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ALKYLATION OF SOME PYRIMIDINE AND PURINE DERIVATIVES USING MICROWAVE-ASSISTED METHODS

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Abstract- *N*-Alkylation of adenine (**1**), guanine (**2**) and 6-amino-2-thiouracil (**3**) with different halides has been carried out using microwave-assisted methods in the presence of small amounts of DMF to improve energy transfer and in the case of **3** by coupling with phase transfer catalysis. The results obtained show high yields and selectivities.

INTRODUCTION

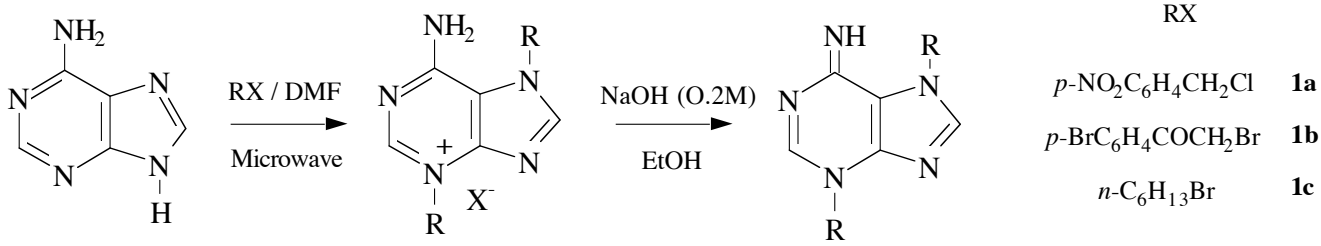
Several works have been reported on the alkylation of *N*-containing heterocycles.[1,12] In this regard, microwave (MW) activation has been successfully applied to the synthesis of such derivatives.[1-3] In previous works, we have described[4] the *N*-alkylation of azoles with 4-bromophenacyl bromide using microwave irradiation under solvent-free conditions and the results obtained show high yields and selectivities. Following our interest in this topic, pyrimidine and purine alkylated products seem to be attractive structures in connection with the investigation of carcinogenesis[5] and as an access to therapeutic agents such as derivatives of antiviral adenines[6] and antimycotic pyrimidines.[7]

The most frequently used method for the synthesis of purine and pyrimidine derivatives is the direct *N*-alkylation by a suitable functionnalized alkylating agent,[8] in the presence of a strong base like potassium fluoride on alumina[1-3] or tetra-*n*-butylammonium fluoride.[10] Phase transfer catalysis (PTC) techniques were applied successfully to a great variety of *N*-alkylation reactions,[11,12] possibly in the absence of solvent,[11-16] especially for the alkylation of theophylline, uracil, adenine and other *N*-containing heterocyclic compounds.

We describe here an easy and efficient microwave-assisted method to obtain *N*-alkylated derivatives from adenine (**1**), guanine (**2**) and 6-amino-2-thiouracil (**3**), under solvent-free conditions, by direct reaction of amines with different alkylating agents. In the case of 6-aminothiouracil, selected instead of natural uracil and cytosine because its importance for medicinal purposes,[17] we used alternately the coupling of microwave irradiation and PTC methods in the presence of a base.[3,18]

RESULTS AND DISCUSSION

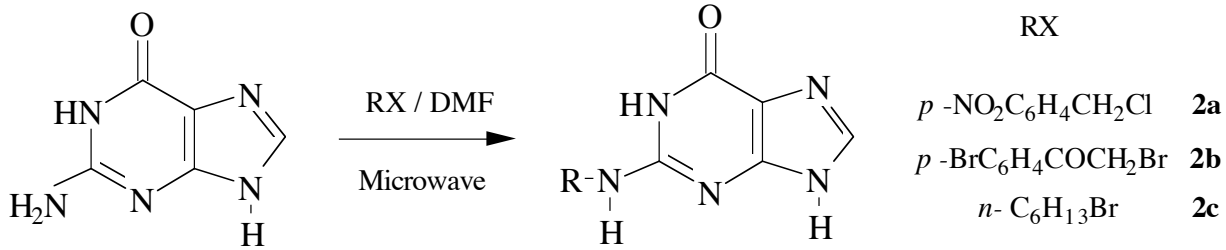
Alkylation of adenine (**1**) with several alkylating agents using a microwave assisted method was performed in the presence of small amounts of DMF. This polar molecule (i.e. highly sensitive to MW irradiation) was added to improve the energy transfer and to allow higher temperatures.[19-22] The reaction led to the dialkylated product as a salt (**A**) which was subsequently extracted with ethanol and treated with NaOH solution (0.2M) to obtain the 3,7-disubstituted adenine (**1a-1c**) with 16, 23 and 14% when the reaction were performed using relative amounts **1**/RX 1:1 and 74, 82 and 72% using **1**/RX 1:2 (Table 1 and Scheme 1).



