Synthesis of 5-Amino-4-(2-azacycloalkylidene)-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-ones

Konstantin G. Nazarenko,*[a] Sergey I. Bova,[b] Vitaliy Polovinko,[c] Andrey A. Tolmachev[c]

[a] Institute of Organic Chemistry, National Academy of Sciences of Ukraine, 5 Murmanska st., Kyiv 02094, Ukraine
Fax +380(44)5732643; E-mail: nazarenko@ioch.kiev.ua

[b] Chernigiv State Technological University, 95 Shevchenko st., Chernigiv 14027, Ukraine

[c] Research and Development Center for Chemistry and Biology, National Taras Shevchenko University, 62 Volodymyrska st., Kyiv 01033, Ukraine

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Abstract: The reaction 5-amino-2-phenyl-3,4-dihydro-3*H*-pyrazol-3-one with activated lactams (lactim ethers, lactam acetals, and methylthioalkylidene iminium salts) was investigated. It occurs on the active methylene group of 5-amino-2-phenyl-3,4-dihydro-3*H*-pyrazol-3-one to furnish cyclic enamines, 5-amino-4-(2-azacycloalkylidene)-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-ones and 5-amino-4-(1-methyl-2-azacycloalkylidene)-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-ones.

Key words: lactams, pyrazolone, cyclic enamine, ring opening, heterocycles

Compounds **1** representing bridged 1,3-dicarbonyl heteroanalogues (Figure 1) are conveniently employed in the synthesis of various heterocyclic ω-aminoalkyl derivatives, synthetic pharmaceuticals, unnatural α-amino acids, etc.[1] One of the synthetic routes to **1** involves the reaction between lactim ethers **2** or lactam acetals **3** and 1,3-dinucleophiles, with the latter mostly exemplified by 1,3-SCN (thioamides) and 1,3-NCN (α-aminoazaheterocycles) compounds. The resultant substituted amidines **1** (X = N, Y = S, NR) have been widely used to prepare ω-aminoalkyl-functionalized thiazoles,[2] imidazoles,[3] isoxazoles,[4] 1,2,4-triazoles,[5] 1,2,4-thiadiazoles,[6] and bicyclic heterocycles.[7]

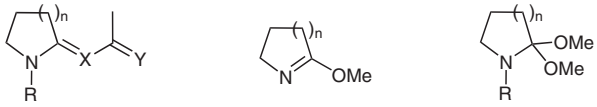

Figure 1 Amidines **1**, lactim ethers **2**, and lactam acetals **3**

Much less attention has been given to the reaction of **2** or **3** with 1,3-CCN dinucleophiles represented, as a rule, by cyanoacetamides[8] and 2-hetarylacetonitriles.[9] The literature reports a nontrivial example in which *O*-methylcaprolactam (**2c**) is reacted with 5-amino-2-phenyl-3,4-dihydro-5*H*-pyrazol-3-one (**4**), a compound bearing several nucleophilic centers including an active methylene and an amino group.[10] The reaction in question proceeds in two steps: compound **4** is first heated to 145 °C with an excess of **2c** to form a product, presumably the O-substituted 3-aminopyrazole **5** (Figure 2), which, if heated further with **2c** at 180 °C for 6 hours, furnishes compound **6** patented as a muscle relaxant. Structures **5** and **6** assigned to the products in the literature[11] appear unsupported by any evidence and hence doubtful. According to literature data, the carbonyl oxygen atom of **4** can be electrophilically attacked only in acylation reactions (which provide a mixture of *N*-acyl and *N*,*O*-diacyl derivatives),[11] whereas reactions with amides and their activated forms (in DMF-DMA)[12] involve the methylene group. As compound **2c** is the activated form of caprolactam, one can assume that its reaction with **4** begins with an attack on the 4-C atom of the pyrazolone ring. To verify this conjecture and to obtain new pyrazole-based building blocks for the synthesis of ω-aminoalkyl-substituted heterocycles, we have studied the reaction of 5-amino-2-phenyl-3,4-dihydro-5*H*-pyrazol-3-one (**4**) with a number of activated lactams, namely, lactim ethers **2a–d**, lactam acetals **3**, and methylthioalkylidene iminium salts **9c–d**.

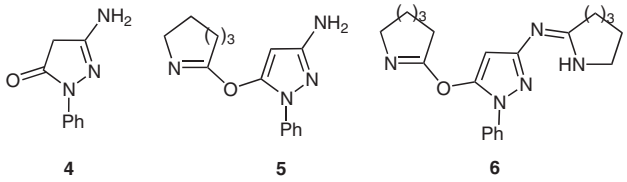

Figure 2 Pyrazoles **4–6**

First of all, we reacted **4** with **2c** under various conditions including heating at 150 °C with **2c** used as a solvent and also in refluxing DMF, toluene, and dioxane. In all cases, the same product was formed, its melting point coinciding with that of compound **5**.[10] However, IR, ^{1}H, and ^{13}C NMR spectra as well as the data of 2D NMR (NOESY and HMBC) experiments suggest that the compound obtained has the structure of 5-amino-4-(hexahydro-2*H*-azepin-2-ylidene)-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (**7c**) (see Figure 3) rather than 3-amino-1-phenyl-5-(3,4,5,6-tetrahydro-2*H*-azepin-7-yloxy)-1*H*-pyrazole (**5**). In particular, the ^{1}H NMR signal of the perhydroazepine NH group appears at 11.2 ppm as a triplet (J = 5.2 Hz) due to

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spin-spin coupling with the neighboring 7-CH_2 group of the same ring. The amino group gives rise to a broad singlet at 4.96 ppm which disappears on adding D_2O. The ^{13}C NMR spectrum exhibits a signal at 90.6 ppm assigned to the pyrazolone 4-C atom. As seen from ^1H-^{13}C HMBC data, this atom shows a cross-peak with the 3-CH_2 group of the perhydroazepine ring at 2.87 ppm (Figure 3). Out of two theoretically possible isomers of such enamines,[13] only the *Z*-isomer was always formed for **7c**, with the NH group and the carbonyl oxygen atom intramolecularly H-bonded. This relative disposition of the perhydroazepine and pyrazolone rings was determined from the ^1H-^1H NOESY correlation between the amino and perhydroazepine 3-CH_2 groups (Figure 3).

