Bioorganic & Medicinal Chemistry Letters 28 (2018) 2302–2313

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Adamantyl thioureas as soluble epoxide hydrolase inhibitors

Vladimir Burmistrov[a,b], Christophe Morisseau[a], Dmitry Pitushkin[b], Dmitry Karlov[c,d,e], Robert R. Fayzullin[f], Gennady M. Butov[b], Bruce D. Hammock[a,*]

[a] Department of Entomology and Nematology, and Comprehensive Cancer Center, University of California, Davis, CA 95616, USA
[b] Department of Chemistry, Technology and Equipment of Chemical Industry, Volzhsky Polytechnic Institute (Branch) Volgograd State Technical University, Volzhsky 404121, Russia
[c] Skolkovo Institute of Science and Technology, Skolkovo Innovation Center, Moscow 143026, Russia
[d] Department of Chemistry, Lomonosov Moscow State University, Moscow 119991, Russia
[e] Institute of Physiologically Active Compounds, Russian Academy of Sciences, Chernogolovka, Moscow Region 142432, Russia
[f] Arbuzov Institute of Organic and Physical Chemistry, FRC Kazan Scientific Center of Russian Academy of Sciences, Kazan 420088, Russia

ARTICLE INFO

Keywords:
Soluble epoxide hydrolase
Inhibitor
Adamantane
Isothiocyanate
Thiourea

ABSTRACT

A series of inhibitors of the soluble epoxide hydrolase (sEH) containing one or two thiourea groups has been developed. Inhibition potency of the described compounds ranges from 50 μM to 7.2 nM. 1,7-(Heptamethylene) bis[(adamant-1-yl)thiourea] (**6f**) was found to be the most potent sEH inhibitor, among the thioureas tested. The inhibitory activity of the thioureas against the human sEH is closer to the value of activity against rat sEH rather than murine sEH. While being less active, thioureas are up to 7-fold more soluble than ureas, which makes them more bioavailable and thus promising as sEH inhibitors.

Mammalian soluble epoxide hydrolase (sEH, E.C. 3.3.2.10) is involved in the metabolism of epoxy-fatty acids to the corresponding vicinal diols through the reaction with a water molecule.[1,2] Endogenous substrates for the sEH include cytochrome P450 metabolites of arachidonic (epoxyeicosatrienoic acids, EETs) and docosahexaenoic (epoxydocosatrienoic acids, EDPEs) acids.[3,4] EETs possess vasodilatory effects through the activation of the calcium dependent broad K^+-channels in endothelial cells, which are beneficial in many renal and cardiovascular diseases.[5,6] Furthermore, the EETs have some anti-inflammatory and analgesic properties.[7] Their conversion to dihydroxyeicosatrienoic acids (DHETs) by sEH reduces those beneficial activities. The inhibition of sEH *in vivo* by highly selective inhibitors results in an increase of the concentration of the EETs and other epoxy fatty acids and is accompanied by a reduction in angiotensin driven blood pressure in rodents, but also reduction of inflammatory and painful states, thereby suggesting that sEH is a target for the treatment of hypertension, inflammatory diseases and pain.[8–10]

Most of compounds reported as sEH inhibitors are 1,3-disubstituted ureas.[11–15] To our knowledge, only 10 thioureas have been reported as sEH inhibitors[16,17] compared to thousands of ureas. Thus, a systematic investigation of thioureas as sEH inhibitors is needed. Separately, ureas are difficult to formulate because of their high melting points and low water solubility. Herein, we investigate the influence of a thiourea function on the physical properties in comparison to ureas.

The common structure of known sEH thiourea based inhibitor is Ad-NHC(S)NH-R, where Ad is adamantan-1-yl, R is alkyl, aryl or heterocyclic group.[18–21] While the R-group was altered, the left (adamantane) part of the thiourea molecules was the same in almost all known thioureas based sEH inhibitors. Thus, the impact of alterations in adamantyl part of the thioureas on their potency and properties has never been investigated.

