Chemistry of Heterocyclic Compounds **2020**, *56*(4), 473–481

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SUPPLEMENTARY INFORMATION

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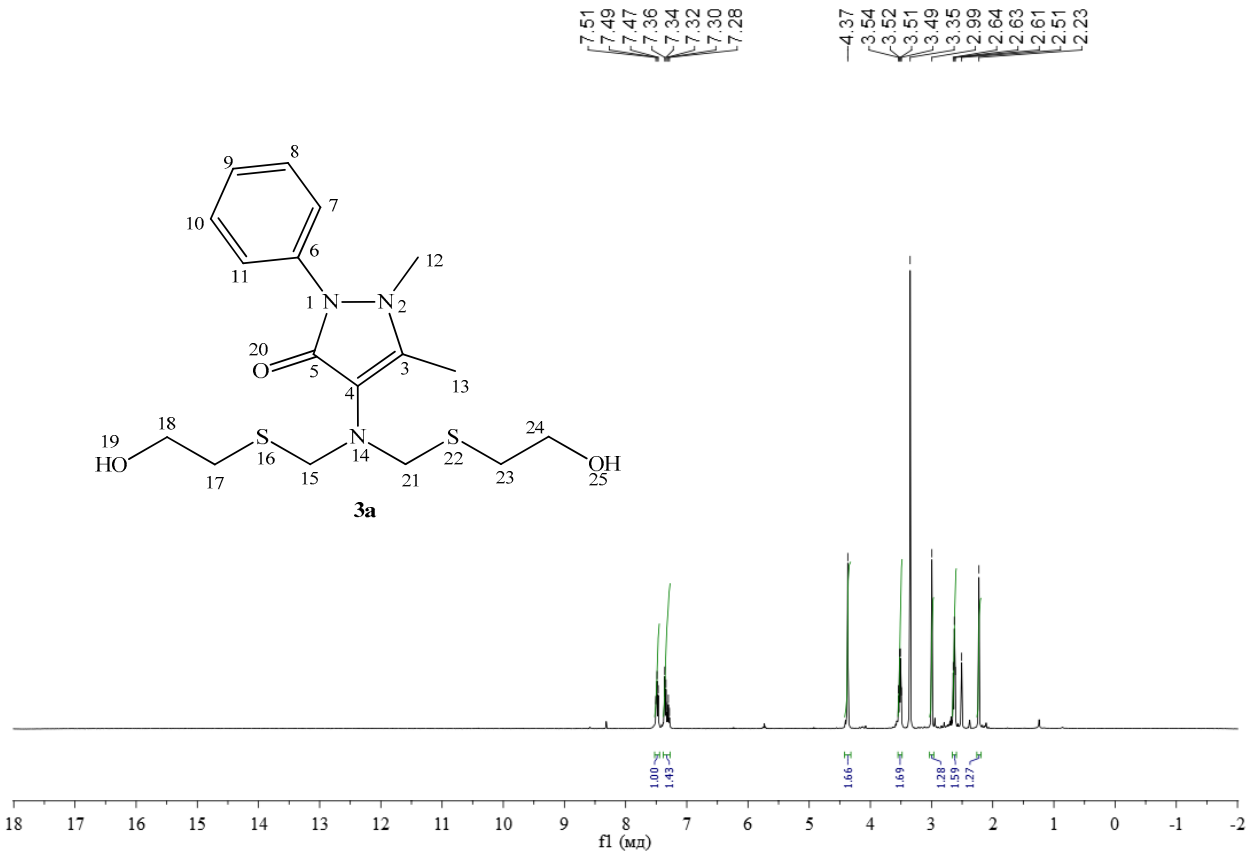

Fig. S1. ^{1}H NMR spectrum of compound **3a** in DMSO-d_6 (400 MHz)

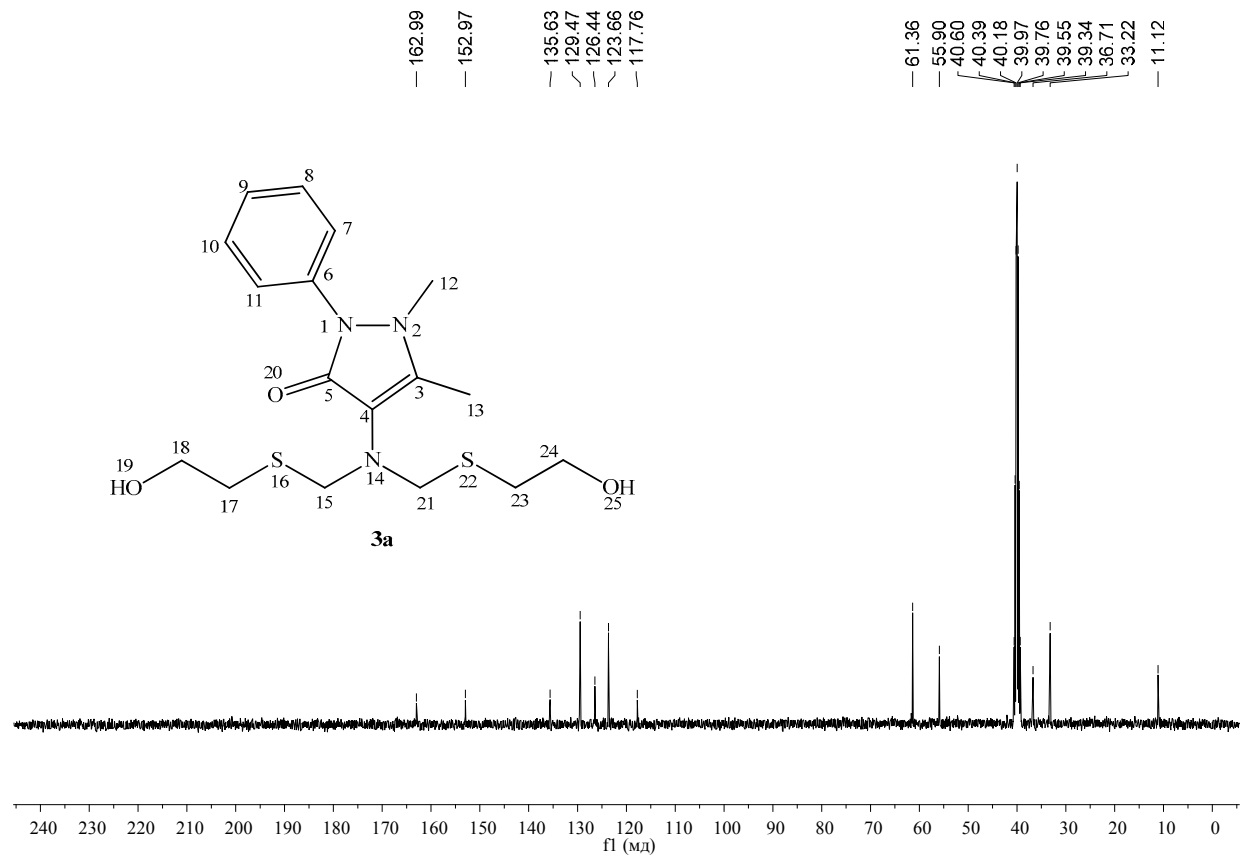

Fig. S2. ^{13}C NMR spectrum of compound **3a** in DMSO-d_6 (100 MHz)