1 **A**

Scheme 1

The *N*-alkylation of guanine (**2**) occurred on the amino group on C2 leading to **2a** with *p*-nitrobenzyl chloride, to **2b** with *p*-bromophenacyl bromide and to **2c** with 1-bromo hexane under similar conditions (Scheme 2) in moderate yields (Table 1).



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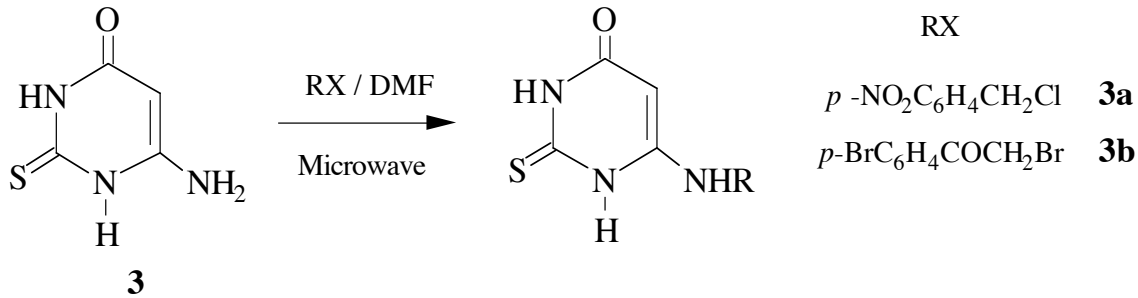
Scheme 2

The results obtained in the alkylation of 6-amino-2-thiouracil (**3**) showed excellent yields in the corresponding N7-monosubstituted thiouracil derivatives (Table 1 and Scheme 3).



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Scheme 3

The syntheses were carried out in good yields within very short reaction times. All reactions were followed by TLC and the products were characterized by ^{1}H, ^{13}C-NMR and MS studies.

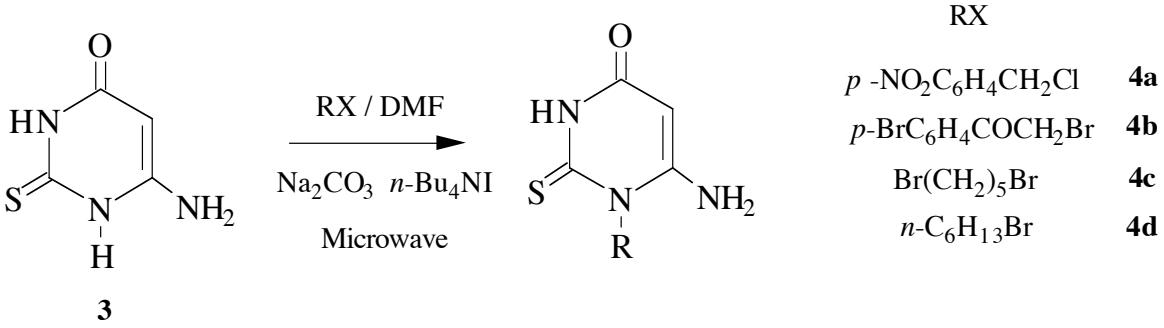
Table 1. Alkylation of pyrimidine and purine derivatives under microwave irradiation in dry media (power 665 W).

