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Synthesis of New 5-Acetyl(arylmethyliden)-4-thiazolidones

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ABSTRACT: *A new approach to the synthesis of new heterocyclic compounds with triazine and 4-thiazolidone fragments in one molecule is developed. The synthesis methods comprise [2+3]-cyclocondensation reactions essential in the preparative synthesis of 4-thiazolidone derivatives. The reactions of S,N-nucleophiles with C_2-cyclization agents for the synthesis of a number of biologically active 2-triazin-4-thiazolidones were investigated. The interaction of thiosemicarbazone of sym-triazine with derivatives of α-halogencarboxylic acids and maleic anhydride resulted in correspondent (2-[2-(4,6-dichloro-1,3,5-triazin-2-yl)hydrazino]-5-(3,4,5-R-p-phenyl-methyliden)-1,3-thiazol-4-ones obtained in the one-step synthesis.* © 2010 Wiley Periodicals, Inc. Heteroatom Chem 21:392–396, 2010; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.20631

INTRODUCTION

Considerable interest in the derivatives of 1,3,5-triazine as half products for the synthesis of substances with a wide spectrum of biological activity arises from the reactivity of the 2,4,6-trichloro-1,3,5-triazine molecule, where at certain reaction conditions all chlorine atoms could be substituted by identical or different substituents. The adducts of 1,3,5-triazine and 4-thiazolidone revealed potential antiinflammatory, antimicrobial, antiviral, cardiovascular, and trombolytic activity, indicating the significance of synthesis and investigation of new substances from the order of 1,3,5-triazine derivatives in the view of organic, combinatorial, and pharmaceutical chemistry.

From the pharmacological point of view, 2,4,6-trichloro-1,3,5-triazine is an object of outstanding interest, offering a possibility to combine several biologically active fragments in one molecule. The derivatives of *sym*-triazine revealed potential anticancer [1–4] and antimicrobial [4–9] activity, whereas aryl- and acetyl-substituted 4-thiazolidones are high-specific ligands to a number of cellular biotargets, predetermining antidiabetic [10,11], antitumor [12–15], antimicrobial [16,17], and other types of pharmacological activity. Aryl- and acetyl-substituted triazin-4-thiazolidones meet the criteria of "drug-similarity" for chemical structures according to Lipinskiy rules [18]. Therefore, such a unique opportunity to combine in one molecule pharmacophores with manifold activity provided by reactive triazin-4-thiazolidones opens potential for synthesis of new polyfunctional preparations.

RESULTS AND DISCUSSION

In this work, we describe the application of the Michael condensation reactions for the synthesis of new heterocyclic compounds with triazine and 4-thiazolidone heterocyclic fragments

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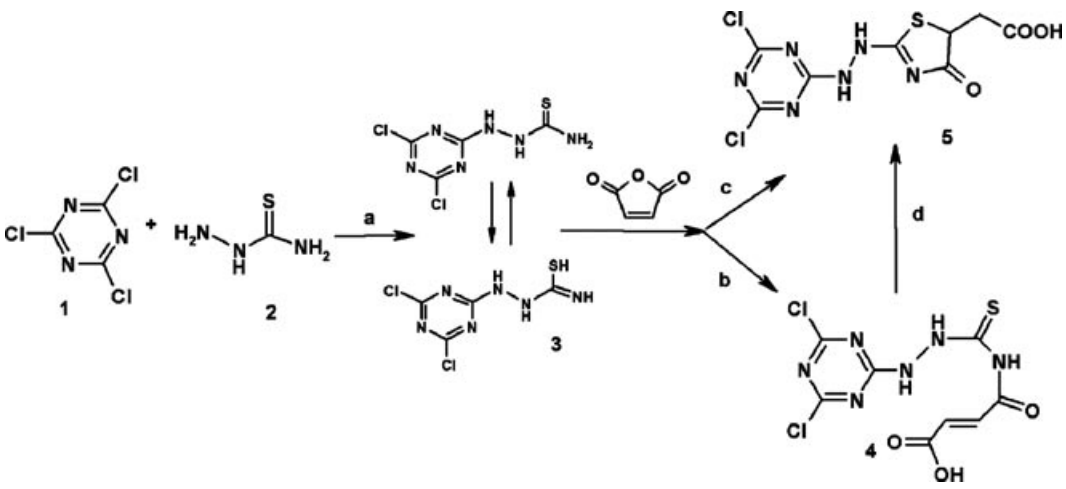