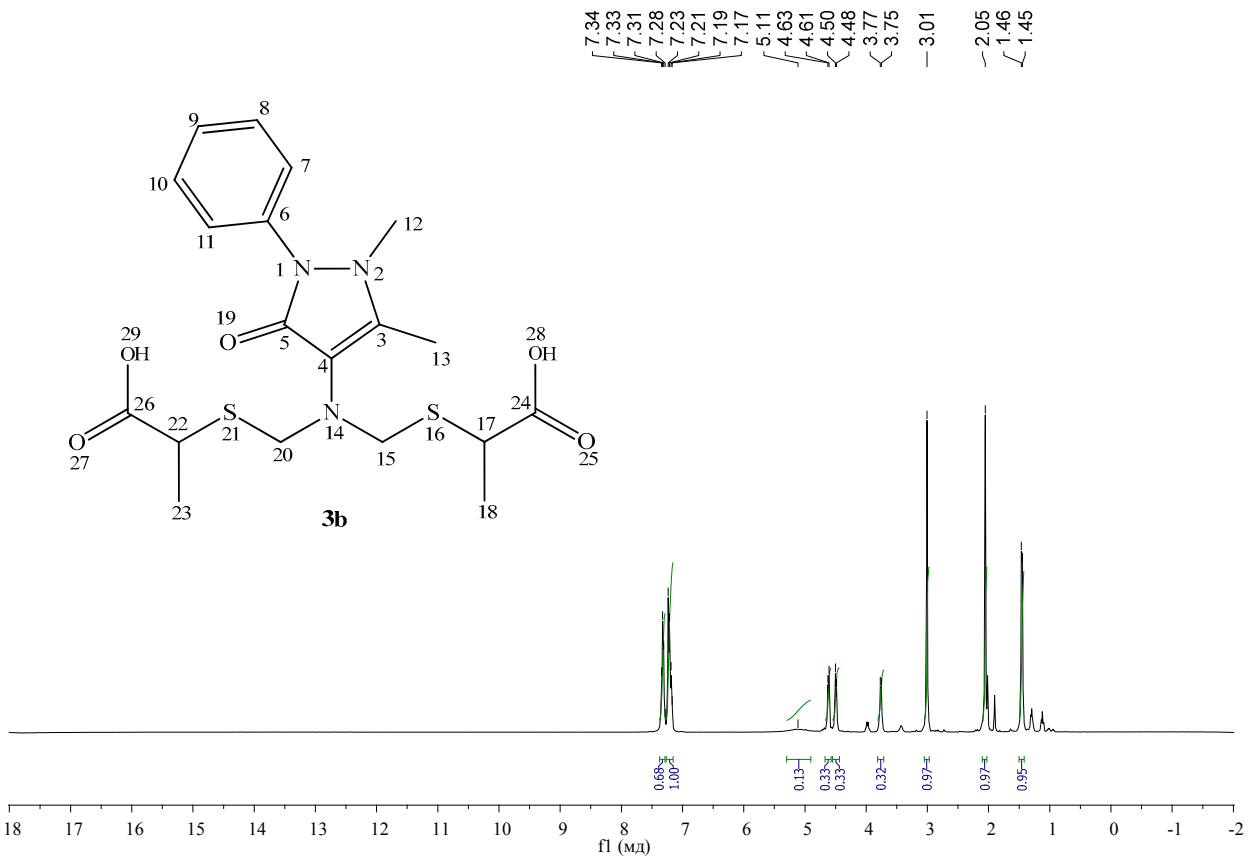

Fig. S3. ^{1}H NMR spectrum of compound **3b** in $CDCl_3$ (400 MHz)

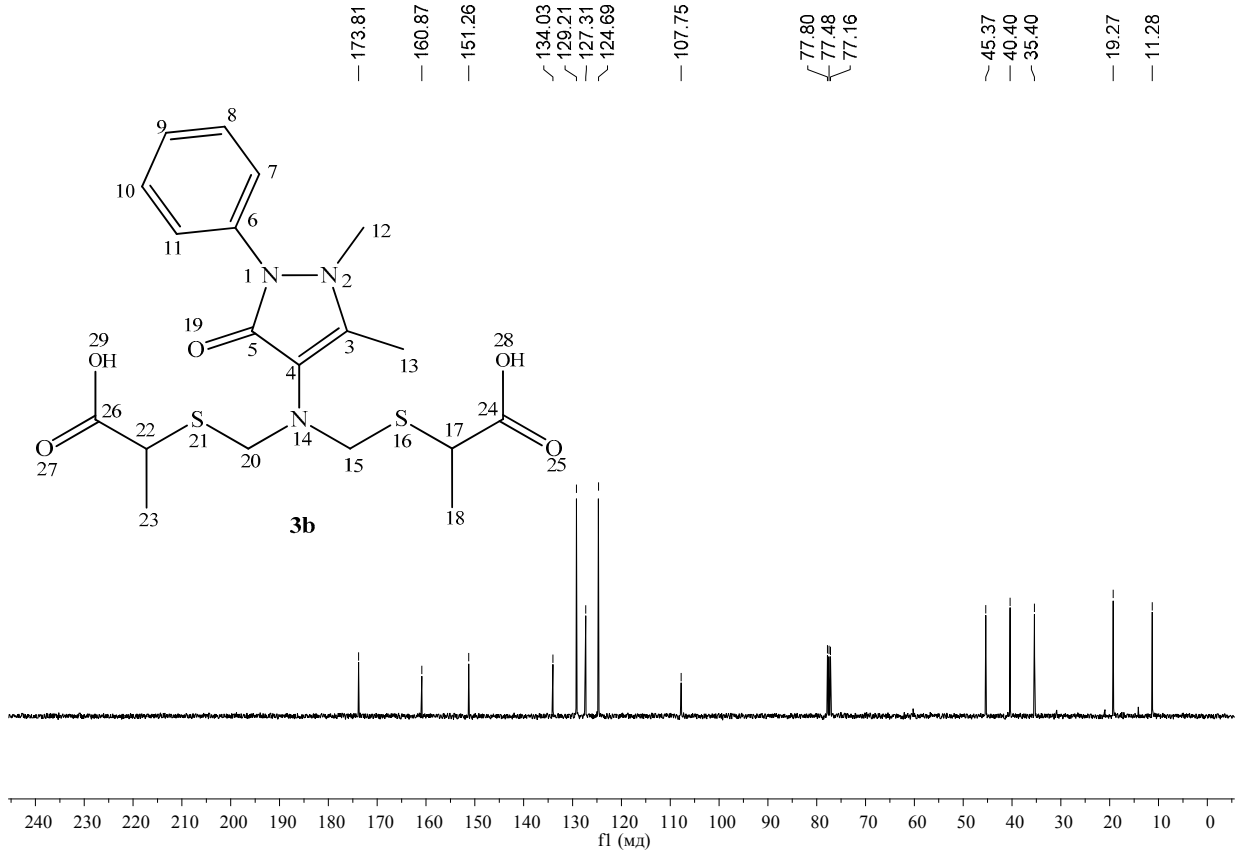

Fig. S4. ^{13}C NMR spectrum of compound **3b** in $CDCl_3$ (100 MHz)