Product	Reaction time (min)	Temperature (°C)[a]	Yield[b] (%)
1a	8	120-125	74
1b	7	130-135	82
1c	7	120-125	72
2a	8	120-125	21
2b	6	145-150	70
2c	9	115-120	52
3a	9	100-110	84
3b	11	105-110	83

[a] Measured immediately after the reaction using a glass thermometer.

[b] No reaction occurred in an oil bath under identical conditions of time and temperature.

The alkylation of 6-amino-2-thiouracil in the presence of a base using microwave irradiation under PTC conditions led to the N1-alkylthiouracil derivatives with excellent yields (Scheme 4 and Table 2).



Scheme 4

The results are very satisfactory taking in account the short reaction times and good yields in *N*-alkylated products. In order to check the possibility of intervention of specific (non-purely thermal) MW effects, the synthesis of these compounds were performed, changing only the heating mode, using a thermoregulated oil bath for the same reaction times and temperatures as involved in microwave experiments. In all cases no reaction was detected by TLC. The reaction times were next extended up to 12 hours without any success as only minor amounts of products were detected. In the case of reaction with dibromopentane, no dialkylated product (1,5-bis(2-thiouracil)) was

detected by TLC or MS. It is evident here that specific "non thermal" effect produced by microwave is of prime importance as no reaction occurred under the same conditions (time and temperature) by conventional heating.

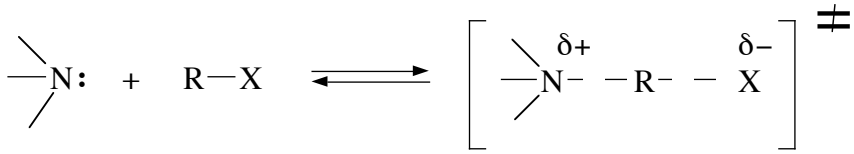
Table 2. Alkylation of 6-amino-2-thiouracil using the coupling of PTC (Na_2CO_3 as the base and catalytic amount of *n*-Bu_4NI) and microwave irradiation in dry media (power 665 W).

Product	Reaction time (min)	Temperature (°C)[a]	Yield[b] (%)
4a	6	70-75	91
4b	6	70-75	95
4c	10	80-85	87
4d	9	105-110	91

[a] Measured immediately after the reaction using a glass thermometer.

[b] No reaction occurred in an oil bath under the same conditions of time and temperature.

This observation is consistent with the consideration of mechanisms and with the assumption that MW effects are increased when the polarity of a system is enhanced.[23,24] In the case of reaction between neutral reactants (amines and alkylating agent), a dipole is developed in the transition state which is consequently more polar than the ground state and therefore more prone to stabilizing effect with MW due to dipole-dipole interactions (Scheme 5). When the anion is concerned (PTC conditions), the polarity of the system is increased in relation with the involvement of charged species, and especially in this case of charge-delocalized ones.



Scheme 5

Table 3. Total atomic charges calculated for the most relevant atoms for adenine (**1**) and guanine (**2**).[25-28]

Atom	**1**	**2**
N1	-0.38	-0.22
C2	0.15	0.17
N3	**-0.48**	-0.39
C4	0.26	0.27
C5	-0.36	-0.35
C6	0.10	0.12
N7	**-0.49**	-0.37
C8	0.32	0.25
N9	-0.37	-0.40
N10	-0.27	**-0.46**

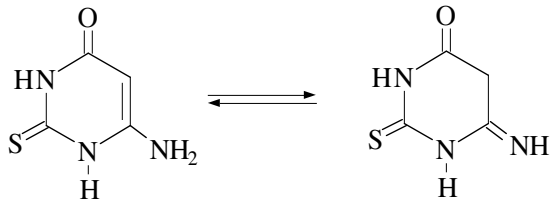
The observed regioselectivity of alkylation of adenine occurring on N3 and N7 atoms and on exocyclic N atom of guanine are consistent with the consideration of atomic charges on the relevant atoms of these molecules as previously reported from ab initio calculations (Table 3).

The N3 and N7 atoms have the most important negative charge in adenine as well as the N10 (exocyclic) in guanine. These results can explain the attack of these atoms by an electrophile under charge controlled reaction.