SCHEME 1 Interaction of 1-(4,6-dichloro-1,3,5-triazin-2-yl)thiosemicarbazide (**3**) with maleic anhydride.

combined in one molecule. The above-mentioned group of methods includes mainly reactions of [2+3]-cyclocondensation, which are preparatively the most essential in the synthesis of 4-thiazolidone derivatives including 2-triazin-5-acetyl(arylmethyliden)-4-thiazolidone. These synthetic approaches include an interaction of S,N-binucleophiles with different equivalents of bielectrophylic synthon $[C_2]^{2+}$. Particularly for the synthesis of several biologically active 2-triazin-4-thiazolidones, the interaction of thiosemicarbazone of *sym*-triazine with the derivatives of α-halogencarboxylic acids [19–21] and maleic anhydride [22] is used (Schemes 1 and 2). These schemes show that 1-(4,6-dichloro-1,3,5-triazin-2-yl)thiosemicarbazide **3** as the active S,N-binucleophil is a promising synthon for the synthesis of new heterocyclic compounds. 1-(4,6-Dichloro-1,3,5-triazin-2-yl)thiosemicarbazide **3** was obtained by nucleophilic substitution of one chlorine atom in 2,4,6-trichloro-1,3,5-triazine by thiosemicarbazide in acetonitrile as a solvent at -7°C in the presence of equimolar amount of $NaHCO_3$ (Scheme 1, way a).

The interaction of 1-(4,6-dichloro-1,3,5-triazin-2-yl)thiosemicarbazide **3** with maleic anhydride as a C_2-cyclization agent depending on the reaction conditions results in the formation of a carboxyl compound with the acyclic structure 4-({[2-(4,6-dichloro-1,3,5-triazin-2-yl)hydrazino] carbonothioyl}amino)-4- oxobut-2-enoic acid **4**, or a cyclization product {2-[2-(4,6-dichloro-1,3,5-triazin-2-yl) hydrazino]-4-oxo-4,5-dihydro-1, 3-thiazol-5-yl} acetic acid **5**.

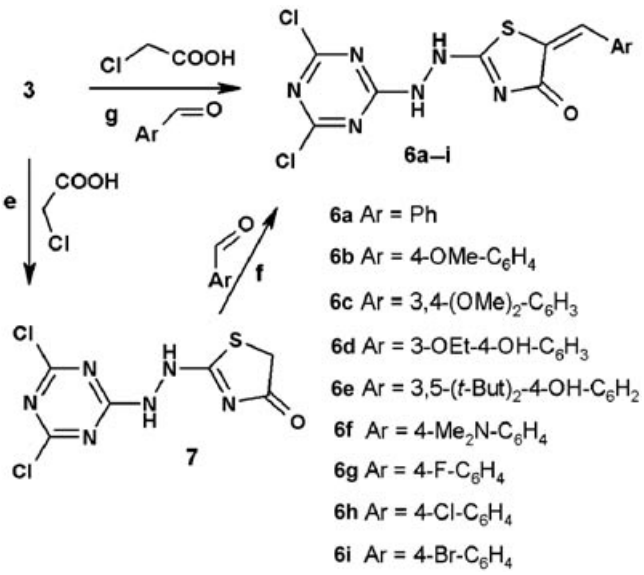
Acylation adduct 4-({[2-(4,6-dichloro-1,3,5-triazin-2-yl)hydrazino]carbonothioyl}amino)-4-oxobut-2-enoic acid **4** was synthesized in mild reaction conditions in DMF at room temperature for 12–18 h or at a temperature 45–55°C for 1 h (Scheme 1, way b).

The reaction of [3+2]-cyclocondensation of 1-(4,6-dichloro-1,3,5-triazin-2-yl)thiosemicarbazide **3** with maleic anhydride, resulting in a cyclic structure {2-[2-(4,6-dichloro-1,3,5-triazin-2-yl)hydrazino]-4-oxo-4,5-dihydro-1,3-thiazol-5-yl}acetic acid **5** was carried out in DMF at 100–110°C for 4 h (Scheme 1, way c).

