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Discovery of Soluble Epoxide Hydrolase Inhibitors from Chemical Synthesis and Natural Products

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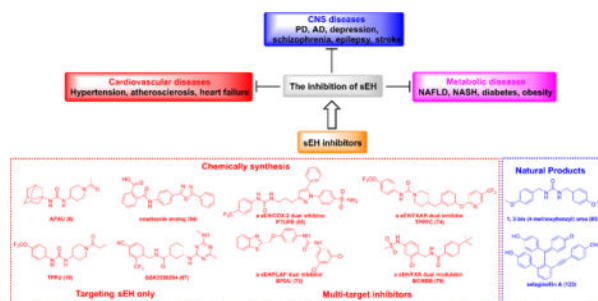
Abstract

Soluble epoxide hydrolase (sEH) is an α/β hydrolase fold protein and widely distributed in numerous organs including the liver, kidney, and brain. The inhibition of sEH can effectively maintain endogenous epoxyeicosatrienoic acids (EETs) levels and reduce dihydroxyeicosatrienoic acids (DHETs) levels, resulting in therapeutic potentials for cardiovascular, central nervous system, and metabolic diseases. Therefore, since the beginning of this century, the development of sEH inhibitors is a hot research topic. A variety of potent sEH inhibitors have been developed by chemical synthesis or isolated from natural sources. In this review, we mainly summarized the interconnected aspects of sEH with cardiovascular, central nervous system, and metabolic diseases, and then focus on representative inhibitors, which would provide some useful guidance for the future development of potential sEH inhibitors.

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Graphical Abstract



Keywords

Soluble epoxide hydrolase (sEH); Natural products; Pharmacology; Structure-activity relationship; Biological activity

1. Introduction

Epoxide hydrolases are widely distributed enzymes responsible for the rapid hydrolysis of epoxides to the corresponding vicinal diols.^{1,2} In mammals, soluble epoxide hydrolase (sEH), an α/β hydrolase fold protein, is expressed in the cytosol, and sometimes also in the peroxisome, of numerous tissues, such as liver, kidney, lungs, heart, brain, spleen, adrenals, and intestine.³ Beside mammals, the sEH is present in all vertebrates; however, only the mammalian sEH has phosphatase activity.^{4–14} Expression levels varies among species; for example, the sEH is much lower in rats than in mice.¹⁵ Furthermore, the sEH expression can be induced by angiotensin II and peroxisome proliferator-activated receptor α (PPAR α) and PPAR γ agonists, such as fibrates and glitazones,^{3, 16} but also by sexual hormones.¹⁷ Notably, the expression of sEH is upregulated by PPAR γ agonists in adipose tissues, while the opposite result is observed in cardiomyocytes.¹⁸ Additionally, inflammation also increases its expression, therefore, sEH can be considered a marker of inflammation.¹⁹

The mammalian sEH comprises of two 62.5 kDa monomers, containing 555 amino acids each, and it is a bifunctional enzyme that possesses a 25 kDa *N*-terminal phosphatase region and a 35 kDa *C*-terminal hydrolase domain (Figure 1A).²⁰ The *C*-terminal hydrolase catalyzes the hydrolysis of epoxy-fatty acids (EpFAs), such as epoxyeicosatrienoic acids (EETs), metabolized from arachidonic acid (AA), to the corresponding diols, such as dihydroxyeicosatrienoic acids (DHETs) (Figure 2).²⁰ The hydrolase catalytic pocket of the *C*-terminal hydrolase consists of two tyrosine residues (Tyr381 and Tyr465) that interact with the oxygen atom of the epoxide *via* two hydrogen bonds. The nucleophilic carboxylic acid Asp333 of the catalytic triad Asp333-Asp495-His523, located on the opposite side of Tyr381 and Tyr465, is oriented and activated by His523 and Asp495, and attacks the epoxide carbon backbone to form an ester bond with the opened epoxide (Figure 1C). The following hydrolysis of this ester results in the production of the corresponding diols.^{21, 22} Compared with the well-understood function of the *C*-terminal hydrolase domain, the role of the *N*-terminal phosphatase domain is still unclear.^{21, 22} Cronin *et al.* and Newman *et al.* independently discovered that the *N*-terminal domain of sEH exhibits phosphatase activity to

hydrolyze diverse lipid phosphates *in vitro*, including farnesyl pyrophosphate, sphingosine-1-phosphate, and lysophosphatidic acid, whereas its physiological and possibly pathophysiological role are still not well understood.^{23, 24}

EPHX2, the human gene encoding sEH, is a 19-exon gene (45 kb) localized in the chromosomal region 8p21–12.²⁵ So far, seven single-nucleotide polymorphisms (SNPs) of sEH have been discovered, including K55R, R103C, C154Y, R287E, R287E/R103C, V422A, and E470G.²⁶ Compared with the wild-type (WT) protein, the mutants the strong reduction of its phosphatase activity in R103C and R287E significantly decreased the phosphatase activity of sEH, and its hydrolase activity is increased in R287E/R103C, while the increasing of its *N*-terminal activity in K55R and C154Y.^{12, 27} Among them, K55R, R103C, and R287Q have been verified in connection with several diseases,^{28, 29} including heart failure, ischemic stroke, anorexia nervosa, and nephropathy.

In response to infection or damage, the body generates an inflammatory response. The central to this response is the production of bioactive lipids from AA (Figure 2).³⁰ Eicosanoids possess a series of protective effects and are defined to be vital metabolites from AA *via* three metabolic pathways: 1) the cytochrome P450 (CYP) pathway forms EETs and hydroxy eicosatetraenoic acids (HETEs); 2) Lipoxygenases (LOXs) catalyze the formation of lipoxins (LXs) and leukotrienes;³¹ 3) Cyclooxygenases (COXs) pathway produces prostanoids.³² The above-mentioned pathways can also metabolize eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and other unsaturated fatty acids.^{30, 32–34}

All these bioactive lipids, called oxylipins, have strong roles in the inflammatory response.³⁵ For example, EETs, synthesized by CYP450s, such as CYP2C8, CYP2C9, and CYP2J2, activate guanine nucleotide-binding protein (G-protein) *G*_s *via* ADP-ribosylation, resulting in the activation of the smooth muscle large conductance Ca²⁺-activated K⁺ channels (BK_{Ca}), to produce vasodilation and lowering blood pressure.^{36–39} Furthermore, EETs increase Ca²⁺ influx, enhance fibrinolysis, and stimulate tube formation in the endothelium.^{40, 41} In addition, EETs prevent I κ B degradation *via* suppressing I κ B kinase, inhibit nuclear transcription factor- κ B (NF- κ B) responsible for cytokine-mediated inflammation, and further inhibits NF- κ B-mediated gene transcription, allowing in the anti-inflammatory effect.^{42, 43} Compared with bioactive substrate EETs, DHETs are inactivation products of EETs,^{37, 44} because their activities are reduced in many systems, such as relaxation of the preglomerular vasculature and the bovine coronary artery,^{45, 46} inhibition of Na⁺ channel and cyclooxygenase,^{47, 48} and Ca²⁺ uptake.⁴⁹ In addition, DHETs produce functional effects in several other systems as well, including the inhibition of hydroosmotic action of arginine vasopressin,⁵⁰ relaxation of canine and porcine coronary arterioles^{51, 52} and activation of the BK_{Ca} channel.^{48–51}

Because sEH can rapidly metabolize or inactivate EETs to produce DHETs, nowadays, sEH inhibition or knockout has become an experimental approach to investigate the biological roles of EpFAs, especially EETs. For example, inflammatory pain can be ameliorated by increasing levels of EETs or inhibiting sEH to stabilize EETs.⁵³ Furthermore, the sEH expression level is upregulated in angiotensin II (Ang II)-induced lung injury mice, levels of tumor necrosis factor- α (TNF- α) and interleukin-1 beta (IL-1 β) are significantly increased,

and the *Ephx2* (the gene name of mouse sEH) knockout can remarkably alleviate the lung injury.⁵⁴ In addition, sEH is found to be expressed in the cerebral cortex and hippocampus as well as striatum (STR). Therefore, it is speculated that sEH is closely related to central nervous systems (CNS) diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD), depression, and stroke.³⁰ In this review, we summarized recent findings of sEH inhibitors from chemical synthesis and natural products, which provided useful guidance for the future development of potential sEH inhibitors, and the relationship between sEH and cardiovascular, CNS, and metabolic diseases.

2. sEH inhibitors

EETs exhibit potential biological functions in dilating blood vessels, and protecting neurons. Numerous studies indicated that inhibiting sEH to stabilize EETs can significantly reduce inflammation and pain.^{54, 55} Therefore, sEH inhibitors are considered as promising and effective treatment for various diseases and its development has become a hot topic in the research field since the beginning of this century. So far, sEH inhibitors have been discovered from a variety of pathways, such as synthesis and natural products,⁵⁶ therefore, we summarized the recent progress in the design and development of sEH inhibitors.

2.1 Targeting sEH only

2.1.1 Urea sEH inhibitors—The earliest selective sEH inhibitors reported are substituted chalcone oxides (such as compound **1**) and phenylglycidols, rather than ureas. 4-Phenyl-chalcone oxide (**1**, Figure 3) is a sEH substrate, and forms a covalent intermediate, allowing in low turnover and transient inhibition. However, they are unstable in the presence of glutathione, and slowly hydrolyzed by sEH, therefore, their use *in vivo* is limited.⁵⁷ The first potent and stable inhibitors of sEH were reported in 1999 based on the urea skeleton (**1**) (Figure 3), such as *N,N'*-dicyclohexyl-urea (**2**, DCU) and *N*-cyclohexyl-*N'*-(3-phenylpropyl)-urea (**3**, CPU).⁵⁸ They display significant inhibitory potency against the mouse and human sEH with IC₅₀ values in the tens of nanomolar. Their kinetic constants (K_i) are in the low nanomolar and are 20- to 150-fold better than **1** ($K_d = 430$ nM), revealing that compounds like DCU (**2**) or CPU⁵⁹ act as competitive inhibitors at stoichiometric concentrations,^{56, 60} and have a tight association with the target enzyme.⁵⁹ DCU (**2**) was first to be used *in vivo*, and could significantly inhibit the conversion from 14,15-EET to 14,15-DHET in spontaneously hypertensive rat, then leading to an antihypertensive effect.⁶¹ In porcine coronary endothelial cells, DCU (**2**) led to the decrease of the EETs conversion rate by 3-fold.⁶² While it demonstrated the usefulness of the urea inhibitors to affect the metabolism of EpFAs *in vitro* and *in vivo*, the early sEH inhibitors, such as DCU (**2**), had poor water solubility and high melting point (mp) due to its rigid structure and non-polar groups, which affected its oral availability and bioavailability. To date, the urea derivatives are the most abundant and effective sEH inhibitors, because the central urea group can bind strongly to the catalytic pocket of sEH (Figure 1B).⁶³ The oxygen atom on the urea group formed two hydrogen bonds with amino acid residues Tyr381 and Tyr465 in the catalytic pocket of sEH.⁶³ Moreover, the N-H of the urea group acts as the hydrogen bond donor of Asp333.⁶³ Because of their high potency, urea derivatives have been continuously

developed, especially to improve solubility and bioavailability to apply them for the treatment of EpFA-related diseases.^{56, 64}

From DCU (**2**), the first improvement in the design of sEH inhibitors was the introduction on one side of the urea function of a flexible chain, such as 12-(3-adamantan-1-yl-ureido)dodecanoic acid (**4**, AUDA). The introduction of a flexible side chain significantly improved the water solubility of AUDA (**4**) and reduced the mp while maintaining the inhibitory effect.⁶⁵ AUDA (**4**) continuously administered to mice *via* drinking water (25 mg/L) for 14 days, and finally achieved the purpose of reducing blood pressure. Although AUDA (**4**) was easier to formulate and to dose animals with (it could be given in the drinking water at 25 mg/L),⁶⁶ it was extremely sensitive to β -oxidation and therefore it was easily metabolized and excreted,³² thus limiting its application in clinic. Nevertheless, AUDA *n*-butyl ester prodrug (**5**, AUDA-nBE) has a relatively good pharmacokinetic⁶⁷ allowing *in vivo* application. AUDA-nBE (**5**) and its *in vivo* metabolite AUDA (**4**) reduced ischemic cerebral infarct size in stroke-prone spontaneously hypertensive rats, and prevented death and restore systolic blood pressure in lipopolysaccharide (LPS)-stimulated mice as well as the inhibition on the tumor growth.^{68, 69}

Based on the analysis of the structure activity of 348 urea-based inhibitors,⁷⁰ and in order to improve physical properties while reducing metabolism, polar functional groups were incorporated into one of the alkyl chains of 1,3-disubstituted ureas.⁶⁴ This study revealed that a representative sEH inhibitor could possess a secondary pharmacophore (a polar functional group) that is incorporated at least five atoms (about 7.5 Å) from the primary pharmacophore (the central urea carbonyl) which effectively improved aqueous solubility and PK properties (Figure 3) while maintaining potency. Solubility could even be enhanced with a polar tertiary pharmacophore that is 13 atoms or ~17 Å away from the primary pharmacophore, without affecting much the inhibitor potency.⁶⁴

To reduce metabolism, in addition to the introduction of polar groups, Jones *et al.* proposed in 2006 conformationally constrained human sEH inhibitors,⁷¹ which have the central pharmacophore and secondary pharmacophore connected by saturated rings, such as piperidine or other unsaturated rings. APAU (**6**) and TPAU (**7**) (Figure 3) are examples of the first series of piperidine-based urea inhibitors. These compounds are not only very potent inhibitors (IC₅₀s in the low nanomolar) but have better PK characteristics, such as 10-fold higher area under the curve (AUC)⁷² compared to AUDA (**4**) (Figure 3), underlying the benefits of conformationally constrained inhibitors.⁷¹

In order to further investigate the influence of conformationally constrained groups towards sEH inhibition, Hwang *et al.* used a cyclohexyl group as a linker instead of a piperidinyll group because of their structural similarity, and designed a series of *cis*- or *trans*-1,4-cyclohexyloxy-*N,N'*-disubstituted urea derivatives based on the skeleton of APAU (**6**, Figure 3).⁷³ These inhibitors not only have a good water solubility, but also resolve the problem that flexible alkyl chains are easily oxidized and metabolized rapidly, increase bioavailability *in vivo* and significantly improve metabolic stability.⁷³ Among them, a pair of epimers *trans*-4-[4-(3-adamantan-1-ylureido)cyclohexyloxy]benzoic acid (**8**, *t*-AUCB) and *cis*-4-[4-(3-adamantan-1-ylureido)cyclohexyloxy]benzoic acid (**9**, *c*-AUCB) shows low

nanomolar inhibitory effects (**8**, $IC_{50} = 1.3$ nM; **9**, $IC_{50} = 0.89$ nM) and desired PK properties, especially *t*-AUCB (**8**). It is notable that the 1,4-*trans* cyclohexane urea *t*-AUCB (**8**) is more stable than its isomer *c*-AUCB (**9**) in human liver microsome (HLM), and the AUC of the former in dogs increases about by 40-fold compared with that of AUDA (**4**). *t*-AUCB (**8**) at a dose of 1 mg/kg also shows the same therapeutic effect of returning blood pressure to normal as AUDA-nBE (**5**) at a dose of 10 mg/kg in LPS-induced hypotension model. An analysis of their structures indicates that the introduced free carboxyl group forms an additional hydrogen bond with Met418 in addition of the classical hydrogen bonds of the urea function with Asp333 and Tyr381.⁷³ In addition, *t*-AUCB (**8**) displays remarkable biological effects, including anti-fibrosis and anti-inflammatory activities, as well as protective effects against liver and cardiovascular diseases.^{74–78} *t*-AUCB (**8**) can down-regulate muscle-specific miR-133 expression level in the myocardial infarction mouse established by ligating the coronary artery, allowing in the reducing infarct size and preventing the development of cardiac arrhythmias.⁷⁴ Moreover, *t*-AUCB (**8**) reduces adipose tissue inflammation, prevents hepatic steatosis and the increased fasting glycemia, improved glucose tolerance, and decreases gluconeogenesis in high-fat diet (HFD) mice.⁷⁷

In addition to the cyclohexyl group, an aromatic ring and an isoxazolyl group were also used as the replacement of the piperidinyl group at the right side of *N*-adamantyl-*N'*-piperidinyl-ureas such as APAU (**6**) in view of their limited solubility and rapid metabolism (Figure 3), which reduced mp of the inhibitors and should enhance the stability.⁷⁹ Despite the potent inhibitory activity observed in this series of compounds, such as 1-(adamant-1-ylmethyl)-3-[[5-(furan-2-yl)isoxazol-3-yl]methyl]urea (**10**, AFMU), and 1-(adamant-1-ylmethyl)-3-[(3-methylisoxazol-5-yl)methyl]urea (**11**, AMMU), their stability was not improved in HLM with nicotinamide adenine dinucleotide phosphate (NADPH).⁷⁹

The next step in sEH inhibitor development involved the optimization of the adamantyl-ureas *via* adding the substitution to the bridgehead of the adamantane to afford a library of this type compounds (Figure 4).⁸⁰ Interestingly, the substitution influenced greatly the potency, physical properties, and metabolic stability of ureas and diureas. Interestingly, a methyl or chloride substitution on the bridgehead of the adamantane is to the benefit of the potency, and the adamantane and urea functions are linked *via* a methylene, which is in favor of potency and physical properties. These findings provide a new path to further design sEH inhibitors.⁸⁰

Although the above-mentioned adamantyl-urea sEH inhibitors have excellent potency, this type of inhibitors is easily oxidized and metabolized, resulting in low drug concentrations and short *in vivo* half-life ($t_{1/2}$). Therefore, in the next iteration of compounds design, aromatic or other aliphatic moieties were used instead of the adamantyl group based on the structure of *t*-AUCB (**8**).⁸¹ A library of aromatic- and other aliphatic-ureas were synthesized (Figure 5; compounds **14–20**). While the replacement of the adamantyl group by aromatic groups did not significantly improve the inhibitory potencies, the PK properties were dramatically improved, especially for TPPU (**19**) and TPCU (**20**). The AUC/ IC_{50} of TPCU (**20**), a metric of the inhibitory effect, is 5,500-fold higher than that of APAU (**6**), and a similar result is obtained in the PK of TPPU (**19**) as well. These compounds have become

commercial inhibitors of sEH and been used in a wide variety of studies to test for sEH biological activities.⁸¹

Although acyl piperidine ureas have good inhibitory effects, they show unsatisfactory PK properties in dog model.⁸² Hammock's team designed a series of piperidyl-urea derivatives for the treatment of diabetic neuropathic pain based on the skeleton of *N*-phenyl-*N'*-piperidyl-urea in 2014.⁸³ The potency of sEH inhibitors does not only consider IC_{50} or K_i , but also depends on how long the target is occupied by the inhibitor, because the catalysis is blocked only when the enzyme is occupied. In these 1,3-disubstituted ureas (Figure 5), the dissociation rate constant (k_{off}) of compounds **21–23** increase 2.4–4.4 fold compared with that of a previous inhibitor TPAU (**7**, $k_{off} = 19.2 \times 10^{-4} \text{ s}^{-1}$). An analysis of the interaction between their analog TPPU (**19**, $k_{off} = 10.2 \times 10^{-4} \text{ s}^{-1}$) and human sEH reveals a small secondary binding site next to the α -carbon of its amide, which provides the possibility of additional binding. The hydrophobic 4-trimethoxyphenyl group binds closely to the right side of the binding pocket with a little extra binding space, which may be the reason why it stays on the target for a long time and shows excellent inhibitory effect.⁸³

CYP enzymes can metabolize AA to produce four regioisomers and each isomer has different proportions of *S/R*- or *R/S*-enantiomers (Figure 6). Because the production rate and ratio of stereoisomers of these diol products are closely related to the stereochemistry of substrates and epoxy ring substitution, stereoselectivity is also an important factor in the design of sEH inhibitors.⁸⁴ Manickam *et al.* designed a series of pairs of enantiomers with a chiral center close to urea nitrogen atoms.⁸⁴ There are significant differences in the inhibitory activity of enantiomers, for example, the inhibitory activity of (*S*)-1-(1-phenylethyl)-3-(3-phenylpropyl) urea (**24**, *S*-PPU) is 40-fold higher than that of its enantiomer (**25**). This similar result is also observed by Lukin *et al.*, which indicates that the chirality of the α -carbon of urea nitrogen atoms can affect the inhibition of inhibitors on sEH.⁶⁰ Among the synthesized compounds, ITBU (**26**) possesses a potent sEH inhibitory activity and an excellent bioavailability in mice. However, the further analysis reveals that ITBU (**26**) is a racemic inhibitor, and can be isolated to afford (+)-ITBU [(+)-**26**] and (–)-ITBU [(–)-**26**]. The inhibitory potency of the former is 11-fold higher than that of the latter. All the above-mentioned suggests that the selective sEH inhibition by different enantiomers provides more possibilities for the binding sites of sEH and a new direction for the development of sEH inhibitors.⁶⁰

Except for the above-mentioned modification, the urea moiety was also altered by replacing the oxygen atom of urea with the sulfur atom to afford thiourea-based sEH inhibitors (Figure 7).⁸⁵ Among the thioureas, 1-(adamantan-2-yl)-3-phenethylthiourea (**27**, APU) and 1,1'-(heptane-1,7-diyl)bis(3-(adamantan-1-yl)thiourea) (**28**, HBAU) are found to be potent sEH inhibitors. Although their potencies less than the previous described as TPPU (**19**), they have better water solubility and are easier to be prepared, which is one of the ideal properties of an ideal inhibitor.⁸⁵

2.1.2 Amide sEH inhibitors—In addition to the urea-based sEH inhibitors, amides have been also widely developed as sEH inhibitors by removing one of the NH group of the ureas (Figure 8), yielding compounds **29–32**.⁸⁶ The primary structure-activity relationship

