3-(2-Heteroaryl)-pyrazolotetrazoles — a subunits for losartan-like structures

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Abstract: A modification of biphenylyltetrazole moiety of Losartan ***(A)*** by 3-(2-heteroaryl)-pyrazolotetrazole ***(B)*** is described. Ketone semicarbazones react with two moles of phosphorus oxychloride-dimethylformamide with the formation of 3-substituted pyrazol-4-carbaldehydes. The transformations of 3-substituted pyrazole-4-carboxaldehydes to 3-substituted pyrazole-4-nitriles were carried out by reaction of hydroxylamine in DMFA. The prepared cyano pyrazoles were converted to tetrazoles by heating with trimethylsilylazide and dibuthyltinoxide in toluene.

Keywords: Angiotensin II receptor antagonists, 3-, 4-substituted pyrazoles, tetrazoles

Introduction

Over the several years, angiotensin II (AII) receptor antagonists have been considered a reliable alternative to inhibitors of angiotensin-converting enzyme and renin, designed to influence the renin-angiotensin system, which plays a pivotal role in the regulation of blood pressure and fluid balance. (Duncia et al. 1990, Thomas et al. 1992, Wexler et al. 1996) Especially the DuPont group discovery of a series of (biphenylmethyl) imidazoles as nonpeptide, potent and orally active AII receptor antagonists has provided an important advance in the area, and stimulated a profusion of research. (Duncia et al. 1990, Thomas et al. 1992, Wexler et al. 1996, Bräse et al. 2010, Roh et al. 2012) The discovery of Losartan has led to a large effort in the pharmaceutical industry to find other AII receptor antagonists.

Recently numerous compounds possessing various spacer have been introduced as new angiotensin II receptor antagonist. Our research efforts have been focused on the modification of the biphenylyltetrazole moiety which in our case has been replaced by 3-(2-heteroaryl) pyrazolo-4-tetrazoles (Figure 1). As a biosteric replacement of biphenyl moiety in the losartan the heterocyclic rings were used to extend the group of AII type receptor antagonists. We are specially interested in the pyrazole derivatives because are important applications in the field of coordination chemistry, photographic industry and medicinal chemistry.

