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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 2,5-BIS(PYRAZOL-3-YL OR TRIAZOL-4-YL)-1,3,4-OXADIAZOLES

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Abstract – The reaction of pyrazole-3-carbohydrazide (**1**) or 1,2,3-triazole-4-carbohydrazides **5a,b** and 2-(ethoxymethylene)malononitrile (**2**) in ethanol under reflux conditions afforded the corresponding *N,N'*-diacylhydrazines **3** or **6a,b**, respectively in high yields. Ring closure of **3** or **6a,b** in the presence of phosphorus oxychloride furnished the corresponding 2,5-*bis*(heterocyclic)-1,3,4-oxadiazoles **4** or **7a,b**, respectively in good yields. The synthesized heterocyclic compounds showed moderate activity against *Staphylococcus aureus*, *Listeria monocytogenes*, and *Escherichia coli*.

INTRODUCTION

Diacylhydrazines are common insecticides and have been used as a biologically active component in insect growth regulators.¹⁻³ 1,2-Diacylhydrazines are commonly synthesized through coupling between carbohydrazides and acyl chlorides, dimerization of carbohydrazides, and reactions between carboxylic acids or isocyanates and hydrazine hydrate.⁴⁻⁷ Diacylhydrazines are common precursors for the production of many heterocyclic ring systems.⁴

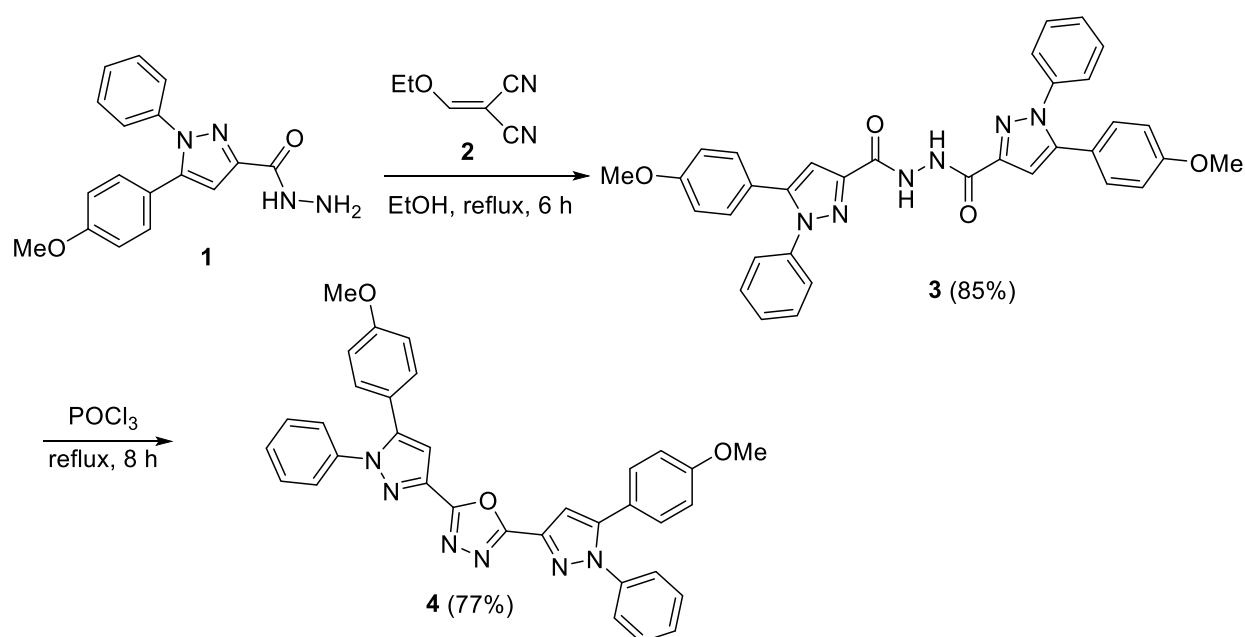
1,3,4-Oxadiazole represents an important class of heterocycles that exhibits pesticidal, antibacterial, and antiviral activities.⁸⁻¹⁰ Various medications containing 1,3,4-oxadiazole ring systems are available and can be used as antiretroviral and anticancer agents.¹¹⁻¹³ 1,2-Diacylhydrazines have been used as precursors for the production of 1,3,4-oxadiazoles using a dehydrating agent (e.g., phosphorus pentoxide, polyphosphoric acid, phosphorus oxychloride, thionyl chloride, iodine or bromine, triflic anhydride, or

