DOI 10.1007/s10593-019-02428-2

Chemistry of Heterocyclic Compounds **2019**, *55*(2), 129–134

Synthesis and properties of 1-[(adamantan-1-yl)methyl]-3-pyrazolyl ureas

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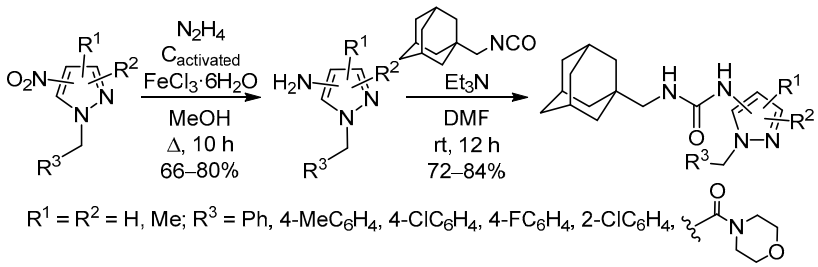
Translated from Khimiya Geterotsiklicheskikh Soedinenii, 2019, *55*(2), 129–134

Submitted October 15, 2018
Accepted December 21, 2018



A series of 1,3-disubstituted ureas containing 1,3,5-trisubstituted pyrazole and (adamantan-1-yl)methyl fragments were synthesized in the reaction of 1-(isocyanatomethyl)adamantane with 3- or 4-aminopyrazoles under mild conditions in 67–92% yields. The inhibitory activity of the obtained compounds with respect to human soluble epoxide hydrolase (sEH) was 16.2–50.2 nmol/l, with solubility in water of 45–85 μmol/l.

Keywords: adamantane derivatives, amines, 1,3-disubstituted ureas, isocyanates, pyrazoles, soluble epoxide hydrolase (sEH), inhibitors.

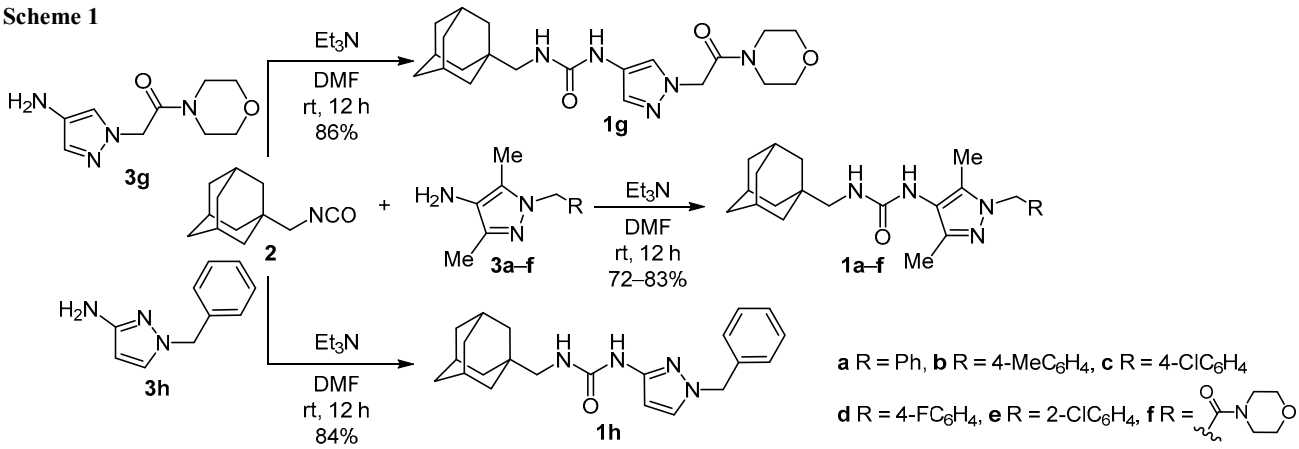
Substituted pyrazoles exhibit diverse biological activity such as analgesic and anti-inflammatory,[1] antibacterial,[2] antifungal,[3] antitumor,[4] and antiviral,[5] and are also being investigated as inhibitors of human soluble epoxide hydrolase (sEH) (IC_{50} 220–224 nmol/l).[6] The data of inhibitory activity of pyrazole-containing compounds toward protein kinase p38 MAPKα, as well as the results of molecular docking showed that the high activity of these compounds is due to the ability of the pyrazole pharmacophoric center to bind up to two amino acid residues in the active center of the enzyme.[7]

1,3-Disubstituted ureas comprising a pyrazole group in their structure were studied as inhibitors of cyclin-dependent kinase CDK5 and glycogen synthase kinase GSK3α/β,[8] inhibitors of viral oncogene sarcoma BRAF,[9] inhibitors of tyrosine kinase activity of VEGFR-2 receptors,[10] and selective dual inhibitor of complexes 1 and 2 (mTORC1 and mTORC2), rapamycin targets in mammals.[11] Inhibition of kinase JNK3 with such structures is a promising strategy in the treatment of neuro-degeneration.[12] A number of ureas containing 1,5-di-arylpyrazole group in their structure were studied as dual cyclooxygenase-2 (COX-2) and sEH inhibitors.[13]

Human sEH is an enzyme involved in the metabolism of epoxy fatty acids (arachidonic acid metabolites) to the corresponding vicinal diols by catalytic addition of a water molecule.[14] Inhibition of human sEH with target-oriented inhibitors has a positive effect on the treatment of hypertension and kidney disease,[15] inflammatory and painful conditions,[16] as well as other socially significant diseases. Analysis of the sEH gene structure shows that it consists of two globular proteins, each of which contains its own C-terminal epoxide hydrolase and N-terminal phosphatase domains for binding to substrates of different nature.[17]

1,3-Disubstituted ureas occupy an important place among the existing inhibitors of the C-terminal epoxide hydrolase domain. For example, small symmetrical ureas, such as 1,3-dicyclohexylurea, are potent inhibitors of sEH.[18] However, their low solubility in water severely limits their use as dosage forms. Asymmetrical ureas with a flexible side chain, such as 12-(1-adamantan-1-ylureido)-dodecanoic acid (AUDA), have been developed to increase solubility. Despite the fact that this class of sEH inhibitors shows high activity in *in vivo* tests, they are extremely rapidly metabolized, which reduces their applicability.[19]

Scheme 1



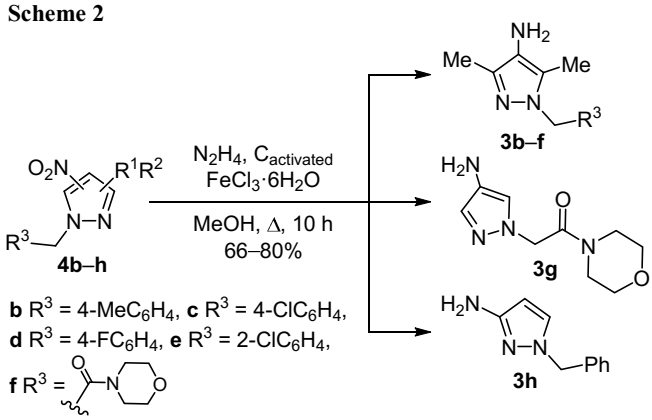
To date, more than 3000 disubstituted ureas containing aliphatic, aromatic, and heterocyclic fragments have been investigated as sEH inhibitors.[20] Many of the synthesized inhibitors of sEH are adamantyl ureas with the ureid pharmacophoric center. However, compounds that combine high activity, solubility in water, and resistance to metabolism were not found among them.

