Chemistry of Heterocyclic Compounds, Vol. 47, No. 3, June, 2011 (Russian Original Vol. 47, No. 3, March, 2011)

A NEW ROUTE FOR THE SYNTHESIS OF SUBSTITUTED 5-AMINO-4-CYANOIMIDAZOL-2-ONES – PRECURSORS FOR THE PREPARATION OF 3,6,7,9-TETRAHYDRO-8H-PURIN-8-ONES DERIVATIVES

S. A. Chumachenko[1], O. V. Shablykin[1], A. P. Kozachenko, T. V. Osadchuk, and V. S. Brovarets[1]*

5-Alkyl(aryl)amino-4-cyanoimidazol-2-ones were obtained on the basis of 2-alkoxycarbonylamino-3,3-dichloroacrylonitriles. They were then used for the synthesis of derivatives of 3,6,7,9-tetrahydro-8H-purin-8-ones.

Keywords: 5-alkyl(aryl)amino-2-oxoimidazole-4-thioamides, 5-alkyl(aryl)amino-4-cyanoimidazol-2-ones, 2-alkoxycarbonylamino-3,3-dichloroacrylonitriles, 3,6,7,9-tetrahydro-8H-purin-8-ones, triethyl orthoformate, heterocyclization.

It was shown previously [1,2] that compounds **1** [3-6] react readily with primary amines to form the aminals **2**.

Using method [2] we have obtained a series of compounds **2** containing aliphatic amine groups (**2a-d**, **i**), aromatic amine groups (**2e**,**f**), and also cyclic amines (**2g**,**h**), with the object of synthesizing heterocyclic compounds based on them.

Thus, we first showed that heating the aminals **2a-f** in dilute alkali was accompanied by intramolecular cyclization into the imidazol-2-ones **3a-f** (cf. [7-9]. The possible mechanism, shown below, consists of consecutive reactions: deprotonation (**A**) and cyclization (**A→B→C**) into an imidazolone with loss of a molecule of an alcohol. Further protonation of the intermediate **C** leads to products **3**.

For successful conversion of reagents **2a-f** to compounds **3a-f** the leaving group (RO) should possess notable nucleophilicity, therefore introduction of the benzyloxycarbonyl derivative **2i** (R = Bn) should facilitate cyclization. However, apparently because of the steric effect of the benzyl group, the cyclization did not occur and compound **2i** decomposed under the reaction conditions. Similar instability under alkaline conditions occurred with the cyclic aminals **2g**,**h**.

The proposed approach gives the possibility of preparing a series of imidazolones **3a-f**. Compound **3a** had been synthesized previously by other methods [10-12]. The presence of some functional groups in the

* To whom correspondence should be addressed, e-mail: brovarets@bpci.kiev.ua

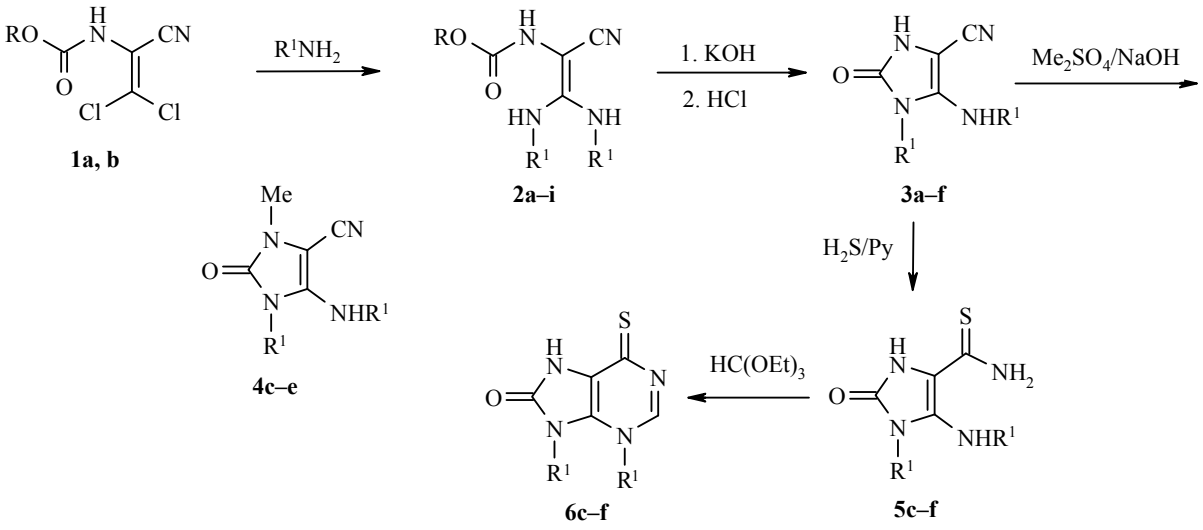
[1]Institute of Bioorganic Chemistry and Petrochemistry, National Academy of Sciences of Ukraine, 1 Murmanskaya St., Kyiv 02660, Ukraine.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, 410-416, March, 2011. Original article submitted October 5, 2010

TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %				mp, ºC*	Yield, %
		C	H	N	S		
2a	$C_7H_{12}N_4O_2$	45.70 / 45.65	6.62 / 6.57	30.43 / 30.42	—	160-161	35
2b	$C_{11}H_{20}N_4O_2$	54.87 / 54.98	8.31 / 8.39	23.26 / 23.31	—	113-115	40
2c	$C_{19}H_{20}N_4O_2$	67.80 / 67.84	5.87 / 5.99	16.59 / 16.65	—	152-153	73
2d	$C_{21}H_{24}N_4O_2$	69.18 / 69.21	6.53 / 6.64	15.29 / 15.37	—	136-137	65
2e	$C_{17}H_{16}N_4O_2$	66.18 / 66.22	5.18 / 5.23	18.12 / 18.17	—	150-152	75
2f	$C_{19}H_{20}N_4O_2$	67.80 / 67.84	5.89 / 5.99	16.59 / 16.65	—	181-183	75
2g	$C_7H_{10}N_4O_2$	46.02 / 46.15	5.50 / 5.53	30.71 / 30.75	—	193-195	40
2h	$C_8H_{12}N_4O_2$	48.88 / 48.97	6.08 / 6.16	28.47 / 28.55	—	177-179	38
2i	$C_{25}H_{24}N_4O_2$	72.73 / 72.80	5.78 / 5.86	13.49 / 13.58	—	108-110	64
3a	$C_6H_8N_4O$	47.28 / 47.36	5.23 / 5.30	36.77 / 36.82	—	240-241	45
3b	$C_{10}H_{16}N_4O$	57.63 / 57.67	7.68 / 7.74	26.85 / 26.90	—	145-147	50
3c	$C_{18}H_{16}N_4O$	71.00 / 71.04	5.23 / 5.30	18.37 / 18.41	—	137-138	85
3d	$C_{20}H_{20}N_4O$	72.21 / 72.27	6.01 / 6.06	16.78 / 16.85	—	135-136	80
3e	$C_{16}H_{12}N_4O$	69.47 / 69.55	4.31 / 4.38	20.22 / 20.28	—	113-115	85
3f	$C_{18}H_{16}N_4O$	71.01 / 71.04	5.21 / 5.30	18.36 / 18.41	—	186-189	75
4c	$C_{19}H_{18}N_4O$	71.62 / 71.68	5.63 / 5.70	17.53 / 17.16	—	118-119	78
4d	$C_{21}H_{22}N_4O$	72.78 / 72.81	6.32 / 6.40	16.11 / 16.17	—	90-92	74
4e	$C_{17}H_{14}N_4O$	70.31 / 70.33	4.82 / 4.86	19.26 / 19.30	—	185-186	75
5c	$C_{18}H_{18}N_4OS$	63.81 / 63.88	5.29 / 5.36	16.48 / 16.55	9.49 / 9.47	173-175 (dec.)	56
5d	$C_{20}H_{22}N_4OS$	65.56 / 65.55	6.04 / 6.05	15.26 / 15.29	8.77 / 8.75	120-122 (dec.)	25
5e	$C_{16}H_{14}N_4OS$	61.87 / 61.92	4.51 / 4.55	17.98 / 18.05	10.27 / 10.33	130-131 (dec.)	45
5f	$C_{18}H_{18}N_4OS$	63.81 / 63.88	5.29 / 5.36	16.48 / 16.55	9.49 / 9.47	140-142 (dec.)	45
6c	$C_{19}H_{16}N_4OS$	65.44 / 65.50	4.57 / 4.63	16.02 / 16.08	9.25 / 9.20	236-237	80
6d	$C_{21}H_{20}N_4OS$	66.94 / 67.00	5.31 / 5.35	14.81 / 14.88	8.57 / 8.52	120-122	75
6e	$C_{17}H_{12}N_4OS$	63.68 / 63.73	3.71 / 3.78	17.42 / 17.49	10.10 / 10.01	282-283	82
6f	$C_{19}H_{16}N_4OS$	65.44 / 65.50	4.57 / 4.63	16.02 / 16.08	9.25 / 9.20	310-312	85

