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The synthesis of new acyclic analogs of 3-phenacyluridine and comparative evaluation of their *in vivo* biological activity

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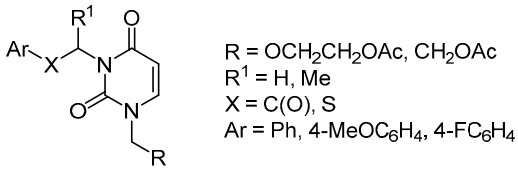


New structural analogs of 3-phenacyluridine were obtained as a result of *N*(3)-alkylation of 1-(2-acetoxyethyl)- and 1-(2-acetoxyethoxymethyl)uracil. Biological studies of the title compounds in an acute *in vivo* experiment did not reveal their hypnotic properties and ability to enhance the effects of diazepam and chloral hydrate.

Keywords: 3-phenacyluridine, alkylation, biological activity, hypnotics, uridine receptor.

The search for new sleeping pills that are not addictive is an important area of medicinal chemistry. As promising hypnotics that can compete with the traditionally used derivatives of barbituric acid, 1,4-benzodiazepine, or Z-drugs, a number of compounds with different structure and mechanism of action are considered,[1] including derivatives of the natural nucleoside uridine.

Data on the hypnotic effects of 3-phenacyluridine (Fig. 1) upon intracerebral administration were first published in 1994.[2] For a long time, the question of the biomolecular mechanism of action of 3-phenacyluridine, which has a structure different from other known hypnotics, remained open. When studying its effect on benzodiazepine receptors, an insignificant affinity for them was discovered,[3] and only a few years later it was found that the affinity of this compound for specific CNS uridine receptors determine its hypnotic properties.[4] It was shown that the metabolic reduction product of the keto group of 3-phenacyluridine also has an affinity for these receptors, and the *S*-isomer exceeds the *R*-isomer of the corresponding alcohol by 187 times in affinity for uridine receptors and 15 times in duration of hypnotic action.[5] As a result of the study, it was established that the formed alcohols are pharmacologically active metabolites of the starting ketone.[6]

In the course of studying the structure–activity relationship, it was shown that the replacement of D-ribose fragment with 2-deoxy-D-ribose or uracil fragment with 6-azauracil fragment[7] in the structure of the prototype substance leads to a sharp decrease in hypnotic activity.

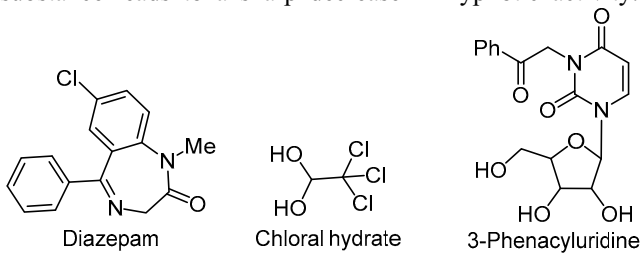
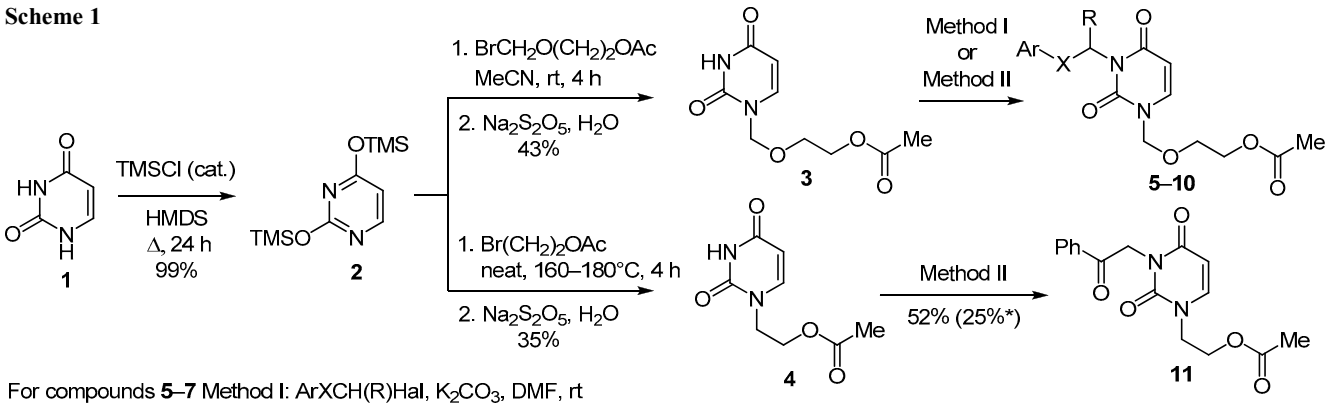


Figure 1. Structures of known hypnotics.

