# Benzimidazoles and related heterocycles
## 10.* A novel acid-catalyzed rearrangement in the system 3-(α-aminobenzyl)quinoxalin-2(1*H*)-one—ethyl acetoacetate as a simple and efficient method for synthesizing 2-(pyrrol-3-yl)benzimidazoles

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A reaction of 3-(α-aminobenzyl)quinoxalin-2(1*H*)-one with ethyl acetoacetate in boiling acetic acid is accompanied by contraction of the pyrazine ring. A rearrangement involving the fragment C(2)—C(3)—C($NH_2$)Ph of the quinoxaline system and the fragment C(2)—C(3) of ethyl acetoacetate yields 2-(4-ethoxycarbonyl-5-methyl-2-phenylpyrrol-3-yl)benzimidazole. Possible pathways of this reaction are considered.

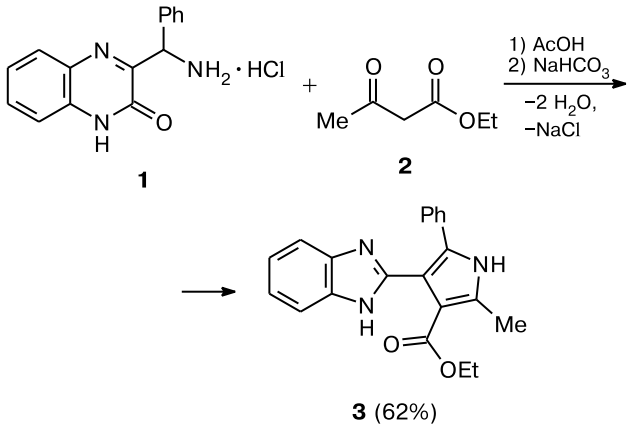
**Key words:** 3-(α-aminobenzyl)quinoxalin-2(1*H*)-one, ethyl acetoacetate, acid-catalyzed rearrangement, spiro[pyrroline-3,2′-quinoxalin]-3′(4′*H*)-one, 2-(pyrrol-3-yl)benzimidazole, X-ray diffraction analysis.

The benzimidazole system is found in many physiologically active compounds, including vitamin $B_{12}$,[2] antiviral[3,4] and antitumor agents,[5—8] drugs used in veterinary medicine,[9—12] and fungicides.[13] Two classic methods most commonly employed for the synthesis of the benzimidazole system are the Phillips—Ladenburg synthesis from diaminobenzenes and carboxylic acid derivatives and the Weidenhagen reaction of *ortho*-phenylenediamine and its derivatives with aldehydes.[14—16] However, the scope of these methods is limited by low yields of the target products and the impossibility of introducing the benzimidazole fragment into various heterocyclic systems. Hetarylbenzimidazoles can be obtained by the classic methods *via* introduction of either a hetaryl fragment into the benzimidazole system or a benzimidazole fragment into a desired heterocyclic system, which must be preceded by development of methods for the synthesis of the heterocyclic system. This results in lowered yields of the target products.

In the present work, we propose a simple and efficient route to 2-(pyrrol-3-yl)benzimidazoles *via* a novel rearrangement occurring in the system ethyl acetoacetate—3-(α-aminobenzyl)quinoxalin-2(1*H*)-one (**1**).[17]

A reaction of quinoxalin-2(1*H*)-one hydrochloride **1** with ethyl acetoacetate (**2**) in boiling acetic acid for 15 h gave 2-(pyrrol-3-yl)benzimidazole **3** in 62% yield (Scheme 1). Its molecular formula was determined from elemental analysis data; its structure was proved by IR and $^1$H NMR spectroscopy and X-ray diffraction.

**Scheme 1**




The formation of the benzimidazole system was confirmed by the $^1$H NMR spectrum of the reaction product: the signals for the protons of the phenylene fragment resonate, owing to benzimidazole tautomerism, as symmetrical multiplets of the AA′XX′ system[1,18] at δ 7.55—7.57 and 7.79—7.81 (rather than as multiplet signals of the ABCD system as for the protons of the phenylene ring in quinoxaline derivatives[19—20]). In addition, the spectrum shows multiplets for the phenyl protons at δ 7.30—7.33

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and 7.35—7.38, a triplet and a quartet for the protons of the ethoxy group at δ 0.87 and 4.02 ($^3J$ = 7.2 Hz), respectively, and a singlet for the methyl protons at δ 2.62.