*Recrystallization solvents: ethyl acetate (compounds **2a-i**), benzene (compounds **3a-f**, **4c-e**), acetone (compounds **6c-f**). Compounds **5c-f** were used for further conversions without further purification. The mp of compounds **2a**,**c**,**d** corresponded to those cited in [2], and compound **3a** to that in [10-12].

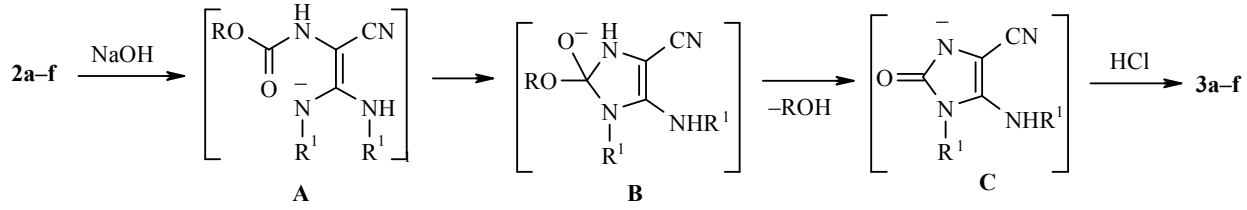


1a, 2a–h R = Me, **1b, 2i** R = Bn; **2,3 a** R^1 = Me, **b** R^1 = Pr; **2c,i, 3c–6c** R^1 = Bn, **2, 3–6 d** R^1 = $PhCH_2CH_2$, **2, 3–6 e** R^1 = Ph, **2, 3, 5**, **6 f** R^1 = 4-MeC_6H_4; **2g** R^1+R^1 = $(CH_2)_2$, **2h** R^1+R^1 = $(CH_2)_3$

