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SYNTHESIS OF 5-[2-(PHENOXY)ETHYL] DERIVATIVES OF 6-METHYLURACIL, 6-METHYL-2-THIOXO-2,3-DIHYDRO-1H-PYRIMIDIN-4-ONE, AND 2-IMINO-6-METHYL-2,3-DIHYDRO-1H-PYRIMIDIN-4-ONE

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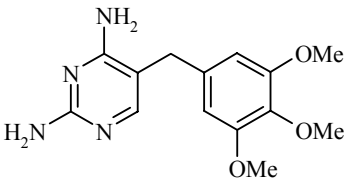
A synthesis of novel derivatives of 6-methyluracil, 6-methyl-2-thioxo-, and 2-imino-6-methyl-2,3-dihydro-1H-pyrimidin-4-one containing a 2-(phenoxy)ethyl substituent at position 5 of the pyrimidine ring has been carried out. It was found that 5-[2-(phenoxy)ethyl] derivatives of 6-methyl-2-thioxo- and 2-imino-6-methyl-2,3-dihydro-1H-pyrimidin-4-one are obtained by the condensation of the corresponding ethyl 3-oxo-2-(2-phenoxyethyl)butanoates with thiourea or guanidine. 6-Methyl-5-[2-(phenoxy)ethyl]uracils can be prepared by treating 6-methyl-5-[2-(phenoxy)ethyl]-2-thioxo-2,3-dihydro-1H-pyrimidin-4-ones with an excess of aqueous monochloroacetic acid solution.

Keywords: 2-imino-6-methyl-5-[2-(phenoxy)ethyl]-2,3-dihydro-1H-pyrimidin-4-ones, 6-methyl-2-thioxo-5-[2-(phenoxy)ethyl]-2,3-dihydro-1H-pyrimidin-4-ones, 6-methyl-5-[2-(phenoxy)ethyl]-2,3-dihydro-1H-pyrimidin-4-ones, synthesis.

The occurrence of AIDS is accompanied by the appearance of secondary opportunistic infections [1]. The etiological agents of such infections are frequently *Pneumocystis carinii* and *Toxoplasma gondii*. Dihydrofolate reductase [2] is a promising target for chemotherapeutic action on the reproduction of these microorganisms. Trimethoprim (**1**) and piritrexim (**2**) are known inhibitors of dihydrofolate reductase. However, their use for prophylaxis and for the treatment of illness caused by *Pneumocystis carinii* and *Toxoplasma gondii* is often of low effectivity due to the features of the life cycle of the pathogens. It is believed that the reason for this is the relatively high polarity of compounds **1** and **2** [3]. Analogs of trimethoprim **1** with such lipophilic substituents as ω-carboxyalkoxy- (**3**) [4] or ω-carboxyalkyl (**4**) (n = 2-5 [5]) groups in the benzene fragment prove to be markedly more efficient as inhibitors of these microorganisms.



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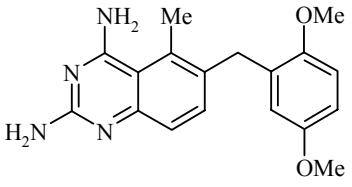

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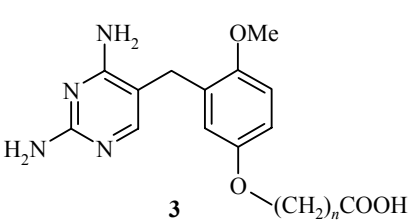

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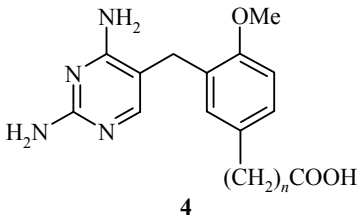

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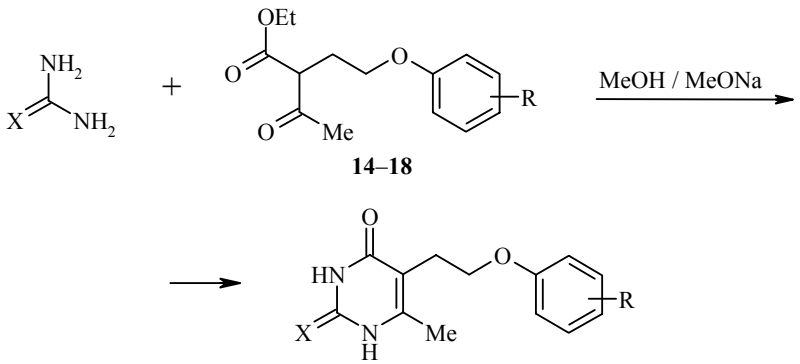
With the object of searching for novel antitumor and antibacterial agents (likely inhibitors of dihydrofolate reductase) we have synthesized novel pyrimidine derivatives containing a lipophilic 2-phenoxyethyl substituent at position 5.

