** (Fig. 2) exhibits highly potent sEH inhibitory activity. A docking study of **1** with human sEH indicated that the oxygen atom of the compound's urea moiety binds to Tyr381 and Tyr465 in the hydrolase catalytic pocket of sEH (Fig. 3). We then designed 1-oxa-4,9-diazaspiro[5.5]undecane-based trisubstituted urea derivative **2**. Because of its introduced oxygen atom, **2** has lower *c*Log*P* than **1** and thus would have higher aqueous solubility (Fig. 2). A docking study of **2** with human sEH (Fig. 3) suggested that the two carbonyl oxygen atoms of **2** bind to the hydrolase catalytic pocket in the same manner as **1**. Under this hypothesis, we began to explore 1-oxa-4,9-diazaspiro[5.5]undecane-based trisubstituted urea derivatives.

The general procedure for the synthesis of 1-oxa-4,9-diazaspiro[5.5]undecane-based trisubstituted urea derivatives **2**, **19–40** and **8** is shown in Scheme 1. Starting material **3** was synthesized by a reported method.[9] Treatment of **3** with isocyanate afforded **4**. Removal of the benzyl protecting group by $Pd(OH)_2$-catalyzed hydrogenation provided **5**. Then, condensation with carboxylic acid or acyl chloride led to **2** and **19–40**. Treatment of **3** with benzoyl chloride afforded **6**. Removal of the benzyl protecting group by $Pd(OH)_2$-catalyzed hydrogenation provided **7**. Then, treatment with isocyanate led to **8**. The synthesis of 2,9-diazaspiro[5.5]undecane-based trisubstituted urea derivatives **15** and **18** is shown in Scheme 2. Oxidation of alcohol **9** with Dess–Martin periodinane afforded **10**. Michael addition to acrylonitrile provided **11**. Then, sequential reduction of nitrile group and cyclization via

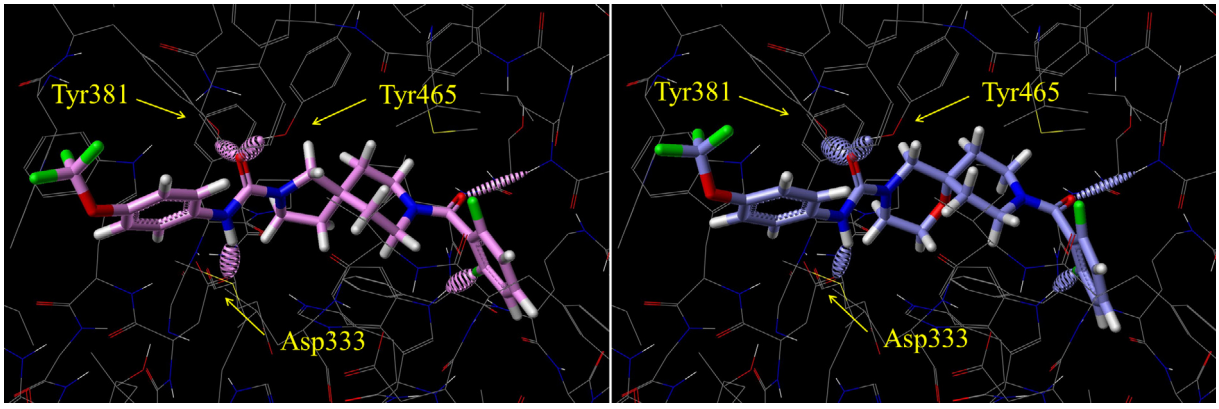
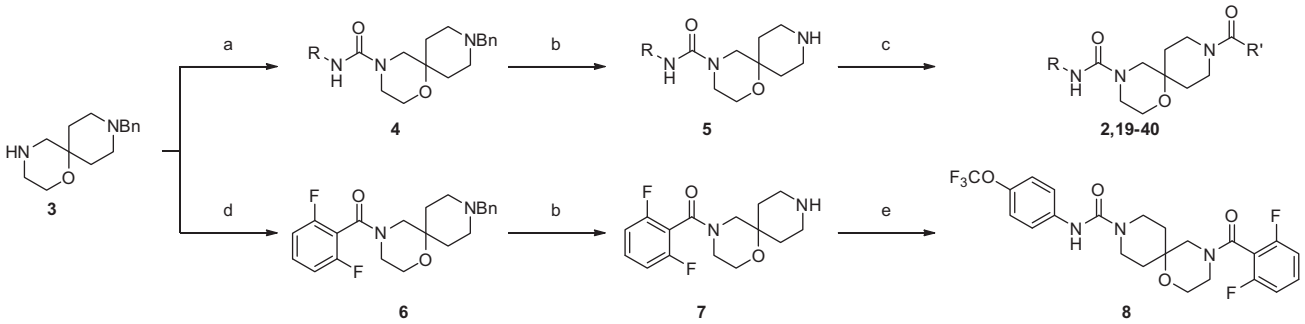


Figure 3. Docking studies of human sEH (PDB code: 1VJ5) with **1** (left) and **2** (right).



Scheme 1. Synthesis of 1-oxa-4,9-diazaspiro[5.5]undecane-based trisubstituted urea derivatives **2**, **19–40** and **8**. Reagents and conditions: (a) R-NCO, DIPEA, $CHCl_3$; (b) H_2, $Pd(OH)_2$, MeOH; (c) R′COOH, HATU, DIPEA, DMF or R′COCl, Et_3N, CH_2Cl_2; (d) 2,6-difluorobenzoyl chloride, Et_3N, CH_2Cl_2; (e) 4-(trifluoromethoxy)phenyl isocyanate, DIPEA, $CHCl_3$, 37% for three steps.