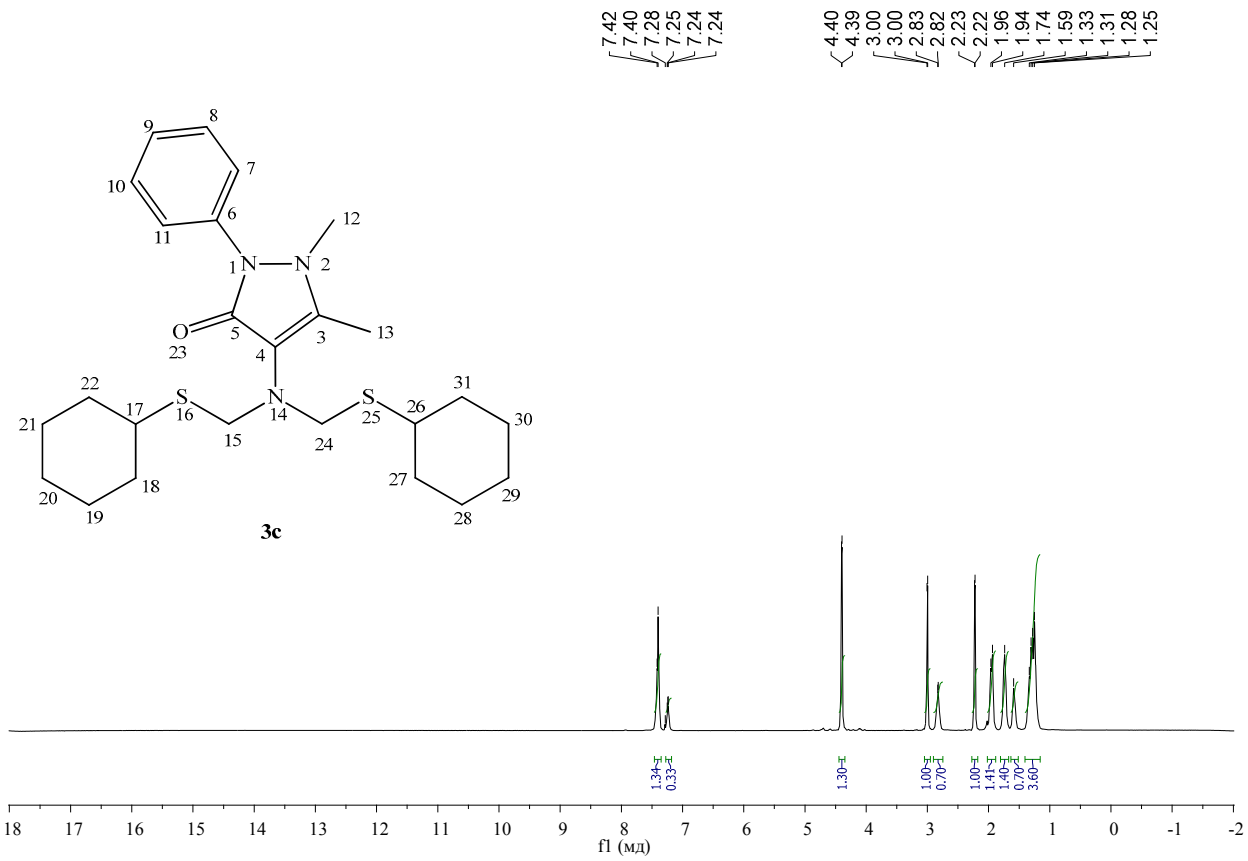

Fig. S5. ^{1}H NMR spectrum of compound **3c** in $CDCl_3$ (400 MHz)

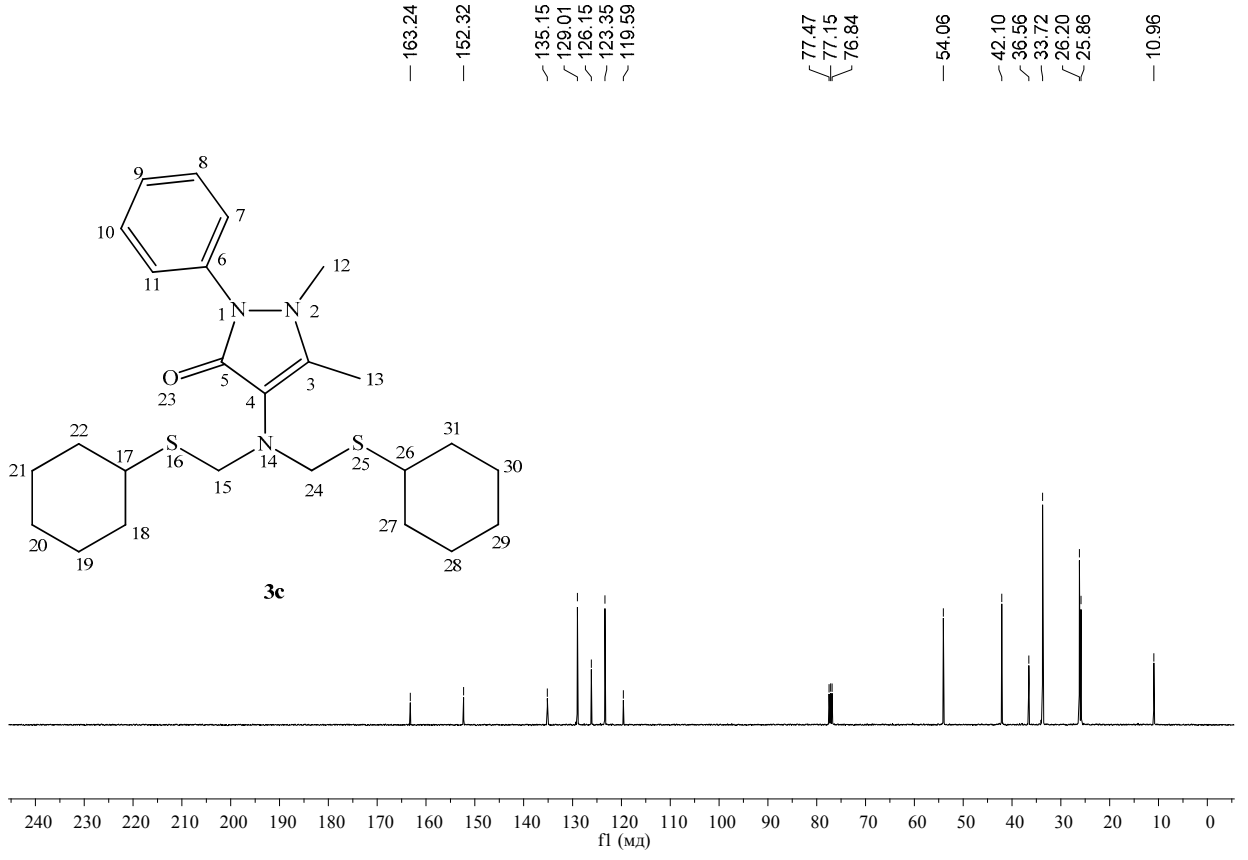

Fig. S6. ^{13}C NMR spectrum of compound **3c** in $CDCl_3$ (100 MHz)

