DOI 10.1007/s10593-017-2098-5

Chemistry of Heterocyclic Compounds **2017**, *53*(5), 604–607

Synthesis of 3-arylamino-6-phenyl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine derivatives as potential bioactive molecules

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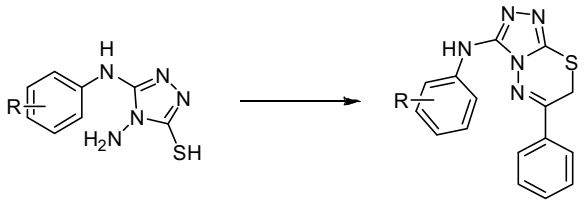
Published in Khimiya Geterotsiklicheskikh Soedinenii, 2017, *53*(5), 604–607

Submitted June 29, 2016
Accepted after revision April 1, 2017



4-Amino-3-arylamino-5-mercapto-1,2,4-triazoles have been used as synthons for the synthesis of fused ring system of 3-arylamino-6-phenyl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines. The reaction in high yield produces compounds with bridgehead nitrogen and two separate hydrazine units in the molecule making them potential candidates for possessing various biological activities.

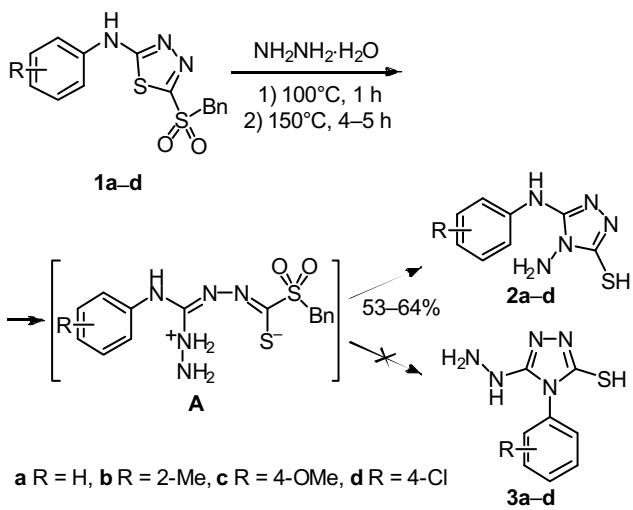
Keywords: 4-amino-3-arylamino-5-mercapto-1,2,4-triazoles, 3-arylamino-6-phenyl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines, (2-arylamino-1,3,4-thiadiazol-5-yl)(benzyl)sulfones.

In the last few decades, the chemistry of N-bridgehead heterocycles and their fused derivatives have received significant attention owing to their structural and biological characteristics. The presence of thiol unit in such compounds in general induces excellent bactericidal and anti-inflammatory activity.[1] In addition, hydrazine moiety has been considered as an essential structural unit in many pharmacophores.[2] 1,2,4-Triazole nucleus has been incorporated into diverse therapeutically vital drug candidates possessing various types of biological activity including H1/H2 histamine receptor blocking, cholinesterase inhibitory, CNS stimulating, antianxiety, anti-inflammatory, sedative, antimicrobial,[3,4] antileishmanial, antitubercular,[5] and antiviral[6] activities. Drugs containing the 1,2,4-triazole moiety, e.g., triazolam,[7] alprazolam,[8] etizolam,[9] and furacrylin[10] have entered pharmaceutical market. Due to the presence of both triazole and thiadiazine rings, triazolothiadiazines are known to exhibit a wide gamut of biological properties.[11]

5-Substituted 4-amino-3-mercapto-1,2,4-triazoles have attracted the attention of many researchers due to the presence of reactive groups at positions 3 and 4 of the triazole ring, as they can serve as building blocks for synthesis of large number of heterocyclic compounds which have wide range of biological activities.[12–14]

4-Amino-3-anilino-4*H*-1,2,4-triazole-5-thiol (**2a**) was reported in 1968 by Kurzer et al.[15] 4-Amino-3-arylamino-5-mercapto-1,2,4-triazoles **2a**–**d** were synthesized by the hydrazinolysis of *N*-aryl-5-(benzylsulfonyl)-1,3,4-thiadiazol-2-amines **1a**–**d**. According to that report, hydrazinolysis of compounds **1a**–**d** could result in the formation of two alternative products, namely, 4-amino-3-arylamino-4*H*-1,2,4-triazole-5-thiols **2a**–**d** and 4-aryl-3-hydrazinyl-4*H*-1,2,4-triazole-3-thiols **3a**–**d** (Scheme 1). Several compounds having 5-substituted 4-amino-3-mercapto-1,2,4-