The synthesis of 5-[2-(phenoxy)ethyl] derivatives of 6-methyl-2-thioxo-2,3-dihydro-1H-pyrimidin-4-one **5-8** and 2-imino-6-methyl-2,3-dihydro-1H-pyrimidin-4-one **9-13** consists of condensation of the ethyl 3-oxo-2-(2-phenoxyethyl)butanoates **14-18** with a 2.5-fold molar excess of thiourea or guanidine. The reaction occurs successfully in refluxing absolute methanol with a 2.6-2.8-fold molar excess of sodium methylate as reported using known methods [6-8]. The corresponding 2-thioxo-2,3-dihydro-1H-pyrimidin-4-ones **5-8** and 2-imino-6-methyl-5-[2-(phenoxy)ethyl]-2,3-dihydro-1H-pyrimidin-4-ones **9-13** were prepared in this way (Table 1).

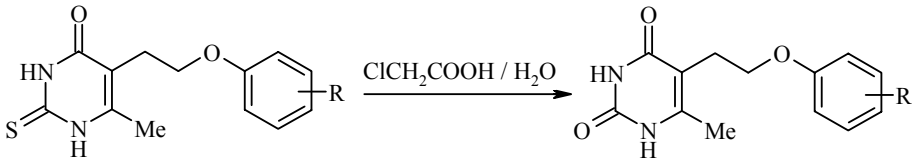


14–18

5–13

5, **9**, **14** R = H; **6**, **10**, **15** R = 2-Me; **7, 11**, **16** R = 3-Me; **12**, **17** R = 4-Me; **8**, **13**, **18** R = 3,5-Me_2;
5-8 X = S; **9-13** X = NH

Since urea takes part in the condensation reaction with β-keto esters with much greater difficulty than thiourea or guanidine, the synthesis of the 5-[2-(phenoxy)ethyl] derivatives of 6-methyluracil **19-22** was carried out by treatment of the thioureas **5-8** with an aqueous solution of monochloroacetic acid, as reported in the literature [8, 9] (Table 1).



5–8

19–22

5, **19** R = H; **6**, **20** R = 2-Me; **7**, **21** R = 3-Me; **8**, **22** R = 3,5-Me_2

TABLE 1. Parameters for the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
5	$C_{13}H_{14}N_2O_2S$	59.74 / 59.52	5.49 / 5.38	10.49 / 10.68	225-226	77
6	$C_{14}H_{16}N_2O_2S$	60.97 / 60.85	5.71 / 5.84	10.02 / 10.14	223-226	71
7	$C_{14}H_{16}N_2O_2S$	60.66 / 60.85	5.73 / 5.84	10.30 / 10.14	229-230	75
8	$C_{15}H_{18}N_2O_2S$	62.25 / 62.04	6.34 / 6.25	9.47 / 9.65	238-239	90
9	$C_{13}H_{15}N_3O_2$	63.42 / 63.66	6.24 / 6.16	17.28 / 17.13	267-269	78
10	$C_{14}H_{17}N_3O_2$	64.98 / 64.85	6.76 / 6.61	16.03 / 16.20	273-274	64
11	$C_{14}H_{17}N_3O_2$	65.01 / 64.85	6.73 / 6.61	16.05 / 16.20	269-271	65
12	$C_{14}H_{17}N_3O_2$	64.69 / 64.85	6.70 / 6.61	16.34 / 16.20	259-260	55
13	$C_{15}H_{19}N_3O_2$	66.14 / 65.91	7.24 / 7.01	15.20 / 15.37	272-274	77
19	$C_{13}H_{14}N_2O_3$	63.53 / 63.40	5.88 / 5.73	11.29 / 11.38	208-210	82
20	$C_{14}H_{16}N_2O_3$	64.76 / 64.60	6.35 / 6.20	10.91 / 10.76	225-226	75
21	$C_{14}H_{16}N_2O_3$	64.46 / 64.60	6.03 / 6.20	10.87 / 10.76	204-205	89
22	$C_{15}H_{18}N_2O_3$	65.77 / 65.68	6.50 / 6.61	10.42 / 10.21	214-215	82

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Bruker DRX-500 (500 MHz) spectrometer using DMSO-d_6 and with TMS as internal standard. The interpretation of the spectra was made using the ACD/HNMR Predictor 3.0 licensed program from Advanced Chemistry Development (Canada). Mass spectra were obtained on a Varian MAT-111 spectrometer (direct introduction, EI ionization method, 70 eV). Melting points were measured in glass capillaries on a Mel-Temp 3.0 instrument (Laboratory Devices Inc., USA).

