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FULL PAPER

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Discovery of phthalimide derivatives as novel inhibitors of a soluble epoxide hydrolase

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Abstract

Soluble epoxide hydrolase (sEH) inhibitors are effective in reducing blood pressure, inflammation, and pain in a number of mammalian disease models. As most classical urea-based sEH inhibitors suffer from poor solubility and pharmacokinetic properties, the development of novel sEH inhibitors with an improved pharmacokinetic specification has received a great deal of attention. In this study, a series of amide-based sEH inhibitors bearing a phthalimide ring as the novel secondary pharmacophore (P_2) was designed, synthesized, and evaluated. Docking results illustrated that the amide group as the primary pharmacophore (P_1) was placed at a suitable distance from the three key amino acids (Tyr383, Tyr466, and Asp335) for an effective hydrogen bonding. In agreement with these findings, most of the newly synthesized compounds demonstrated moderate to high sEH inhibitory activities, relative to 12-(3-adamantan-1-yl-ureido)dodecanoic acid as the reference standard. Compound **12e** with a 4-methoxybenzoyl substituent exhibited the highest sEH inhibitory activity, with an IC_{50} value of 1.06 nM. Moreover, the ADME properties of the compounds were evaluated in silico, and the results revealed appropriate predictions.

KEYWORDS
docking, inhibitor, phthalimide, soluble epoxide hydrolase, synthesis

1 | INTRODUCTION

In mammalian tissues, several types of epoxide hydrolases (EHs) have been identified, including leukotriene A_4 hydrolase, cholesterol EH, hepoxilin A_3 hydrolase, microsomal EH, and soluble epoxide hydrolase (sEH), which differ in their substrate specificity.[1,2] The sEH (E.C. 3.3.2.10), which belongs to the α/β-hydrolase family, is involved in the metabolic conversion of endogenous epoxyeicosatrienoic acids (EETs) into the physiologically inactive dihydroxy eicosatrienoic acids through the reaction with a water molecule.[3–5] EETs exert a wide range of biological effects, including suppression of reactive oxygen species,[6] enhancement of the fibrinolytic pathway,[7,8] and vasodilation through the activation of potassium channels.[9] Furthermore, EETs were reported to regulate leukocyte recruitment,[10] platelet aggregation,[11] and vascular smooth muscle cell migration[12] in several studies. Considering the definite role of sEH in the management of these physiological processes, exhaustive efforts have been made to design novel sEH inhibitors. It was discovered that the hydrolase active site of sEH possesses a catalytic triad consisting of one aspartate and two tyrosine residues, which play a pivotal role in epoxide ring opening.[13–15] Most of the sEH inhibitor scaffolds employ urea-, amide- or imide-containing pharmacophores, which function as an active-site transition-state mimic.[16] They fit well into the hydrolase catalytic pocket to interact with the aforementioned residues.

Specifically, the carbonyl oxygen of urea/amide/imide is engaged in a hydrogen bonding interaction with tyrosine, and the N–H moiety donates its covalently bonded hydrogen atom to aspartate.[13] Urea-, carbamate-, and amide-containing compounds substituted

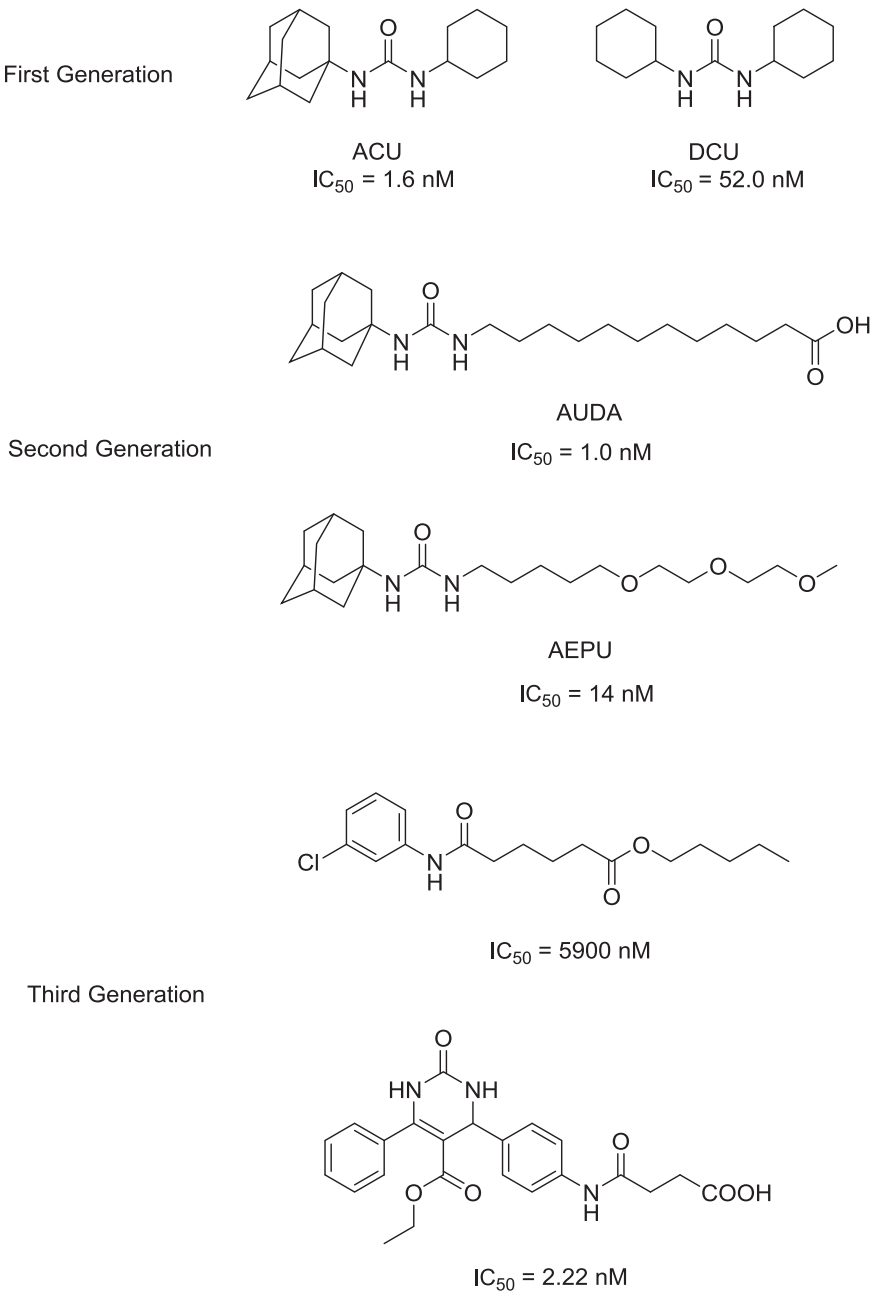


FIGURE 1 Chemical structures of some soluble epoxide hydrolase inhibitors. ACU, N-adamantyl-N′-cyclohexylurea; AEPU, 1-adamantan-3-(5-(2-(2-ethylethoxy)ethoxy) pentyl)urea; AUDA, 12-(3-adamantane-1-yl-ureido)-dodecanoic acid; DCU, N, N′-dicyclohexylurea

with hydrophobic groups (Figure 1) appeared to be good and stable sEH inhibitors, which showed satisfactory in vivo activity.[17,18] However, their clinical use has been restricted due to poor pharmacokinetic and physical properties, such as rapid in vivo metabolism, low solubility, and relatively high melting points.[17,19] With the help of a structure-based drug design approach, polar functional groups with a proper distance from the pharmacophore moieties were added at specific positions of the hydrophilic moieties to improve the solubility and bioavailability of these sEH inhibitors, besides keeping high potency.[20–22]