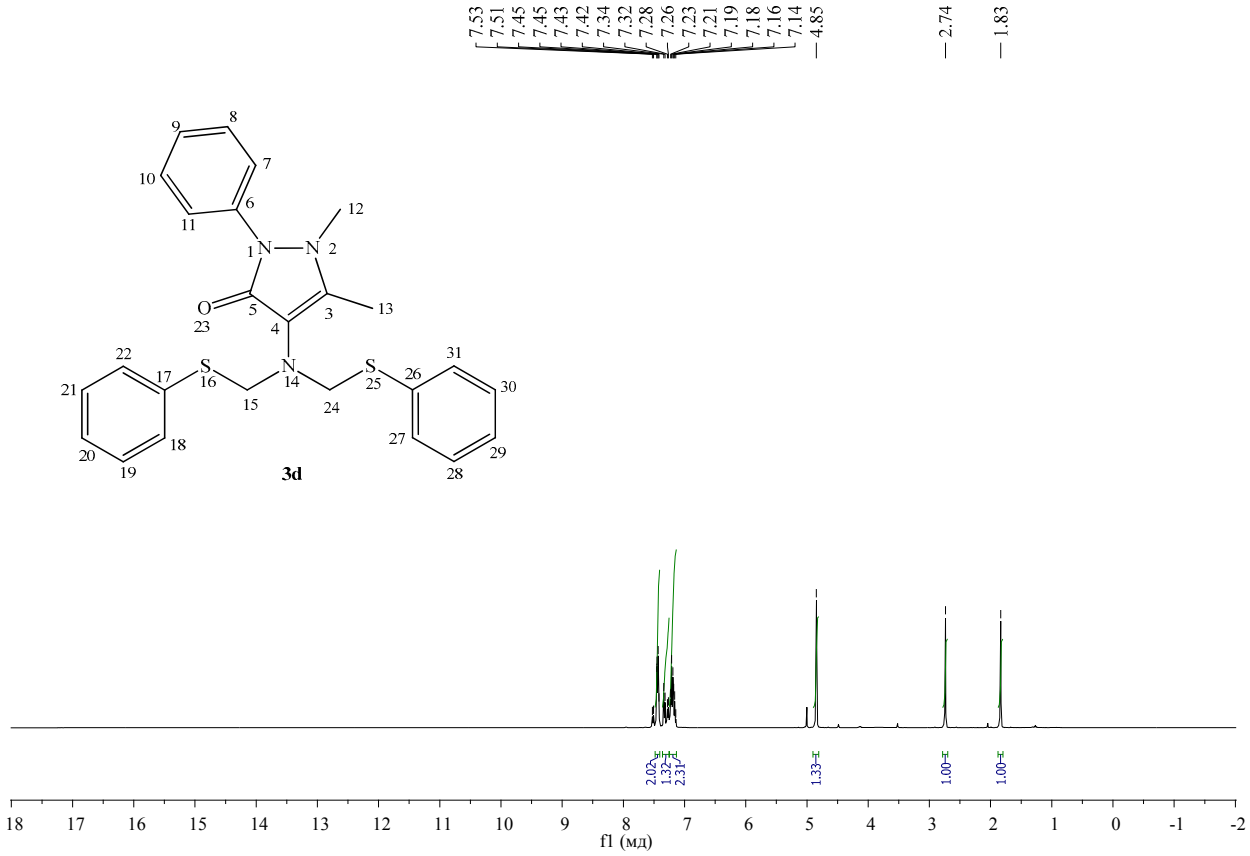

Fig. S7. ^{1}H NMR spectrum of compound **3d** in $CDCl_3$ (400 MHz)

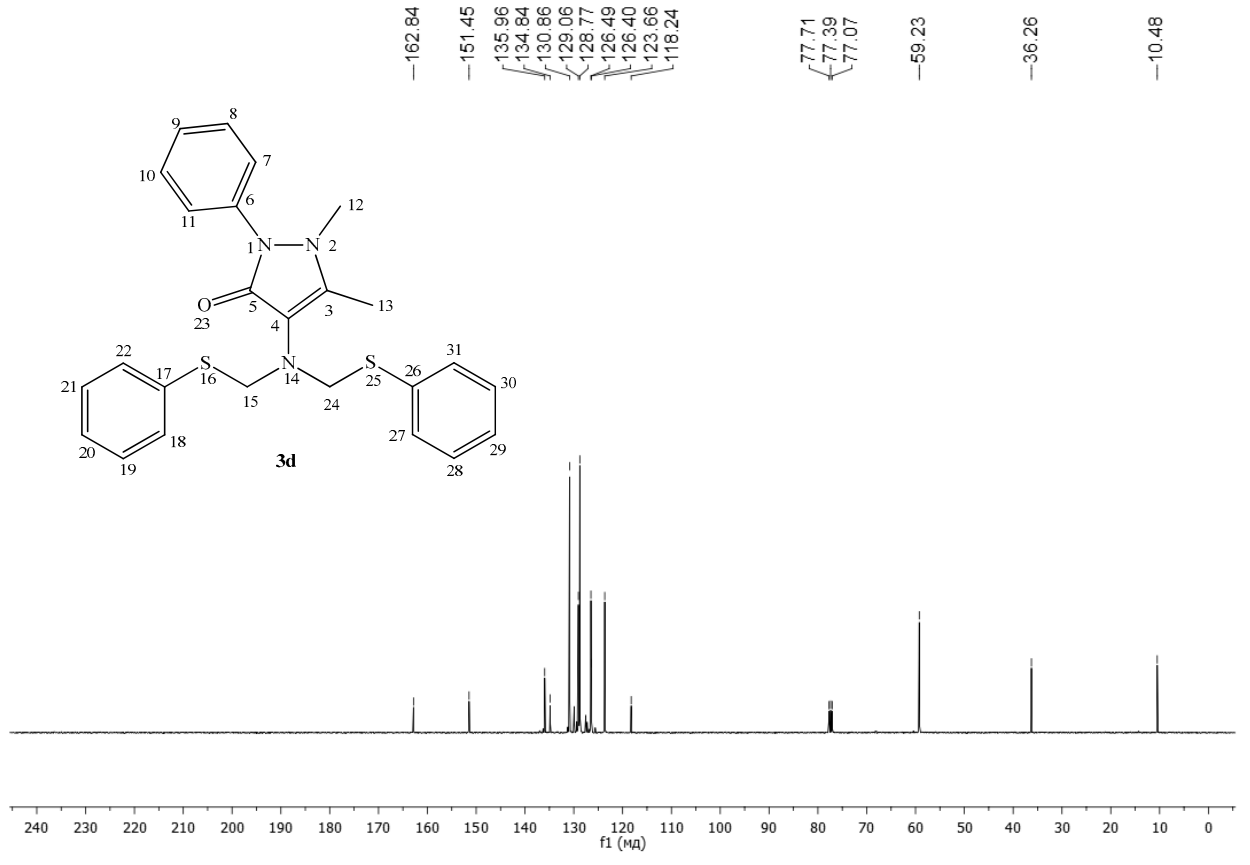

Fig. S8. ^{13}C NMR spectrum of compound **3d** in $CDCl_3$ (100 MHz)