In continuation of our work on the synthesis of adamantyl-containing 1,3-disubstituted ureas with a heterocyclic fragment[21] and the study of their properties, a series of 1,3-disubstituted ureas **1a**–**h** containing the pyrazole fragment were obtained for the first time (Scheme 1). The synthesis of products **1a**–**h** was carried out by stirring 1-(isocyanatomethyl)adamantane (**2**) and the corresponding aminopyrazoles **3a**–**h** in anhydrous DMF in the presence of Et_3N with the molar ratio of reagents **2**:**3**:Et_3N of 1:1:1 for 12 h at room temperature. During the reaction, precipitation of 1,3-disubstituted ureas **1a**–**h** in the form of white crystals was observed. At the end of the reaction, the products were filtered off and washed with EtOAc, 1 N aqueous HCl to remove the residual amine, and a small amount of H_2O. The yields of the obtained compounds **1a**–**h** were 67–92%. The structure of the obtained compounds was confirmed using IR spectroscopy, ^1H, ^{13}C NMR spectroscopy, and elemental analysis.

1-(Adamantan-1-yl)-3-(1-alkyl-1*H*-pyrazolyl)ureas described in the literature were studied as inhibitors of human sEH (IC_{50} 488–2512 nmol/l) and had water solubility values of 4.5–149.3 μmol/l.[22] In order to increase the inhibitory activity against human sEH, we carried out screening of the initial reagents for inhibitor synthesis. The choice of isocyanate **2** is due to the presence of a methylene bridge between the isocyanate group and the adamantyl fragment, which increases the conformational mobility of the pharmacophoric fragment and contributes to a better adjustment of the inhibitor in the active center of sEH.[23] Benzyl-substituted aminopyrazoles **3a**–**e**,**h** as well as aminopyrazoles **3f**,**g**, containing *N*-[2-(morpholin-4-yl)-2-oxoethyl] group were selected as the pyrazole component (Scheme 1); such pyrazoles are widely used in the synthesis of biologically active compounds.[24] It is known that the presence of the methyl group, as well as halogen atoms (chlorine, fluorine) in the aromatic ring increases the inhibitory activity of compounds with respect to sEH.[19] In addition, pyrazoles **3a**–**f** contain methyl substituents in positions 3 and 5 of the pyrazole ring, which, in our opinion, will help to protect it from the oxidative effects of cytochromes P450. The selected series of compounds **3a**–**h** will allow to study the effect of the structure of substituted pyrazoles on the properties of 1,3-disubstituted ureas **1a**–**h** and on their inhibitory activity against human sEH.

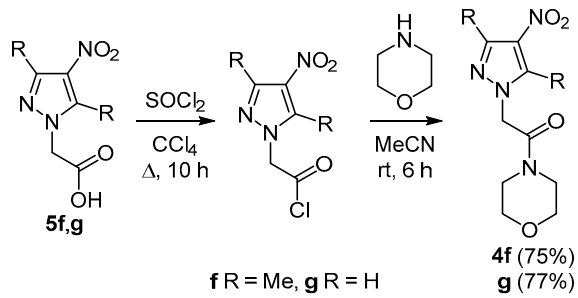
Mild reduction with hydrazine, well proven for nitropyrazoles,[25] was used to obtain the starting aminopyrazoles **3b**–**h**. Indeed, treatment of nitro derivatives **4b**–**h** with hydrazine on activated carbon in the presence of $FeCl_3 \cdot 6H_2O$ as a catalyst allowed us to obtain the desired amines **3b**–**h** in high yields (Scheme 2).

Scheme 2



Nitropyrazoles **4f**,**g** with an *N*-[2-(morpholin-4-yl)-2-oxoethyl] substituent were obtained by a known method from nitropyrazolylacetic acids **5f**,**g**[26] synthesized by us earlier (Scheme 3).

Scheme 3



The obtained series of 1,3-disubstituted ureas **1a**–**h** was investigated *in vitro* as a target-oriented sEH inhibitors. It was established that the inhibitory activity against human sEH for the obtained products **1a**–**h** ranges from 16.2 to 50.2 nmol/l. Other properties of compounds **1a**–**e**,**h** are presented in Table 1. For compounds **1a**–**e**, the introduction of 4-Me, 4-Cl, 4-F, and 2-Cl substituents into the aromatic ring reduces the solubility in water. Water solubility decreases when replacing a fluorine atom with a chlorine atom. The position of the substituent in the aromatic ring (*para*- or *ortho*-) hardly affects the solubility. Urea based on unsubstituted pyrazole **1h** dissolves worse compared to 3,5-dimethylpyrazole-substituted analogs **1a**–**e**. The obtained pyrazole-containing 1,3-disubstituted ureas **1a**–**e**,**h** dissolve better in water in comparison with the known analogs,[22] which suggests their higher bioavailability.

Table 1. Properties of 1,3-disubstituted ureas **1a**–**e**,**h**

Compound	Substituents in benzene ring	Water solubility, μmol/l	cLogP
1a	–	85 ± 3	4.80
1b	4-Me	75 ± 2	5.25
1c	4-Cl	65 ± 4	5.48
1d	4-F	75 ± 3	4.96
1e	2-Cl	65 ± 4	5.43
1h	–	45 ± 2	4.35

To conclude, 1,3-disubstituted ureas were synthesized by reacting 1-(isocyanatomethyl)adamantane with 3- or 4-aminopyrazoles in anhydrous DMF in the presence of Et_3N for 12 h at room temperature. The high inhibitory activity of the obtained compounds in combination with increased bioavailability makes them promising for further study as inhibitors of human sEH.

