A Simple Synthesis of 5-(2-Aminophenyl)-1*H*-pyrazoles

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A four-step synthesis of 1-substituted 5-(2-aminophenyl)-1*H*-pyrazoles **5** as a novel type of histamine analogs and versatile building blocks for further transformations was developed. The synthesis starts from commercially available 2-nitroacetophenone (**12**), which is converted into the enamino ketone **13** as the key intermediate. Cyclization of the key intermediate **13** with monosubstituted hydrazines **14a**–**14l** afforded the 5-(2-nitrophenyl)-1*H*-pyrazoles **17a**–**17l**. Finally, catalytic hydrogenation of the nitro compounds **17a**, **17c**–**17e**, and **17g**–**17j** furnished the title compounds **5a**, **5c**–**5e**, and **5g**–**5j**, respectively, in good yields. As demonstrated by some further transformations, additional functionalization of compounds **17** and **5** is feasible, either by electrophilic substitution at C(4) of the pyrazole ring, or at the NH_2 group.

Introduction. – In biological processes, histamine, tyramine, dopamine, tryptamine, serotonin, and melatonin play a crucial role as chemical messengers. Therefore, preparation of their novel synthetic analogs based on the 2-(heteroaryl)ethylamine scaffold is an important target in medicinal and synthetic organic chemistry [1].

Pyrazoles are an important class of heterocyclic compounds. Despite their rare occurrence in nature, numerous pyrazole derivatives have found use in various applications, and a general interest in their chemistry is still continuing (for a review, see [2]). Among numerous synthetic options for the construction of the pyrazole ring, two classical approaches are most frequently employed: *a*) cyclocondensation of a 1,3-dicarbonyl compound with a hydrazine derivative and *b*) 1,3-dipolar cycloaddition of a C–N–N type 1,3-dipole (diazoalkane, nitrile imine, or azomethine imine) to a C,C multiple bond [2].

Recently, a part of our research has been focused on the synthesis of functionalized pyrazoles utilizing the [3+2] cycloaddition and cyclocondensation approach [3][4]. Within this context, pyrazole derivatives functionalized with an amino acid [5], β-amino alcohol [6], 2-phenylethylamine [6a], terpene [7], and dipeptide structural motif [3][4][8] have been prepared. In continuation, we reported a 'ring switching' synthesis of 1-substituted 4-(2-aminoethyl)-1*H*-pyrazol-5-ols **2** [9] as the pyrazole analogs of histamine **1** and, soon after, a one-pot parallel solution-phase synthesis of compounds **2** [10]. Next, the syntheses of 1-substituted 5-(2-aminoethyl)-1*H*-pyrazol-4-carboxamides **3** [11] and their bicyclic analogs, 1,5-disubstituted 6,7-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-4(5*H*)-ones **4** [12] have been reported. In continuation of our work in this field, we focused our attention on 5-(2-aminophenyl)-1*H*-pyrazole derivatives **5** as

another type of histamine analogs. The structures of histamine (**1**) and its analogs **2**–**5** are depicted in *Fig. 1*. Compounds **5** are interesting for several reasons: *a*) to the best of our knowledge, only a handful of these simple compounds were already known, *b*) compounds **5** should be easily accessible from 2-aminoacetophenone (**6**) or its synthetic equivalent, *c*) although a few examples of enaminone-based synthesis of target compounds **5** were known, the literature did not provide sufficient experimental and characterization data, and *d*) because 5-(2-aminophenyl)-1*H*-pyrazole derivatives could be useful building blocks for further transformations including combinatorial studies. As a result of our efforts in this field, we now report a simple enaminone-based synthesis and some further transformations of 1-substituted 5-(2-aminophenyl)-1*H*-pyrazoles **5** as novel histamine analogs.

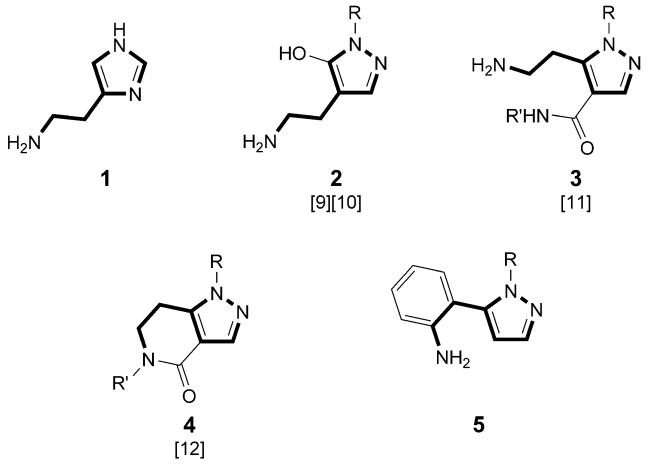
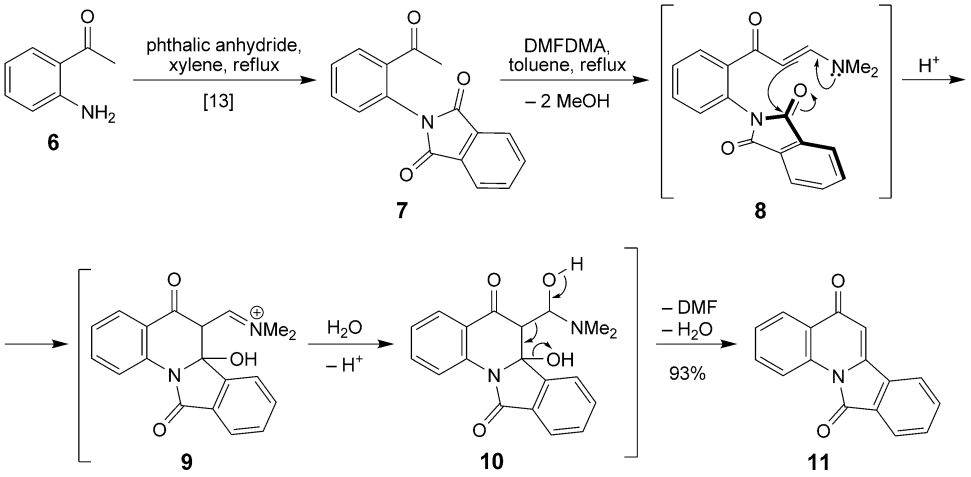


Fig. 1. *Histamine* (**1**) *and its pyrazole analogs* **2**–**5**

Results and Discussion. – First, we tried to synthesize the target compounds from 2-(2-acetylphenyl)-1*H*-isoindole-1,3(2*H*)-dione (**7**), which was prepared by phthaloylation of 2-aminoacetophenone (**6**) according to the procedure described in [13]. Unfortunately, further treatment of **7** with *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) in refluxing toluene gave isoindolo[2,1-*a*]quinoline-5,11-dione (**11**) instead of the desired enamino ketone **8**. This result was not very surprising, since two examples of base-catalyzed cyclizations of **7** into **11** have already been reported [14]. The reaction mechanism can be rationalized by initial formation of enaminone **8** (activated analog of **7**), which cyclizes to **9**, followed by β-elimination of DMF and H_2O to give **11** (*Scheme 1*).

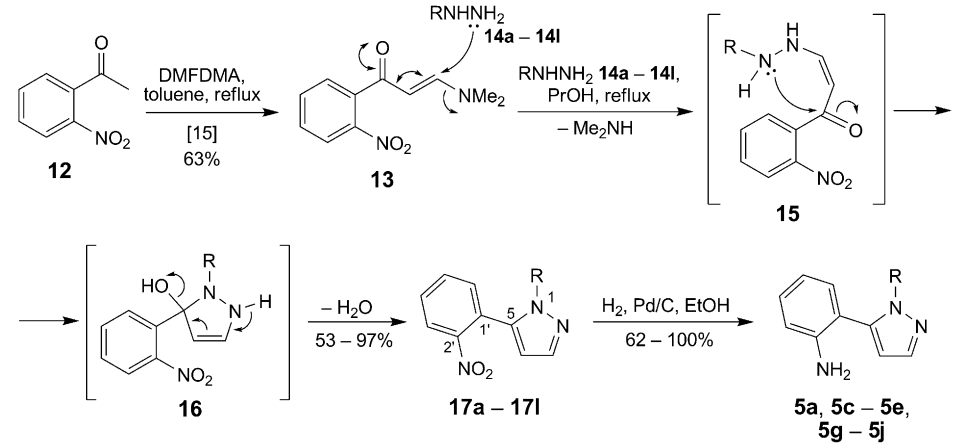
Because the attempted synthesis of target compounds from the *N*-phthaloylated 2-aminoacetophenone **7** failed in the very beginning, we turned our attention to commercially available 2-nitroacetophenone (**12**) as another suitable starting material. Following a slightly modified literature procedure [15], **12** was reacted with DMFDMA to give (*E*)-3-(dimethylamino)-1-(2-nitrophenyl)prop-2-en-1-one (**13**) in 63% yield. Treatment of the key intermediate **13** with $NH_2NH_2 \cdot H_2O$ (**14a**) and a series of alkyl- and arylhydrazines **14b**–**14f** and **14g**–**14l**, respectively, in refluxing PrOH gave

Scheme 1



1-substituted 5-(2-nitrophenyl)pyrazoles **17a**–**17l** in 53–97% yields. The mechanism of formation of pyrazoles **17** can be explained by initial substitution of the dimethylamino group to give the ene-hydrazine **15**. Intramolecular addition of the hydrazino group to the C=O group gives the intermediate 2,3-dihydro-3-hydroxy-1*H*-pyrazole **16**, from which H_2O is eliminated to produce the 1*H*-pyrazole **17**. This proposed mechanism is in agreement with the mechanism determined previously for reaction of related enamino ketones with hydrazines [16]. Finally, reduction of the (nitrophenyl)-1*H*-pyrazoles **17** to the title compounds **5** was carried out by catalytic hydrogenation in the presence of Pd/C. In this manner, 5-(2-aminoethyl)-1*H*-pyrazoles **5a**, **5c**–**5e**, and **5g**–**5j** were prepared in 62–100% yields (*Scheme 2* and *Table 1*).