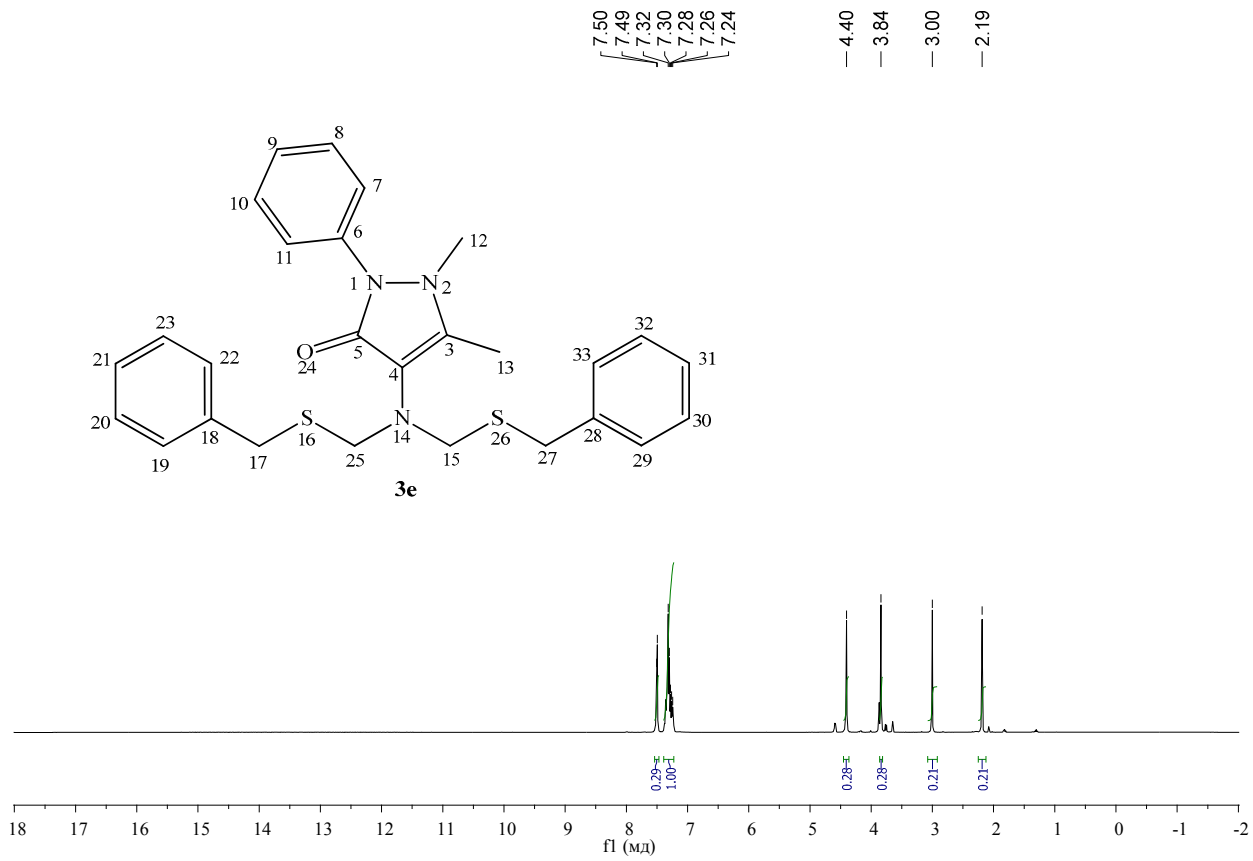

Fig. S9. ^{1}H NMR spectrum of compound **3e** in $CDCl_3$ (400 MHz)

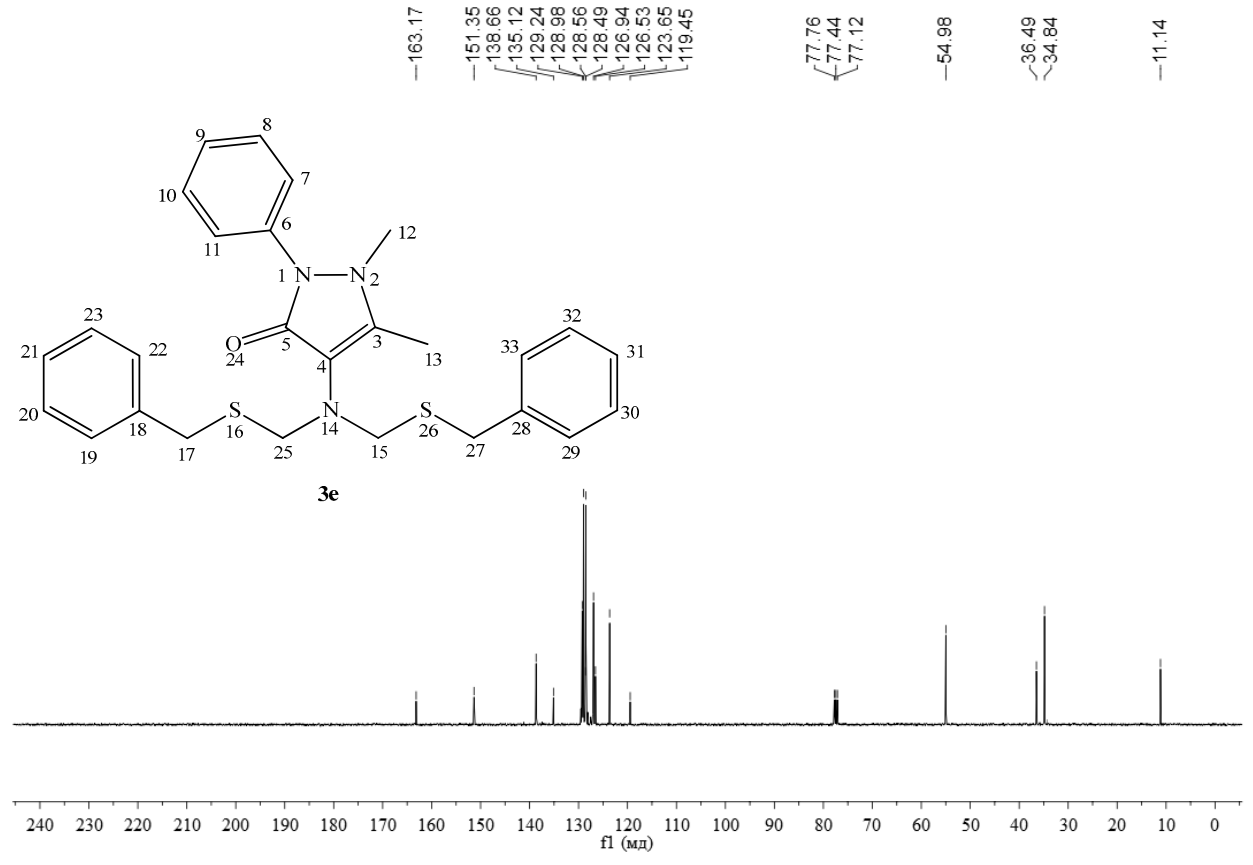

Fig. S10. ^{13}C NMR spectrum of compound **3e** in $CDCl_3$ (100 MHz)

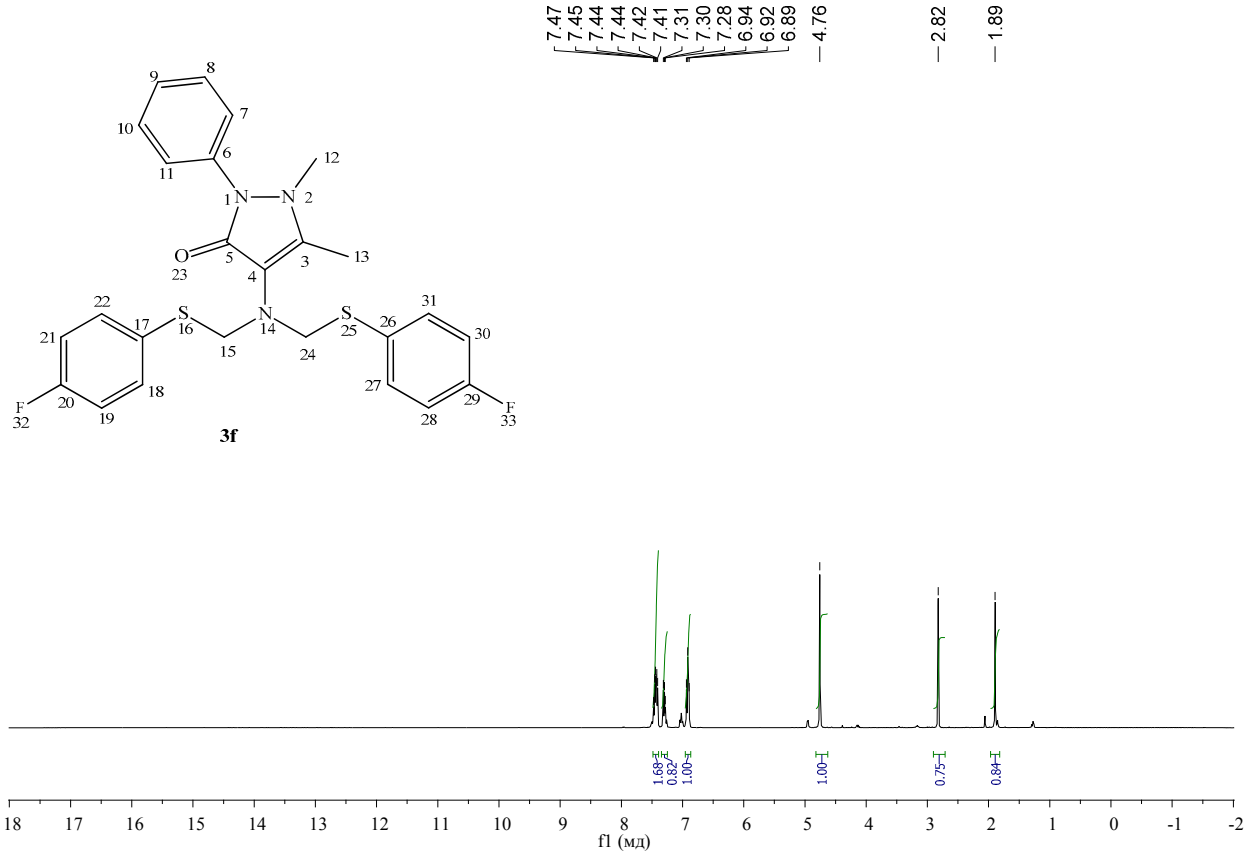

Fig. S11. ^{1}H NMR spectrum of compound **3f** in $CDCl_3$ (400 MHz)