According to X-ray diffraction data, benzimidazole **3** crystallizes with a solvate methanol molecule in a ratio of 1 : 1 to form triclinic crystals (space group *P*-1). The molecular structure of compound **3** is shown in Fig. 1.

In structure **3**, the angle between the plane of the phenyl substituent and the plane of the central pyrrole ring is 21.3° and the plane of the benzimidazole fragment is nearly orthogonal to the pyrrole ring, making a dihedral angle of 77.3°. The planar ethoxycarbonyl group is also noncoplanar with the central pyrrole ring: the dihedral angle between their planes is 7.2°. Such relative positions of the above fragments preclude intramolecular hydrogen bonding N—H...O between the H atom of the amino group of the benzimidazole fragment and the O atom of the ethoxycarbonyl group. This gives rise to a centrosymmetric H-dimer due to intermolecular pair interactions of this type (Fig. 2). The parameters of the hydrogen bond N(1)—H(1)...O(13′) (–*x*, 1 – *y*, 1 – *z*) are as follows: N(1)...O(13′), 2.959(3) Å; H(1)...O(13′), 2.09(3) Å; the angle N(1)—H(1)...O(13′), 168(2)°. The H(8) atom of the amino group of the pyrrole ring forms a classic hydrogen bond to the O(23) atom of the solvate methanol molecule (N(8)...O(23), 2.854(3) Å; H(8)...O(23), 1.98(3) Å; the angle N(8)—H(8)...O(23), 170(3)°.

An analysis of the intermolecular interactions suggests a crucial role of solvate methanol molecules in the formation of a supramolecular structure in the crystal of benzimidazole **3**. Having a hydroxy group, the methanol molecule acts as both a donor and an acceptor in classic hydrogen bonding. One molecule of benzimidazole **3** is hydrogen-bonded to methanol according to the earlier described type of bonding (N—H...O) and the O(23) atom of the methanol molecule acts as a proton acceptor; for a second

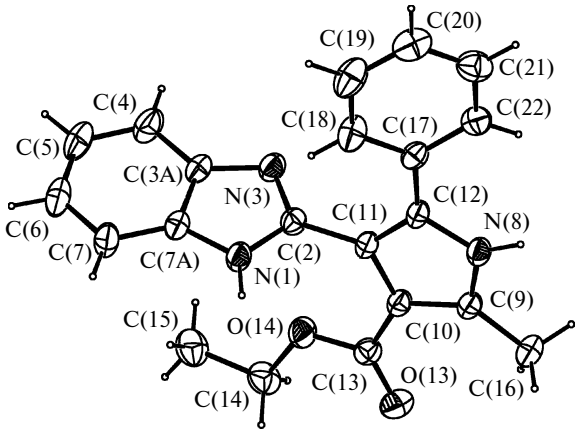



**Fig. 1.** Molecular structure of benzimidazole **3** in the crystal with thermal displacement ellipsoids for the non-hydrogen atoms ($p$ = 50%). The hydrogen atoms are represented by spheres of arbitrary radii. The solvate methanol molecule is omitted.

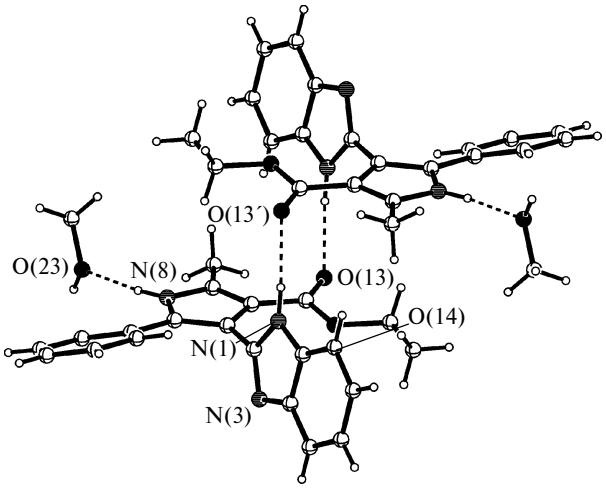



**Fig. 2.** Dimerization of benzimidazole **3** in the crystal through N—H...O hydrogen bonding (the bonds are indicated with dashed lines).