4-methylbenzenesulfonyl chloride) in the presence of a base (e.g., triethylamine, potassium carbonate, or pyridine) or Vilsmeier reagent.^{14–16}

1,2,3-Triazoles exhibit a variety of biological activities and act as antibacterial, antitubercular, and antiviral agents.^{17–22} In addition, pyrazoles act as inhibitors of protein glycation, antibacterial, antifungal, and antiviral agents.^{4,8} Therefore, the synthesis of novel heterocycles containing 1,3,4-oxadiazole, 1,2,3-triazole, or pyrazoles is of interest.^{23,24} Here, we report the synthesis of novel heterocycles containing 1,3,4-oxadiazole moiety using a simple procedure as a continuation of our long-term interest in the synthesis of bioactive molecules.^{25–27}

RESULTS AND DISCUSSION

Reaction of 5-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazole-3-carbohydrazide (**1**) and 2-(ethoxymethylene)malononitrile (**2**) in ethanol (EtOH) under reflux conditions for 6 h afforded 5-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazole-3-carboxylic acid 2-[[5-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-3-yl]carbonyl]hydrazide (**3**) in 85% yield. Dehydration of **3** took place in the presence of boiling phosphorus oxychloride (POCl₃) for 8 h to give 2,5-bis(5-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-3-yl)-1,3,4-oxadiazole (**4**) in 77% yield (Scheme 1).



Scheme 1. Synthesis of **3** and **4**

The ¹H NMR spectrum of **3** showed two characteristic singlet singlets at 10.07 and 10.69 ppm corresponding to the two NH protons. The NH protons were absent in the ¹H NMR spectrum of **4**. In addition, it shows two singlets at 3.71 and 3.78 ppm corresponding to the two OMe groups. The structures of **3** and **4** were confirmed further using the ¹³C NMR spectra and single-crystal X-ray crystallography.

The independent part of the crystal structure of **3** is half a molecule with the rest being generated by symmetry (Figure 1). The molecule comprises three unique rings, 3A (C2—C7), 3B (C8—C10, N1, and N2) and 3C (C12—C17), with twist angles between the planes of neighboring rings in the molecule between 44–49° (Table 1).

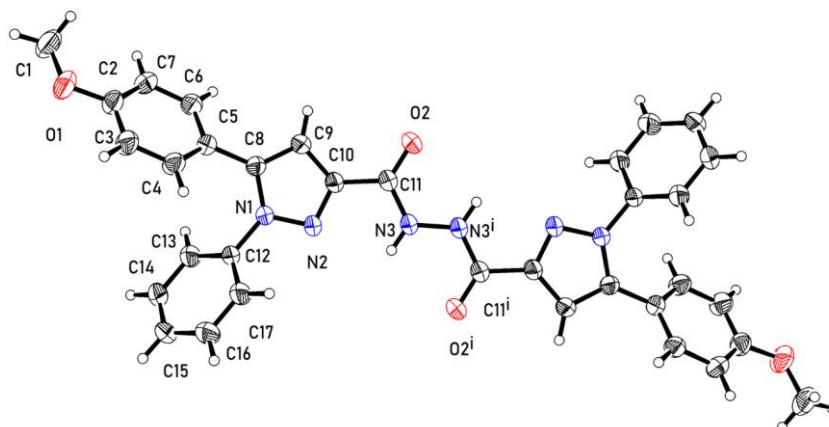


Figure 1. A 50% probability ellipsoid ORTEP representation of the molecule of **3** showing atom numbering

The molecule in the structure of **4** is shown in Figure 2. The molecule comprises seven rings, 4A (C2—C7), 4B (C8—C10, N1, and N2), 4C (C11—C16), 4D (C17, C18, N3, and N4, O2), 4E (C19—C21, N5, and N6), 4F (C22—C27), 4G (C28—C33). The twist angles between the planes of adjacent rings are between 5–54° (Table 1).