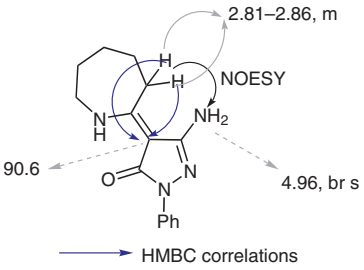
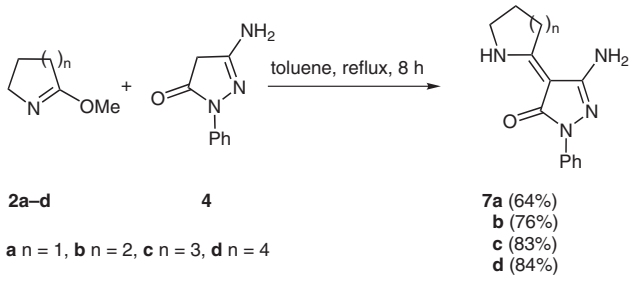


Figure 3 NOESY and HMBC correlations for **7c**

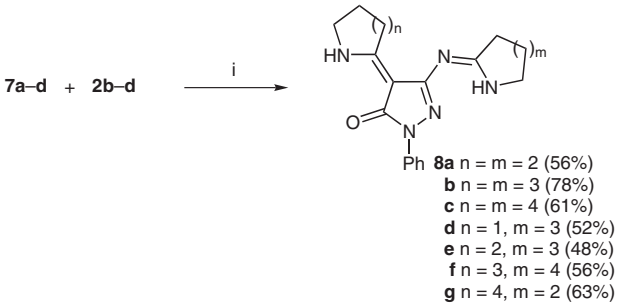
Like **2c**, the other lactim ethers **2a**,**b**,**d** react with pyrazolone **4** via initial attack on its active methylene group leading to the *Z*-isomers of enamines **7a**,**b**,**d** (see Scheme 1). Compounds **7** are most conveniently obtained by boiling **4** with a slight excess of lactim ether **2** in toluene for 7–8 hours. On cooling the reaction mixture, the resulting products precipitate in a fairly pure state and in 64–83% yields.



Scheme 1 Reaction of lactim ethers **2a–d** with **4**

The second stage of the reaction involves the amino group and requires more severe conditions than the condensation at the active methylene group. On boiling enamines **7a–d** at 160–170 °C in a three-fold excess of an appropriate lactim ether, the alkoxy group of the latter is replaced by the amino group to give compounds **8a–g** (Scheme 2). Depending on the reagents used, products **8** contain two saturated rings of the same (m = n) or different (m ≠ n) sizes. In the former case, it is unnecessary to carry out the reaction in two stages: initial pyrazolone **4** is merely boiled in an excess of appropriate lactim ether **2** at 170 °C.

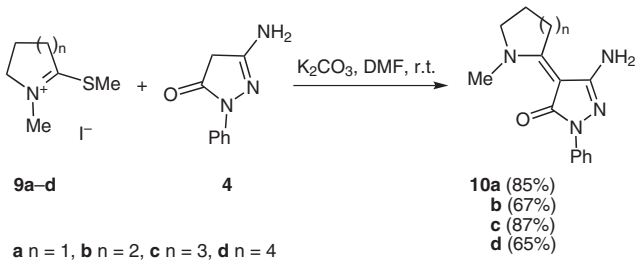
At the same time, we failed to prepare any of pyrrolidine derivatives **8** (m = 1). As *O*-methylbutyrolactim (**2c**) needed to obtain the corresponding product is not sufficiently high-boiling, the reaction was run in a closed reactor or, alternatively, with *S*-methylbutyrothiolactim having a higher boiling point. Nevertheless, complex mixtures of products resulted in all cases; they contained compounds with an open polymethylene chain, as evidenced by ^1H NMR spectra. Products of this kind are probably formed by an intramolecular reaction between the enamine and amidine moieties in compounds **8** at m = 1, which should lead to the formation of the pyrazolo[3,4-*d*]pyrimidine nucleus[12b] and, accordingly, to the cleavage of one pyrrolidine ring.



Scheme 2 Reagents and conditions: (i) oil bath, 160 °C, 6–8 h

Compounds **8** were structurally determined by a combination of spectral methods. Unlike the starting enamines **7a–d**, which do not exhibit enamine-imine tautomerism, products **8** exist as two tautomers, with the endo- and exocyclic double bond, due to the N,N-prototropic shift in the amidine moiety.[14] As a result, two characteristic signal sets are observed in their ^1H and ^{13}C NMR spectra.