Scheme 2[a])



[a]) For R and yields of **17** and **5**, see *Table 1*.

Table 1. *Yields of Compounds* **5** *and* **17**

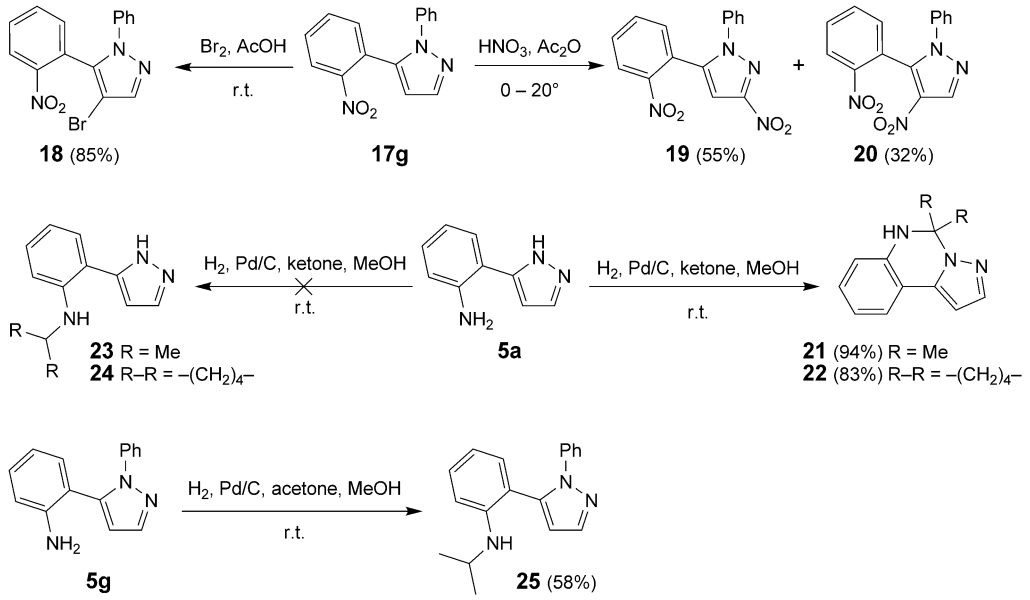
Compound	R	Yield [%]	
		17	**5**
17a, **5a**	H	53	94
17b	Me	74	–
17c, **5c**	Cyclohexyl	61	62
17d, **5d**	*t*Bu	70	92
17e, **5e**	$HOCH_2CH_2$	69	95
17f	CH_2COOEt	83	–
17g, **5g**	Ph	97	93
17h	4-NO_2–C_6H_4	73	–
5h	4-NH_2–C_6H_4	–	88
17i, **5i**	3-MeO–C_6H_4	89	95
17j, **5j**	4-MeO–C_6H_4	79	100
17k	2-Cl–C_6H_4	75	–
17l	3-Cl–C_6H_4	81	–

Next, some further transformations of the intermediates **17** and final products **5** were carried out. Electrophilic bromination of **17g** proceeded selectively at the pyrazole ring to afford the 4-Br analog **18** in 85% yield. Nitration of **17g** took place at the heteroaromatic part of the molecule to produce a mixture of regioisomeric products **19** and **20**. Subsequent chromatographic separation furnished pure compounds **19** and **20** in 55 and 32% yield, respectively. Loss of regioselectivity in nitration was somewhat surprising, yet explainable. Nitronium ion as a strong and hard electrophile can attack free positions in pyrazole **17g**, more nucleophilic C(4) and less nucleophilic C(3). However, C(4) in **17g** is hindered, sterically as well as electrostatically, by the 2-nitrophenyl group at C(5). Consequently, nitration also takes place at less nucleophilic, yet sterically more accessible C(3). Finally, we tried to perform reductive isopropylation of the amines **5a** and **5g**. Catalytic hydrogenation of the 1-unsubstituted compound **5a** in the presence of acetone and cyclopentanone afforded stable tricyclic aminals **21** and **22**, and not the expected 5-[2-(1-methylethylamino)phenyl]-1*H*-pyrazoles **23** and **24**. On the other hand, reductive isopropylation of the 1-phenyl analog **5g** in acetone in the presence of 10% Pd/C furnished the desired *N*-isopropylated derivative **25** in 58% yield (*Scheme 3*).

The structures of novel compounds **17c**–**17f**, **17h**–**17l**, **5b**–**5l**, **18**–**20**, **22** and **25** were determined by spectroscopic methods (IR, ^{1}H- and ^{13}C-NMR, and NOESY spectroscopy, and MS) and by elemental analyses. Compounds **17e**, **17f**, **5d**, **5e**, **5h**, **18**, **20**, and **22** were not obtained in analytically pure form. Their identities were confirmed by ^{13}C-NMR and/or EI-HR-MS. Physical and spectroscopic data for known compounds **10** [14], **13** [15], **17a** [17], **17b** [18], **17g** [15], **5a** [19], and **21** [20] were in agreement with the literature data.

The (*E*)-configuration of the C=C bond in the enaminone **13** was determined by ^{1}H-NMR on the basis of the vicinal coupling constant, $^3J(2,3) = 12.7$ Hz, which was in agreement with the (*E*)-configuration. The 'regiochemistry' of pyrazoles **17b** and **17d** was confirmed by NOESY spectroscopy. The absence of NOE between the 1-alkyl

Scheme 3



group (Me or ^{t}Bu), and H–C(4) and H–C(3) was in agreement with the proposed structure (*Fig. 2*).

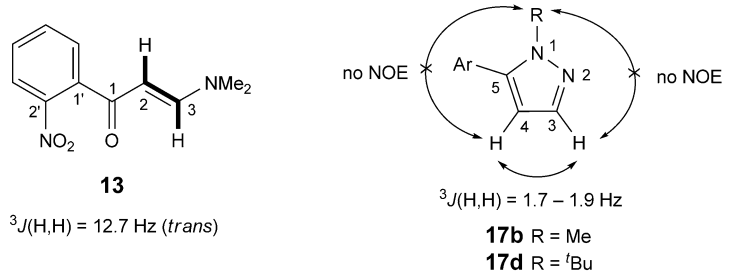


Fig. 2. *Coupling constants and NOESY results for* **13**, **17b** *and* **17d**

The structures of compounds **13**, **17a**, **17j**, and **22** were determined by X-ray crystallography (*Figs. 3–6*).

Conclusions. – In summary, a simple three-step synthesis of 1-substituted 5-(2-aminophenyl)-1*H*-pyrazoles **5** as novel conformationally constrained analogs of histamine was developed. The synthesis comprises condensation of commercially available 2-nitroacetophenone (**12**) with DMFDMA to give the enamino ketone **13**, followed by regioselective cyclization with monosubstituted hydrazines **14** to give the 5-(2-nitrophenyl)-1*H*-pyrazoles **17**. Subsequent reduction of the NO_2 group by catalytic hydrogenation afforded the title compounds **5**, in good overall yields. Compounds **17**

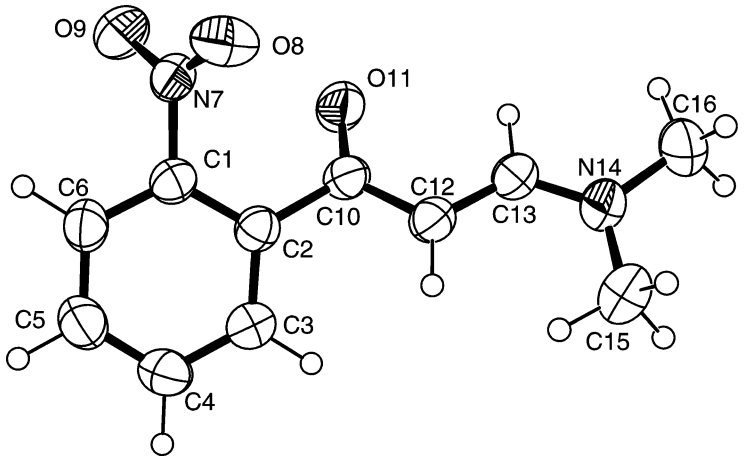


Fig. 3. *Molecular structure of compound* **13**. Ellipsoids are plotted at 50% probability level. H-Atoms are drawn as circles of arbitrary radii.

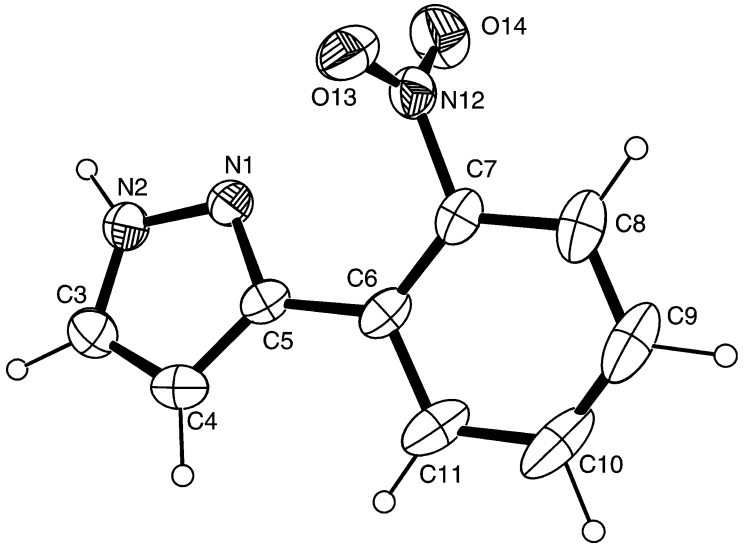


Fig. 4. *Molecular structure of compound* **17a**. Ellipsoids are plotted at 50% probability level. H-Atoms are drawn as circles of arbitrary radii.

and **5** are also useful building blocks, which can easily be derivatized, either at the amino function, or at C(3) and C(4) of the pyrazole ring. In conclusion, this work represents another useful synthetic application of enaminones as versatile reagents in the diversity-oriented synthesis of histamine analogs and other functionalized heterocycles.