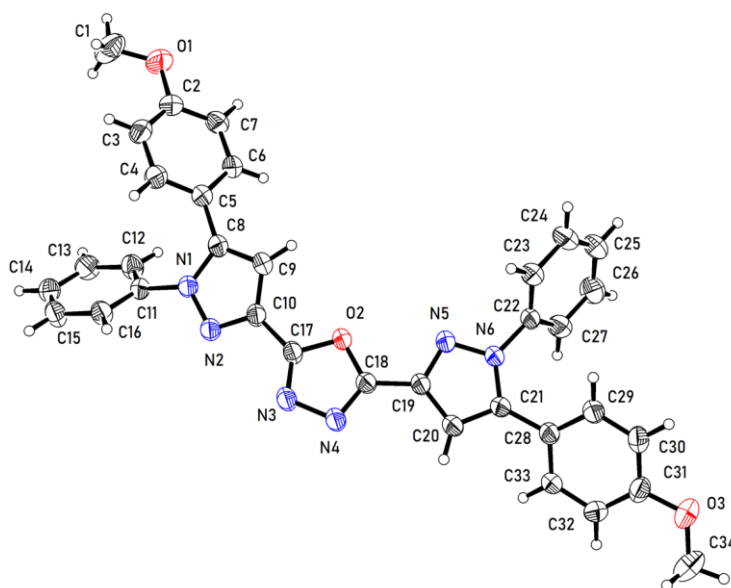
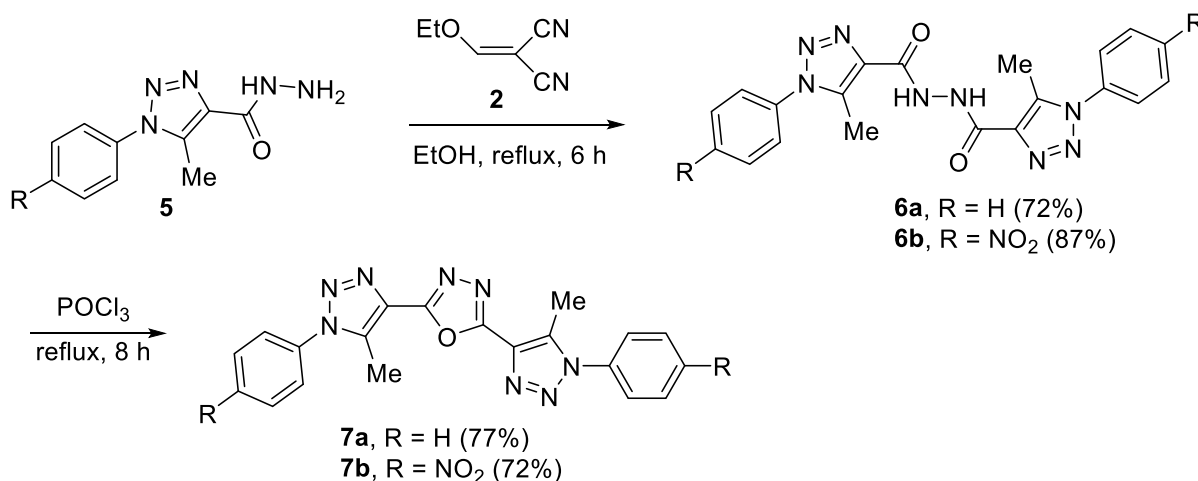


Figure 2. A 50% probability ellipsoid ORTEP representation of the molecule of **4** showing atom numbering

Table 1. Twist angles ($^{\circ}$) between adjacent planes in the structures of **3**, **4**, and **7a**. The geometry after local optimization of geometry. The planes are defined in the discussion.