Experimental

IR spectra were registered on a Bruker Alpha spectrometer in KBr pellets. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker AM300 (300 and 75 MHz, respectively) spectrometer in DMSO-d_6 and $CDCl_3$ at 25°C with TMS as internal standard. Assignment of signals in the ^{13}C NMR spectra were made on the basis of literature data.[25,27] Mass spectra were recorded on a Finnigan MAT Incos 50 apparatus with direct sample injection in EI ionization mode (70 eV). Melting points were determined on a Boetius heating bench (4°C/min heating rate) and are uncorrected. Elemental analysis was performed on a Perkin Elmer Series II 2400 Elemental analyzer. Monitoring of the reaction progress and assessment of the purity of synthesized compounds were done by TLC on Merck Silica-gel 60 F_{254} plates, eluent MeCN–$CHCl_3$, 1:5.

Precursors 1-(isocyanatomethyl)adamantane (**2**)[23] and nitropyrazolylacetic acids **5f**,**g**[26] were obtained according to literature methods, pyrazoles **3a** and **4b**–**e**,**h** were supplied by Crea-Chim.

Synthesis of 1,3-disubstituted ureas 1a–h (General method). Aminopyrazole **3a**–**h** (0.5 mmol) and Et_3N (70 μl, 0.5 mmol) were added to a solution of 1-(isocyanatomethyl)-adamantane (**2**) (96 mg, 0.5 mmol) in anhydrous DMF (5 ml) at 0°C. The mixture was stirred at room temperature for 12 h. The formed white crystals were filtered off, washed with EtOAc (10 ml), 1 N aqueous HCl (10 ml), and H_2O (10 ml), then air-dried.

1-[(Adamantan-1-yl)methyl]-3-[1-benzyl-3,5-dimethyl-1*H*-pyrazol-4-yl]urea (1a). Yield 160 mg (81%), mp 200–202°C. IR spectrum, ν, cm^{-1}: 3318, 2901, 2847, 1643, 1572, 1451, 1301, 1246, 1095, 649. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 7.31 (3H, t, *J* = 7.0, H Ph); 7.12 (2H, d, *J* = 6.9, H Ph); 5.51 (1H, br. s, NH); 5.26 (2H, s, NC$\underline{H}_2$Ph); 4.51 (1H, br. s, N$\underline{H}$CH$_2$); 2.89 (2H, d, *J* = 5.8, NHC$\underline{H}_2$); 2.24 (3H, s, CH_3); 2.13 (3H, s, CH_3); 1.95 (3H, br. s, CH Ad); 1.72–1.54 (6H, m, CH_2 Ad); 1.38 (6H, s, CH_2 Ad). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 157.1 (C=O); 143.2; 137.9; 134.6; 128.5 (CH Ph); 127.3 (CH Ph); 127.0 (CH Ph); 116.8; 52.3 (CH_2); 51.0 (CH_2); 39.8 (CH_2 Ad); 36.7 (CH_2 Ad); 33.7 (C Ad); 27.8 (CH Ad); 11.2 (CH_3); 9.1 (CH_3). Mass spectrum, *m*/*z* (I_{rel}, %): 392 [M]$^+$ (100). Found, %: C 73.30; H 8.29; N 14.14. $C_{24}H_{32}N_4O$. Calculated, %: C 73.42; H 8.22; N 14.27.

1-[(Adamantan-1-yl)methyl]-3-[3,5-dimethyl-1-(4-methylbenzyl)-1*H*-pyrazol-4-yl]urea (1b). Yield 166 mg (81%), mp 223–225°C. IR spectrum, ν, cm^{-1}: 3311, 2901, 2845, 1642, 1576, 1473, 1449, 1303, 1248, 1108, 730. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 7.12 (2H, d, *J* = 7.7, H Ar); 7.02 (2H, d, *J* = 7.8, H Ar); 5.46 (1H, s, NH); 5.20 (2H, s, NC$\underline{H}_2$Ar); 4.48 (1H, br. s, N$\underline{H}$CH$_2$); 2.88 (2H, d, *J* = 5.8, NHC$\underline{H}_2$); 2.33 (3H, s, CH_3); 2.23 (3H, s, CH_3); 2.12 (3H, s, CH_3); 1.94 (3H, br. s, CH Ad); 1.72–1.51 (6H, m, CH_2 Ad); 1.37 (6H, s, CH_2 Ad). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 158.2 (C=O); 144.3; 137.6; 135.9; 135.6; 130.2 (CH Ar); 128.1 (CH Ar); 117.8; 53.2 (CH_2); 52.1 (CH_2); 40.9 (CH_2 Ad); 37.8 (CH_2 Ad); 34.9 (C Ad); 28.9 (CH Ad); 21.8 (4-$\underline{C}H_3C_6H_4$); 12.3 (CH_3); 10.2 (CH_3). Mass spectrum, *m*/*z* (I_{rel}, %): 406 [M]$^+$ (100). Found, %: C 73.69; H 8.54; N 13.74. $C_{25}H_{34}N_4O$. Calculated, %: C 73.85; H 8.43; N 13.78.

1-[(Adamantan-1-yl)methyl]-3-[1-(4-chlorobenzyl)-3,5-dimethyl-1*H*-pyrazol-4-yl]urea (1c). Yield 162 mg (76%), mp 253–255°C. IR spectrum, ν, cm^{-1}: 3310, 2907, 2845, 1642, 1573, 1490, 1448, 1314, 1249, 1093, 1016, 803, 732. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 7.40 (2H, d, *J* = 8.1, H Ar); 7.16 (2H, d, *J* = 8.1, H Ar); 7.09 (1H, s, NH); 5.74 (1H, t, *J* = 5.1, N$\underline{H}$CH$_2$); 5.18 (2H, s, NC$\underline{H}_2$Ar); 2.75 (2H, d, *J* = 5.9, NHC$\underline{H}_2$); 2.02 (3H, s, CH_3); 2.01 (3H, s, CH_3); 1.93 (3H, br. s, CH Ad); 1.70–1.56 (6H, m, CH_2 Ad); 1.42 (6H, s, CH_2 Ad). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 7.30 (2H, d, *J* = 8.8, H Ar); 7.06 (2H, d, *J* = 8.3, H Ar); 5.50 (1H, s, NH); 5.21 (2H, s, NC$\underline{H}_2$Ar); 4.46 (1H, br. s, N$\underline{H}$CH$_2$); 2.89 (2H, d, *J* = 5.7, NHC$\underline{H}_2$); 2.23 (3H, s, CH_3); 2.12 (3H, s, CH_3); 1.95 (3H, br. s, CH Ad); 1.73–1.53 (6H, m, CH_2 Ad); 1.38 (6H, s, CH_2 Ad). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 157.0 (C=O); 143.4; 136.8; 134.4; 131.9; 128.8 (CH Ar); 128.4 (CH Ar); 116.7; 51.4 (CH_2); 50.9 (CH_2); 39.7 (CH_2 Ad); 36.6 (CH_2 Ad); 33.6 (C Ad); 27.8 (CH Ad); 11.1 (CH_3); 8.9 (CH_3). Mass spectrum, *m*/*z* (I_{rel}, %): 426 [M(^{35}Cl)]$^+$ (100), 428 [M(^{37}Cl)]$^+$ (100). Found, %: C 67.59; H 7.23; N 13.07. $C_{24}H_{31}ClN_4O$. Calculated, %: C 67.51; H 7.32; N 13.12.