Just as lactim ethers **2** react with pyrazolones **4** attacking their active methylene group, so do lactam acetals **3**. For instance, boiling compound **4** in toluene with a 10% excess of the dimethyl acetal of *N*-methylcaprolactam **3** (R = Me) furnishes condensation product **10c** in 65% yield, along with a small amount of unreacted **4** (Scheme 3). As found, compounds **10** are prepared more easily using methylthioalkylidene iminium salts **9** instead of lactam acetals **3** in the reaction with pyrazolones **4**. Salts **9a–d**, readily formed by the alkylation of the corresponding thiolactams[15] or thiolactim ethers,[16] are stable in storage and smoothly react with active methylene compounds in the presence of bases.[17] We have established that their condensation with **4** occurs already at room temperature, if conducted in DMF in the presence of excess potassium carbonate. The reaction proceeds exclusively at the active methylene group of **4** to afford products **10a–d** in yields up to 80–85%. Their ^1H and ^{13}C NMR spectra are similar to those of compounds **7a–d**, and the NOESY cross-peaks between the amino group and the 3-CH_2 group of the saturated ring suggest the *Z*-configuration, as in **7**.



9a–d **4** **10a** (85%) **b** (67%) **c** (87%) **d** (65%)

a n = 1, **b** n = 2, **c** n = 3, **d** n = 4

Scheme 3 Reaction of methylthioalkylidene iminium salts **9a–d** with **4**

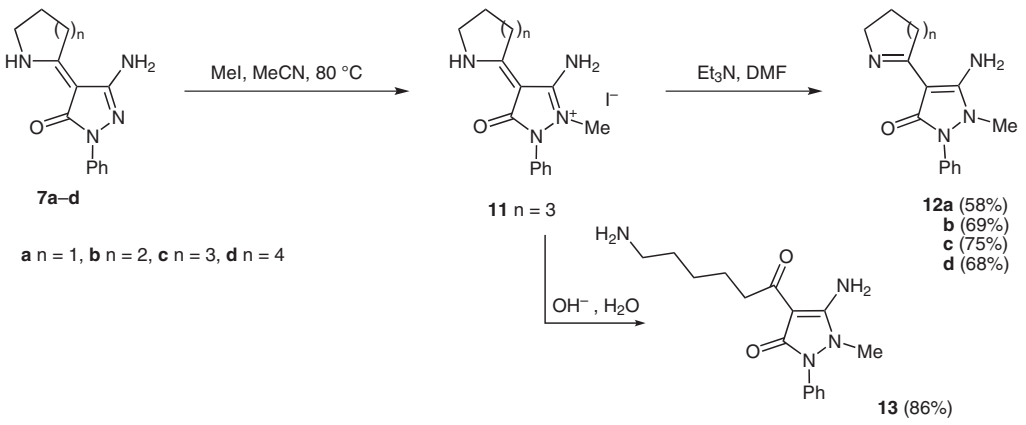
One of the main objectives of the present study was to obtain the pyrazole derivatives, which could be further used in the synthesis of heterocyclic ω-aminoalkyl compounds. In this context, the alkylation products of enamines **7** appear to be relevant intermediates. We have found that the regioselective 1-N methylation of the pyrazolone ring is achieved by boiling **7** with an excess of methyl iodide in acetonitrile (Scheme 4). The resultant (unpurified) salts **11** were cautiously treated with triethylamine to provide the corresponding bases **12a–d**.

Unlike cyclic enamines **7** and **10**, compounds **12** exist as imines with the endocyclic double bond in the saturated ring. The most essential indication of the imine form is given by the spectral characteristics of **12** different from those of **7** and **10**. The ^{1}H NMR spectra of **12** lack the NH signal at 11.2 ppm, whereas the broad singlet of the amino group is observed in the region 8.0–8.5 ppm. The ^{13}C NMR spectra of the products mainly differ by the resonances of the pyrazolone ring: for compounds **12**, the 5-C signal is found in the region 163–165 ppm (cf. 152 ppm for **7** and **10**) and the 4-C signal at 85 ppm (5 ppm upfield from the corresponding peak of **7** and **10**).

The presence of the imine function in compounds **12a–d** is also evidenced by their higher sensitivity to nucleophiles as compared to enamines **7** and **10**. To exemplify, treatment of compound **12c** or the corresponding salt **11** with aqueous alkali yields 5-amino-4-(6-aminohexanoyl)-1-methyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one (**13**) as a result of opening of the saturated ring. This conversion of **12c** goes to completion within 2–2.5 h at room temperature and 10–15 minutes at boiling in 10% aqueous alkali, whereas **7c** and **10c** remain unchanged under the same conditions. It is evident that the endocyclic C=N bond in **12c** undergoes hydrolytic cleavage in alkaline medium, in contrast to the alkali-resistant enamine moiety in **7c** and **10c**.

In conclusion, we have established that lactim ethers **2**, lactam acetals **3**, and methylthioalkylidene iminium salts **9** react with 5-amino-2-phenyl-3,4-dihydro-3*H*-pyrazol-3-one (**4**) via initial attack on its active methylene group to furnish enamines **7** and **10**. Compounds **7** can be converted to derivatives **8** by the reaction with the second equivalent of the lactim ether under more severe conditions. Treatment of **7** with methyl iodide leads to alkylation at the pyrazolone 1-N atom thus affording derivatives **12a–d**. As a further research, newly obtained compounds **7a–d**, **8a–d**, **10a–d**, and **12a–d** will be used to prepare fused pyrazoles and their ω-aminoalkyl derivatives.