Scheme 1



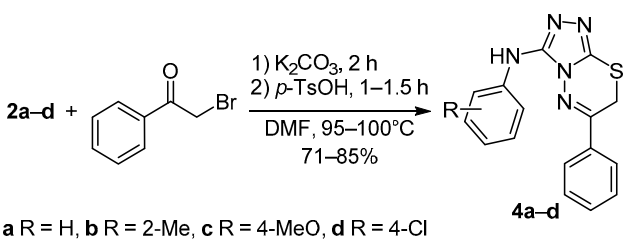
triazole unit have been used as a building blocks for formation of [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines derivatives. Surprisingly, 4-aryl-3-hydrazinyl-4*H*-1,2,4-triazole-3-thiols, though have similar structural features, have not been used for preparation of triazolothiadiazine derivatives. When the reaction of 5-(benzylsulfonyl)-*N*-phenyl-1,3,4-thiadiazol-2-amine (**1a**) and hydrazine hydrate was carried out as reported,[15] we could isolate only one product (Scheme 1), and the melting point of the compound conformed to that which was reported for compound **2a** by Kurzer.[15] Compound **3a** was not formed in the reaction.

Kurzer has proposed an open-chain intermediate **A** (Scheme 1), which further cyclizes to afford compounds **2a**–**d** and **3a**–**d**. We support this hypothesis and are convinced that the same intermediate must be responsible for the formation of compounds **2a**–**d** in our experiments, too. From the two possible nucleophilic nitrogens, $NHNH_2$ and ArNH, the hydrazine nitrogen, being the more nucleophilic one, participates in the ring closure preferentially with elimination of $BnSO_2H$ which results in the formation of compounds **2a**–**d**. In difference to the literature method, we have used a large excess of hydrazine for the reaction, which appears to be the primary reason for the selective formation of compounds **2a**–**d** over isomeric compounds **3a**–**d**.

The structures of compounds **2a**–**d** were confirmed by analytical and spectral data. Although these compounds were reported earlier,[15] their characterization was based on IR spectra and elemental analysis. We have unambiguously characterized compounds **2a**–**d**. Apart from the satisfactory ^{1}H and ^{13}C NMR spectra, the electron impact mass spectrum exhibited the expected $[M]^+$ peaks, and a significant daughter ion fragment at *m*/*z* 118 for compound **2a** which indicated presence of the fragment Ph–NH–C=N as a part of molecule **2a**. Analogous peaks were observed in the mass spectra of compounds **2b**–**d**. The mass spectrum of compound **2a** also gave major ion peaks at *m*/*z* 161, 104, 92, 77, and 51. This combination of mass spectral data confirmed that the compound isolated as the sole product was 4-amino-5-anilino-4*H*-1,2,4-triazole-5-thiol (**2a**).

Compounds **2a**–**d** were reacted further with α-bromoacetophenone for the synthesis of *N*-aryl-6-phenyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-amine **4a**–**d** (Scheme 2). All the reactions proceeded with satisfactory yields. The products were characterized on the basis of ^{1}H and ^{13}C NMR spectra, mass spectra, and elemental analysis. ^{13}C DEPT experiments confirmed the presence of one methylene (7-CH_2) group in compounds **4a**–**d** by means of a negative phase ^{13}C signal at 61.2–64.4 ppm.

Scheme 2



Based on the earlier reported bioactivities of 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazine derivatives, it is reasonable to expect the new compounds of this class, reported in the present work, to exhibit good bioactivities. The compounds have been adequately characterized. Thus, this work has resulted into establishing yet another route to 1,2,4-triazolo-[3,4-*b*][1,3,4]thiadiazines with possibility to introduce diverse heterocyclic substituents.