1-[(Adamantan-1-yl)methyl]-3-[1-(4-fluorobenzyl)-3,5-dimethyl-1*H*-pyrazol-4-yl]urea (1d). Yield 156 mg (76%), mp 218–220°C. IR spectrum, ν, cm^{-1}: 3318, 2901, 2847, 1643, 1604, 1573, 1510, 1481, 1449, 1314, 1297, 1248, 1230, 1157, 1104, 833, 764, 721, 532. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 7.12 (2H, dd, *J* = 8.4, *J* = 5.4, H Ar); 7.01 (2H, t, *J* = 8.5, H Ar); 5.50 (1H, s, NH); 5.21 (2H, s, NC$\underline{H}_2$Ar); 4.47 (1H, br. s, N$\underline{H}$CH$_2$); 2.88 (2H, d, *J* = 6.0, NHC$\underline{H}_2$); 2.23 (3H, s, CH$_3$); 2.13 (3H, s, CH$_3$); 1.94 (3H, br. s, CH Ad); 1.72–1.50 (6H, m, CH$_2$ Ad); 1.38 (6H, s, CH$_2$ Ad). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 162.6 (d, *J* = 242.9, C-4' Ar); 158.2 (C=O); 144.5; 135.6; 135.1; 130.3 (d, *J* = 8.0, C-2',6' Ar); 117.9; 116.4 (d, *J* = 21.4, C-3',5' Ar); 52.6 (CH$_2$); 52.1 (CH$_2$); 40.9 (CH$_2$ Ad); 37.8 (CH$_2$ Ad); 34.9 (C Ad); 28.9 (CH Ad); 12.3 (CH$_3$); 10.2 (CH$_3$). Mass spectrum, *m*/*z* (I_{rel}, %): 410 [M]$^+$ (100). Found, %: C 70.31; H 7.52; N 13.68. $C_{24}H_{31}FN_4O$. Calculated, %: C 70.22; H 7.61; N 13.65.

1-[(Adamantan-1-yl)methyl]-3-[1-(2-chlorobenzyl)-3,5-dimethyl-1*H*-pyrazol-4-yl]urea (1e). Yield 144 mg (67%), mp 213–215°C. IR spectrum, ν, cm^{-1}: 3304, 2906, 2842, 1635, 1573, 1488, 1445, 1314, 1248, 1110, 1088, 1018, 830, 725, 696. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J,* Hz): 7.41 (1H, d, *J* = 7.6, H Ar); 7.25 (2H, d, *J* = 6.9, H Ar); 6.81 (1H, d, *J* = 6.9, H Ar); 5.44 (2H, s, NC$\underline{H}_2$Ar); 5.40 (1H, s, NH); 5.17 (1H, br. s, N$\underline{H}$CH$_2$); 2.71 (2H, d, *J* = 4.0, NHC$\underline{H}_2$); 2.29 (3H, s, CH$_3$); 2.18 (3H, s, CH$_3$); 1.96 (3H, br. s, CH Ad); 1.73–1.50 (6H, m, CH$_2$ Ad); 1.44 (6H, s, CH$_2$ Ad). Mass spectrum, *m*/*z* (I_{rel}, %): 426 [M(^{35}Cl)]$^+$ (100), 428 [M(^{37}Cl)]$^+$ (100). Found, %: C 67.66; H 7.24; N 13.01. $C_{24}H_{31}ClN_4O$. Calculated, %: C 67.51; H 7.32; N 13.12.

1-[(Adamantan-1-yl)methyl]-3-{3,5-dimethyl-1-[2-(morpholin-4-yl)-2-oxoethyl]-1*H*-pyrazol-4-yl}urea (1f). Yield 146 mg (68%). IR spectrum, ν, cm^{-1}: 3328, 2901, 2847, 1651, 1634, 1571, 1450, 1345, 1311, 1277, 1244, 1117. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 5.78 (1H, br. s, NH); 4.93 (2H, s, NCH$_2$C(O)); 4.86 (1H, br. s, N$\underline{H}$CH$_2$); 3.72 (4H, t, *J* = 4.4, 2OC$\underline{H}_2$CH$_2$N); 3.59 (4H, t, *J* = 4.4, 2OCH$_2$C$\underline{H}_2$N); 2.91 (2H, d, *J* = 5.8, NHC$\underline{H}_2$); 2.89 (3H, s, CH$_3$); 2.21 (3H, s, CH$_3$); 1.95 (3H, br. s, CH Ad); 1.76–1.60 (6H, m, CH$_2$ Ad); 1.50 (6H, s, CH$_2$ Ad). Mass spectrum, *m*/*z* (I_{rel}, %): 429 [M]$^+$ (100). Found, %: C 64.22; H 8.12; N 16.38. $C_{23}H_{35}N_5O_3$. Calculated, %: C 64.31; H 8.21; N 16.30.