The starting lactim ethers **1a–d** were prepared as reported.[18] Aminophenylpyrazol-3-one was commercially available. All solvents were purified by standard methods. All melting points were determined in open capillary tubes in a Thiele apparatus and are uncorrected. IR spectra for KBr tablets were obtained on a Pye Unicam SP 3-300 apparatus. ^{1}H NMR (400 MHz) spectra were recorded on a Varian Mercury-400 spectrometer in DMSO-d_6 solution with TMS as an internal standard. ^{13}C NMR (125 MHz) spectra were recorded on a Bruker Avance DRX 500 spectrometer in DMSO-d_6 solution with TMS as an internal standard. LC/MS spectra were recorded using chromatography/mass spectrometric system that consists of high-performance liquid chromatograph 'Agilent 1100 Series' equipped with diode-matrix and mass-selective detector 'Agilent LC/MSD SL'. The parameters of chromatography-mass analysis are: column: Zorbax SB-C18, 1.8 μm × 4.6 mm × 15 mm; solvents: A, MeCN–H_2O (95:5), 0.1% TFA; B, H_2O (0.1% of TFA); eluent flow: 3 mL/sec; volume of injected sample: 1 μL; UV-detectors at 215, 254, and 265 nm; ionization method: chemical ionization under atmospheric pressure (APCI); ionization mode: simultaneous scanning of positive and negative ions in the mass range of 80–1000 *m*/*z*. Microanalyses were performed in the Microanalytical Laboratory of the Institute of Organic Chemistry, National Academy of Sciences of Ukraine.



7a–d

a n = 1, **b** n = 2, **c** n = 3, **d** n = 4

11 n = 3

12a (58%) **b** (69%) **c** (75%) **d** (68%)

13 (86%)

Scheme 4 Alkylation of enamines **7** with MeI

Compounds 7a–d; General Procedure
An appropriate lactim ether **2a–d** (60 mmol) was added to a stirred suspension of **4** (8.75 g, 50 mmol) in toluene (300 mL) and the mixture was refluxed for 8 h. After cooling to r.t., the precipitate was filtered, washed with *i*-PrOH (2 × 25 mL), and recrystallized from *i*-PrOH.

5-Amino-2-phenyl-4-(2-pyrrolidinylidene)-2,4-dihydro-3*H*-pyrazol-3-one (7a)
Yield: 7.74 g (32 mmol, 64%); brown solid; mp 232 °C.

IR (KBr): 3430, 3320, 3280, 3200, 2960, 1640, 1590 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.02 (quint, *J* = 7.6 Hz, 2 H, CH_2), 3.08 (t, *J* = 8.2 Hz, 2 H, CH_2), 3.62 (t, *J* = 7.6 Hz, 2 H, CH_2), 5.15 (s, 2 H, NH_2), 6.96 (t, *J* = 7.2 Hz, 1 H, Ar), 7.29 (t, *J* = 8.0 Hz, 2 H, Ar), 7.97 (d, *J* = 7.6 Hz, 2 H, Ar), 9.85 (br s, 1 H, NH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 20.7, 31.9, 48.3, 88.9, 117.3, 122.2, 128.9, 140.6, 152.5, 164.7, 167.3.

MS (APSI): *m*/*z* = 243 $[M + 1]^+$.

Anal. Calcd for $C_{13}H_{14}N_4O$: C, 64.25; H, 5.82; N, 23.13. Found: C, 64.41; H, 5.78; N, 23.21.

5-Amino-2-phenyl-4-(2-piperidinylidene)-2,4-dihydro-3*H*-pyrazol-3-one (7b)
Yield: 9.72 g (38 mmol, 76%); yellow solid; mp 179 °C.

IR (KBr): 3400, 3320, 3230, 3080, 2970, 1625, 1595 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.78–1.84 (m, 4 H, CH_2), 2.89–2.93 (m, 2 H, CH_2), 3.47–3.51 (m, 2 H, CH_2), 4.94 (s, 2 H, NH_2), 6.96 (t, *J* = 7.2 Hz, 1 H, Ar), 7.29 (t, *J* = 8.1 Hz, 2 H, Ar), 7.32 (d, *J* = 7.8 Hz, 2 H, Ar), 11.14 (br s, 1 H, NH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 18.7, 21.3, 28.1, 41.7, 90.0, 117.6, 122.5, 128.9, 140.4, 152.5, 164.7, 165.8.

MS (APSI): *m*/*z* = 257 $[M + 1]^+$.

Anal. Calcd for $C_{14}H_{16}N_4O$: C, 61.61; H, 6.29; N, 21.86. Found: C, 61.58; H, 6.34; N, 21.83.

5-Amino-4-hexahydro-2*H*-azepin-2-ylidene-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (7c)
Yield: 11.20 g (41.4 mmol, 83%); yellow solid; mp 191 °C.

IR (KBr): 3370, 3320, 3230, 3080, 3050, 2940, 1620, 1595 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.59–1.78 (m, 6 H, CH_2), 2.81–2.86 (m, 2 H, CH_2), 3.56–3.61 (m, 2 H, CH_2), 4.96 (s, 2 H, NH_2), 6.96 (t, *J* = 7.2 Hz, 1 H, Ar), 7.27 (t, *J* = 8.1 Hz, 2 H, Ar), 7.95 (d, *J* = 7.8 Hz, 2 H, Ar), 11.24 (br s, 1 H, NH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 24.7, 28.4, 28.9, 30.1, 44.1, 90.6, 117.7, 122.7, 128.9, 140.1, 152.4, 164.9, 171.7.

MS (APSI): *m*/*z* = 271 $[M + 1]^+$.

Anal. Calcd for $C_{15}H_{18}N_4O$: C, 66.64; H, 6.71; N, 20.73. Found: C, 66.58; H, 6.73; N, 20.76.

5-Amino-4-hexahydro-2(1*H*)-azocinylidene-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (7d)
Yield: 11.50 g (40.4 mmol, 81%); yellow solid; mp 165 °C.