Experimental

IR spectra were obtained in KBr pellets on a PerkinElmer Frontier Optica FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra of compounds **2a**–**d**, **4a**–**d** were recorded on a Bruker Avance II-300 spectrometer (300 and 75 MHz, respectively) in $CDCl_3$+DMSO-d_6 using TMS as internal standard. ^{13}C NMR and DEPT-135 spectra of compound **4a** were recorded on a Bruker Avance 200 spectrometer (50 MHz) and those of compounds **4b**–**d** – on a Jeol ECX 400 spectrometer (100 MHz) in $CDCl_3$+DMSO-d_6 using TMS as internal standard. The ^{13}C NMR signals were assigned using DEPT-135 experiment. Mass spectra were recorded on a GC-MSQP-1000 spectrometer using electron impact ionization with direct sample introduction (70 eV). Elemental analyses were carried out on a Carlo Erba EA-1108 elemental analyzer. Monitoring of the course of reactions and purity of the compounds obtained was carried out by TLC on silica gel plates (eluents petroleum ether – $CHCl_3$ or petroleum ether – AcOEt in various proportions). Melting points were taken on a Lab-Hosp melting point apparatus. Compounds **2a**–**d** were synthesized according to the literature procedure.[15] Other chemicals were purchased and used without any further purification.

Synthesis of 4-amino-3-arylamino-4*H*-1,2,4-triazole-5-thiols 2a–d (General method).[15] A mixture of compound **1a**–**d** (10.06 mmol) and hydrazine hydrate (80%, 20 ml, 320 mmol) was taken into 50-ml round-bottom flask. The reaction mixture was refluxed initially for 1 h at 100°C. Then the temperature was increased gradually up to 150°C, and the refluxing continued for 4–5 h. The course of reaction was monitored by TLC. On completion of reaction, the mixture was poured onto crushed ice and concd HCl was added dropwise until the pH of the mixture reached 8. The colorless precipitate obtained was filtered off and air-dried.

4-Amino-5-anilino-4*H*-1,2,4-triazole-5-thiol (2a). Yield 53%, mp 202–204°C (mp 203–205°C[15]). IR spectrum, ν, cm^{-1}: 3339, 3317, 2957, 1621. ^{1}H NMR spectrum, δ, ppm: 4.03 (2H, s, NH_2); 6.82–7.50 (5H, m, H Ar); 8.12 (1H, s, NH); 12.82 (1H, s, SH). ^{13}C NMR spectrum, δ, ppm: 117.3; 121.5; 128.8; 139.2; 148.2. Mass spectrum, *m*/*z* (I_{rel}, %): 207 $[M]^+$ (100), 161 (15), 135 (27), 118 $[Ph–NH–C=N]^+$ (58), 104 (22), 92 (28), 77 $[C_6H_5]^+$ (100), 51 (34). Found, %: C 46.26; H 4.29; N 33.86; S 15.59. $C_8H_9N_5S$. Calculated, %: C 46.36; H 4.38; N 33.79; S 15.47.

4-Amino-5-(2-methylphenyl)amino-4*H*-1,2,4-triazole-5-thiol (2b). Yield 53%, mp 185–187°C. IR spectrum, ν, cm^{-1}: 3376, 3341, 2949, 1637, 1599. ^{1}H NMR spectrum, δ, ppm: 2.22 (3H, s, CH_3); 5.18 (2H, s, NH_2); 6.83–7.08 (4H, m, H Ar'); 7.81 (1H, s, NH); 12.82 (1H, s, SH). ^{13}C NMR spectrum,

δ, ppm: 17.3 (CH_3); 117.6; 122.2; 126.9; 130.3; 136.7; 148.1; 164.0. Mass spectrum, *m*/*z* (I_{rel}, %): 221 $[M]^+$ (100), 190 (18), 175 (22), 149 (11), 132 $[CH_3C_6H_4–NH–C=N]^+$ (24), 118 (27), 91(57), 65 (22). Found, %: C 48.97; H 4.95; N 31.53; S 14.55. $C_9H_{11}N_5S$. Calculated, %: C 48.85; H 5.01; N 31.65; S 14.49.