Scheme 1



For compounds **5**–**7** Method I: ArXCH(R)Hal, K_2CO_3, DMF, rt
For compounds **8**–**10** Method II: ArXCH(R)Hal, K_2CO_3,MeCN, Δ

5 Ar = Ph, R = H, X = C(O), 48% (23%*); **6** Ar = 4-$MeOC_6H_4$, R= H, X = C(O), 42% (27%*);
7 Ar = 4-FC_6H_4, R = H, X = C(O), 73% (30%*); **8** Ar = Ph, R = Me, X = C(O), 42% (41%*);
9 Ar = 4-$MeOC_6H_4$, R = Me, X = C(O), 41% (19%*); **10** Ar = 4-FC_6H_4, R = H, X = S, 72% (35%*)
* Yield after preparative HPLC.

However, some hypnotic activity was retained in derivatives of 2'-deoxy-2'-fluoro-3-phenacyluridine, although they showed more antiviral activity against HIV-1.[8] Analogs of 3-phenacyluridine, in the structure of which the glycosyl fragment is replaced by heteroarylmethyl moiety, have pronounced hypnotic effect, which also enhance the action of pentobarbital and diazepam under the conditions of an acute experiment.[9] It is known from literature that 3-phenacyluridine derivatives containing one or more MeO groups in the benzene ring have an antinociceptive activity.[10] The corresponding 3-benzyl-substituted derivatives of uridine, for which hypnotic activity upon intracerebral administration has been established,[11] do not show hypnotic properties with other routes of administration. This is probably due to their high hydrophilicity and low ability to cross the blood-brain barrier. At the same time, their analogs, in which the hydroxy groups of the ribose fragment are methylated or acylated, retain their activity when administered intravenously.[12] Replacing the ribose fragment with a hydrocarbon substituent results in compounds exhibiting hypnotic properties upon intraperitoneal administration, equal in activity and toxicity to barbital.[13] In contrast to the derivatives of 6-aza-3-phenacyluridine and 3-phenacylthymidine,[7] the corresponding derivatives of 6-aza-3-benzyluracil[14] and 3-benzylthymine[15] exhibit hypnotic activity and enhance the action of pentobarbital. Similar biological properties are also characteristic of arabinosides of 3-benzyluracil derivatives.[16]

Based on the data described above, the objective of our study was to obtain compounds with both high hypnotic activity of 3-phenacyluridine and lipophilicity of 1-alkyl-3-benzyluracils. The purpose of the work was to create a potential sleeping pill effective when administered *per os* and acting on the uridine receptor system of CNS. Thus, we obtained and studied *in vivo* analogs of 3-phenacyluridine containing a bioisostere acyclic fragment at position 1 of the pyrimidine ring (Scheme 1).

To access the target substances **5**–**11**, uracil (**1**) was used as the starting compound, silylation of which in hexamethyldisilazane (HMDS) under reflux in the presence of a catalytic amount of trimethylsilyl chloride (TMSCl) led to the formation of 2,4-bis[(trimethylsilyl)oxy]-pyrimidine (**2**). As a result of the subsequent alkylation of pyrimidine **2** with 2-(bromomethoxy)ethyl acetate in MeCN at room temperature[17] or 2-bromoethyl acetate at 160–180°C in neat,[18] the corresponding 1-[(2-hydroxyethoxy)methyl]- and 1-(2-hydroxyethyl)uracil acetates **3**, **4** were isolated after hydrolysis and chromatographic purification. Then, the obtained compounds **3**, **4** were subjected to *N*(3)-alkylation using phenacyl halides, α-bromopropiophenones, or (chloromethyl)(4-fluorophenyl)-sulfane in the presence of K_2CO_3.

It should be noted that the reaction proceeds regioselectively. When using phenacyl bromides, stirring at room temperature in anhydrous DMF was sufficient, while heating under reflux in anhydrous MeCN was necessary employing the rest of the alkylating agents with lower reactivity. The obtained compounds, with the exception of product **7**, were viscous syrups, the purification of which was difficult and was carried out in two stages: column chromatography followed by preparative HPLC.

The results of the study of the biological activity of compounds **5**, **8**, **11** in the open field test after a single intragastric administration are presented in Table 1. Compound **11** at a dose of 10 mg/kg during intragastric administration significantly reduced vertical activity and the number of racks, which indicates the possible hypnotic effect of target compound **11** on the animal's body.