IR (KBr): 3370, 3320, 3230, 3080, 3050, 2940, 1620, 1595 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.47–2.01 (m, 8 H, CH_2), 2.84–2.87 (m, 2 H, CH_2), 3.64–3.73 (m, 2 H, CH_2), 4.97 (s, 2 H, NH_2), 6.94 (t, *J* = 7.2 Hz, 1 H, Ar), 7.25 (t, *J* = 8.1 Hz, 2 H, Ar), 7.94 (d, *J* = 7.8 Hz, 2 H, Ar), 11.20 (br s, 1 H, NH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 25.1, 25.4, 25.6, 29.3, 32.4, 44.7, 90.2, 117.6, 122.7, 128.9, 140.2, 152.1, 165.1, 170.2.

MS (APSI): *m*/*z* = 286 $[M + 1]^+$.

Anal. Calcd for $C_{16}H_{20}N_4O$: C, 67.58; H, 7.09.71; N, 19.70. Found: C, 67.61; H, 7.11; N, 19.74.

Compounds 8a–g; General Procedure
A mixture of compound **7a–d** (10 mmol) and the appropriate lactim ether **2b–d** (30 mmol) was heated in an oil bath at 160 °C for 6–8 h. After cooling, resulting solid was recrystallized from MeCN. The compounds were prepared as a mixture of two isomers. ^1H and ^{13}C NMR signals of major isomers are given.

2-Phenyl-4-(2-piperidinylidene)-5-(2-piperidinylideneamino)-2,4-dihydro-3*H*-pyrazol-3-one (8a)
Yield: 1.89 g (5.6 mmol, 56%); yellow solid; mp 178 °C.

IR (KBr): 2950, 2880, 1660, 1620, 1600 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.56–1.75 (m, 6 H, CH_2), 2.49–2.58 (m, 6 H, CH_2), 3.09–3.26 (m, 2 H, CH_2), 3.31–3.46 (m, 2 H, CH_2), 6.97 (t, *J* = 7.0 Hz, 1 H, Ar), 7.28 (t, *J* = 7.5 Hz, 2 H, Ar), 7.98 (d, *J* = 7.8 Hz, 2 H, Ar), 9.72 (br s, 1 H, NH), 11.28 (br s, 1 H, NH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 17.6, 19.6, 20.9, 21.6, 25.2, 30.6, 39.5, 41.3, 90.3, 117.5, 122.4, 128.3, 140.1, 155.2, 160.7, 162.8, 166.9.

MS (APSI): *m*/*z* = 338 $[M + 1]^+$.

Anal. Calcd for $C_{19}H_{23}N_5O$: C, 67.63; H, 6.87; N, 20.76. Found: C, 67.58; H, 6.79; N, 20.72.

4-Hexahydro-2*H*-azepin-2-ylidene-5-(hexahydro-2*H*-azepin-2-ylideneamino)-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (8b)
Yield: 2.85 g (7.8 mmol, 78%); yellow solid; mp 194 °C.

IR (KBr): 2940, 2860, 1650, 1620, 1590 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 1.62–1.79 (m, 12 H, CH_2), 2.57–2.62 (m, 2 H, CH_2), 3.43–3.56 (m, 6 H, CH_2), 6.99 (t, *J* = 7.0 Hz, 1 H, Ar), 7.29 (t, *J* = 7.5 Hz, 2 H, Ar), 7.93 (d, *J* = 7.8 Hz, 2 H, Ar), 9.87 (br s, 1 H, NH), 11.43 (br s, 1 H, NH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 23.9, 24.1, 24.5, 25.1, 28.1, 29.2, 29.8, 30.0, 36.3, 43.4, 90.8, 117.7, 122.3, 128.2, 139.8, 155.7, 162.7, 167.1, 173.2.

MS (APSI): *m*/*z* = 366 $[M + 1]^+$.

Anal. Calcd for $C_{19}H_{23}N_5O$: C, 68.35; H, 7.17; N, 19.93. Found: C, 68.38; H, 7.15; N, 19.92.

4-Hexahydro-2(1*H*)-azocinylidene-5-[hexahydro-2(1*H*)-azocinylideneamino]-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (8c)
Yield: 2.40 g (6.1 mmol, 61%); yellow solid; mp 174 °C.

IR (KBr): 2940, 2870, 1660, 1620, 1600 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.51–1.79 (m, 16 H, CH_2), 2.53–2.57 (m, 2 H, CH_2), 3.20–3.37 (m, 6 H, CH_2), 7.03 (t, *J* = 7.2 Hz, 1 H, Ar), 7.32 (t, *J* = 8.2 Hz, 2 H, Ar), 7.93 (d, *J* = 7.8 Hz, 2 H, Ar), 9.71 (br s, 1 H, NH), 11.40 (br s, 1 H, NH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 24.0, 24.6, 24.7, 25.0, 25.6, 29.8, 30.0, 30.4, 32.2, 32.8, 39.5, 43.5, 91.1, 118.0, 123.3, 129.0, 140.4, 156.5, 163.0, 166.4, 172.1.

MS (APSI): *m*/*z* = 394 $[M + 1]^+$.

Anal. Calcd for $C_{23}H_{31}N_5O$: C, 70.20; H, 7.97; N, 17.80. Found: C, 70.18; H, 7.95; N, 17.75.

5-(Hexahydro-2*H*-azepin-2-ylideneamino)-2-phenyl-4-(2-pyrrolidinylidene)-2,4-dihydro-3*H*-pyrazol-3-one (8d)
Yield: 1.75 g (5.2 mmol, 52%); yellow solid; mp 211 °C.