In the case of 6-amino-2-thiouracil, the difference in regioselectivity obtained by the two methods employed for the synthesis of *N*-alkylated derivatives was a consequence of the basic medium. When the reaction is performed in the absence of a base, the selectivity is clearly different from the one observed from the anionic species (PTC conditions). Alkylation occurs selectively at position 6 on the neutral 6-amino-2-thiouracil and at position 1 from its anion. Such a change in selectivity was already described in the case of alkylations of some azoles according to basic or neutral conditions.[29]

We have tried to justify these effects on the selectivity of alkylation by considering a theoritical approach taking into account the orbital coefficients on the nitrogen atoms of 6-amino-2-thiouracil (**3**). Some calculations have been performed using the HF/6-31** *ab initio* program (Gaussian 94).[30]

A previous calculation has allowed to suggest the **3 (A)** geometry to be more stable than its tautomer **3 (B)** (imino form) by 1.50 kcal/mol (cf. tautomerism equilibrium as depicted in Scheme 6).



3(A) **3(B)**

Scheme 6

In order to explain the site of electrophilic attack of **3 (A)** or its anion **3 (-)**, the values of atomic orbital coefficients are given in the highest occupied levels (Table 4).

Table 4. HF/6-31G** orbital coefficients of the highest energy levels of the 6-amino-2-thiouracil (**3**), 6-imino-5H-thiouracil (**3B**) and the 6-amino-2-thiouracil anion (**3-**).

		3 (A)	**3 (B)**	**3 (A)**	**3 (B)**	**3 (-)**
Orbital energy level		35		37 (HOMO)		
Energy (Hartrees)		0.37	0.42	0.33	0.35	0.37
Coefficients	N1	0.09	0.37	0.31	0.34	0.34
	C2	0.18	0.01	0.11	0.18	0.02
	N3	0.25	0.39	0.23	0.21	0.13
	C4	0.02	0.01	0.02	0.02	0.05
	C5	0.38	0.07	0.37	0.01	0.37
	C6	0.21	0.23	0.15	0.07	0.05
	N7	0.26	0.42	0.12	0.20	0.04

Taking into account the values of the orbital coefficients in the near highest energy level (orbital No 35) for the neutral molecule, we would suggest that this orbital takes part in this reaction, justifying the regioselectivity (attack by N7). The N7 orbital atomic coefficient is important in this orbital, suggesting thus a subjacent orbital contribution of the reaction, whereas the highest coefficient in the HOMO orbital (orbital No 37) lies on N1 atom.

On the other hand, the alkylation reaction in the 6-amino-2-thiouracil anion has to be favored by N1 and C5 atoms, which have the highest orbital coefficients in the HOMO.

In the same way, the atomic charge of the most relevant atoms was calculated and is reported in Table 5. In 6-amino-2-thiouracil, the N1, N3 and N7 atoms have the most negative charge values. The behavior is the same for 6-imino-5*H*-thiouracil (**3B**) and 6-amino-2-thiouracil anion. In all cases, the atomic charge in C5 is significantly lower than on N atoms. These values could explain, for the anion, the attack by the nitrogen atoms and to reject the possible attack by the C5 atom.

Table 5. Total atomic charges calculated for the most relevant atoms.

Atoms	**3 (A)**	**3 (B)**	**3 (-)**
N1	-0.76	-0.70	-0.69
C2	0.49	0.47	0.46
N3	-0.75	-0.74	-0.74
C4	0.82	0.78	0.80
C5	-0.39	-0.41	-0.41
C6	0.70	0.57	0.58
N7	-0.75	-0.61	-0.74

In summary, the procedure described here, leading to high yields, does only require the use of a small amount of solvent within very short reaction times and with simplified and safe work-up. It constitutes a clear improvement and involves " green chemistry " techniques.