Accordingly, and in continuance of our previous studies on sEH inhibitors,[23–26] various phthalimide derivatives have been developed as reversible sEH inhibitors (Figure 2). The amide and imide groups in the represented structures were considered as the primary (P_1) and secondary pharmacophores (P_2), respectively, which have a proper distance from each other. A phenyl/benzyl motif (L_1) as a lipophilic spacer linked P_1 and P_2, and the phenylene group incorporated as a terminal pharmacophore (L_2/P_3).[27]

2 | RESULTS AND DISCUSSION

2.1 | Chemistry

The designed compounds were synthesized in a good yield according to Scheme 1. Compound **3** was prepared from the reaction of

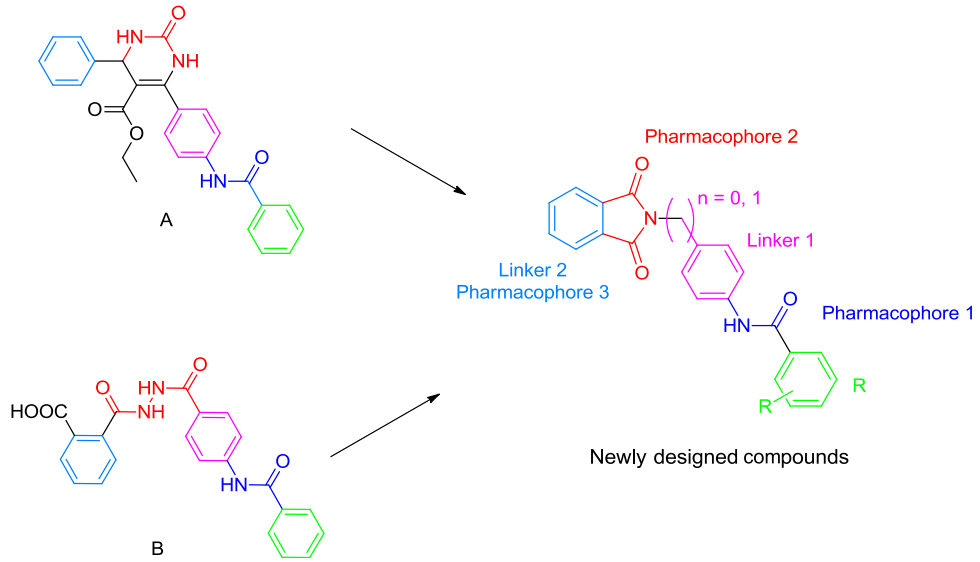


FIGURE 2 The design of novel phthalimide derivatives as soluble epoxide hydrolase inhibitors

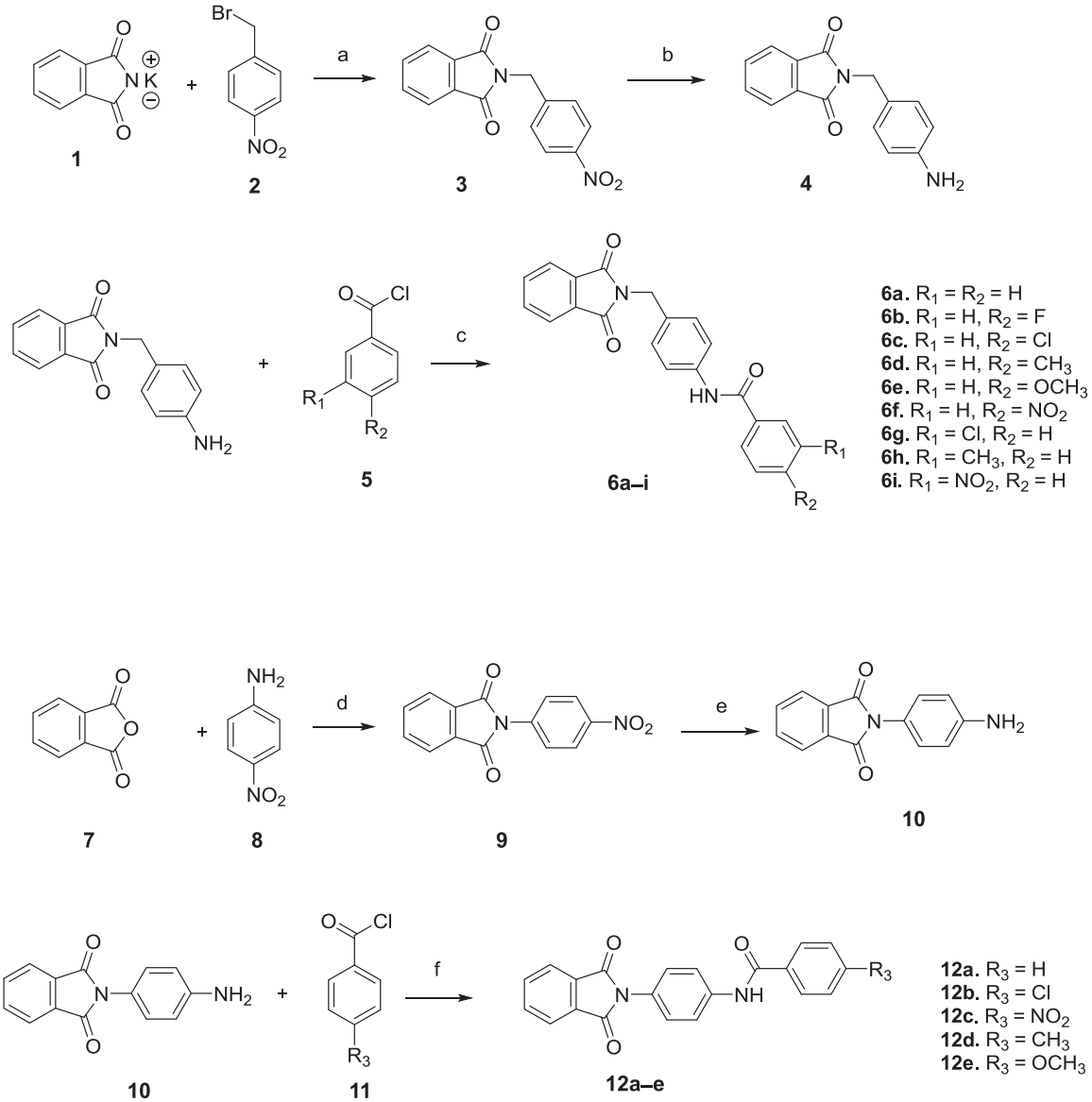
potassium 1,3-dioxoisoindolin-2-ide (compound **1**) with 4-nitrobenzyl bromide (compound **2**). Compounds **6a**–**i** were synthesized through the reduction of the nitro group present in compound **3** by $SnCl_2$ in ethanol, followed by treatment of the corresponding amine **4** with properly substituted benzoyl chloride derivatives. Compounds **12a**–**e** were also obtained from the reaction of 4-nitroaniline with phthalic anhydride, followed by the reduction of the nitro group to amine and subsequently the reaction of corresponding amine **10** with various benzoyl chloride analogs.