To confirm our assumption, the next step was the open field test for compound **11** with intraperitoneal and intragastric administration at a dose of 50 mg/kg. Thus, with intragastric administration, compound **11** does not exert a depressing effect on the indications of vertical activity, as with intraperitoneal administration, but on the contrary, its increase relative to intact control was recorded (Table 2). Perhaps this reverse reaction of increasing the amount of vertical activity is associated with a dose-dependent manifestation of side effects. Such a phenomenon has been described for some groups of tranquilizers, including uridine.[19]

Table 1. The effect of compounds **5**, **8**, **11** on the locomotor response of animals in the open field test after a single intragastric administration at a dose of 10 mg/kg (n = 8, duration 2 min)*

Test indicators	Intact control	Compound			Level of reliability in comparison with intact control		
					Compound		
		5	**8**	**11**	**5**	**8**	**11**
Total locomotor activity, number of locomotor acts	78.25 ± 8.35	75.43 ± 7.11	84.25 ± 3.58	84.25 ± 3.58	0.54	0.96	0.16
Locomotor activity, s	79.84 ± 3.73	79.89 ± 3.40	83.71↑ ± 2.89	77.09 ± 4.40	0.96	0.03	0.23
Distance traveled, cm	40.16 ± 3.73	40.11 ± 3.40	36.29↓ ± 2.89	42.91 ± 4.40	0.96	0.03	0.23
Average speed, cm/s	578.64 ± 96.56	484.63 ± 74.19	499.13 ± 66.96	422.14↓ ± 41.05	0.07	0.15	0.00
Vertical activity, number of racks	4.78 ± 0.82	3.99 ± 0.61	4.10 ± 0.56	3.48↓ ± 0.34	0.05	0.15	0.00
Time of vertical activity, s	20.00 ± 4.14	18.43 ± 3.31	16.00 ± 5.13	14.25↓ ± 4.17	0.54	0.12	0.03
Looking into the holes, number of times	18.81 ± 4.30	19.36 ± 3.97	13.68 ± 5.63	15.97 ± 6.12	0.87	0.15	0.38
Time of looking into the holes, s	8.63 ± 2.50	10.14 ± 3.44	14.29↑ ± 5.38	10.75 ± 4.20	0.34	0.02	0.28
Number of jumps	3.50 ± 0.94	5.68↑ ± 1.97	9.86↑ ± 3.95	6.34 ± 3.34	0.03	0.01	0.06
Vertical distance, cm	5.13 ± 4.52	1.29 ± 1.50	0.57↓ ± 0.79	1.50 ± 1.20	0.09	0.03	0.16

* Up arrow (↑) shows increase of indicator, down arrow (↓) shows decrease, confidence level $p < 0.05$ in comparison with intact control.

Table 2. Comparison of intragastric (i/g) and intraperitoneal (i/p) administration at a dose of 50 mg/kg of compound **11** in the open field test after a single injection (n = 8, duration 2 min)*

Test indicators	Intact control	Compound		Level of reliability in comparison with intact control	
				Compound	
		11 (i/g)	**11** (i/p)	**11** (i/g)	**11** (i/p)
Total locomotor activity, number of locomotor acts	80.88 ± 8.34	76.13 ± 3.60	75.86 ± 6.47	0.279	0.336
Locomotor activity, s	72.38 ± 7.36	76.66 ± 5.11	80.00 ± 5.42	0.234	0.054
Distance traveled, cm	47.63 ± 7.36	43.34 ± 5.11	40.00 ± 5.42	0.234	0.054
Average speed, cm/s	480.00 ± 116.90	463.25 ± 42.60	528.90 ± 85.62	0.574	0.397
Vertical activity, number of racks	3.95 ± 0.98	3.81 ± 0.36	4.36 ± 0.70	0.645	0.463
Time of vertical activity, s	15.88 ± 5.54	18.00 ± 4.31	24.71↑ ± 8.73	0.279	0.040
Looking into the holes, number of times	16.44 ± 5.63	20.38 ± 8.07	25.79↑ ± 6.39	0.382	0.014
Time of looking into the holes, s	6.88 ± 3.83	11.50 ± 6.09	11.71↑ ± 2.50	0.130	0.021
Number of jumps	2.53 ± 1.27	6.50↑ ± 3.55	7.25↑ ± 1.49	0.003	0.000
Vertical distance, cm	3.25 ± 3.45	0.88 ± 0.83	3.57 ± 3.91	0.234	0.867

* Up arrow (↑) shows increase of indicator, down arrow (↓) shows decrease, confidence level $p < 0.05$ in comparison with intact control.

The study also determined the effect of the test compound on locomotor activity against the background of diazepam. Compounds **5**, **8**, **11** were administered intraperitoneally at a dose of 50 mg/kg 30 min before the administration of diazepam. After administration of diazepam, animals were tested after 30 min. As a result of the experiment, it was found that compounds **5**, **8**, **11** did not significantly aggravate or stop the relaxing effect of diazepam (Table 3).