EXPERIMENTAL

Starting materials came from commercial sources. Melting points were determined on an Electrothermal 9100 apparatus and are uncorrected. The reactions were carried out in a Sanyo domestic microwave oven, which allows the selection of output power up to 800 Watts. TLC analyses were run on 60 F254 silica gel chromatoplates from Merck using a mixture of n-hexane:ethyl acetate 4:1 as an eluent. ^{1}H-NMR spectra were recorded on a Bruker AC 250 using TMS as an internal standard and DMSO-*d6* as a solvent. Mass spectra were obtained with a Hewlett Packard 5890 spectrometer. Microanalyses were performed by the Servicio de Microanálisis of Centro de Ingeniería Genética y Biotecnología. HF/6-31G** calculations were carried out in order to determine the orbital coefficients of the highest occupied molecular orbitals and the atomic charges in 6-amino-2-thiouracil and its tautomer using Gaussian 94 program.[30] Previously, MP2/6-31G** calculations were done in order to optimized the structure of the molecules.

Procedure to obtain 3,7-bis-alkyladenine (**1a-c**): 2.5 mmol (337.5 mg) of adenine and 5 mmol of alkylating agent and 1 mmol (73 mg) of DMF were smoothly mixed, placed into a pyrex-glass open vessel and irradiated in a domestic microwave oven. When the irradiation was stopped, the final temperature was measured by introducing a glass thermometer into the reaction mixture, homogenizing it in order to obtain a temperature value representative of the whole mass. The mixture was extracted with ethanol (3x10 mL). The extract was evaporated under vacuum and the final products obtained after washing with a solution of NaOH (0.2 M). The resulting solid was filtered off and conveniently dried and then recrystallized from water.

3,7-Bis(4-nitrobenzyl)adenine (**1a**): mp: 258-260°C; νmax (KBr)/cm^{-1}: 3100, 1662, 1508, 1348; Anal. Calcd for $C_{19}H_{15}N_7O_4$: C, 56.30; H, 3.72; N, 24.19. Found: C, 56.51; H, 3.87; N, 24.42.^{1}H-NMR (DMSO-d_6) δ, (ppm): 5.6 (s, 4H), 8.0 (br s, NH), 7.7 (d, J = 8.7 Hz, 2H), 8.19 (d, J = 8.7 Hz, 2H), 8.6 (s, 1H, H-8), 9.1 (s, 1H, H-2); ^{13}C-NMR (DMSO-d_6) δ, (ppm): 51.6 (C10, C15), 116.7 (C5), 123.5 (C13, C13', C18, C18'), 128.9 (C12, C12', C17, C17'), 139.5 (C8), 142.2 (C16), 145.0 (C14), 147.1 (C19), 148.0 (C11), 151.7 (C2), 153.5 (C4), 153.7 (C6); MS (m/z): 405 (M^+), 269, 223.

3,7-Bis(4-bromophenacyl)adenine (**1b)** : mp: 286-287°C; Anal. Calcd for $C_{21}H_{15}N_5O_2Br_2$: C, 47.66; H, 2.86; N, 13.23. Found: C, 47.78; H, 2.95; N, 13.41. νmax (KBr)/cm-1:3320, 2860, 1825, 1620; ^{1}H-NMR (DMSO-d_6) δ, (ppm): 5.5 (s, 4H), 8.0 (br s, NH), 7.8 (d, *J* = 8.4 Hz, 2H), 8.1 (d, J=8.4 Hz, 2H), 8.6 (s, 1H, H-8), 9.1 (s, 1H, H-2); ^{13}C-NMR (DMSO-d_6) δ, (ppm): 52.3 (C10, C16), 115.8 (C5), 128.9 (C21), 130.4 (C14, C14â, C20, C20â), 132.1 (C18), 132.8 (C15), 134.1 (C13, C13â, C19, C19â), 136.2 (C12), 139.4 (C8), 152.0 (C2), 153.4 (C4), 153.7 (C6) 188.5 (C11), 188.8 (C17); MS(m/z): 529/531 M^+, 331/332, 133.