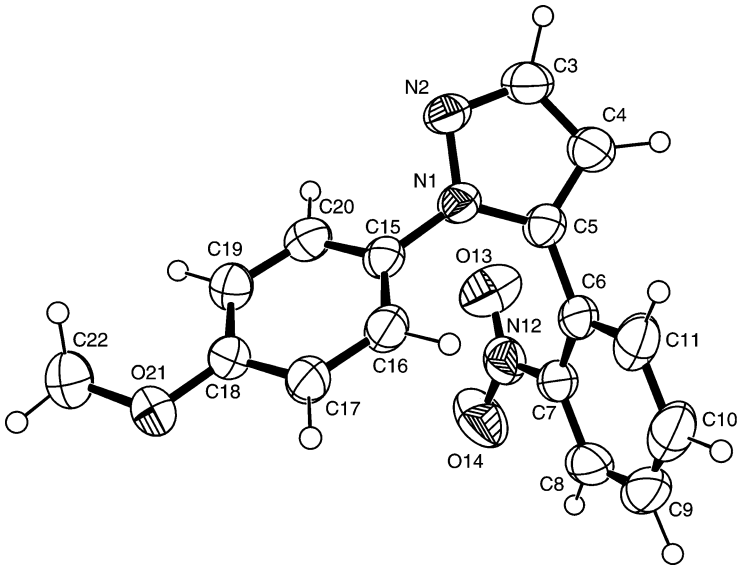


Fig. 5. *Molecular structure of compound* **17j**. Ellipsoids are plotted at 50% probability level. H-Atoms are drawn as circles of arbitrary radii.

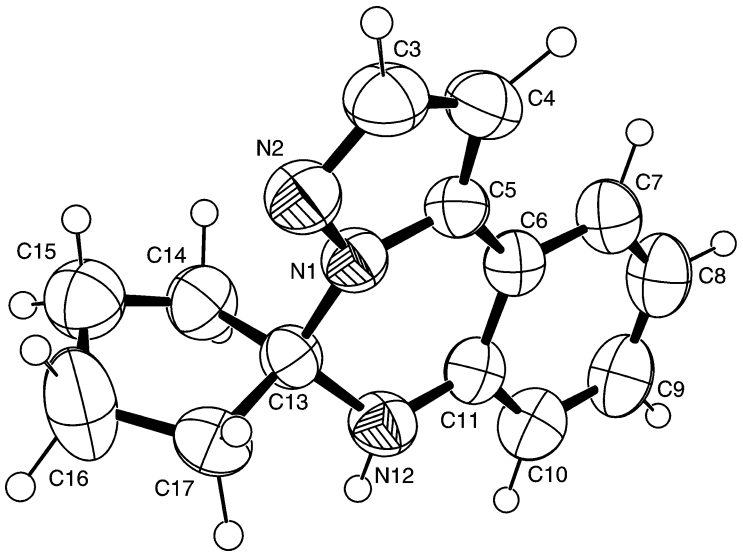


Fig. 6. *Molecular structure of compound* **22**. Ellipsoids are plotted at 50% probability level. H-Atoms are drawn as circles of arbitrary radii.

Experimental Part

1. *General.* Catalytic hydrogenations: *Parr Pressure Reaction Hydrogenation Apparatus 500 ml 3916EF.* Column chromatography (CC): silica gel (*Fluka*, silica gel *60*, particle size: 0.035 – 0.070 mm).

TLC: aluminium sheets, silica gel *60 F_{254}* (*Fluka*). M.p.: *Kofler* micro hot stage and *Stanford Research Systems MPA100 OptiMelt* automated melting point system; uncorrected. IR Spectra: *Perkin-Elmer Spectrum BX FTIR* spectrophotometer; in cm^{-1}. ^1H- and ^{13}C-NMR spectra: *Bruker Avance DPX 300* instrument (300 and 75.5 MHz, resp.) in (D_6)DMSO and $CDCl_3$ with TMS as the internal standard (=0 ppm), *J* in Hz. MS and HR-MS: *AutoSpecQ* spectrometer; in *m*/*z*. Elemental analyses: *Perkin-Elmer CHN Analyser 2400 II*.

2. *Starting Materials. 2-Aminoacetophenone* (**6**), *2-nitroacetophenone* (**12**), DMFDMA, hydrazines **14a**–**14l**, and 10% Pd/C are commercially available (*Sigma–Aldrich*). *2-(2-Acetylphenyl)-1*H*-isoindole-1,3(2*H*)-dione* (**7**) was prepared from **6** according to the procedure described in [13].

3. *Synthesis of Isoindolo[2,1-*a*]quinoline-5,11-dione* (**11**). A mixture of **7** (2.650 g, 10 mmol), anh. toluene (15 ml), and DMFDMA (1.5 ml, 10 mmol) was heated under reflux for 3 h. Volatile components were evaporated *in vacuo*, and the solid residue was crystallized from AcOEt to give **11**. Yield: 2.981 g (93%). Yellow solid. M.p. 260–263° ([14c]: 260–263°). R_f (AcOEt) 0.32. IR (KBr): 3051, 1741 (C=O), 1648 (C=O), 1592, 1477, 1407, 1344, 1291, 1269, 1190, 1167, 1138, 1094, 1061, 907, 772, 756, 698, 571. ^1H-NMR ($CDCl_3$): 6.74 (*s*, H–C(6)); 7.43 (*ddd*, *J* = 0.9, 7.2, 8.0, H–C(3)); 7.66 (*dt*, *J* = 1.1, 7.4, H–C(8)); 7.70–7.78 (*m*, H–C(7), H–C(9)); 7.82 (*td*, *J* = 0.8, 7.4, H–C(10)); 7.97 (*td*, *J* = 0.9, 7.4, H–C(4)); 8.30 (*dd*, *J* = 1.4, 8.0, H–C(2)); 9.11 (*dd*, *J* = 0.4, 8.5, H–C(1)).

4. *Synthesis of (*E*)-3-(Dimethylamino)-1-(2-nitrophenyl)prop-2-en-1-one* (**13**). Compound **13** was prepared according to a slightly modified literature procedure [15a]. A mixture of **12** (3.30 g, 20 mmol), anh. toluene (20 ml), and DMFDMA (3 ml, 20 mmol) was stirred under reflux for 4 h. Volatile components were evaporated *in vacuo*, and the solid residue was crystallized from AcOEt/hexanes to give **13**. Yield: 2.77 g (63%). Yellow solid. M.p. 127–129° ([15a]: 128–129°, [15c]: 129–132°). R_f (AcOEt) 0.25. IR (KBr): 3031, 2884, 2806, 1640(C=O), 1549, 1523, 1142, 1412, 1364, 1243, 1103, 1051, 974, 855, 729. ^1H-NMR ($CDCl_3$): 2.87, 3.09 (2*s*, 1:1, Me_2N); 5.27 (*d*, *J* = 12.7, H–C(2)); 7.45–7.65 (*m*, C_6H_4); 7.96 (*d*, *J* = 12.7, H–C(3)).

5. *Preparation of 1-Substituted 5-(2-Nitrophenyl)-1*H*-pyrazoles* **17a**–**17d** *and* **17g**–**17l**. *General Procedure 1 (GP 1)*. Enaminone **13** (1.10 g, 5 mmol) was added to a stirred suspension of hydrazine derivative[1]) **14a**–**14d** and **14g**–**14l** (5 mmol) in PrOH (20 ml), and the mixture was stirred under reflux for 2–5 h. Volatile components were evaporated *in vacuo*, and the solid residue was crystallized from EtOH/H_2O to give **17a**–**17d** and **17g**–**17l**.

5.1. *5-(2-Nitrophenyl)-1*H*-pyrazole* (**17a**). Prepared from **13** (1.100 g, 5 mmol) and **14a** (0.335 g, 5 mmol) by *GP 1* (reflux for 2.5 h). Yield: 503 mg (53%). Yellowish solid. M.p. 75–78° ([17]: 74–76°). R_f (AcOEt) 0.57. IR (KBr): 3524, 3292, 1636, 1612, 1523, 1462, 1381, 1068, 953, 772, 745. ^1H-NMR ($CDCl_3$): 6.52 (*d*, *J* = 2.4, H–C(4)); 7.47 (*dt*, *J* = 1.5, 7.9, 1 H, C_6H_4); 7.60 (*dt*, *J* = 1.2, 7.6, 1 H, C_6H_4); 7.63 (*d*, *J* = 2.4, H–C(3)); 7.74 (*dd*, *J* = 1.4, 7.7, 1 H, C_6H_4); 7.75 (*dd*, *J* = 1.2, 7.9, 1 H, C_6H_4); 10.70 (br. *s*, H–N(1)). ^{13}C-NMR ($CDCl_3$): 104.8; 123.7; 127.1; 128.8; 131.0; 132.0; 149.3. ESI-MS: 190 ($[M+H]^+$). HR-ESI-MS: 190.0500 ($[M+H]^+$, $C_9H_8N_3O_2^+$; calc. 190.0617). Anal. calc. for $C_9H_7N_3O_2$ (189.17): C 57.14, H 3.73, N 22.21; found: C 56.90, H 3.63, N 22.06.

5.2. *1-Methyl-5-(2-nitrophenyl)-1*H*-pyrazole* (**17b**) [18]. Prepared from **13** (1.100 g, 5 mmol), **14b** (0.23 g, 0.265 ml, 5 mmol), and 37% aq. HCl (10 drops, *ca.* 3 mmol) by *GP 1* (reflux for 4 h). Yield: 755 mg (74%). Yellowish solid. M.p. 99–101°. R_f (AcOEt) 0.63. IR (KBr): 3408, 3265, 1636, 1614, 1526, 1483, 1362, 1187, 984, 851, 754. ^1H-NMR ($CDCl_3$): 3.70 (*s*, Me); 6.24 (*d*, *J* = 1.9, H–C(4)); 7.44 (*dd*, *J* = 1.5, 7.5, 1 H, C_6H_4); 7.53 (*d*, *J* = 1.9, H–C(3)); 7.65 (*dd*, *J* = 1.7, 7.7, 1 H, C_6H_4); 7.72 (*dd*, *J* = 1.5, 7.5, 1 H, C_6H_4); 8.07 (*dd*, *J* = 1.4, 8.0, 1 H, C_6H_4). ^{13}C-NMR ($CDCl_3$): 37.1; 106.9; 124.7; 125.8; 130.4; 132.9; 133.1; 138.2; 138.8; 149.3. ESI-MS: 204 ($[M+H]^+$). Anal. calc. for $C_{10}H_9N_3O_2^+$ (203.20): C 59.11, H 4.46, N 20.68; found: C 58.97, H 4.38, N 20.57.