(SAR) indicates that their inhibition potencies almost does not affect for mouse sEH compared to the corresponding ureas, whereas this modification leads to the 2.5-fold decrease inhibition potency for human sEH. On the other hand, the amide function can significantly improve the physical property compared to the corresponding ureas, such as solubility and mp, for example AABA-PE (**31**; mp, oil; solubility, 17.4 $\mu\text{g/mL}$).⁸⁶

Eldrup and colleagues screened in-house compounds with drug-like characteristics for sEH inhibition, and found that *N*-(3,3-diphenyl-propyl)-nicotinamide (**33**, DPN) could be regarded as a new starting point for an optimization process.⁸⁷ According to the X-ray crystal result of DPN (**33**) and sEH as shown in Figure 9, a library of amide inhibitors were designed and synthesized *via* the introduction of methanesulfonyl and fluorine at two benzene rings based on the structural core of DPN (**33**), yielding compounds **34–37** (Figure 9). They showed similar inhibitory potencies as DPN (**33**), whereas their metabolic stability was significantly improved in HLM and rat liver microsome.⁸⁸ CFMB (**36**) as a potential sEH inhibitor was found to have a low drug-drug interaction potential with selectivity for CYP enzymes.⁸⁷ In addition, DPN (**33**) was further optimized based on the structure of urea analog (**38**) with good metabolic stabilities ($t_{1/2}$, 185 min in HLM; 105 min in RLM), resulting in the production of a series of nicotinamide analogs.⁸⁹ Among them, nicotinamide analog (**39**) showed a low nanomolar inhibitory effect and a great metabolic stability, and had also acceptable ($t_{1/2}$, 185 min in HLM and 105 min in RLM) plasma exposure.⁸⁹

Anandan *et al.* analyzed previous urea inhibitors, such as CPU,⁵⁹ AUDA (**4**), and TPPU (**19**), and summarized the pharmacophore model comprising of a primary, secondary, and tertiary pharmacophores, and two linkers, therefore, they developed a series of urea, amide, sulfonamide, thiourea, sulfonyl urea, hydroxyamide, and ketoamide inhibitors based on the skeleton (**II**, Figure 10).⁹⁰ A detailed analysis of SAR reveals that no less of inhibitory potency is observed when the *N* atom on the left side of the carbonyl group of urea is replaced by a *C* atom, whereas the decrease of inhibitory potency is present when the urea group is substituted with other groups, such as sulfonamide, thiourea, sulfonyl urea, hydroxyamide, and ketoamide. A methylene group occurs between adamantyl and hydroxyamide or ketoamide group, which will be to the benefit of inhibitory potency, except for amides (**40** and **45**). However, the inhibition potency is decreased when the adamantyl group is replaced by other groups, including cyclohexyl, 4-trifluoromethylphenyl, 4-chlorophenyl, and 4-trifluoromethoxyphenyl group.⁹¹

Based on these findings, the subsequent researches focused on the secondary pharmacophore to optimize the inhibition potency of amides.^{92–96} Firstly, an oxyoxalamide functional group was used to design and develop sEH inhibitors as the secondary pharmacophore according to the skeleton (**III**) by Kim and co-workers (Figure 11).⁹⁴ Among the synthesized compounds, **50** (MMMO) and **51** (PMMO) show low nanomolar inhibitory activities as similar as that of AUDA (**4**), and their physical property has been greatly improved compared to AUDA (**4**), especially their solubility. The new skeleton (**IV**) by modifying the secondary pharmacophore was constructed using the phosphonate function in place of the oxyoxalamide group,⁹⁵ to afford potent sEH inhibitors, such as **52** (DPDP) and **53** (DAPDP). In addition, Zavareh *et al.* also tried to develop the novel skeleton (**V**) *via* using an oxadiazole ring as a novel secondary pharmacophore,^{93, 96} yielding a series of potent

oxadiazole-base amide inhibitors, such as oxadiazole analogs **54** ($IC_{50} = 0.91$ nM) and **55** ($IC_{50} = 0.83$ nM). Molecular docking indicates that amino acid residues Asp335, Tyr383, and Tyr466 play a crucial role in the interaction with sEH, and Val498, His524, and Trp525 also form additional hydrogen bond interaction with an oxadiazole group. These findings have great importance in the design of sEH inhibitors.⁹⁶

Kim and co-workers carried out the structural modification on both sides of the amide pharmacophore of 1,3-bicycloalkyl substituted amides to improve the inhibitory effect on sEH.⁹⁷ According to the SAR result (Figure 12), potent sEH inhibitors **56** (TPNC) and **57** (MTCMB) are obtained with reasonable physical properties. For example, mp of MTCMB (**57**) is reduced (115 °C) and the water solubility (125 μ M) is 2-fold higher than that of AUDA (**4**). This shows that amide inhibitors can achieve similar inhibitory potency as urea inhibitors while having better physical properties. In addition, this study opened the door to numerous possibilities for the design of potent amide inhibitors, especially through combinatorial chemistry.⁹⁷

For finding new structures, Landry *et al.* tested a library of 130,000 chemicals, provided by the National Institutes of Health Roadmap project, for sEH inhibition. They obtained a lead compound **58** (Figure 13) with nanomolar potency that contains a sulfonyl isonipicotamide that is resembling APAU (**6**). Further optimization of **58** resulted in the production of three subnanomolar inhibitors (**59–61**).^{98, 99} Xing *et al.* designed a combinatorial library of benzoxazole derivatives, and screened the potential sEH inhibitors *via* a virtual screening (Figure 14).¹⁰⁰ The X-ray crystal structure (PDB code 3PDC) of the human sEH with compound **62** revealed unique interactions between the enzyme and the benzoxazole group. In addition to the classic hydrogen bonds between the amide group and active site residues (Asp333, Tyr381, and Tyr465), the oxygen of the benzoxazole ring forms a hydrogen bond interaction with His523, one of the catalytic triad Asp333-Asp495-His523 (Figure 14). These additional hydrogen bonds may account for the enhanced potency of the amide-based inhibitors containing a benzoxazolyl group.¹⁰⁰

Marino and co-workers used encoded library technology to discover a sEH inhibitor (**64**) featuring a piperidinecarboxamide skeleton *via* high throughput screening (HTS, Figure 15),^{101, 102} and optimized this skeleton to yield compounds **65** and **66** displaying low nanomolar inhibitory potencies.¹⁰³ The X-ray crystal structure of MTTP (**65**) with sEH (PDB code 4JNC) showed that **65** formed H-bonds with Asp335, Tyr383, and Tyr466 at the active site (Figure 15). The further optimization of this skeleton led to the production of a low picomolar sEH inhibitor GSK2256294 (**67**). The result of *in vivo* study indicated that GSK2256294 (**67**) could dose-dependent reduce pulmonary leukocyte and keratinocyte chemoattractant levels in cigarette smoke-induced mice, suggesting that GSK2256294 (**67**) would be an appropriate agent for the treatment of chronic obstructive pulmonary and cardiovascular diseases.⁵⁹ This compound has been tested in clinical trials.

2.2. Multi-target inhibitors

Highly effective drugs with a single biological target are the mainstream of drug research and development.¹⁰⁴ However, they also have some limitations. By targeting a single

enzyme or receptor only, a drug could lack efficacy on complex diseases, and may cause additional adverse reactions when used in combination with other drugs.^{104, 105} In order to solve these problems, research is focusing now on multi-target drugs with higher safety and effectiveness.^{105, 106} In recent years, several multi-target drugs have shown excellent therapeutic ability in meddling with the AA cascade. The sEH plays a crucial role in the AA cascade and participates in the pathological process of numerous diseases. In addition, the effectiveness of sEH inhibitors has been verified *in vivo*.¹⁰⁴ By combining the inhibition of sEH with the inhibition of another actor of the AA cascade, such as COX-2, 5-LOX, and FLAP, one could expect a greater effect for the treatment of complex diseases, such as neuro-inflammation or cancer.^{107, 108}

2.2.1 sEH/COX-2 dual inhibitors—COX-2 is an enzyme in which expression is induced by the stimulation of inflammation, hormones, or growth factors.¹⁰⁹ COX-2 is highly expressed in inflammation and proliferative diseases, such as various cancers, therefore, it is a target to develop anti-inflammatory and anti-tumor agents.¹⁰⁴ A recent study has demonstrated that co-administration of EETs and COX inhibitors exerts a better effect than the single administration of COX inhibitors to reduce LPS-induced pain and hypotension.^{79, 84} Accordingly, a series of sEH/COX-2 dual inhibitors based on the structural skeletons of celecoxib and *t*-AUCB (**8**, Figure 16), were designed and found that **68** (PTUPB) displayed potent inhibitory activities against both sEH and COX-2. Molecular stimulation shows that PTUPB (**68**) forms hydrogen bond interactions with amino acid residues Asp333, Tyr381, and Tyr465 of human sEH, and His90 and Tyr335 of mouse COX-2. In a nociceptive assay, PTUPB (**68**) enhances *in vivo* anti-allodynia effects compared to both the individual and combination therapies of celecoxib and *t*-AUCB (**8**).^{107, 110}

PTUPB (**68**) was found to be beneficial to sepsis, non-alcoholic fatty liver disease, pulmonary fibrosis, and cancer.^{33, 107, 111–116} PTUPB (**68**) inhibits tumor growth and metastasis by suppressing endothelial cell proliferation, and it also improves survival rate, delays the onset of debris-stimulated ovarian tumor growth, and reduces ascites.^{107, 115, 116} In addition to the treatment of cancers, PTUPB (**68**) suppresses the activation of NLRP3 inflammasome,¹¹¹ allowing in improving the survival rate, reducing the clinical scores and systemic inflammatory response, and alleviating the multiple-organ injury in sepsis mice.¹¹² Therefore, sEH and COX-2 dual inhibition may be an approach to treat inflammation and cancer diseases.

2.2.2 sEH/5-LOX dual inhibitors—5-LOX as a dioxygenase, play a catalytic role in two steps of the biosynthesis of LTs which progress regulate the innate immune response and play a pathophysiological role in chronic inflammatory diseases, such as asthma and atherosclerosis.¹⁰⁴ To date, a 5-LOX inhibitor zileuton is used in the clinic for the treatment of asthma with restrictions.¹¹⁷ Co-administration of an sEH inhibitor *t*-AUCB (**8**) with a 5-LOX inhibitor showed a significant enhancement of the anti-inflammatory response.¹⁰⁹ Therefore, the sEH/5-LOX dual inhibitor has caught the attention of medicinal chemists. Moser and co-workers applied the pharmacophores of sEH and 5-LOX for screening 37,429 compounds *in silico* to afford a poor sEH/5-LOX dual inhibitor (sEH IC₅₀ = 3.5 μM; 5-LOX

IC₅₀ = 36 μM), which, nevertheless, led to the new era of discovery dual inhibitors.¹¹⁸ Based on the key pharmacophores, an imidazo[1,2-*a*] pyridine motif of a 5-LOX inhibitor EP6 (5-LOX IC₅₀ = 59 nM) and a urea group of AUDA (**4**), a library of compounds were designed and synthesized by Meirer *et al.*¹⁰⁹ The SAR indicated that two pharmacophores required an *n*-propyl linker to maintain both sEH and 5-LOX inhibition. Among them, compound **69** showed high inhibitory potency against both 5-LOX and sEH (Figure 17). Although CMMPPU (**69**) exhibited high potency *in vitro*, it was not stability in plasma.¹⁰⁹ Subsequently, Meirer *et al.* designed KM55 (**70**), which showed a strong anti-inflammatory effect *in vitro*.¹¹⁷

Achenbach *et al.* used saturation transfer difference (STD)-NMR and activity-based assays (Figure 18), and found that a compound featuring an aminothiazole skeleton had better inhibitory activities towards sEH (IC₅₀ = 170 nM) and 5-LOX (IC₅₀ = 30 nM).¹¹⁹ Nandha *et al.* designed and developed a potential sEH/5-LOX dual inhibitor (FFBMB, **71**) based on the structure of the 5-LOX inhibitor RWJ-63556 (Figure 19), a benzimidazole analog, and the sEH inhibitor *t*-TUCB. The *in vivo* study confirmed that FFBMB (**71**) possessed significant inhibition of carrageenan-induced rat paw edema.¹²⁰

2.2.3 sEH/FLAP dual inhibitors—5-LOX-activating protein (FLAP) is a nuclear membrane-anchored protein responsible for transferring AA to 5-LOX that produces pro-inflammatory LTs. The inhibition of FLAP by FLAP inhibitors or genetic knockout can abolish the production of pro-inflammatory LTs. Meanwhile, a FLAP inhibitor, GSK2190915, has completed phase II trials for the treatment of asthma.^{121, 122} Recent studies have indicated that co-administration of a sEH inhibitor *t*-AUCB (**8**) and MK886, a FLAP inhibitor, enhances anti-inflammatory activities in a murine model, yielding interest in sEH/FLAP dual inhibitors.¹²³ Temml *et al.* used a pharmacophore-based virtual screening to afford a first sEH/FLAP dual inhibitor diflapolin (**72**) (Figure 20), which did not affect other enzymes of the AA cascade, suggesting that (**72**) is very selective for sEH and FLAP.¹²⁴ Investigation of its *in vivo* biological effects indicates that diflapolin (**72**) ameliorates vascular permeability, inhibits the formation of pro-inflammatory factors cysteinyl-LTs and leukotriene B4 (LTB4), suppresses neutrophil infiltration in the zymosan-induced peritonitis mouse model.¹²⁴ Subsequently, Vieider and colleagues designed a library of diflapolin derivatives, leading to BPDU (**73**) (Figure 20), a more potent sEH/FLAP dual inhibitor.¹²⁵

2.2.4 sEH/FAAH dual inhibitors—Fatty acid amide hydrolase (FAAH) is a membrane-bound serine hydrolase responsible for the deactivating metabolism of endogenous cannabinoids, such as oleamide, anandamide, and myristic amide.¹⁰⁴ Both EpFAs and endocannabinoids exert anti-inflammatory effects, therefore, elevating their concentrations by inhibiting both sEH and FAAH should be a good method to treat inflammation and neuropathic pain.¹⁰⁴ Indeed, co-administration of a FAAH inhibitor and a sEH inhibitor elicited a synergistic analgesic response in acute inflammatory and chronic pain mice,¹²⁶ and thus, sEH/FAAH dual inhibitors had attracted more attention. Interestingly, because *t*-TUCB, a potent sEH inhibitor (IC₅₀ = 0.4 nM), has a *N*-(3-trifluoromethoxyphenyl) moiety, which is a good leaving group for FAAH, it has also reasonable inhibitory potency against FAAH (IC₅₀ = 260 nM).¹⁰⁵ Further chemical modifications resulted in a 6-fold increase

potency against FAAH while retaining *l*-TUCB intrinsic sEH inhibitory effect (Figure 21).¹⁰⁵

Separately, a series of sEH/FAAH dual inhibitors were developed based on the cores of a FAAH inhibitor PF-3845 and sEH inhibitor TPPU (**19**, Figure 22). Kodani *et al.* found that TPPPC (**74**) is a low nanomolar inhibitor for both FAAH and sEH inhibitions (Figure 22). Further investigation suggested that TPPPC (**74**) possesses a good target selectivity, PK property (AUC = 1200 nM*h; C_{max} = 98 nM; t_{1/2} = 4.9 h in mice), and *in vivo* target engagement.¹²⁷

2.2.5 sEH/PPAR γ dual modulators—PPAR γ is a nuclear receptor that can be activated by EETs allowing the inhibition of NF- κ B pathway and anti-inflammatory effects.¹²⁸ Some studies have indicated that the sEH expression level is increased and the PPAR γ transcriptional activity is decreased in obese patients, suggesting that simultaneous regulation of sEH and PPAR γ has a therapeutic potential for metabolic diseases.¹²⁸ Recently, Imig and co-workers co-administrated thiazolidinedione (TZD), a PPAR γ agonist, and *l*-AUCB(**8**), a sEH inhibitor, to spontaneously hypertensive obese rats, resulting in protective effects towards vascular function and kidney,¹²⁹ supporting the idea of sEH/PPAR dual modulators.¹⁰⁴ Proschak *et al.* designed a library of sEH/PPAR dual modulators based on the sEH pharmacophore 4-(trifluoromethoxy)phenyl ureas and PPAR modulator structures (Figure 23), and obtained compounds, such as TPUBPC (**75**) and AUBPC (**76**), that display inhibition on sEH and activation on PPAR α/γ (Figure 24).¹⁰⁸

Subsequently, Blöcher *et al.* also designed a series of sEH/PPAR dual modulators with a benzylamide structure, a merged pharmacophore for sEH and PPAR γ , on the basis of the structure of the PPAR γ agonist GSK1997132B, such as RB394 (Figure 24) with good potencies against sEH and PPAR γ . In addition to its good PK and pharmacodynamic profile,¹³⁰ RB394 could also ameliorate the development of hypertension, insulin resistance, and hyperlipidaemia in obese spontaneously hypertensive and obese diabetic Zucker fatty/spontaneously hypertensive heart failure F1 hybrid rats, which suggested that it could be regarded as a potential agent to treat metabolic syndromes.¹³¹

Afterwards Schierle *et al.* found that zafirlukast, an antagonist of cysteinyl leukotriene receptor 1, also possesses an agonistic effect towards PPAR γ and inhibitory effect towards sEH (Figure 25). Further structural optimization led to the production of compound **77**. Its potencies on sEH and PPAR γ was increased by 46.5- and 8.1- fold compared to zafirlukast, respectively, and it also exerted an anti-inflammatory potency in the zymosan-induced paw edema.¹³²

2.2.6 sEH/FXR dual modulators—Farnesoid X receptor (FXR), known as the bile acid receptor, is a ligand-activated nuclear receptor.¹³³ Clinical trials have reported that administration of FXR agonists could improve histological features and clinical markers of non-alcoholic fatty liver disease (NAFLD) as well as metabolic parameters, revealing that FXR can be served as a potential target for fatty liver disorders and metabolic diseases.

Interestingly, an antagonist of cysteinyl leukotriene receptor 1, zafirlukast, also has an agonistic effect against FXR ($EC_{50} = 3.9 \mu\text{M}$) and inhibitory effect against sEH ($IC_{50} = 2.0 \mu\text{M}$). The optimization of zafirlukast structure lead to a 15-fold increase of its agonistic effect against FXR with a similar potency toward sEH (Figure 26).¹³⁴

Separately, based on the structure of a sEH inhibitor (GSK2188931B, Figure 27) and a FXR agonist, Schmidt *et al.* extracted their similar structural characteristics and combined them in the dual pharmacophore *N*-benzylamide. This finding led to the production of a sEH/FXR dual modulator BCMBB (**79**).¹³⁵ Extensive *in vitro* characterization confirmed its potency and favorable PK (Figure 27).¹³⁴

2.2.7 sEH/c-RAF dual inhibitors—RAF is a proto-oncogene serine/threonine-protein kinase (c-RAF or RAF1),¹³⁶ and is the target for antitumor drugs because its inhibition or knockout regulates the RAS-RAF-MEK-ERK pathway to suppress lung and ovarian tumors growth.¹³⁷ Sorafenib (**80**), the first FDA-approved inhibitor of c-RAF,¹³⁸ possesses a similar urea pharmacophore as a selective sEH inhibitor *t*-TUCB, and it was founded to exhibit potent inhibitory activity towards sEH as well (Figure 28).¹³⁹ Structural optimization leads to the design and synthesis of a sEH/c-RAF dual inhibitor *t*-CUPM (**81**, Figure 28).¹⁴⁰ Compared to sorafenib (**80**), *t*-CUPM (**81**) is 25-folds more potent toward sEH while displaying similar potency toward c-RAF, while having satisfying PK properties. The subsequent *in vivo* study in LSL-KrasG^{12D}/Pdx-1-Cre mice indicated that *t*-CUPM (**81**) significantly alleviated chronic pancreatitis by suppressing mutant Kras-transmitted phosphorylations of cRAF/MEK/ERK.¹⁴⁰

2.3 Natural (or naturally occurring) products as sEH inhibitors

Natural products play an important role in drug discovery, and about 50% of drugs in clinic are natural products, such as artemisinin, taxol, andrographolide, and penicillin.^{141, 142} Accordingly, numerous compounds from natural resources also display inhibition of sEH, including natural ureas, triterpenoids, flavones, and phenyl-propionic acids.^{143–146} Interestingly, numerous compounds reported as sEH inhibitor have a weak potency with IC_{50} or K_i in the micromolar range, thus limiting their usefulness for eventually treating patients.

2.3.1 Natural ureas and amides—So far, as described above, ureas and amides have been most widely studied as sEH inhibitors. To date, natural urea-containing compounds also are discovered from the genera *Pentadiplandra*, *Salvadora*, *Lepidium*, and *Moringa* (Figure 29),^{145, 147–151} whereas only five ureas (**82–86**), isolated from *P. brazzeana* and *L. meyenii*, were screened for their sEH inhibitory activities and possess potent human and rat sEH inhibitory activities (Figure 29).¹⁵² These are the only reported natural compounds that inhibit sEH with IC_{50} in the nanomolar range.