The interaction of 1-(4,6-dichloro-1,3,5-triazin-2-yl)thiosemicarbazide **3** with maleic anhydride is a [2+3]-cyclocondensation reaction. It is known that thiourea occurs in thione and thiol tautomeric forms being active in the Michael reactions of S—H addition. The formation of product **4** with a linear structure in mild reaction conditions witnesses the progress of acylation with opening of anhydride cycle (Scheme 1, way b), whereas in harsh conditions it results in the product of cyclocondensation **5** (Scheme 1, way d). From these data, we can conclude that the [2+3]-cyclocondensation reaction between 1-(4,6-dichloro-1,3,5-triazin-2-yl)thiosemicarbazide **3** and maleic anhydride (Scheme 1, way c) passes through the stage of intermediate product **4** formation.

The interaction of 1-(4,6-dichloro-1,3,5-triazin-2-yl)thiosemicarbazide **3** with monochloroacetic acid occurs as [3+2]-cyclocondensation of S,N-binucleophiles with formation of corresponding 2-[2-(4,6-dichloro-1,3,5-triazin-2-yl)hydrazino]-1,3-thiazol-4-one **7**. A reaction was carried out in DMF with an equimolar amount of triethylamine at the temperature 100–110°C (Scheme 2, way e).

The product (Scheme 2, way e) 2-[2-(4,6-dichloro-1,3,5-triazin-2-yl)hydrazino]-1,3-thiazol-4-one **7** contains a methylene fragment active in



SCHEME 2 Synthesis of 5-arylmethyliden-2-[2-(4,6-dichloro-1,3,5-triazin-2-yl)hydrazino]-1,3-thiazol-4-ones (**6a–i**).

the Knoevenagel reaction and, therefore, is easily transformed in situ in arylmethyliden derivatives by addition of corresponding R-substituted aromatic aldehydes into the reaction mixture. A reaction was carried out also in DMF with the presence of triethylamine at the temperature 100–110°C, resulting in 5-arylmethyliden-2-[2-(4,6-dichloro-1,3,5-triazin-2-yl)hydrazino]-1,3-thiazol-4-ones **6a–i** (Scheme 2, way f).

The products **6a–i** were synthesized in an alternative way by the interaction of an initial 1-(4,6-dichloro-1,3,5-triazin-2-yl)thiosemicarbazide **3** with monochloroacetic acid and a number of aromatic aldehydes in one stage in DMF in the presence of double the amount of triethylamine at 100–110°C (Scheme 2, way g).

Therefore, new application of the [2+3]-cyclocondensation reaction of S,N-nucleophiles and C_2-cyclization agents for the synthesis a number of biologically active 2-triazin-4-thiazolidones using the interaction of thiosemicarbazone of *sym*-triazine with monochloroacetic acid and maleic anhydride was reported.

EXPERIMENTAL

Melting points were determined in open capillary tubes. Infrared (IR) spectrums were recorded on a Specord-80M spectrophotometer in potassium bromide pellets as described elsewhere. ^{1}H NMR spectra were recorded on a Varian VXR (300 MHz). The reaction progress was monitored by thin-layer chromatography on 0.2-mm silica gel (Silufol UV-254).

1-(4,6-Dichloro-1,3,5-triazin-2-yl)thiosemicarbazide **3**

To a suspension of 10 mmol of 2,4,6-trichloro-1,3,5-triazine in 15 mL of anhydrous acetonitrile, 10 mmol of thiosemicarbazide was added the and the mixture was stirred at temperature −7°C in the presence of $NaHCO_3$ for 1 h. The obtained precipitate was filtered and washed with cold water. Yield 71%, mp = 177°C. IR (KBr), cm^{-1}: 3200, 1650 (NH), 1450 (C=S), 1410, 1230, 820 (C=N triazine), 720 (C—Cl), 680 (C—SH).