Compound		Experimental	Optimized
3	3A/3B	44.78(9)	61.90
	3B/3C	48.57(8)	16.57
4	4A/4B	44.60(9)	63.03
	4B/4C	50.72(8)	16.02
	4B/4D	18.32(13)	0
	4D/4E	5.24(16)	0
	4E/4F	53.82(8)	16.23
	4E/4G	33.55(10)	62.41
7	7A/7B	30.68(8)	19.08
	7B/7C	7.51(11)	3.80
	7C/7D	21.14(9)	3.73
	7D/7E	42.96(5)	18.92

The synthesis of 5-methyl-1-phenyl-1*H*-1,2,3-triazole-4-carboxylic acid 2-[(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)carbonyl]hydrazide (**6a**) in 72% from reaction of 5-methyl-1-phenyl-1*H*-1,2,3-triazole-4-carbohydrazide (**5a**) and 2-(ethoxymethylene)malononitrile (**2**) has been reported.²⁸ Similarly, *N,N'*-diacylhydrazine **6b** was synthesized in 87% yield (Scheme 2) from reaction of 5-methyl-1-(4-nitrophenyl)-1*H*-1,2,3-triazole-4-carbohydrazide (**5b**). Ring closure of both **6a** and **6b** in boiling in POCl₃ for 8 h gave the corresponding 1,3,4-oxadiazoles **7a** and **7b** in 77 and 72% yields, respectively (Scheme 2).



Scheme 2. Synthesis of **6** and **7**

The ¹H NMR spectrum of **6b** showed a characteristic singlet at 10.59 ppm corresponding to the two NH protons. The carbonyl carbon appears at 160.5 ppm in its ¹³C NMR spectrum. The ¹H NMR spectra of both **7a** and **7b** showed the absence of NH protons.

The structure of **7a** was confirmed further using crystal X-ray crystallography. The molecule in the structure of **7a** is shown in Figure 3. The molecule comprises five rings, 7A (C1—C6), 7B (N1—N3 and C7—C9), 7C (O1, N4, N5, C10, and C11), 7D (N6, N7, N8, and C12—C14), 7E (C15—C20). The twist angles between the planes of adjacent rings are between 7–43° (Table 1).

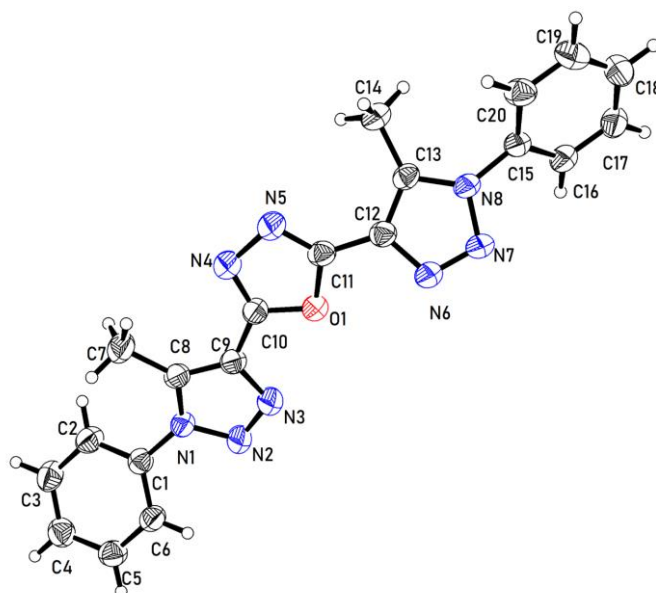


Figure 3. A 50% probability ellipsoid ORTEP representation of the molecule of **7a** showing atom numbering

In addition to the elemental composition, the biological activity of a molecule may be influenced by its flexibility. Local optimization of molecules isolated from the crystal structures of **3**, **4** and **7a** using Avogadro²⁹ gave the results shown in Table 1. The calculations showed that the molecules in the crystal structure were not at the lowest energy conformations, indicating that the geometry may adopt to that of the pathogen.