Capsaicin (**87**) and dihyrocapsainin (**88**), isolated from *Capsicum chinense*, are competitive-type inhibitors with K_i values of 7.3 and 4.7 μM , respectively.¹⁵³ In addition, three amide derivatives piperlonguminine (**89**), piperlonguminine (**90**), and futoamide (**91**) from the traditional Chinese medicine *Scutellaria baicalensis*, are weak sEH inhibitors.¹⁴⁴

2.3.2 Flavonoids—Some of flavonoids, isolated and identified from the genera *Scutellaria*, *Tetrastigma*, *Epimedium*, *Apios*, *Kaempferia*, *Boscia*, and so on, exhibited sEH inhibitory potencies (Figure 30).^{144, 145, 154–158}

The investigation on *T. hemsleyanum* led to the isolation of kaempferol (**92**) and apigenine (**93**), and they were defined as noncompetitive-type inhibitors with K_i values of 18.6 and 24.4 μM , respectively.¹⁴⁵ In addition, 3,5,7-trimethoxyflavone (**94**), 5,7,4'-trimethoxyflavone (**95**), 3,5,7,4'-tetramethoxyflavone (**96**), 3,5,7,3',4'-pentamethoxyflavone (**97**), and 4',5-dihydroxy-3,3',7-trimethoxyflavone (**98**), isolated from *K. parviflora*, displayed potent inhibitory potentials with K_i values ranging from 0.1 μM to 1.7 μM .¹⁵⁵

2.3.3 Triterpenoids—Thao and co-workers studied the constituents of *Cimicifuga dahurica* to afford cycloartuane-type triterpenoids (**99–107**, Figure 31).^{159, 160} It was found that compounds **99–107** were mixed-type inhibitors and their IC_{50} values were 0.4–4.8 μM . Protostane-type triterpenoids are characteristic constituents of the genus *Alimisa*, and twenty-five of them were assayed for their inhibitory effects against sEH.¹⁶¹ Among them, 11-deoxy-25-anhydro alisol E (**108**, $\text{IC}_{50} = 3.4 \mu\text{M}$) and 11-deoxy alisol B (**109**, $\text{IC}_{50} = 5.9 \mu\text{M}$) significantly suppressed sEH activity. As mixed-type inhibitors, 11-deoxy-25-anhydro alisol E (**108**, $K_i = 12.6 \mu\text{M}$) and 11-deoxy alisol B (**109**, $K_i = 3.5 \mu\text{M}$) are hypothesized to form hydrogen bonds with amino acid residues Asp335, Trp336, Tyr383, and Tyr466, respectively.

2.3.4 Phenylpropionic acids—Six phenylpropionic acids from *T. hemsleyanum*, such as (1 α ,3 R ,4 α ,5 R)-4-*O*-(*E*)-caffeoylquinic acid methyl ester (**110**) and caffeic acid (**111**, Figure 32), showed weak inhibitory activities towards sEH.¹⁴⁵ In order to discover more potent sEH inhibitors from natural resources, the subsequent investigation on *Polygala tenuifolia* led to the isolation of nine analogues, such as 6-*O*-(*O*-methyl-pbenzoyl)-3'-*O*-(*O*-methylsinapoyl)sucrose (**112**), and 6,3'-di-*O*-sinapoylsucrose (**113**).¹⁴⁶ Kim and co-workers investigated the constituents of *C. dahurica* and *Gentiana scabra* to obtain cimicifiphenone (**114**), cimircemate A (**115**), 3,5-di-*O*-caffeoylquinic acid (**116**), and ferulic acid methyl ester (**117**).^{162, 163} Compounds **114–117** could significantly inhibit sEH activity (Figure 32).

2.3.5 Anthraquinones—*Aloe* is a short-stemmed succulent herb mainly used in traditional medicine to treat various diseases. Anthraquinones are considered as the major active constituents of the genus *Aloe* (Figure 33). Sun *et al.* obtained three anthraquinones, desoxyaloin (**118**), aloinosides C (**119**), and elgonica dimer A (**120**), from *Aloe*.¹⁶⁴ Among them, desoxyaloin (**118**) showed the most potent inhibitory activity against sEH with a mixed-type inhibitor behavior. Molecular docking suggested that desoxyaloin (**118**) could bond to sEH with hydrogen bond interactions with Tyr343 and Pro361. Besides, emodin (**121**), an anthraquinone derivative isolated from *P. multiflorum*, also displayed inhibitory potency against sEH.¹⁶⁵

2.3.6 Stilbenes—The investigation on *Rheum undulatum* resulted in the isolation of astringin (**122**, Figure 34), which was found to inhibit sEH.¹⁶⁶ Molecular docking suggests

seven hydrogen bonds between astringin (**122**) and Ser415, Leu417, Met419, Tyr466, Lys495, and His524 residues of sEH. In addition, three noncompetitive inhibitors of sEH, selaginellin A (**123**), selaginellin B (**124**), and selaginellin (**125**) were isolated from *Selaginella tamariscina*.¹⁶⁴ *In silico* investigation suggests that they bonded to a complex of sEH and substrate *via* hydrogen bond interactions.

2.3.7 alkaloids—Investigation of the phytochemical constituents of traditional Chinese medicines *C. daturica* and *Glycosmis stenocarpa*, resulted in the isolation and identification of four alkaloids (**126–129**) (Figure 35) that inhibits sEH.^{160, 167}

2.3.8 Others—Besides all the above-mentioned compounds, some other type of compounds isolated from *G. scabra*, *Magnolia officinalis*, *Callistemon citrinus* and *Cassia tora*,^{163, 168, 169} also displayed some inhibition on sEH, such as berchemol (**130**), honokiol (**131**), callistenone B (**132**), and cassitoroside (**133**) (Figure 36).

2.4 Selectivity of sEH inhibitors

High selectivity of pharmacological inhibitors as an important factor limit off-target non-desirable side effects in clinic. Here, we are mostly concentrating on the urea-based sEH inhibitors. Because urea function is also the central pharmacophore for compounds that inhibit proteases and kinases,¹⁷⁰ and bind to cannabinoid receptors 1,¹⁷¹ it is possible that inhibitors for sEH could also alter the function of these other proteins. It is interesting that the Raf-1 kinase inhibitor sorafenib (**80**), used to treat some cancer, was found to inhibit sEH also.¹³⁹ A commonly use sEH inhibitor, TPPU (**19**), was recently reported to also inhibit significantly the P38 kinase, influencing its action in Alzheimer disease model.¹⁷² The selectivity of a particular compound is not only dependent of the central pharmacophore but also of the chemical groups present on both side of the urea. As these groups are becoming more complex and establishing additional bond with sEH, the likelihood of a compound to bind to another protein decrease. However, any compound developed as a pharmacological sEH inhibitor should be tested for its selectivity especially for its ability to inhibit or not proteases and kinases.¹⁷³

3. Biological potentials for sEH inhibition

EpFAs play a crucial role in biological functions, such as reducing inflammation and pain, dilating blood vessels, and protecting neurons. A growing body of studies indicated that many cardiovascular, CNS, and metabolic diseases, such as hypertension, arteriosclerosis, AD, PD, NAFLD, and diabetes, are related to the level of EpFAs in the human body and the expression of sEH.^{32, 174–176} Moreover, chemical inhibition or genetic knockout sEH, which yield a steady state of EpFAs level in the body, have beneficial effects on the physiological environment and greatly influence the above-mentioned diseases.¹⁷⁷

3.1 Cardiovascular diseases

The abnormal function of vascular endothelial cells plays a crucial role in the occurrence and development of cardiovascular diseases. The prevention of endothelial cell dysfunction is one of the key problems related to cardiovascular diseases to solve. EETs synthesized in

endothelial cells act as an autocrine and paracrine mediator of cardiovascular system, which has vasodilation and anti-inflammatory effects.¹⁷⁴ Therefore, sEH is considered in the treatment of cardiovascular diseases *via* improving the bioavailability of endothelium-derived hyperpolarization and relaxing factor EETs.³²

Hypertension is caused by a complex interaction of genes and several environmental factors, and is also one of the important causes of heart remodeling. Hypertension not only reduces the quality of life, but also increases the risk of other cardiovascular diseases.¹⁷⁸ Extensive researches have verified that endogenous EETs contribute to vasodilation in various organs, such as brain, kidney, intestine, and heart,^{45, 179, 180} especially 14,15-EET. They activate BK_{Ca} in vascular smooth muscle cells to promote K⁺ efflux and membrane hyperpolarization *via* modulating cAMP-mediated protein kinase A and ADP ribosylation of G_{αs} pathway, leading to the relaxation of blood vessels.^{40, 181–185} However, DHETs, sEH-mediated hydrolysates of EETs, exhibit weak relaxant effect,¹⁸⁴ which suggests that inhibition of sEH to stabilize levels of EETs is a therapeutic strategy for hypertension.¹⁷⁹ Present series of studies provide evidence that the expression level of sEH is increased in hypertensive rats.^{61, 186} For example, the increasing of sEH expression was observed in the kidney of spontaneously hypertensive rats and Ang II-induced hypertension rodent model.^{187, 188} The similar result was also found in aortic specimens from saline-fed and Ang II-infused rats,^{189, 190} demonstrating the presence of the relationship between sEH and hypertension. The *Ephx2* abolishment significantly decreases systolic blood pressure, and enhances the ratio of EETs/DHETs in a saline-fed-induced hypertensive model.¹⁹¹ Moreover, a great increase of evidence demonstrated that administration of sEH inhibitors, such as AUDA (**4**), TPPU (**19**), and *c*-AUCB (**9**), lowered blood pressure in the hypertensive mice model.^{67,192, 193} An orally administered sEH inhibitor AR9281 (APAU, **6**) developed by Arête Therapeutics Inc finished the Phase I and II clinical trials. AR9281 is safe and well tolerated for healthy volunteers, even administration with a high dose (single oral dose, 1000 mg; multiple dose, 400 mg every 8 hours for 7 days) in the Phase I clinical trial, whereas does not display thrilling efficacy in early-stage hypertension during the Phase II clinical trial.¹⁹⁴

Atherosclerotic diseases are the major causes of mortality worldwide. Atherosclerosis is a progressive disease characterized by the formation of foam cells, dyslipidemia, and accumulation of lipid plaques in the arterial wall.¹⁹⁵ Extensive epidemiological studies clearly revealed the correlation of the plasma cholesterol profile with atherosclerosis. In the course of atherosclerosis, low-density lipoprotein (LDL), especially oxidized-LDL, activates inflammation and foam cell formation, but high-density lipoprotein (HDL) has a protective effect on atherosclerosis. sEH inhibitors reduced atherosclerotic lesion formation in the deficient of apolipoprotein E (*apoE*^{-/-}) or LDL receptor (*Ldlr*^{-/-}) mice; these mice exhibited advanced lesions and increased in the LDL level.¹⁹⁶ In *apoE*^{-/-} mice, administration of a sEH inhibitor significantly decreased serum LDL concentrations and secretion of inflammatory factors.¹⁹⁶ In order to reveal the protective mechanism for inhibition of sEH, a study by Xu *et al.* reported that administration of *t*-AUCB (**8**) could enhance CD36-mediated recognition and interpretation of oxidized-LDL through the activation of PPAR γ , and further improve cholesterol outflow by increasing the ATP cassette A1 expression level,

which reduced the formation of atherosclerotic lesions in *Ldlr*^{-/-} mice.¹⁹⁷ Similarly, Shen *et al.* found that *t*-AUCB (**8**) treatment alleviated atherosclerosis symptoms in *Ldlr*^{-/-} mice as well *via* modulating the expression of ATP binding cassette transporter A1, cholesterol efflux, and plasma HDL levels.¹⁹⁸ In addition, inhibition of sEH with *t*-TUCB delayed the formation of hyperlipidemia and atherosclerosis in *Ldlr*^{-/-} mice, and *Ephx2* genetic abolishment significantly alleviated the symptoms of atherosclerosis as well.¹⁹⁵

Heart failure is caused by blocking blood flow to the heart, results in coronary heart disease, myocardial infarction, arrhythmia, viral myocarditis, and genetic cardiomyopathies.¹⁹⁹ A study by Seubert *et al.* has demonstrated the increasing of sEH activity in animal models of myocardial infarction, and the increasing of sEH expression was observed in the human hearts of patients with ischemic cardiomyopathy. Moreover, increasing EET levels protected against myocardial infarction and left ventricular dysfunction after ischemic injury in *Ephx2*^{-/-} mice.²⁰⁰ Inhibition of sEH with GSK2188931B and TUPS both protected heart failure.^{201, 202} For example, TUPS treatment reduced the thickness of heart wall, down-regulated the expression of hypertrophy markers atrial and brain natriuretic peptides, and regulated negative autophagy *via* activating mammalian target of rapamycin (mTOR) signaling, allowing in preventing myocardial hypertrophy induced by isoproterenol.²⁰² These data all suggested the therapeutic potential of sEH in heart failure.

Preclinical results have demonstrated that inhibition of sEH by inhibitors or *Ephx2* genetic knockout possesses beneficial effects, such as vasodilation, antihypertension, and anti-atherosclerotic effects. Although inhibition of sEH to treat human diseases still remains to be demonstrated in clinical trials, the increasing of positive effects of sEH inhibitors in cardiovascular diseases strongly supports the clinical role of sEH in cardiovascular diseases.

3.2 CNS diseases

EETs play an important role in CNS diseases, it can regulate angiogenesis and cerebral blood flow (CBF), and affect signal transduction process. Because of the abundant expression of sEH in various parts of the brain, the neuroprotective effect of sEH inhibitors has become an important research direction in the treatment of CNS diseases. In recent years, sEH inhibitors have been used in the treatment of CNS diseases, such as AD, PD, and depression with satisfactory performance.^{175, 203–205}

PD, one of the most common neurodegenerative diseases, leads to progressive motor deficits and non-motor symptoms, including speech, motor, and mental disorders.^{203, 204} In the course of onset, dopaminergic neurons in substantia nigra (SN) prematurely die and Lewy bodies accumulate in the brain.⁷¹ The current treatment works by increasing dopamine concentration and/or stimulating its receptors, but this treatment only targets basal ganglia and dopamine, but does not involve more neurons associated with PD. Therefore, this therapy is generally not very effective. In human and animal PD models, the expression level of sEH in brain regions is associated with dopaminergic death, endoplasmic reticulum (ER) stress, and tyrosine hydroxylase positive cell death, which can be alleviated by administration of AUDA (**4**), TPPU (**19**) or 14,15-EET.^{206, 207} EETs stimulate astrocytes to secrete nerve growth factors (NGFs), including vascular endothelial growth factor and brain-derived neurotrophic factor, which promotes the growth and differentiation of nerve cells

and protects neurons.¹⁷⁷ Administration of AUDA (**4**) reduced MPTP-mediated loss of TH positive cells in SN.²⁰⁷ Furthermore, the *Ephx2* abolishment protected against MPTP-induced neurotoxicity in STR, while overexpression of sEH in STR significantly enhanced MPTP-induced neurotoxicity.²⁰⁶ Moreover, the expression of the sEH protein in STR from MPTP-treated mice was significantly higher than control group. Interestingly, there was a positive correlation between sEH expression and p- α -synuclein in STR, suggesting that sEH may play a role in the phosphorylation of α -synuclein in STR. In model animals, administration of TPPU (**19**) increased dopamine, 3,4-dihydroxyphenylacetic acid, and homovanillic acid levels, and inhibited the apoptosis of parkinson disease protein 2 (PARK2) neurons. Accordingly, it is likely that sEH can act as a potential target for the treatment of PD.

AD is a neurodegenerative disease characterized by impaired learning, memory, and cognitive abilities. As our acknowledge, neuroinflammation is a critical factor causing AD and plays a crucial role in the development course of AD,^{208–210} therefore, 16% of currently on-going clinical trials for the treatment of AD is correlate with inflammation.²¹¹ Neuroinflammation is intimately linked to the oxidative stress associated with AD,^{212, 213} and controls the interactions between the immune system and the nervous system.²¹⁴ The senescence-accelerated mouse prone 8 (SAMP8) is a paradigm of late-onset AD and cognitive impairment in age, causing oxidative stress, neuroinflammation, tau hyperphosphorylation, and proamilodogenic APP processing.^{215–219} Gríñán-Ferré *et al.* found the increasing of sEH expression in the hippocampus of SAMP8 mice, and inhibition of sEH with TPPU (**19**), AS2586114, or UB-EV52 could reduce biomarkers of inflammation, oxidative stress, and ER stress.²²⁰ Similarly, these positive results also were observed in a 5 \times FAD mouse model of early-onset AD after administration of sEH inhibitors.²²⁰ A recent study has revealed that sEH level was increased in the brain and predominantly appeared in hippocampal astrocytes of APP/PS1 Tg mice.²²¹ Genetic deletion of sEH alleviates behavior outcomes and amyloid β (A β) accumulation, increases astrogliosis and the production of anti-inflammatory cytokines IL-4 and IL-10, and inhibits NF- κ B signaling pathway, resulting in a protective effect against AD.¹⁷⁵ Additionally, compared with healthy human, the analysis of clinical specimens demonstrated that sEH were overexpressed in Braak III and V phases of AD patients' brains,²²⁰ which confirmed the correlation of sEH with AD.

Depression and schizophrenia both have high mortality rates and involve a wide range of severe chronic mental illness.²⁰⁵ The pro-inflammatory cytokines in serum and cerebrospinal fluid are increased, and the sEH level is significantly increased in the parietal cortex of the brain of deceased-patients suffering of these diseases.²²² It strongly suggests that sEH is likely involved in the pathophysiological process of depression and schizophrenia. In LPS-treated depressed mice, TPPU (**19**), a sEH inhibitor, can significantly improve depressive symptoms by reducing the level of TNF- α , up-regulating the expression of BDNF in mouse hippocampus and PC12 cells, and enhancing NGF-induced neuronal growth in PC12 cells. Moreover, sEH knockout ameliorates symptoms of depression as well.²²³ Chemical inhibition on sEH by AS2586114 decreases levels of 11,12-DHET and 14,15-DHET, and improves hyperactivity and pre-pulse inhibition defects in phencyclidin-induced

schizophrenia.²²⁴ Thus, the inhibition of sEH appears to exert anti-depressant and anti-schizophrenic effects by increasing the concentration of EETs, regulating BDNF-tropomyosin receptor kinase B (BDNF-TrkB) signaling pathway, and preventing oxidative stress.²²²

Additionally, sEH is also involved in epilepsy and stroke. Administration of sEH inhibitors could prevent neuroinflammation and reduce the number and duration of seizures of epilepsy.^{55, 225} After treatment with AUDA (**4**), the expression of inflammatory factors decreased and the EETs/DHETs ratio increased, while at the same time, the epileptic induction threshold was increased and the epileptic sensitivity was decreased. There is a correlation between the mutation of Arg287Gln of sEH, which led to a decrease of sEH activity and a reduced risk of stroke.³⁰ Chemical inhibition can reduce astrocyte infiltration, glial scar formation, microglial activation, neuronal death, insufficient blood flow, and behavioral disorder after cerebral ischemia.²²⁶ Put together, sEH has a clear role in CNS health and diseases, and represent a potential target for treatment.

3.3 Metabolic diseases

Besides cardiovascular and CNS diseases, sEH is closely related to metabolic diseases, including NAFLD, diabetes, and obesity. Many studies have shown overexpression of sEH in many liver diseases, such as NAFLD, non-alcoholic steatohepatitis²²⁷, and hepatic fibrosis.²²⁷⁻²³¹ NAFLD is caused by excessive fat accumulation in hepatocytes, affecting approximately 25% of the global adult population. Some of preclinical results verified that sEH inhibition was to the benefit of NAFLD and NASH. Iyer *et al.* investigated the role of sEH inhibition in high-carbohydrate and high-fat diet (HCHFD)-induced rat model.³³ The inhibition of sEH with *t*-AUCB (**8**) alleviated HCHF -induced liver hypertrophy and steatosis, had significant improvements in plasma lipid levels and insulin sensitivity, and suppressed the increasing of aspartate aminotransferase (AST) and lactate dehydrogenase (LDH) levels.³³ Similarly, chemical inhibition of sEH or *Ephx2* genetic abolishment has a protective role in high-fat diet (HFD)-induced NAFLD.²³² *t*-AUCB (**8**) could reduce HFD-induced macrophage accumulation, downregulate mRNA expression levels of pro-inflammatory cytokines TNF- α , IL-6, MCP-1, and IFN, leading to the improvement of HFD-induced inflammation *via* the activation of MAPK pathway (JNK and p38).²³² However, overexpression of sEH by the injection of adenoviruses encoding human sEH resulted in the aggravation of metabolic syndromes, such as the increasing of triglyceride and pro-inflammatory cytokine and the upregulation of JNK and p38.²³² Conversely, the *Ephx2* deletion alleviated hepatic steatosis and tissue inflammatory described as administration of *t*-AUCB (**8**), which suggested the role of sEH-mediated hepatic steatosis. The role of sEH in NAFLD also was supported in a high methionine diet-induced hyperhomocysteinemia and hepatic steatosis.²³³ Accumulating evidence revealed that hyperhomocysteinemia disturbs lipid metabolism in the liver and is served as a significant risk factor. A study by Yao *et al.* demonstrated that sEH inhibition by TPPU (**19**) ameliorated hyperhomocysteinemia-induced lipid accumulation, further mechanism investigation suggested that the increase of EETs through the inhibition of sEH by TPPU (**19**), especially 11,12-EET, elevated the expression levels of PPAR α target genes and activated PPAR α .²³³ These findings suggested that the increase of sEH activity was a

critical threaten in hyperhomocysteinemia-induced hepatic steatosis, and sEH inhibition might be regarded as an effective means to treat hyperhomocysteinemia-induced hepatic steatosis.

Inflammasome is responsible for the modulation of the adaptive response of the liver to pathogenic challenge, and a library of evidences demonstrated that sEH inhibition could suppress inflammasome activation to reduce hepatic inflammation.²³⁰ Administration of PTUPB (**68**), a sEH/COX-2 dual inhibitor, could block fibrotic progression by suppressing collagen deposition and down-modulating Col1a1, Col1a1a3, and α -SMA expression levels. The dual inhibition of sEH and COX-2 also suppressed the NLRP3 inflammasome activation through the decrease of Nlrp3/NLRP3 and Asc expression, and reduced the downstream target protein of NLRP3, pro-caspase 1, pro-IL-1 β , and pro-IL-18. Besides, PTUPB (**68**) treatment decreased the release of pro-inflammatory cytokines IL-6 and MCP-1.²³⁰ Accordingly, it was worth noting that the role of sEH in inflammasome activation still need further be studied.