5.3. *1-Cyclohexyl-5-(2-nitrophenyl)-1*H*-pyrazole* (**17c**). Prepared from **13** (1.100 g, 5 mmol) and **14c** (573 mg, 5 mmol) by *GP 1* (reflux for 5 h). Yield: 595 mg (61%). Yellowish solid. M.p. 60–62°. R_f (AcOEt) 0.56. IR (KBr): 3451, 3427, 1607, 1524, 1480, 1437, 1375, 1350, 1281, 1207, 1034, 973, 833, 784, 746. ^1H-NMR ($CDCl_3$): 1.08–1.33 (*m*, 3 H, C_6H_{11}); 1.67–1.68 (*m*, 1 H, C_6H_{11}); 1.76–2.07 (*m*, 6 H,

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[1]) Hydrazine hydrochlorides **14a**, **14c**, **14d**, **14g**, and **14i**–**14l** were used. In the case of free hydrazines **14b** and **14h**, 37% aq. HCl (10 drops, *ca.* 3 mmol) was also added.

C_6H_{11}); 3.61–3.74 (*tt*, *J* = 4.2, 11.3, 1 H, C_6H_{11}); 6.17 (*d*, *J* = 1.9, H–C(4)); 7.40 (*dd*, *J* = 1.5, 7.5, 1 H, C_6H_4); 7.57 (*d*, *J* = 1.9, H–C(3)); 7.64 (*dt*, *J* = 1.7, 7.7, 1 H, C_6H_4); 7.71 (*dt*, *J* = 1.5, 7.5, 1 H, C_6H_4); 8.03 (*dd*, *J* = 1.4, 7.9, 1 H, C_6H_4). ^{13}C-NMR ($CDCl_3$): 25.2; 25.7; 33.1; 58.1; 105.9; 124.5; 126.0; 130.2; 132.8; 132.9; 136.9; 138.6; 149.5. ESI-MS: 272 ($[M+H]^+$). HR-ESI-MS: 272.1399 ($[M+H]^+$, $C_{15}H_{18}N_3O_2^+$; calc. 272.1409). Anal. calc. for $C_{15}H_{17}N_3O_2$ (271.31): C 66.40, H 6.37, N 15.49; found: C 66.32, H 6.37, N 15.46.

5.4. *1-(*tert*-Butyl)-5-(2-nitrophenyl)-1*H*-pyrazole* (**17d**). Prepared from **13** (1.100 g, 5 mmol) and **14d** (624 mg, 5 mmol) by *GP 1* (reflux for 4.5 h). Yield: 853 mg (70%). Yellowish solid. M.p. 67–71°. R_f (AcOEt) 0.64. IR (KBr): 3534, 3466, 2985 1616, 1573, 1528, 1445, 1362, 1261 1130, 924, 853, 781, 755. ^{1}H-NMR ($CDCl_3$): 1.47 (*s*, *t*-Bu); 6.07 (*d*, *J* = 1.7, H–C(4)); 7.47 (*dd*, *J* = 1.8, 7.3, 1 H, C_6H_4); 7.52 (*d*, *J* = 1.7, H–C(3)); 7.58 (*dt*, *J* = 1.9, 7.5, 1 H, C_6H_4); 7.63 (*dt*, *J* = 1.6, 7.4, 1 H, C_6H_4); 8.05 (*dd*, *J* = 1.7, 7.8, 1 H, C_6H_4). ^{13}C-NMR ($CDCl_3$): 30.8; 61.7; 108.2; 124.5; 129.4; 130.0; 132.3; 133.3; 136.6; 137.2; 148.9. ESI-MS: 246 ($[M+H]^+$). HR-ESI-MS: 246.1240 ($[M+H]^+$, $C_{13}H_{16}N_3O_2^+$; calc. 246.1243). Anal. calc. for $C_{13}H_{15}N_3O_2$ (245.28): C 63.66, H 6.16, N 17.1; found: C 63.51, H 6.13, N 16.93.

5.5. *5-(2-Nitrophenyl)-1-phenyl-1*H*-pyrazole* (**17g**). Prepared from **13** (1.100 g, 5 mmol) and **14g** (536 mg, 5 mmol) by *GP 1* (reflux for 2 h). Yield: 951 mg (97%). Yellowish solid. M.p. 120–122° ([15c]: 66–70°). R_f (33% AcOEt/hexanes) 0.33. IR (KBr): 3410, 3343, 2977, 1648, 1593, 1530, 1495, 1441, 1383, 1337, 1136, 1088, 1049, 808, 756. ^{1}H-NMR ($CDCl_3$): 6.47 (*d*, *J* = 1.9, H–C(4)); 7.20–7.32 (*m*, Ph); 7.40 (*dd*, *J* = 1.5, 7.5, 1 H, C_6H_4); 7.55 (*dt*, *J* = 1.7, 7.7, 1 H, C_6H_4); 7.62 (*dd*, *J* = 1.5, 7.5, 1 H, C_6H_4); 7.76 (*d*, *J* = 1.9, H–C(3)); 7.90 (*dd*, *J* = 1.4, 8.0, 1 H, C_6H_4). ^{13}C-NMR ($CDCl_3$): 108.5; 124.5; 124.6; 126.0; 127.7; 129.1; 130.0; 132.8; 133.0; 138.0; 139.4; 140.4; 148.8. ESI-MS: 266 ($[M+H]^+$). Anal. calc. for $C_{15}H_{11}N_3O_2$ (265.27): C 67.92, H 4.18, N 15.84; found: C 67.79, H 4.12, N 15.78.

5.6. *5-(2-Nitrophenyl)-1-(4-nitrophenyl)-1*H*-pyrazole* (**17h**). Prepared from **13** (1.100 g, 5 mmol), **14h** (624 mg, 5 mmol), and 37% aq. HCl (10 drops, *ca.* 3 mmol) by *GP 1* (reflux for 4 h). Yield: 675 mg (73%). Red-brown solid. M.p. 176–179°. R_f (AcOEt) 0.60. IR (KBr): 3468, 3436, 1596, 1520, 1499, 1383, 1349, 853, 751. ^{1}H-NMR ($CDCl_3$): 6.52 (*d*, *J* = 1.8, H–C(4)); 7.44 (*dd*, *J* = 1.5, 7.5, 1 H, C_6H_4); 7.45 (*dt*, *J* = 2.2, 9.2, 2 H, C_6H_4); 7.66 (*dt*, *J* = 1.8, 7.6, 1 H, C_6H_4); 7.71 (*dt*, *J* = 1.6, 7.5, 1 H, C_6H_4); 7.82 (*d*, *J* = 1.8, H–C(3)); 8.02 (*dd*, *J* = 1.5, 7.8, 1 H, C_6H_4); 8.17 (*dt*, *J* = 2.2, 9.2, 2 H, C_6H_4). ^{13}C-NMR ($CDCl_3$): 110.5; 124.1; 125.0; 125.3; 125.6; 131.2; 133.0; 133.9; 138.8; 142.0; 144.7; 146.4; 148.9. ESI-MS: 311 ($[M+H]^+$). HR-ESI-MS: 311.0776 ($[M+H]^+$, $C_{15}H_{11}N_4O_4^+$; calc. 311.0780). Anal. calc. for $C_{15}H_{10}N_4O_4^+$ (310.26): C 58.07, H 3.25, N 18.06; found: C 57.82, H 3.33, N 17.68.

5.7. *1-(3-Methoxyphenyl)-5-(2-nitrophenyl)-1*H*-pyrazole* (**17i**). Prepared from **13** and **14i** (697 mg, 5 mmol) by *GP 1* (reflux for 2 h). Yield: 1.035g (89%). Yellowish solid. M.p. 112–116°. R_f (AcOEt) 0.61. IR (KBr): 3455, 1607, 1525, 1491, 1439, 1377, 1351, 1283, 1210, 1035, 972, 785. ^{1}H-NMR ($CDCl_3$): 3.70 (*s*, Me); 6.46 (*d*, *J* = 1.9, H–C(4)); 6.77 (*ddd*, *J* = 0.9, 1.9, 7.9, 1 H, C_6H_4); 6.82 (*ddd*, *J* = 0.9, 2.5, 8.3, 1 H, C_6H_4); 6.85 (br. *t*, *J* = 2.2, 1 H, C_6H_4); 7.14 (*t*, *J* = 8.1, 1 H, C_6H_4); 7.40 (*dd*, *J* = 1.5, 7.5, 1 H, C_6H_4); 7.55 (*dt*, *J* = 1.7, 7.7, 1 H, C_6H_4); 7.63 (*dd*, *J* = 1.5, 7.5, 1 H, C_6H_4); 7.75 (*d*, *J* = 1.8, H–C(3)); 7.92 (*dd*, *J* = 1.4, 8.0, 1 H, C_6H_4). ^{13}C-NMR ($CDCl_3$): 55.4; 108.5; 109.9; 113.9; 116.5; 124.5; 126.0; 129.7; 130.0; 132.7; 133.0; 138.0; 140.3; 140.4; 148.8; 160.0. ESI-MS: 296 ($[M+H]^+$). Anal. calc. for $C_{16}H_{13}N_3O_3$ (295.29): C 65.08, H 4.44, N 14.23; found: C 65.02, H 4.34, N 14.08.