molecule of benzimidazole **3**, methanol acts as a proton donor (O—H...N). Thus, methanol molecules bridge the H-dimers of benzimidazole **3**. This gives rise to a supramolecular structure as zigzag chains of H-bonded molecules of benzimidazole **3** and methanol along the crystallographic axis 0*b* (Fig. 3). The parameters of the bond O—H...N between the H(23) atom of the hydroxy group of MeOH and the N(3″) atom of the imidazole ring are as follows: O(23)...N(3″), 2.816(3) Å; H(23)...N(3″), 1.91(4) Å; the angle O(23)—H(23)...N(3″), 168(4)° (1 – *x* ,1 – *y*, 1 – *z*).

The supramolecular structure is additionally stabilized by pair π—π-contacts between the aromatic systems of the pyrrole ring C(9)—N(8) and the benzene ring C(17)—C(22) of symmetrically related molecules (–*x*, 1 – *y*, 1 – *z*). The shortest distance between the planes of the corresponding rings is 2.88 Å; the dihedral angle between these planes is 21.2°.

Surprisingly, although the fragments of the molecules are not disordered, the calculated packing factor (0.62) is appreciably lower than the lower bound of the range characteristic of the crystals of organic compounds (0.65—0.75). The free volume, which is potentially accessible in the crystal to solvent molecules, is small (51.8 Å$^3$).

With free quinoxalin-2(1*H*)-one instead of its hydrochloride **1** in a reaction with ethyl acetoacetate, the yield of the rearrangement product remains virtually unchanged; apparently, this is due to various acid-catalyzed reactions involving ethyl acetoacetate.

To increase the yield of the rearrangement product, we recurred to our hypothesis[21] that any spiro derivative of quinoxalin-3(4*H*)-one with at least one acidic H atom in its spiro-fused component tends to rearrange itself into a benzimidazole derivative spiro-fused at position 2 (Scheme 2).

According to this hypothesis, our aim was to obtain a spiro[4-pyrroline-3,2′-quinoxalin]-3′(4′*H*)-one deriv-

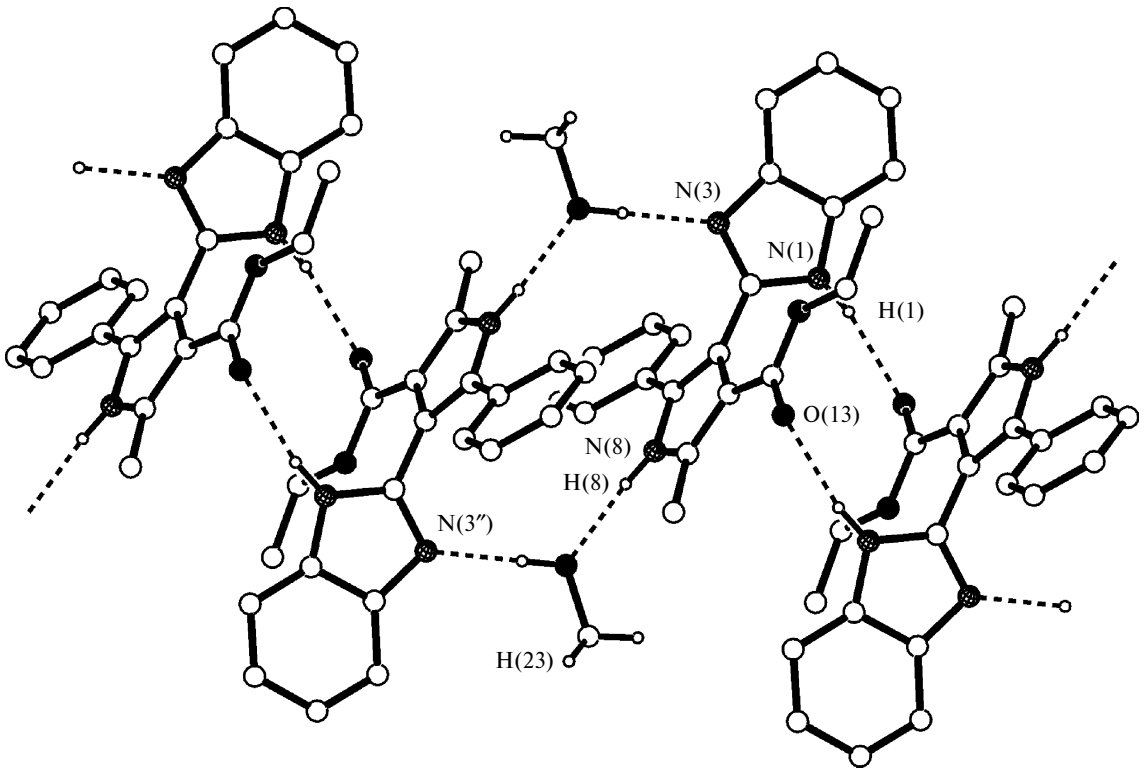
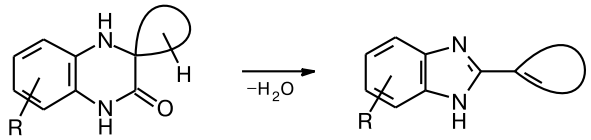