4-({[2-(4,6-Dichloro-1,3,5-triazin-2-yl)hydrazino]carbonothioyl}amino)-4-oxobut-2-enoic Acid **4**

A mixture of 1-(4,6-dichloro-1,3,5-triazin-2-yl)thiosemicarbazide **3** (10 mmol) and maleic anhydride (10 mmol) in DMF (20 mL) was stirred at temperature 20–25°C for 14 h or 45–55°C for 1 h. The solid product formed was collected by filtration. Yield 57%, mp >250°C. IR (KBr), cm^{-1}: 3210, 1650 (NH), 1740, 1680 (C=O), 1640, 1600 (C=C), 1615 (—COOH), 1410, 1230, 820 (C=N triazine), 720 (C—Cl). ^{1}H NMR DMSO-d_6 (δ, ppm): 10.21 (s, 1H, COOH), 10.02 (s, 1H, NH), 9.48 (s, 1H, NH), 8.75 (s, 1H, NH), 6.95, 6.90 (dd, 2H, J = 15.2 Hz).

{2-[2-(4,6-Dichloro-1,3,5-triazin-2-yl)hydrazino]-4-oxo-4,5-dihydro-1,3-thiazol-5-yl}acetic Acid **5**

Way c. A mixture of 1-(4,6-dichloro-1,3,5-triazin-2-yl)thiosemicarbazide **3** (10 mmol) and maleic anhydride (10 mmol) in DMF (20 mL) was stirred at temperature 100–110°C for 4 h. The solid product formed was collected by filtration.

Way d. A mixture of 4-({[2-(4,6-dichloro-1,3,5-triazin-2-yl)hydrazino]carbonothioyl}amino)-4-oxobut-2-enoic acid **4** (10 mmol) in DMF (20 mL) was stirred at temperature 100–110°C for 3 h. The solid product formed was collected by filtration. Yield 73%, mp = 221°C. IR (KBr), cm^{-1}: 3200, 1650 (NH), 1740, 1690 (C=O), 1610 (–COOH), 1410, 1230, 820 (C=N triazine), 720 (C—Cl). ^{1}H NMR DMSO-d_6 (δ, ppm): 10.12 (s, 1H, COOH), 9.78 (s, 1H, NH), 8.85 (s, 1H, NH), 2.81 d, 2.98 d, 4.25 m (CH_2CH J_{AB} = 15.0 Hz, J_{AX} = 9.0 Hz, J_{BX} = 4.5 Hz).

2-[2-(4,6-Dichloro-1,3,5-triazin-2-yl)hydrazino]-1,3-thiazol-4-one **7**

A mixture of 1-(4,6-dichloro-1,3,5-triazin-2-yl)thiosemicarbazide **3** (10 mmol) and chloroacetic acid (10 mmol) in DMF (20 mL) was stirred at temperature 100–110°C for 3 h in the presence of a equimolar amount of triethylamine. The solid product formed was collected by filtration. Yield 76%, mp = 212°C. IR (KBr), cm^{-1}: 3200, 1650 (NH), 1740, 1690 (C=O), 1410, 1230, 820 (C=N triazine), 720 (C—Cl). ^1H NMR DMSO-d_6 (δ, ppm): 9.18 (s, 1H, NH), 8.67 (s, 1H, NH), 4.47 (s, 2H, CH_2).

General Methods of Synthesis of 5-Arylmethyliden-2-[2-(4,6-dichloro-1,3,5-triazin-2-yl)hydrazino]-1,3-thiazol-4-ones **6a–i**

Way f. A mixture of 2-[2-(4,6-dichloro-1,3,5-triazin-2-yl)hydrazino]-1,3-thiazol-4-one **7** (10 mmol) and aromatic aldehyde (12 mmol) in DMF (20 mL) was stirred at temperature 100–110°C for 4 h in the presence of an equimolar amount of triethylamine. The solid product formed was collected by filtration.

Way g. A mixture of 1-(4,6-dichloro-1,3,5-triazin-2-yl)thiosemicarbazide **3** (10 mmol), chloroacetic acid (10 mmol), and aromatic aldehyde (12 mmol) in DMF (20 mL) was stirred at temperature 100–110°C for 4–7 h in the presence of triethylamine (20 mmol). The solid product formed was collected by filtration.