The antimicrobial activities of **3**, **4**, **6a**, **6b**, **7a**, and **7b** were assessed against some pathogenic microorganisms obtained from the American type culture collection (ATCC; Rockville, MD, USA). The organisms used were *Staphylococcus aureus* ATCC-47077 (*S. aureus*), *Listeria monocytogenes* ATCC-35152 (*L. monocytogenes*), *Escherichia coli* ATCC-25922 (*E. coli*), *Salmonella typhi* ATCC-15566, and *Candida albicans* ATCC-10231 (*C. albicans*). Ampicillin and vancomycin were used reference antibiotics for comparison. Compared with the reference drugs, the tested compounds showed moderate activity against the microorganisms (Table 2).

Table 2. Antimicrobial activity of the synthesized heterocycles

Compound	Gram-positive bacteria		Gram-negative bacteria		Fungi
	<i>S. aureus</i>	<i>L. monocytogenes</i>	<i>E. coli</i>	<i>S. Typhi</i>	<i>C. albicans</i>
3	10	11	10	10	10
4	11	12	10	—	12
6a	12	12	10	12	13
6b	13	15	14	—	14
7a	10	10	9	—	10
7b	12	11	11	—	13
Ampicillin	15	20	16	19	19
Vancomycin	14	15	15	17	15

CONCLUSIONS

Novel 2,5-bis(pyrazol-3-yl)-1,3,4-oxadiazoles and 2,5-bis(1,2,3-triazol-4-yl)-1,3,4-oxadiazoles were synthesized in high yields from the appropriate carbonylhydrazide using simple procedures. The synthesized heterocycles showed moderate activity against *Staphylococcus aureus*, *Listeria monocytogenes*, and *Escherichia coli*.

EXPERIMENTAL

General Melting points were determined using an Electrothermal (variable heater) melting point apparatus. The NMR spectra were measured on a JEOLNMR 500 MHz spectrometer. ¹H (500 MHz) and ¹³C NMR (125 MHz) spectra were recorded in deuterated dimethyl sulfoxide (DMSO-*d*₆) using tetramethylsilane as a standard. The chemical shift (δ) is reported in ppm and the coupling constant (*J*) in Hz. Compounds **1**,³⁰ **2**,³¹ **5a,b**,^{32,33} and **6a**²⁸ were prepared following literature procedures.

Synthesis of *N,N'*-diacylhydrazines **3 and **6b**.** A mixture of **1** or **5b** (5 mmol) **2** (0.61 g, 5 mmol) in dry EtOH (25 mL) was heated under reflux conditions for 6 h. The mixture was left overnight and the product obtained was collected by filtration, washed with EtOH, and dried to give a colorless solid.

5-(4-Methoxyphenyl)-1-phenyl-1*H*-pyrazole-3-carboxylic acid 2-[[5-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-3-yl]carbonyl]hydrazide (3**)** Yield 85%, mp 218–220 °C. ¹H NMR: 10.69 (s, exch., 1H, NH), 10.07 (s, exch., 1H, NH), 7.71–7.68 (m, 12H, Ar), 7.25 (d, 4H, *J* = 8.5 Hz, Ar), 6.90–6.89 (m, 4H, Ar), 3.78 (s, 3H, OMe), 3.71 (s, 3H, OMe). ¹³C NMR: 161.4, 160.6, 154.8, 137.8, 135.3, 134.6, 130.3, 127.7, 127.3, 122.8, 115.6, 115.1, 55.8. Anal. Calcd for C₃₄H₂₈N₆O₄ (584.22): C, 69.85; H, 4.83; N, 14.38; Found: C, 69.99; H, 4.92; N, 14.49%.