2.2 | In vitro biological activity

The results of the sEH enzyme inhibitory assay appeared to be promising. As shown in Table 1, most of the novel synthesized compounds have appropriate IC_{50} values (1.06–22.88 nM) as compared with 12-(3-adamantan-1-yl-ureido)dodecanoic acid (AUDA), the potent urea-based inhibitor with an IC_{50} value of 1.00 nM in our experimental condition. Generally, the *N*-[4-(1,3-dioxoisoindolin-2-yl) phenyl]benzamide derivatives (**12a**–**e**, Series 2) were found to be more potent than the corresponding *N*-{4-[(1,3-dioxoisoindolin-2-yl) methyl]phenyl}benzamide derivatives (**6a**–**i**, Series 1). The most potent compounds were those with a methoxy substituent on the 4-position of the benzoyl moiety (**6e** and **12e**). The observed rank order for the contribution of 4-positioned substituents to the enzyme inhibitory in Series 1 and 2 is as follows: $OCH_3 > Cl > CH_3 > H > F > NO_2$ and $OCH_3 > Cl > CH_3 > H > NO_2$, respectively. Out of all the compounds, the most potent were those with methoxy substituents on the 4-position of the benzoyl ring (**6e** and **12e**) with IC_{50} values of 2.50 and 1.06 nM, respectively. There was also a noticeable decrease in the activity of the newly synthesized analogs in Series 1 with a change in the *para* substituents of the phenyl ring, suggesting that there may be an improper conformation or steric hindrance induced by *meta*-substitution on the benzoyl moiety. The results confirmed the importance of the P_1 moiety in the binding of the designed structures to the enzyme. In brief, it seems that inserting lipophilic, electron-donating substitutes in the R_3 position of the benzoyl moiety leads to an increased inhibitory activity. Thus, these derivatives could be appropriate candidates for further investigations to find new sEH inhibitors.

2.3 | Docking studies

Molecular docking at the sEH active site was performed for all newly synthesized analogs. As indicated in Table 1, approximately all compounds possessed a comparable affinity to AUDA reference standard, and Series **12a**–**e** possessed a generally better affinity for the enzyme of interest than **6a**–**i**. Interestingly, the docking results for the Series **12a**–**e** were in agreement with the biological assessment findings, and the observed orders in both studies were similar. Docking results of the newly designed sEH inhibitors confirmed that all the ligands were oriented in sEH binding site in a similar way, fitted into the hydrolase catalytic pocket of the simulated 3D model of sEH. Obviously, the amide group (P_1) was located properly at the active site pocket and placed at proper distances from the three amino acids, Tyr383 (2.66 Å), Tyr466 (2.71 Å), and Asp335 (3.06 Å), for hydrogen bonding, and additional hydrogen bonds could be formed between imide group (P_2 in Figure 3a) and Asp335 of the catalytic site. Moreover, phthalimide and benzoyl rings may have a lipophilic interaction with Trp336, Val380, Phe497, and Leu463 of the active site (Figure 3b). Compound **6i**, which was substituted with nitro on benzoyl group in three positions, and compound **12a**, with an unsubstituted benzoyl moiety, indicated the lowest affinities as well as different orientations in docking study as compared with the other analogs (Figure 3c).



SCHEME 1 The synthesis of novel phthalimide derivatives. Reagents and conditions: (a) anhydrous DMF, reflux, 1 hr, 87%; (b) $SnCl_2{\cdot}2H_2O$, absolute ethanol, reflux, 1 hr, 84%; (c) , DCM, RT, 12 hr, 72–89%; (d) CuI, glacial acetic acid, reflux, 4 hr, 90%; (e) $SnCl_2{\cdot}2H_2O$, absolute ethanol, reflux, 1 hr, 95%; (f) triethylamine, DCM, RT, 12 hr, 71–92%. DCM, dichloromethane; DMF, dimethylformamide; RT, room temperature

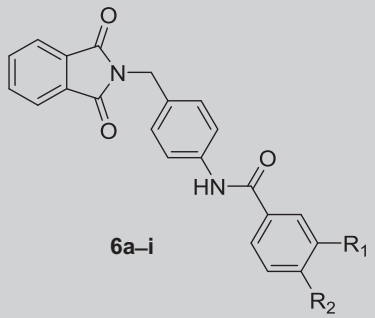
2.4 | ADME (absorption, distribution, metabolism, and excretion) properties

An in silico study of the final products was carried out for the prediction of ADME properties. As shown in Table 2, all synthesized compounds were found to have good druglikeness as well as a moderate to high percentage of absorption (% ABS), ranging from 69.67% to 85.48%. By definition, no more than one violation of the following four criteria should be shown in a molecule that is likely to develop as an orally active candidate: molecular weight ≤500, miLog *P* (octanol–water partition coefficient) ≤5, number of hydrogen bond donors ≤5, and number of hydrogen bond acceptors ≤10.[28] Interestingly, all of our synthesized compounds followed the criteria for orally active drugs. Therefore, such compounds have good potential for development as new oral sEH inhibitors.

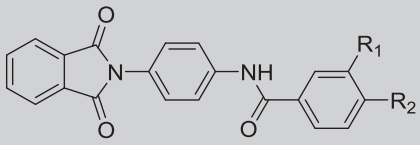
3 | CONCLUSIONS

In this study, we designed and synthesized a novel group of amide-based phthalimide analogs to identify a new scaffold as sEH inhibitors. All the designed compounds were docked, and docking scores suggested that all newly designed compounds possess an appropriate affinity to the hydrolase catalytic site of sEH enzyme and they might interact with key amino acid residues in the enzyme active site. The compounds were then evaluated for their in vitro sEH inhibitory activity, and the findings revealed that all the synthesized compounds exhibited a high sEH inhibitory activity as compared with AUDA. Compounds **6e** and **12e** were found to be the most potent sEH inhibitors, with IC_{50} values of 2.50 and 1.06 nM, respectively. In addition, the computational ADME prediction of synthesized analogs was performed, suggesting that the compounds could be exploited as orally

TABLE 1 Inhibitory activities and docking results of compounds **6a–i** and **12a–e**



6a–i



12a–e

Compound	R_1	R_2	IC_{50}[a] (nM)	ΔG[b] (kcal/mol)
6a	H	H	4.08	−11.7
6b	H	F	8.49	−12.0
6c	H	Cl	3.53	−12.0
6d	H	CH_3	3.69	−12.1
6e	H	OCH_3	2.50	−11.7
6f	H	NO_2	10.68	−11.5
6g	Cl	H	11.16	−11.7
6h	CH_3	H	14.30	−11.8
6i	NO_2	H	22.88	−11.8
12a	H	H	3.43	−8.1
12b	H	Cl	2.50	−10.3
12c	H	NO_2	8.5	−9.8
12d	H	CH_3	2.65	−10.5
12e	H	OCH_3	1.06	−11.3
AUDA[c]			1.00	−8.3

[a]IC_{50} values are an average of two experiments, and Cayman-based Human Soluble Epoxide Hydrolase Assay Kit (item number: 10011671) was used to assess inhibitory concentrations.
[b]The Gibbs free energy was obtained from docking results.
[c]A potent soluble epoxide hydrolase inhibitor, named 12-(3-adamantan-1-yl-ureido)dodecanoic acid (AUDA), was used as a reference inhibitor.

active sEH inhibitors. It was concluded that the designed structures have the potential to act as promising starting points for the development of more active sEH inhibitors with improved pharmacokinetic properties in the future.