To determine the effect of target compound **11** on the relaxing effect of chloral hydrate, a chloral hydrate sleep test was performed. It is important to note that there were no significant deviations in sleep time caused by chloral hydrate under the influence of the studied compounds.

The obtained 1-(2-acetoxyethyl)uracil derivatives are similar in pharmacological activity to the previously described related *N*(3)-(phenylcarbamoyl)methylquinazolin-4(3*H*)-ones[20–22] possessing antidepressant and nootropic properties, rather than to 3-phenacyluridine and its analogs. It should be noted that an important component of the final product structure, which determines the psychopharmacological effect, is the presence of an acetylated or nonacetylated 1-(2-hydroxyethyl)uracil fragment. The obtained compounds contain a fragment of α-aminoacetophenone, which makes them related to the psychostimulants of the cathinone group; however, a decrease in the basicity of the nitrogen atom due to its inclusion in the pyrimidine ring significantly weakens the psychostimulating properties of the prototype substances. We believe that the target compounds may be of more interest as probable antiviral agents, similar in structure to the previously studied substances with the corresponding

Table 3. The effect of compounds **5**, **8**, **11** on the locomotor response of animals in the open field test after a single intraperitoneal injection at a dose of 50 mg/kg against diazepam at a dose of 10 mg/kg (n = 8, duration 2 min)

Test indicators	Intact control	Compound			
		5	**8**	**11**	Diazepam
Total locomotor activity, number of locomotor acts	68.00#↑ ± 5.15	54.00*↓ ± 15.3	63.13 ± 23.62	52.38*↓ ± 19.11	49.25*↓ ± 9.03
Locomotor activity, s	82.94 ± 6.64	75.06 ± 29.62	57.06 ± 25.76	70.72 ± 27.90	73.81 ± 26.59
Distance traveled, cm	37.06 ± 6.64	44.94 ± 29.62	62.94 ± 25.76	49.28 ± 27.90	46.19 ± 26.59
Average speed, cm/s	573.46 ± 90.91	690.41 ± 354.55	456.83 ± 281.69	552.29 ± 249.44	585.80 ± 301.93
Vertical activity, number of racks	4.74 ± 0.76	5.73 ± 2.92	3.76 ± 2.33	4.54 ± 2.07	4.83 ± 2.52
Time of vertical activity, s	17.25#↑ ± 5.60	11.50 ± 12.24	2.50#↓*↓ ± 6.68	5.25*↓ ± 4.53	4.75*↓ ± 3.10
Looking into the holes, number of times	17.94#↑ ± 4.79	8.75 ± 9.04	2.13#↓*↓ ± 5.62	4.06*↓ ± 5.0	2.94*↓ ± 1.53
Time of looking into the holes, s	10.13#↑ ± 1.25	4.50*↓ ± 4.84	2.63*↓ ± 2.56	3.63*↓ ± 3.50	1.75*↓ ± 0.96
Number of jumps	4.44#↑ ± 1.05	1.59*↓ ± 2.10	1.06*↓ ± 1.05	1.25*↓ ± 1.32	0.69*↓ ± 0.43
Vertical distance, cm	2.25 ± 2.87	8.25#↑*↑ ± 3.65	9.88*↑ ± 9.03	3.63 ± 3.42	3.00 ± 2.00

Reliability level $p < 0.05$ compared with diazepam, #↓ – decrease of indicator relative to diazepam, #↑ – increase of indicator relative to diazepam.
* confidence level $p < 0.05$ in comparison with intact control, *↓ – decrease of indicator relative to intact control, *↑ – increase of indicator relative to intact control.

activity,[8,23–27] rather than as the basis for the construction of new hypnotic agents.

To conclude, the title compounds are not of interest as hypnotics, but seem to be enough promising as potential antiviral agents.

Experimental

^{1}H and ^{13}C NMR spectra were acquired on a Bruker AM 360 spectrometer (360 and 90 MHz, respectively) in $CDCl_3$, with TMS as internal standard. HPLC control was performed using a chromatographic system consisting of a Jasco PU-980 pumping unit, Jasco UV-975 UV detector, and Rheodyne injection systems under the following conditions: Reprosil C18 AQ (150 × 4.6 mm) column, 3 μm, 0.9 ml/min, λ 220 nm, 30°C temperature, mobile phase: H_2O–MeCN–H_3PO_4 (85%) in a 200:200:1 ratio. HPLC-MS analysis was performed on an Agilent 1200 instrument under the following conditions: Reprosil-Pur Basic C18 (250 × 4.6 mm) column, 5 μm (Dr. Maisch GmbH); eluents: 0.01% CF_3COOH–H_2O (A), 0.01% CF_3COOH–MeCN (B); 1 ml/min flow rate; a VWD single-wave UV/VID detector, ELSD-detector, and Agilent 6310 Ion Trap LCMS (in positive ion mode) were used for detection. Preparative HPLC separation of reaction products was carried out on a semipreparative system with Gilson pumps (blocks 305 and 306), Gilson 805 manometric module, Jetchrom UVV-105 detector, ReproSil Pure Basic C 18 column (250 × 20 mm), 10 nm; 10 ml/min flow rate, with UV detection at λ 220 nm. Elemental analysis was performed on a vario EL cube. TLC was performed on Polygram Sil G/UV254 and Merck TLC F_{254} plates, visualization under UV light. Silica gel L14002 (Alfa Aesar) with a dispersion of 0.06–0.20 mm (70–230 mesh) was used for column chromatography.