5-Methyl-1-(4-nitrophenyl)-1*H*-1,2,3-triazole-4-carboxylic acid 2-[(5-methyl-1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)carbonyl]hydrazide (6b**)** Yield 87%, mp > 300 °C. ¹H NMR: 10.59 (s, exch., 2H, 2 NH), 8.46 (d, 4H, *J* = 8.6 Hz, Ar), 7.99 (d, 4H, *J* = 8.6 Hz, Ar), 2.46 (s, 6H, 2 Me). ¹³C NMR: 160.5, 148.4, 140.7,

138.6, 137.9, 127.0, 125.6, 10.0. Anal. Calcd for C₂₀H₁₆N₁₀O₆ (492.12): C, 48.78; H, 3.28; N, 28.45; Found: C, 48.87; H, 3.40; N, 28.66%.

2,5-Bis(heterocyclic)-1,3,4-oxadiazoles 4 and 7a,b. A mixture of **3** or **6a,b** (2 mmol) and POCl₃ (20 mL) was refluxed for 8 h. The product obtained on cooling was collected by filtration, washed with EtOH, and dried to give the corresponding product **4** or **7a,b**.

2,5-Bis[5-(4-methoxyphenyl)-1-phenyl-1H-pyrazol-3-yl]-1,3,4-oxadiazole (4) Yield 77%, mp 233–235 °C. ¹H NMR: 7.49–36 (m 8H, Ar), 7.26 (s, 2H, Ar), 7.22 (d, 4H, *J* = 8.5 Hz, Ar), 6.91 (d, 4H, *J* = 9.5 Hz, Ar), 3.72 (s, 6H, 2 OMe). ¹³C NMR: 162.8, 160.3, 160.0, 139.8, 137.7, 130.6, 129.8, 129.2, 126.2, 121.4, 114.7, 107.7, 55.8. Anal. Calcd for C₃₄H₂₆N₆O₃ (566.21): C, 72.07; H, 4.63; N, 14.83; Found: C, 72.37; H, 4.72; N, 14.95%.

2,5-Bis(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-1,3,4-oxadiazole (7a) Yield 72%, mp 220–222 °C. ¹H NMR: 7.70–7.63 (m, 10H, Ar), 2.46 (s, 6H, 2 Me). ¹³C NMR: 160.7, 158.4, 137.2, 130.8, 130.3, 126.0, 125.9, 10.3. Anal. Calcd for C₂₀H₁₆N₈O (384.14): C, 62.49; H, 4.20; N, 29.15; Found: C, 62.52; H, 4.33; N, 29.33%.

2,5-Bis[5-methyl-1-(4-nitrophenyl)-1H-1,2,3-triazol-4-yl]-1,3,4-oxadiazole (7b) Yield 75%, mp > 300 °C. ¹H NMR: 8.49 (d, 4H, *J* = 8.6 Hz, Ar), 7.99 (d, 4H, *J* = 8.6 Hz, Ar), 2.45 (s, 6H, 2 Me). ¹³C NMR: 160.5, 148.4, 140.4, 138.6, 137.8, 127.0, 125.6, 10.0. Anal. Calcd for C₂₀H₁₄N₁₀O₅ (474.11): C, 50.64; H, 2.97; N, 29.53; Found: C, 20.73; H, 3.08; N, 29.66%.

Antimicrobial Activity. The agar well diffusion procedure was employed to investigate the antimicrobial activities of **3**, **4**, **6a**, **6b**, **7a**, and **7b**.^{34,35} Ampicillin and vancomycin were used as standards for comparison. Bacterial (70 μL) and yeast (106 CFU/mL) cells were spread on plates containing nutrient agar. The wells (6 mm diameter) were excavated on the injected agar plates then each sample (200 mg) in DMSO (1 mL) was added. The reference antibiotics disks (10 and 30 μg/disk of ampicillin and vancomycin, respectively) were introduced on the surface of agar inoculated plates. The plates were kept at 4 °C for 2 h before incubation to permit diffusion to occur. The plates were kept at 37 °C for 24 h except for yeast strains that were incubated at 28 °C for 24 h. The diameter of the inhibition zone (mm) was measured. The tests were replicated five times and the averages were calculated.