TABLE 2. IR and Mass Spectra of Synthesized Compounds

Compound	IR spectrum, ν, cm^{-1}	Mass spectrum, *m/z* $[M]^+$
2a	1747* (C=O), 2189 (CN), 3007-3327 (NH)	184
2b	1716 (C=O), 2147 (CN), 2963-3378 (NH)	240
2c	1716 (C=O), 2147 (CN), 2949-3342 (NH)	336
2d	1710 (C=O), 2175 (CN), 3022-3360 (NH)	364
2e	1726* (C=O), 2182 (CN), 3289-3376 (NH)	308
2f	1697 (C=O), 2183 (CN), 3024-3327 (NH)	336
2g	1730 (C=O), 2149 (CN), 3292-3411 (NH)	182
2h	1702* (C=O), 2142 (CN), 3254-3551 (NH)	196
2i	1719* (C=O), 2154 (CN), 3029-3350 (NH)	412
3a	1749* (C=O), 2190 (CN), 3005-3326 (NH)	152
3b	1721* (C=O), 2187 (CN), 2967-3330 (NH)	208
3c	1692* (C=O), 2198 (CN), 3201-3325 (NH)	304
3d	1710* (C=O), 2175 (CN), 3025-3360 (NH)	332
3e	1694* (C=O), 2206 (CN), 3279-3383 (NH)	276
3f	1704 (C=O), 2203 (CN), 3158-3397 (NH)	304
4c	1711 (C=O), 2186 (CN), 3070-3565 (NH)	318
4d	1707 (C=O), 2171 (CN), 3274-3505 (NH)	346
4e	1702 (C=O), 2211 (CN), 3036-3218 (NH)	290
5c	1719* (C=O), 3215-3583 (NH, NH_2)	338
5d	1721* (C=O), 3184-3553 (NH, NH_2)	366
5e	1719* (C=O), 3202-3353 (NH, NH_2)	310
5f	1695* (C=O), 3146-3380 (NH, NH_2)	338
6c	1710 (C=O), 3134 (NH)	348
6d	1715 (C=O), 3120 (NH)	376
6e	1721 (C=O), 3130 (NH)	320
6f	1717 (C=O), 3030 (NH)	348

* Band with shoulder.



structure of the 5-alkyl(aryl)amino-4-cyanoimidazol-2-ones prepared (**3a-f**) allows their use as starting materials for the synthesis of other examples of the imidazole series. Thus, in aqueous alkali compounds **3c-e** were alkylated with dimethyl sulfate to form 1-alkyl(aryl)-3-methylimidazol-2-ones **4c-e.** The regioselective alkylation of imidazolones is confirmed by a number of literature analogs [13-15] and also by ^{1}H NMR spectral data: the signals of the protons of the NMe group are found in the 3.03-3.23 ppm region. The thioamides **5c-f** were formed by the reactions of compounds **3c-f** with hydrogen sulfide. We used the presence of the vicinal thioamide and alkylamino groups in compounds **5c-f** to obtain the purine analogs **6c-f**, which are potential biologically active compounds (cf. [16-18]).

Preliminary investigations of compounds **3** as inhibitors of furin showed that they had inhibitory effects in the experimental conditions at 28.0-31.7%, which shows that these compounds have prospects for the creation of modern medicinal preparations [19-22]. It should be noted that the N-methyl derivatives **4** show practically no inhibition of furin under analogous conditions.

EXPERIMENTAL

IR spectra of KBr disks were recorded with a Vertx-70 spectrometer. ^{1}H NMR spectra were obtained on a Varian-300 (300 MHz) instrument with TMS as the internal standard. Chromato-mass spectra were obtained using liquid chromato-mass spectrometer system based on an Agilent 1100 Series high efficiency liquid chromatograph equipped with a diode matrix with an Agilent LC/MSD SL mass-selective detector. Parameters of the chromato-mass analysis: Zorbax SB-C18 column, 1.8μm, 4.6×15 mm (PN 821975-932); solvents: A – acetonitrile–water, 95:5, 0.1% trifluoroacetic acid, B – 0.1% aqueous trifluoroacetic acid, flow of eluent 3 ml/min, injection volume 1 μl; UV detectors – 215, 254, 285 nm; method of ionization – chemical ionization at atmospheric pressure (APCI), scanning range *m/z* 80-1000. Melting points were measured with a Fisher-Johns apparatus.

2-Alkyloxycarbonylamino-3,3-di[alkyl(aryl)amino]acrylonitriles 2a-i. To a suspension of compound **1a,b** (0.05 mol) in tetrahydrofuran (100 ml), triethylamine (0.11 mol) was added with stirring and cooling (10-15°C), followed by the corresponding amine (0.11 mol). The mixture was stirred for 12 h, the solvent was evaporated in vacuum, the precipitate was washed with water and purified by recrystallization.

