New 6-Azauracil Derivatives

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Six new 6-azauracil derivatives have been obtained through the nucleophilic substitution of 5-bromo-6-azauracil with various aromatic amines and phenols. These compounds have been characterized by means of UV-VIS, IR and ^{1}H-NMR spectroscopy.

Keywords: 6-azauracil derivatives; 5-bromo-6-azauracil; substituted 1,2,4-triazine-3,5-dione

The interest shown toward 6-azauracil and its compounds resides in their biological properties, including antiviral, antimetabolite, anticarcinogenic properties and cell growth inhibitor character [1].

Recent investigations towards 3-derivatives of 8-aryl-2,6,7,8-tetrahydroimidazo[2,1-c][1,2,4]triazin-4(3H)-one have demonstrated the presence of antibacterial, antiviral [2] and antitumor properties [3].

In recent years, it has been shown that low molecular weight copper (II) complexes containing asymmetrical triazine ligands posses antiviral and anti-inflammatory properties. These properties arise from a N_2O_2 square – planar coordination around the Cu atom [4].

Our research has been aimed at obtaining some 6-azauracil based derivatives containing the necessary scaffolding for acting as ligands in Cu (II) complexes with antiviral properties. We have investigated the simple, yet powerful nucleophilic substitutions of 5-bromo-6-azauracil with corresponding aromatic amines and phenols in order to obtain the desired compounds.

Experimental part

Materials

The raw starting materials have been chloral hydrate and semicarbazide hydrochloride, used as purchased from Fluka, without further purification. Their reaction in aqueous media afforded glyoxylic acid semicarbazone **1** which yielded 6-azauracil **2** in basic medium, in accordance with the method previously described in [5]. 5-Bromo-6-azauracil **3** has been synthesized by direct bromination of 2 as described in [6]. Compounds **4 - 7** have been prepared by nucleophilic substitution of the bromine atom from 3 with an aromatic amine moiety, while compounds **8** and **9** have been obtained from phenols (fig. 1.).

Unless stated otherwise, all amines and phenols have been used without further purification, as purchased from *Sigma*-Aldrich.

Procedures

5-Bromo-6-azauracil (3)

2.5 g (0.0022 mol) 6-azauracil **3** were suspended in 30 mL water. 4.6 mL Br_2 (0.00545 mol) were added. The reaction mixture was stirred for 24h at room temperature. The precipitate was collected by suction, while the remaining solution was distilled. From the combined precipitates, 5-bromo-6-azauracil was obtained through recrystallized from 85 mL water.

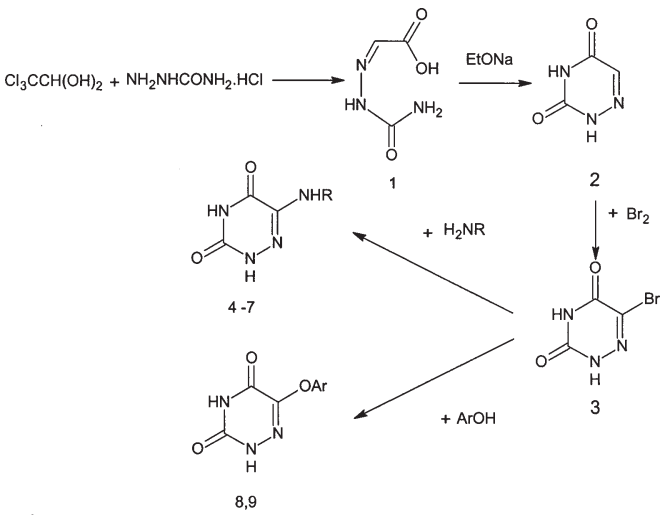

Fig.1. General synthetic route for the obtaining of 5-substituted-6-azauracil

3-[(3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazin-6-yl)amino]benzoic acid (4)

1.00 g (0.0052 mol) 5-bromo-6-azauracil and 1.80 g (0.0104 mol) 3-aminobenzoic acid chlorohydrate were added to a solution containing 0.62 g (0.0011 mol) KOH in 15 mL water. The mixture was heated at reflux for 24 h. The precipitate was collected by distillation and recrystallized from 15 mL water.

6-[(2-aminophenyl)amino]-1,2,4-triazine-3,5(2H,4H)-dione (5)

1.16 g (0.006 mol) 5-bromo-6-azauracil and 0.65 g (0.006 mol) 1,2-phenylenediamine were added to a solution containing 0.34 g (0.006 mol) KOH in 20 mL water. The solution was heated at reflux for 24 h. The precipitate was collected by suction and recrystallized from ethanol.

6-[(4-aminophenyl)amino]-1,2,4-triazine-3,5(2H,4H)-dione (6)

1.16 g (0.006 mol) 5-bromo-6-azauracil and 0.65 g (0.006 mol) 1,4-phenylenediamine were added to a solution containing 0.34 g (0.006 mol) KOH in 20 mL water. The solution was heated under reflux for 27 h. The precipitate is collected by suction and recrystallized from ethanol.

6,6'-(benzene-1,4-diyldiimino)bis(1,2,4-triazine-3,5(2H,4H)-dione) (7)

1.16 g (0.006 mol) 5-bromo-6-azauracil and 1.30 g (0.006 mol) 1,4-phenylenediamne were added in 20 mL water. The solution was heated under reflux for 24 h. The precipitate was collected by suction and recrystallized from ethanol.