6-Methyl-5-(2-phenoxyethyl)-2-thioxo-2,3-dihydro-1H-pyrimidin-4-one (5). Thiourea (8.9 g, 117 mmol) and ethyl 3-oxo-2-(2-phenoxyethyl)butanoate (**14**) (11.5 g, 45.95 mmol) were added to a solution of sodium (2.7 g, 117 mmol) in methanol (100 ml) and refluxed with protection from the moisture of the air for 48 h. The reaction product was evaporated in vacuo and the residue was dissolved in water (200 ml), acidified with a 3% solution of hydrochloric acid, and the precipitate was filtered off, dried at 60-70°C, and recrystallized from a mixture of DMF and water (5:1). Yield 9.3 g of finely crystalline, light yellow material; mp 225-226°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.21 (3H, s, 6-CH_3); 2.75 (2H, t, *J* = 5, C$\underline{H_2}$CH_2O); 4.00 (2H, t, *J* = 5, CH_2O); 6.84-7.21 (5H, m, C_6H_5), 11.96 (1H, br. s, 3-NH), 12.04 (1H, br. s, 1-NH). Mass spectrum, *m/z*: 262 $[M]^+$.

Compounds 6-8 were prepared similarly.

6-Methyl-5-[2-(2-methylphenoxy)ethyl]-2-thioxo-2,3-dihydro-1H-pyrimidin-4-one (6). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.10 (3H, s, 2-CH_3); 2.19 (3H, s, 6-CH_3); 2.68 (2H, t, *J* = 5, C$\underline{H_2}$CH_2O); 3.97 (2H, t, *J* = 5, CH_2O); 6.85-6.96 (2H, m, arom. H); 7.23-7.30 (2H, m, arom. H); 10.61 (1H, br. s, 1-NH); 10.89 (1H, br. s, 3-NH). Mass spectrum, *m/z*: 276 $[M]^+$.

6-Methyl-5-[2-(3-methylphenoxy)ethyl]-2-thioxo-2,3-dihydro-1H-pyrimidin-4-one (7). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.18 (3H, s, 6-CH_3); 2.26 (3H, s, 3-CH_3); 2.70 (2H, t, *J* = 5, C$\underline{H_2}$CH_2O); 3.98 (2H, t, *J* = 5, CH_2O); 6.68-6.77 (3H, m, arom. H-2',4',6'); 7.14 (1H, m. arom. H-5'); 12.05 (1H, br. s, 3-NH); 12.28 (1H, br. s, 1-NH). Mass spectrum, *m/z*: 276 $[M]^+$.

6-Methyl-5-[2-(3,5-dimethylphenoxy)ethyl]-2-thioxo-2,3-dihydro-1H-pyrimidin-4-one (8). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.20 (3H, s, 6-CH_3); 2.27 (6H, s, 3-CH_3); 2.69 (2H, t, *J* = 5, C$\underline{H}_2$CH_2O); 3.98 (2H, t, *J* = 5, CH_2O); 6.69 (3H, s, arom. H); 11.33 (1H, br. s, 3-NH); 11.45 (1H, br. s, 1-NH). Mass spectrum, *m/z*: 290 $[M]^+$.

2-Imino-6-methyl-5-[2-(phenoxy)ethyl]-2,3-dihydro-1H-pyrimidin-4-one (9). Guanidine acetate (5.1 g, 42.81 mmol) and ethyl 3-oxo-2-(2-phenoxyethyl)butanoate (**14**) (4.2 g, 16.78 mmol) was added to a solution of sodium (1.0 g, 43.48 mmol) in methanol (50 ml) and refluxed with protection from the moisture of the air for 48 h. The reaction product was evaporated in vacuo and the residue was dissolved in water (200 ml), acidified with a 3% solution of hydrochloric acid, and the precipitate was filtered off, dried in air, and recrystallized from a mixture of DMF and water (5:1). Yield 3.2 g of finely crystalline material, light yellow material; mp 267-269°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.17 (3H, s, 6-CH_3); 2.72 (2H, t, *J* = 5, C$\underline{H}_2$CH_2O); 3.95 (2H, t, *J* = 5, CH_2O); 6.23 (2H, br. s, NH_2); 6.89-7.20 (5H, m, C_6H_5); 10.54 (1H, br. s, 1-NH). Mass spectrum, *m/z*: 245 $[M]^+$.

Compounds 10-13 were prepared similarly

2-Imino-6-methyl-5-[2-(2-methylphenoxy)ethyl]-2,3-dihydro-1H-pyrimidin-4-one (10). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.10 (3H, s, 6-CH_3); 2.23 (3H, s, 2-CH_3); 2.73 (2H, t, *J* = 5, C$\underline{H}_2$CH_2O); 3.96 (2H, t, *J* = 5, CH_2O); 5.27 (2H, br. s, NH_2); 6.90 (2H, m, arom. H); 7.25 (2H, m, arom. H); 10.72 (1H, br. s, 3-NH). Mass spectrum, *m/z*: 259 $[M]^+$.