1-Alkyl(aryl)-5-alkyl(aryl)amino-2-oxo-2,3-dihydro-1H-imidazole-4-carbonitriles 3a-f. Potassium hydroxide (0.015 mol) in water (2 ml) was added to a suspension of one of compounds **2a-f** (0.005 mol) in ethanol (10 ml) and the mixture was boiled for 10 min. The solution was cooled and water (5 ml) and 10% hydrochloric acid (5.5 ml) were added. The precipitate was filtered off, washed with water and purified by recrystallization.

1-Alkyl(aryl)-5-alkyl(aryl)amino-3-methyl-2-oxo-2,3-dihydro-1H-imidazole-4-carbonitriles 4c-e. Dimethyl sulfate (0.015 mol) was added dropwise with stirring to a solution of one of the compounds **3c-e** (0.005 mol) in 5% aqueous sodium hydroxide solution (15 ml), the reaction mixture was stirred for a further 4 h at 20-25°C, the precipitate formed was filtered off, washed with water and purified by recrystallization.

1-Alkyl(aryl)-5-alkyl(aryl)amino-2-oxo-2,3-dihydro-1H-imidazole-4-thioamides 5c-f. One of compounds **3c-f** (0.005 mol) was dissolved in a mixture of pyridine (10 ml) and triethylamine (1ml). A rapid flow