4 | EXPERIMENTAL

4.1 | Chemistry

4.1.1 | General

All laboratory-grade chemicals and reagents were supplied commercially from Sigma-Aldrich® or Merck® companies and used without further purification. Melting points were measured with an Electrothermal 9100 apparatus and were not corrected. Analytical thin-layer chromatography, performed on commercially available Merck precoated plates (silica gel 60 F254, 0.25 mm), was used to monitor the progression of reactions. The synthesized analogs were visualized by illumination with short-wavelength UV light, and their structures were confirmed by infrared (IR), liquid chromatography/mass spectrometry (LC/MS), ^{1}H nuclear magnetic resonance (NMR), ^{13}C NMR spectroscopy (see Supporting Information Data), and elemental analysis methods. The IR and LC–MS spectra were recorded on PerkinElmer 843 IR and Agilent 6410 Triple Quadrupole LC/MS with an electrospray ionization (ESI) interface, respectively. A Bruker FT 400-MHz instrument (Bruker Biosciences) was used to obtain ^{1}H NMR and ^{13}C NMR spectra in dimethyl sulfoxide (DMSO)-d_6 or $CDCl_3$, using tetramethylsilane (TMS) as an internal standard. Chemical shifts were expressed in ppm against TMS as the internal standard. Coupling constant (J) increments are estimated in hertz (Hz), and spin multiples are expressed as follows: "s" for "singlet," "d" for "doublet," "t" for "triplet," "q" for the "quartet," "m" for "multiplet," and "br" for "broad" signal. The spectral data of all newly synthesized

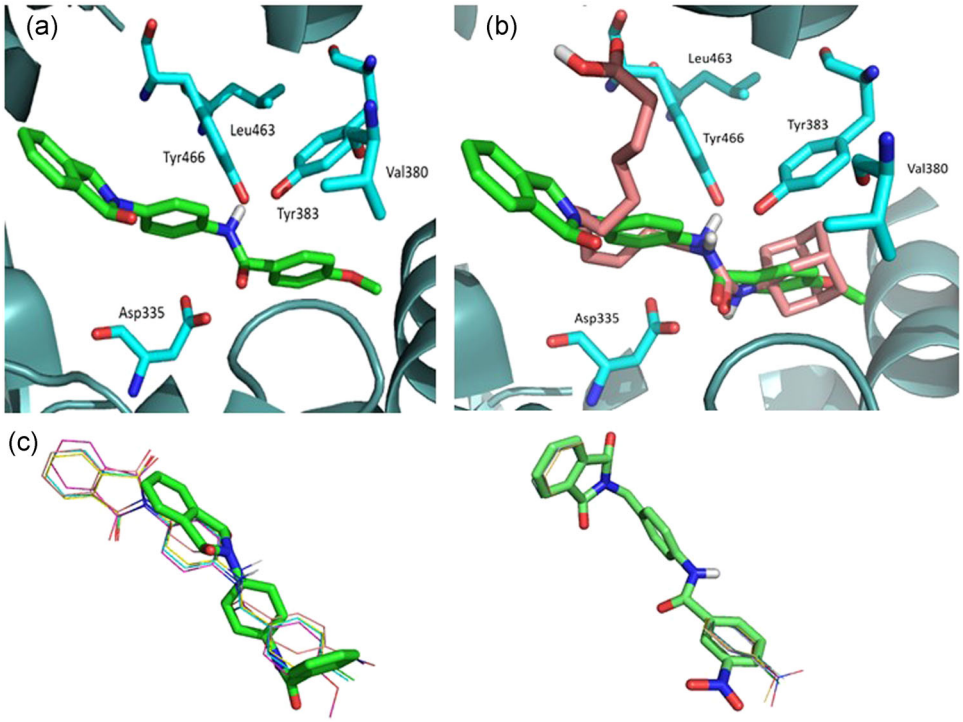


FIGURE 3 (a) The most potent analog **12e** containing a 4-methoxybenzoyl motif docked into the catalytic site of the co-crystal structure of human soluble epoxide hydrolase (PDB code: 3ANS). The amide group has a suitable distance from the three amino acids, Tyr383, Tyr466, and Asp335, for hydrogen bonding. (b) The overlay of compound **12e** (green) with AUDA (pink) in the active site of the enzyme. (c) Superimposition of all designed analogs in Series **6a–i** (right) and **12a–e** (left). The weakest affinities were observed from the compounds **6i** and **12a** (sticks), which showed different orientations from the other ligands (lines). AUDA, 12-(3-adamantan-1-yl-ureido)dodecanoic acid

compounds were consistent with the proposed structure. The elemental analysis was conducted using the elemental analyzer apparatus (Costech®, Italy), and its data were within ±0.4% of the theoretical values.

The InChI keys of the investigated compounds, together with some biological activity data, are provided as Supporting Information Data.

4.1.2 | Procedure for the preparation of 2-(4-nitrobenzyl)isoindoline-1,3-dione (3)

A solution of phthalimide (3.7 g, 20 mmol) and 4-nitrobenzyl bromide (3.72 g, 20 mmol) in 20 ml of anhydrous dimethylformamide was refluxed for 1 hr. After completion of the reaction, a mixture of ice and water was added to the reaction system. The residue was filtered and recrystallized from ethyl acetate to yield the desired product as a cream-colored solid (87% yield); m.p. 161–163°C; IR (KBr) υ_{max}/cm^{-1}: 1,700 (C═O), 1,509, 1,344 (N═O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.94 (s, 2H, CH_2-benzyl), 7.59 (d, J = 8 Hz, 2H, $H_{2,6}$-benzyl), 7.76 (dd, J = 8, 4 Hz, 2H, $H_{3,4}$-phenylene), 7.87 (dd, J = 8, 4 Hz, 2H, $H_{2,5}$-phenylene), 8.18 (d, J = 12 Hz, 2H, $H_{3,5}$-benzyl); LC–MS $[M+1]^+$: m/z 283.1; anal. calcd. for $C_{15}H_{10}N_2O_4$: C, 63.83; H, 3.57; N, 9.92; found: C, 63.95; H, 3.54; N, 9.85.

4.1.3 | Procedure for the preparation of 2-(4-aminobenzyl)isoindoline-1,3-dione (4)

In 30 ml of absolute ethanol, 2.8 g (10.0 mmol) of compound **3** and 11.5 g of $SnCl_2{\cdot}2H_2O$ (50.0 mmol) were added, and the mixture was refluxed at 75°C for 50 min. Afterward, the solvent was evaporated and the residue was extracted with a mixture of dichloromethane and ammonia aqueous solution (15 M). The organic phase was separated, dried over anhydrous sodium sulfate, and concentrated to afford compound **4** as a yellow solid (yield: 84%); m.p. 202–203°C; IR (KBr) υ_{max}/cm^{-1}: 3,444, 3,357 (NH_2), 1,754 (C═O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.65 (bs, 2H, NH_2), 4.73 (s, 2H, CH_2-benzyl), 6.61 (d, J = 8 Hz, 2H, $H_{3,5}$-benzyl), 7.26 (d, J = 8 Hz, 2H, $H_{2,6}$-benzyl), 7.79 (dd, J = 8, 4 Hz, 2H, $H_{3,4}$-phenylene), 7.83 (dd, J = 8, 4 Hz, 2H, $H_{2,5}$-phenylene); ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.2, 115.03, 123.22, 126.46, 130.13, 132.23, 133.84, 146.08, 168.15; LC–MS $[M+1]^+$: m/z 252.9; anal. calcd. for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10; found: C, 71.25; H, 4.81; N, 11.16.

4.1.4 | General procedure for the preparation of derivatives 6a–i

In dichloromethane, 0.5 g (2.0 mmol) of compound **4** was dissolved and 6.0 mmol of various benzoyl chloride derivatives were added to

TABLE 2 Pharmacokinetic parameters important for good oral bioavailability of the synthesized compounds

Compound	% ABS	TPSA (A^2)	*n*-ROTB	MV	MW	miLog *P*	*n*-ON acceptors	*n*-OHNH donors	Lipinski's violations
6a	85.48	68.17	4	314.96	356.38	4.01	5	1	0
6b	85.48	68.17	4	319.89	374.37	4.17	5	1	0
6c	85.48	68.17	4	328.49	390.83	4.69	5	1	0
6d	85.48	68.17	4	331.52	370.41	4.46	5	1	0
6e	82.29	77.41	5	340.50	386.41	4.07	6	1	0
6f	69.67	114.00	5	338.29	401.38	3.97	8	1	0
6g	85.48	68.17	4	328.49	390.83	4.66	5	1	0
6h	85.48	68.17	4	331.52	370.41	4.43	5	1	0
6i	69.67	114.00	5	338.29	401.38	3.94	8	1	0
12a	85.48	68.17	3	298.16	342.35	3.69	5	1	0
12b	85.48	68.17	3	311.69	376.80	4.37	5	1	0
12c	69.67	114.00	4	321.49	387.35	3.65	8	1	0
12d	85.48	68.17	3	314.72	356.38	4.14	5	1	0
12e	82.29	77.41	4	323.70	372.38	3.75	6	1	0
AUDA	81.94	78.42	13	403.52	392.58	6.50	5	3	1

Abbreviations: AUDA, 12-(3-adamantan-1-yl-ureido)dodecanoic acid; miLog *P*, logarithm of *n*-octanol/water partition coefficient; MV, molecular volume; MW, molecular weight; *n*-OHNH donors, the number of hydrogen bond donors; *n*-ON acceptors, the number of hydrogen bond acceptors; *n*-ROTB, the number of rotatable bonds; TPSA, the topological polar surface area; % ABS, percentage absorption.

it. A catalytic amount of triethylamine was also added and the mixture was stirred for 12 hr at room temperature. The solvent was evaporated under a stream of nitrogen gas, and the residue was washed with distilled water, weak acid, and base solutions. The resulting crude solid was recrystallized from ethanol to afford the final products **6a–i**.