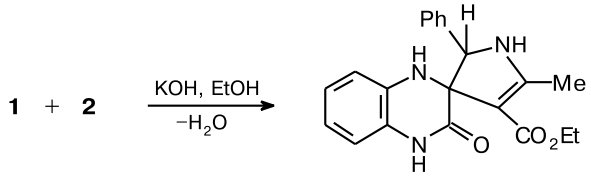

**Fig. 3.** Hydrogen-bonded chains in the crystal of compound **3** (hydrogen bonds are indicated with dashed lines).

**Scheme 2**




ative. Considering 3-(α-aminobenzyl)quinoxalin-2(1*H*)-one (**1**) to be a hetero analog to the α-amino carbonyl component of the Knorr reaction[22—24] (synthesis of pyrroles by condensation of α-amino ketones with active methylene ketones), we carried out a reaction of quinoxalinone **1** with ethyl acetoacetate (**2**) in EtOH in the presence of KOH (Scheme 3). The reaction occurred smoothly to give the desired spiro compound 4-ethoxycarbonyl-5-methyl-2-phenyl-1′*H*-spiro[4-pyrroline-3,2′-quinoxalin]-3′(4′*H*)-one (**4**) in high yield (88%). Note that the reaction takes place both at room temperature (12 h) and in boiling ethanol (4 h).

**Scheme 3**



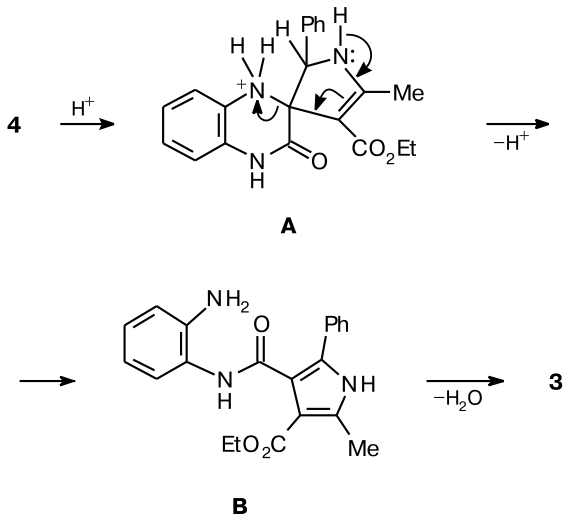

**4**

The $^1$H NMR spectrum of spiro compound **4** shows multiplet signals for the phenyl and phenylene protons at δ 7.26—7.83, a triplet and a quartet for the protons of the ethoxy group at δ 1.19 and 4.05 ($^3J$ = 7.2 Hz), respectively, two doublets of the AB system for the CH—NH fragment at δ 6.26 and 9.91 ($^3J$ = 8.6 Hz), and singlets for the methyl and two NH protons at δ 1.90, 4.47, and 12.56, respectively.

Reflux of compound **4** in acetic acid for 1 h gave the expected benzimidazole **3** in 95% yield. Apparently, the reaction of 3-(α-aminobenzyl)quinoxalin-2(1*H*)-one (**1**) with ethyl acetoacetate (**2**) initially produces spiro compound **4**, which undergoes *in situ* acid-catalyzed rearrangement into benzimidazole **3**. The rearrangement steps include (1) opening of the pyrazine ring of the quinoxaline system through cleavage of the N(1)—C(2) bond in intermediate salt **A** and (2) closure of the imidazole ring by intramolecular cyclization involving the newly formed amino group and the carbamoyl CO group in pyrrole derivative **B** (Scheme 4).