5.8. *1-(4-Methoxyphenyl)-5-(2-nitrophenyl)-1*H*-pyrazole* (**17j**). Prepared from **13** (1.100 g, 5 mmol) and **14j** (697 mg, 5 mmol) by *GP 1* (reflux for 2 h). Yield: 931 mg (79%). Yellowish solid. M.p. 126–128°. R_f (AcOEt) 0.60. IR (KBr): 3528, 3410, 1636, 1616, 1528, 1515, 1454, 1393, 1340, 1249, 1028, 837, 793, 757. ^{1}H-NMR ($CDCl_3$): 3.77 (*s*, Me); 6.45 (*d*, *J* = 1.9, H–C(4)); 6.80 (*dt*, *J* = 2.8, 9.0, 2 H, C_6H_4); 7.16 (*dt*, *J* = 2.8, 9.0, 2 H, C_6H_4); 7.39 (*dd*, *J* = 1.5, 7.5, 1 H, C_6H_4); 7.53 (*dt*, *J* = 1.7, 7.7, 1 H, C_6H_4); 7.61 (*dt*, *J* = 1.5, 7.5, 1 H, C_6H_4); 7.73 (*d*, *J* = 1.9, H–C(3)); 7.89 (*dd*, *J* = 1.3, 8.0, 1 H, C_6H_4). ^{13}C-NMR ($CDCl_3$): 55.5; 108.0; 114.2; 124.5; 126.0; 126.1; 129.9; 132.5; 132.8; 132.9; 138.1; 140.1; 148.9; 159.0. ESI-MS: 296 ($[M+H]^+$). HR-ESI-MS: 296.1033 ($[M+H]^+$, $C_{16}H_{14}N_3O_3^+$; calc. 296.1035). Anal. calc. for $C_{16}H_{13}N_3O_3^+$ (295.29): C 65.08, H 4.44, N 14.23; found: 65.08, H 4.36, N 14.20.

5.9. *1-(2-Chlorophenyl)-5-(2-nitrophenyl)-1*H*-pyrazole* (**17k**). Prepared from **13** (1.100 g, 5 mmol) and **14k** (884 mg, 5 mmol) by *GP 1* (reflux for 2.5 h). Yield: 1.116 g (75%). Yellowish solid. M.p. 116–118°. R_f (AcOEt) 0.56. IR (KBr): 3497, 3444, 1617, 1524, 1491, 1439, 1383, 1352, 788. ^{1}H-NMR ($CDCl_3$): 6.51 (*d*, *J* = 1.9, H–C(4)); 7.24–7.59 (*m*, 7 H, C_6H_4); 7.81 (*d*, *J* = 1.9, H–C(3)); 7.84 (*dd*, *J* = 1.3, 8.0, 1 H,

C_6H_4). ESI-MS: 300 ($[M+H]^+$). HR-ESI-MS: 300.0542 ($[M+H]^+$, $C_{15}H_{11}ClN_3O_2^+$; calc. 300.0540). Anal. calc. for $C_{15}H_{10}ClN_3O_2$ (299.71): C 60.16, H 3.36, N 14.02; found: C 59.82, H 3.14, N 13.77.

5.10. *1-(3-Chlorophenyl)-5-(2-nitrophenyl)-1*H*-pyrazole* (**17l**). Prepared from **13** (1.100 g, 5 mmol) and **14l** (884 mg, 5 mmol) by *GP 1* (reflux for 2.5 h). Yield: 1.209 mg (81%). Yellowish solid. M.p. 95–97°. R_f (AcOEt) 0.54. IR (KBr): 3516, 3410, 1619, 1593, 1528, 1485, 1428, 1373, 1356, 872, 793. ^{1}H-NMR ($CDCl_3$): 6.47 (*d*, *J* = 1.8, H–C(4)); 7.09 (*dt*, *J* = 1.7, 7.6, 1 H, C_6H_4); 7.18 (*t*, *J* = 7.8, 1 H, C_6H_4); 7.26 (*dt*, *J* = 1.6, 8.1, 1 H, C_6H_4); 7.32 (*t*, *J* = 1.9, 1 H, C_6H_4); 7.40 (*dd*, *J* = 1.7, 7.4, 1 H, C_6H_4); 7.59 (*dt*, *J* = 1.7, 7.7, 1 H, C_6H_4); 7.66 (*dt*, *J* = 1.5, 7.5, 1 H, C_6H_4); 7.76 (*d*, *J* = 1.8, H–C(3)); 7.96 (*dd*, *J* = 1.4, 7.9, 1 H, C_6H_4). ^{13}C-NMR ($CDCl_3$): 109.0; 122.3; 124.7; 124.8; 125.7; 127.8; 130.0; 130.3; 132.8; 133.2; 134.8; 138.2; 140.5; 140.9; 148.8. ESI-MS: 300 ($[M+H]^+$). HR-ESI-MS: 300.0543 ($[M+H]^+$, $C_{15}H_{11}ClN_3O_2^+$; calc. 300.0540). Anal. calc. for $C_{15}H_{10}ClN_3O_2$ (299.71): C 60.11, H 3.36, N 14.02; found: C 60.00, H 3.30, N 13.94.

6. *Preparation of 1-Substituted 5-(2-Nitrophenyl)-1*H*-pyrazoles* **17e** *and* **17f**. *General Procedure 2 (GP 2)*. Enaminone **13** (1.100 g, 5 mmol) was added to a stirred suspension of hydrazine derivative[2]) **14** (5 mmol) in PrOH (20 ml), and the mixture was stirred under reflux for 2–5 h. Volatile components were evaporated *in vacuo*, and the oily residue was purified by CC (AcOEt). Fractions containing the product were combined and evaporated *in vacuo* to give **17e** and **17f**.

6.1. *1-(2-Hydroxyethyl)-5-(2-nitrophenyl)-1*H*-pyrazole* (=*2-[5-(2-Nitrophenyl)-1*H*-pyrazol-1-yl]-ethanol*; **17e**). Prepared from **13** (1.100 g, 5 mmol) and **14e** (380 mg, 5 mmol) by *GP 2* (reflux for 4 h). Yield: 753 mg (69%). Yellow oil. R_f (AcOEt) 0.43. IR (NaCl): 3356, 2945, 1615, 1573, 1528, 1406, 1349, 1063, 852, 786, 752. ^{1}H-NMR ($CDCl_3$): 3.47 (br. *t*, *J* = 5.6, OH); 3.92–3.98 (*m*, CH_2); 4.00–4.05 (*m*, CH_2); 6.26 (*d*, *J* = 1.9, H–C(4)); 7.45 (*dd*, *J* = 1.6, 7.4, 1 H, C_6H_4); 7.59 (*d*, *J* = 1.9, H–C(3)); 7.66 (*dd*, *J* = 1.7, 7.7, 1 H, C_6H_4); 7.72 (*dtd*, *J* = 1.5, 7.5, 1 H, C_6H_4); 8.05 (*dd*, *J* = 1.4, 8.0, 1 H, C_6H_4). ^{13}C-NMR ($CDCl_3$): 51.3; 61.5; 106.7; 124.6; 125.3; 130.6; 133.1; 138.7; 139.2; 149.3; 162.4. EI-MS: 233 (M^+). HR-EI-MS: 233.0810 (M^+, $C_{11}H_{11}N_3O_3^+$; calc. 233.0800).

6.2. *1-(2-Ethoxy-2-oxoethyl)-5-(2-nitrophenyl)-1*H*-pyrazole* (= *Ethyl [5-(2-Nitrophenyl)-1*H*-pyrazol-1-yl]acetate*; **17f**). Prepared from **13** (1.100 g, 5 mmol) and **14f** (779 mg, 5 mmol) by *GP 2* (reflux for 2 h). Yield: 1.146 g (83%). Brownish oil. R_f (AcOEt) 0.61. IR (NaCl): 3458, 3104, 2984, 1715, 1616, 1573, 1530, 1478, 1458, 1407, 1351, 1203, 1025, 928, 852, 787, 750. ^{1}H-NMR ($CDCl_3$): 1.22 (*t*, *J* = 7.1, CH_2*Me*); 4.15 (*q*, *J* = 7.1, C*H*$_2$Me); 4.76 (*s*, C*H*$_2$COOEt); 6.29 (*d*, *J* = 1.9, H–C(4)); 7.52 (*dd*, *J* = 1.8, 7.2, 1 H, C_6H_4); 7.61 (*d*, *J* = 1.9, H–C(3)); 7.64 (*dt*, *J* = 1.9, 7.4, 1 H, C_6H_4); 7.69 (*dt*, *J* = 1.7, 7.5, 1 H, C_6H_4); 8.02 (*dd*, *J* = 1.6, 7.7, 1 H, C_6H_4). ^{13}C-NMR ($CDCl_3$): 14.2; 51.3; 61.9; 107.7; 124.4; 124.9; 130.7; 132.9; 133.4; 138.7; 139.8; 149.4; 167.8. EI-MS: 275 (M^+). HR-EI-MS: 275.0913 (M^+, $C_{13}H_{13}N_3O_4^+$: 275.0906).

7. *Reduction of 1-Substituted 5-(2-Nitrophenyl)-1*H*-pyrazoles* **17**. *General Procedure for the Preparation of 1-Substituted 5-(2-Aminophenyl)-1*H*-pyrazoles* **5a**, **5c**–**5e**, *and* **5g**–**5j**. A mixture of **17a**, **17c**–**17e**, and **17g**–**17j** (1 mmol), EtOH (10 ml), and 10% Pd/C (100 mg) was hydrogenated (3 bar of H_2) at r.t. for 3 h. The catalyst was removed by filtration through a fritted funnel, washed with EtOH (5 ml), and the combined filtrate was evaporated *in vacuo* to give **5a**, **5c**–**5e**, and **5g**–**5j**. Amine **5c** was dissolved in EtOH (3 ml), and a 3.6M soln. of HCl in Et_2O (10 ml) was added. The precipitate was collected by filtration to give **5c** hydrochloride.