N-*{4-[(1,3-Dioxoisoindolin-2-yl)methyl]phenyl}benzamide (**6a**)*

White solid; yield: 72%; m.p. 213–217°C; IR (KBr) υ_{max}/cm^{-1}: 3,302 (NH), 1,659, 1,701 (C═O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.76 (s, 2H, CH_2-benzyl), 7.44 (m, 7H, $H_{2,3,5,6}$-benzyl, $H_{3,4,5}$-benzoyl), 7.63 (dd, J = 8, 4 Hz, 2H, $H_{2,6}$-benzoyl), 7.76 (m, 4H, $H_{2,3,4,5}$-phenylene), 7.82 (s, 1H, NH-amide); ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.16, 120.36, 123.38, 127.03, 128.80, 129.57, 131.91, 132.11, 132.56, 134.04, 134.85, 137.58, 165.67, 168.07; LC–MS $[M+1]^+$: *m/z* 357.9, $[M+23]^+$: *m/z* 379; anal. calcd. for $C_{22}H_{16}N_2O_3$: C, 74.15; H, 4.53; N, 7.86; found: C, 74.27; H, 4.50; N, 7.89.

4-Fluoro-N-*{4-[(1,3-dioxoisoindolin-2-yl)methyl]phenyl}-benzamide (**6b**)*

White solid; yield: 89%; m.p. 223–226°C; IR (KBr) υ_{max}/cm^{-1}: 3,302 (NH), 1,659 (C═O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.75 (s, 2H, CH_2-benzyl), 7.31 (d, J = 8 Hz, 2H, $H_{3,5}$-benzyl), 7.36 (t, J = 8 Hz, 2H, $H_{3,5}$-benzoyl), 7.72 (d, J = 12 Hz, 2H, $H_{2,6}$-benzyl), 7.86 (m, 4H, $H_{2,3,4,5}$-phenylene), 8.03 (dd, J = 8, 4 Hz, 2H, $H_{2,6}$-benzoyl), 10.29 (s, 1H, NH-amide); ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.99, 115.61, 115.83, 121.05, 123.67, 128.26, 130.89, 130.98, 131.63, 131.66, 132.03, 132.35, 135.01, 138.86, 163.29, 164.79, 165.77, 168.17; LC–MS $[M+1]^+$: *m/z* 375.9, $[M+23]^+$: *m/z* 397; anal. calcd. for $C_{22}H_{15}FN_2O_3$: C, 70.58; H, 4.04; N, 7.48; found: C, 70.15; H, 4.07; N, 7.52.

4-Chloro-N-*{4-[(1,3-dioxoisoindolin-2-yl)methyl]phenyl}-benzamide (**6c**)*

White solid; yield: 87%; m.p. 240–244°C; IR (KBr) υ_{max}/cm^{-1}: 3,339 (NH), 1,690 (C═O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.74 (s, 2H, CH_2-benzyl), 7.30 (d, J = 8 Hz, 2H, $H_{3,5}$-benzyl), 7.57 (d, J = 8 Hz, 2H, $H_{2,6}$-benzoyl), 7.77 (d, J = 8 Hz, 2H, $H_{2,6}$-benzyl), 7.86 (m, 4H, $H_{2,3,4,5}$-phenylene), 8.02 (d, J = 8 Hz, 2H, $H_{3,5}$-benzoyl), 10.49 (s, 1H, NH-amide); ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.98, 121.09, 123.66, 128.27, 128.83, 129.58, 130.19, 132.01, 132.43, 133.88, 134.99, 136.86, 138.79, 164.78, 168.16; LC–MS $[M+23]^+$: *m/z* 413.0; anal. calcd. for $C_{22}H_{15}ClN_2O_3$: C, 67.61; H, 3.87; N, 7.17; found: C, 67.31; H, 3.90; N, 7.25.

4-Methyl-N-*{4-[(1,3-dioxoisoindolin-2-yl)methyl]phenyl}-benzamide (**6d**)*

White solid; yield: 73%; m.p. 211–213°C; IR (KBr) υ_{max}/cm^{-1}: 3,381 (NH), 1,704 (C═O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 3H, CH_3), 4.85 (s, 2H, CH_2-benzyl), 7.28 (d, J = 8 Hz, 2H, $H_{3,5}$-benzoyl), 7.46 (d, J = 8 Hz, 2H, $H_{3,5}$-benzyl), 7.61 (d, J = 8 Hz, 2H, $H_{2,6}$-benzyl), 7.72 (dd, J = 8, 4 Hz, 2H, $H_{3,5}$-phenylene), 7.47 (d, J = 8 Hz, 2H, $H_{2,6}$-benzoyl), 7.85 (m, 3H, $H_{2,4}$-phenylene, NH-amide); ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.16, 45.78, 120.45, 123.35, 127.19, 129.37, 129.41, 131.92, 132.10, 132.29, 134.03, 137.84, 142.36, 165.65, 168.05; LC–MS $[M+1]^+$: *m/z* 371; anal. calcd. for $C_{23}H_{18}N_2O_3$: C, 74.58; H, 4.90; N, 7.56; found: C, 74.28; H, 4.94; N, 7.63.

4-Methoxy-N-*{4-[(1,3-dioxoisoindolin-2-yl)methyl]phenyl}-benzamide (**6e**)*

White solid; yield: 75%; m.p. 208–211°C; IR (KBr) υ_{max}/cm^{-1}: 3,307 (NH), 1,694 (C═O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.79 (s, 3H, OCH_3), 4.76 (s, 2H, CH_2-benzyl), 6.88 (d, J = 12 Hz, 2H, $H_{3,5}$-benzoyl), 7.37 (d, J = 8 Hz, 2H, $H_{3,5}$-benzyl), 7.51 (d, J = 8 Hz, 2H, $H_{2,6}$-benzyl), 7.70 (m, 7H, $H_{2,3,4,5}$-phenylene, $H_{2,6}$-benzoyl, NH-amide); ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.16, 55.48, 113.99, 120.27, 123.27, 126.99, 128.90, 129.57, 132.13, 132.33, 134.02, 137.75, 162.53, 168.06; LC–MS $[M+1]^+$: *m/z* 387, $[M+23]^+$: *m/z* 409; anal. calcd. for $C_{23}H_{18}N_2O_4$: C, 74.58; H, 4.90; N, 7.56; found: C, 74.67; H, 4.88; N, 7.54.