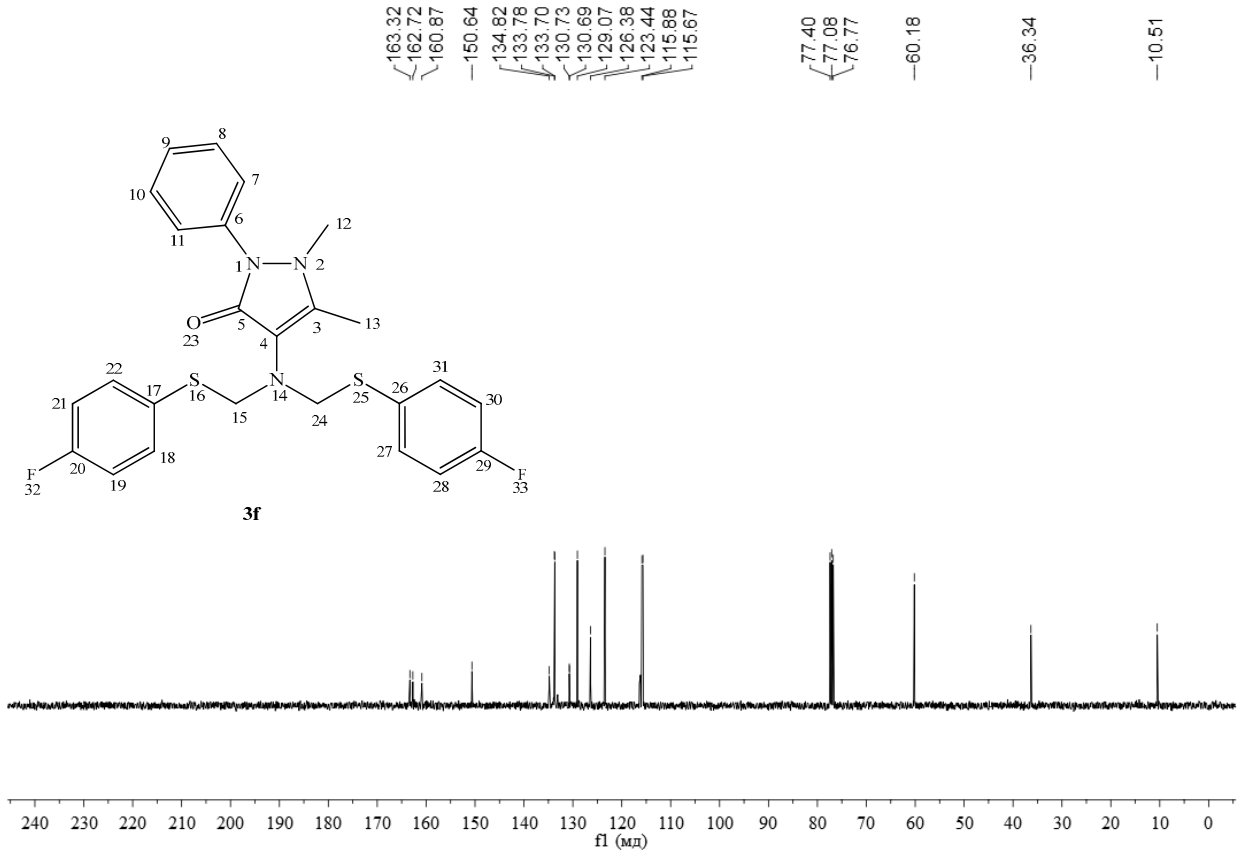

Fig. S12. ^{13}C NMR spectrum of compound **3f** in $CDCl_3$ (100 MHz)

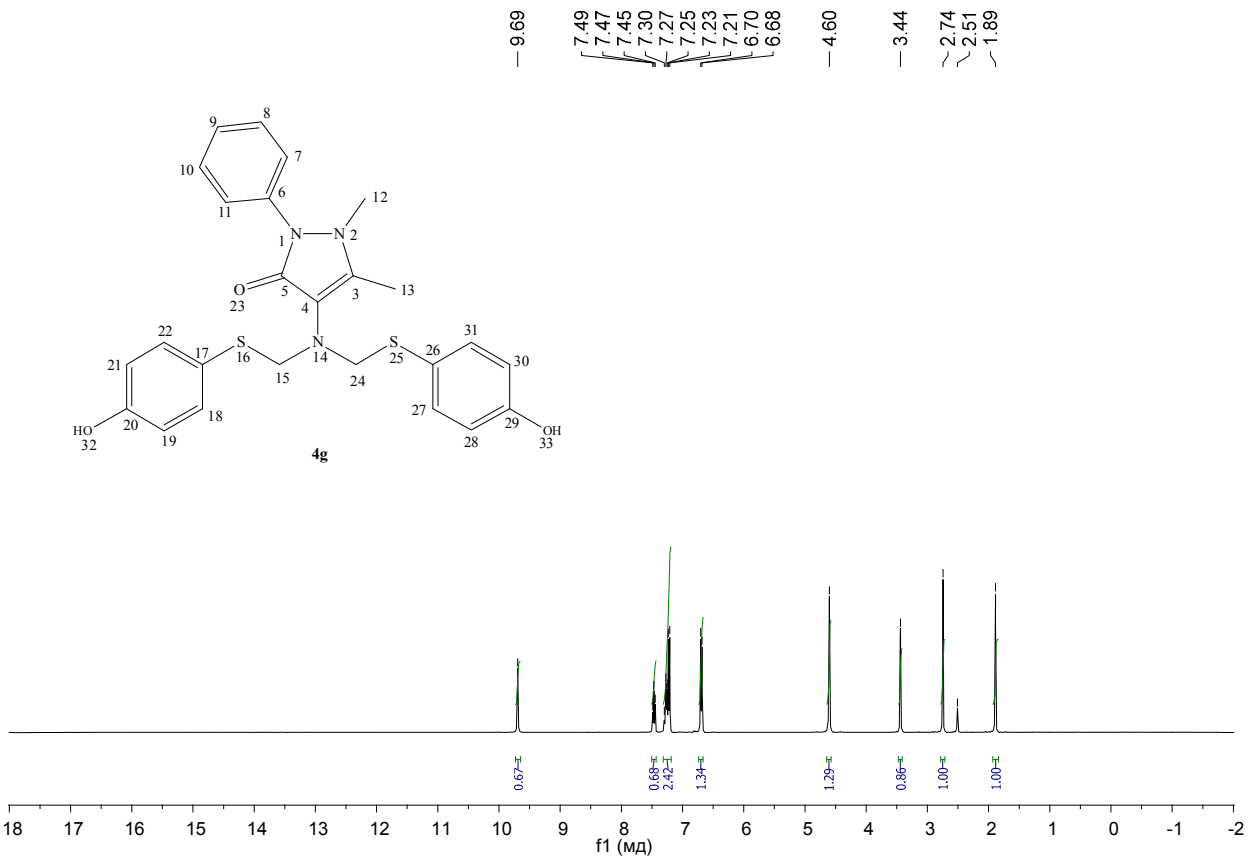

Fig. S13. ^{1}H NMR spectrum of compound **3g** in DMSO-d_6 (400 MHz)