TABLE 3. ^{1}H NMR Spectra of Synthesized Compounds

Com-pound	Chemical shifts (DMSO-d_6), δ, ppm (J, Hz)
2a	2.83 (3H, s, CH_3); 3.05 (3H, s, CH_3); 3.34 (3H, s, CH_3); 6.07 (2H, br. s, 2NH); 7.81 (1H, br. s, NH)
2b	0.74-0.85 (6H, m, $2CH_3$); 1.35-1.60 (4H, m, $2CH_2$); 2.85-2.92 (2H, m, CH_2); 3.05-3.16 (2H, m, CH_2); 3.54 (3H, s, CH_3); 5.40-5.60 (2H, br. s, 2NH); 7.55 (1H, s, NH)
2c	3.55 (3H, s, CH_3); 4.27 (2H, d, J = 5.9, CH_2); 4.32 (2H, d, J = 5.9, CH_2); 6.23 (1H, br. s, NH); 6.33 (1H, br. s, NH); 7.08-7.32 (10H, m, H arom); 7.72 (1H, s, NH)
2d	2.63 (2H, m, CH_2); 2.82 (2H, m, CH_2); 3.15-3.25 (2H, m, CH_2); 3.40-3.52 (2H, m, CH_2); 3.56 (3H, s, CH_3); 5.61 (1H, br. s, NH); 5.77 (1H, br. s, NH); 10.07-10.21 (10H, m, H arom); 7.61 (1H, s, NH)
2e	3.50 (3H, s, CH_3); 6.95-7.22 (10H, m, H arom); 8.03 (1H, s, NH); 8.57 (1H, s, NH); 8.72 (1H, s, NH)
2f	2.18 (6H, s, $2CH_3$); 3.57 (3H, s, CH_3); 6.92-7.05 (8H, m, H arom); 7.95 (1H, s, NH); 8.43 (1H, s, NH); 8.49 (1H, s, NH)
2g	3.37-3.49 (4H, m, $2CH_2$); 3.55 (3H, s, CH_3); 6.48 (1H, br. s, NH); 6.64 (1H, br. s, NH); 7.42 (1H, s, NH)
2h	1.73 (2H, m, CH_2); 3.07-3.17 (4H, m, $2CH_2$); 3.55 (3H, s, CH_3); 6.23 (1H, br. s, NH); 6.42 (1H, br. s, NH); 7.32 (1H, s, NH)
2i	4.18 (2H, d, J = 5.4, CH_2); 4.28 (2H, d, J = 4.7, CH_2); 5.05 (2H, s, CH_2); 6.25 (1H, br. s, NH); 7.11 (1H, br. s, NH); 7.21-7.33 (15H, m, H arom); 7.82 (1H, s, NH)
3a	2.87 (3H, d, J = 3.5, CH_3); 2.97 (3H, s, CH_3); 6.52 (1H, br. s, NH); 9.77 (1H, s, NH)
3b	0.85-0.92 (6H, m, $2CH_3$); 1.50-1.60 (4H, m, $2CH_2$); 3.10-3.16 (2H, m, CH_2); 3.43-3.47 (2H, m, CH_2); 6.46 (1H, br. s, NH); 9.72 (1H, s, NH)
3c	4.36 (2H, d, J = 4.4, CH_2); 4.83 (2H, s, CH_2); 7.25-7.38 (10H, m, H arom); 7.43 (1H, br. s, NH); 10.02 (1H, s, NH)
3d	2.73 (2H, m, CH_2); 2.85 (2H, m, CH_2); 3.39 (2H, m, CH_2); 3.74 (2H, m, CH_2); 6.72 (1H, br. s, NH); 7.27-7.43 (10H, m, H arom); 9.90 (1H, s, NH)
3e	6.65-7.58 (10H, m, H arom); 8.30 (1H, s, NH); 11.02 (1H, s, NH)
3f	2.18 (3H, s, CH_3); 2.31 (3H, s, CH_3); 6.77 and 6.98 (4H, two d, J = 7.5, C_6H_4); 7.23 (4H, s, C_6H_4); 8.08 (1H, s, NH); 10.88 (1H, s, NH)
4c	3.07 (3H, s, CH_3); 4.45 (2H, d, J = 6.1, CH_2); 4.92 (2H, s, CH_2); 7.23-7.52 (10H, m, H arom); 8.35 (1H, br. s, NH)
4d	2.73 (2H, m, CH_2); 2.88 (2H, t, J = 7.2, CH_2); 3.03 (3H, s, CH_3); 3.39 (2H, m, CH_2); 3.75 (2H, t, J = 7.2, CH_2); 7.91 (1H, s, NH); 7.25-7.33 (10H, m, H arom)
4e	3.23 (3H, s, CH_3); 6.75-7.47 (10H, m, H arom); 8.38 (1H, s, NH)
5c	4.37 (2H, d, J = 6.1, CH_2); 4.95 (2H, s, CH_2); 7.23-7.33 (10H, m, H arom); 7.46 (1H, br. s, NH); 7.78 (1H, br. s, NH); 9.83 (1H, br. s, NH); 10.15 (1H, br. s, NH)
5d	2.76 (2H, m, CH_2); 2.91 (2H, t, J = 6.9, CH_2); 3.42-3.49 (2H, m, CH_2); 3.75 (2H, t, J = 6.9, CH_2); 7.09-7.51 (10H, m, H arom); 7.53 (1H, br. s, NH); 7.83 (1H, br. s, NH); 9.86 (1H, br. s, NH); 10.22 (1H, br. s, NH)
5e	9.02-9.62 (10H, m, H arom); 7.95 (1H, br. s, NH); 8.87 (1H, br. s, NH); 10.13 (1H, br. s, NH); 10.42 (1H, br. s, NH)
5f	2.09 (3H, s, CH_3); 2.19 (3H, s, CH_3); 6.63 and 6.82 (4H, two d, J = 6.5, C_6H_4); 7.04 and 7.15 (4H, two d, J = 6.0, C_6H_4); 7.93 (1H, br. s, NH); 8.82 (1H, br. s, NH); 10.18 (1H, br. s, NH); 10.28 (1H, br. s, NH)
6c	4.83 (2H, s, CH_2); 5.43 (2H, s, CH_2); 6.96-7.42 (10H, m, H arom); 8.23 (1H, s, NH); 11.73 (1H, s, CH)
6d	2.94 (2H, t, J = 7.4, CH_2); 3.18 (2H, t, J = 7.1, CH_2); 4.08 (2H, t, J = 7.4, CH_2); 4.35 (2H, t, J = 7.1, CH_2); 6.85-7.40 (10H, m, H arom); 7.84 (1H, s, NH); 11.43 (1H, s, CH)
6e	7.08-7.40 (10H, m, H arom); 8.23 (1H, s, NH); 11.63 (1H, s, CH)
6f	2.20 (6H, s, $2CH_3$); 6.88 (4H, s, C_6H_4); 6.92 and 7.14 (4H, two d, J = 7.5, C_6H_4); 8.16 (1H, s, NH); 11.57 (1H, s, CH)

of hydrogen sulfide was passed through this solution for 1 h, it was stirred for a further 2 h at 20-25°C, water (50 ml) was added, the precipitate was filtered off, and compounds **5c-f** were used in further reactions without additional purification.