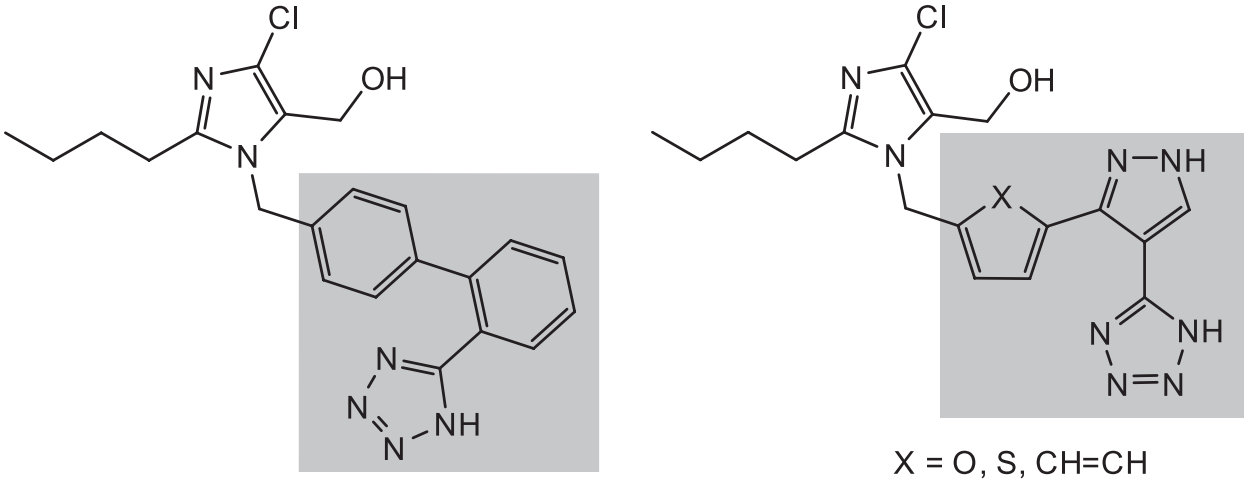
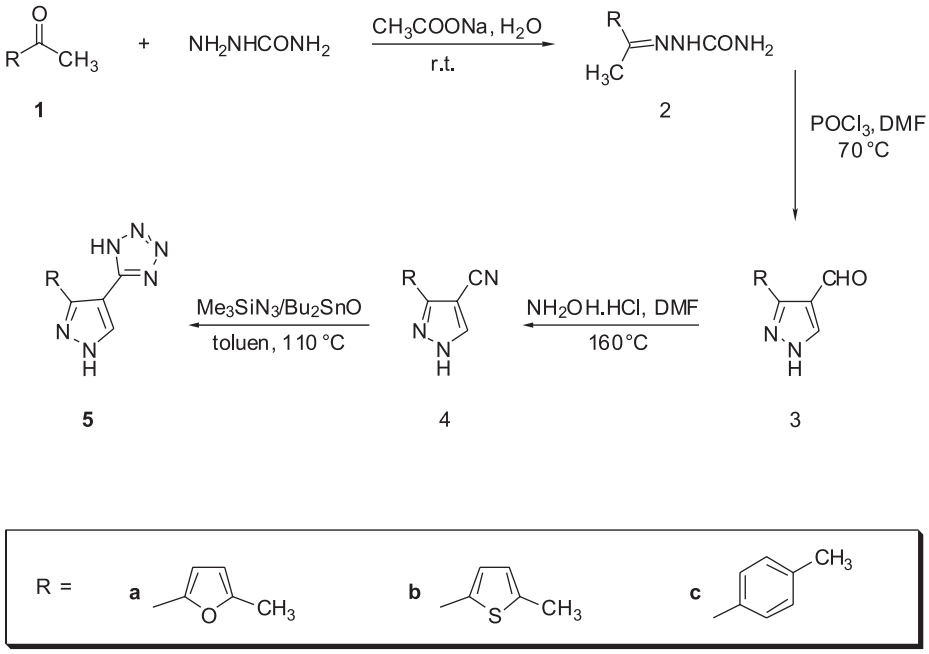


Fig. 1. ***A***: Losartan — active nonpeptide AII receptor antagonist. ***B***: potential AII receptor antagonist.

Results and Discussion

We utilized the procedure of (Kira et al. 1970, Lásiková et al. 1998) for the preparation of 3-substituted pyrazol-4-carbaldehydes. The starting methylketones reacted with the semicarbazide in aqueous solution to give rise to the respective semicarbazones (**2a-c**), isolated in 75—95 % yields, which after having been isolated, were submitted to cyclization by phosphoryl chloride in dimethylformamide to give the 3-substituted pyrazol-4-carbaldehydes (**3a-c**) in 61—92 % yield. After transformation to 3-substituted pyrazol-4-nitriles (**4a-c**) in 50—82 % yield and 3-substituted pyrazol-4-tetrazoles (**5a-c**) were obtained in 72—88 % yield.

Structures of **3a-c**, **4a-c**, **5a-c** were confirmed by means of spectroscopic characterisation (UV-Vis, IR, NMR). ^{1}H NMR data showed that **3a-c**, **4a-c**, **5a-c** were the only structures present at room temperature (singlet of the CH-proton). Tetrazoles were identified by IR, ^{1}H, ^{13}C NMR and by elemental analysis. The typical characteristic change of the cyano group to tetrazole manifested itself in infrared spectra. The band of the CN group at 2100—2200 cm^{-1} disappeared and a new broad band appeared at 3400 cm^{-1}. The analysis of ^{1}H NMR spectra of the compound **5c**, taken in DMSO-d_6 failed to unequivocally identify the signal of proton of pyrazol. Instead of the expected sharp singlet we observed a small broad signal, resembling readily exchangeable protons, such as those in amino group. The structure of **5c** in solid state was characterized by single crystal X-ray diffraction analysis (Figure 2).