4-Amino-5-(4-methoxyphenyl)amino-4*H*-1,2,4-triazole-5-thiol (2c). Yield 63%, mp 177–179°C. IR spectrum, ν, cm^{-1}: 3320, 3129, 2963, 1626. ^1H NMR spectrum, δ, ppm: 3.67 (3H, s, OCH_3); 5.12 (2H, s, NH_2); 6.71–7.40 (4H, m, H Ar); 7.78 (1H, s, NH); 12.73 (1H, s, SH). ^{13}C NMR spectrum, δ, ppm: 55.4 (OCH_3); 114.1; 118.9; 134.1; 148.5; 154.5. Mass spectrum, *m*/*z* (I_{rel}, %): 237 $[M]^+$ (100), 191 (8), 165 (12), 148 $[CH_3OC_6H_4–NH–C=N]^+$ (24), 134 (28), 107 (16), 92 (20), 60 (10). Found, %: C 46.68; H 4.72; N 29.58; S 13.40. $C_9H_{11}N_5SO$. Calculated, %: C 46.56; H 4.67; N 29.51; S 13.51.

4-Amino-5-(4-chlorophenyl)amino-4*H*-1,2,4-triazole-5-thiol (2d). Yield 64%, mp 201–203°C. IR spectrum, ν, cm^{-1}: 3352, 3316, 3047, 1634. ^1H NMR spectrum, δ, ppm: 4.13 (2H, s, NH_2); 7.11–7.53 (4H, m, H Ar); 8.48 (1H, s, NH); 12.85 (1H, s, SH). ^{13}C NMR spectrum, δ, ppm: 118.8; 125.8; 128.6; 138.2; 148.1. Mass spectrum, *m*/*z* (I_{rel}, %): 241 $[M]^+$ (100), 191 (14), 165 (28), 152 $[ClC_6H_4–NH–C=N]^+$ (52), 134 (24), 105 (40), 92 (54), 60 (16). Found, %: C 39.60; H 3.43; N 28.95; S 13.35. $C_8H_8ClN_5S$. Calculated, %: C 39.75; H 3.34; N 28.97; S 13.27.

Synthesis of *N*-aryl-6-phenyl-7*H*-[1,2,4]triazolo[3,4-*b*]-[1,3,4]thiadiazin-3-amines 4a–d (General method). A mixture of compound **2a**–**d** (1.44 mmol) and K_2CO_3 (0.199 g, 1.44 mmol) was taken into 25-ml round-bottom flask, and dry DMF (5 ml) was added to it. An equimolar quantity of α-bromoacetophenone (0.286 g, 1.44 mmol) was added to the reaction mixture. The flask was protected with freshly prepared calcium chloride guard-tube. The reaction mixture was kept on water bath at 95–100°C for 2 h, then a pinch of toluene-4-sulfonic acid was added, and reaction mixture was stirred for another 1–1.5 h at the same temperature. After the completion of the reaction, crushed ice was added to it. On trituration, a solid precipitated which was filtered, air-dried, and recrystallized from ethanol.

***N*,6-Diphenyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-amine (4a)**. Yield 85%, mp 237–240°C. IR spectrum, ν, cm^{-1}: 3335, 2919, 2849, 1686. ^1H NMR spectrum, δ, ppm: 5.33 (2H, s, CH_2); 6.88–7.39 (10H, m, H Ar); 9.75 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 60.2 (CH_2); 117.1; 122.1; 125.4; 127.3; 127.6; 127.8; 129.8; 138.2; 153.8; 167.8. ^{13}C DEPT-135 spectrum, δ, ppm: 118.1 (2CH Ar); 123.2 (CH Ar); 128.3 (2CH Ar); 128.6 (CH Ar); 128.8 (2CH Ar); 130.9 (2CH Ar); and it showed the negative signal of methylene group (C-7, CH_2) at 61.2 ppm. Mass spectrum, *m*/*z* (I_{rel}, %): 307 $[M]^+$ (100), 275 (18), 230 (12), 203 (40), 118 $[C_6H_5NHCN]^+$ (50), 104 (45), 91 (12), 77 $[C_6H_5]^+$ (100), 51 (32). Found, % : C 62.63; H 4.22; N 22.85; S 10.30. $C_{16}H_{13}N_5S$. Calculated, %: C 62.52; H 4.26; N 22.78; S 10.44.