Diabetes is mainly due to the lack of insulin produced by pancreatic β -cells or the insensitivity of the target tissue to insulin, leading to the severe injuries to organs.²³⁴ A growing body of evidences have demonstrated that the stabilization of EETs, inhibition of sEH by sEH inhibitors or *Ephx2* genetic deletion plays a crucial role in diabetes. A study by Schaefer *et al.* verified that EETs enhanced insulin signaling through the regulation of Akt expression level rather than affecting levels of insulin receptor.⁷² Furthermore, the insulin release was also promoted by 5,6-EET, while 8,9-EET, 11,12-EET, and 14,15-EET might promote the release of glucagon and increase the level of blood glucose, which suggested that increasing the concentration of EETs through inhibiting sEH might be a potential pathway to treat diabetes.³² In streptozotocin (STZ)-induced diabetic mice, administration of *t*-AUCB (**8**) attenuated hyperglycemia and had protective effects against β -cell damage.²³⁵ An investigation by Pardeshi *et al.* has been reported that TPPU (**19**) reduced the level of fasting blood glucose, improved the cognitive impairment and memory impairment by stabilizing EETs to dilate arterioles, and increased cerebral blood perfusion in STZ-induced diabetes.²³⁶ A similar result was also observed after administration of *t*-AUCB (**8**).²³⁷ In addition, inhibition of sEH or *Ephx2* knockout has been found to alleviate symptoms of hyperglycemia and insulin resistance in HFD-induced type 2 diabetes,²³⁸ which might activate insulin signaling in the liver and adipose tissue.

Diabetes also causes many complications, such as retinopathy, nephropathy, and cardiovascular diseases, and seriously affect a patient's quality of life. A great number of studies have verified that inhibition of sEH by inhibitors or genetic knockout sEH is beneficial to diabetic complications.^{228, 239} Diabetic retinopathy is one of diabetic complications caused by progressive loss of vascular cells and slow dissolution of vascular junctions.²⁴⁰ The expression of sEH is increased in human retina and vitreous of diabetic retinopathy. Furthermore, overexpression of sEH in retinal Müller glial cells can result in vascular abnormalities in diabetic retinopathy.²³⁹ Therefore, the overexpression of sEH is a key factor in the pathogenesis of diabetic retinopathy. Jouihan *et al.* found that STZ treatment promoted sEH mRNA expression and reduced EET level in cerebral vessels.²²⁸ Furthermore, brain infarction was exacerbated in STZ-treated mice after middle cerebral

artery occlusion, which was reversed through the inhibition of sEH by *t*-AUCB (**8**). Moreover, sEH is related to diabetic cardiomyopathy since sEH is highly expressed in the heart tissue of type 1 diabetes mice.²³¹ In addition, sEH genetic disruption reduced levels of blood urea nitrogen and creatinine as well *via* suppressing renal tubular apoptosis and enhancing renal endothelial function, allowing in the alleviation of diabetic nephropathy.^{229, 230}

So far, a selective sEH inhibitor GSK2256294 (**67**) has finished its Phase I clinical trial, which clinical experimental data demonstrated its safety and sustained inhibitory effect against sEH.¹⁷³ These results supported further clinical trials in patients with endothelial dysfunction, such as diabetes. In 2018, Vanderbilt University Medical Center sponsored the Phase II clinical trial of GSK2256294 (**67**) to treat diabetes, endocrine system diseases, glucose metabolism disorders, and obesity, and started volunteer recruitment.

Obesity is a global public health problem and a major risk factor for diseases as same as cancer and diabetes. In metabolic disorders, chemical inhibition of sEH or *Ephx2* deletion is capable of lessening body weight gain, lowering blood pressure, and suppressing the production of inflammatory cytokines.^{78, 241, 242} Moreover, the increasing of sEH expression has been found in adipose tissue of obese mice,^{78, 241, 242} revealing the potential correlation of sEH with obese. A growing body of evidence indicates that ER is a known cellular consequence of metabolic diseases, such as obesity and NAFLD.²⁴³ Importantly, sEH deficiency or inhibition in mice attenuated HFD-induced ER stress in liver and adipose tissue. Similarly, the inhibition of sEH in 3T3-L1 preadipocytes mitigated chemical-induced ER stress and activation of JNK, p38, and cell death.⁵⁴ A study by Lopez-Vicario *et al.* has reported that *t*-TUCB could stabilize the levels of EpFAs, 17,18-epoxyeicosatetraenoic acid (17,18-EEQ) and 19,20-epoxydocosapentaenoic (19,20-EDP) derived from omega-3.²⁴⁴ Moreover, *t*-TUCB promoted the polarization of macrophage to anti-inflammatory M2-type cells, induced hepatic autophagy *via* increasing Atg12-Atg5 and LC3-II expression levels, reduced p62 expression and ER stress *via* suppressing p-IRE-1 α and p-eIF2 α expression levels.²⁴⁴ The inhibition of sEH to exert a protective effect was also confirmed in palmitate-primed hepatocytes and adipocytes through the incubation of 19,20-EDP or 17,18-EEQ,²⁴⁴ which suggested that sEH was a physiological modulator of ER stress and a potential target for the treatment of obesity. In short, the inhibition on sEH blocks the progression of obesity, and is of great significance for obesity and related diseases.

4. Conclusion and perspective

In this review, we described a complete picture of chemically synthesized or naturally obtained sEH inhibitors. Among these inhibitors, urea-based compounds are the most prominent because they can accommodate well the active pocket of sEH hydrolase and form stable hydrogen bonds, and have in general a good selectivity for sEH. Besides potency, the main drivers for improvement have been to increase water solubility and other physical properties as well as better bioavailability and PK parameters. Toward solving these problems, amides are good alternatives to ureas for sEH inhibition. In addition, the introduction of secondary polar groups and tertiary pharmacophore into the structure of the inhibitors would greatly help with the design of “Better” inhibitor. Nowadays, Nature is

providing more and more structural skeletons on which to build potent sEH inhibitors besides ureas and amides, such as flavones, and triterpenoids. These compounds have their advantages and disadvantages, which provide more space for the development and optimization of future sEH inhibitors.

Currently, sEH is a potential therapeutic target in multiple diseases related to inflammation, such as cardiovascular (hypertension and arteriosclerosis), CNS (AD, PD, and depression), and metabolic (diabetes, NAFLD, NASH, and obesity) diseases. Moreover, some sEH inhibitors, such as AR9281, EC5026, and GSK2256294, are underway clinical trials to treat heart failure, insulin resistance, glucose intolerance, hypertension, endothelial dysfunction, and pain, while future researches in some key areas are needed to further elucidate its applications and action mechanisms. Compared with the function of C-terminal hydrolase, the role of the N-terminal phosphatase domain is still undetermined. Although Kramer *et al.* has firstly discovered *in vivo* active inhibitors of sEH phosphatase with favorable PK, its N-terminal physiological function needs to be further in-depth investigated. Future studies should consider that inhibition of sEH C-terminal activity remains its phosphatase activity, discovering any differences in phenotype between sEH hydrolase inhibitor-treated and *Ephx2* deficiency animals.

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Biographies

Dr. Cheng-Peng Sun graduated from Shenyang Pharmaceutical University in 2016 and received Ph.D. in Natural Medicinal Chemistry under the guidance of Prof. Feng Qiu. Afterward, he joined the Department of Medicinal Chemistry in Dalian Medical University. In January 2019, he was promoted to Associate Professor of Natural Medicinal Chemistry at Dalian Medical University. So far, he has published more than 40 papers on journals indexed by the Science Citation Index. His major research interests include extraction and isolation of chemical constituents from natural medicines, structural modification of active compositions, and natural modulators of sEH, FXR, and PXR. In addition, he is focusing on the prevention and treatment of neurodegenerative diseases.

Dr. Xin-Yue Zhang graduated from Dalian Medical University and received her Bachelor's degree in 2019. She is pursuing a Master's degree at the Dalian Medical University, in the research group of Professor Xiao-Chi Ma. Her research focuses on the active substances of traditional Chinese medicine and the discovery of sEH inhibitors.

Dr. Christophe Morisseau obtained his Ph.D. in organic chemistry in 1995 from the Université de la Méditerranée in Marseille, and since he has been working with Prof. Hammock at UC Davis. He is now a Professional Researcher faculty. He is working at

understanding the mechanism and biological role of EHs and developing selective tight binding inhibitors for EHs. He developed the first stable highly potent inhibitor of human sEH, obtained the first crystal structures for sEH, the first high-throughput assays for the human sEH and mEH, and developed more biochemical tools to study EHs. Some of the inhibitors he obtained are in development for the treatment of inflammation, cardiovascular disease, pain, and cancer. His work has resulted in more than 250 papers and 20 patents.

Dr. Sung Hee Hwang obtained his Ph.D. in organic chemistry in 2004 from the University of California, Davis. He is an accomplished medicinal chemist. He leads the development of highly potent inhibitors of epoxide hydrolase and cyclooxygenase enzymes. In addition, he has synthesized various fattyacids and their cytochrome P450-metabolite analogs to study their biological activities. His work has resulted in more than 100 publications.

Prof. Zhan-Jun Zhang received his Ph.D. in medicine from Beijing University of Chinese Medicine in 2005, and is the director of the Center for Beijing Aging Brain Rejuvenation Institute and the vice president of State Key Laboratory of Cognitive Neuroscience and Learning Beijing Normal University. He has been engaged in a long-term research of digging the pattern of varied human advanced cognitive functions decline, the degradation mode of brain's structure and function network, the mechanism of genetic variation towards brain and cognitive aging, and the contribution of Chinese medicine in protecting the brain from aging. He is the recipient of the National Science Fund for Distinguished Young Scholars and the New Century Excellent Talents Program of China's Ministry of Education.

Prof. Bruce D. Hammock received his Ph.D. in entomology and toxicology in 1974 from the University of California Berkeley. He is now a Distinguished Professor at the University of California, Davis. Dr. Hammock is an elected member of the National Academy of Sciences, US since 1999. He discovered the sEH and has devoted his career studying the biological roles of this enzyme. He has over 30 years of extensive experience in the field of eicosanoids that has yielded over 1,200 publications and 100 issued patents on synthesis, pharmacology, and biological action of eicosanoids and sEH inhibitors.

Prof. Xiao-Chi Ma received his Ph.D. in phytochemistry from School of Traditional Chinese Medicine, Shenyang Pharmaceutical University in July 2005, under the guidance of Prof. De-An Guo and Li-Jun Wu. He worked as a postdoctor in School of Pharmaceutical Sciences, Peking University, and mainly focused on Biological fermentation, tissue culture of endangered plant medicine, biotransformation of natural products by microorganism and plant suspension cells and phytochemistry. In 2008, he joined in the Dalian medical university, and was promoted to Professor of Natural Medicinal Chemistry at Dalian Medical University in 2012. He is the recipient of the National Science Fund for Excellent Young Scholars. His major research interests include effective substances from traditional Chinese medicine, drug metabolism, development and application of small molecular probe.

ABBREVIATIONS USED

AA	arachidonic acid
A β	amyloid β

AD	Alzheimer's disease
AFIMU	1-(adamant-1-ylmethyl)-3-{{5-(furan-2-yl)isoxazol-3-yl}methyl}urea
AMMU	1-(adamant-1-ylmethyl)-3-[(3-methylisoxazol-5-yl)methyl]urea
Ang II	angiotensin II
APU	1-(adamantan-2-yl)-3-phenethylthiourea
AUC	area under the curve
AUDA	12-(3-adamantan-1-yl-ureido) dodecanoic acid
AUDA-nBE	AUDA <i>n</i> -butyl ester
BDNF-TrkB	BDNF-tropomyosin receptor kinase B
c-AUCB	<i>cis</i> -4-[4-(3-adamantan-1-ylureido)cyclohexyloxy]benzoic acid
CBF	cerebral blood flow
CNS	central nervous system
CPU	<i>N</i> -cyclohexyl- <i>N'</i> -(3-phenylpropyl)-urea
COXs	cyclooxygenases
CYP	cytochrome P450
DCU	<i>N,N'</i> -dicyclohexyl-urea
DHA	docosahexaenoic acid
DHETs	dihydroxyeicosatrienoic acids
DPN	<i>N</i> -(3,3-diphenyl-propyl)-nicotinamide
EETs	epoxyeicosatrienoic acids
EpFAs	epoxy-fatty acids
FAAH	fatty acid amide hydrolase
FLAP	5-LOX-activating protein
HBAU	1,1'-(heptane-1,7-diyl)bis(3-(adamantan-1-yl)thiourea)
HCHFD	high-carbohydrate and high-fat diet
HDL	high-density lipoprotein
HETEs	hydroxy eicosatetraenoic acids
HFD	high-fat diet
HLM	human liver microsome

ITBU	<i>N</i> -[9-(isopropylsulfonyl)-1-oxa-9-azaspiro[5.5]undec-4-yl]- <i>N'</i> -[4-(trifluoromethoxy)benzyl]urea
K_i	kinetic constant
k_{off}	dissociation rate constant
LDL	low-density lipoprotein
IL-1β	interleukin-1 beta
LOXs	lipoxygenases
LXs	lipoxins
LPS	lipopolysaccharide
LTB4	leukotriene B4
LTs	leukotrienes
mp	melting point
mTOR	mammalian target of rapamycin
NADPH	nicotinamide adenine dinucleotide phosphate
NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
NF-κB	nuclear factor-kappa B
PD	Parkinson's disease
PK	pharmacokinetic
PARK2	parkinson disease protein 2
PPARγ	peroxisome proliferator-activated receptor gamma
RLM	rat live microsome
sEH	soluble epoxide hydrolase
S-PPU	(<i>S</i>)-1-(1-phenylethyl)-3-(3-phenylpropyl) urea
STZ	streptozotocin
<i>t</i>-AUCB	<i>trans</i> -4-[4-(3-adamantan-1-ylureido)cyclohexyloxy]benzoic acid
TNF-α	tumor necrosis factor- α
TZD	thiazolidinedione

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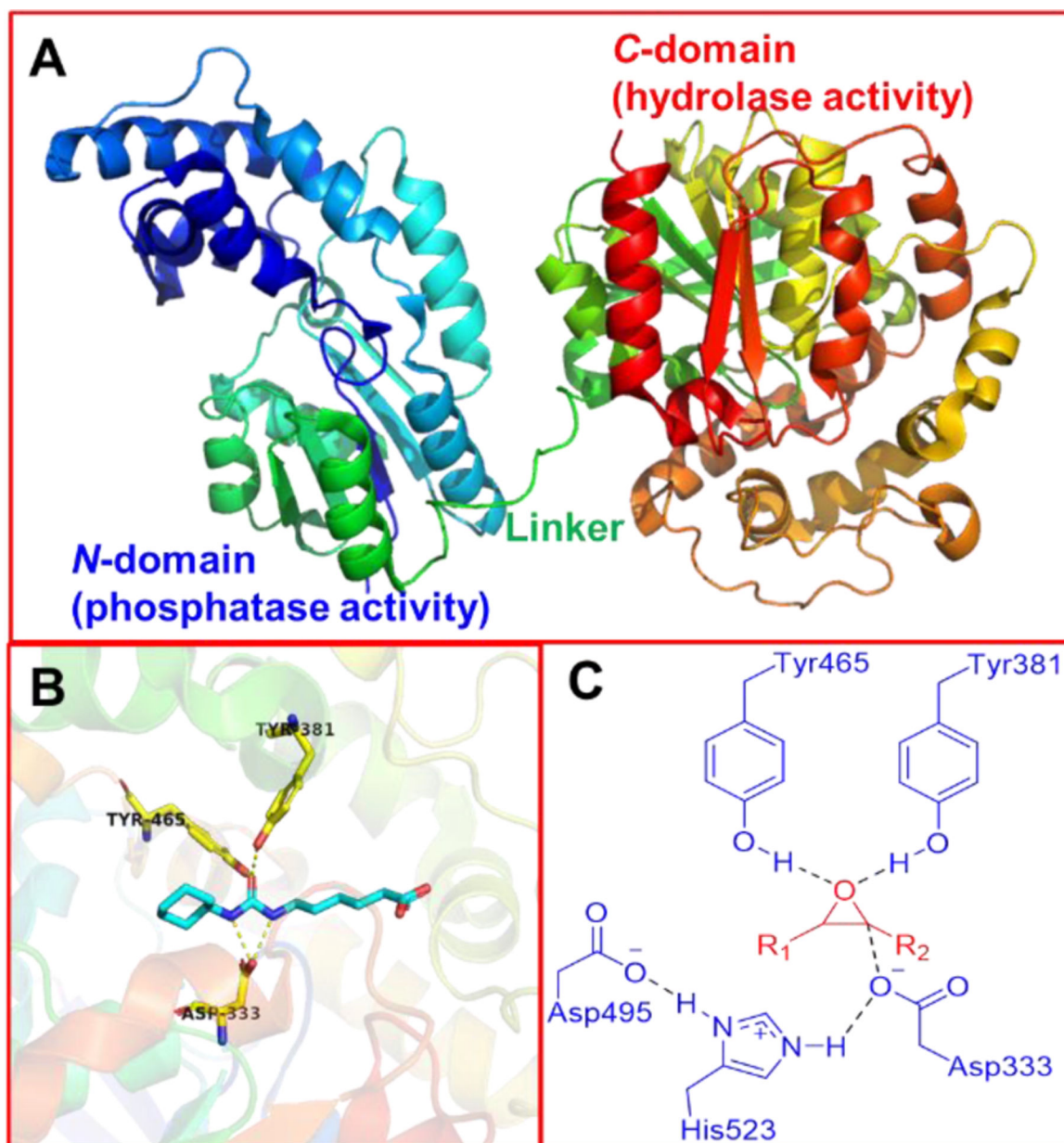


Figure 1.

(A) X-ray cocrystal structure of a single subunit of the human sEH (PDB code 1ZD4). (B) X-ray cocrystal structure of human sEH C-domain showing the binding site (PDB code 1ZD4). (C) The potential interactions between epoxides and human sEH C-domain.