Scheme 1. Synthesis of 3-substituted pyrazol-4-tetrazoles (**5a-c**).

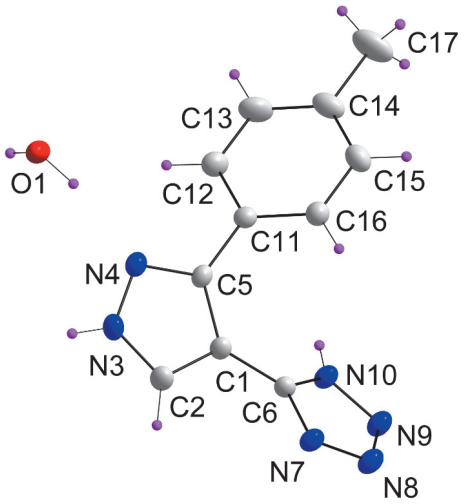


Figure 2. ORTEP drawing (Brandenburg 2002) of the **5c** with 50 % probability thermal displacement ellipsoids. Hydrogen atoms are represented by circles of an arbitrary radius. Selected bond lengths [Å]: C1—C2 1.376(19); C1—C5 1.418(19); C1—C6 1.453(19); C2—N3 1.331(19); N3—N4 1.346(17); N4—C5 1.335(18); C6—N7 1.323(18); C6—N10 1.332(18); N7—N8 1.360(17); N8—N9 1.291(18); N9—N10 1.339(16). Selected torsion angles [°]: C1—C5—C11—C16 -34.2(2); C5—C1—C6—N10 -33.9(2).

Conclusions

In this study we presented the new key intermediates for the synthesis of losartan — like angiotensin II receptor antagonists. In a variation of the biphenyl part of different combinations of the heterocycle is expected to increase biological activity. Selected heterocycles such as pyrazole, thiophen and furan are a part of pharmacophore at modeling in drug design.

Experimental Section

All melting points were taken on a Kofler hot stage and are uncorrected; IR spectra were determined on a Perkin-Elmer 1600 FT-IR system (KBr pellets); NMR (^{1}H at 300, ^{13}C at 75 MHz) spectra were measured on a Varian VXR 300 spektrometer with $CDCl_3$ or DMSO-d_6 solvent (TMS as internal reference). Elemental analyses were obtained using a Carlo Erba Elemental Analyzer 1108. Silica gel 60 (230—400 mesh, Merck) was used for column chromatography. Reactions and the collected fraction samples were monitored by TLC (Merck 60 F254 silica gel). Visualization was made with UV light. MS spectra were measured a GS/MS 25 RFA instrument (Kratos Analytical, Manchester). Crystal and experimental data for compound **5c** are given on Table 1. Semicarbazones **2a-c** were prepared according to the literature (Vogel 1975), all the other starting material were commercially available.

General method for the preparation of aldehydes 3a-c: To a vigorously stirred mixture of $POCl_3$-DMF [prepared by the slow addition of $POCl_3$ (32.32 g, 0.21 mol) to DMF (30 mL)] cooled below 5 °C, semicarbazones **2a-c** (0.088 mol) were added portionwise. The mixture was heated at 60 °C for about 4h, and poured onto crushed ice (1000 g). The mixture was then neutralized with NaOH (20 g in 75 mL of water), heated to 50—60 °C for 5 min, cooled down, and acidified to pH = 6 with 10 M HCl. The solution was extracted with EtOAc (3 × 200 mL) and the combined organic layers were dried and concentrated *in vacuo*. The crude residue was purified by chromatography ($Et_2O/CHCl_3$, 9/1) to give the aldehydes **3a-c**.