The reagents and solvents used were supplied by Alfa Aesar and Acros Organics. For HPLC, MeCN supplied by Panreac (221074, HPLC-gradient grade) and orthophosphoric acid supplied by "Komponent-Reaktiv" (extra pure 17-4) were used. Solvents were dried according to standard methods.[28]

The starting 2,4-bis[(trimethylsilyl)oxy]pyrimidine (**2**),[29] 1-[(2-hydroxyethoxy)methyl]uracil acetate (**3**)[17] and 1-(2-hydroxyethyl)uracil acetate (**4**)[18] were obtained in accordance with the methods described earlier.

Synthesis of pyrimidine-2,4(1*H*,3*H*)-diones 5–7 (General procedure). Method I. A suspension of K_2CO_3 (0.44 g, 3.18 mmol) in a solution of 1-[2-(acetoxyethoxy)-methyl]uracil (**3**) (0.6 g, 2.63 mmol) and the respective alkylating agent (2.76 mmol) in anhydrous DMF (30 ml) was stirred under protection from atmospheric moisture until HPLC analysis of an aliquot of the reaction mixture showed the absence of the starting compound **3**. The resulting mixture was filtered, the filter cake was washed with DMF (2×10 ml), and the filtrate was evaporated to dryness under reduced pressure. Traces of DMF were removed by coevaporation of the residue with PhMe (2×15 ml) under reduced pressure. The crude product was treated with H_2O (120 ml) and extracted with EtOAc (3×75 ml). Organic extracts were combined, washed with H_2O (2×25 ml), saturated aqueous NaCl (3×25 ml), filtered, and dried over anhydrous Na_2SO_4. The desiccant was separated by filtration, the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in a minimum volume of THF and sorbed on silica gel. The product was purified by column chromatography by gravity elution with EtOAc. The product is then further purified by preparative HPLC.

2-{[2,4-Dioxo-3-(2-oxo-2-phenylethyl)-3,4-dihydropyrimidin-1(2*H*)-yl]methoxy}ethyl acetate (5). Yield 440 mg (48%), assay 79% (UV). Yield after preparative HPLC 210 mg (23%), colorless syrup, assay 100% (ELSD). R_f 0.52 (EtOAc), 0.40 (EtOAc–cyclohexane, 4:1). ^{1}H NMR spectrum,

δ, ppm (*J*, Hz): 2.07 (3H, s, CH_3); 3.77–3.80 (2H, m, $OCH_2C\underline{H}_2$); 4.21–4.23 (2H, m, $OC\underline{H}_2CH_2$); 5.23 (2H, s, NCH_2O); 5.38 (2H, s, $NCH_2C(O)$); 5.88 (1H, d, *J* = 8.3, 6-CH pyrimidine); 7.35 (1H, d, *J* = 7.9, 5-CH pyrimidine); 7.46–7.51 (2H, m, H-3,5); 7.58–7.63 (1H, m, H-4); 7.97–8.00 (2H, m, H-2,6). ^{13}C NMR spectrum, δ, ppm: 20.7 ($\underline{C}H_3C(O)O$); 46.9 ($\underline{C}H_2C(O)$); 62.9 (CH_2); 67.6 (CH_2); 77.3 (CH_2); 102.6 (6-CH pyrimidine); 128.0 (2CH Ar); 128.7 (2CH Ar); 133.7 (CH Ar); 134.8; 141.2 (5-CH pyrimidine); 151.6; 162.1; 170.6; 191.3 (C(O) Ar). Found, %: C 59.14; H 5.40; N 7.89. $C_{17}H_{18}N_2O_6$. Calculated, %: C 58.96; H 5.24; N 8.09.