2-Imino-6-methyl-5-[2-(3-methylphenoxy)ethyl]-2,3-dihydro-1H-pyrimidin-4-one (11). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.10 (3H, s, 6-CH_3); 2.26 (3H, s, 3-CH_3); 2.72 (2H, t, *J* = 5, C$\underline{H}_2$CH_2O); 3.93 (2H, t, *J* = 5, CH_2O); 6.21 (2H, br. s, NH_2); 6.66-6.78 (3H, m, arom. H-2',4',6'); 7.10-7.16 (1H, m, arom. H-3'); 10.64 (1H, br. s, 3-NH). Mass spectrum, *m/z*: 259 $[M]^+$.

2-Imino-6-methyl-5-[2-(4-methylphenoxy)ethyl]-2,3-dihydro-1H-pyrimidin-4-one (12). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.19 (3H, s, 6-CH_3); 2.22 (3H, s, 4-CH_3); 2.72(2H, t, *J* = 5, C$\underline{H}_2$CH_2O); 3.92 (2H, t, *J* = 5, CH_2O); 6.23 (2H, br. s, NH_2); 6.81 (2H, m, arom. H); 7.07 (2H, m, arom. H); 10.68 (1H, br. s, 3-NH). Mass spectrum, *m/z*: 259 $[M]^+$.

5-[2-(3,5-Dimethylphenoxy)ethyl]-2-imino-6-methyl-2,3-dihydro-1H-pyrimidin-4-one (13). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.10 (3H, s, 6-CH_3); 2.22 (6H, s, 3-, 5-CH_3); 2.71 (2H, t, *J* = 5, C$\underline{H}_2$CH_2O); 3.92 (2H, t, *J* = 5, CH_2O); 6.20 (2H, br. s, NH_2); 6.52 (3H, s, arom. H-2',4',6'); 10.67 (1H, br. s, 3-NH). Mass spectrum, *m/z*: 273 $[M]^+$.

6-Methyl-5-[2-phenoxy)ethyl]uracil (19). A mixture of compound **5** (1.7 g, 6.48 mmol) and monochloroacetic acid (3.1 g, 32.81 mmol) in water (30 ml) was refluxed for 12 h, cooled to ~ 20°C, and the precipitate was filtered off, washed with water (2 × 20 ml), dried in air, and recrystallized from a mixture of DMF and water (5:1) to give white, finely divided crystals (1.3 g). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.11 (3H, s, 6-CH_3); 2.75 (2H, t, *J* = 5, C$\underline{H}_2$CH_2O); 4.00 (2H, t, *J* = 5, CH_2O); 6.84-7.21 (5H, m, C_6H_5); 10.60 (1H, br. s, 1-NH); 10.82 (1H, br. s, 3-NH). Mass spectrum, *m/z*: 246 $[M]^+$.

Compounds 20-22 were prepared similarly.

6-Methyl-5-[2-(2-methylphenoxy)ethyl]uracil (20). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.12 (3H, s, 6-CH_3); 2.22 (3H, s, 2-CH_3); 2.74 (2H, t, *J* = 5, C$\underline{H}_2$CH_2O); 4.02 (2H, t, *J* = 5, CH_2O); 6.85-6.96 (2H, m, arom. H); 7.23-7.30 (2H, m, arom. H); 10.53 (1H, br. s, 1-NH); 10.79 (1H, br. s, 3-NH). Mass spectrum, *m/z*: 260 $[M]^+$.

6-Methyl-5-[2-(3-methylphenoxy)ethyl]uracil (21). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.13 (3H, s, 6-CH_3); 2.24 (3H, s, 3-CH_3); 2.73 (2H, t, *J* = 5, C$\underline{H}_2$CH_2O); 3.99 (2H, t, *J* = 5, CH_2O); 6.70-6.78 (3H, m, arom. H-2',4',6'); 7.10 (1H, m, arom. H-5');10.55 (1H, br. s, 3-NH); 11.02 (1H, br. s, 1-NH). Mass spectrum, *m/z*: 260 $[M]^+$.

5-[2-(3,5-Dimethylphenoxy)ethyl]-6-methyluracil (22). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.18 (3H, s, 6-CH_3); 2.25 (6H, s, 3-, 5-CH_3); 2.71 (2H, t, *J* = 5, C$\underline{H}_2$CH_2O); 4.00 (2H, t, *J* = 5, CH_2O); 6.72 (3H, s, arom. H); 10.36 (1H, br. s, 3-NH); 10.65 (1H, br. s, 1-NH). Mass spectrum, *m/z*: 274 $[M]^+$.

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