7.1. *5-(2-Aminophenyl)-1*H*-pyrazole* (=*2-(1*H*-Pyrazol-5-yl)benzenamine*; **5a**). Prepared from **17a** (189 mg, 1 mmol). Yield: 149 mg (94%). White solid. M.p. 124–126° (from EtOH/H_2O) ([18]: 122–123°). R_f (AcOEt) 0.59. IR (KBr): 3407, 3266, 3177, 1607, 1591, 1530, 1507, 1470, 1446, 1350, 1309, 1194, 1153, 1065, 1039, 947, 765. ^{1}H-NMR ((D$_6$)DMSO): 6.29 (*s*, NH_2); 6.55 (*dt*, *J* = 1.1, 7.4, 1 H, C_6H_4); 6.68 (*d*, *J* = 1.8, H–C(4)); 6.71 (*dd*, *J* = 0.9, 8.1, 1 H, C_6H_4); 6.97 (*dt*, *J* = 1.4, 7.6, 1 H, C_6H_4); 7.50 (*dd*, *J* = 1.3, 7.8, 1 H, C_6H_4); 7.78 (*d*, *J* = 2.3, H–C(3)); 12.83 (*s*, H–N(1)). ^{13}C-NMR ((D$_6$)DMSO): 102.1; 115.4; 115.5; 115.6; 127.8; 128.9; 145.6; 145.7; 151.5. EI-MS: 159 (M^+). HR-EI-MS: 159.0796 (M^+, $C_9H_9N_3^+$; calc. 159.0803). Anal. calc. for $C_9H_9N_3 \cdot {}^1/_8\,H_2O$ (159.19): C 66.96, H 5.78, N 26.03; found: C 66.94, H 5.54, N 26.14.

7.2. *5-(2-Aminophenyl)-1-cyclohexyl-1*H*-pyrazole Hydrochloride* (=*2-(1-Cyclohexyl-1*H*-pyrazol-5-yl)benzenamine Hydrochloride*; **5c**·HCl). Prepared from **17c** (271m g, 1 mmol). Yield: 196 mg (62%).

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[2]) Hydrazine hydrochlorides **14e** and **14f** were used.

Beige solid. M.p. 124–126°. R_f (AcOEt) 0.57. IR (KBr): 3473, 3419, 3146, 1622, 1597, 1550, 1513, 1494, 1472, 1406, 1254, 1192, 1164, 919, 808, 772. ^{1}H-NMR ((D$_6$)DMSO): 0.93 (*m*, 4 H, C_6H_{11}); 1.61 (*m*, 6 H, C_6H_{11}); 3.60 (*m*, 1 H, C_6H_{11}); 5.68 (br. *s*, NH_3^+); 6.29 (*d*, *J* = 1.8, H–C(4)); 6.97–7.06 (*m*, 2 H, C_6H_4); 7.15 (br. *d*, *J* = 7.9, 1 H, C_6H_4); 7.19–7.27 (*m*, 1 H, C_6H_4); 7.38 (*d*, *J* = 1.8, H–C(3)). ^{13}C-NMR ((D$_6$)DMSO): 24.9; 25.1; 33.0; 57.5; 107.6; 124.4; 124.7; 128.0; 130.3; 131.2; 131.5; 136.1; 137.7. EI-MS: 241 (M^+). HR-EI-MS: 241.1584 (M^+, $C_{15}H_{19}N_3^+$; calc. 241.1579). Anal. calc. for $C_{15}H_{19}N_3 \cdot 2\,HCl$ (314.25) C 57.33, H 6.74, N 13.37; found: C 57.64, H 6.84, N 13.38.

7.3. *5-(2-Aminophenyl)-1-(*tert*-butyl)-1*H*-pyrazole* (=*2-[1-(*tert*-Butyl)-1*H*-pyrazol-5-yl]benzenamine*; **5d**). Prepared from **17d** (245 mg, 1 mmol). Yield: 197 mg (92%). Beige solid. M.p. 119–123° (from EtOH/H_2O). R_f (AcOEt) 0.65. IR (KBr): 3458, 3317, 3198, 2990, 2970, 1628, 1574, 1532, 1485, 1452, 1344, 1310, 1236, 1126, 974, 787, 756. ^{1}H-NMR ((D$_6$)DMSO): 1.41 (*s*, *t*-Bu); 4.57 (*s*, NH_2); 6.08 (*d*, *J* = 1.7, H–C(4)); 6.59 (*dt*, *J* = 1.1, 7.4, 1 H, C_6H_4); 6.71 (*dd*, *J* = 0.9, 8.1, 1 H, C_6H_4); 6.95 (*dd*, *J* = 1.5, 7.5, 1 H, C_6H_4); 7.11 (*dt*, *J* = 1.6, 7.8, 1 H, C_6H_4); 7.46 (*d*, *J* = 1.7, H–C(3)). ^{13}C-NMR ((D$_6$)DMSO): 30.0; 60.4; 108.3; 114.4; 115.5; 117.6; 129.5; 131.1; 136.6; 138.7; 146.8. EI-MS: 215 (M^+). HR-EI-MS: 215.1422 (M^+, $C_{13}H_{17}N_3^+$; calc. 215.1430). Anal. calc. for $C_{13}H_{17}N_3 \cdot {}^1/_3\,H_2O$ (215.29): C 70.56, H 8.05, N 18.99; found: C 70.78, H 7.76, N 18.99.

7.4. *5-(2-Aminophenyl)-1-(2-hydroxyethyl)-1*H*-pyrazole* (=*2-[5-(2-Aminophenyl)-1*H*-pyrazol-1-yl]ethanol*; **5e**). Prepared from **17e** (233 mg, 1 mmol). Yield: 194 mg (95%). White solid. M.p. 123–126°. R_f (AcOEt) 0.17. IR (KBr): 3456, 3343, 3217, 1634, 1575, 1487, 1453, 1395, 1312, 1217, 1136, 1055, 935, 758. ^{1}H-NMR ((D$_6$)DMSO): 3.67 (*q*, *J* = 6.1, CH_2CH_2OH); 3.93 (*t*, *J* = 6.3, CH_2CH_2OH); 4.79 (*s*, NH_2); 4.81 (br. *s*, OH); 6.22 (*d*, *J* = 1.8, H–C(4)); 6.62 (*dt*, *J* = 1.1, 7.4, 1 H, C_6H_4); 6.77 (*dd*, *J* = 0.9, 8.1, 1 H, C_6H_4); 7.01 (*dd*, *J* = 1.5, 7.6, 1 H, C_6H_4); 7.12 (*dt*, *J* = 1.6, 7.7, 1 H, C_6H_4); 7.53 (*d*, *J* = 1.8, H–C(3)). ^{13}C-NMR ((D$_6$)DMSO): 50.9; 59.9; 105.8; 114.3; 115.0; 116.0; 129.7; 130.9; 138.5; 140.5; 146.6. EI-MS: 203 (M^+). HR-EI-MS: 203.1065 (M^+, $C_{11}H_{13}N_3O^+$; calc. 203.1059). Anal. calc. for $C_{11}H_{13}N_3O \cdot {}^1/_4\,H_2O$ (203.24): C 63.60, H 6.55, N 20.23; found: C 63.57, H 6.26, N 20.24.

7.5. *5-(2-Aminophenyl)-1-phenyl-1*H*-pyrazole* (=*2-(1-Phenyl-1*H*-pyrazol-5-yl)benzenamine*; **5g**). Prepared from **17g** (265 mg, 1 mmol). Yield: 218 mg (93%). White solid. M.p. 100–103°. R_f (AcOEt) 0.73. IR (KBr): 3462, 3373, 1614, 1600, 1487, 1456, 1384, 1306, 1228, 1135, 959, 919, 797, 763, 692. ^{1}H-NMR ((D$_6$)DMSO): 4.86 (*s*, NH_2); 6.47 (*dt*, *J* = 1.1, 7.4, 1 H, C_6H_4); 6.52 (*d*, *J* = 1.8, H–C(4)); 6.71 (*dd*, *J* = 0.8, 8.1, 1 H, C_6H_4); 6.75 (*dd*, *J* = 1.5, 7.6, 1 H, C_6H_4); 7.05 (*ddd*, *J* = 1.6, 7.4, 8.1, 1 H, C_6H_4); 7.22–7.37 (*m*, Ph); 7.77 (*d*, *J* = 2.3, H–C(3)). ^{13}C-NMR ((D$_6$)DMSO): 108.4; 114.5; 114.9; 115.9; 123.8; 126.9; 128.7; 129.6; 130.7; 139.8; 139.9; 140.1; 146.4. EI-MS: 235 (M^+). HR-EI-MS: 235.1115 (M^+, $C_{15}H_{13}N_3^+$; calc. 1235.1109). Anal. calc. for $C_{15}H_{13}N_3$ (235.28): C 76.57, H 5.57, N 17.86; found: C 76.30, H 5.40, N 17.77.

7.6. *5-(2-Aminophenyl)-1-(4-aminophenyl)-1*H*-pyrazole* (=*2-[1-(4-Aminophenyl)-1*H*-pyrazol-5-yl]benzenamine*; **5h**). Prepared from **17h** (310 mg, 1 mmol). Yield: 220 mg (88%). Gray solid. M.p. 194–197°. R_f (AcOEt) 0.42. IR (KBr): 3375, 2863, 2588, 1626, 1568, 1514, 1450, 1389, 1138, 964, 832, 766. ^{1}H-NMR ((D$_6$)DMSO): 4.76, 5.16 (2*s*, 1:1, 2 NH_2); 6.42 (*d*, *J* = 1.8, H–C(4)); 6.44 (*dt*, *J* = 2.4, 8.8, 2 H, *p*-C_6H_4); 6.47 (br. *dt*, *J* = 1.1, 7.8, 1 H, *o*-C_6H_4); 6.68 (*dd*, *J* = 0.9, 8.1, 1 H, *o*-C_6H_4); 6.73 (*dd*, *J* = 1.5, 7.6, 1 H, *o*-C_6H_4); 6.91 (*dt*, *J* = 2.4, 8.8, 2 H, *p*-C_6H_4); 7.01 (*ddd*, *J* = 1.6, 7.6, 8.1, 1 H, *o*-C_6H_4); 7.65 (*d*, *J* = 1.8, H–C(3)). ^{13}C-NMR ((D$_6$)DMSO): 109.8; 122.5; 122.6; 123.5; 125.4; 126.0; 130.1; 131.6; 133.9; 137.6; 138.5; 140.4; 142.1. EI-MS: 250 (M^+). HR-EI-MS: 250.1219 (M^+, $C_{15}H_{14}N_4^+$; calc. 250.1218).