2-({3-[2-(4-Methoxyphenyl)-2-oxoethyl]-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl}methoxy)ethyl acetate (6). Yield 420 mg (42%), assay 83% (UV). Yield after preparative HPLC 270 mg (27%), colorless syrup, assay 100% (ELSD). R_f 0.45 (EtOAc), 0.31 (EtOAc–cyclohexane, 4:1). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.07 (3H, s, CH_3); 3.77–3.80 (2H, m, $OCH_2C\underline{H}_2$); 3.87 (3H, s, OCH_3); 4.20–4.23 (2H, m, $OC\underline{H}_2CH_2$); 5.22 (2H, s, NCH_2O); 5.34 (2H, s, $NCH_2C(O)$); 5.87 (1H, d, *J* = 7.9, 6-CH pyrimidine); 6.93–6.97 (2H, m, H-3,5); 7.34 (1H, d, *J* = 7.9, 5-CH pyrimidine); 7.94–7.98 (2H, m, H-2,6). ^{13}C NMR spectrum, δ, ppm: 20.7 ($\underline{C}H_3C(O)O$); 46.5 ($\underline{C}H_2C(O)$); 55.4 (CH_3O); 62.9 (CH_2); 67.5 (CH_2); 77.3 (CH_2); 102.6 (6-CH pyrimidine); 113.9 (2CH Ar); 127.9; 130.2 (2CH Ar); 141.2 (5-CH pyrimidine); 151.6; 162.1; 163.9; 170.6; 189.7 (C(O)Ar). Found, %: C 57.76; H 5.50; N 7.80. $C_{18}H_{20}N_2O_7$. Calculated, %: C 57.44; H 5.36; N 7.44.

2-({3-[2-(4-Fluorophenyl)-2-oxoethyl]-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl}methoxy)ethyl acetate (7). Yield 700 mg (73%), assay 81% (UV). Yield after preparative HPLC 291 mg (30%), white crystals, assay 100% (ELSD). Mp 105.6–106.2°C. R_f 0.51 (EtOAc), 0.38 (EtOAc–cyclohexane, 4:1). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.07 (3H, s, CH_3); 3.77–3.79 (2H, m, $OCH_2C\underline{H}_2$); 4.20–4.23 (2H, m, $OC\underline{H}_2CH_2$); 5.22 (2H, s, NCH_2O); 5.34 (2H, s, $NCH_2C(O)$); 5.87 (1H, d, *J* = 7.9, 6-CH pyrimidine); 7.13–7.19 (2H, m, H-3,5); 7.35 (1H, d, *J* = 7.9, 5-CH pyrimidine); 7.99–8.04 (2H, m, H-2,6). ^{13}C NMR spectrum, δ, ppm: 20.7 ($\underline{C}H_3C(O)O$); 46.7 ($\underline{C}H_2C(O)$); 62.8 (CH_2); 67.6 (CH_2); 77.3 (CH_2); 102.5 (6-CH pyrimidine); 115.8 (CH Ar); 116.0 (CH Ar); 131.2 (2CH Ar); 131.3; 141.3 (5-CH pyrimidine); 151.6; 162.0; 164.6; 167.4; 170.6; 189.8 (C(O) Ar). Found, %: C 55.89; H 4.82; N 7.41. $C_{17}H_{17}FN_2O_6$. Calculated, %: C 56.04; H 4.70; N 7.69.

Synthesis of pyrimidine-2,4(1*H*,3*H*)-diones 8–10 (General procedure). Method II. Similar to method I, except for using anhydrous MeCN (40 ml) as the solvent and carrying out the synthesis at reflux.

2-{[2,4-Dioxo-3-(1-oxo-1-phenylpropan-2-yl)-3,4-dihydropyrimidin-1(2*H*)-yl]methoxy}ethyl acetate (8). Yield 400 mg (42%), assay 87% (UV). Yield after preparative HPLC 390 mg (41%), colorless syrup, assay 100% (ELSD). R_f 0.69 (EtOAc), 0.44 (EtOAc–cyclohexane, 4:1). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.61 (3H, d, *J* = 6.8, $C\underline{H}_3CH$); 2.02 (3H, s, $CH_3C(O)O$); 3.07–3.39 (2H, m, $OCH_2C\underline{H}_2$); 3.92–4.05 (2H, m, $OC\underline{H}_2CH_2$); 4.97 (2H, dd, ^1J = 10.4, ^2J = 10.4, NCH_2O); 5.78 (1H, d, *J* = 7.9, 6-CH pyrimidine); 5.96 (1H, q, *J* = 6.5, $CH_3C\underline{H}$); 7.16 (1H, d, *J* = 7.9, 5-CH pyrimidine); 7.30–7.35 (2H, m, H-3,5); 7.41–7.46 (1H, m, H-4); 7.62–7.65 (2H, m, H-2,6). ^{13}C NMR spectrum, δ, ppm: 13.1 ($\underline{C}H_3CH$); 20.7 ($\underline{C}H_3C(O)O$); 53.3 ($CH_3\underline{C}H$); 62.5 (CH_2); 66.8 (CH_2); 76.9 (CH_2); 102.6 (6-CH pyrimidine); 127.2 (2CH Ar); 128.2 (2CH Ar); 132.1 (CH Ar); 136.3; 136.3 (5-CH pyrimidine); 150.5; 161.7; 170.4; 196.8 (C(O) Ar). Found, %: C 60.21; H 5.81; N 8.00. $C_{18}H_{20}N_2O_6$. Calculated, %: C 59.99; H 5.59; N 7.77.