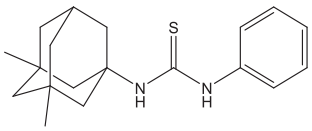
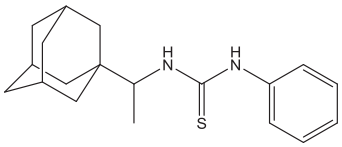
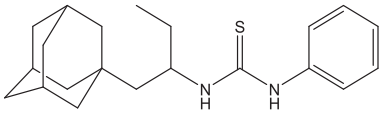
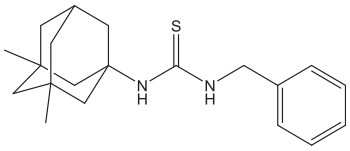
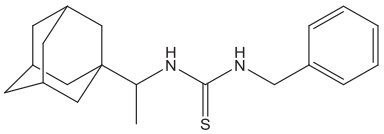
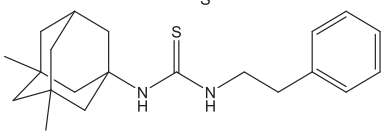
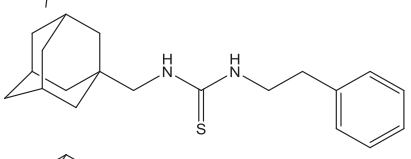
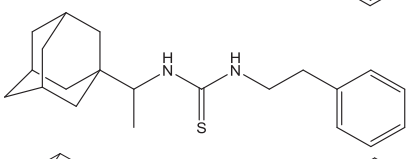
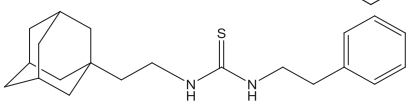
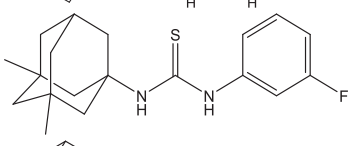
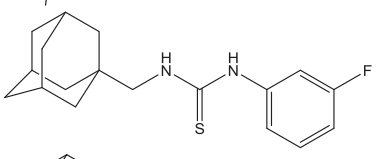
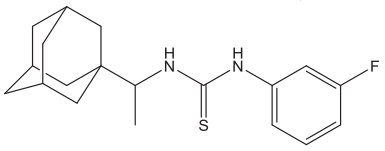
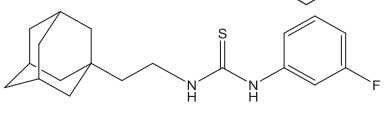
In this work we prepared and systematically studied new structural types of adamantyl thioureas with the following features: (*i*) spacers between adamantyl substituent and thiourea group to enhance conformational mobility; (*ii*) alkyl substituents in the bridgehead positions of adamantane to alter its lipophilicity; (*iii*) two adamantyl parts in a single molecule; (*iv*) adamantyl fragment linked with thioureas group by the bridge carbon; (*v*) aromatic fragments to regulate lipophilicity.

Reaction of amines with isothiocyanates is among the most widely used procedures for the preparation of thioureas. In contrast to isocyanates, isothiocyanates are less reactive and do not react with water in common conditions.[22] Due to the bimolecular nature of this reaction, the adamantane moiety can be introduced in to the molecule of thiourea either with adamantyl amine or with adamantyl isothiocyanate. In this case, it is reasonable to use adamantyl amines, which are quite available in contrast to the adamantyl isothiocyanates.[23] Since the mechanism of thiourea formation is nucleophilic addition to thiocarbonyl group, the most significant factors

* Corresponding author.
E-mail address: bdhammock@ucdavis.edu (B.D. Hammock).

https://doi.org/10.1016/j.bmcl.2018.05.024
Received 26 February 2018; Received in revised form 30 March 2018; Accepted 10 May 2018
Available online 23 May 2018
0960-894X/

Table 1
IC_{50} values and some physico-chemical properties for adamantyl-aryl sEH inhibitors **1a–q**.

#	Structure	mp (°C)	Solubility (μM)[a]	Human sEH IC_{50} (nM)[b]
1a		146–147	40–60	1224
1b		174–175	–	2592
1c		148–149	–	50,248
1d		117–118	10–15	58
1e		167–168	40–50	234
1f		75–76	8–12	216
1g		138–139	25–30	133
1h		126–127	20–30	345
1i		67–68	60–80	52
1j		147–148	50–60	58
1k		153–154	30–40	281
1l		161–162	35–45	451
1m		69–70	80–90	160

(*continued on next page*)