2-[2-(4,6-Dichloro-1,3,5-triazin-2-yl)hydrazino]-5-benzylidene-1,3-thiazol-4-one **6a**. Yield 76%, mp = 187°C. IR (KBr), cm^{-1}: 3190, 1650 (NH), 1730, 1690 (C=O), 1410, 1220, 820 (C=N triazine), 720 (C—Cl). ^1H NMR DMSO-d_6 (δ, ppm): 9.24 (s, 1H, NH), 8.85 (s, 1H, NH), 7.65 (d, 2H, J = 8.6 Hz, arom.), 7.33 (t, 2H, arom.), 7.11 (t, 1H, arom.), 7.47 (s, 1H, CHAr).

2-[2-(4,6-Dichloro-1,3,5-triazin-2-yl)hydrazino]-5-(4-methoxybenzylidene)-1,3-thiazol-4-one **6b**. Yield 71%, mp = 198°C. IR (KBr), cm^{-1}: 3210, 1660 (NH), 1750, 1690 (C=O), 1410, 1230, 810 (C=N triazine), 710 (C—Cl). ^1H NMR DMSO-d_6 (δ, ppm): 9.18 (s, 1H, NH), 8.67 (s, 1H, NH), 7.15 (d, 2H, J = 8.2 Hz, arom.), 6.96 (d, 2H, J = 8.2 Hz, arom.), 7.40 (s, 1H, CHAr), 3.77 (s, 3H, OCH_3).

2-[2-(4,6-Dichloro-1,3,5-triazin-2-yl)hydrazino]-5-(3,4-(dimethoxy)benzylidene)-1,3-thiazol-4-one **6c**. Yield 73%, mp = 176°C. IR (KBr), cm^{-1}: 3220, 1670 (NH), 1730, 1690 (C=O), 1420, 1230, 820 (C=N triazine), 720 (C—Cl). ^1H NMR DMSO-d_6 (δ, ppm): 10.11 (s, 1H, NH), 8.77 (s, 1H, NH), 6.92 (d, 1H, J = 7.2 Hz, arom.), 6.83 (m, 2H, arom.), 3.76 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 7.41 (s, 1H, CHAr).

2-[2-(4,6-Dichloro-1,3,5-triazin-2-yl)hydrazino]-5-(3-ethoxy-4-hydroxybenzylidene)-1,3-thiazol-4-one **6d**. Yield 65%, mp = 211°C. IR (KBr), cm^{-1}: 3210, 1650 (NH), 1730, 1690 (C=O), 1410, 1230, 820 (C=N triazine), 710 (C—Cl). ^1H NMR DMSO-d_6 (δ, ppm): 10.17 (s, 1H, NH), 8.97 (s, 1H, NH), 8.86 (s, 1H, OH), 6.73 (d, 1H, J = 8.0 Hz, arom.), 6.71 (s, 1H, arom.), 6.63 (d, 1H, J = 8.0 Hz, arom.), 4.02 (m, 2H, CH_2CH_3), 5.45 (s, 1H, CHAr), 1.19 (t, 3H, CH_2CH_3).

2-[2-(4,6-Dichloro-1,3,5-triazin-2-yl)hydrazino]-5-(3,5-di-tert-butyl-4-hydroxybenzylidene)-1,3-thiazol-4-one **6e**. Yield 55%, mp = 157°C. IR (KBr), cm^{-1}: 3210, 1650 (NH), 1740, 1690 (C=O), 1410, 1230, 810 (C=N triazine), 720 (C—Cl). ^1H NMR DMSO-d_6 (δ, ppm): 10.01 (s, 1H, NH), 8.95 (s, 1H, NH), 8.06 (s, 1H, OH), 7.68 (s, 2H, arom.), 7.58 (s, 1H, CHAr), 1.42 (s, 18H, $C(CH_3)_3$).