4-Nitro-N-*{4-[(1,3-dioxoisoindolin-2-yl)methyl]phenyl}benzamide (**6f**)*

White solid; yield: 72%; m.p. 252–256°C; IR (KBr) υ_{max}/cm^{-1}: 3,368 (NH), 1,709 (C═O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.77 (s, 2H, CH_2-benzyl), 7.33 (d, J = 8 Hz, 2H, $H_{3,5}$-benzyl), 7.74 (d, J = 8 Hz, 2H, $H_{2,6}$-benzoyl), 7.90 (m, 4H, $H_{2,3,4,5}$-phenylene), 8.21 (d, J = 8 Hz, 2H, $H_{2,6}$-benzyl), 8.36 (d, J = 8 Hz, 2H, $H_{3,5}$-benzoyl), 10.60 (d, J = 8 Hz, 1H, NH-amide); ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.98, 121.11, 123.70, 124.00, 128.36, 129.68, 132.06, 132.88, 135.04, 138.42, 140.94, 149.62, 164.27, 168.19; LC–MS $[M+23]^+$: *m/z* 424; anal. calcd. for $C_{22}H_{15}N_3O_5$: C, 65.83; H, 3.77; N, 10.47; found: C, 65.89; H, 3.75; N, 10.38.

3-Chloro-N-*{4-[(1,3-dioxoisoindolin-2-yl)methyl]phenyl}-benzamide (**6g**)*

White solid; yield: 81%; m.p. 196–198°C; IR (KBr) υ_{max}/cm^{-1}: 3,327 (NH), 1,705 (C═O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.75 (s, 2H, CH_2-benzyl), 7.31 (d, J = 8 Hz, 2H, $H_{3,5}$-benzyl), 7.55 (t, J = 8 Hz, 1H, H_5-benzoyl), 7.64 (d, J = 8 Hz, 1H, H_6-benzoyl), 7.75 (d, J = 8 Hz, 2H, $H_{2,6}$-benzyl), 7.86 (m, 5H, $H_{2,3,4,5}$-phenylene, H_4-benzoyl), 7.92 (s, 1H, H_2-benzoyl), 10.43 (s, 1H, NH-amide); ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.98, 121.06, 123.67, 126.98, 127.90, 128.31, 130.81, 131.85, 132.03, 132.57, 133.65, 135.00, 137.19, 138.65, 164.41, 168.16; LC–MS $[M+23]^+$: *m/z* 413; anal. calcd. for $C_{22}H_{15}ClN_2O_3$: C, 67.61; H, 3.87; N, 7.17; found: C, 67.27; H, 3.90; N, 7.25.

3-Methyl-N-*{4-[(1,3-dioxoisoindolin-2-yl)methyl]phenyl}-benzamide (**6h**)*

White solid; yield: 79%; m.p. 182–186°C; IR (KBr) υ_{max}/cm^{-1}: 3,413 (NH), 1,703 (C═O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 3H, CH_3), 4.85 (s, 2H, CH_2-benzyl), 7.36 (d, J = 8 Hz, 2H, $H_{3,5}$-benzyl), 7.46 (d, J = 8 Hz, 2H, $H_{2,6}$-benzyl), 7.68 (m, 6H, $H_{2,4,5,6}$-benzoyl, $H_{3,4}$-phenylene), 7.86 (m, 3H, $H_{2,5}$-phenylene, NH-amide); ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.13, 45.82, 120.63, 123.31, 124.29, 128.06, 128.48, 129.23, 132.05, 132.23, 132.49, 134.05, 134.71, 137.94, 138.49, 165.99, 168.02; LC–MS $[M+1]^+$: *m/z* 371, $[M+23]^+$: *m/z* 393;

anal. calcd. for $C_{23}H_{18}N_2O_3$: C, 74.58; H, 4.90; N, 7.56; found: C, 74.37; H, 5.00; N, 7.65.

*3-Nitro-*N*-{4-[(1,3-dioxoisoindolin-2-yl)methyl]phenyl}benzamide (**6i**)*

White solid; yield: 84%; m.p. 239–241°C; IR (KBr) υ_{max}/cm^{-1}: 3,341 (NH), 1,701 (C═O); ^1H NMR (400 MHz, $CDCl_3$): δ 4.75 (s, 2H, CH_2-benzyl), 7.33 (d, J = 12 Hz, 2H, $H_{3,5}$-benzyl), 7.75 (d, J = 8 Hz, 2H, $H_{2,6}$-benzyl), 7.86 (m, 5H, $H_{2,3,4,5}$-phenylene, H_5-benzoyl), 8.40 (m, 2H, $H_{4,6}$-benzoyl), 8.78 (s, 1H, H_2-benzoyl), 10.59 (s, 1H, NH-amide); ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.96, 121.16, 122.87, 123.64, 126.59, 128.38, 130.56, 132.01, 132.80, 134.62, 134.95, 136.57, 138.44, 148.15, 163.64, 168.14; LC–MS $[M+1]^+$: m/z 402; anal. calcd. for $C_{22}H_{15}N_3O_5$: C, 74.58; H, 4.90; N, 7.56; found: C, 74.80; H, 4.84; N, 7.51.

4.1.5 | Procedure for the preparation of 2-(4-nitrophenyl)isoindoline-1,3-dione (9)

In 7 ml of glacial acetic acid, 0.148 g (1.0 mmol) of phthalic anhydride and 0.138 g (1.0 mmol) of 4-nitroaniline were dissolved, and 0.019 g (0.1 mmol) of cuprous iodide was added as the catalyst. The mixture was refluxed for 4 hr. The resulting precipitate was filtered and recrystallized from absolute ethanol to afford the product **9** as a white solid (90% yield); m.p. 171–173°C; IR: (KBr) υ (cm^{-1}) 1,700 (C═O), 1,510, 1,354 (N═O); ^1H NMR (400 MHz, DMSO-d_6): δ 7.79–7.82 (d, J = 12 Hz, 2H, $H_{2,6}$-phenyl), 7.93–7.97 (m, 2H, $H_{3,4}$-phenylene), 8.00–8.03 (m, 2H, $H_{2,5}$-phenylene), 8.40–8.43 (d, J = 12 Hz, 2H, $H_{3,5}$-phenyl); ^{13}C NMR (100 MHz, DMSO-d_6): δ 124.17, 124.66, 128.20, 131.96, 135.46, 138.20, 146.62, 166.87; LC–MS $[M+1]^+$: m/z 269.1; anal. calcd. for $C_{14}H_8N_2O_4$: C, 62.69; H, 3.01; N, 10.44; found: C, 63.05; H, 3.10; N, 10.56.

4.1.6 | Procedure for the preparation of 2-(4-aminophenyl)isoindoline-1,3-dione (10)

In 30 ml of absolute ethanol, 2.7 g (10.0 mmol) of compound **9** and 11.5 g of $SnCl_2{\cdot}2H_2O$ (50.0 mmol) were added, and the mixture was stirred at 75°C for 50 min. Afterward, the solvent was evaporated and the residue was extracted with a mixture of dichloromethane and ammonia aqueous solution (15.0 M). The organic phase was separated, dried over anhydrous sodium sulfate, and concentrated to afford compound **10** as a white solid (92% yield); m.p. 208–210°C; IR (KBr) υ_{max}/cm^{-1}: 3,355 (NH), 1,705 (C═O); ^1H NMR (400 MHz, DMSO-d_6): δ 7.44–7.46 (d, J = 8.8 Hz, 2H, $H_{3,5}$-phenyl), 7.51–7.53 (d, J = 8.8 Hz, 2H, $H_{2,6}$-phenyl), 7.91–7.93 (q, J = 3.6, 3.2, 1.2 Hz, 2H, $H_{5,6}$-phenylene), 7.97–7.98 (d, J = 2.8 Hz, 2H, $H_{4,7}$-phenylene), 10.01 (bs, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ 123.07, 123.94, 129.08, 130.43, 132.00, 134.22, 135.25, 167.42; LC–MS $[M+1]^+$: m/z 239; anal. calcd. for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76; found: C, 70.91; H, 4.17; N, 11.69.