3,7-Bis(hexyl)adenine (**1c)**: mp: 218-219°C; Anal. Calcd for $C_{17}H_{29}N_5$: C, 67.29; H, 9.63; N, 23.08. Found: C, 67.36; H, 9.72; N, 23.17. ^{1}H-NMR (DMSO-d_6) δ, (ppm): 0.5 (t, J = 6.6 Hz, 3H), 0.7 (t, J = 6.6 Hz, 3H), 0.9-1.7 (m, 16H), 4.6 (t, J = 6.8 Hz, 2H), 4.8 (t, J = 6.9 Hz, 2H), 7.8 (br s, NH), 8.5 (s, 1H, H-8), 9.1 (s, 1H, H-2); ^{13}C-NMR (DMSO-d_6) δ, (ppm): 12.9 (C21), 13.1 (C15), 20.5 (C14), 20.9 (C20), 21.6 (C11), 21.9 (C17), 27.5 (C12), 28.1 (C18), 28.3 (C13), 28.9 (C19), 29.5 (C10), 30.2 (C16), 116.6 (C5), 139.8 (C8), 151.5 (C2), 153.8 (C4), 154.2 (C6); MS (m/z): 303 M^+, 218, 118.

General procedure to obtain *N*2-monoalkylguanines: 2.5 mmol (378 mg) of guanine and 2.5 mmol of alkylating agent and 2.5 mmol (183 mg) of DMF were gently mixed, placed into a pyrex-glass open vessel and irradiated in a domestic microwave oven. When the irradiation was stopped, the final temperature was immediately measured by introducing a glass thermometer into the reaction mixture, homogenizing it in order to obtain a temperature value representative of the whole mass. The mixture was extracted with adequate solvents (3x10 mL). The extract was evaporated under vacuum and the final products obtained by washing with acetone (3x10 mL). The remaining solids were filtered off and conveniently dried and subsequently recrystallized from water.

*N*2-(4-Nitrobenzyl)guanine (**2a**): mp: 263-264°C; Anal. Calcd for $C_{12}H_{10}N_6O_3$: C, 50.35; H, 3.52; N, 29.36. Found: C, 50.41; H, 3.60; N, 29.42. ^{1}H-NMR (DMSO-d_6) δ, (ppm): 5.6 (d, J = 0.9 Hz, 2H), 7.6 (d, J = 8.6 Hz, 2H), 8.2 (d, J = 8.6 Hz, 2H), 8.8 (s, 1H, H-8), 9.6 (s, 1H, H-9); ^{13}C-NMR (DMSO-d_6) δ, (ppm): 46.3 (C11), 107.5 (C9), 123.7 (C14,14'), 128.8 (C5), 129.2 (C8), 129.3 (C13,13'), 146.1 (C15), 149.7 (C12), 153.1 (C6), 155.0 (C2).

*N*2-(4-Bromophenacyl)guanine (**2b**): mp: 293-294°C; νmax (KBr)/cm^{-1}: 3330, 2870, 1710, 1650; Anal. Calcd for $C_{13}H_{10}N_6OBr$: C, 45.11; H, 2.91; N, 24.28. Found: C, 45.32; H, 3.07; N, 24.46. ^{1}H-NMR (DMSO-d_6) δ, (ppm): 5.4 (d, J = 0.9 Hz, 2H), 7.05 (br s, NH), 7.8 (d, J = 8.4 Hz, 2H), 8.0 (d, J = 8.4 Hz, 2H), 8.8 (s, 1H, H-8), 9.2 (s, 1H, H-9); ^{13}C-NMR (DMSO-d_6) δ, (ppm): 51.5 (C11), 107.5 (C9), 128.9 (C8), 129.0 (C5), 130.1 (C16), 130.3 (C15,15'), 131.9 (C13), 132.5 (C14,14'), 136.9 (C4), 153.2 (C6), 156.0 (C2), 189.9 (C12); MS(m/z): 347/349 (M^+), 151, 81/82.