It should be noted that substituted 3-(α-aminobenzyl)-quinoxalin-2(1*H*)-ones successfully react with both ethyl acetoacetate and other β-oxo acid esters to give the corresponding 2-(pyrrol-3-yl)benzimidazoles in high yields. These data suggest the general character of the reaction under study and will be discussed elsewhere.

**Scheme 4**




## Experimental

Melting points were determined on a Boetius instrument. IR spectra were recorded on a Vector-22 FTIR spectrometer (Bruker) in KBr pellets. The $^1$H NMR spectra of compounds **3** and **4** were recorded on a Bruker Avance-600 spectrometer (600.13 MHz) in DMSO-$d_6$. Chemical shifts δ are referenced to the signals of residual solvent protons ($\delta_H$ 2.50).

**2-(4-Ethoxycarbonyl-5-methyl-2-phenylpyrrol-3-yl)benzimidazole (3).** ***A.*** Quinoxalin-2(1*H*)-one hydrochloride **1** (0.2 g, 0.7 mmol) and ethyl acetoacetate (**2**) (0.1 mL, 0.77 mmol) were refluxed in acetic acid (6 mL) for 15 h and then kept at room temperature for 12 h. The crystals that formed were filtered off and dried in air. Compound **3** was analytically pure. To collect an additional crop of product **3**, the reaction mixture was evaporated to dryness in a water aspirator vacuum and the residue was treated with water. The resulting crystals were filtered off, washed with 5% aqueous $NaHCO_3$ (3×10 mL), dried in air, and recrystallized from AcOH. The total yield of compound **3** was 0.15 g (62%), m.p. 270—272 °C. Found (%): C, 72.92; H, 5.60; N, 12.08. $C_{21}H_{19}N_3O_2$. Calculated (%): C, 73.03; H, 5.54; N, 12.17. IR, ν/cm$^{-1}$: 3208, 2818, 2729, 2638, 2589, 1704, 1630, 1581, 1458, 1446, 1385, 1301, 1262, 1208, 1140, 1095, 895, 867, 780, 761, 738, 694, 683, 618. $^1$H NMR, δ: 0.87 (t, 3 H, $OCH_2C\underline{H}_3$, $J$ = 7.2 Hz); 2.62 (s, 3 H, $CH_3$); 4.02 (q, 2 H, $OC\underline{H}_2CH_3$, $J$ = 7.2 Hz); 7.30—7.33 (m, 3 H); 7.35—7.38 (m, 2 H); 7.55—7.57 (m, 2 H, benzimidazole); 7.79—7.81 (m, 2 H, benzimidazole).

***B.*** A solution of spiroquinoxaline **4** (0.1 g, 0.28 mmol) in acetic acid (10 mL) was refluxed for 6 h, kept at ~20 °C for 18 h, and concentrated *in vacuo*. The resulting crystalline precipitate was dried in air. The yield of compound **3** was 0.09 g (95%).

**4-Ethoxycarbonyl-5-methyl-2-phenyl-1′*H*-spiro[4-pyrroline-3,2′-quinoxalin]-3′(4′*H*)-one (4).** Ethyl acetoacetate (**2**) (0.1 mL, 0.77 mmol) and a solution of KOH (0.08 g, 1.4 mmol) in EtOH (1 mL) were added to a solution of quinoxalin-2(1*H*)-one hydrochloride **1** (0.2 g, 0.7 mmol) in EtOH (6 mL). The reaction mixture was stirred at room temperature for 12 h or refluxed for 4 h and then concentrated to half its initial volume. The residue was treated with 5% aqueous HCl. The crystals that formed were filtered off, washed with water, and dried in air. The yield of compound **4** was 0.22 g (88%), m.p. 113—115 °C. Found (%): C, 69.09; H, 5.88; N, 11.54. $C_{21}H_{21}N_3O_3$. Calculated (%): C, 69.41; H, 5.82; N, 11.56. IR, ν/cm$^{-1}$: 3437, 2974, 2928, 1664, 1595, 1494, 1448, 1293, 1256, 1170, 1122, 1098, 1026, 786, 758, 699, 583. $^1$H NMR, δ: 1.19 (t, 3 H, $OCH_2C\underline{H}_3$, $J$ = 7.2 Hz); 1.90 (s, 3 H, $CH_3$); 4.05 (q, 2 H, $OC\underline{H}_2CH_3$, $J$ = 7.2 Hz); 4.47 (s, 1 H, $NH_{quinox}$); 6.26 (d, 1 H, CH, $J$ = 8.6 Hz); 7.26 (dd, 1 H, H(6), $J$ = 7.2 Hz, $J$ = 7.2 Hz); 7.31—7.36 (m, 4 H); 7.45 (d, 2 H, *o*-HPh, $J$ = 7.7 Hz); 7.54 (dd, 1 H, H(7), $J$ = 6.8 Hz, $J$ = 7.2 Hz); 7.83 (d, 1 H, H(5), $J$ = 8.1 Hz); 9.91 (d, 1 H, NH, $J$ = 8.6 Hz); 12.56 (br.s, 1 H, $NH_{carbamoyl}$).