4.1.7 | General procedure for the preparation of derivatives 12a–e

In dichloromethane, 0.5 g (2.1 mmol) of compound **10** was dissolved and 6.0 mmol of various benzoyl chloride derivatives were added to it. A catalytic amount of triethylamine was also added and the mixture was stirred for 12 hr at room temperature. The solvent was evaporated under a stream of nitrogen gas, and the residue was washed with distilled water, weak acid, and base solutions. The resulting crude solid was recrystallized from ethanol to afford the final products **12a–e**.

N-*[4-(1,3-Dioxoisoindolin-2-yl)phenyl]benzamide (**12a**)*

White solid; yield: 71%; m.p. 351–355°C; IR (KBr) υ_{max}/cm^{-1}: 3,330 (NH), 1,654, 1,704 (C═O); ^1H NMR (400 MHz, DMSO-d_6): δ 7.33–7.36 (d, 2H, J = 12 Hz, $H_{3,5}$-phenyl), 7.46–7.56 (m, 3H, $H_{3,5}$-benzoyl), 7.81–7.91 (m, 8H, $H_{4,5,6,7}$-phenylene, $H_{2,6}$-phenyl, and $H_{2,6}$-benzoyl), 10.37 (s, 1H, NH-amide); ^{13}C NMR (100 MHz, DMSO-d_6): δ 121.01, 123.88, 127.57, 128.21, 128.92, 132.04, 132.21, 135.18, 135.22, 139.37, 166.17, 167.63, 185.22; LC–MS $[M+1]^+$: m/z 343.0; anal. calcd. for $C_{21}H_{14}N_2O_3$: C, 73.68; H, 4.12; N, 8.18; found: C, 73.41; H, 4.15; N, 8.24.

*4-Chloro-*N*-[4-(1,3-dioxoisoindolin-2-yl)phenyl]benzamide (**12b**)*

White solid; yield: 84%; m.p. 330–350°C (decomposed); IR (KBr) υ_{max}/cm^{-1}: 3,347 (NH), 1,657, 1,704 (C═O); ^1H NMR (400 MHz, DMSO-d_6): δ 7.34–7.36 (d, J = 4 Hz, 2H, $H_{3,5}$-benzoyl), 7.54–7.57 (d, J = 12 Hz, 2H, $H_{2,6}$-phenyl), 7.80–7.84 (m, 4H, $H_{2,6}$-benzoyl and $H_{3,5}$-phenyl), 7.88–7.90 (m, 2H, $H_{5,6}$-phenylene), 7.92–7.95 (d, J = 12 Hz, 2H, $H_{4,7}$-phenylene), 11.02 (s, 1H, NH-amide); ^{13}C NMR (100 MHz, DMSO-d_6): δ 121.09, 123.88, 127.75, 128.22, 129.00, 130.18, 132.04, 133.90, 135.18, 137.03, 139.16, 167.05, 168.09; LC–MS $[M+1]^+$: m/z 377.0; anal. calcd. for $C_{21}H_{13}ClN_2O_3$: C, 66.94; H, 3.48; N, 7.43; found: C, 66.74; H, 3.53; N, 7.50.

*4-Nitro-*N*-[4-(1,3-dioxoisoindolin-2-yl)phenyl]benzamide (**12c**)*

White solid; yield: 78%; m.p. 334–345°C; IR (KBr) υ_{max}/cm^{-1}: 3,358 (NH), 1,691, 1,712 (C═O); ^1H NMR (400 MHz, DMSO-d_6): δ 7.87–7.99 (m, 4H, $H_{2,3,4,5}$-phenylene), 8.12–8.14 (d, J = 8 Hz, 4H, $H_{2,3,5,6}$-phenyl), 8.25–8.27 (d, J = 8 Hz, 4H, $H_{2,3,5,6}$-benzoyl), 11.02 (s, 1H, NH-amide); ^{13}C NMR (100 MHz, DMSO-d_6): δ 113.95, 119.96, 123.66, 123.89, 128.70, 129.93, 130.87, 132.05, 134.99, 135.20, 149.34, 167.05, 168.09; LC–MS $[M+1]^+$: m/z 388.09; anal. calcd. for $C_{21}H_{13}N_3O_5$: C, 65.12; H, 3.38; N, 10.85; found: C, 65.04; H, 3.40; N, 10.88.

*4-Methyl-*N*-[4-(1,3-dioxoisoindolin-2-yl)phenyl]benzamide (**12d**)*

White solid; yield: 81%; m.p. 326–332°C; IR (KBr) υ_{max}/cm^{-1}: 3,326 (NH), 1,654, 1,697 (C═O); ^1H NMR (400 MHz, DMSO-d_6): δ 2.41 (s, 3H, CH_3), 7.36–7.38 (d, J = 8 Hz, 2H, $H_{3,5}$-benzoyl), 7.41–7.44 (d, J = 12 Hz, 2H, $H_{2,6}$-phenyl), 7.90–7.94 (m, 6H, $H_{2,6}$-benzoyl, $H_{3,5}$-phenyl, and $H_{5,6}$-phenylene), 7.96–7.99 (m, 2H, $H_{4,7}$-phenylene),

10.36 (s, 1H, NH-amide); ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.51, 120.99, 123.87, 127.47, 128.17, 128.24, 129.43, 132.04, 132.32, 135.17, 139.45, 142.24, 165.96, 167.63; LC–MS $[M+1]^+$: *m/z* 357.12; anal. calcd. for $C_{22}H_{16}N_2O_3$: C, 74.15; H, 4.53; N, 7.86; found: C, 73.95; H, 4.59; N, 7.90.

*4-Methoxy-N-[4-(1,3-dioxoisoindolin-2-yl)phenyl]benzamide (**12e**)*
White solid; yield: 92%; m.p. 396–400°C (decomposed); IR (KBr) υ_{max}/cm^{-1}: 2,635–3,837 (NH), 1,648, 1,708 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.91 (s, 3H, OCH_3), 7.14–7.16 (d, *J* = 8 Hz, 2H, $H_{3,5}$-benzoyl), 7.46–7.48 (d, *J* = 8 Hz, 2H, $H_{3,5}$-phenyl), 7.94–7.99 (m, 4H, $H_{2,6}$-phenyl and $H_{2,6}$-benzoyl), 8.01–8.07 (m, 4H, $H_{4,5,6,7}$-phenylene), 10.34 (s, 1H, NH-amide); ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.93, 114.12, 120.96, 123.86, 127.22, 127.35, 128.13, 130.16, 132.05, 135.17, 139.57, 162.49, 165.50, 167.63; LC–MS $[M+1]^+$: *m/z* 373.0, $[M+23]^+$: *m/z* 395.0, $[2M+23]^+$: *m/z* 767.0; anal. calcd. for $C_{22}H_{16}N_2O_4$: C, 70.96; H, 4.33; N, 7.52; found: C, 71.03; H, 4.28; N, 7.47.

4.2 | In vitro biological activity

The biological evaluation was carried out by Cayman Spectrofluorometric Assay Kit (item number: 10011671), using the synthetic substrate 3-phenyl-cyano(6-methoxy-2-naphthalenyl)methyl ester-2-oxiraneacetic acid (PHOME). The enzyme and inhibitors were incubated in 200 μl of Bis-Tris/HCl-buffered solution (25 mM, pH 7.0) at 30°C for 5 min. AUDA, a well-known sEH inhibitor with an IC_{50} of 1 nM, was used as the positive control for the assay. The enzyme activity was determined through monitoring the appearance of 6-methoxy-2-naphthaldehyde by fluorescence detection with excitation and emission wavelengths of 330 and 465 nm, respectively. All test samples and AUDA were dissolved in DMSO.