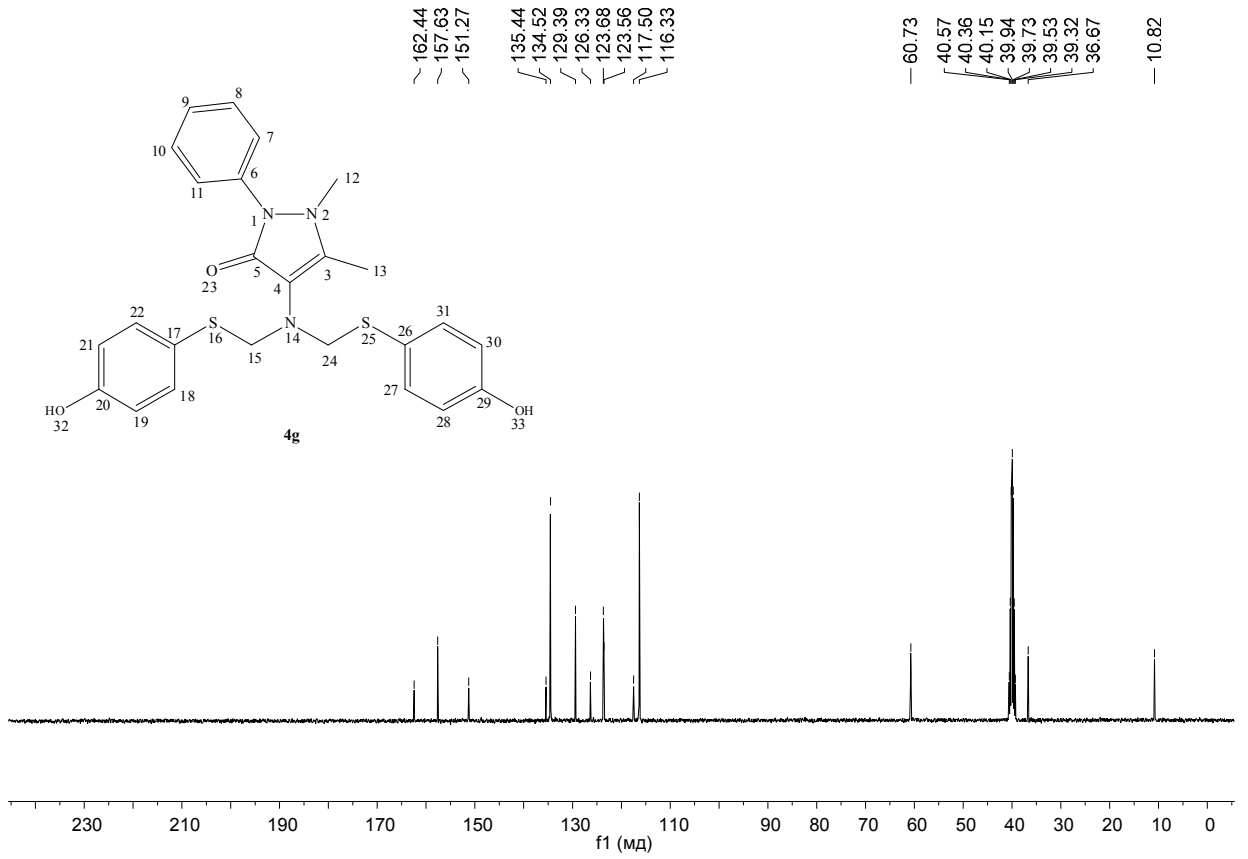

Fig. S14. ^{13}C NMR spectrum of compound **3g** in DMSO-d_6 (100 MHz)

Table S1. Acute toxicity prediction results for ampiron derivatives using the GUSAR program on the way2drug.com web-platform

The method of administration of substance	Acute toxicity to rats predicted by GUSAR, in units of LD_{50} (mg/kg)				Rat toxicity classification under the OECD project			
	IP[1]	IV[2]	Oral[3]	SC[4]	IP[1]	IV[2]	Oral[3]	SC[4]
3a	1597	357.3	1519	994.5	–	Class 5	Class 4	Class 4
3b_Stereo	1491	432.1	1221	616.8	Non toxic	Class 5	Class 4	Class 4
3c	1395	195.8	1407	585.7	Non toxic	Class 4	Class 4	Class 4
3d	1082	400.6	1005	1206	Class 5	Class 5	Class 4	Class 5
3e	952.5	239.6	1534	911	Class 5	Class 4	Class 4	Class 4
3f	–	113.9	1766	–	–	Class 4	Class 4	–
3g	1467	186.5	1719	–	Non toxic	Class 4	Class 4	–
Phenazon	638.2	223.6	889.6	487.1	Class 5	Class 4	Class 4	Class 4
Ampiron	651.6	201.4	796.2	476.1	Class 5	Class 4	Class 4	Class 4
Propiphenazon	531.9	195.3	1110	396.2	Class 5	Class 4	Class 4	Class 4

1 - intraperitoneal route of administration
2 - intravenous route of administration
3 - oral route of administration
4 - subcutaneous route of administration

Table S2. Prediction of the biological activity spectra for ampiron derivatives via the PASS program

3c	0.943	0.004	Analgesic, non-opioid
	0.940	0.004	Analgesic
	0.912	0.004	Antiinflammatory
	0.907	0.003	Antipyretic
	0.846	0.003	CYP2A8 substrate
	0.841	0.003	Antihypoxic
	0.836	0.004	Autoimmune disorders treatment
	0.808	0.003	CYP2A2 substrate
	0.807	0.004	Rheumatoid arthritis treatment
	0.718	0.004	Leukopoiesis inhibitor
	0.712	0.004	CYP2A1 substrate
	0.705	0.005	Antiviral (Picornavirus)
3d	0.963	0.004	Analgesic, non-opioid
	0.955	0.004	Analgesic
	0.943	0.004	Antiinflammatory
	0.930	0.003	Antipyretic
	0.906	0.003	Rheumatoid arthritis treatment
	0.887	0.004	CYP2B substrate
	0.881	0.003	Flavin-containing monooxygenase substrate
	0.881	0.004	Autoimmune disorders treatment
	0.879	0.002	CYP2A8 substrate
	0.864	0.003	Antihypoxic
	0.831	0.003	CYP2A2 substrate
	0.818	0.005	Anticonvulsant
	0.812	0.003	CYP2C18 substrate
	0.816	0.009	CYP2C substrate
	0.810	0.005	CYP3A1 substrate
	0.804	0.003	Leukopoiesis inhibitor
	0.774	0.004	Insulysin inhibitor
	0.760	0.003	CYP2A1 substrate
	0.756	0.009	CYP2C9 substrate
	0.733	0.008	CYP2A6 substrate
	0.730	0.005	CYP2C19 substrate
	0.731	0.009	CYP3A2 substrate
	0.731	0.009	CYP2C8 substrate
	0.715	0.005	Antiviral (Picornavirus)