3-(5-Methyl-furan-2-yl)-1*H*-pyrazole-4-carbaldehyde (3a): yield 61 %; mp 131—133 °C; IR (ν, cm^{-1}): 3140 (NH), 2919—2762 (s, br), 1686 (s), 1676 (s), 1655 (s), 1570 (s), 1510 (s), 1482 (s), 1333 (m), 1024 (s), 953 (s), 947 (s), 799 (s), 768 (s). ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 2.34 (3H, s, C<u>H</u>$_3$), 6.12 (1H, d, $^3J_{H,H}$ = 3.3 Hz, H_{furan}), 7.22 (1H, d, $^3J_{H,H}$ = 3.0 Hz, H_{furan}), 8.04 (1H, s, $H_{pyrazole}$), 10.08 (1H, s, C<u>H</u>O). ^{13}C NMR (75 MHz, $CDCl_3$), δ_C 13.5 (<u>C</u>H$_3$), 107.8, 113.4, 118.6, 139.4, 139.2, 142.8, 154.2, 184.9 (<u>C</u>HO). MS, m/z (%): 176 M$^+$**.** Anal. calcd. for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90 %. Found: C, 61.22; H, 4.55; N, 15.62 %.

3-(5-Methyl-thiophen-2-yl)-1*H*-pyrazole-4-carbaldehyde (3b): yield 92 %; mp 95—97 °C; IR (ν, cm^{-1}): 3123 (NH), 2950—2861 (s, br), 1709 (s), 1688 (s), 1682 (s), 1674 (s), 1667 (s), 1661 (s), 1651 (s), 1645 (s), 1597 (s), 1526 (s), 1499 (s), 1454 (s), 1435 (s), 808 (s), 772 (s). ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 2.50 (3H, s, C<u>H</u>$_3$), 6.77 (1H, d, $^3J_{H,H}$ = 3.6 Hz, $H_{thiophen}$), 7.52 (1H, d, $^3J_{H,H}$ = 3.6 Hz, $H_{thiophen}$), 8.12 (1H, s, $H_{pyrazol}$), 10.02 (1H, s, C<u>H</u>O), 11.89 (1H, br, NH). ^{13}C NMR (75 MHz, $CDCl_3$), δ_C 15.3 (<u>C</u>H$_3$), 119.7, 126.4, 128.3, 129.1, 138.1, 142.9, 145.0, 184.5 (<u>C</u>HO). MS, m/z (%): 192 M+. Anal. calcd. for $C_9H_8N_2OS$: C, 56.23; H, 4.19; N, 14.57 %. Found: C, 56.22; H, 4.02; N, 14.29 %.

3-p-Tolyl-1*H*-pyrazole-4-carbaldehyde (3c): yield 81 %; mp 123—125 °C; IR (ν, cm^{-1}): 3183 (s), 3131 (s), 3048 (s), 2926 (s), 1653 (s, C═O), 1512 (m), 1487 (s), 1377 (s), 1202 (s), 934 (s), 878 (s), 830 (s), 822 (s), 768 (s). ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 2.34 (3H, s, C<u>H</u>$_3$), 7.29 (2H$_{arom}$, d, $^3J_{H,H}$ = 8.1 Hz), 7.42 (2H$_{arom}$, d, $^3J_{H,H}$ = 8.1 Hz), 8.31 (1H, s, $H_{pyrazol}$), 9.87 (1H, s, C<u>H</u>O). ^{13}C NMR (75 MHz, $CDCl_3$), δ_C 20.9 (<u>C</u>H$_3$), 119.7, 125.2, 128.6, 129.3, 138.9, 149.0 163.1, 184.8 (d, <u>C</u>HO). MS, m/z (%): 186 M+. Anal. calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04 %. Found: C, 70.51; H, 5.31; N, 14.97 %.