7.7. *5-(2-Aminophenyl)-1-(3-methoxyphenyl)-1*H*-pyrazole* (=*2-[1-(3-Methoxyphenyl)-1*H*-pyrazol-5-yl]benzenamine*; **5i**). Prepared from **17i** (295 mg, 1 mmol). Yield: 251 mg (95%). Beige solid. M.p. 80–83° (from EtOH/H_2O). R_f (AcOEt) 0.61. IR (KBr): 3443, 3319, 3219, 1611, 1577, 1536, 1491, 1462, 1435, 1379, 1290, 1221, 1041, 968, 929, 800, 756. ^{1}H-NMR ((D$_6$)DMSO): 3.62 (*s*, MeO); 4.85 (*s*, NH_2); 6.50 (*dt*, *J* = 1.2, 7.3, 1 H, C_6H_4); 6.51 (*d*, *J* = 1.8, H–C(4)); 6.72 (*dd*, *J* = 0.9, 8.1, 1 H, C_6H_4); 6.78 (*dd*, *J* = 1.4, 7.5, 1 H, C_6H_4); 6.82 (*ddd*, *J* = 0.8, 2.5, 8.3, 1 H, C_6H_4); 6.88 (*dd*, *J* = 1.4, 2.6, 1 H, C_6H_4); 6.89 (*ddd*, *J* = 1.4, 2.5, 10.9, 1 H, C_6H_4); 7.07 (*ddd*, *J* = 1.6, 7.3, 8.2, 1 H, C_6H_4); 7.22 (*dt*, *J* = 0.6, 8.1, 1 H, C_6H_4); 7.77 (*d*, *J* = 1.8, H–C(3)). ^{13}C-NMR ((D$_6$)DMSO): 55.0; 108.6; 109.2; 112.6; 114.7; 114.9; 115.7; 116.0; 129.4; 129.7; 130.7; 139.9; 140.0; 140.9; 146.5; 159.1. EI-MS: 265 (M^+). HR-EI-MS: 265.1221 (M^+, $C_{16}H_{15}N_3O^+$; calc. 265.1215). Anal. calc. for $C_{16}H_{15}N_3O$ (265.31): C 72.43, H 5.70, N 15.84; found: C 72.05, H 5.53, N 15.64.

7.8. *5-(2-Aminophenyl)-1-(4-methoxyphenyl)-1*H*-pyrazole* (=*2-[1-(4-Methoxyphenyl)-1*H*-pyrazol-5-yl]benzenamine*; **5j**). Prepared from **17j** (295 mg, 1 mmol). Yield: 265 mg (100%). White solid. M.p.

113–115° (from EtOH/H_2O). R_f (AcOEt) 0.58. IR (KBr): 3464, 3368, 3233, 1616, 1578, 1516, 1487, 1440, 1387, 1302, 1246, 1179, 1023, 926, 837, 751. ^{1}H-NMR ((D$_6$)DMSO): 3.73 (*s*, Me); 4.83 (*s*, NH_2); 6.47 (*dt*, *J* = 1.1, 7.9, 1 H, C_6H_4); 6.48 (*d*, *J* = 1.9, H–C(4)); 6.69 (*dd*, *J* = 0.8, 8.1, 1 H, C_6H_4); 6.75 (*dd*, *J* = 1.5, 7.6, 1 H, C_6H_4); 6.88 (*dt*, *J* = 2.8, 9.0, 2 H, C_6H_4); 7.04 (*dt*, *J* = 1.6, 8.3, 1 H, C_6H_4); 7.21 (*dt*, *J* = 2.8, 9.0, 2 H, C_6H_4); 7.72 (*d*, *J* = 1.8, H–C(3)). ^{13}C-NMR ((D$_6$)DMSO): 55.2; 107.8; 113.8; 114.5; 114.9; 115.9; 125.4; 129.5; 130.7; 133.1; 139.6; 139.7; 146.4; 158.0. EI-MS: 265 (M^+). HR-EI-HR: 265.1222 (M^+, $C_{16}H_{15}N_3O^+$; calc. 265.1215). Anal. calc. for $C_{16}H_{15}N_3O$ (265.31): C 72.43, H 5.70, N 15.84; found: C 72.15, H 5.51, N 15.83.

8. *Synthesis of 4-Bromo-5-(2-nitrophenyl)-1-phenyl-1*H*-pyrazole* (**18**). A soln. of Br_2 (2M in AcOH, 1 ml, 2 mmol) was added to a stirred soln. of **17g** (265 mg, 1 mmol) in AcOH (100%, 2 ml), and the mixture was stirred at r.t. for 48 h. Volatile components were evaporated *in vacuo*, and the residue was purified by CC (20% AcOEt/hexanes). Fractions containing the product were combined and evaporated *in vacuo* to give **18**. Yield: 291 mg (85%). Yellow oil. R_f (20% AcOEt/hexanes) 0.27. IR (NaCl): 3098, 3068, 2922, 2867, 1596, 1528, 1498, 1385, 1349, 1070, 952, 852, 756. ^{1}H-NMR ($CDCl_3$): 7.20–7.29 (*m*, Ph); 7.38 (*dd*, *J* = 1.8, 7.3, 1 H, C_6H_4); 7.59 (*dt*, *J* = 1.7, 7.6, 1 H, C_6H_4); 7.66 (*dt*, *J* = 1.6, 7.5, 1 H, C_6H_4); 7.76 (*s*, H–C(3)); 8.06 (br. *dd*, J = 1.5, 7.9, 1 H, C_6H_4). ^{13}C-NMR ($CDCl_3$): 96.7; 124.4; 124.5; 125.3; 128.3; 129.4; 130.9; 133.5; 133.7; 137.4; 139.5; 141.1; 148.9. ESI-MS: 344 ($[M+H]^+$). HR-ESI-MS: 344.0044 ($[M+H]^+$, $C_{15}H_{10}BrN_3O_2^+$; calc. 344.0035).

9. *Synthesis of 3-Nitro-5-(2-nitrophenyl)-1-phenyl-1*H*-pyrazole* (**19**) *and Its 4-Nitro Isomer* **20**. Conc. HNO_3 (65%, 0.4 ml) was added to a stirred soln. of **17g** (265 mg, 1 mmol) in Ac_2O (2.5 ml) at −5°. The mixture was stirred at r.t. for 12 h, poured on crushed ice (*ca.* 75 g), and then left at r.t., until all the ice had melted. The product was extracted with CH_2Cl_2 (3 × 20 ml), the combined org. phases were washed with sat. aq. $NaHCO_3$ (2 × 20 ml), dried (Na_2SO_4), filtered, and the filtrate was evaporated *in vacuo* to give a mixture of regioisomers **19** and **20**, which were separated by CC (33% AcOEt/hexanes). Fractions containing the products were combined and evaporated *in vacuo* to give **19** and **20**.

9.1. *3-Nitro-5-(2-nitrophenyl)-1-phenyl-1*H*-pyrazole* (**19**). Yield: 170 mg (55%). Yellow solid. M.p. 118–130°. R_f (33% AcOEt/hexanes) 0.32. IR (NaCl): 3149, 2925, 2855, 1595, 1574, 1529, 1497, 1455, 1411, 1374, 1337, 1252, 1204, 1089, 1075, 999, 972, 912, 853, 827, 766, 751, 732, 689. ^{1}H-NMR ($CDCl_3$): 7.08 (*s*, H–C(4)); 7.22–7.36 (*m*, Ph); 7.51 (*dd*, *J* = 1.7, 7.3, 1 H, C_6H_4); 7.66 (*dt*, *J* = 1.6, 7.6, 1 H, C_6H_4); 7.74 (*dt*, *J* = 1.5, 7.5, 1 H, C_6H_4); 8.02 (*dd*, *J* = 1.3, 8.0, 1 H, C_6H_4). ^{13}C-NMR ($CDCl_3$): 104.3; 123.7; 125.1; 125.4; 129.6; 129.6; 131.7; 133.1; 134.1; 138.1; 141.7; 148.4; 156.5. ESI-MS: 333 ($[M+Na]^+$), 311 ($[M+H]^+$). Anal. calc. for $C_{15}H_{10}N_4O_4$ (310.26): C 58.07, H 3.25, N 18.06; found: C 57.94, H 3.09, N 17.88.

9.2. *4-Nitro-5-(2-nitrophenyl)-1-phenyl-1*H*-pyrazole* (**20**). Yield: 99 mg (32%). Yellow oil. R_f (33% AcOEt/hexanes) 0.38. IR (NaCl): 3127, 2924, 1617, 1595, 1558, 1529, 1504, 1458, 1399, 1348, 1325, 1201, 1087, 1008, 955, 912, 854, 826, 788, 765, 731, 709, 692. ^{1}H-NMR ($CDCl_3$): 7.25–7.35 (*m*, Ph, 1 H, C_6H_4); 7.59–7.68 (*m*, 2 H, C_6H_4); 8.19–8.24 (*m*, 1 H, C_6H_4); 8.38 (*s*, H–C(4)). ^{13}C-NMR ($CDCl_3$): 122.6; 124.7; 125.0; 125.1; 125.3; 129.3; 131.4; 132.3; 133.7; 137.1; 137.7; 137.9; 148.4. ESI-MS: 333 ($[M+Na]^+$), 311 ($[M+H]^+$). HR-ESI-MS: 311.0785 ($[M+H]^+$, $C_{15}H_{10}N_4O_4^+$; calc. 311.0780).