***N*-(2-Methylphenyl)-6-phenyl-7*H*-[1,2,4]triazolo[3,4-*b*]-[1,3,4]thiadiazin-3-amine (4b)**. Yield 71%, mp 83–85°C. IR spectrum, ν, cm^{-1}: 3375, 3059, 2920. ^1H NMR spectrum, δ, ppm: 2.41 (3H, s, CH_3); 4.33 (2H, s, CH_2); 7.10–7.41 (9H, m, H Ar); 8.92 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 16.1 (CH_3); 59.5 (CH_2); 121.0; 124.0; 125.1; 125.3; 126.7; 127.0; 129.1; 129.2; 129.4; 136.4; 153.1; 170.1. ^{13}C DEPT-135 spectrum, δ, ppm: 18.2 (CH_3); 123.1 (CH Ar); 126.2 (CH Ar); 127.2 (CH Ar); 128.9 (2CH Ar); 129.2 (CH Ar); 131.3 (CH Ar); 131.6 (2CH Ar); and it showed the negative signal of methylene group (C-7, CH_2) at 61.6 ppm. Mass spectrum, *m*/*z* (I_{rel}, %): 321 $[M]^+$ (90), 289 (18), 217 (42), 132 (40), 118 $[C_6H_5NHCN]^+$ (20), 105 (100), 91 (32), 77 $[C_6H_5]^+$ (90), 51 (28). Found, %: C 63.41; H 4.79; N 21.90; S 9.90. $C_{17}H_{15}N_5S$. Calculated, %: C 63.53; H 4.70; N 21.79; S 9.98.

***N*-(4-Methoxyphenyl)-6-phenyl-7*H*-[1,2,4]triazolo[3,4-*b*]-[1,3,4]thiadiazin-3-amine (4c)**. Yield 76%, mp 113–115°C. IR spectrum (KBr), ν, cm^{-1}: 3387, 3059, 2928, 1601. ^1H NMR spectrum, δ, ppm: 3.69 (3H, s, OCH_3); 4.27 (2H, s, CH_2); 6.74–7.36 (9H, m, H Ar); 9.76 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 53.7 (OCH_3); 60.4 (CH_2); 112.5; 117.8; 125.9; 126.9; 127.4; 132.4; 135.1; 149.5; 153.2; 164.4. ^{13}C DEPT-135 spectrum, δ, ppm: 55.5 (OCH_3); 114.4 (2CH Ar), 119.7 (2CH Ar); 127.8 (CH Ar); 128.7 (2CH Ar); 129.2 (2CH Ar); and it showed the negative signal of methylene group (C-7, CH_2) at 64.4 ppm. Mass spectrum, *m*/*z* (I_{rel}, %): 337 $[M]^+$ (100), 318 (60), 305 (32), 233 (32), 148 (90), 133 (50), 105 (26), 77 $[C_6H_5]^+$ (52), 51 (18). Found, %: C 60.61; H 4.35; N 20.70; S 9.60. $C_{17}H_{15}N_5SO$. Calculated, %: C 60.52; H 4.48; N 20.76; S 9.50.

***N*-(4-Chlorophenyl)-6-phenyl-7*H*-[1,2,4]triazolo[3,4-*b*]-[1,3,4]thiadiazin-3-amine (4d)**. Yield 78%, mp 125–127°C. IR spectrum, ν, cm^{-1}: 3395, 3059, 2924, 1598. ^1H NMR spectrum, δ, ppm: 4.67 (2H, s, CH_2); 7.13–7.69 (9H, m, H Ar); 10.80 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 59.7 (CH_2); 117.7; 125.2; 126.9; 127.0; 127.2; 127.3; 128.9; 129.6; 154.2; 166.8. ^{13}C DEPT-135 spectrum, δ, ppm: 120.0 (2CH Ar); 128.8 (CH Ar); 128.9 (2CH Ar); 129.1 (2CH Ar); 131.5 (2CH Ar); and it showed the negative signal of methylene group (C-7, CH_2) at 61.6 ppm. Mass spectrum, *m*/*z* (I_{rel}, %): 343 $[M(^{37}Cl)]^+$ (33), 341 $[M(^{35}Cl)]^+$ (100), 309 (20), 237 (30), 152 (20), 117 (12), 105 (22), 77 $[C_6H_5]^+$ (32), 51 (12). Found, %: C 56.30; H 3.50; N 20.55; S 9.28. $C_{16}H_{12}ClN_5S$. Calculated, %: C 56.22; H 3.54; N 20.49; S 9.38.