IR (KBr): 2940, 2880, 1660, 1620, 1600 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.63–1.81 (m, 6 H, CH_2), 2.12 (quint, *J* = 7.6 Hz, 2 H, CH_2), 2.57 (t, *J* = 7.8 Hz, 2 H, CH_2), 3.28–3.44 (m, 4 H, CH_2), 3.66 (t, *J* = 7.2 Hz, 2 H, CH_2), 7.04 (t, *J* = 7.0 Hz, 1 H, Ar), 7.32 (t, *J* = 8.0 Hz, 2 H, Ar), 7.98 (d, *J* = 6.4 Hz, 2 H, Ar), 9.76 (br s, 1 H, NH), 9.96 (br s, 1 H, NH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 20.4, 24.7, 29.5, 31.1, 36.0, 39.5, 43.1, 47.8, 90.3, 117.3, 122.0, 128.3, 140.0, 155.8, 163.6, 167.2, 169.1.

MS (APSI): *m*/*z* = 338 $[M + 1]^+$.

Anal. Calcd for $C_{19}H_{23}N_5O$: C, 67.63; H, 6.87; N, 20.76. Found: C, 67.59; H, 6.78; N, 20.74.

5-(Hexahydro-2*H*-azepin-2-ylideneamino)-2-phenyl-4-(2-piperidinylidene)-2,4-dihydro-3*H*-pyrazol-3-one (8e)
Yield: 1.68 g (4.8 mmol, 48%); yellow solid; mp 198 °C.

IR (KBr): 2950, 2870, 1670, 1620, 1600 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.67–1.77 (m, 8 H, CH_2), 2.49–2.60 (m, 2 H, CH_2), 3.09–3.19 (m, 4 H, CH_2), 3.38–3.47 (m, 4 H, CH_2), 6.97 (t, *J* = 7.2 Hz, 1 H, Ar), 7.28 (t, *J* = 8.1 Hz, 2 H, Ar), 7.94 (d, *J* = 7.8 Hz, 2 H, Ar), 9.86 (br s, 1 H, NH), 11.20 (br s, 1 H, NH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 17.6, 20.9, 24.6, 25.2, 29.6, 29.8, 36.8, 41.11, 43.2, 90.5, 117.5, 122.7, 128.3, 139.9, 155.2, 162.7, 166.9, 167.1.

MS (APSI): *m*/*z* = 352 $[M + 1]^+$.

Anal. Calcd for $C_{19}H_{23}N_5O$: C, 68.35; H, 7.17; N, 19.93. Found: C, 68.38; H, 7.15; N, 19.92.

4-Hexahydro-2*H*-azepin-2-ylidene-5-[hexahydro-2(1*H*)-azocinylideneamino]-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (8f)
Yield: 2.12 g (5.6 mmol, 56%); yellow solid; mp 145 °C.

IR (KBr): 2940, 2860, 1660, 1620, 1590 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.54–1.80 (m, 14 H, CH_2), 2.57–2.68 (m, 2 H, CH_2), 3.45–3.56 (m, 6 H, CH_2), 7.04 (t, *J* = 7.2 Hz, 1 H, Ar), 7.32 (t, *J* = 8.2 Hz, 2 H, Ar), 7.95 (d, *J* = 7.8 Hz, 2 H, Ar), 9.73 (br s, 1 H, NH), 11.51 (br s, 1 H, NH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 24.1, 25.2, 27.9, 28.2, 29.6, 30.0, 31.7, 32.2, 39.9, 41.2, 43.6, 90.7, 117.6, 122.3, 128.3, 139.8, 156.0, 163.9, 165.9, 173.1.

MS (APSI): *m*/*z* = 380 $[M + 1]^+$.

Anal. Calcd for $C_{22}H_{29}N_5O$: C, 69.63; H, 7.70; N, 18.45. Found: C, 69.58; H, 7.74; N, 18.43.

4-Hexahydro-2(1*H*)-azocinylidene-2-phenyl-5-(2-piperidinylideneamino)-2,4-dihydro-3*H*-pyrazol-3-one (8g)
Yield: 2.29 g (6.3 mmol, 63%); yellow solid; mp 191 °C.

IR (KBr): 2950, 2870, 1660, 1620, 1600 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.51–1.80 (m, 12 H, CH_2), 2.45–2.56 (m, 2 H, CH_2), 3.18–3.49 (m, 6 H, CH_2), 6.99 (t, *J* = 7.2 Hz, 1 H, Ar), 7.29 (t, *J* = 8.0 Hz, 2 H, Ar), 7.95 (d, *J* = 7.6 Hz, 2 H, Ar), 9.64 (br s, 1 H, NH), 11.28 (br s, 1 H, NH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 19.6, 21.6, 23.5, 24.6, 25.1, 28.6, 30.7, 31.6, 41.1, 41.4, 90.5, 117.6, 122.2, 128.3, 139.4, 155.8, 159.5, 160.8, 171.4.

MS (APSI): *m*/*z* = 366 $[M + 1]^+$.

Anal. Calcd for $C_{21}H_{27}N_5O$: C, 69.01; H, 7.45; N, 19.16. Found: C, 69.08; H, 7.51; N, 19.22.

Compounds 10a–d; General Procedure
A solution of compound **9a–d** (10 mmol) in anhyd DMF (50 mL) was added in one portion to a suspension of **4** (1.75 g, 10 mmol) and K_2CO_3 (1.38 g, 10 mmol) in DMF (50 mL) at r.t. The resulting mixture was stirred for 5 h. H_2O (300 mL) was added and solid was isolated by filtration, washed with H_2O (1 × 50 mL), and recrystallized from DMF.

5-Amino-4-(1-methyl-2-pyrrolidinylidene)-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (10 a)
Yield: 2.18 g (8.5 mmol, 85%); yellow solid; mp 239 °C.