*N*2-(Hexyl)guanine **(2c)**: mp: 182-183 °C; νmax (KBr)/cm^{-1}:3310, 3230, 1750, 1560; Anal. Calcd for $C_{11}H_{17}N_5O$: C, 56.15; H, 7.28; N, 29.76. Found: C, 56.33; H, 7.42; N, 29.89.^{1}H-NMR (DMSO-d_6) δ, (ppm): 0.6 (t, J = 6.9 Hz, 3H), 0.9-1.5 (m, 8H), 4.3 (t, J = 6.5 Hz, 2H), 7.0 (brs, NH), 8.9 (s, 1H, H-8); ^{13}C-NMR (DMSO- d_6) δ, (ppm): 12.8 (C16), 13.4 (C15), 22.1 (C12), 26.8 (C13), 28.0 (C14), 31.0 (C11), 78.4 (C5), 161.7 (C6), 163.5 (C4), 178.2 (C2); MS(m/z): 235 M^+, 150, 135.

General procedure to obtain *N*6-monoalkylthiouracil: 2.5 mmol (358 mg) of 6-amino-2- thiouracil and 2.5 mmol (430 mg or 695 mg respectively) of 4-nitrobenzyl chloride or 4-bromophenacyl bromide and 2.5 mmol (183 mg) of DMF were gently mixed, placed into a pyrex-glass open vessel and irradiated in a domestic microwave oven. When the irradiation was stopped, the final temperature was measured by introducing a glass thermometer into the reaction mixture, homogenizing it in order to obtain a temperature value representative of the whole mass. The mixture was extracted with the adequate solvents (3x10 mL). The extract was evaporated under vacuum, washed with acetone and filtered. Finally, they were recrystallized from ethanol.

*N*6-(4-Nitrobenzyl)amino-2-thiouracil (**3a**): mp: 186-187°C; νmax (KBr)/cm^{-1}: 3220, 2840, 1530, 1370; Anal. Calcd for $C_{11}H_{10}N_4O_3S$: C, 47.48; H, 3.62; N, 20.13. Found: C, 47.56; H, 3.77; N, 20.32.^{1}H-NMR (DMSO-d_6) δ, (ppm): 4.4 (s, 2H, CH_2), 5.6 (s, 1H, H-5), 7.5 (br s, NH-7), 7.7-8.2 (m, 4H, $C_6H_4NO_2$), 11.9 (br s, NH-1/NH-3); ^{13}C-NMR (DMSO-d_6) δ, (ppm): 32.9 (C8), 81.2 (C5), 123.5 (C11, C11´), 130.8 (C10,C10´), 145.9 (C12), 146.7 (C9), 155.1 (C6), 163.5 (C4), 174.5 (C2); MS (m/z): 278/279 (M^+), 144, 122.

*N*6-(4-Bromophenacyl)amino-2-thiouracil (**3b**): mp: 199-201°C; νmax (KBr)/cm^{-1}: 3310, 2810, 1824, 1560; Anal. Calcd for $C_{12}H_{10}N_3O_2BrS$: C, 42.24; H, 2.95; N, 12.31. Found: C, 42.35; H, 3.06; N, 12.41. ^{1}H-NMR (DMSO-d_6) δ, (ppm): 4.5 (s, 2H), 5.6 (s, 1H), 7.5 (br s, NH-7), 7.7 (d, J = 8.5 Hz, 2H), 8.0 (d, J = 8.4 Hz, 2H), 11.9 (br s, NH-1/ NH-3); ^{13}C-NMR (DMSO-d_6 δ, (ppm): 78.1 (C8), 81.0 (C5), 127.9 (C13), 130.4 (C12, C12´), 132.0 (C11, C11´), 134.5 (C10), 154.9 (C6), 163.2 (C4), 174.4 (C2), 192.0 (C9); MS (m/z): 341/342 (M^+), 308, 185.

General procedure to obtain *N*1-alkylthiouracil: 2.5 mmol (358 mg) of 6-amino-2-thiouracil, 2.5 mmol of alkylating agent, 2.5 mmol (183 mg) of DMF, 2.5 mmol (265 mg) of sodium carbonate and 5% (46 mg) of tetra-*n*-butylammonium iodide were gently mixed and placed into a pyrex-glass open vessel and irradiated in a domestic microwave oven. When the irradiation was stopped, the final temperature was measured by introducing a glass thermometer into the reaction mixture, homogenizing it in order to obtain a temperature value representative of the whole mass. The mixture was extracted with adequate solvents (3x10 mL). The extract was evaporated in vacuum, washed with ether, filtered, then recrystallized from ethanol.