References

1. (a) Maddila, S.; Pagadala, R.; Jonnalagadda, S. B. *Lett. Org. Chem*. **2013**, *10*, 693. (b) Holla, B. S.; Poorjary, N. K.; Rao, S. B.; Shivananda, M. K. *Eur. J. Med. Chem*. **2002**, 37, 511.
2. Koçyiğit-Kaymakçıoğlu, B.; Oruç, E.; Unsalan, S.; Kandemirli, F.; Shvets, N.; Rollas, S.; Dimoglo, A. *Eur. J. Med. Chem.* **2006**, *41*, 1253.
3. (a) Birnkammer, T.; Spickenreither, A.; Brunskole, I.; Lopuch, M.; Kagermeier, N.; Bernhardt, G.; Dove, S.; Seifert, R.; Elz, S.; Buschauer, A. *J. Med. Chem.* **2012**, *55*, 1147. (b) Heindel, N. D.; Reid, J. R. *J. Heterocycl. Chem.* **1980**, *17*, 1087.
4. (a) Demirbaş, N.; Uğuruoğlu, R.; Demirbaş, A. *Bioorg. Med. Chem.* **2002**, *10*, 3717. (b) Shivarama Holla, B.;

Sooryanayarana Rao, B.; Sarojini, B. K.; Akberali, P. M.; Sucheta Kumari, N. *Eur. J. Med. Chem.* **2006**, *41*, 657.
5. Shiradkar, M. R.; Murahari, K. K.; Gangadasu, H. R.; Suresh, T.; Kalyan, C. A.; Panchal, D.; Kaur, R.; Burange, P.; Ghogare, J.; Mokale, V.; Raut, M. *Bioorg. Med. Chem.* **2007**, *15*, 3997.
6. Al-Soud, Y. A.; Al-Dweri, M. N.; Al-Masoudi, N. A. *Farmaco* **2004**, *59*, 775.
7. Brucato, A.; Coppola, A.; Gianguzza, S.; Provenzano, P. M. *Bull. Soc. Ital. Biol. Sper.* **1978**, *54*, 1051.
8. Coffen, D. L.; Fryer, R. I. US Patent 3849434.
9. Shiroki, M.; Tahara, T.; Araki, K. JP Patent 50100096; *Chem. Abstr.* **1976**, *84*, 59588k.
10. Povelitsa, F. D.; Gural, A. G. *Antibiotiki (Moscow)* **1973**, *18*, 71; *Chem. Abstr.* **1973**, *78*, 93044.
11. (a) Nanjunda Swamy, S..; Basappa, B. S.; Prabhuswamy, B.; Doreswamy, B. H.; Shashidhara Prasad, J.; Rangappa, K. S. *Eur. J. Med. Chem.* **2006**, *41*, 531. (b) Mathew, V.; Keshavayya, J.; Vaidya, V. P. *Eur. J. Med. Chem.* **2006**, *41*, 1048.
12. (a) Yanchenko, V. A.; Demchenko, A. M.; Lozinskii, M. O. *Chem. Heterocycl. Compd.* **2004**, *40*, 516. [*Khim. Geterotsikl. Soedin.* **2004**, 614.] (b) Özil, M.; Bodur, O.; Ülker, S.; Kahveci, B. *Chem. Heterocycl. Compd.* **2015**, *51*, 88. [*Khim. Geterotsikl. Soedin.* **2015**, *51*, 88.] (c) Dilanyan, E. R.; Hovsepyan, T. R.; Melik-Ohanjanyan, R. G. *Chem. Heterocycl. Compd.* **2008**, *44*, 1395. [*Khim. Geterotsikl. Soedin.* **2008**, 1712.]
13. Elwahy, A. H.; Abbas, A. A.; Ibrahim, Y. A. *J. Chem. Res., Synop.* **1996**, 182.
14. (a) Turan-Zitouni, G.; Kaplancikli, Z. A.; Erol, K.; Kiliç, F. S. *Farmaco* **1999**, *54*, 218. (b) Kritsanida, M.; Mouroutsou, A.; Marakos, P.; Pouli, N. Papakonstantinou-Garoufalias, S.; Pannecouque, C.; Witvrouw, M.; De Clercq, E. *Farmaco* **2002**, 57, 253.
15. Kurzer, F.; Wilkinson, M. *J. Chem. Soc. C* **1968**, 2099.