**Single-crystal X-ray diffraction study** of compound **3** was performed at the Crystallographic Division of the Collective Use Center of the Spectroanalytical Center based on the Diffraction Investigations Laboratory of the A. E. Arbuzov Institute of Organic and Physical Chemistry (Kazan Research Center, Russian Academy of Sciences).

The crystals of compound **3**, $C_{21}H_{19}N_3O_2 \cdot CH_4O$, are triclinic. The unit cell parameters at 23 °C: $a$ = 9.526(1) Å, $b$ = 10.954(1) Å, $c$ = 11.833(2) Å, α = 111.561(2)°, β = 94.151(2)°, γ = 105.140(2)°, $V$ = 1088.7(3) Å$^3$, $Z$ = 2, $d_{calc}$ = 1.151 g cm$^{-3}$, M = 377.43, space group $P$-1. The intensities of 7529 reflections ($R_{int}$ = 0.0445) were measured on a Bruker Smart Apex II CCD diffractometer (Mo-$K\alpha$ radiation, graphite monochromator, λ = 0.71073 Å, ω scan mode, scan ranges: $-11 \le h \le 10$, $-13 \le k \le 13$, $-14 \le l \le 13$, $1.88 \le \theta \le 25.50°$). The number of independent reflections was 3813 (2329 reflections with $I \ge 2\sigma(I)$). An absorption correction was applied semiempirically with the SADABS program[25] (μMo = 0.78 cm$^{-1}$). The structure was solved by the direct method and refined by the least-squares method first isotropically and then anisotropically for all non-hydrogen atoms. The H atoms at the N(1), N(8), and O(23) atoms were located from difference electron-density maps and refined isotropically. The positions of the other H atoms were calculated from stereochemical considerations and refined using appropriate riding models. The final residuals are $R_1$ = 0.0530 and $wR_2$ = 0.1362 for 2329 independent reflections with $I > 2\sigma(I)$ and $R_1$ = 0.0983 and $wR_2$ = 0.1646 for all reflections; GOOF = = 1.005, the number of parameters refined is 268. The maximum and minimum residual electron densities are 0.189 and −0.177 e Å$^{-3}$, respectively. Reflection intensity data were collected and edited, and the unit cell parameters were refined, with the APEX2 program.[26] All calculations were performed with the SHELXTL[27] and WinGX programs.[28] Intermolecular interactions were analyzed and the molecules were imaged with the PLATON program.[29] The atomic coordinates and thermal parameters for structure **3** have been deposited with the Cambridge Crystallographic Data Center (http://www.ccdc.cam.ac.uk; CCDC No. 773036).

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## References

1. V. A. Mamedov, A. M. Murtazina, A. T. Gubaidullin, E. A. Hafizova, I. Kh. Rizvanov, *Tetrahedron Lett.*, 2009, **50**, 5186.