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Compound	ϵ_{max} [L·mol^{-1}·cm^{-1}]	λ_{max} [nm]	Λ [nm]
3	5594	276	-
4	4788	320	
5	6146	277	-
6	3640	261	572
7	3420	259	568
8	4148	277	-
9	4354	240	286

Table 1
UV - VIS SPECTRA FOR THE 6-AZAURACIL DERIVATIVES

Compound	IR bands (cm^{-1})					
	νNH	νCH	νC=O, C=N	νC=C$_{arom}$	νCBr	νC-O-C
3	3257; 3173	-	1728;1686	1565	641	
4	3320 (wide)	3083	1684	1570;1551		
5	3257; 3163	3078	1684	1562		
6	3321; 3183	2993	1688	1599;1545		
7	3544; 3461; 3403; 3285	2922	1701	1609;1511		
8	3132 (wide)	2948	1680	1570;1453		1226
9	3371; 3188; 3124;	3055	1695	1606;1565		1267

Table 2
6-AZAURACIL DERIVATIVES IR SPECTRA PEAKS

3-[(3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazin-6-yl)oxy]benzaldehyde (8)

1.00 g (0.0052 mol) 5-bromo-6-azauracil and 0.64 g (0.0052 mol) 4-hydroxybenzaldehide were added to a solution containing 0.50 g (0.00175 mol) Na_2CO_3.10 H_2O in 10 mL water. The mixture was heated at reflux for 24 h. The precipitate was collected by suction and recrystallized from ethanol.

4-amino-3-[(3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazin-6-yl)oxy]benzene sulfonic acid (9)

1.92 g (0.01 mol) 5-bromo-6-azauracil and 3.78 g (0.02 mol) 3-amino-4-hydroxybenzenesulfonic acid were added to a solution containing 1.14 g (0.02 mol) KOH in 30 mL water. The solution was heated at reflux for 32 h. The excess water was removed by distillation and the product was collected and recrystallized from ethanol.

Characterization

The IR spectra have been recorded using a Bruker apparatus, endowed with an ATR device. The UV – VIS spectra have been recorded in EtOH, using a JASCO V550 spectrometer. The ^{1}H-NMR spectra were obtained in DMSO d6, at 300 MHz using a Varian Gemini-300 spectrometer. The melting points have been measured on a Boetius stage apparatus and are uncorrected.

Results and discussions

Six new compounds have been obtained from the substitution of 5-bromo-6-azauracil with various amines and phenols.

The substances obtained, as well as the intermediate **3** have been characterized by means of UV – VIS and IR spectra. The UV – VIS spectra and the corresponding molar extinction coefficient are presented in table 1. The IR spectra of the 6-azauracil derivatives are presented in table 2.

The formation of C-N bond for compounds **4** -**7** is indicated by the presence of additional N-H vibration peaks in the 3000 – 3500 cm^{-1} region of the IR spectra [7], as opposed to 5-bromo-6-azauracil (**3**).

Likewise, the formation of C-O-C bonds in compounds **8** and **9** is evidenced by the intense peaks in the 1200cm^{-1} region, corresponding to the aromatic C-O-C ether bond vibration.

For compounds **4** and **5**, the ^{1}H-NMR spectra were recorded and compared to predicted spectra using the method described in [8]. From the results presented in table 3 it can be concluded that the substances obtained correspond to their proposed formulae.

The formula for the compounds obtained and their respective yields are presented in table 4.

Compound	Predicted spectra (δ,ppm)	^{1}H-NMR spectra (δ,ppm)
4	8.443 (1H, s)	8.461 (1H, s)
	7.828 (1H, d)	7.855 (1H, d)
	7.550 (1H, d)	7.514 (2H, m)
	7.507 (1H, t)	
5	6.989 (1H, t)	7.590 (1H, dd)
	6.942 (1H, q)	7.530 (1H, q)
	6.672 (1H, t) 6.644 (1H, t)	7.22 (2H, m)

Table 3
^{1}H-NMR SPECTRA

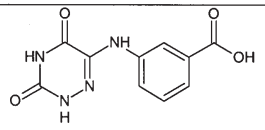
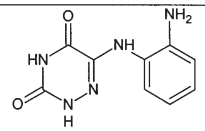
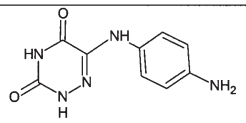
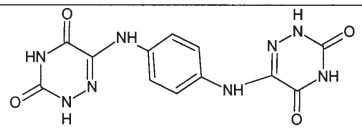
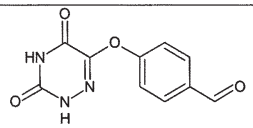
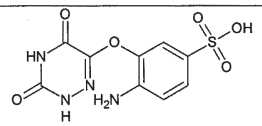
Compound	Proposed structure	m.p. [°C]	Yield [%]
4		215-217	54
5		> 300	35
6		> 300	51
7		> 300	32
8		> 300	25
9		> 300	52

Table 4
COMPOUNDS OBTAINED

Conclusions

Starting from 5-bromo-6-azauracil, six new 6-azauracil compounds have been obtained through nucleophilic substitution reactions with various amines and phenols.

The yields of the reactions cannot be explained solely by the nucleophilicity of the amines or phenols used as reactants.

These compounds have been characterized by means of UV – VIS and IR spectroscopy and in 2 cases by ^{1}H-NMR. From the spectral characterization it can be concluded that the nucleophilic substitution method is a viable synthetic route to obtaining new 5-substituted 6-azauracil derivatives.

Containing a 6-azauracil moiety, as well as sites capable to bind transition metals and thus to form complexes, the obtained derivatives might lead to compounds with interesting biological properties, such as antiviral, oxygen radical scavenging or anticarcinogenic properties.

The presence of reactive groups (COOH, NH_2, CHO) enables the aforementioned compounds to act as intermediates and as ligands for various transitional metals, potentially yielding compounds with biological properties.

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