2-({3-[1-(4-Methoxyphenyl)-1-oxopropan-2-yl]-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl}methoxy)ethyl acetate (9). Yield 420 mg (41%), assay 74% (UV). Yield after preparative HPLC 201 mg (19%), colorless syrup, assay 100% (ELSD). R_f 0.62 (EtOAc), 0.34 (EtOAc–cyclohexane, 4:1). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.59 (3H, d, *J* = 6.8, $C\underline{H}_3CH$); 2.02 (3H, s, $CH_3C(O)O$); 3.14–3.44 (2H, m, $OCH_2C\underline{H}_2$); 3.80 (3H, s, OCH_3); 3.93–4.06 (2H, m, $OC\underline{H}_2CH_2$); 5.05 (2H, dd, ^1J = 10.4, ^2J = 10.4, NCH_2O); 5.79 (1H, d, *J* = 7.9, 6-CH pyrimidine); 5.93 (1H, q, *J* = 6.6, $CH_3C\underline{H}$); 6.80–6.84 (2H, m, H-3,5); 7.18 (1H, d, *J* = 7.6, 5-CH pyrimidine); 7.61–7.65 (2H, m, H-2,6). ^{13}C NMR spectrum, δ, ppm: 13.2 ($\underline{C}H_3CH$); 20.7 ($\underline{C}H_3C(O)O$); 53.1 ($CH_3\underline{C}H$); 55.3 (OCH_3); 62.6 (CH_2); 66.9 (CH_2); 76.9 (CH_2); 102.6 (6-CH pyrimidine); 113.5 (CH Ar); 128.8; 129.4 (CH Ar); 141.4 (5-CH pyrimidine); 150.5; 161.7; 162.8; 170.4; 195.2 (C(O) Ar). Found, %: C 58.31; H 5.30; N 6.97. $C_{19}H_{22}N_2O_7$. Calculated, %: C 58.46; H 5.68; N 7.18.

2-[(3-{[(4-Fluorophenyl)sulfanyl]methyl}-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)methoxy]ethyl acetate (10). Yield 700 mg (72%). Yield after preparative HPLC 340 mg (35%), yellowish oil, assay 100% (ELSD). R_f 0.67 (EtOAc), 0.38 (EtOAc–cyclohexane, 4:1). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.04 (3H, s, CH_3); 3.68–3.71 (2H, m, $OCH_2C\underline{H}_2$); 4.17–4.19 (2H, m, $OC\underline{H}_2CH_2$); 5.15 (2H, s, NCH_2O); 5.25 (2H, s, NCH_2S); 5.76 (1H, d, *J* = 7.9, 6-CH pyrimidine); 6.93–6.99 (2H, m, H-3,5); 7.24 (1H, d, *J* = 7.9, 5-CH pyrimidine); 7.46–7.52 (2H, m, H-2,6). ^{13}C NMR spectrum, δ, ppm: 20.7 ($\underline{C}H_3C(O)O$); 46.1 (CH_2S); 62.7 (CH_2); 67.6 (CH_2); 77.5 (CH_2); 102.4 (6-CH pyrimidine); 115.7 (CH Ar); 116.0 (CH Ar); 128.8; 135.1 (2CH Ar); 141.0 (5-CH pyrimidine); 150.9; 161.3; 164.0; 170.5. Found, %: C 51.98; H 4.31; N 7.61; S 9.00. $C_{16}H_{17}FN_2O_5S$. Calculated, %: C 52.17; H 4.65; N 7.60; S 8.70.