10. *Synthesis of 5,6-Dihydropyrazolo[1,5-*c*]quinazolines* **21** *and* **22**. A mixture of **5** (1 mmol), EtOH (10 ml), 10% Pd/C (20 mg), and acetone or cyclopentanone (2 ml) was hydrogenated (3 bar of H_2) at r.t. for 5 h. The catalyst was removed by filtration through a fritted funnel and washed with EtOH (2 × 5 ml). The combined filtrate was evaporated *in vacuo* to give **21** and **22**.

10.1. *5,6-Dihydro-5,5-dimethylpyrazolo[1,5-*c*]quinazoline* (**21**) [20]. Prepared from **5a** (159 mg, 1 mmol) and acetone. Yield: 187 mg (94%). White solid. M.p. 104–106° ([20]: 116°). R_f (AcOEt) 0.60. IR (KBr): 3370, 3251, 3217, 1614, 1587, 1503, 1480, 1383, 1311, 1270, 1196, 1050, 785, 757. ^{1}H-NMR ($CDCl_3$): 1.73 (*s*, $CHMe_2$); 4.31 (*s*, H–N(6)); 6.48 (*d*, *J* = 1.9, H–C(1)); 6.70 (br. *d*, *J* = 8.0, H–C(7)); 6.85 (br. *t*, *J* = 7.2, H–C(9)); 7.12 (*dt*, *J* = 1.3, 7.9, H–C(8)); 7.44 (br. *d*, *J* = 7.6, H–C(10)); 7.53 (*d*, *J* = 1.8, H–C(2)). ^{13}C-NMR ($CDCl_3$): 28.0; 72.3; 99.9; 114.9; 115.5; 119.9; 124.1; 129.3; 136.5; 139.3; 139.4. EI-MS: 200 ($[M+H]^+$). HR-ESI-MS: 200.1176 ($[M+H]^+$, $C_{12}H_{14}N_3^+$; calc. 200.1188). Anal. calc. for $C_{12}H_{13}N_3 \cdot {}^1/_{10}\,H_2O$ (199.25): C 71.69, H 6.62, N 21.09; found: C 71.67, H 6.42, N 21.00.

10.2. *6′*H*-Spiro[cyclopentane-1,5′(6′*H*)-pyrazolo[1,5-*c*]quinazoline]* (**22**). Prepared from **5a** (159 mg, 1 mmol) and cyclopentanone. Yield: 227 mg (83%). White solid. M.p. 75–77°. R_f (AcOEt) 0.68. IR (KBr): 3289, 2957, 2872, 1616, 1590, 1550, 1496, 1480, 1436, 1379, 1333, 1306, 1264, 1196, 1155, 1097, 1042,

999, 954, 928, 779, 750. ^{1}H-NMR ($CDCl_3$): 1.72–1.84 (*m*, 2 H, cyclopent.); 1.86–1.99 (*m*, 4 H, cyclopent.); 2.42–2.55 (*m*, 2 H, cyclopent.); 4.33 (br. *s*, H–C(6′)); 6.49 (*d*, *J* = 1.8, H–C(1′)); 6.73 (br. *d*, *J* = 8.0, H–C(7′)); 6.87 (br. *t*, *J* = 7.2, H–C(9′)); 7.12 (*dt*, *J* = 1.2, 7.9, H–C(8′)); 7.44 (br. *d*, *J* = 7.6, H–C(10′)); 7.50 (*d*, *J* = 1.8, H–C(2′)). ^{13}C-NMR ($CDCl_3$): 24.1; 38.7; 82.5; 100.2; 115.8; 115.9; 120.2; 124.1; 129.1; 137.2; 139.3; 139.7. ESI-MS: 226 ($[M+H]^+$). HR-ESI-MS: 226.1337 ($[M+H]^+$, $C_{14}H_{16}N_3^+$; calc. 226.1344). Anal. calc. for $C_{14}H_{15}N_3 \cdot {}^1/_3\, H_2O$ (225.29): C 72.70, H 6.83, N 18.17; found: C 72.78, H 6.64, N 18.21.

11. *Synthesis of 5-[2-(Isopropylamino)phenyl]-1-phenyl-1*H*-pyrazole* (= N-*(1-Methylethyl)-2-(1-phenyl-1*H*-pyrazol-5-yl)benzenamine*; **25**) *Solvate with Hexane.* A mixture of **5g** (235 mg, 1 mmol), acetone (25 ml), and 10% Pd/C (70 mg) was hydrogenated (3 bar of H_2) at r.t. for 24 h. The catalyst was removed by filtration through a fritted funnel and washed with acetone (2 × 10 ml). The combined filtrate was evaporated *in vacuo*, and the residue was purified by CC (20% AcOEt/hexanes). Fractions containing the product were combined and evaporated *in vacuo* to give **25**. Yield: 161 mg (58%) of yellowish solid. M.p. 84–88°. R_f (20% AcOEt/hexanes) 0.43. IR (KBr): 3450, 2963, 2926, 1636, 1498, 1458, 1379, 1318, 1261, 1176, 1096, 958, 924, 912, 796, 764, 754. ^{1}H-NMR ($CDCl_3$): 0.88 (*m*, 2.2 H, 2 Me of hexane); 0.96 (*d*, *J* = 6.2, CH*Me*$_2$); 1.26 (*m*, 3 H, 4 Me of hexane); 3.53 (*sept.*, *J* = 6.2, C*H*Me$_2$); 3.66 (br. *s*, NH); 6.46 (*d*, *J* = 1.8, H–C(4)); 6.58 (*dt*, *J* = 1.1, 7.4, 1 H, C_6H_4); 6.60 (*dd*, *J* = 1.3, 8.5, 1 H, C_6H_4); 6.96 (*dd*, *J* = 1.6, 7.7, 1 H, C_6H_4); 7.18–7.35 (*m*, Ph, 1 H, C_6H_4); 7.78 (*d*, *J* = 1.8, H–C(3)). ^{13}C-NMR ($CDCl_3$): 14.3 (2 Me of hexane); 22.5, 22.8 (2 CH_2 of hexane); 30.1 (2 CH_2 of hexane); 43.5; 108.8; 111.0; 115.7; 116.1; 123.4; 126.9; 128.7; 130.2; 131.2; 139.9; 140.0; 140.6; 145.1. ESI-MS: 278 ($[M+H]^+$). HR-ESI-MS: 278.1646 ($[M+H]^+$, $C_{18}H_{20}N_3^+$; calc. 278.1657). Anal. calc. for $C_{18}H_{19}N_3 \cdot {}^3/_8$ hexane (277.36) C 78.54, H 7.89, N 13.57; found: C 78.72, H 7.58, N 13.18.

Table 2. *Crystal Data, Data Collection, and Structure Refinement for Compounds* **13**, **17a**, **17j**, *and* **22**

	13	**17a**	**17j**	**22**
Formula	$C_{11}H_{12}N_2O_3$	$C_9H_7N_3O_2$	$C_{16}H_{13}N_3O_3$	$C_{14}H_{15}N_3$
Rel. formula weight	220.23	189.17	295.30	225.29
Crystal system	Orthorhombic	Monoclinic	Orthorhombic	Trigonal
Space group	$P2_12_12_1$, No. 19	$P2_1/n$, No. 14	$Pna2_1$, No. 33	$R\bar{3}$, No. 148
a [Å]	7.4332(2)	11.4686(3)	17.5869(4)	31.9814(5)
b [Å]	11.8131(2)	5.1831(1)	12.1416(2)	31.9814(5)
c [Å]	12.6750(2)	5.9689(4)	6.6759(1)	6.6003(1)
β [°]	90.00	110.348(1)	90.00	90
V [Å^3]	1112.98(4)	890.00(4)	1425.53(5)	5846.4(2)
Z	4	4	4	18
D_x [Mg m^{-3}]	1.314	1.412	1.376	1.150
μ [mm^{-1}]	0.097	0.104	0.098	0.071
T [K]	293(2)	293(2)	293(2)	293(2)
θ_{max} [°]	26.4	27.5	27.5	27.5
Integrated refl.	30494	16320	16994	37197
R_{int}	0.031	0.028	0.035	0.036
Independent refl.	1311	2021	1768	2966
Observed refl.	1256	1592	1485	2199
Threshold criterion	$F^2 > 2.0\sigma(F^2)$	$F^2 > 2.0\sigma(F^2)$	$F^2 > 2.0\sigma(F^2)$	$F^2 > 2.0\sigma(F^2)$
Refinement on	*F*	*F*	*F*	*F*
No. of contrib. refl.	1296	1869	1674	2705
No. of parameters	145	127	199	158
Final *R*, R_w	0.044, 0.031	0.044, 0.043	0.045, 0.028	0.083, 0.056
$\Delta\rho_{max}$, $\Delta\rho_{min}$ [e Å^{-3}]	0.16, −0.23	0.19, −0.22	0.24, −0.33	0.50, −0.62

12. *X-Ray Crystal-Structure Analysis for Compounds* **13**, **17a**, **17j**, *and* **22**. Single-crystal X-ray diffraction data of compounds **13**, **17a**, **17j**, and **22** were collected at r.t. on a *Nonius Kappa CCD* diffractometer using the *Nonius* Collect Software [21]. DENZO and SCALEPACK [22] were used for indexing and scaling of the diffraction data. All structures were solved by direct methods using SIR97 [23] and refined by Xtal3.6 [24] program package. Structures were refined on *F* values using the full-matrix least-squares procedure. Some of the positions of H-atoms were obtained from difference *Fourier* map, and some were geometrically calculated. The non-H-atoms were refined anisotropically, while the positional and isotropic atomic displacement parameters of H-atoms were not refined. The resulting crystal data, and details concerning data collection and refinement for all four compounds are compiled in *Table 2*. The structure **22** is slightly disordered. This is reflected mainly in the fact that most of the solvent ($CHCl_3$) molecules left the structure. They were originally positioned in the channels parallel to *c* axis. Crystallographic data (excluding structure factors) for compounds **13**, **17a**, **17j**, and **22** have been deposited with the *Cambridge Crystallographic Data Centre* as supplementary publication Nos. CCDC 788696–788699, resp. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk.

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