3,9-Dialkyl(aryl)-6-thioxo-3,6,7,9-tetrahydro-8H-purin-8-ones 6c-f. A solution of the corresponding imidazolone **5c-f** in ethyl orthoformate (15 ml) was boiled for 4 h, the precipitate formed was filtered off, washed with ether, and recrystallized.

REFERENCES

1. O. Diels and A. Gukassianz, *Ber.,* **43**, 3317 (1910).
2. B. S. Drach, E. P. Sviridov, and T. Ya. Lavrenyuk, *Zh. Org. Khim.,* **10**, 1271 (1974).
3. O. Diels and J. Seib, *Ber.,* **42**, 4068 (1909).
4. B. S. Drach, E. P. Sviridov, A. A. Kisilenko, and A. V. Kirsanov, *Zh. Org. Khim.,* **9**, 1818 (1973).
5. V. S. Brovarets, S. G. Pil'o, A. N. Chernega, E. A. Romanenko, and B. S. Drach, *Zh. Obshch. Khim,* **69**, 1646 (1999).
6. J. Perronnet and A. Teche, *J. Chem. Res. (S)*, 44 (1977).
7. T. Kovac, M. Oklobdzija. G. Comisso, E. Decorte, and T. Fajdiga, *J. Heterocycl. Chem.,* **20**, 1339 (1983).
8. V. K. Agrawal, S. Sharma, and R. N. Iyer, *Indian J. Chem.,* **20B**, 398 (1981).
9. K. Kubo, Y. Kohara, E. Imamiya, Y. Sugiura, and Y. Inada, *J. Med. Chem.,* **36**, 2182 (1993).
10. T. Itaya and T. Harada, *Tetrahedron Lett.,* **23**, 2203 (1982).
11. T. Itaya and T. Harada*, Chem. Pharm. Bull.,* **38**, 2971 (1990).
12. T. Itaya, T. Kanai, M. Iwata, and M. Azuma, *Chem. Pharm. Bull.,* **45**, 75 (1997).
13. M. Bianchi, A. Butti, S. Rossi, F. Barzaghi, and V. Marcaria, *Eur. J. Org. Chem.,* **18**, 501 (1983).
14. N. N. Smolyar, Kh. Ya. Lopatinskaya, A. B. Vasilechko, D. A. Lomov, and Yu. M. Yutilov, *Russ. J. Org. Chem.,* **43**, 417 (2007).
15. J. P. Beck, A. G. Arvanitis, M. A. Curry, J. T. Rescinito, and L. W. Fitzgerald, *Bioorg. Med. Chem. Lett.,* **9**, 967 (1999).
16. M. Rinaldi, P. Pecorari, L. Constantino, A. Provvisionato, M. Malagoli, and C. Cermelli, *Farmaco,* **47**, 1315 (1992).
17. D. J. K. Crawford, J. L. Maddocks, D. N. Jones, and P. Szawlowski, *J. Med. Chem.,* **39**, 2690 (1996).
18. K. Kazaoka, H. Sajiki, and K. Hirota, *Chem. Pharm. Bull.,* **51**, 608 (2003).
19. K. Nakayama, *Biochem. J.,* **327**, 625 (1997).
20. F. Bergeron, R. Leduc, and R. Day, *J. Mol. Endocrin.,* **24**, 1 (2000).
21. G. Thomas, *Nat. Rev. Mol. Cell. Biol.,* **3**, 753 (2002).
22. V. K. Kibirev, T. V. Osadchuk, and Yu. L. Radavskii, *Ukr. Biokhim., Zh.,* **79**, 5 (2007).