Crystal Structure Determination. Single-crystal XRD data were collected at room temperature on an Agilent SuperNova Dual Atlas diffractometer with a mirror monochromator using Mo radiation. The crystal structures were solved by SHELXS³⁶ and refined using SHELXL³⁷ Non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were inserted in idealized positions, and a riding model was used with *U*_{iso} set at 1.2 or 1.5 times the value of *U*_{eq} for the atom to which they are bonded.

3: C₁₇H₁₄N₃O₂, FW = 292.31, T = 293(2) K, λ = 0.71073 Å, monoclinic, P2₁/n, a = 6.4199(4) Å, b =

9.6695(5) Å, $c = 23.5094(15)$ Å, $\beta = 93.691(6)^\circ$, $V = 1456.37(15)$ Å³, $Z = 4$, density (cal) = 1.333 mg/m³, absorption coefficient = 0.090 mm⁻¹, $F(000) = 612$, crystal size = 0.320 × 0.146 × 0.069 mm³, reflections collected = 13237, independent reflections = 3660, $R(\text{int}) = 0.0293$, parameters = 201, goodness-of-fit on $F^2 = 1.052$, $R1 = 0.0586$, $wR2 = 0.1472$ based on ($I > 2\sigma(I)$), $R1 = 0.0881$, $wR2 = 0.1684$ based on all data, largest diff. peak and hole = 0.219 and -0.178 e.Å⁻³. **4:** C₃₄H₂₆N₆O₃, FW = 566.61, T = 293(2) K, $\lambda = 0.71073$ Å, triclinic, $P\bar{1}$, $a = 8.3728(6)$ Å, $b = 13.3452(9)$ Å, $c = 13.6662(9)$ Å, $\alpha = 75.407(6)^\circ$, $\beta = 77.290(6)^\circ$, $\gamma = 89.585(5)^\circ$, $V = 1439.66(18)$ Å³, $Z = 2$, density (cal) = 1.307 mg/m³, absorption coefficient = 0.086 mm⁻¹, crystal size = 0.319 × 0.203 × 0.050 mm³, reflections collected = 12111, independent reflections = 6838, $R(\text{int}) = 0.0327$, parameters = 391, goodness-of-fit on $F^2 = 1.038$, $R1 = 0.0614$, $wR2 = 0.1382$ based on ($I > 2\sigma(I)$), $R1 = 0.1006$, $wR2 = 0.1656$ based on all data, largest diff. peak and hole = 0.265 and -0.199 e.Å⁻³. **7a:** C₂₀H₁₆N₈O, FW = 384.41, T = 296(2) K, $\lambda = 0.71073$ Å, monoclinic, $P2_1/n$, $a = 11.9990(8)$ Å, $b = 7.8858(5)$ Å, $c = 19.4028(12)$ Å, $\beta = 98.952(6)^\circ$, $V = 1813.6(2)$ Å³, $Z = 4$, density (cal) = 1.408 mg/m³, absorption coefficient = 0.095 mm⁻¹, $F(000) = 800$, crystal size = 0.400 × 0.280 × 0.196 mm³, reflections collected = 15595, independent reflections = 4562, $R(\text{int}) = 0.0422$, parameters = 265, goodness-of-fit on $F^2 = 1.051$, $R1 = 0.0546$, $wR2 = 0.1103$ based on ($I > 2\sigma(I)$), $R1 = 0.1131$, $wR2 = 0.1387$ based on all data, largest diff. peak and hole = 0.165 and -0.157 e.Å⁻³. The crystal structures have been deposited in the Cambridge Structural Database under reference CCDC 2162219–2162221.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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