General method for the preparation of nitriles 4a-c: To a vigorously stirred solution of the aldehyde **3a-c** (0.019 mol) in DMFA (20 mL) hydroxylamine hydrochloride (1.48 g, 0.021 mol) was added portionwise. Then Et_3N (2.63 mL, 0.019 mol) was added droppwise. The reaction mixture was stirred at the room temperature for 1 hour and then at the 160 °C for 2 hours. The reaction mixture was poured on ice and extracted with Et_2OAc (3 × 50 mL). Combined organic layers were dried with Na_2SO_4, filtrated and concentrated *in vacuo*. The crude residue was purified by crystallization from toluene.

3-(5-Methyl-furan-2-yl)-1*H*-pyrazole-4-carbonitrile (4a): yield 65 %; mp 115—117 °C; IR (ν, cm^{-1}): 3142 (NH), 3083—2676 (s, br), 2223 (CN), 1578 (s), 1439 (s), 1073 (s), 1067 (m), 1030 (s), 951 (s), 830 (w), 785 (s). ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 2.36 (3H, s, C<u>H</u>$_3$), 6.29 (1H, d, $^3J_{H,H}$ = 3.0 Hz, H_{furan}), 6.85 (1H, d, $^3J_{H,H}$ = 3.3 Hz, H_{furan}), 8.46 (1H, s, $H_{pyrazol}$). ^{13}C NMR (75 MHz, $CDCl_3$), δ_C 13.3 (q, <u>C</u>H$_3$), 86.3, 101.2, 108.2, 110.1, 114.4 (CN), 153.1. MS, m/z (%): 173 M+. Anal. calcd. for $C_9H_7N_3O$: C, 65.42; H, 4.07; N, 23.74 %. Found: C, 61.99; H, 4.01; N, 23.74 %.

3-(5-Methyl-thiophen-2-yl)-1*H*-pyrazole-4-carbonitrile (4b): yield 50 %; mp 143—147 °C; IR (ν, cm^{-1}): 3164 (s, br, NH), 3139 (s), 2955 (s), 2921 (s), 2234 (s, CN), 1570 (w), 1508 (s), 1312 (m), 1069 (s), 1059 (s),

938 (s), 787 (s), 712 (s), 613 (s), 490 (m). ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 2.53 (3H, s, C$\underline{H}_3$), 6.87 (1H, d, $^3J_{H,H}$ = 3.5 Hz, $H_{thiophen}$), 7.52 (1H, d, $^3J_{H,H}$ = 3.5 Hz, $H_{thiophen}$), 8.36 (1H, s, $H_{pyrazol}$). ^{13}C NMR (75 MHz, $CDCl_3$), δ_C 14.9 (q, $\underline{C}H_3$), 86.6, 114.8 (s, CN), 125.8, 126.4, 138.2, 141.0 (not all quaternary carbons are visible in the spectrum). MS, m/z (%): 189 M+. Anal. calcd. for $C_9H_7N_3S$: C, 57.12; H, 3.73; N, 22.21 %. Found: C, 57.87; H, 3. 90; N, 22.67 %.

3-p-Tolyl-1*H*-pyrazole-4-carbonitrile (4c): 82 % yield, mp 125—127 °C; IR (ν, cm^{-1}): 3194 (s), 3127 (s), 3046 (s), 2972 (s), 2919 (s), 2899 (s), 2861 (s), 2838(s), 2234 (s, CN), 1620 (m), 1514 (m), 1499 (m), 1439 (m), 1096 (m), 955 (s), 818 (s), 721 (m), 492 (m). ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 2.41 (3H, s, C$\underline{H}_3$), 7.30 (2H_{arom}, d, $^3J_{H,H}$ = 8.7 Hz), 7.75 (2H_{arom}, d, $^3J_{H,H}$ = 8.4 Hz), 7.95 (1H, s, $H_{pyrazol}$). ^{13}C NMR (75 MHz, $CDCl_3$), δ_C 21.4 (q, $\underline{C}H_3$), 114.9 (s, CN), 125.4, 126.6, 129.9, 140.4, 150.3 (not all quaternary carbons are visible in the spectrum). MS, m/z (%): 183 M+. Anal. calcd. for $C_{11}H_9N_3$: C, 72.11; H, 4.95; N, 22.94 %. Found: C, 71.67; H, 4.83; N, 22.67 %.