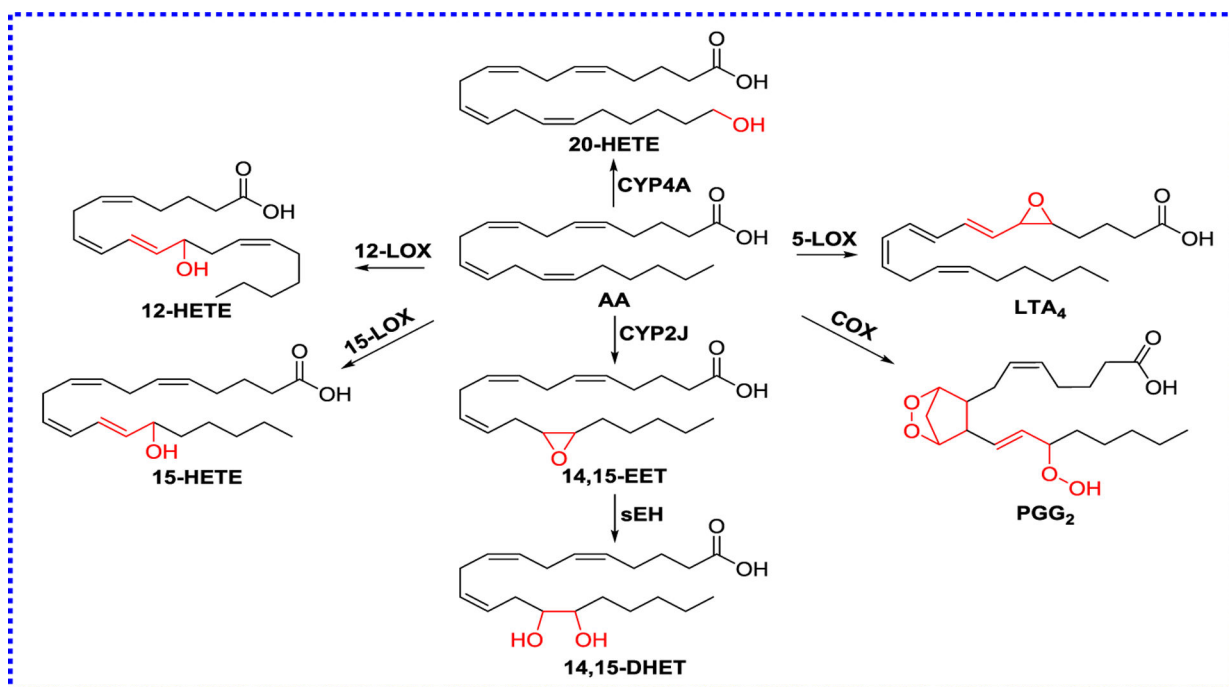


Figure 2.
The metabolic pathways of AA

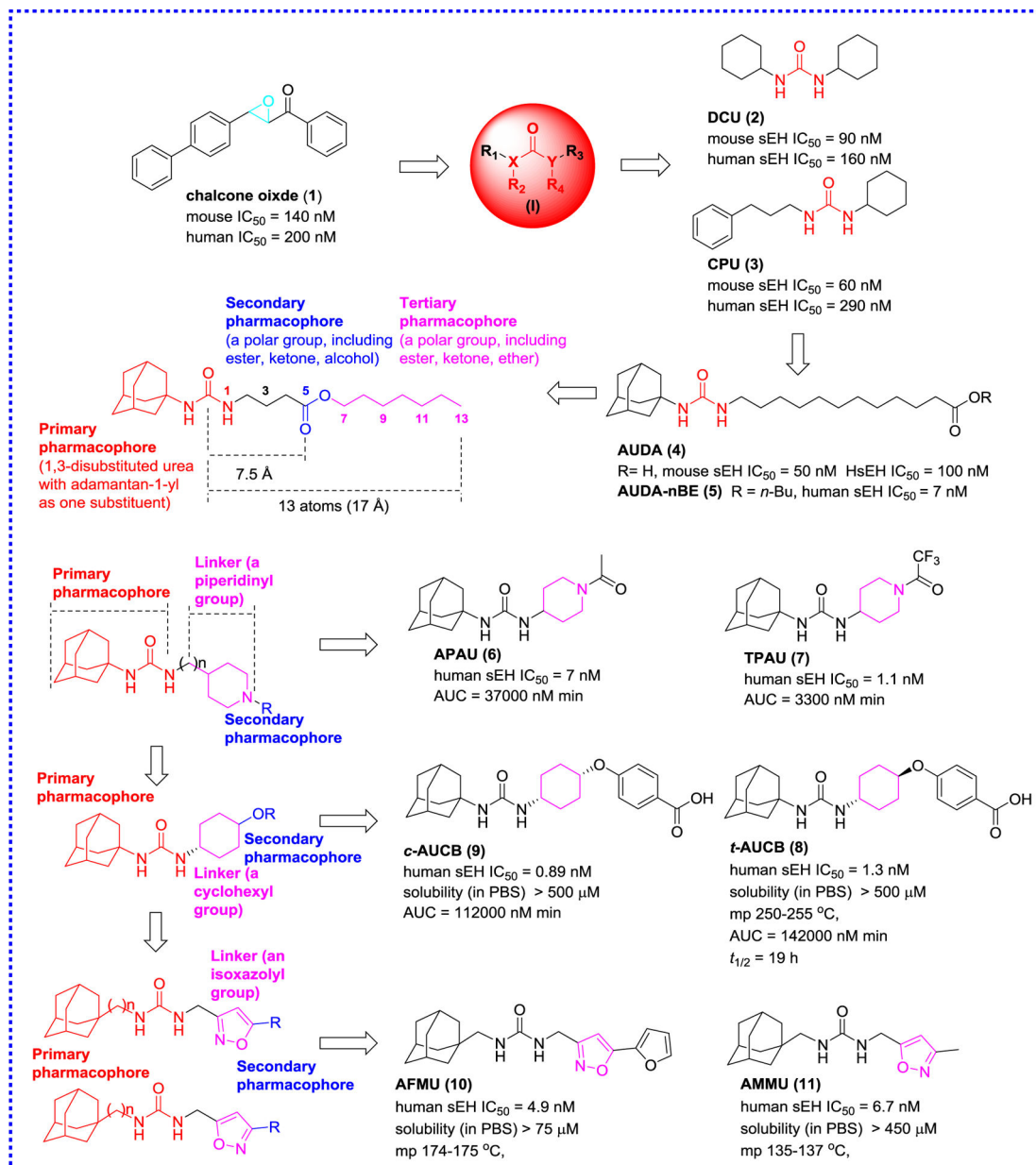


Figure 3. Representative sEH inhibitors and development of early sEH inhibitors

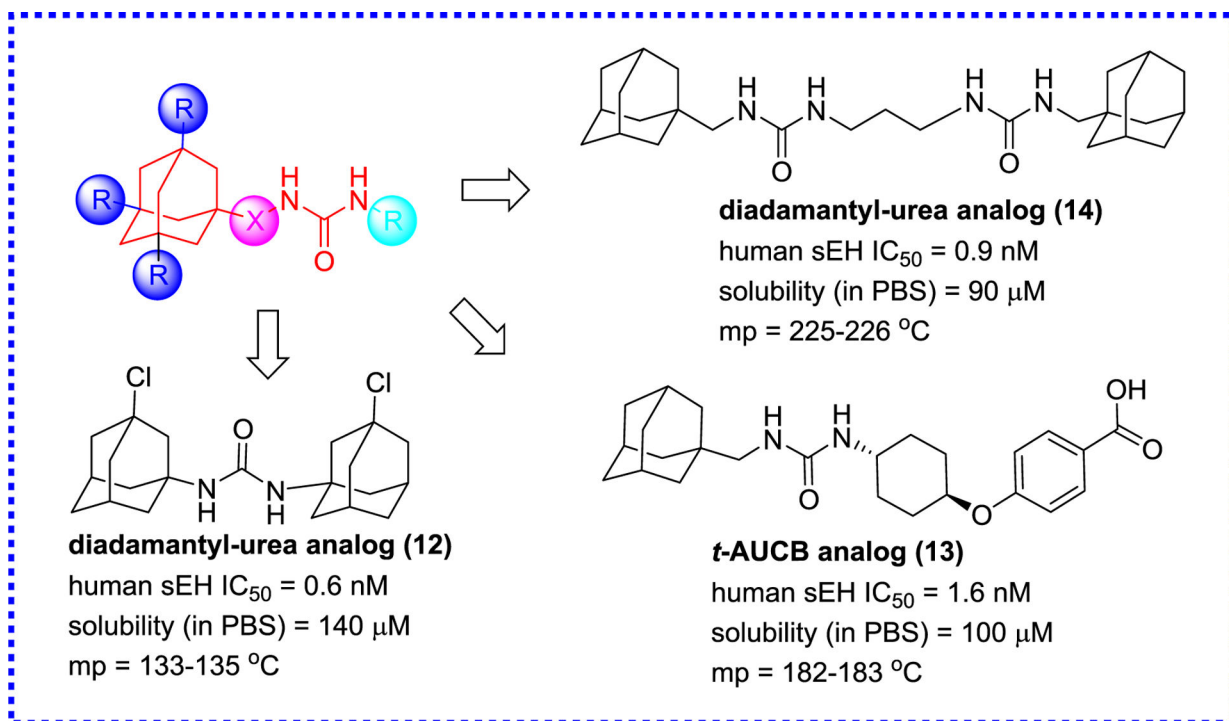


Figure 4.
 Optimization of adamantyl-ureas

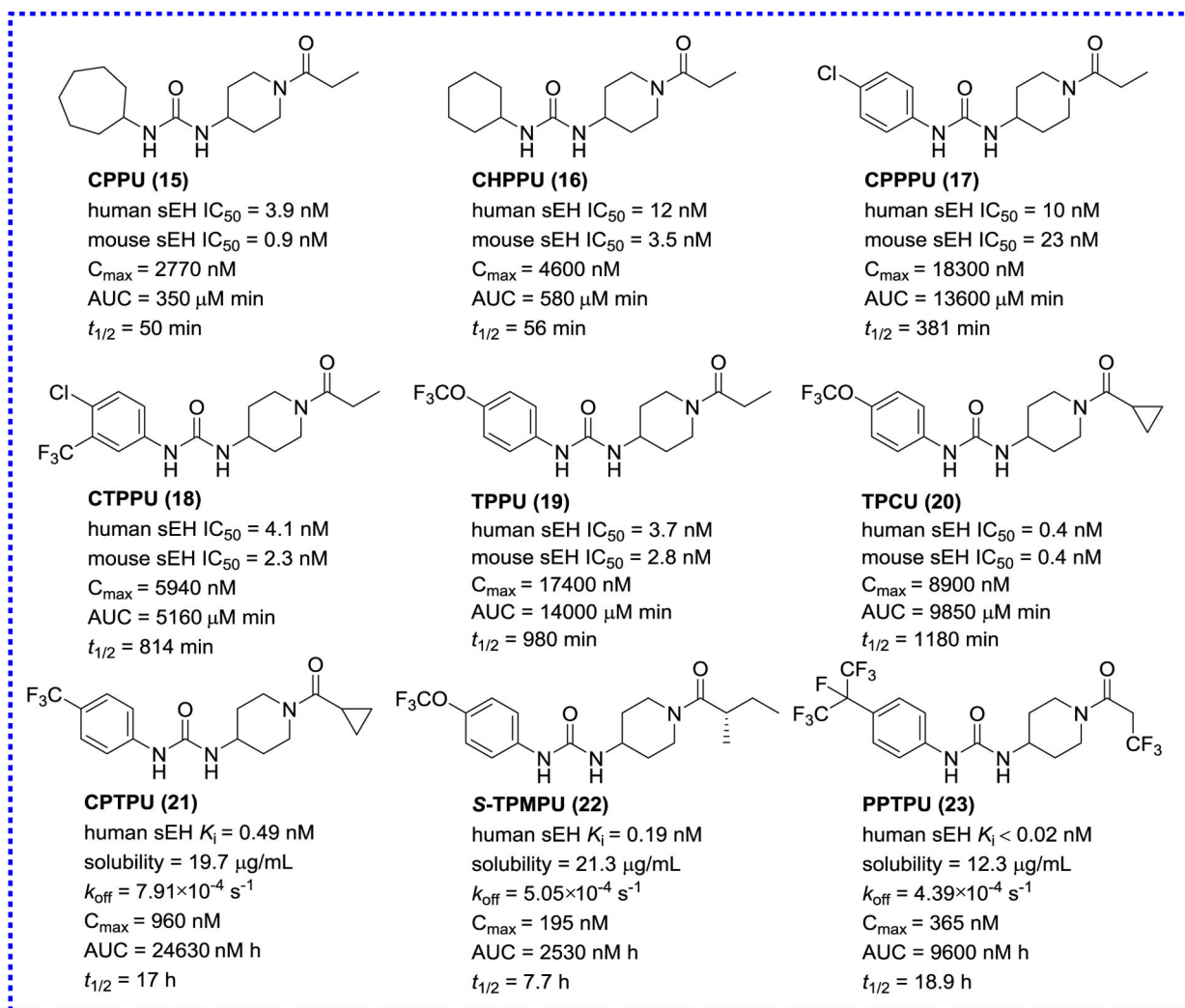


Figure 5.
 Representative urea sEH inhibitors

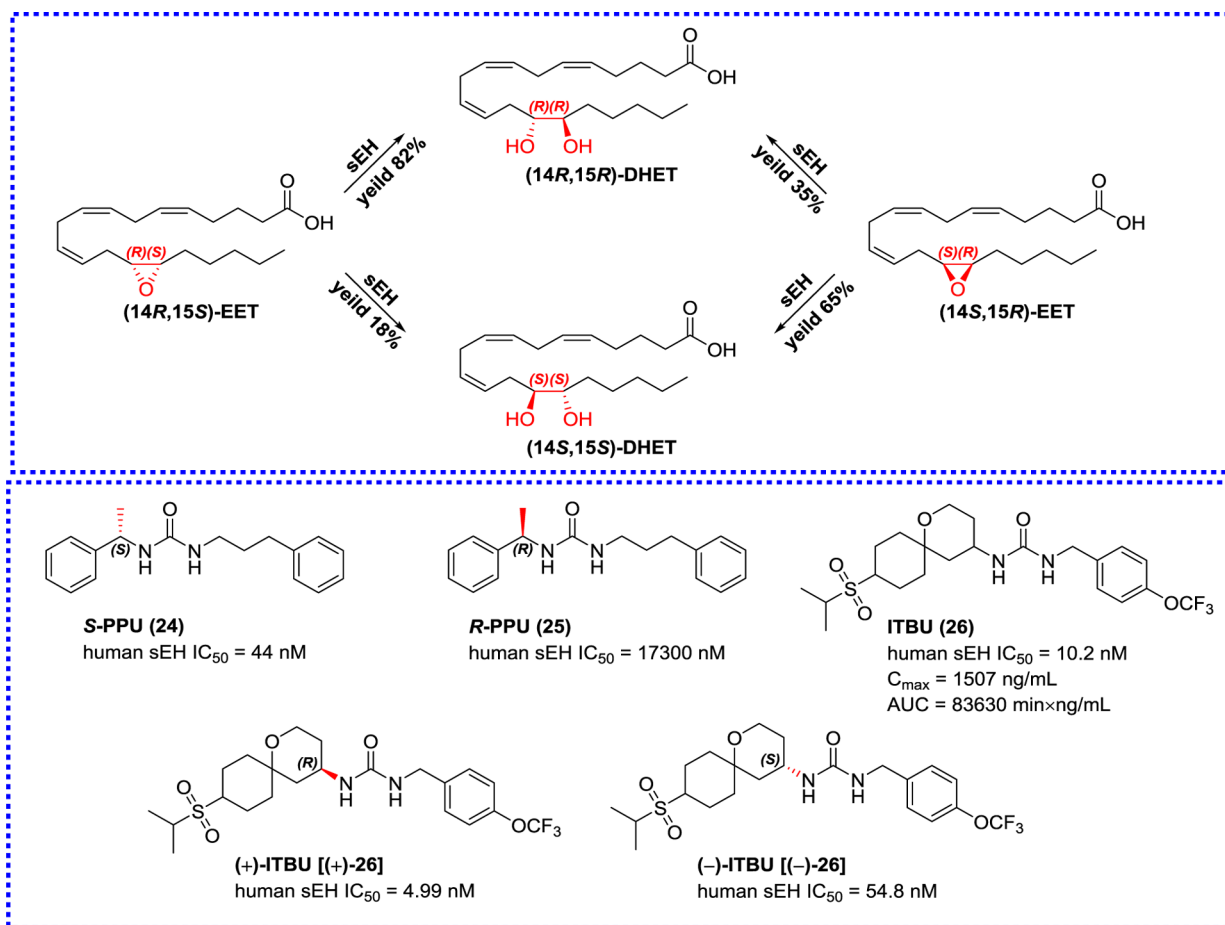


Figure 6.
The influence of stereo configurations on inhibitory potentials and representative sEH inhibitors

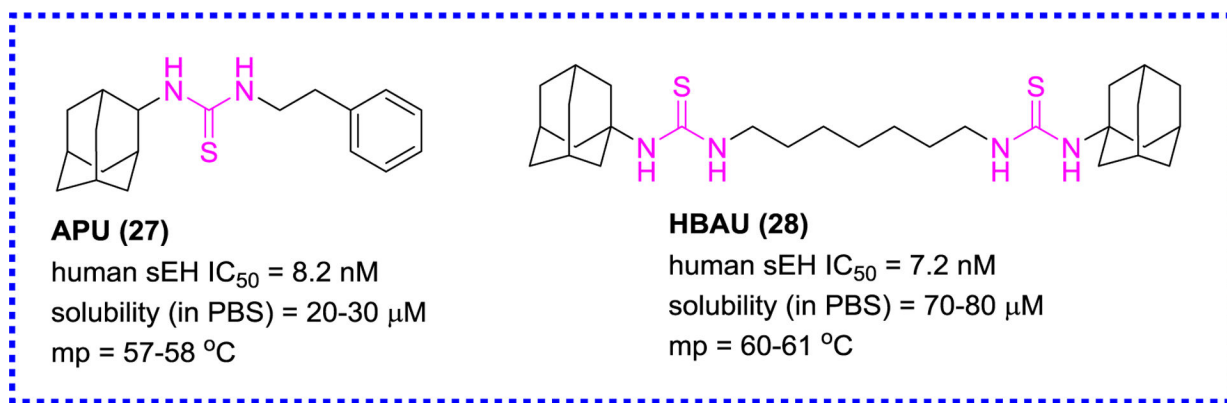


Figure 7.
Representative thiourea-based sEH inhibitors

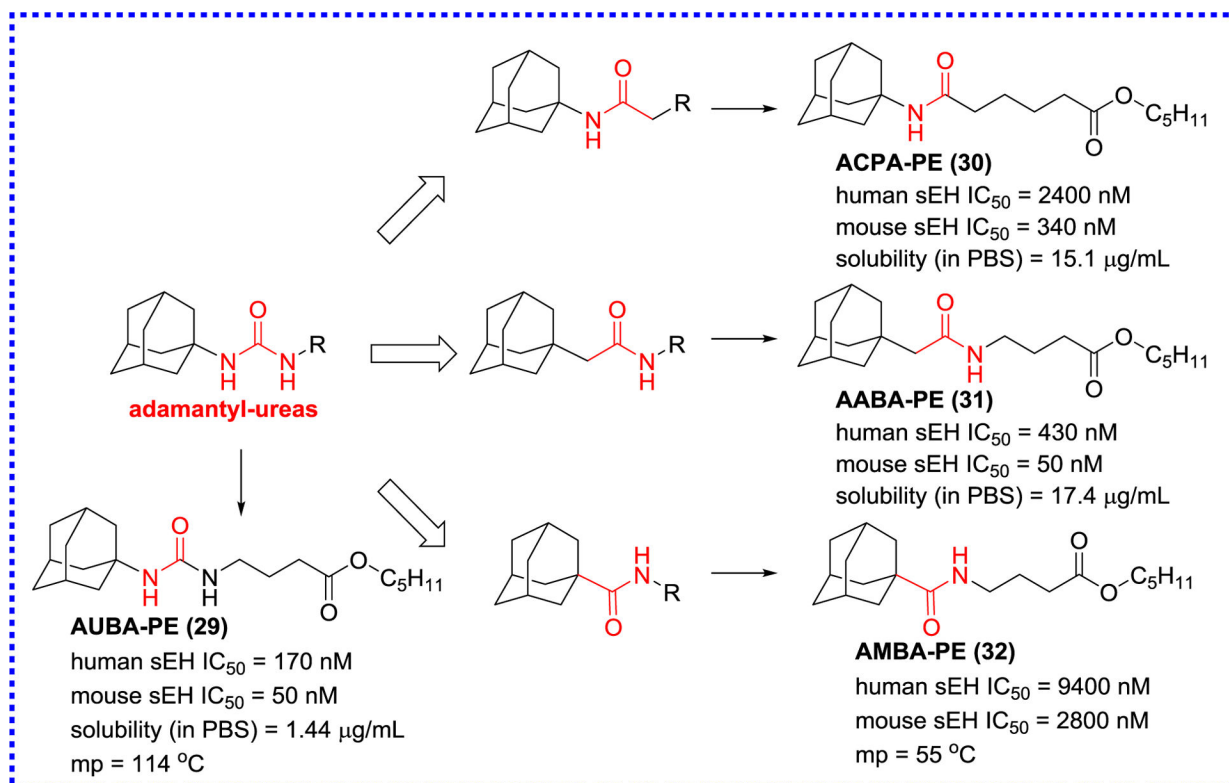


Figure 8.
 The modification of adamantyl-ureas to afford amide inhibitors

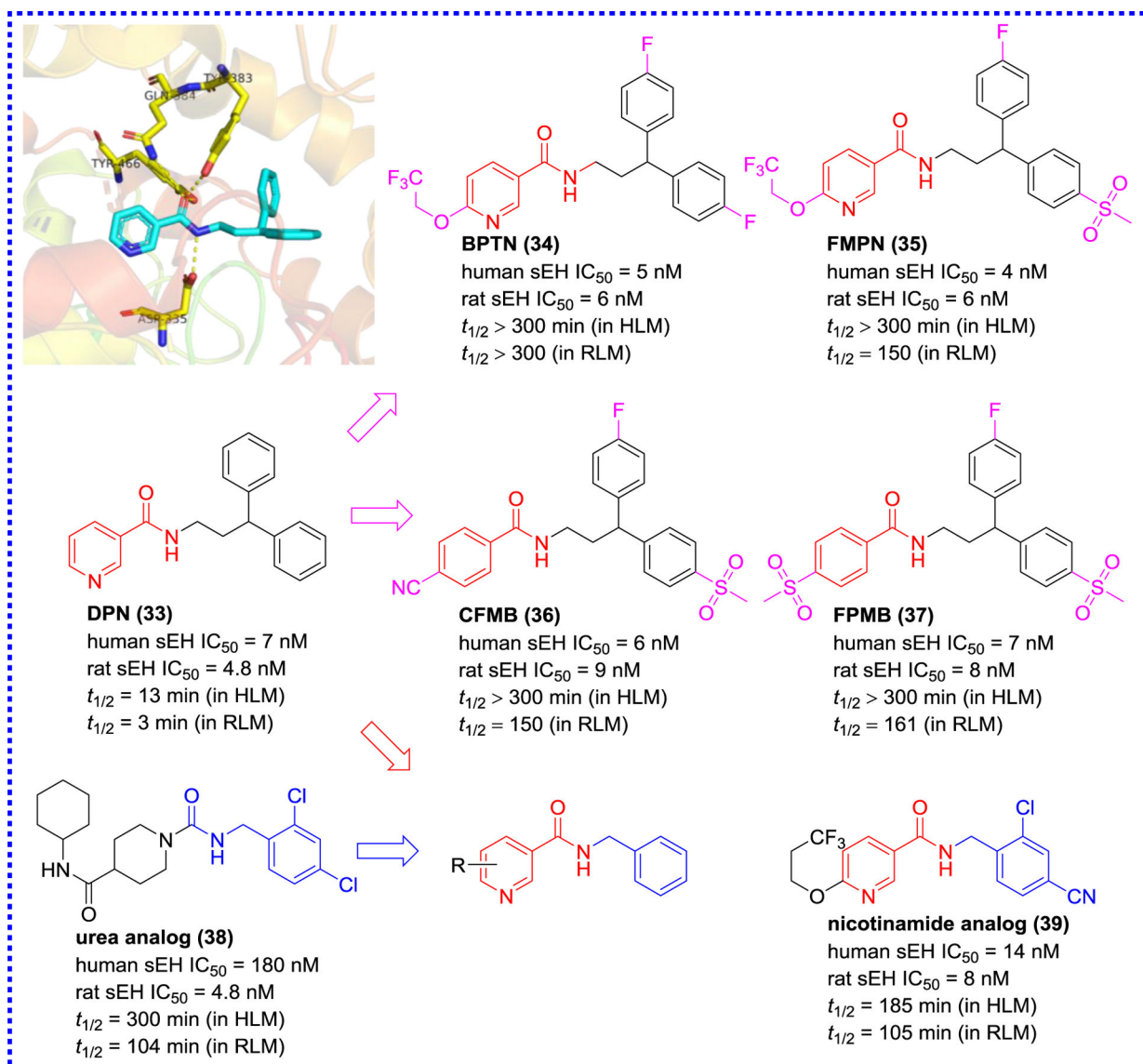


Figure 9. X-ray co-crystal structure of DPN (33) with sEH (PDB code 311Y) and its optimization.