2. N. G. Brink, F. W. Holly, C. H. Shunk, E. W. Peel, J. J. Cahill, K. Folkers, *J. Am. Chem. Soc.*, 1950, **72**, 1866; D. E. Wolf, W. H. Jones, J. Valiant, K. Folkers, *J. Am. Chem. Soc.*, 1950, **72**, 2820.
3. S. Salluja, R. Zou, J. C. Drach, L. B. Townsend, *J. Med. Chem.*, 1996, **39**, 881.
4. H. Zarrinmayeh, D. M. Zimmerman, B. E. Cantrell, D. A. Schober, R. F. Bruns, S. L. Gackenheimer, P. L. Oznstein, P. A. Hipskind, T. C. Britton, D. R. Gehlert, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 647.
5. I. Antonini, F. Claudi, G. Cristalli, P. Franchetti, M. Grifantini, S. Martelli, *J. Med. Chem.*, 1988, **31**, 260.
6. E. B. Skibo, W. G. Schulz, *J. Med. Chem.*, 1993, **36**, 3050.
7. R. Zhou, E. B. Skibo, *J. Med. Chem.*, 1996, **39**, 4321.
8. W. A. Craigo, B. W. LeSueur, E. B. Skibo, *J. Med. Chem.*, 1999, **42**, 3324.
9. R. Cedillo-Rivera, O. Munoz, *J. Med. Microbiol.*, 1992, 37.
10. B. Chavez, R. Cedillo-Rivera, A. Martinez-Palomo, *J. Protozool.*, 1992, **39**, 510.
11. S. D. Sears, J. O´Hare, *Antimicrob. Agents Chemother.*, 1988, **32**, 144.
12. A. A. Spasov, I. N. Yoshitsa, L. I. Bugaeva, V. A. Anisimova, *Pharm. Chem. J.*, 1999, **33**, 232.
13. P. J. Taggart, L. R. Cooke, P. C. Mercer, M. W. Shaw, *Crop Prot.*, 1998, **17**, 727.
14. J. B. Wright, *Chem. Rev.*, 1951, **48**, 397.
15. P. N. Preston, *Chem. Rev.*, 1974, **74**, 279.
16. R. L. Hudkins, *Heterocycles*, 1995, **41**, 1045.
17. V. A. Mamedov, A. A. Kalinin, N. M. Azancheev, Ya. A. Levin, *Zh. Org. Khim.*, 2003, **39**, 135 [*Russ. J. Org. Chem.* (*Engl. Transl.*), 2003, **39**, 125].
18. V. A. Mamedov, D. F. Saifina, I. Kh. Rizvanov, A. T. Gubaidullin, *Tetrahedron Lett.*, 2008, **49**, 4644.
19. E. A. Gorbunova, V. A. Mamedov, *Zh. Org. Khim.*, 2006, **42**, 1540 [*Russ. J. Org. Chem.* (*Engl. Transl.*), 2006, **42**, 1528].
20. V. A. Mamedov, A. A. Kalinin, A. T. Gubaidullin, E. A. Gorbunova, I. A. Litvinov, *Zh. Org. Khim.*, 2006, **42**, 1543 [*Russ. J. Org. Chem.* (*Engl. Transl.*), 2006, **42**, 1532].
21. V. A. Mamedov, A. M. Murtazina, A. T. Gubaidullin, E. A. Khafizova, I. Kh. Rizvanov, I. A. Litvinov, *Izv. Akad. Nauk, Ser. Khim.*, 2010, 1602 [*Russ. Chem. Bull., Int. Ed.*, 2010, **59**, 1645].
22. L. Knorr, *Ber.*, 1884, **17**, 1635.
23. A. Castro, D. D. Giannin, W. F. Greenlee, *J. Org. Chem.*, 1970, **35**, 2815.
24. A. F. Mironov, Kh. Kh. Alarkon, R. P. Evstigneeva, *Khim. Geterotsikl. Soedin.*, 1973, 1643 [*Chem. Heterocycl. Compd.* (*Engl. Transl.*), 1973, **12**, 1643].
25. G. M. Sheldrick, *SADABS, Program for Empirical X-Ray Absorption Correction*, Bruker-Nonius, 1990—2004.
26. *APEX2 (Version 2.1), SAINTPlus, Data Reduction and Correction Program (Version 7.31A), Bruker Advanced X-Ray Solutions*, Bruker AXS, Inc., Madison (WI), USA, 2006.
27. G. M. Sheldrick, *SHELXTL v.6.12, Structure Determination Software Suite*, Bruker AXS, Madison (WI), USA, 2000.
28. L. J. Farrugia, *J. Appl. Cryst.*, 1999, **32**, 837.
29. A. L. Spek, *Acta Crystallogr., Sect. A: Found. Crystallogr.*, 1990, **46**, 34.

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