1-[(Adamantan-1-yl)methyl]-3-{1-[2-(morpholin-4-yl)-2-oxoethyl]-1*H*-pyrazol-4-yl}urea (1g). Yield 172 mg (85%). IR spectrum, ν, cm^{-1}: 3324, 2901, 2848, 1636, 1596, 1568, 1450, 1400, 1252, 1119, 1041, 645. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 8.03 (1H, s, H-5 Pz); 7.62 (1H, s, H-3 Pz); 7.29 (1H, s, NH); 5.98 (1H, br. s, N$\underline{H}$CH$_2$); 5.02 (2H, s, NCH$_2$C(O)); 3.59 (4H, s, OC$\underline{H}_2$CH$_2$N); 3.48 (2H, s, OCH$_2$C$\underline{H}_2$N); 3.46 (2H, s, OCH$_2$C$\underline{H}_2$N); 2.78 (2H, d, *J* = 5.7, NHC$\underline{H}_2$); 1.94 (3H, br. s, CH Ad); 1.71–1.58 (6H, m, CH$_2$ Ad); 1.44 (6H, s, CH$_2$ Ad). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 165.7 (C=O); 155.4 (C=O); 129.4 (CH Pz); 123.0 (C-4 Pz); 120.4 (CH Pz); 65.9 (OCH$_2$); 52.7 (CH$_2$); 50.9 (CH$_2$); 44.8 (CH$_2$); 41.8 (CH$_2$); 39.7 (CH$_2$ Ad); 36.6 (CH$_2$ Ad); 33.5 (C Ad); 27.7 (CH Ad). Mass spectrum, *m*/*z* (I_{rel}, %): 401 [M]$^+$ (100). Found, %: C 62.74; H 7.90; N 17.53. $C_{21}H_{31}N_5O_3$. Calculated, %: C 62.82; H 7.78; N 17.44.

1-[(Adamantan-1-yl)methyl]-3-(1-benzyl-1*H*-pyrazol-3-yl)urea (1h). Yield 168 mg (92%), mp 165–167°C. IR spectrum, ν, cm^{-1}: 3360, 3281, 3245, 3137, 3122, 2901, 2848, 1673, 1639, 1573, 1552, 1533, 1453, 1407, 1355, 1345, 1312, 1295, 759, 716. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 8.76 (1H, s, H-5 Pz); 8.69 (1H, s, H-4 Pz); 7.31 (3H, t, *J* = 6.8, H Ph); 7.12 (2H, d, *J* = 6.9, H Ph); 7.01 (1H, br. s, NH); 6.05 (1H, br. s, N$\underline{H}$CH$_2$); 5.18 (2H, s, NC$\underline{H}_2$Ph); 2.82 (2H, d, *J* = 5.9, NHC$\underline{H}_2$); 1.93 (3H, br. s, CH Ad); 1.70–1.52 (6H, m, CH$_2$ Ad); 1.40 (6H, s, CH$_2$ Ad). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 159.8; 155.9 (C=O); 150.3; 138.8; 132.2 (CH Ph); 129.6 (CH Ph); 128.7 (CH Ph); 95.3; 55.6 (CH$_2$); 52.1 (CH$_2$); 40.9 (CH$_2$ Ad); 37.7 (CH$_2$ Ad); 34.5 (C Ad); 28.8 (CH Ad). Mass spectrum, *m*/*z* (I_{rel}, %): 364 [M]$^+$ (100). Found, %: C 72.42; H 7.79; N 15.30. $C_{22}H_{28}N_4O$. Calculated, %: C 72.50; H 7.74; N 15.37.

Synthesis of aminopyrazoles 3b–h by reduction of nitropyrazoles 4b–h (General method). Nitropyrazole **4b**–**h** (3.2 mmol) was added to a solution of $N_2H_4 \cdot H_2O$ (0.48 ml, 9.6 mmol) in MeOH (30 ml) at room temperature, followed by $FeCl_3 \cdot 6H_2O$ (22 mg, 0.08 mmol) and activated carbon (160 mg, 13.2 mmol). The reaction mixture was heated to boiling point, refluxed for 10 h, then cooled. The precipitate was filtered off, washed with EtOH (3×20 ml). The combined filtrates were evaporated under reduced pressure. The residue was dissolved in H_2O (5 ml) and acidified with aqueous HCl to pH 3–4. The formed precipitate was filtered off, washed with cold water H_2O (2 ml), and air-dried.

3,5-Dimethyl-1-(4-methylbenzyl)-1*H*-pyrazol-4-amine (3b). Yield 551 mg (80%), white powder, mp 108–109°C. IR spectrum, ν, cm^{-1}: 3377, 3275, 3205, 2920, 1629, 1595, 1515, 1474, 1426, 1374, 1359, 1325, 1255, 1233, 1116, 830, 797, 675, 471. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 7.10 (2H, d, *J* = 7.6, H Ar); 6.92 (2H, d, *J* = 7.7, H Ar); 5.05 (2H, s, NCH$_2$); 3.38 (2H, br. s, NH$_2$+H$_2$O); 2.23 (3H, s, 4-C$\underline{H}_3$C$_6$H$_4$); 2.04 (6H, s, 2CH$_3$). Mass spectrum, *m*/*z* (I_{rel}, %): 215 [M]$^+$ (100). Found, %: C 72.35; H 8.06; N 19.68. $C_{13}H_{17}N_3$. Calculated, %: C 72.52; H 7.96; N 19.52.

1-(4-Chlorobenzyl)-3,5-dimethyl-1*H*-pyrazol-4-amine (3c). Yield 581 mg (77%), cream-colored powder, mp 62–63°C. IR spectrum, ν, cm^{-1}: 3382, 3269, 3199, 1627, 1595, 1509, 1492, 1475, 1425, 1375, 1361, 1324, 1255, 1098, 1018, 811, 797, 672, 484, 438. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 7.38 (2H, d, *J* = 8.3, H Ar); 7.02 (2H, d, *J* = 8.4, H Ar); 5.06 (2H, s, NCH$_2$); 3.38 (br. s, NH$_2$+H$_2$O); 2.00 (6H, s, CH$_3$). Mass spectrum, *m*/*z* (I_{rel}, %): 235 [M(^{35}Cl)]$^+$ (100), 237 [M(^{37}Cl)]$^+$ (33). Found, %: C 61.19; H 6.04; N 17.93. $C_{12}H_{14}ClN_3$. Calculated, %: C 61.15; H 5.99; N 17.83.

1-(4-Fluorobenzyl)-3,5-dimethyl-1*H*-pyrazol-4-amine (3d). Yield 519 mg (74%), light-brown powder, mp 45–46°C. IR spectrum, ν, cm^{-1}: 3385, 3333, 1605, 1510, 1476, 1439, 1380, 1320, 1252, 1159, 1114, 949, 822, 760, 666, 520, 481. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.15–7.05 (4H, m, H Ar); 5.06 (2H, s, NCH$_2$); 3.38 (br. s, NH$_2$+H$_2$O); 1.98 (6H, s, CH$_3$). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 161.3 (d, *J* = 242.6, C-4' Ar); 136.9; 134.7 (d, *J* = 2.9, C-1' Ar); 128.7 (d, *J* = 8.2, C-2',6' Ar); 125.3; 124.6;

115.2 (d, J = 21.3, C-3',5' Ar); 51.1 (NCH_2); 10.9 (CH_3); 8.5 (CH_3). Mass spectrum, m/z (I_{rel}, %): 219 $[M]^+$ (100). Found, %: C 65.80; H 6.42; N 19.29. $C_{12}H_{14}FN_3$. Calculated, %: C 65.73; H 6.44; N 19.16.