2-[2,4-Dioxo-3-(2-oxo-2-phenylethyl)-3,4-dihydropyrimidin-1(2*H*)-yl]ethyl acetate (11). Obtained according to method II from 1-(2-acetoxyethyl)uracil (**4**) (0.62 g, 3.13 mmol), K_2CO_3 (0.52 g, 3.29 mmol), 2-bromo-1-phenylethan-1-one (0.65 g, 3.75 mmol), and anhydrous MeCN (75 ml). Yield 510 mg (52%). Yield after preparative HPLC 250 mg (25%), colorless syrup, assay 100% (ELSD). R_f 0.53 (EtOAc). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.07 (3H, s, CH_3); 3.90 (2H, t, *J* = 1.9, $OCH_2C\underline{H}_2$); 4.30 (2H, t, *J* = 1.9, $OC\underline{H}_2CH_2$); 5.38 (2H, s, $NCH_2C(O)$); 5.79–5.81 (1H, d, *J* = 2.9, 6-CH pyrimidine); 7.19–7.21 (1H, d, *J* = 2.8, 5-CH pyrimidine); 7.46–7.51 (2H, m, H-2,6); 7.58–7.62 (1H, m, H-4); 7.97–8.00 (2H, m,

H-3,5). ^{13}C NMR spectrum, δ, ppm: 20.6 ($\underline{C}H_3C(O)$); 47.0 ($\underline{C}H_2C(O)$); 61.7 (CH_2); 77.0 (CH_2); 101.4 (6-CH pyrimidine); 128.0 (2CH Ar); 128.7 (2CH Ar); 133.6 (CH Ar); 134.8; 142.8 (5-CH pyrimidine); 151.2; 162.3; 170.3; 191.8 (C(O) Ar). Found, %: C 61.00; H 4.89; N 9.01. $C_{16}H_{16}N_2O_5$. Calculated, %: C 60.76; H 5.10; N 8.86.

Biological activity of the obtained compounds was studied on female outbred (nonlinear) laboratory mice (CD-1) weighing 20–25 g. Animals were obtained from the vivarium of the Federal Research Center of the Institute of Cytology and Genetics, Siberian Branch of the Russian Academy of Sciences, where they were kept under standard vivarium conditions with free access to water and granular feed. After quarantine, animals were randomized by weight and divided into groups of 8–10 mice. Work with animals was carried out in strict accordance with the Order of the Ministry of Health of the Russian Federation No. 199н dated April 1, 2016 "Rules of Good Laboratory Practice" and the provisions of Directive 2010/63/EU of the European Parliament (Directive 2010/63/EU on the protection of animals used for scientific purposes) and the Council of the European Union of 22 September 2010 on the protection of animals used for scientific purposes.

Test compounds were administered in two ways:

1. Intragastrically (i/g) with a probe, once, in the form of a thin suspension in Tween-20 with a volume of 0.2 ml per 10 g of body weight at a dose of 10 or 50 mg/kg. The control group of animals were injected with an equal volume of aqueous Tween solution intragastrically.

2. Intraperitoneally (i/p) with an insulin syringe, once, sterile solution of 0.9% NaCl was used as the solvent with a volume of 0.1 ml per 10 g of body weight at a dose of 10 or 50 mg/kg. An equal volume of solvent was also administered intraperitoneally to the control group of animals.

The choice of doses was justified by the literature data for 3-phenacyluridine and its analogs.[2,15,16]

The following tests were used to determine the effect of the test compounds on the central nervous system:

1. Determination of the locomotor response of animals in the open field test[30] using an automated TruScan photosensor installation (Coulbourn, USA), which is a square arena measuring 26 × 26 × 33 cm (length × width × height) and contains 16 evenly spaced holes (burrows) with a diameter of 2.2 cm. The test animal was placed in the center of the installation with its tail to the experimenter one hour after a single intragastric administration of the studied agents. Within 2 min, the following indicators were recorded: total locomotor activity (number of locomotor acts), time of locomotor activity (s), distance traveled (cm), average speed (cm/s), number of jumps, vertical activity (number of racks), time of vertical activity (s), number and time of looking (s) into holes, vertical distance (cm).

2. Locomotor activity against the background of diazepam (diazepam was administered intraperitoneally at a dose of 10 mg/kg.[31] Locomotor response of animals was evaluated 30 min after the administration of diazepam by the open field test[30] using an automated TruScan photosensor system (Coulbourn, USA).

3. "Chloral hydrate sleep" was caused by intraperitoneal administration of the hypnotic chloral hydrate in a dose of 325 mg/kg. The criterion for evaluating the effect was the time of loss and restoration of the reflex of turning of the mice from a lateral position.[31] The time of falling asleep, awakening, and duration of sleep were estimated. The duration of sleep was calculated by the difference between the indicator of time falling asleep (the moment of loss of the flipping reflex) and the time of awakening (reflex recovery).

Chloral hydrate and diazepam were administered after 1 h for intragastric administration and after 30 min for intraperitoneal administration of the test compounds.

Statistical data processing was carried out using the program Statistica 6.0. Data are presented as the arithmetic mean and standard error of the mean. Comparisons between groups were performed using the nonparametric Mann–Whitney U test. For a significant level of significance, $p \leq 0.05$. Differences at the trend level were considered at $0.05 < p < 0.1$.

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