IR (KBr): 3320, 3200, 3080, 2970, 1640, 1590 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.02 (quint, *J* = 7.2 Hz, 2 H, CH_2), 3.18 (t, *J* = 8.2 Hz, 2 H, CH_2), 3.40 (s, 3 H, CH_3), 3.67 (t, *J* = 7.6 Hz, 2 H, CH_2), 4.99 (s, 2 H, NH_2), 6.95 (t, *J* = 8.0 Hz, 1 H, Ar), 7.26 (t, *J* = 7.0 Hz, 2 H, Ar), 7.95 (d, *J* = 7.0 Hz, 2 H, Ar).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 20.7, 35.6, 40.0, 58.1, 88.1, 117.6, 122.0, 128.7, 140.9, 153.4, 162.1, 168.6.

MS (APSI): *m*/*z* = 257 $[M + 1]^+$.

Anal. Calcd for $C_{14}H_{16}N_4O$: C, 65.61; H, 6.29; N, 21.86. Found: C, 65.58; H, 6.35; N, 21.89.

5-Amino-4-(1-methyl-2-piperidinylidene)-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (10b)
Yield: 1.80 g (6.7 mmol, 67%); yellow solid; mp 239 °C.

IR (KBr): 3330, 3200, 2960, 1630, 1595, 1560 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.69–1.80 (m, 4 H, CH_2), 3.10–3.13 (m, 2 H, CH_2), 3.35 (s, 3 H, CH_3), 3.50–3.53 (m, 2 H, CH_2), 4.76 (s, 2 H, NH_2), 6.88 (t, *J* = 7.5 Hz, 1 H, Ar), 7.24 (t, *J* = 7.0 Hz, 2 H, Ar), 7.98 (d, *J* = 8.5 Hz, 2 H, Ar).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 18.0, 21.4, 29.1, 45.6, 51.9, 89.5, 116.8, 120.1, 128.1, 140.7, 152.0, 162.7, 169.2.

MS (APSI): *m*/*z* = 271 $[M + 1]^+$.

Anal. Calcd for $C_{15}H_{18}N_4O$: C, 66.64; H, 6.71; N, 20.73. Found: C, 66.58; H, 6.78; N, 20.69.

5-Amino-4-(1-methylhexahydro-2*H*-azepin-2-ylidene)-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (10c)
Yield: 2.47 g (8.7 mmol, 87%); yellow solid; mp 222 °C.

IR (KBr): 3390, 3320, 3200, 3070, 3040, 2970, 2920, 1630, 1590, 1560 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.59–1.81 (m, 6 H, CH_2), 3.12–3.15 (m, 2 H, CH_2), 3.35 (s, 3 H, CH_3), 3.53–3.68 (m, 2 H, CH_2), 4.76 (s, 2 H, NH_2), 6.90 (t, *J* = 7.2 Hz, 1 H, Ar), 7.21 (t, *J* = 8.0 Hz, 2 H, Ar), 7.93 (d, *J* = 8.2 Hz, 2 H, Ar).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 24.0, 24.7, 28.2, 31.3, 46.1, 53.9, 91.8, 116.8, 121.4, 128.0, 140.5, 151.9, 161.5, 172.6.

MS (APSI): *m*/*z* = 285 $[M + 1]^+$.

Anal. Calcd for $C_{16}H_{20}N_4O$: C, 67.58; H, 7.09; N, 19.70. Found: C, 67.51; H, 7.12; N, 19.69.

5-Amino-4-[1-methylhexahydro-2(1*H*)-azocinylidene]-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (10d)
Yield: 1.94 g (6.5 mmol, 65%); yellow solid; mp 177 °C.

IR (KBr): 3410, 3280, 3230, 3070, 3050, 2940, 1630, 1590, 1540 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.33–1.44 (m, 4 H, CH_2), 1.72–1.76 (m, 4 H, CH_2), 3.04–3.07 (m, 2 H, CH_2), 3.38 (s, 3 H, CH_3), 3.75–3.83 (m, 2 H, CH_2), 4.95 (s, 2 H, NH_2), 6.90 (t, *J* = 7.0 Hz, 1 H, Ar), 7.25 (t, *J* = 7.5 Hz, 2 H, Ar), 7.96 (d, *J* = 8.2 Hz, 2 H, Ar).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 20.9, 25.2, 28.5, 29.9, 31.3, 43.9, 51.2, 89.7, 116.7, 120.9, 128.1, 140.6, 151.9, 161.5, 173.5.

MS (APSI): m/z = 299 $[M + 1]^+$.

Anal. Calcd for $C_{16}H_{20}N_4O$: C, 68.43; H, 7.43; N, 18.78. Found: C, 68.45; H, 7.39; N, 18.73.

Compounds 12a–d; General Procedure

To a stirred solution of **7a–d** (20 mmol) in MeCN (70 mL) was added a solution of MeI (3.12 g, 22 mmol) in MeCN (20 mL) in one portion. The mixture was refluxed for 3 h whereupon a precipitate was formed during the course of the reaction. Upon cooling, the mixture was filtered and the solid was washed with Et_2O (2 × 30 mL). The crude product was dissolved in DMF (10 mL) and Et_3N (3 mL, 22 mmol) was added. After the exothermal reaction had ceased, the mixture was diluted with H_2O (80 mL) and the solid was isolated by filtration and recrystallized from *i*-PrOH.

5-Amino-4-(3,4-dihydro-2*H*-pyrrol-5-yl)-1-methyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one (12a)

Yield: 2.97 g (11.5 mmol, 58%); white solid; mp 258 °C.

IR (KBr): 3250, 3120, 2980, 1620, 1600 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.75 (quint, J = 7.2 Hz, 2 H, CH_2), 2.81 (t, J = 8.2 Hz, 2 H, CH_2), 3.06 (s, 3 H, CH_3), 3.73 (t, J = 7.6 Hz, 2 H, CH_2), 7.20 (t, J = 7.6 Hz, 1 H, Ar), 7.29 (d, J = 7.5 Hz, 2 H, Ar), 7.73 (t, J = 7.6 Hz, 2 H, Ar), 8.23 (br s, 2 H, NH_2).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 21.4, 35.4, 36.3, 58.5, 83.1, 121.9, 124.8, 128.8, 137.7, 163.0, 165.8, 168.9.