General procedure for conversion of nitriles (4a-c) to tetrazoles (5a-c): To a solution of the nitrile (**4a-c**) and trimethylsilylazide (2.0 equiv) in toluene was added dibutyltin oxide (0.2 equiv), and the mixture was heated for 24—72 h until the nitrile was consumed (TLC analysis). The reaction mixture was concentrated *in vacuo*. The residue was dissolved in methanol and reconcentrated. The residue was partitioned between ethyl acetate and 10 % sodium bicarbonate solution (1:1). The combined aqueous extracts were dried over sodium sulfate, filtered, and concentrated to give the 5-substituted tetrazole **5a-c**.

5-[3-(5-Methyl-furan-2-yl)-1*H*-pyrazol-4-yl]-1*H*-tetrazole (5a): 72 % yield, mp 235—237 °C; IR (ν, cm^{-1}): 3120 (s), 3061 (s), 2868 (s), 2734 (s), 1640 (s), 1606 (s), 1578 (s), 1436 (s), 1371 (m), 1218 (m), 1098 (s), 1060 (s), 1027 (s), 953 (s), 804 (s), 756 (m), 711 (m), 557 (m). ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 2.39 (3H, s, C$\underline{H}_3$), 6.15 (1H, d, $^3J_{H,H}$ = 2.4 Hz), 7.39 (1H, d, $^3J_{H,H}$ = 3.3 Hz), 8.08 (1H, s, $H_{pyrazol}$). ^{13}C NMR (75 MHz, $CDCl_3$), δ_C 13.6 (q, $\underline{C}H_3$), 101.3, 108.4, 112.7, 137.0, 142.8, 150.1, 153.4 (not all quaternary carbons are visible in the spectrum). MS, m/z (%): 216 M+. Anal. calcd. for $C_9H_8N_6O$: C, 50.00 ; H, 3.73; N, 38.87 %. Found: C, 49.93; H, 3.74; N, 38.89 %.

5-[3-(5-Methyl-tiofen-2-yl)-1*H*-pyrazol-4-yl]-1*H*-tetrazole (5b): 88 % yield, mp 123—125 °C; IR (ν, cm^{-1}): 3356 (s), 3172 (s), 2953 (s), 2804 (s), 1616(s), 1505 (s), 1086 (m), 1024 (m), 943 (s), 918 (s), 808 (s), 754 (s), 615 (m). ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 2.48 (3H, s, C$\underline{H}_3$), 4.81 (1H, br, NH), 6.73 (1H, d, $^3J_{H,H}$ = 3.0Hz), 7.47 (1H, d, $^3J_{H,H}$ = 3.5Hz), 8.06 (1H, s, $H_{pyrazol}$); ^{13}C NMR (75 MHz, $CDCl_3$), δ_C 14.9 (q, $\underline{C}H_3$), 125.9, 128.0, 128.0, 128.1, 128.7, 129.4, 141.6, 150.0 (not all quaternary carbons are visible in the spectrum). MS, m/z (%): 232 M+. Anal. calcd. for $C_9H_8N_6S$: C, 46.54; H, 3.47; N, 36.18 %. Found: C, 36.18; H, 3.46; N, 36.39 %.