1-(2-Chlorobenzyl)-3,5-dimethyl-1*H*-pyrazol-4-amine (3e). Yield 543 mg (72%), white powder, mp 98–99°C. IR spectrum, ν, cm^{-1}: 3346, 3297, 3211, 1591, 1574, 1472, 1445, 1390, 1352, 1331, 1255, 1116, 1048, 1036, 797, 754, 748, 683. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (J, Hz): 7.47 (1H, d, J = 6.5, H Ar); 7.32–7.19 (2H, m, H Ar); 6.50 (1H, d, J = 7.0, H Ar); 5.12 (2H, s, NCH_2); 3.61 (br. s, NH_2+H_2O); 2.03 (6H, s, CH_3). Mass spectrum, m/z (I_{rel}, %): 235 $[M(^{35}Cl)]^+$ (100), 237 $[M(^{37}Cl)]^+$ (33). Found, %: C 61.07; H 5.91; N 17.88. $C_{12}H_{14}ClN_3$. Calculated, %: C 61.15; H 5.99; N 17.83.

2-(4-Amino-3,5-dimethyl-1*H*-pyrazol-1-yl)-1-(morpholin-4-yl)ethan-1-one (3f). Yield 503 mg (66%), light-yellow powder, mp 121–122°C. IR spectrum, ν, cm^{-1}: 3382, 3331, 3201, 2973, 2920, 2866, 1655, 1477, 1445, 1352, 1275, 1242, 1116, 1038, 962, 916, 842, 791, 631, 569. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 4.81 (2H, s, $NCH_2C(O)$); 3.59–3.42 (10H, m, NH_2, OCH_2CH_2N); 1.97 (3H, s, CH_3); 1.96 (3H, s, CH_3). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 166.0 (C=O); 136.9 (C Pz); 126.1 (C Pz); 123.8 (C Pz); 66.1 (CH_2); 66.0 (CH_2); 50.2 (CH_2); 44.9 (CH_2); 41.8 (CH_2); 11.0 (CH_3); 8.5 (CH_3). Mass spectrum, m/z (I_{rel}, %): 238 $[M]^+$ (100). Found, %: C 55.30; H 7.70; N 23.74. $C_{11}H_{18}N_4O_2$. Calculated, %: C 55.44; H 7.61; N 23.51.

2-(4-Amino-1*H*-pyrazol-1-yl)-1-(morpholin-4-yl)ethan-1-one (3g). Yield 457 mg (68%), light-brown powder, mp 149–150°C. IR spectrum, ν, cm^{-1}: 3406, 3344, 3241, 3123, 2955, 2856, 1649, 1594, 1459, 1410, 1360, 1269, 1241, 1113, 1039, 1019, 997, 955, 850, 818, 768, 646, 630, 591, 565. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 6.97 (1H, s, H-5 Pz); 6.91 (1H, s, H-3 Pz); 4.89 (2H, s, $NCH_2C(O)$); 3.55–3.33 (10H, m, NH_2, $2OCH_2CH_2N$). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 166.0 (C=O); 131.0 (C-4 Pz); 129.7 (CH Pz); 117.8 (CH Pz); 66.0 (CH_2); 59.9 (CH_2); 52.7 (CH_2); 44.9 (CH_2); 41.8 (CH_2). Mass spectrum, m/z (I_{rel}, %): 210 $[M]^+$. Found, %: C 51.49; H 6.67; N 26.72. $C_9H_{14}N_4O_2$. Calculated, %: C 51.42; H 6.71; N 26.65.

1-Benzyl-1*H*-pyrazol-3-amine (3h). Yield 421 mg (76%), white powder, mp 64–65 °C. IR spectrum, ν, cm^{-1}: 3430, 3274, 3191, 3095, 3068, 3026, 2920, 1618, 1545, 1499, 1456, 1438, 1394, 1359, 1243, 1193, 1057, 990, 745, 730, 696, 658, 597, 582. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (J, Hz): 7.43 (1H, d, J = 2.0, H-5 Pz); 7.34–7.23 (3H, m, H Ph); 7.18 (2H, d, J = 7.1, H Ph); 5.44 (1H, d, J = 2.0, H-4 Pz); 5.03 (2H, s, NCH_2); 4.58 (2H, s, NH_2). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 155.7 (C-3 Pz); 138.4 (C Ph); 130.7 (C-5 Pz); 128.3 (CH Ph); 127.4 (CH Ph); 127.2 (CH Ph); 92.1 (C-4 Pz); 54.2 (NCH_2). Mass spectrum, m/z (I_{rel}, %): 173 $[M]^+$ (100). Found, %: C 69.20; H 6.44; N 24.36. $C_{10}H_{11}N_3$. Calculated, %: C 69.34; H 6.40; N 24.26.

Synthesis of nitropyrazolylacetic acid amides 4f,g (General method). Acid **5f**,**g** (7.5 mmol) was added to CCl_4 (25 ml), and then $SOCl_2$ (1.1 ml, 15 mmol) was added dropwise. The reaction mixture was heated under reflux for 10 h, and the solvent was removed under reduced pressure. The solid residue of acid chloride was dried over P_2O_5 under reduced pressure, and used without additional purification. Morpholine (1.3 ml, 15 mmol) was added to a suspension of the corresponding acid chloride (7.5 mmol) in anhydrous MeCN (15 ml), and the mixture was stirred at room temperature for 6 h. The formed precipitate was filtered, washed with MeCN (1 ml), and recrystallized from H_2O.

2-(3,5-Dimethyl-4-nitro-1*H*-pyrazol-1-yl)-1-morpholinoethan-1-one (4f). Yield 1.51 g (75%), white powder, mp 197–199°C. IR spectrum, ν, cm^{-1}: 3423, 2974, 2864, 1648, 1570, 1496, 1469, 1421, 1376, 1363, 1275, 1242, 1116, 1070, 1041, 1005, 854, 795, 609, 573. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 5.24 (2H, s, $NCH_2C(O)$); 3.68–3.54 (4H, m, $2OCH_2CH_2N$); 3.54–3.40 (4H, m, $2OCH_2CH_2N$); 2.46 (3H, s, CH_3); 2.39 (3H, s, CH_3). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 164.0 (C=O); 144.6 (C-3 Pz); 142.5 (C-5 Pz); 130.3 (C-4 Pz); 66.0 (CH_2); 65.9 (CH_2); 51.0 (CH_2); 44.7 (CH_2); 42.9 (CH_2); 13.7 (CH_3); 10.5 (CH_3). Mass spectrum, m/z (I_{rel}, %): 268 $[M]^+$ (100). Found, %: C 49.32; H 6.06; N 21.02. $C_{11}H_{16}N_4O_4$. Calculated, %: C 49.25; H 6.01; N 20.88.