4.3 | Docking studies

The newly designed structures were drawn using ChemBioDraw® Ultra 16.0, energy-minimized under the MM+ force field in Chem3D Ultra® 16.0 software, and converted to pdbqt format file using AutoDock® Tools version 1.5.6rc3 (http://mgltools.scripps.edu). The published X-ray crystallographic structure of the human sEH (PDB code: 3ANS) complexed with its cognate ligand, 4-cyano-*N*-[(1*S*,2*R*)-2-phenylcyclopropyl]benzamide, was downloaded from RCSB Protein Data Bank[29] and processed using Accelrys ViewerLite® software version 5.0. The structures of compounds were investigated by the Lamarckian genetic algorithm search method implemented in AutoDock4 software. The conformation of the receptor was kept rigid, and ligand molecules were allowed to be flexible. The water molecules were removed. The polar hydrogen atoms were merged and Kollman united partial charges were added to the individual atoms of the protein at pH 7.0. Grid map dimensions (20 × 20 × 20) were set surrounding the active site. Other related parameters were set as default parameters. Docking results were clustered with a root mean square deviation of 0.5 Å and visualized by Pymol® software version 1.5.0.1 (http://pymol.findmysoft.com).

4.4 | ADME properties

The ADME properties of the newly synthesized analogs **6a–i** and **12a–e** were predicted in a computer analysis using the Molinspiration online property calculation toolkit.[30] It determined eight parameters including logarithm of partition coefficient (miLog *P*), molecular volume (MV), molecular weight (MW), the number of hydrogen bond acceptors (*n*-ON), the number of hydrogen bond donors (*n*-OHNH), the topological polar surface area (TPSA), the number of rotatable bonds (*n*-ROTB), and Lipinski's rule of five (ROF).[31] The absorption rate (% ABS) has also been computed with ABS = 109 − (0.345 × TPSA).[32]

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CONFLICT OF INTERESTS
The authors declare that there are no conflicts of interests.

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REFERENCES
[1] C. Morisseau, *Biochimie*. **2013**, *95*, 91.
[2] A. Cronin, M. Decker, M. Arand, *J. Lipid Res.* **2011**, *52*, 712.
[3] J. D. Imig, B. D. Hammock, *Nat. Rev. Drug. Discov.* **2009**, *8*, 794.
[4] N. Chiamvimonvat, C. M. Ho, H. J. Tsai, B. D. Hammock, *J. Cardiovasc. Pharmacol.* **2007**, *50*, 225.
[5] K. Hashimoto, *Front. Pharmacol.* **2019**, *10*, 36.
[6] L. Liu, C. Chen, W. Gong, Y. Li, M. L. Edin, D. C. Zeldin, D. W. Wang, *J. Pharmacol. Exp. Ther.* **2011**, *339*, 451.
[7] A. A. Spector, X. Fang, G. D. Snyder, N. L. Weintraub, *Prog. Lipid Res.* **2004**, *43*, 55.
[8] S. Tacconelli, P. Patrignani, *Front. Pharmacol.* **2014**, *5*, 239.
[9] B. T. Larsen, H. Miura, O. A. Hatoum, W. B. Campbell, B. D. Hammock, D. C. Zeldin, J. R. Falck, D. D. Gutterman, *Am. J. Physiol. Heart Circ. Physiol.* **2006**, *290*, H491.
[10] B. B. Davis, J.-Y. Liu, D. J. Tancredi, L. Wang, S. I. Simon, B. D. Hammock, K. E. Pinkerton, *Biochem. Biophys. Res. Commun.* **2011**, *410*, 494.
[11] M. L. Heizer, J. S. McKinney, E. F. Ellis, *Stroke* **1991**, *22*, 1389.
[12] J. Sun, X. Sui, J. A. Bradbury, D. C. Zeldin, M. S. Conte, J. K. Liao, *Circ. Res.* **2002**, *90*, 1020.
[13] E. R. Zavareh, M. Hedayati, L. H. Rad, S. Shahhosseini, M. Faizi, S. A. Tabatabai, *Iran. J. Pharm. Res.* **2014**, *13*, 51.
[14] M. Nazari, S. A. Tabatabai, E. Rezaee, *ChemistrySelect* **2019**, *4*, 6348.
[15] A. B. Eldrup, F. Soleymanzadeh, S. J. Taylor, I. Muegge, N. A. Farrow, D. Joseph, K. McKellop, C. C. Man, A. Kukulka, S. De Lombaert, *J. Med. Chem.* **2009**, *52*, 5880.

[16] R. H. Ingraham, R. D. Gless, H. Y. Lo, *Curr. Med. Chem.* **2011**, *18*, 587.
[17] V. Burmistrov, C. Morisseau, D. Pitushkin, D. Karlov, R. R. Fayzullin, G. M. Butov, B. D. Hammock, *Bioorg. Med. Chem. Lett.* **2018**, *28*, 2302.
[18] V. Burmistrov, C. Morisseau, D. Danilov, T. R. Harris, I. Dalinger, I. Vatsadze, T. Shkineva, G. M. Butov, B. D. Hammock, *Bioorg. Med. Chem. Lett.* **2015**, *25*, 5514.
[19] N. Tripathi, S. Paliwal, S. Sharma, K. Verma, R. Gururani, A. Tiwari, A. Verma, M. Chauhan, A. Singh, D. Kumar, A. Pant, *Sci. Rep.* **2018**, *8*, 14604.
[20] C. Morisseau, J. W. Newman, H.-J. Tsai, P. A. Baecker, B. D. Hammock, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5439.
[21] I.-H. Kim, F. R. Heirtzler, C. Morisseau, K. Nishi, H.-J. Tsai, B. D. Hammock, *J. Med. Chem.* **2005**, *48*, 3621.
[22] I.-H. Kim, K. Nishi, H.-J. Tsai, T. Bradford, Y. Koda, T. Watanabe, C. Morisseau, J. Blanchfield, I. Toth, B. D. Hammock, *Bioorg. Med. Chem.* **2007**, *15*, 312.
[23] E. Rezaee Zavareh, M. Hedayati, L. Hoghooghi Rad, A. Kiani, S. Shahhosseini, M. Faizi, S. A. Tabatabai, *Lett. Drug. Des. Discov.* **2014**, *11*, 721.
[24] E. Rezaee, M. Hedayati, L. H. Rad, S. Shahhosseini, M. Faizi, S. A. Tabatabai, *MedChemComm* **2016**, *7*, 2128.
[25] L. Hejazi, E. Rezaee, S. A. Tabatabai, *Iran. J. Pharm. Res.* **2019**, *18*, 1759.
[26] E. Rezaee, S. M. Amrolah, M. Nazari, S. A. Tabatabai, *Mol. Divers.* **2019**, 1.
[27] H. C. Shen, B. D. Hammock, *J. Med. Chem.* **2012**, *55*, 1789.
[28] P. Ertl, B. Rohde, P. Selzer, *J. Med. Chem.* **2000**, *43*, 3714.
[29] D. Tanaka, Y. Tsuda, T. Shiyama, T. Nishimura, N. Chiyo, Y. Tominaga, N. Sawada, T. Mimoto, N. Kusunose, *J. Med. Chem.* **2010**, *54*, 851.
[30] M. Cheminformatics, Web-enabled software for large-scale calculation of molecular properties and database searches. Free online molecular descriptor calculations. **2015** (accessed: November 2012).
[31] C. A. Lipinski, F. Lombardo, B. W. Dominy, P. J. Feeney, *Adv. Drug Deliv. Rev.* **1997**, *23*, 3.
[32] Y. H. Zhao, M. H. Abraham, J. Le, A. Hersey, C. N. Luscombe, G. Beck, B. Sherborne, I. Cooper, *Pharm. Res.* **2002**, *19*, 1446.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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