5-[3-(4-Methylphenyl)-1*H*-pyrazol-4-yl]-1*H*-tetrazole (5c): 78 % yield, mp 138—139 °C; IR (ν, cm^{-1}): 3168(s), 3029 (s), 2951 (s), 2928 (s), 1616 (s), 1508 (m), 1458 (m), 1448 (m), 1071 (m), 1046 (m), 966 (w), 947 (w), 822 (s), 754 (w), 733 (m). ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 2.34 (3H, s, C$\underline{H}_3$), 7.25 (2H_{arom}, d, $^3J_{H,H}$ = 7.8 Hz), 7.57 (2H, d, $^3J_{H,H}$ = 8.1 Hz), 8.13 (1H, s, $H_{pyrazol}$). ^{13}C NMR (75 MHz, $CDCl_3$), δ_C 21.0 (q, $\underline{C}H_3$), 102.7, 119.6, 128.1, 129.1, 138.2, 150.4 (not all quaternary carbons are visible in the spectrum). MS, m/z (%): 226 M+. Anal. calcd. for $C_{11}H_{10}N_6$: C, 58.40; H, 4.45; N, 37.15 %. Found: C, 58.65; H, 4.43; N, 37.34 %.

X-ray analysis

A colorless single crystal of **5c** (0.56 × 0.19 × 0.11 mm) was obtained by a slow crystallization from a DMSO at room temperature. X-ray data were collected on the Oxford Diffraction Gemini R diffractometer equipped with R CCD detector using Mo Kα radiation at room temperature Crystal data and structure analysis parameters are summarized in Table 1. Data reduction was performed with Oxford Diffraction *CrysAlis RED version 171.33.34* software (Oxford Diffraction 2009).Crystal structure was determined with direct methods procedure in ShELXS97 and refined with SHELXL97 (Sheldrick 2008).

Tab. 1. Crystal and experimental data for compound **5c**.

Empirical formula	$C_{11}H_{12}N_6O_1$
Formula weight (g.mol^{-1})	244.27
Temperature, T (K)	293(2)
Wavelength, λ (Ĺ)	0.71073
Space group	$P2_12_12_1$
Unit cell dimensions (Ĺ)	a = 7.28242(3) α = β = γ = 90° b = 10.72420(19) c = 15.4735(3)
Unit cell volume, V (Ĺ^3)	1208.4
Formula units per unit cell, Z	4
Calculated density, D_x (g.cm^{-3})	1.343
Absorption coefficient, μ (mm^{-1})	0.094
F(000)	512
Crystal size (mm)	0.56 × 0.19 × 0.11
Goodness-of-fit	1.068
R indices [$I>2\sigma(I)$]	0.0310
R indices for all data	0.0368

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References

Brandenburg K (2002) DIAMOND. Crystal Impact GbH, Bonn, Germany.

Bräse S, Banert K (2010) Organic azides, (pp 37—40) Synthesis and Applications, Wiley, United Kingdom.

Duncia JV, Chiu AT, Carini DJ, Gregory GB, Johnson AL, Price WA, Wells GJ, Wong PC, Calabrese JC, Timmermans PB (1990) *J. Med. Chem. 33*: 1312—1329.

Kira MA, Aboul-Enein MN, Korkor MI (1970) *J. Heterocycl. Chem. 7*: 25—26.

Lásiková A, Végh D (1998) *Chem. Listy 92*: 957.

Oxford Diffraction (2009). CrysAlis CCD and CrysAlis RED. Oxford Diffraction Ltd, Yarnton, Oxfordshire, England.

Roh J, Vávrová K, Hrabálek A (2012) Eur. J. Org. Chem. 6101—6118.

Thomas AP, Allott ChP, Gibson KH, Major JS, Masek BB, Oldham AA, Ratcliffe AH, Roberts DA, Russell ST, Thomason DA (1992) *J. Med. Chem. 35*: 877—885.

Sheldrick GM (2008) Acta Cryst. A64: 112—122.

Vogel AI (1975) A Text Book of Practical Organic Chemistry 3rd edn. Longmann.

Wexler RR, Greenlee WJ, Irvin JD, Goldberg MR, Prendergast K, Smith RD, Timmermans PB (1996) *J. Med. Chem. 39*: 625—656.