3e	0.883	0.004	Analgesic
	0.875	0.005	Antiinflammatory
	0.866	0.004	Analgesic. non-opioid
	0.845	0.003	Antihypoxic
	0.831	0.003	Flavin-containing monooxygenase substrate
	0.813	0.003	CYP2A8 substrate
	0.801	0.004	Rheumatoid arthritis treatment
	0.773	0.004	CYP2A2 substrate
	0.745	0.005	Autoimmune disorders treatment
	0.720	0.006	Insulysin inhibitor
	0.715	0.003	CYP2C18 substrate
	0.714	0.004	Antipyretic
	0.708	0.004	Leukopoiesis inhibitor
3f	0.869	0.005	Analgesic
	0.859	0.004	Analgesic. non-opioid
	0.856	0.005	Antiinflammatory
	0.784	0.004	Rheumatoid arthritis treatment
	0.764	0.005	Antihypoxic
	0.735	0.005	Autoimmune disorders treatment
	0.703	0.004	Flavin-containing monooxygenase substrate
3g	0.849	0.005	Antiinflammatory
	0.838	0.003	Flavin-containing monooxygenase substrate
	0.834	0.003	Antihypoxic
	0.823	0.005	Analgesic
	0.795	0.004	Antipyretic
	0.777	0.005	Analgesic. non-opioid
	0.767	0.008	CYP2B substrate
	0.752	0.004	Rheumatoid arthritis treatment
	0.743	0.005	CYP2A2 substrate
	0.738	0.005	Insulysin inhibitor
3b	0.881	0.005	Antiinflammatory
	0.861	0.003	Antipyretic
	0.852	0.003	Antihypoxic
	0.841	0.005	Analgesic
	0.817	0.005	Analgesic. non-opioid
	0.762	0.005	CYP2E1 substrate
	0.757	0.004	Rheumatoid arthritis treatment
	0.754	0.005	CYP2E substrate

	0.748	0.003	CYP2C18 substrate
	0.745	0.007	CYP3A1 substrate
	0.734	0.003	Leukopoiesis inhibitor
	0.734	0.005	CYP2A2 substrate
	0.722	0.005	Autoimmune disorders treatment
	0.717	0.007	Insulysin inhibitor
	0.714	0.005	Antiviral (Picornavirus)
	0.702	0.004	CYP2A1 substrate
3a	0.884	0.005	Antiinflammatory
	0.852	0.005	Analgesic
	0.848	0.003	Antihypoxic
	0.846	0.004	Analgesic. non-opioid
	0.833	0.005	CYP2E1 substrate
	0.825	0.005	CYP2E substrate
	0.782	0.004	Antipyretic
	0.774	0.004	CYP2A2 substrate
	0.758	0.004	Rheumatoid arthritis treatment
	0.744	0.003	CYP2C18 substrate
	0.731	0.005	Autoimmune disorders treatment
	0.715	0.008	CYP3A1 substrate
	0.711	0.004	CYP2A1 substrate
Phenazone	0.892	0.004	Analgesic
	0.889	0.003	Antipyretic
	0.857	0.005	Antiinflammatory
	0.831	0.005	Analgesic. non-opioid
	0.829	0.003	CYP2A2 substrate
	0.812	0.002	Leukopoiesis inhibitor
	0.760	0.003	CYP2A1 substrate
	0.761	0.007	Anticonvulsant
	0.741	0.005	Insulysin inhibitor
	0.740	0.004	Rheumatoid arthritis treatment
	0.730	0.005	Antihypoxic
	0.731	0.017	5-O-(4-coumaroyl)-D-quinate 3'-monooxygenase inhibitor
	0.714	0.005	Antiviral (Picornavirus)
	0.702	0.009	CYP3A1 substrate

	0.721	0.048	Testosterone 17beta-dehydrogenase (NADP+)
Ampyrone	0.919	0.004	Analgesic
	0.907	0.004	Antiinflammatory
	0.904	0.002	CYP2A8 substrate
	0.904	0.004	Analgesic. non-opioid
	0.898	0.002	CYP2B2 substrate
	0.864	0.002	Antiviral (Picornavirus)
	0.855	0.004	CYP3A1 substrate
	0.848	0.002	CYP2C18 substrate
	0.842	0.003	Antihypoxic
	0.839	0.005	CYP2A6 substrate
	0.834	0.002	CYP2A2 substrate
	0.831	0.005	CYP2B substrate
	0.828	0.005	CYP2E1 substrate
	0.825	0.002	Leukopoiesis inhibitor
	0.825	0.004	CYP2B1 substrate
	0.824	0.005	CYP2E substrate
	0.819	0.004	Rheumatoid arthritis treatment
	0.817	0.005	Autoimmune disorders treatment
	0.814	0.005	CYP2A substrate
	0.810	0.005	CYP1A2 substrate
	0.795	0.005	Anticonvulsant
	0.790	0.007	CYP1A substrate
	0.782	0.003	CYP2A1 substrate
	0.773	0.004	Insulysin inhibitor
	0.762	0.004	Antipyretic
	0.759	0.005	CYP1A1 substrate
	0.763	0.009	CYP2B6 substrate
	0.756	0.005	CYP2C11 substrate
	0.743	0.008	CYP3A2 substrate
	0.740	0.008	CYP2C8 substrate
	0.726	0.010	CYP2C9 substrate
	0.726	0.015	CYP2C substrate
	0.714	0.004	Flavin-containing monooxygenase substrate
Propyphenazone	0.959	0.002	Antipyretic
	0.896	0.002	CYP2A8 substrate

0.858	0.005	Antiinflammatory
0.827	0.005	Analgesic. non-opioid
0.790	0.005	HMGCS2 expression enhancer
0.786	0.004	CYP2A2 substrate
0.754	0.003	CYP2C18 substrate
0.712	0.009	CYP3A1 substrate

Table S3. Results of docking to active centers COX-1 and COX-2 for some drugs

Entry	Drug name	COX-1		COX-2	
		Free binding energy. kcal / mol	RMSD. Å	Free binding energy. kcal / mol	RMSD. Å
1	Celecoxib	-9.3 / -9.4*	1.28 / 1.50*	-10.27 / -10.40*	1.60 / 1.40*
3	Diclofenac	-8.41 / -7.50	1.96 / 2.00*	-7.55 / -8.60*	1.96 / 2.00*
4	Flurbiprophenum	-8.01 / -8.20*	1.18 / 1.20*	-7.05 / -8.80*	1.80 / 2.00*

* Docking solutions found using the evaluation function of AutoDock Vina are indicated.

Table S4. Crystallographic parameters and refinement details of crystal structures of compounds **3c** and **3d**

	3c	**3d**
CCDC	1966864	1966863
Empirical formula	$C_{25}H_{37}N_3OS_2$	$C_{25}H_{25}N_3OS_2$
Formula weight	459.70	447.60
Temperature/K	293(2)	293(2)
Crystal system	monoclinic	monoclinic
Space group	$P2_1$	$P2_1/c$
a/Å	12.4601(11)	14.1759(10)
b/Å	7.4224(5)	7.4161(6)
c/Å	14.6474(15)	22.8208(16)
α/°	90	90
β/°	104.815(10)	98.411(6)
γ/°	90	90
Volume/Å^3	1309.6(2)	2373.3(3)
Z	2	4
ρ_{calc}g/cm^3	1.166	1.253
μ/mm^{-1}	0.224	0.246
F(000)	496.0	944.0
Radiation	MoKα (λ = 0.71073)	MoKα (λ = 0.71073)
$2\Theta_{max}$/°	58.496	58.518
Index ranges	–10 ≤ h ≤ 16, –9 ≤ k ≤ 9, -18 ≤ l ≤ 19	–18 ≤ h ≤ 16, –9 ≤ k ≤ 9, -29 ≤ l ≤ 28
Reflections collected	6504	10994
Independent reflections	5058 (R_{int} = 0.0191)	5430 (R_{int} = 0.0226)

Goodness-of-fit on F^2	1.194	1.101
Final R indexes [I>=2σ (I)]	R_1 = 0.0794, wR_2 = 0.1890	R_1 = 0.0708, wR_2 = 0.1869
Final R indexes [all data]	R_1 = 0.1130, wR_2 = 0.2161	R_1 = 0.1236, wR_2 = 0.2239
Largest diff. peak/hole / e $Å^{-3}$	0.46/–0.26	0.23/–0.40