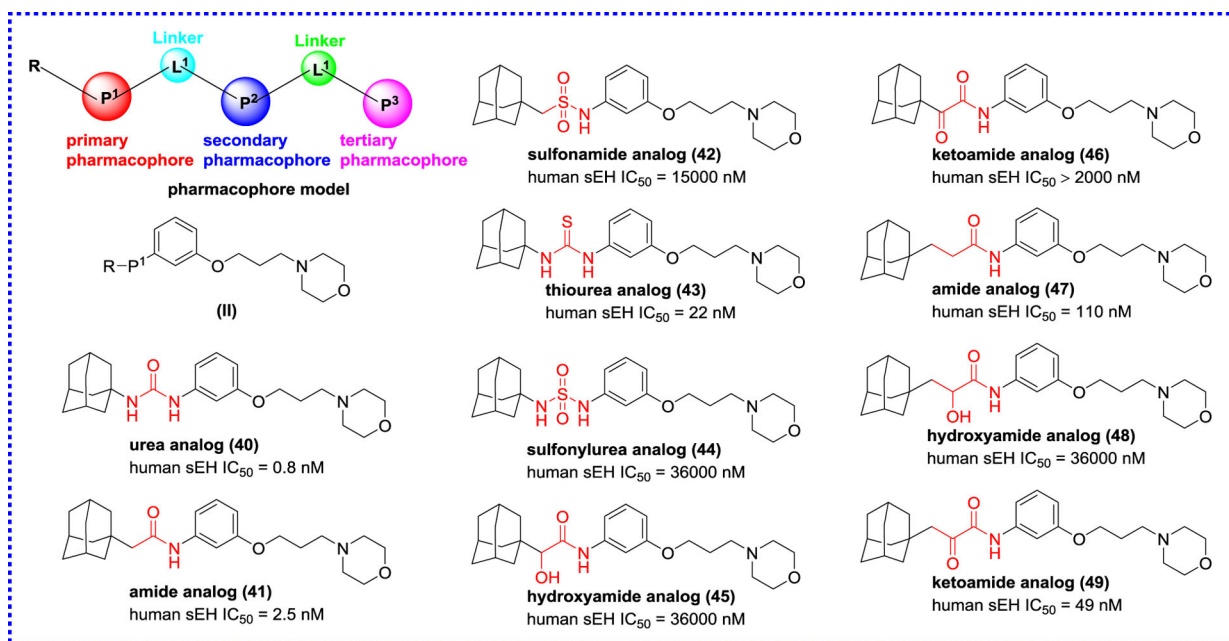


Figure 10.
Modification based on the skeleton.

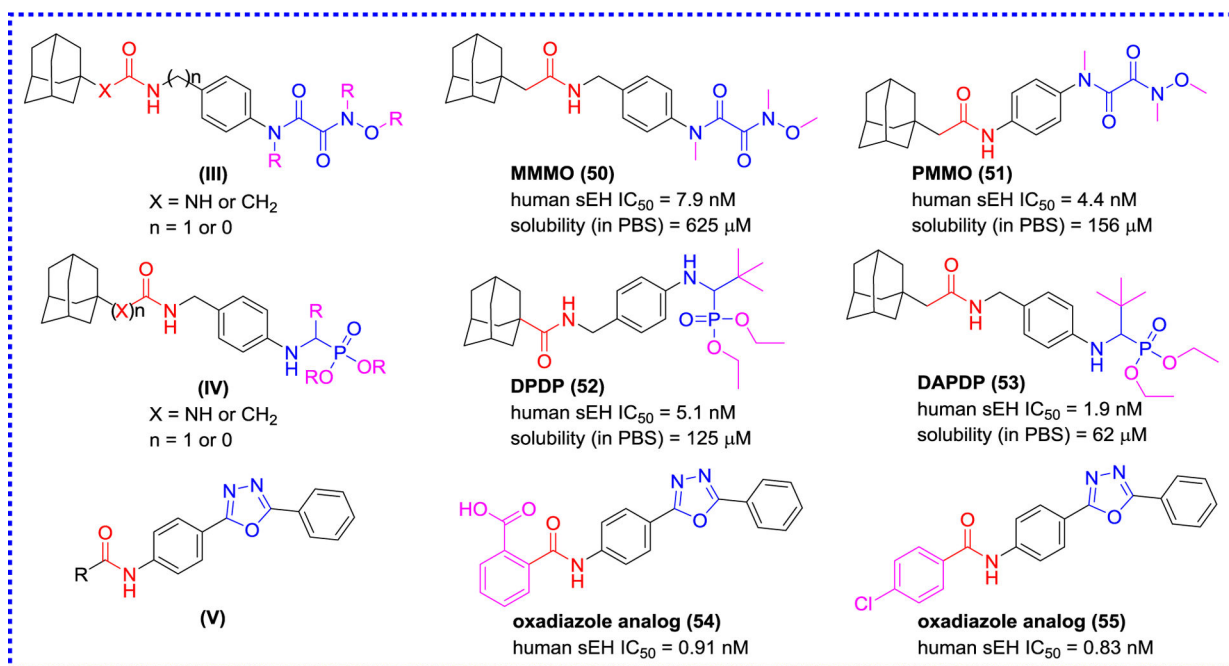


Figure 11.
Modification of the secondary pharmacophore.

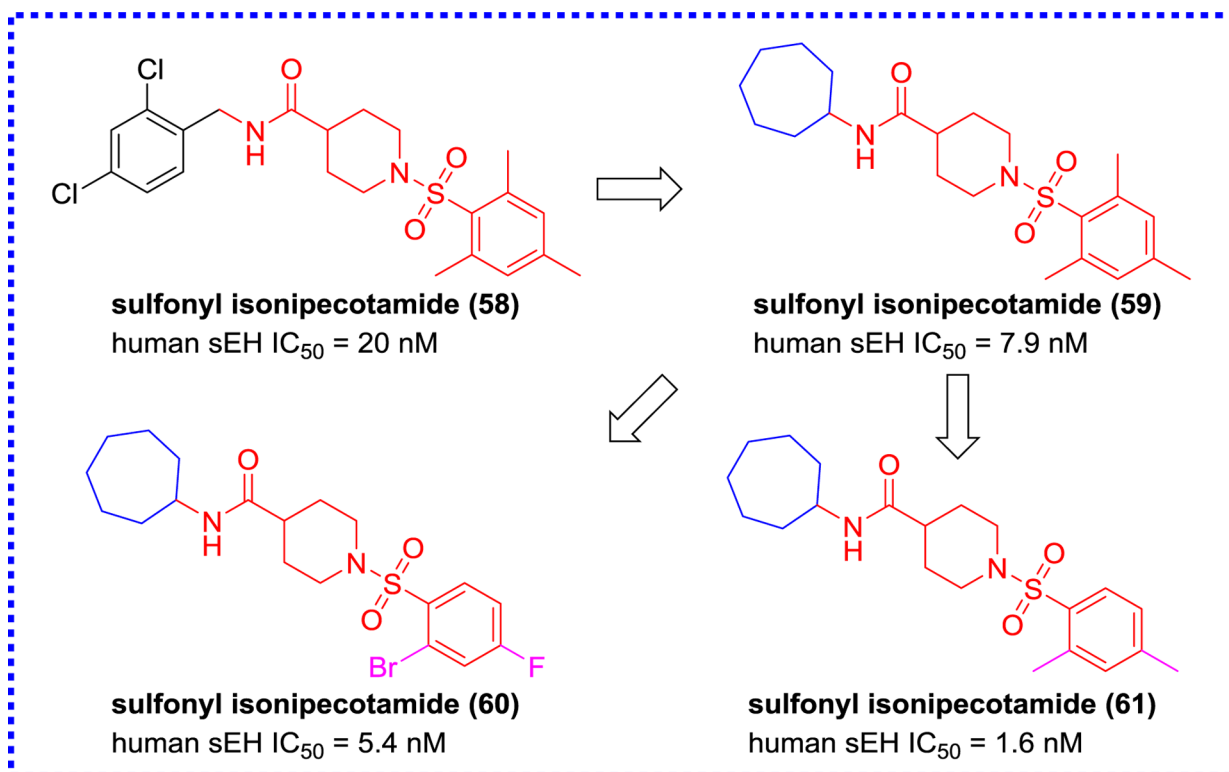


Figure 13.
Chemical structures of sulfonyl isonipecotamides.

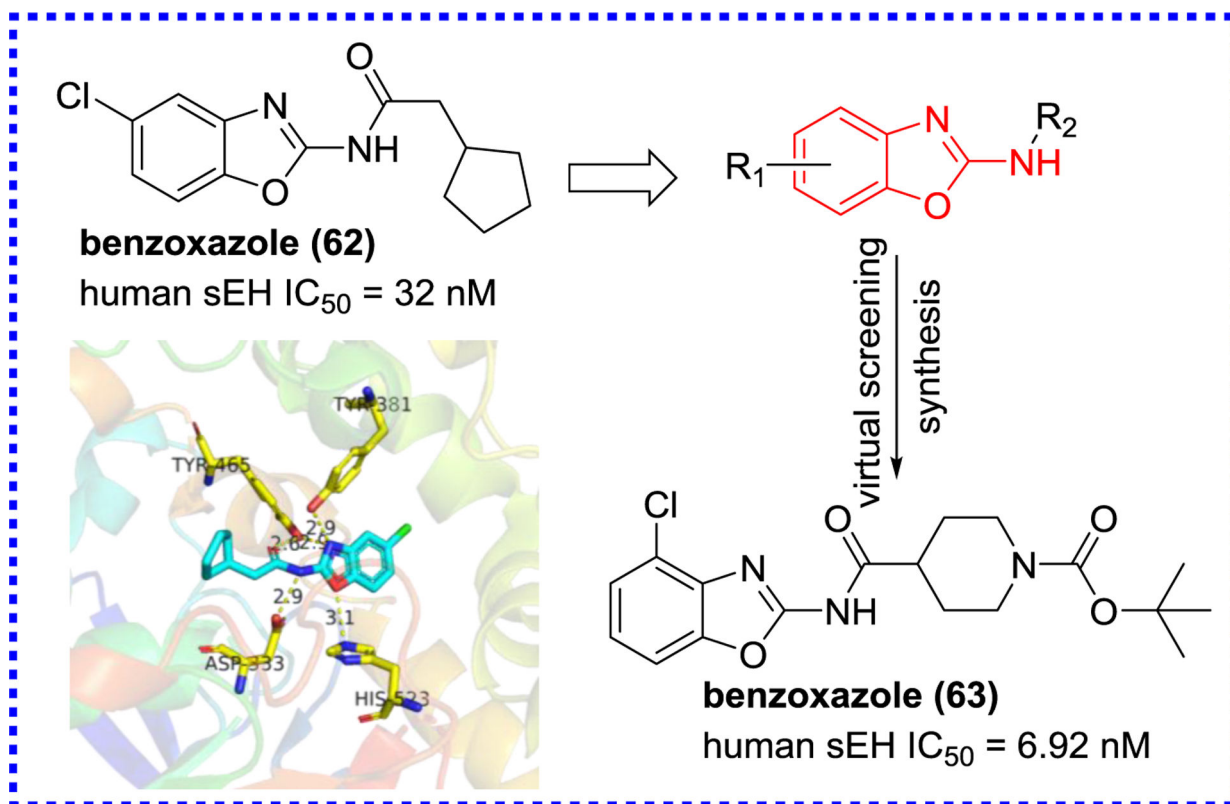


Figure 14. X-ray crystal structure of sEH complexed with the benzoxazole (62) (PDB code 3PDC) and its optimization.

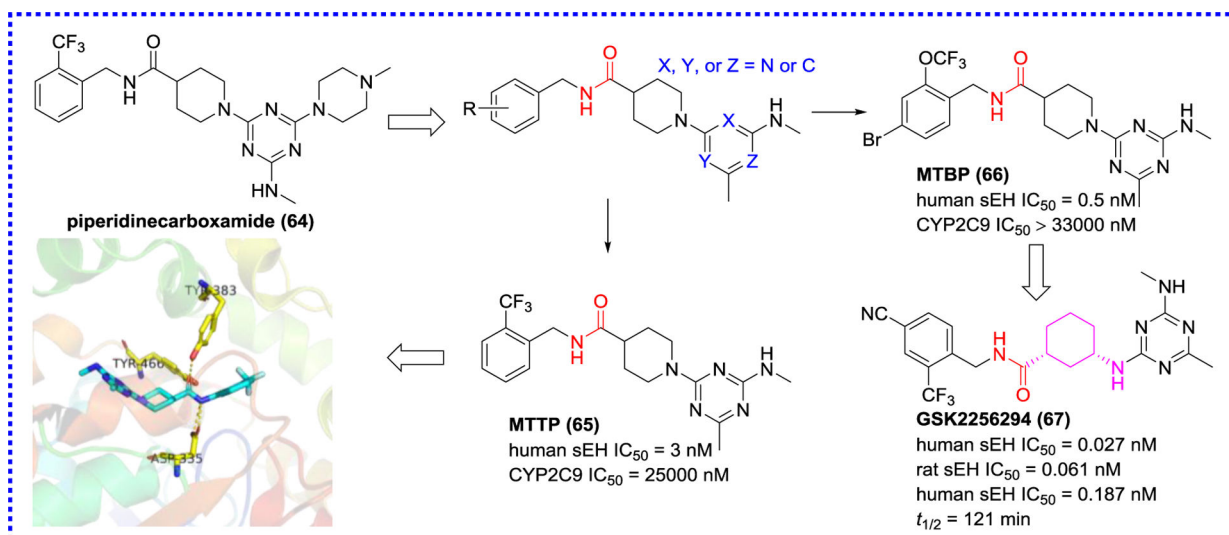


Figure 15. Modification based on the structure of the amide (**64**) and co-crystal structure of MTPP (**65**) and sEH (PDB code 4JNC)

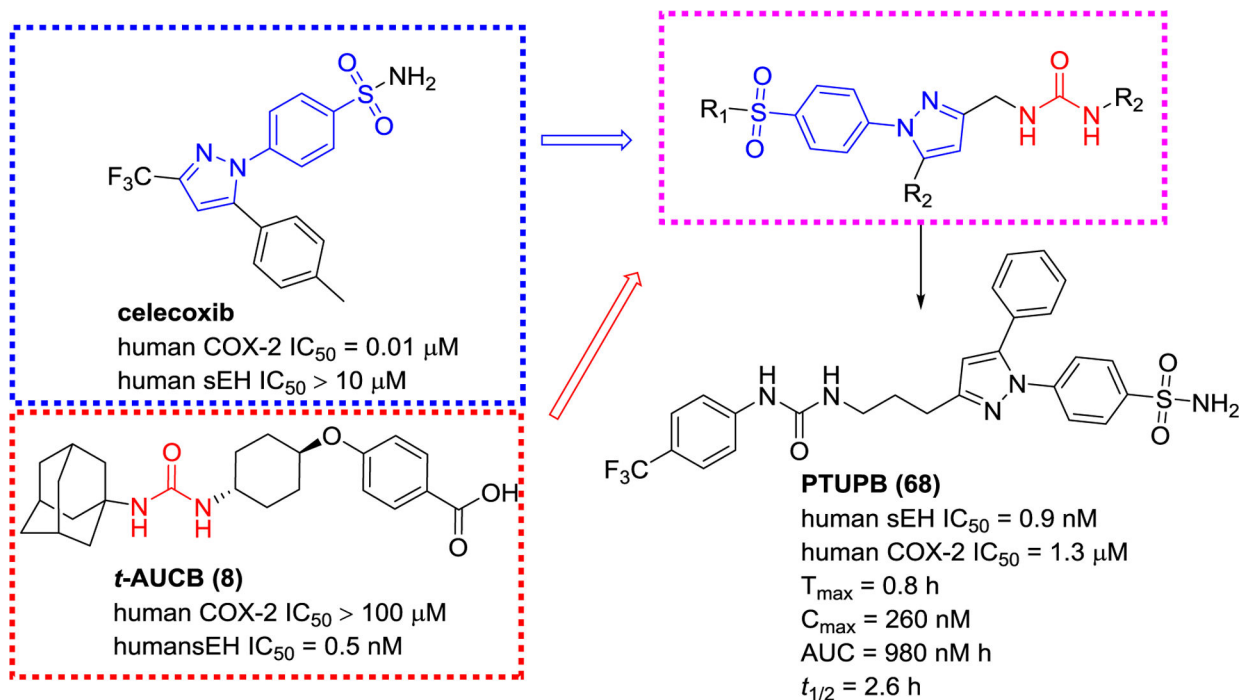


Figure 16.
The design principle of an sEH/COX-2 dual inhibitor PTUPB (**68**)

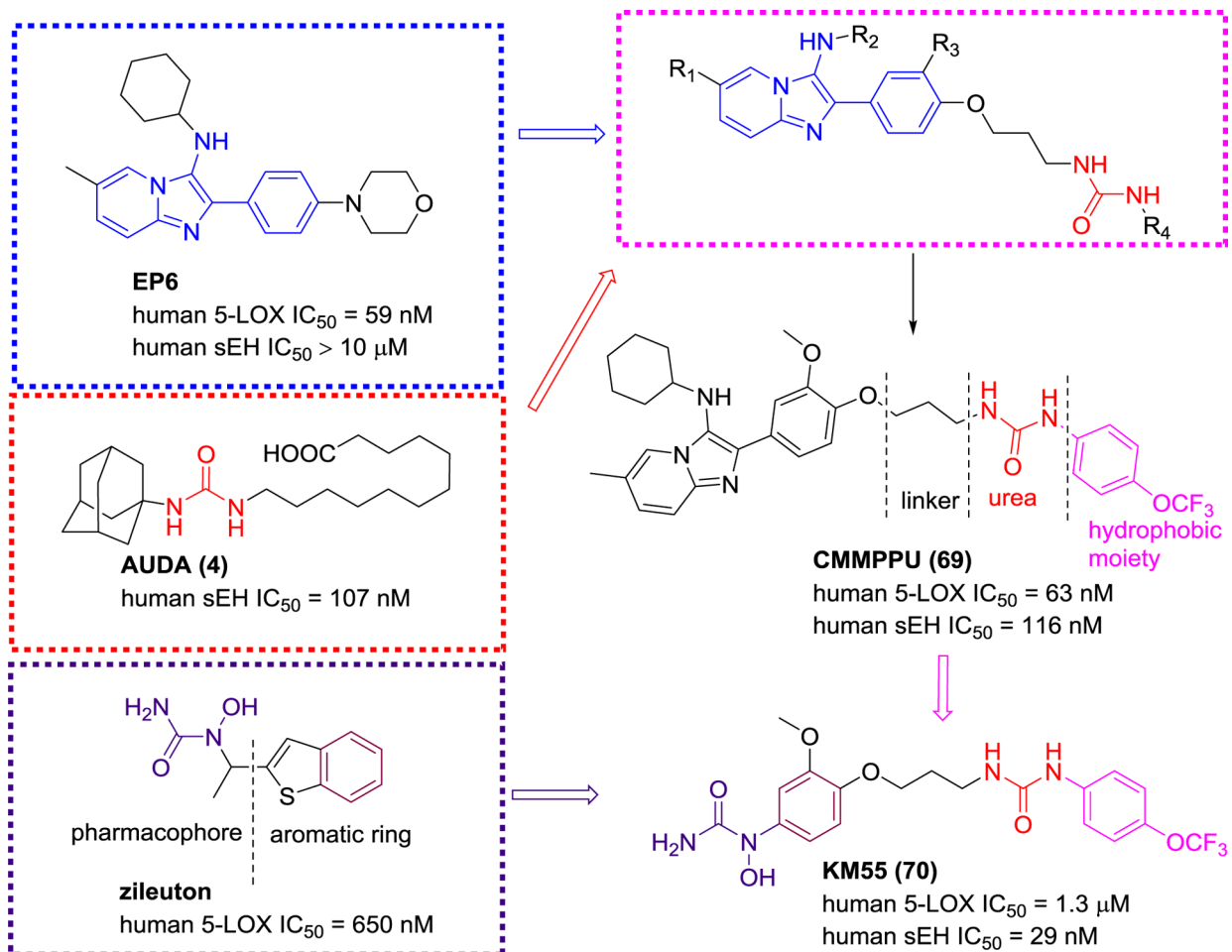


Figure 17.
sEH/5-LOX dual inhibitors that linked two pharmacophores for sEH and 5-LOX.