1-Morpholino-2-(4-nitro-1*H*-pyrazol-1-yl)ethan-1-one (4g). Yield 1.39 g (77%), light-crème-colored powder, mp 160–161°C. IR spectrum, ν, cm^{-1}: 3449, 3127, 2962, 2863, 1655, 1533, 1509, 1474, 1402, 1334, 1307, 1272, 1236, 1218, 1035, 992, 891, 822, 756, 584. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 8.77 (1H, s, H-5 Pz); 8.25 (1H, s, H-3 Pz); 5.28 (2H, s, $NCH_2C(O)$); 3.69–3.54 (4H, m, OCH_2CH_2N); 3.54–3.42 (4H, m, OCH_2CH_2N). Mass spectrum, m/z (I_{rel}, %): 240 $[M]^+$ (100). Found, %: C 44.83; H 5.08; N 23.51. $C_9H_{12}N_4O_4$. Calculated, %: C 45.00; H 5.04; N 23.32.

The study of the inhibitory properties of compounds 1a–h. Half maximal inhibitory concentration (IC_{50}) in regards to human sEH were determined at the Department of Entomology and Nematology of the University of California, Davis (USA) according to the published method.[28]

To determine the solubility in H_2O of the obtained compounds **1a**–**e**,**h**, a series of their solutions in DMSO with concentrations ranging from 0.5 to 100 mmol/l were prepared. Then, 10 μl of the obtained solutions were added to 990 μl of a buffer solution (0.1 mol/l Na_3PO_4, pH 7.4). Thus, the final concentration of the studied compounds ranged from 5 to 1000 μmol/l, while the concentration of DMSO was 1%. Solubility was determined by examining the turbidity (adsorption of light with a wavelength of 590 nm) of the resulting aqueous solutions. A buffer solution containing 1% DMSO was used as the reference point.

The lipophilicity coefficient cLogP was calculated using the Molinspiration program (www.molinspiration.com).

The work was supported by the Ministry of Education and Science of the Russian Federation within the framework of the Basic part of the State assignment for 2017–2019 (No. 4.7491.2017/CU) for V.S.D., D.V.D., V.V.B., G.M.B.

References

1. (a) El-Sehemi, A. G.; Bondock, S.; Ammar, Y. A. *Med. Chem. Res.* **2014**, *23*, 827. (b) Cidade, A. F.; Vasconcelos, P. A.;