2-[2-(4,6-Dichloro-1,3,5-triazin-2-yl)hydrazino]-5-(4-(dimethylamino)benzylidene)-1,3-thiazol-4-one **6f**. Yield 77%, mp = 182–184°C. IR (KBr), cm^{-1}: 3210, 1660 (NH), 1740, 1690 (C=O), 1410, 1210, 820 (C=N triazine), 720 (C—Cl). ^1H NMR DMSO-d_6 (δ, ppm):

TABLE 1 Elemental Analysis of Obtained Compounds

Compounds	*Formula*	*Calculated*	*Found*
3	$C_4H_4Cl_2N_6S$	C 20.10, N 35.15, S 13.41	C 20.24, N 35.03, S 13.25
4	$C_8H_6Cl_2N_6O_3S$	C 28.50, N 24.93, S 9.51	C 28.58, N 24.71, S 9.36
5	$C_8H_6Cl_2N_6O_3S$	C 28.50, N 24.93, S 9.51	C 28.46, N 24.82, S 9.47
6a	$C_{13}H_8Cl_2N_6OS$	C 42.52, N 22.89, S 8.73	C 42.73, N 22.69, S 8.88
6b	$C_{14}H_{10}Cl_2N_6O_2S$	C 42.33, N 21.16, S 8.07	C 42.19, N 21.32, S 8.01
6c	$C_{15}H_{12}Cl_2N_6O_3S$	C 42.17, N 19.67, S 7.50	C 42.03, N 19.86, S 7.39
6d	$C_{15}H_{12}Cl_2N_6O_3S$	C 42.17, N 19.67, S 7.50	C 42.31, N 19.76, S 7.36
6e	$C_{21}H_{24}Cl_2N_6O_3S$	C 50.91, N 16.96, S 6.47	C 50.72, N 16.81, S 6.55
6f	$C_{15}H_{13}Cl_2N_7OS$	C 43.91, N 23.90, S 7.82	C 43.99, N 23.73, S 7.64
6g	$C_{13}H_7Cl_2FN_6OS$	C 40.54, N 21.82, S 8.32	C 40.62, N 21.67, S 8.19
6h	$C_{13}H_7Cl_3N_6OS$	C 38.87, N 20.92, S 7.98	C 38.89, N 20.83, S 7.79
6i	$C_{13}H_7Cl_3BrN_6OS$	C 35.00, N 18.84, S 7.19	C 35.11, N 18.93, S 7.28
7	$C_6H_4Cl_2N_6OS$	C 25.82, N 30.11, S 11.49	C 25.74, N 30.29, S 11.62

10.19 (s, 1H, NH), 8.89 (s, 1H, NH), 7.17 (d, 2H, $J = 8.1$ Hz, arom.), 6.96 (d, 2H, $J = 8.1$ Hz, arom.), 7.51 (s, 1H, CHAr), 2.77 (s, 6H, $N(CH_3)_2$).

2-[2-(4,6-Dichloro-1,3,5-triazin-2-yl)hydrazino]-5-(4-fluorobenzylidene)-1,3-thiazol-4-one **6g**. Yield 78%, mp = 123–125°C. IR (KBr), cm^{-1}: 3195, 1655 (NH), 1730, 1690 (C=O), 1410, 1220, 820 (C=N triazine), 720 (C—Cl). ^{1}H NMR DMSO-d_6 (δ, ppm): 10.07 (s, 1H, NH), 8.54 (s, 1H, NH), 7.96 (t, 2H, $J = 8.5$ Hz, arom.), 7.36 (t, 2H, $J = 8.5$ Hz, arom.), 7.43 (s, 1H, CHAr).

2-[2-(4,6-Dichloro-1,3,5-triazin-2-yl)hydrazino]-5-(4-chlorobenzylidene)-1,3-thiazol-4-one **6h**. Yield 71%, mp = 126–128°C. IR (KBr), cm^{-1}: 3220, 1650 (NH), 1730, 1690 (C=O), 1410, 1230, 810 (C=N triazine), 720 (C—Cl) cm^{-1} ^{1}H NMR DMSO-d_6 (δ, ppm): 10.11 (s, 1H, NH), 8.71 (s, 1H, NH), 7.27 (d, 2H, $J = 8.7$ Hz, arom.), 6.92 (d, 2H, $J = 8.7$ Hz, arom.), 7.55 (s, 1H, CHAr).

2-[2-(4,6-Dichloro-1,3,5-triazin-2-yl)hydrazino]-5-(4-bromobenzylidene)-1,3-thiazol-4-one **6i**. Yield 67%, mp = 142–144°C. IR (KBr), cm^{-1}: 3200, 1660 (NH), 1740, 1670 (C=O), 1410, 1220, 820 (C=N triazine), 720 (C—Cl). ^{1}H NMR DMSO-d_6 (δ ppm): 10.13 (s, 1H, NH), 8.79 (s, 1H, NH), 7.22 (d, 2H, $J = 8.4$ Hz, arom.), 6.98 (d, 2H, $J = 8.4$ Hz, arom.), 7.50 (s, 1H, CHAr).