MS (APSI): m/z = 257 $[M + 1]^+$.

Anal. Calcd for $C_{14}H_{16}N_4O$: C, 65.61; H, 6.29; N, 21.86. Found: C, 65.67; H, 6.31; N, 21.90.

5-Amino-1-methyl-2-phenyl-4-(3,4,5,6-tetrahydro-2-pyridinyl)-1,2-dihydro-3*H*-pyrazol-3-one (12b)

Yield: 3.72 g (13.8 mmol, 69%); white solid; mp 236 °C.

IR (KBr): 3360, 3200, 3120, 2950, 1620, 1600 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.55–1.66 (m, 4 H, CH_2), 2.63–2.66 (m, 2 H, CH_2), 2.99 (s, 3 H, CH_3), 3.56–3.57 (m, 2 H, CH_2), 7.13 (t, J = 7.0 Hz, 1 H, Ar), 7.26 (d, J = 8.5 Hz, 2 H, Ar), 7.37 (t, J = 7.0 Hz, 2 H, Ar), 8.09 (br s, 2 H, NH_2).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 18.8, 21.9, 27.3, 36.3, 46.9, 85.3, 121.9, 124.6, 128.6, 137.9, 163.5, 164.7, 165.9.

MS (APSI): m/z = 271 $[M + 1]^+$.

Anal. Calcd for $C_{15}H_{18}N_4O$: C, 66.64; H, 6.71; N, 20.73. Found: C, 66.70; H, 6.75; N, 20.69.

5-Amino-1-methyl-2-phenyl-4-(3,4,5,6-tetrahydro-2*H*-azepin-7-yl)-1,2-dihydro-3*H*-pyrazol-3-one (12c)

Yield: 4.26 g (15.0 mmol, 75%); white solid; mp 194 °C.

IR (KBr): 3380, 3200, 2920, 1610, 1580 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.46–1.53 (m, 4 H, CH_2), 1.76–1.77 (m, 2 H, CH_2), 2.98 (s, 3 H, CH_3), 3.12–3.17 (m, 2 H, CH_2), 3.56–3.62 (m, 2 H, CH_2), 7.15 (t, J = 7.5 Hz, 1 H, Ar), 7.29 (d, J = 8.0 Hz, 2 H, Ar), 7.37 (t, J = 7.5 Hz, 2 H, Ar), 8.16 (br s, 2 H, NH_2).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 23.7, 20.9, 27.5, 30.73, 36.4, 47.7, 85.0, 121.9, 124.6, 128.6, 138.0, 164.5, 165.8, 165.9.

MS (APSI): m/z = 285 $[M + 1]^+$.

Anal. Calcd for $C_{16}H_{20}N_4O$: C, 67.58; H, 7.07; N, 19.70. Found: C, 67.61; H, 7.12; N, 19.76.

5-Amino-4-(3,4,5,6,7,8-hexahydro-2-azocinyl)-1-methyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one (12d)

Yield: 4.05 g (13.6 mmol, 68%); white solid; mp 206 °C.

IR (KBr): 3380, 3200, 2930, 1610, 1590 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.34–1.35 (m, 4 H, CH_2), 1.55–1.60 (m, 4 H, CH_2), 2.91–2.93 (m, 2 H, CH_2), 2.99 (s, 3 H, CH_3), 3.58–3.60 (m, 2 H, CH_2), 7.17 (t, J = 7.0 Hz, 1 H, Ar), 7.29 (d, J = 7.5 Hz, 2 H, Ar), 7.39 (t, J = 7.5 Hz, 2 H, Ar), 8.21 (br s, 2 H, NH_2).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 24.4, 24.7, 25.6, 28.1, 31.0, 36.3, 45.5, 84.7, 121.8, 124.5, 128.6, 138.0, 164.5, 165.7, 169.4.

MS (APSI): m/z = 299 $[M + 1]^+$.

Anal. Calcd for $C_{17}H_{22}N_4O$: C, 68.43; H, 7.43; N, 18.78. Found: C, 68.51; H, 7.46; N, 18.81.

5-Amino-4-(6-aminohexanoyl)-1-methyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one (13)

A suspension of **11** (2.56 g, 10 mmol) in aq 1 M NaOH (100 mL) was stirred for 3 h. The mixture was filtered and the residue crystallized from EtOH–H_2O; yield: 2.59 g (8.6 mmol, 86%); white solid; mp 180 °C.

IR (KBr): 3370, 3280, 3200, 3120, 2940, 2870, 1620 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.31 (m, 4 H, CH_2), 1.51 (m, 2 H, CH_2), 2.51 (m, 2 H, CH_2), 2.71 (m, 2 H, CH_2), 3.10 (s, 3 H, CH_3), 4.25 (br s, 4 H, 2 × NH_2), 7.25 (t, J = 7.5 Hz, 1 H, Ar), 7.28 (d, J = 8.0 Hz, 2 H, Ar), 7.44 (t, J = 7.5 Hz, 2 H, Ar).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 24.6, 26.8, 32.9, 35.8, 39.4, 41.7, 89.9, 123.3, 126.0, 129.3, 137.6, 163.6, 165.8, 195.9.

MS (APSI): m/z = 303 $[M + 1]^+$.

Anal. Calcd for $C_{16}H_{22}N_4O_2$: C, 63.55; H, 7.33; N, 18.53. Found: C, 63.61; H, 7.35; N, 18.56.

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