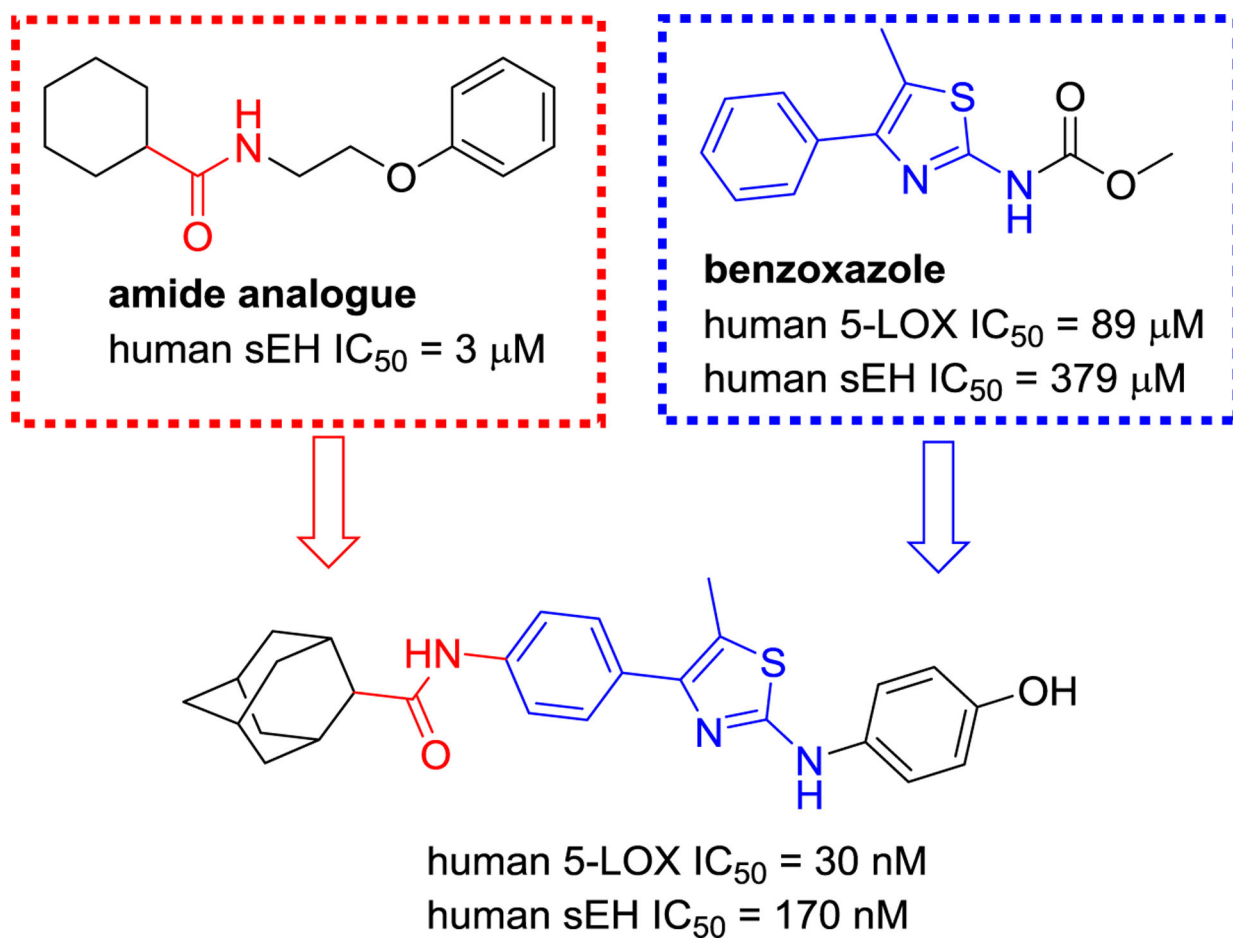


Figure 18.

A sEH/5-LOX dual inhibitor with an amide and an aminothiazole moiety.

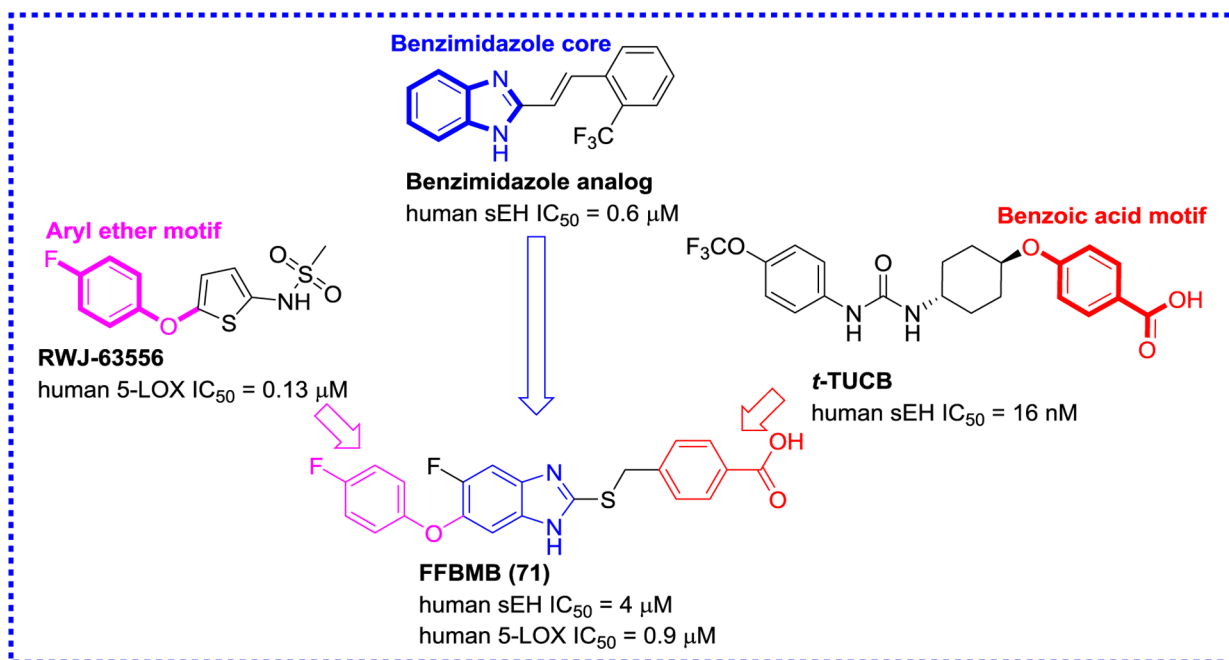


Figure 19.

A sEH/5-LOX dual inhibitor FFBMB (71) based on an aryl ether and a benzoic acid motif and a benzimidazole core.

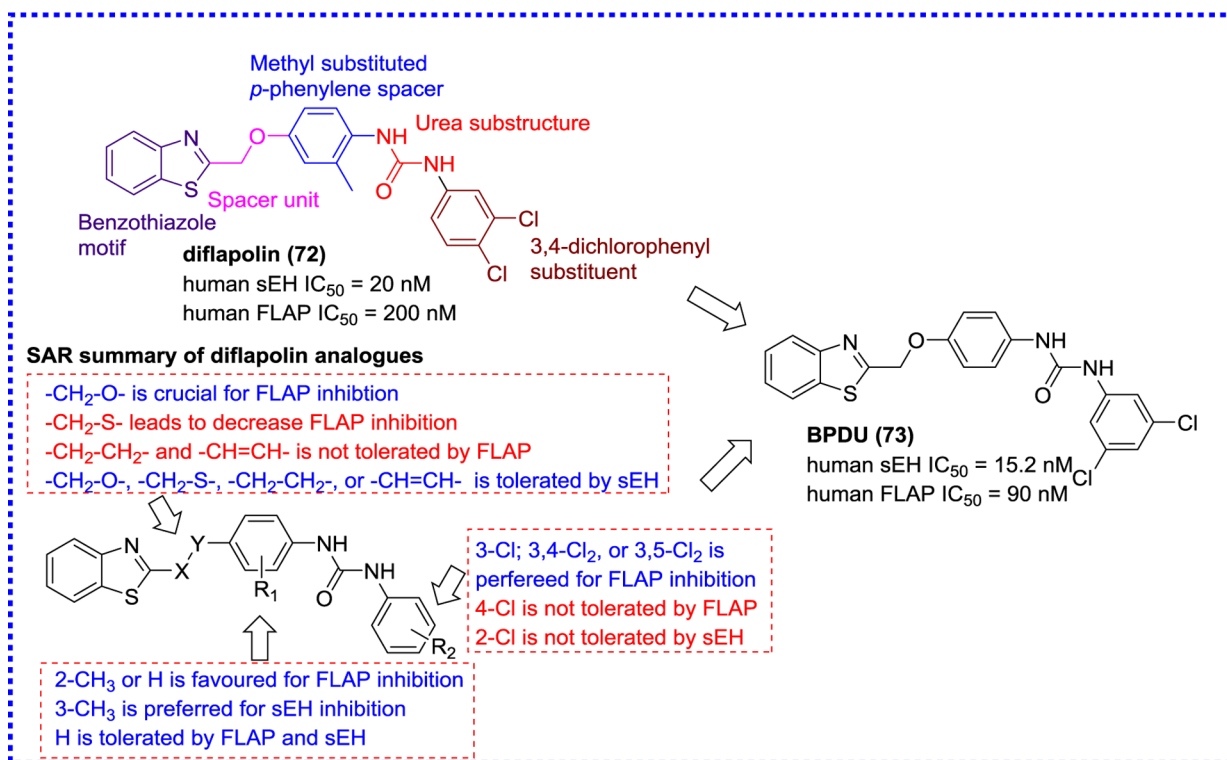


Figure 20.
 sEH/FLAP dual inhibitors diflapolin analogues.

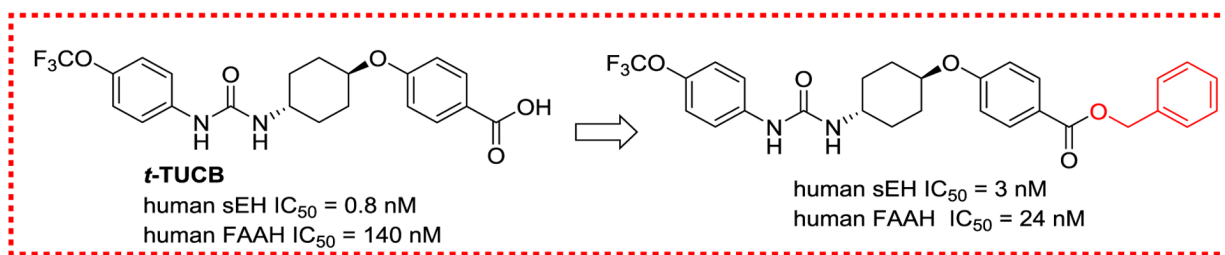


Figure 21.
A sEH/FAAH dual inhibitor derived from *t*-TUCB.

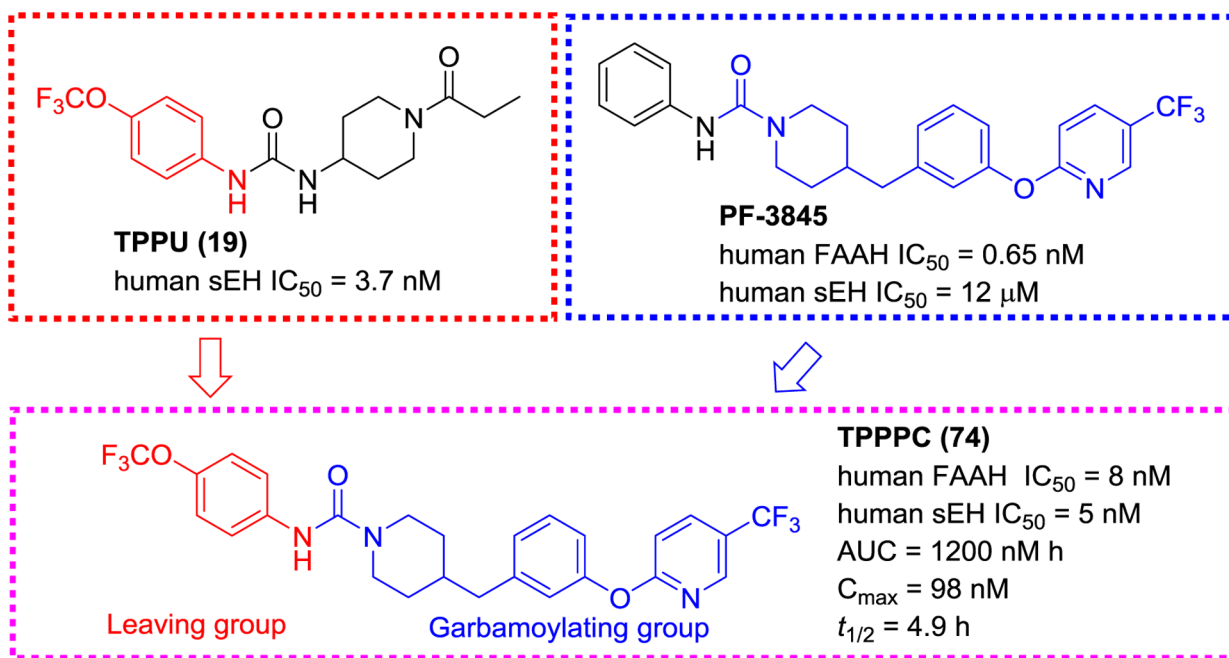


Figure 22.

A selective sEH/FAAH dual inhibitor TPPPC (**74**) derived from TPPU (**19**) and PF-3845.

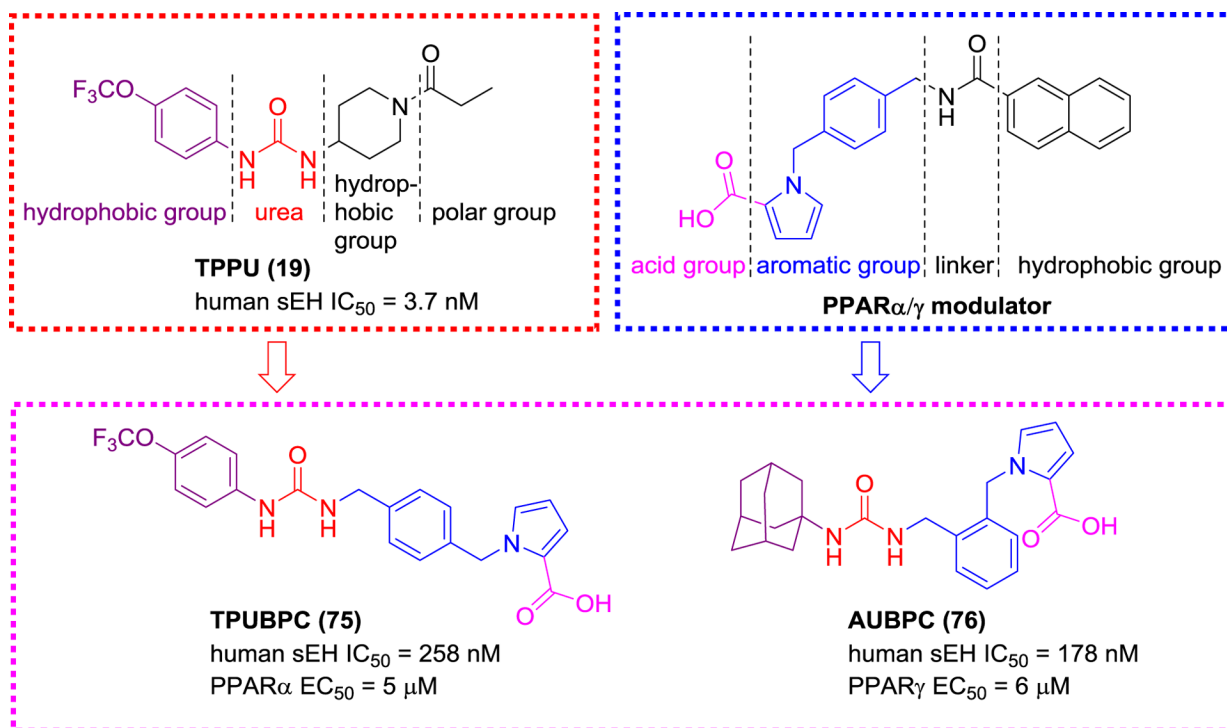


Figure 23.
Selective sEH/PPAR dual modulators TPUBPC (75) and AUBPC (76).

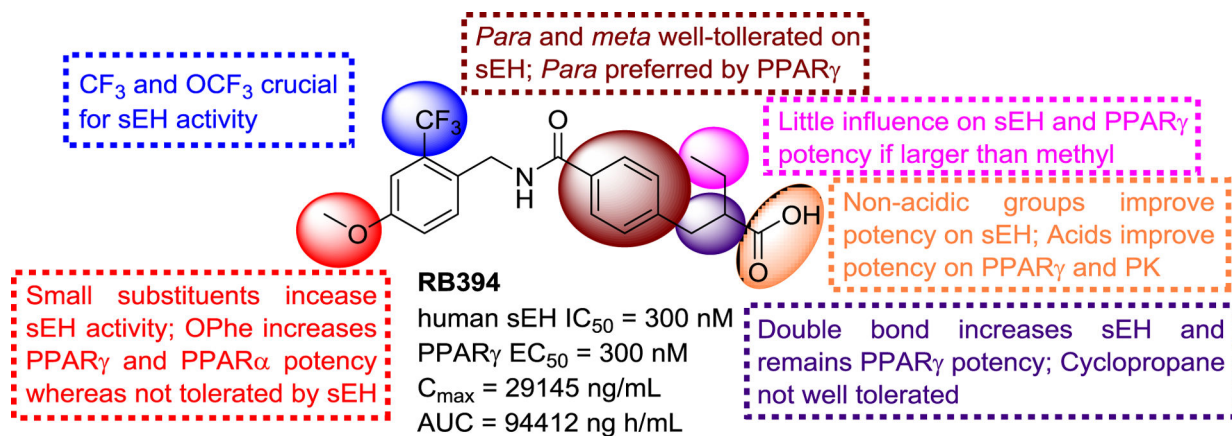


Figure 24.
 SAR of *N*-benzylbenzamides with sEH and PPAR_γ.

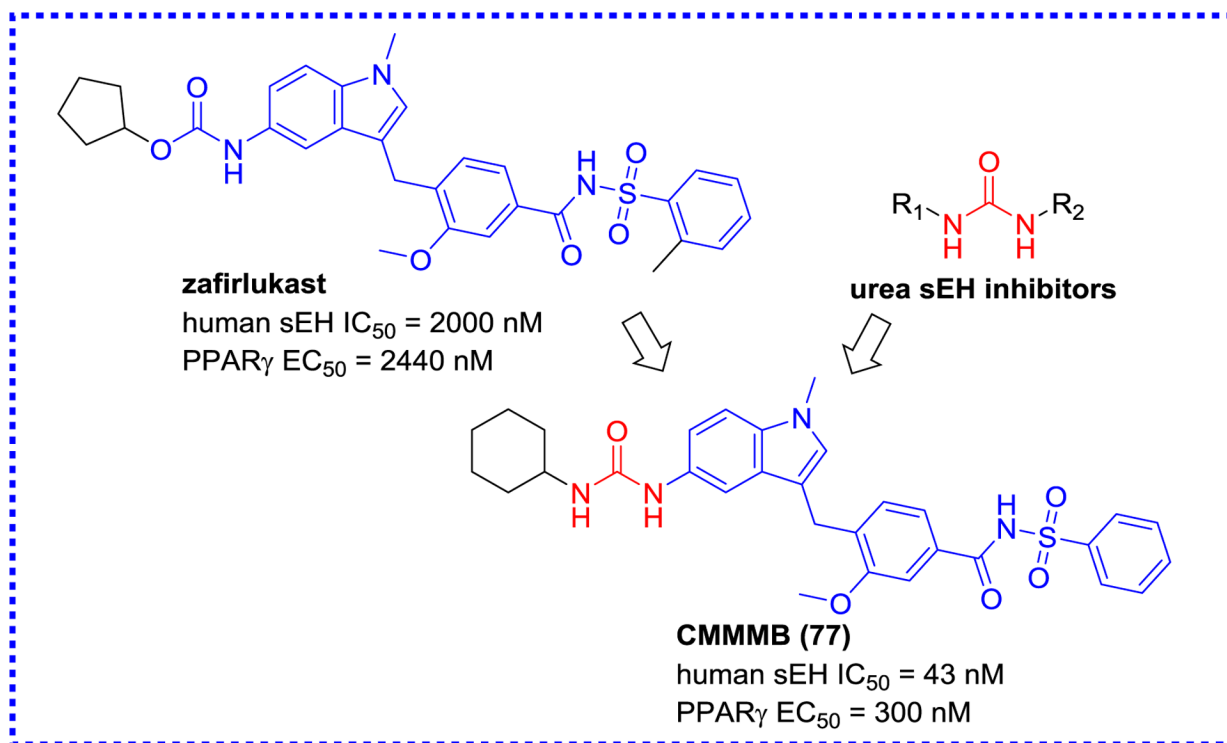


Figure 25.

A selective sEH/PPAR dual modulator CMMMB (77) derived from zafirlukast.

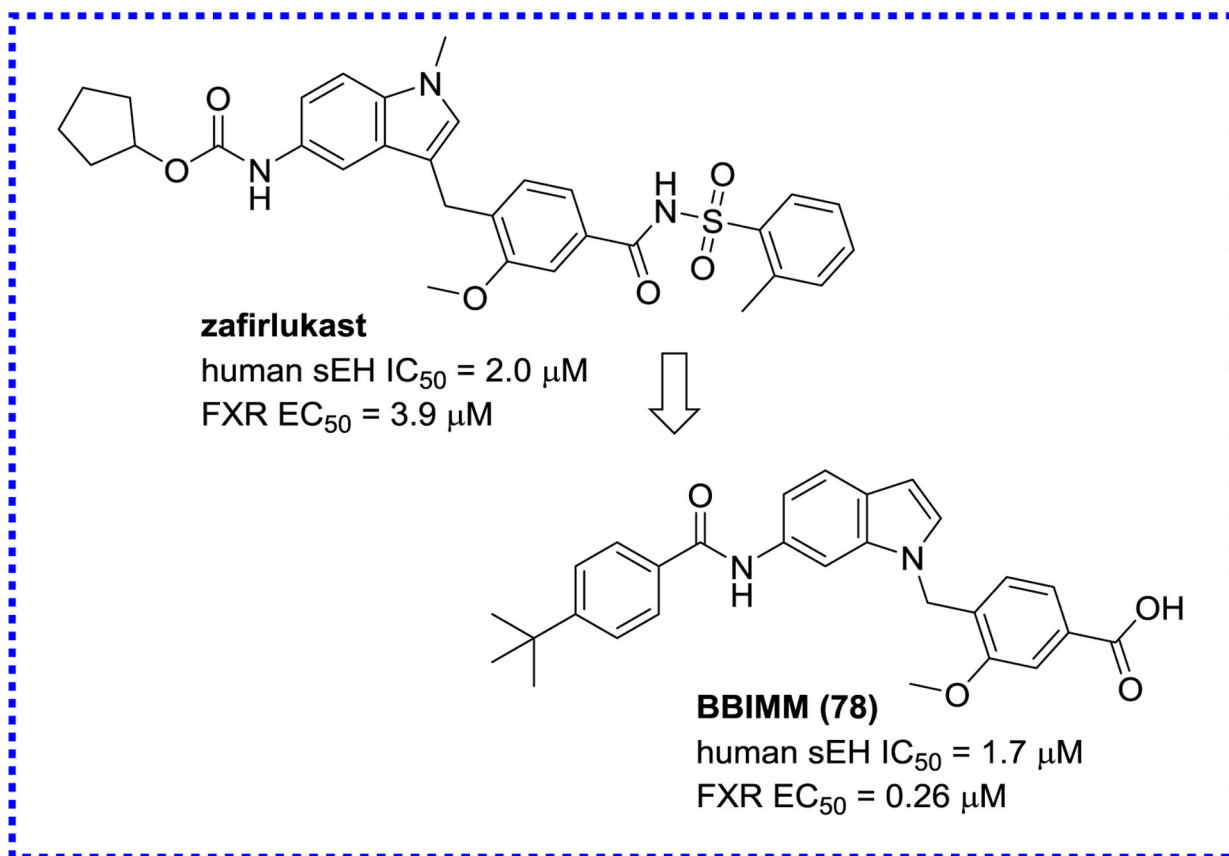


Figure 26.
A sEH/FXR dual modulator BBIMM (78) derived from zafirlukast.