*N*1-(4-Nitrobenzyl)amino-2-thiouracil (**4a**): mp: 201-202°C; νmax (KBr)/cm^{-1}: 3420, 3320, 3070, 1540, 1340; Anal. Calcd for $C_{11}H_{10}N_4O_3S$: C, 47.48; H, 3.62; N, 20.13. Found: C, 47.53; H, 3.71; N, 20.22. ^{1}H-NMR (DMSO-d_6) δ, (ppm): 4.4 (s, 1H), 4.9 (s, 2H), 6.4 (br s, NH_2), 7.7 (d, J = 8.7 Hz, 2H), 8.1 (d, J = 8.7 Hz, 2H), 11.9 (br s, NH); ^{13}C-NMR (DMSO-d_6) δ, (ppm): 32.3 (C8), 81.3 (C5), 123.1 (C11,C11'), 130.2 (C10, C10′), 146.2 (C12), 146.8 (C9), 162.7 (C6), 163.6 (C4), 175.5 (C2); MS (m/z): 278/279 (M^+), 143, 111.

*N*1-(4-Bromophenacyl)amino-2-thiouracil (**4b**): mp: 170-171°C; νmax (KBr)/cm^{-1}: 3310, 3170, 1680, 1411; Anal. Calcd for $C_{12}H_{10}N_3O_2BrS$: C, 42.24; H, 2.95; N, 12.31. Found: C, 42.37; H, 3.09; N, 12.44. ^{1}H-NMR (DMSO-d_6) δ, (ppm): 4.5 (s, 2H), 4.84 (s, 1H), 6.3 (br s, NH_2), 7.7 (d, J = 8.5 Hz, 2H), 7.9 (d, J = 8.5 Hz, 2H), 10.8 (br s, NH); ^{13}C-NMR (DMSO-d_6) δ, (ppm): 43.4 (C8), 82.4 (C5), 130.1 (C13), 130.4 (C12, C12′), 131.6 (C11, C11′), 163.4 (C10), 163.7 (C6), 163.8 (C4), 164.3 (C2), 177.0 (C9); MS (m/z): 341/342 (M^+), 185, 156, 110.
*N*1-(5-Bromopentyl)amino-2-thiouracil (**4c**): mp: 152-153°C; νmax (KBr)/cm^{-1}: 3320, 3220, 2720, 1560; Anal. Calcd for $C_9H_{14}N_3OBrS$: C, 36.99; H, 4.83; N, 14.38. Found: C, 37.11; H, 4.92; N, 14.50; ^{1}H-NMR (DMSO-d_6) δ, (ppm): 0.9-1.8 (m, 6H), 3.3 (t, J = 7.0 Hz, 2H), 4.5 (s, 1H), 4.8 (t, J = 6.7 Hz, 2H), 6.1 (br s, NH_2), 9.9 (br s, NH); ^{13}C-NMR (DMSO-d_6) δ, (ppm): 13.2 (C10), 22.8 (C12), 27.2 (C9), 28.3 (C11), 28.9 (C8), 81.6 (C5), 164.2 (C6), 166.5 (C4), 176.9 (C2).

*N*1-(Hexyl)amino-2-thiouracil (**4d**): mp: 165-167°C; Anal. Calcd for $C_{10}H_{17}N_3OS$: C, 43.31; H, 6.17; N, 15.15. Found: C, 43.46; H, 6.31; N, 15.27. ^{1}H-NMR (DMSO-d_6) δ, (ppm): 0.5-1.4 (m, 11H), 4.4 (s, 1H), 4.8 (t, J = 6.9 Hz, 2H), 6.1 (br s, NH_2), 9.7 (br s, NH); ^{13}C-NMR (DMSO-d_6) δ, (ppm): 13.8 (C13), 22.0 (C12), 28.1 (C9), 28.6 (C10), 28.9 (C11), 31.2 (C8), 78.6 (C5), 161.8 (C6), 163.8 (C4), 176.6 (C2).

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