Silva, D. P. B.; Florentino, I. F.; Vasconcelos, G. A.; Vaz, B. G.; Costa, E. A.; Lião, L. M.; Menegatti, R. *Eur. J. Pharmacol.* **2016**, *791*, 195.
2. Bhavanarushi, S.; Kanakaiah, V.; Bharath, G.; Gangagnirao, A.; Rani, J. V. *Med. Chem. Res.* **2014**, *23*, 158.
3. Mert, S.; Kasımoğulları, R.; Iça, T.; Çolak, F.; Altun, A.; Ok, S. *Eur. J. Med. Chem.* **2014**, *78*, 86.
4. (a) Yang, B.; Liu, W.; Mei, Y.; Huang, D.; Qian, H.; Huang, W.; Gust, R. *Lett. Drug Des. Discovery* **2014**, *11*, 749. (b) Nakao, S.; Mabuchi, M.; Shimizu, T.; Itoh, Y.; Takeuchi, Y.; Ueda, M.; Mizuno, H.; Shigi, N.; Ohshio, I.; Jinguji, K.; Ueda, Y.; Yamamoto, M.; Furukawa, T.; Aoki, S.; Tsujikawa, K.; Tanaka, A. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 1071.
5. Dawood, K. M.; Eldebss, T. M. A.; El-Zahabi, H. S. A.; Yosef, M. H. *Eur. J. Med. Chem.* **2015**, *102*, 266.
6. Nimbarte, V. D.; Murtuza, H.; Phaniraj, S.; Shrivastava, S.; Naidu, V. G. M.; Kumar, N. S.; Atcha, K. R. *Med. Chem. Res*. **2014**, *23*, 2178.
7. Zhu, D.; Xing, Q.; Cao, R.; Zhao, D.; Zhong, W. *Molecules* **2016**, *21*, 677.
8. Boulahjar, R.; Ouach, A.; Matteo, C.; Bourg, S.; Ravache, M.; le Guével, R.; Marionneau, S.; Oullier, T.; Lozach, O.; Meijer, L.; Guguen-Guillouzo, C.; Lazar, S.; Akssira, M.; Troin, Y.; Guillaumet, G.; Routier, S. *J. Med Chem.* **2012**, *55*, 9589.
9. Rowbottom, M. W.; Faraoni, R.; Chao, Q.; Campbell, B. T.; Lai, A. G.; Setti, E.; Ezawa, M.; Sprankle, K. G.; Abraham, S.; Tran, L.; Struss, B.; Gibney, M.; Armstrong, R. C.; Gunawardane, R. N.; Nepomuceno, R. R.; Valenta, I.; Hua, H.; Gardner, M. F.; Cramer, M. D.; Gitnick, D.; Insko, D. E.; Apuy, J. L.; Jones-Bolin, S.; Ghose, A. K.; Herbertz, T.; Ator, M. A.; Dorsey, B. D.; Ruggeri, B.; Williams, M.; Bhagwat, S.; James, J.; Holladay, M. W. *J. Med Chem.* **2012**, *55*, 1082.
10. Zhang, Y.; Chen, Y.; Zhang, D.; Wang, L.; Lu, T.; Jiao, Y. *J. Med. Chem.* **2018**, *61*, 140.
11. Pike, K. G.; Morris, J.; Ruston, L.; Pass, S. L.; Greenwood, R.; Williams, E. J.; Demeritt, J.; Culshaw, J. D.; Gill, K.; Pass, M.; Finlay, M. R. V.; Good, C. J.; Roberts, C. A.; Currie, G. S.; Blades, K.; Eden, J. M.; Pearson, S. E. *J. Med Chem.* **2015**, *58*, 2326.
12. Zheng, K.; Iqbal, S.; Hernandez, P.; Park, H.; LoGrasso, P. V.; Feng, Y. *J. Med Chem.* **2014**, *57*, 10013.
13. Hwang, S. H.; Wagner, K. M.; Morisseau, C.; Liu, J. Y.; Dong, H.; Wecksler, A. T.; Hammock, B. D. *J. Med Chem.* **2011**, *54*, 3037.
14. Arand, M.; Grant, D. F.; Beetham, J. K.; Friedberg, T.; Oesch, F.; Hammock, B. D. *FEBS Lett.* **1994**, *338*, 251.
15. (a) Spector, A. A.; Fang, X.; Snyder, G. D.; Weintraub, N. L. *Prog. Lipid Res*. **2004**, *43*, 55. (b) Fleming, I.; Rueben, A.; Popp, R.; Fisslthaler, B.; Schrodt, S.; Sander, A.; Haendeler, J.; Falck, J. R.; Morisseau, C.; Hammock, B. D.; Busse, R. *Arterioscler., Thromb., Vasc. Biol.* **2007**, *27*, 2612. (c) Imig, J. D. *Expert Opin. Drug Metab. Toxicol*. **2008**, *4*, 165. (d) Yu, Z.; Xu, F.; Huse, L. M.; Morisseau, C.; Draper, A. J.; Newman, J. W.; Parker, C.; Graham, L.; Engler, M. M.; Hammock, B. D.; Zeldin, D. C.; Kroetz, D. L. *Circ. Res*. **2000**, *87*, 992.
16. (a) Spiecker, M.; Liao, J. K. *Arch. Biochem. Biophys.* **2005**, *433*, 413. (b) Imig, J. D.; Zhao, X.; Capdevila, J. H.; Morisseau, C.; Hammock, B. D. *Hypertension* **2002**, *39*, 690. (c) Imig, J. D.; Zhao, X.; Zaharis, C. Z.; Olearczyk, J. J.; Pollock, D. M.; Newman, J. W.; Kim, I. H.; Watanabe, T.; Hammock, B. D. *Hypertension* **2005**, *46*, 975.
17. Decker, M.; Arand, M.; Cronin, A. *Arch. Toxicol*. **2009**, *83*, 297.
18. (a) Morisseau, C.; Goodrow, M. H.; Dowdy, D.; Zheng, J.; Greene, J. F.; Sanborn, J. R.; Hammock, B. D. *Proc. Natl. Acad. Sci. U. S. A*. **1999**, *96*, 8849. (b) Schmelzer, K. R.; Kubala, L.; Newman, J. W.; Kim, I. H.; Eiserich, J. P.; Hammock, B. D. *Proc. Natl. Acad. Sci. U. S. A*. **2005**, *102*, 9772.
19. Hwang, S. H.; Wecksler, A. T.; Zhang, G.; Morisseau, C.; Nguyen, L. V.; Fu, S. H.; Hammock, B. D. *Bioorg. Med. Chem. Lett*. **2013**, *23*, 3732.
20. Kodani, S. D.; Hammock, B. D. *Drug Metab. Dispos.* **2015**, *43*, 788.
21. (a) Butov, G. M.; Burmistrov, V. V.; Dalinger, I. L.; Vatsadze, I. A.; Shkineva, T. K.; Danilov, D. V. *Chem. Heterocycl. Compd.* **2015**, *50*, 1719. [*Khim. Geterotsikl. Soedin.* **2014**, 1869.] (b) Burmistrov, V.; Morisseau, C.; Danilov, D.; Harris, T. R.; Dalinger, I.; Vatsadze, I.; Shkineva, T.; Butov, G. M.; Hammock, B. D. *Bioorg. Med. Chem. Lett*. **2015**, *25*, 5514.
22. North, E. J.; Scherman, M. S.; Bruhn, D. F.; Scarborough, J. S.; Maddox, M. M.; Jones, V.; Grzegorzewicz, A.; Yang, L.; Hess, T.; Morisseau, C.; Jackson, M.; McNeil, M. R.; Lee, R. E. *Bioorg. Med. Chem.* **2013**, *21*, 2587.
23. Burmistrov, V.; Morisseau, C.; Harris, T. R.; Butov, G.; Hammock, B. D. *Bioorg. Chem.* **2018**, *76*, 510.
24. (a) Ai, T.; Willett, R.; Williams, J.; Ding, R.; Wilson, D. J.; Xie, J.; Kim, D.-H.; Puertollano, R.; Chen, L. *ACS Med. Chem. Lett.* **2017**, *8*, 90. (b) Heisler, I.; Mueller, T.; Siebeneicher, H.; Buchmann, B.; Cleve, A.; Guenther, J.; Koppitz, M.; Heroult, M.; Neuhaus, R.; Petrul, H.; Quanz-Schoeffel, M. WO Patent 2015091428. (c) Ramsden, N.; Harrison, R. J.; Oxenford, S.; Bell, K.; Piton, N.; Dagostin, C.; Boussard, C.; Ratcliffe, A. WO Patent 2011048082.
25. (a) Dalinger, I. L.; Kormanov, A. V.; Vatsadze, I. A.; Serushkina, O. V.; Shkineva, T. K.; Suponitsky, K. Yu.; Pivkina, A. N.; Sheremetev, A. B. *Chem. Heterocycl. Compd.* **2016**, *52*, 1025. [*Khim. Geterotsikl. Soedin.* **2016**, *52*, 1025.] (b) Shkineva, T. K.; Kormanov, A. V.; Boldinova, V. N.; Vatsadze, I. A.; Dalinger, I. L. *Chem. Heterocycl. Compd.* **2018**, *54*, 703. [*Khim. Geterotsikl. Soedin.* **2018**, *54*, 703.]
26. Xuan, B.; Wang, T.; Cy Chiou, G.; Dalinger, I. L.; Shkineva, T. K.; Shevelev, S. A. *Acta Pharmacol. Sin*. **2002**, *23*, 705.
27. (a) Zaitsev, A. A.; Dalinger, I. L.; Shevelev, S. A. *Russ. Chem. Rev*. **2009**, *78*, 589. [*Usp. Khim.* **2009**, *78*, 643.] (b) Shevelev, S. A.; Dalinger, I. L. *Russ. J. Org. Chem*. **1998**, *34*, 1071. [*Zh. Org. Khim.* **1998**, *34*, 1127.]
28. Jones, P. D.; Wolf, N. M.; Morisseau, C.; Whetstone, P.; Hock, B.; Hammock, B. D. *Anal. Biochem*. **2005**, *343*, 66.