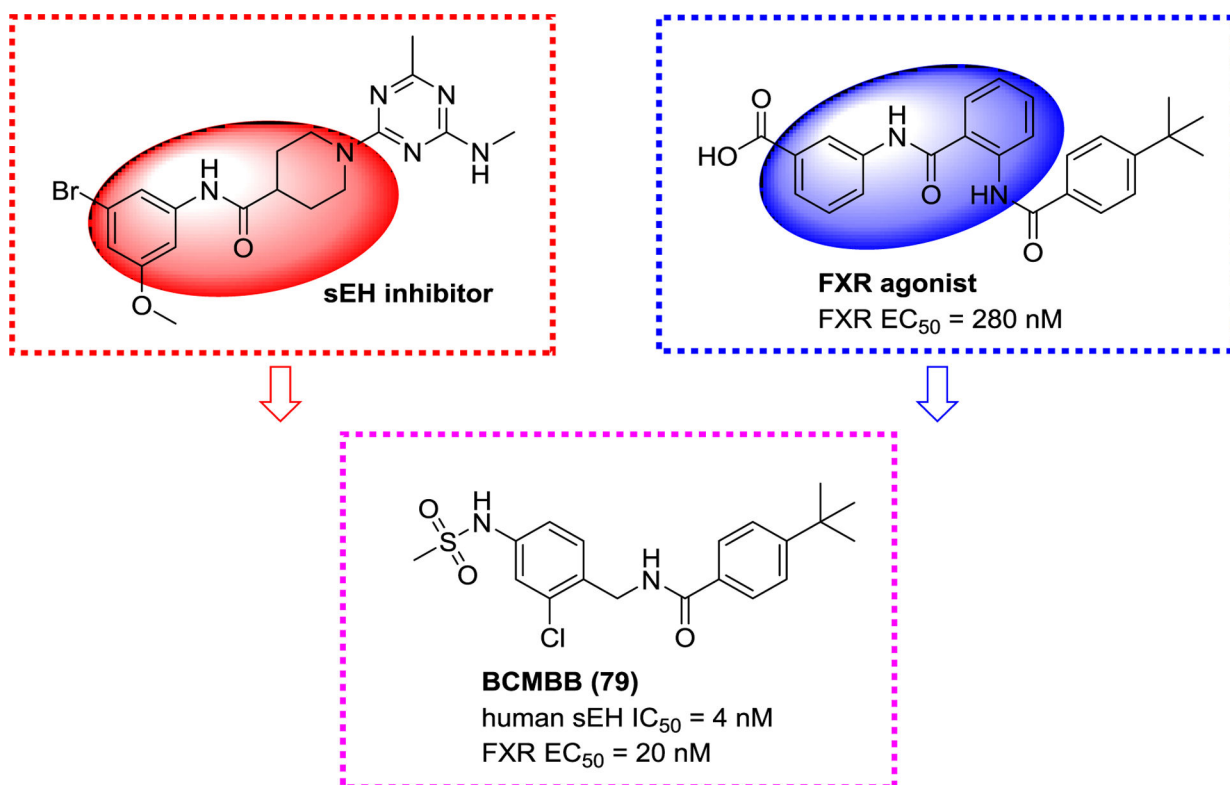
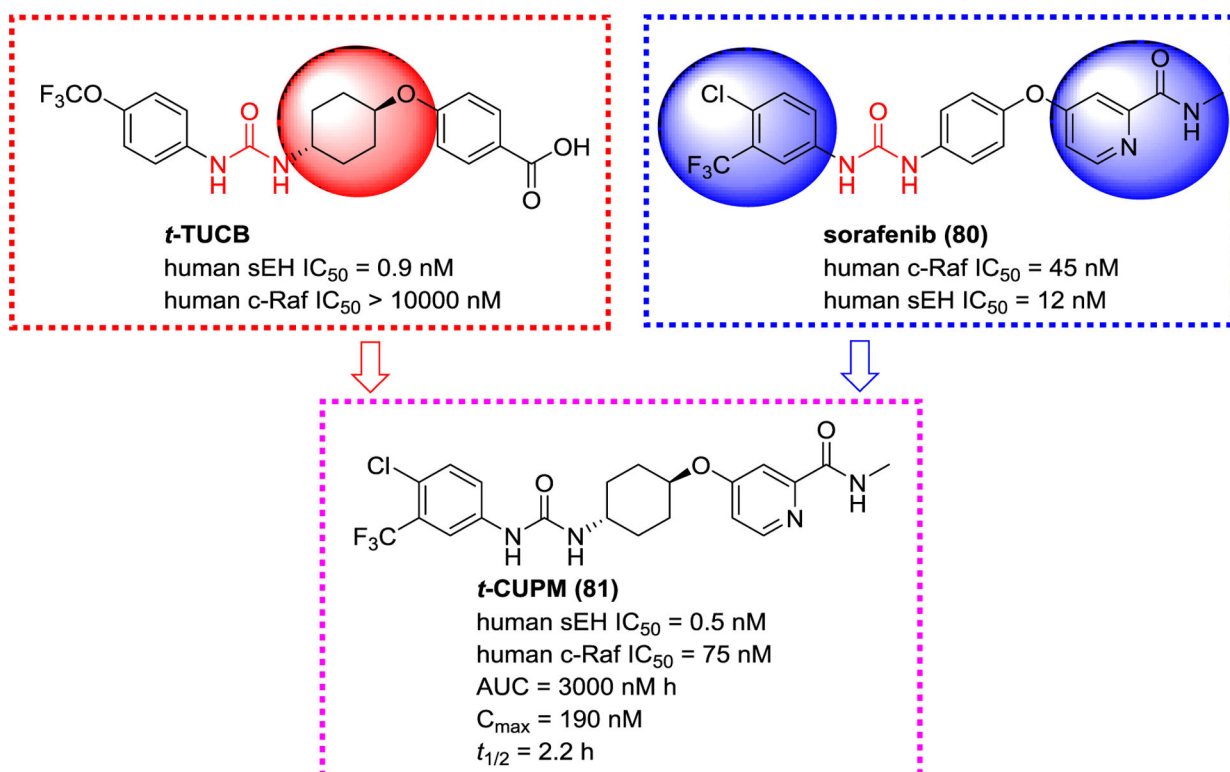


Figure 27.
A sEH/FXR dual modulator BCMBB (79).

**Figure 28.**

A sEH/c-RAF dual modulator *t*-CUPM (**81**) derived from *t*-TUCB and sorafenib (**80**)

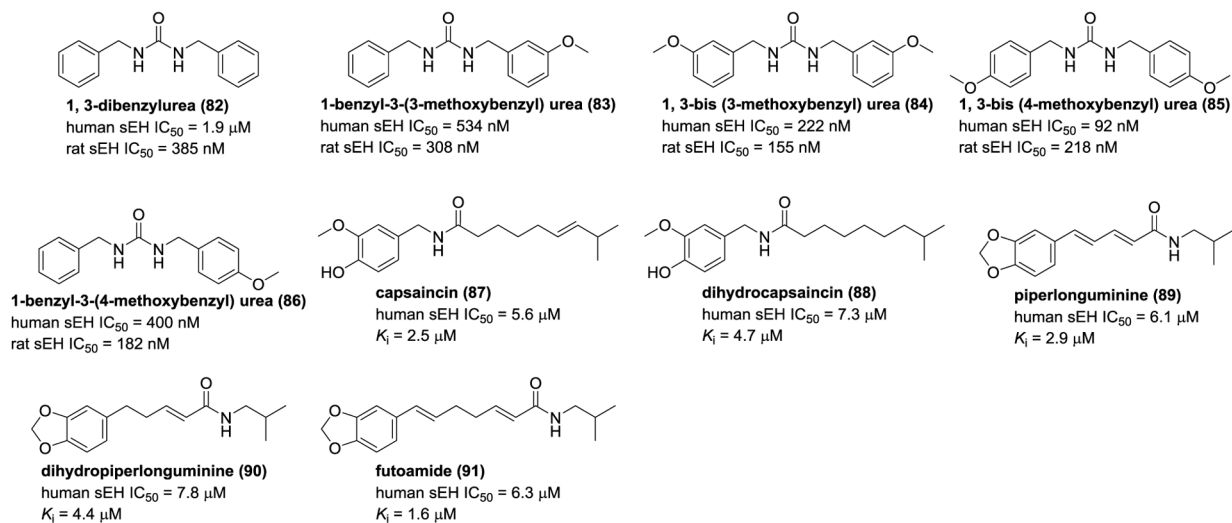


Figure 29.
 Chemical structures of naturally occurring sEH inhibitors: ureas (**82–86**) and amides (**87–91**).

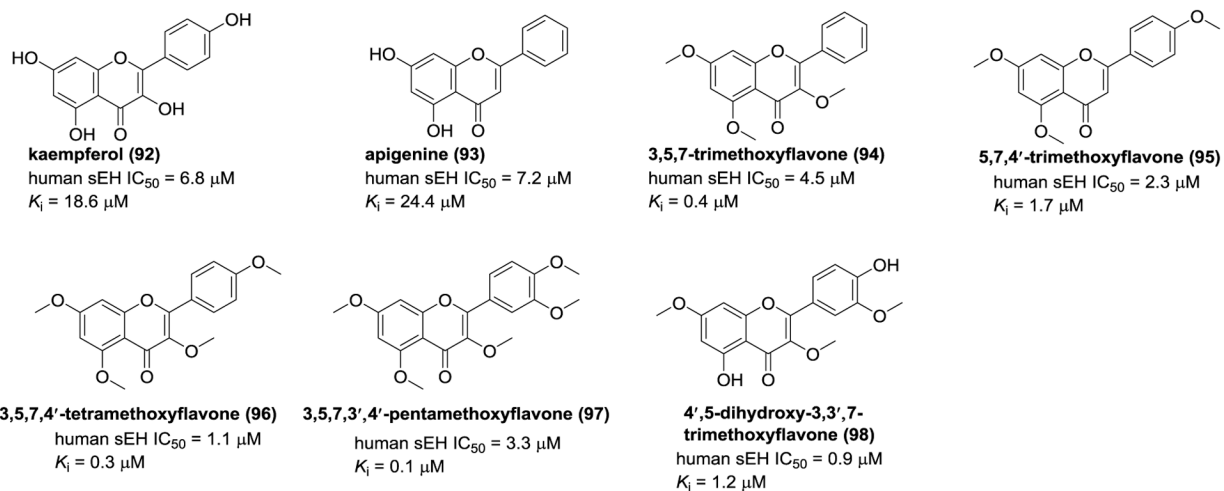


Figure 30.
Chemical structures of naturally occurring sEH inhibitors: flavonoids (**92–98**).

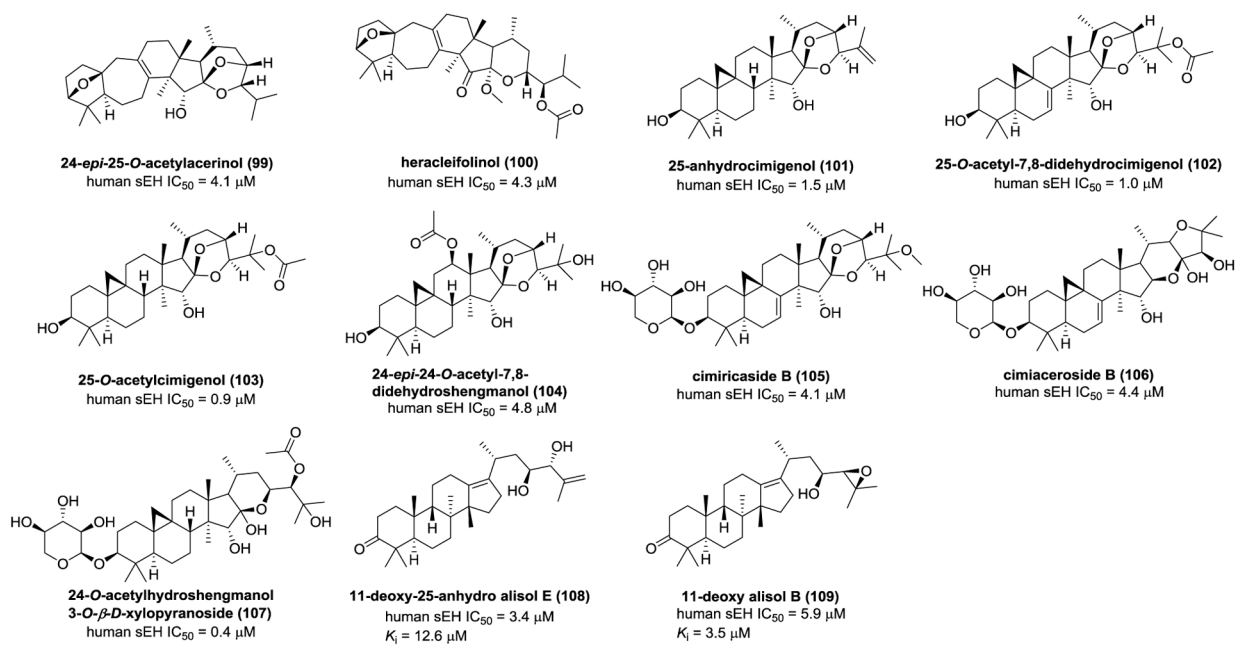


Figure 31.
 Chemical structures of naturally occurring sEH inhibitors: triterpenoids (99–109).

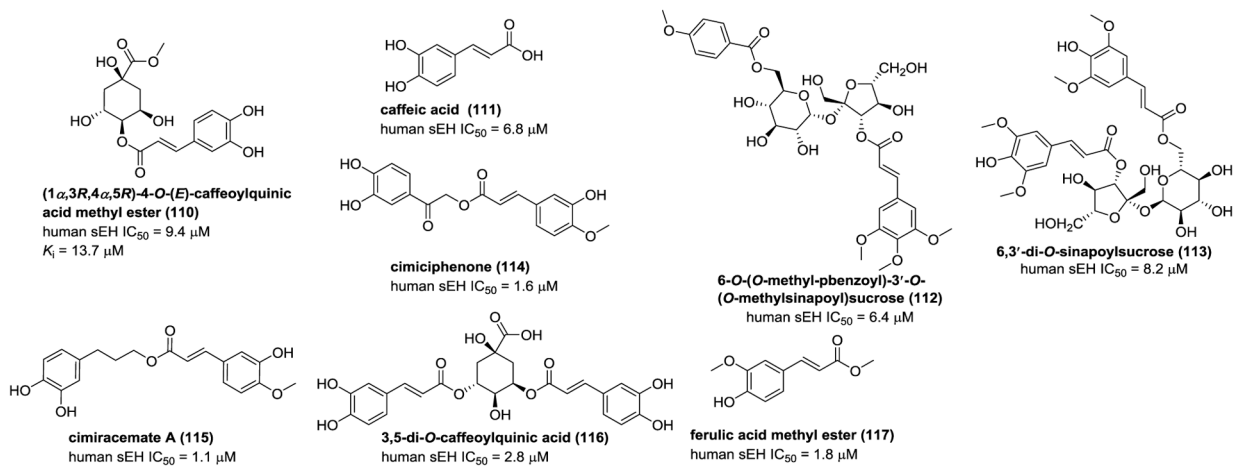


Figure 32.
Chemical structures of naturally occurring sEH inhibitors: phenylpropionic acids (110–117).

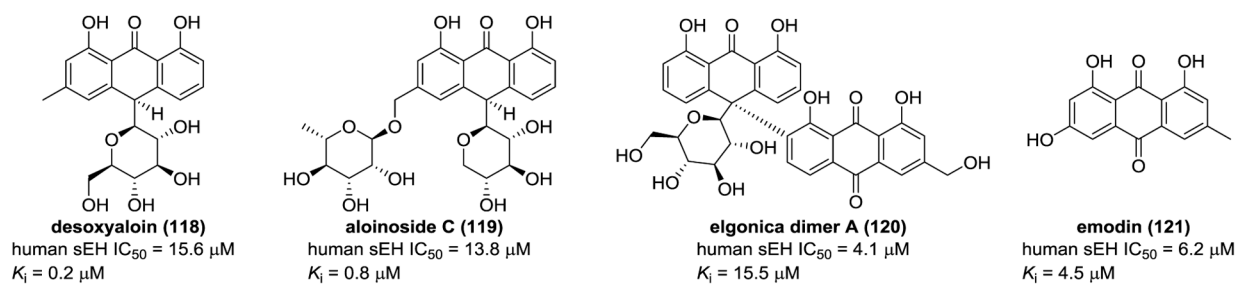


Figure 33.
Chemical structures of naturally occurring sEH inhibitors: anthraquinones (**118–121**).

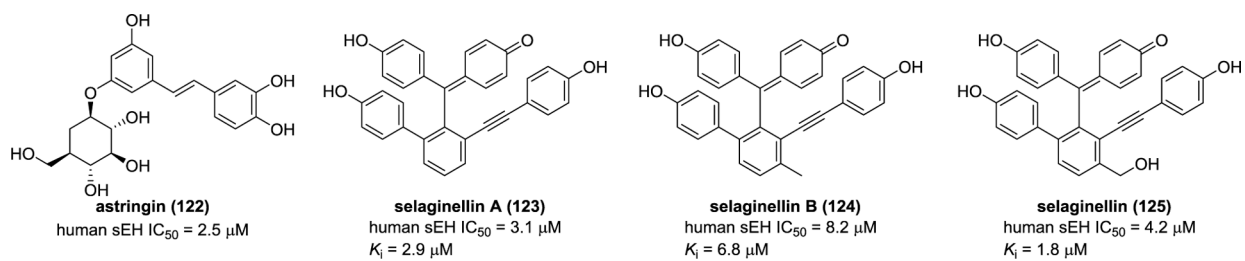


Figure 34.
Chemical structures of naturally occurring sEH inhibitors: stilbenes (122–125).

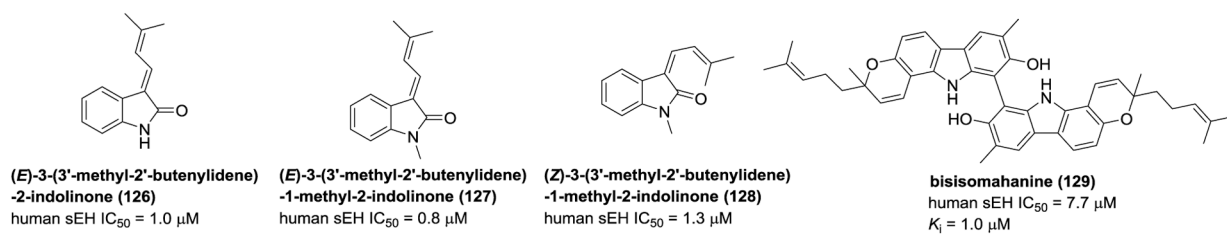


Figure 35.
 Chemical structures of naturally occurring sEH inhibitors: alkaloids (**126–129**).

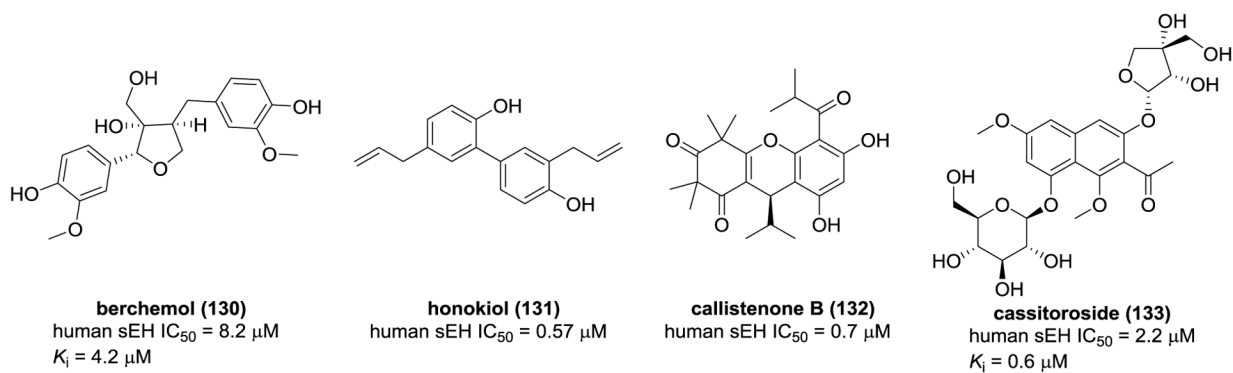


Figure 36.
Chemical structures of naturally occurring sEH inhibitors: others (130–133).