The data of elemental analysis of all obtained compounds are presented in Table 1.

REFERENCES

[1] Goldin, A.; Wolpert-Defilippes, M. K. Bull Cancer 1979, 66, 61–66.
[2] Foster, B. J.; Harding, B. J.; Leyland-Jones, B.; Hoth, D. Cancer Treatment Rev 1986, 13, 197–217.
[3] Menicagli, R.; Samaritani, S.; Signore, G.; Vaglini, F; Dalla Via, L. J Med Chem 2004, 47, 4649–4652.
[4] Saczewski, F.; Bulakowska, A.; Bednarski, P.; Grunert, R. Eur J Med Chem 2006, 41, 219–225.
[5] Kreutzberger, A.; Richter, B. Archiv Pharm 1983, 316, 213–217.
[6] Arenas, J. E.; Cload, S. T.; Fleming, E. S. WO Patent 99/36410, 1999.
[7] Ghaib, A.; Menager, S.; Verite, P.; Lafont, O. Farmaco 2002, 57, 109–116.
[8] Srinivas, K.; Srinivas, U.; Bhanuprakash, K.; Harakishore, K.; Murthy, U. S. N.; Jayathirtha Rao, V. Eur J Med Chem 2006, 41, 1240–1246.
[9] Zhou, Y.; Sun, Z.; Froelich, J. M.; Hermann, T.; Wall, D. Bioorg Med Chem Lett 2006, 16, 5451–5456.
[10] Bailey, C. J. Trends Pharmacol Sci 2000, 21, 259–264.
[11] Reginato, M. J.; Lazar, M. A. Trends Endocrinol Metab 1999, 10, 9–13.
[12] Liu, W. J.; Bulgaru, A.; Haigents, M.; Perez-Soler, R.; Mani, S. Curr Med Chem 2003, 3, 217–223.
[13] Degterev, A.; Lugovskoy, A.; Cardone, M.; Mulley, B.; Wagner, G.; Mitchison, T.; Yuan, J. Nature Cell Biol 2001, 3, 173–182.
[14] Murthy Madiraju, S. R.; Shore Gordon, C.; Johnson Roy, A.; Steenaart Nancy, A. Patent US2003119894 USA A61K31/404, 2003.
[15] Cutshall, N. S.; O'Day, C.; Preshdo, M. Bioorg Med Chem Lett 2005, 15, 3374–3379.
[16] Andres, C. J.; Bronson, J. J.; D'Andrea, S. V.; Deshpande, M. S.; Falk, P. J.; Grant-Young, K. A.; Harte, W. E.; Ho, H. T.; Misco, P. F.; Robertson, J. G.; Stock, D.; Sun, Y.; Walsh, A. W. Bioorg Med Chem Lett 2000, 10, 715–717.
[17] El Zoeiby, A.; Sanschagrin, F.; Levesque, R. C. Mol Microbiol 2003, 47, 1–12.
[18] Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. Adv Drug Delivery Rev 1997, 23, 3–25.
[19] Ottana, R.; Maccari, R.; Barreca, M. L.; Bruno, G.; Rotondo, A.; Rossi, A.; Chiricosta, G.; Di Paola, R.; Sautebin, L.; Cuzzocrea, S.; Vigorita, M. G. Bioorg Med Chem 2005, 13, 4243–4252.
[20] Ram, V. J.; Pandey, H. N.; Singh, S. N. J. Indian Chem Soc 1972, 49, 181–183.
[21] Joshi, C. K.; Pathak, V. N.; Chaturvedi, R. K. Pharmazie 1986, 41, 475–478.
[22] Tenirio, R. P.; Carvalho, C. S.; Pessanha, C. S.; De Lima, J. G.; De Faria, A. R.; Alves, A. J.; De Melo, E. J. T.; Goes, A. J. S. Bioorg Med Chem Lett 2005, 15, 2575–2578.