Regioselective Reaction of Ethyl 5-Acetyl-3,4-dihydropyridine-1(2*H*)-carboxylate with Hydrazines: A Facile Approach to New Pyrazole Derivatives

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Abstract: The reaction of ethyl 5-acetyl-3,4-dihydropyridine-1(2*H*)-carboxylate with diverse aliphatic as well as aromatic monosubstituted hydrazines resulted in the regioselective formation of N-substituted 3-methylpyrazoles.

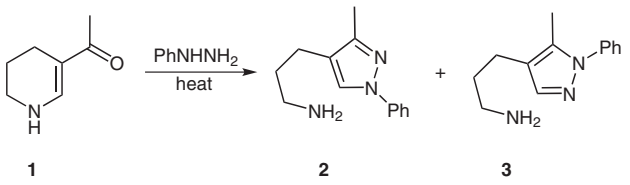
Key words: pyrazole, hydrazine, tetrahydropyridine, regioselectivity

Pyrazoles are an important class of organic compounds used in the pharmaceutical industry. Compounds containing the pyrazole motif are being developed in a wide range of therapeutic areas including CNS, metabolic diseases and endocrine functions, and oncology.[1] A number of pyrazole-containing compounds have been successfully commercialized, such as the blockbuster drugs Viagra, Celebrex, and Acomplia. Substituted pyrazoles have also been applied as ligands for transition-metal-catalyzed cross-coupling reactions.[2]

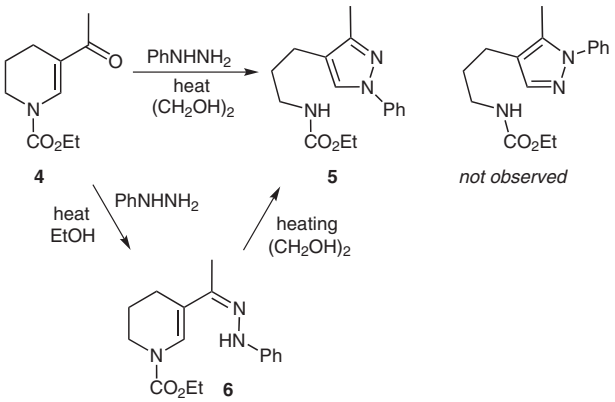
The chemistry of substituted pyrazoles has been extensively studied, and many synthetic strategies for this heterocyclic system are known. One such method is based on the reaction of hydrazines with β-enamino ketones to give the corresponding pyrazoles.[3,4] Herein we report a regioselective synthesis of new pyrazole derivatives from β-enamino ketone **1** and diverse monosubstituted hydrazines.

Despite the structural simplicity of 1-(1,4,5,6-tetrahydropyridin-3-yl)ethanone (**1**) (readily available from 3-acetylpyridine),[3a] there is, to the best of our knowledge, only one report in the literature of the synthesis of pyrazoles from **1** (Scheme 1). In 1970, Quin and Pinion showed, that **1** reacted with phenylhydrazine to form a mixture of two isomeric pyrazoles **2/3** (Scheme 1).[3a] The regioselective synthesis of the individual compounds **2** and **3**, however, was not performed.

We suggested that changing the reactivity of the amino group in **1** by using an N-protecting group might have an influence on the regioselectivity of the reaction. In fact, heating a mixture of N-ethoxycarbonyl-protected compound **4** and phenylhydrazine in aqueous ethylene glycol at 140 °C resulted in the formation of **5** as the sole regioisomer (Scheme 2). Moreover, the expected intermediate **6** was also isolated when the reaction was performed at 78 °C in ethanol. Hydrazone **6** was subsequently transformed into pyrazole **5** by heating at 140 °C in aqueous ethylene glycol (Scheme 2).



Scheme 1 Synthesis of the mixture of pyrazoles **2/3** according to ref. 3a



Scheme 2 Synthesis of pyrazole **5**

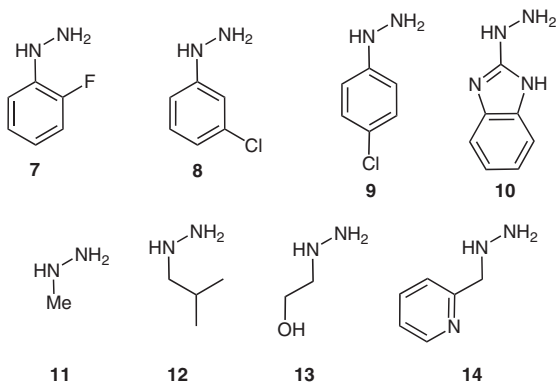


Figure 1 Hydrazines **7**–**14**

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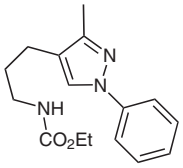
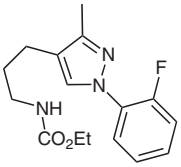
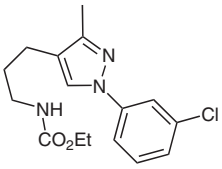
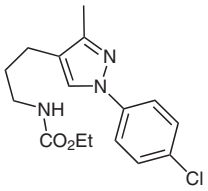
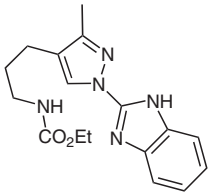
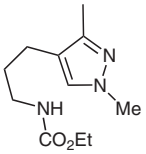
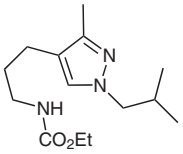
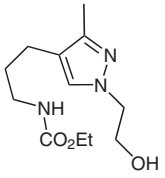
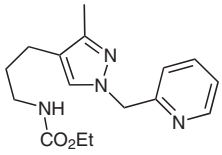
Table 1 Reaction Conditions for the Synthesis of Pyrazoles **5**, **15**–**22** from β-Enamino Ketone **4** and Hydrazines and Formation of Their Hydrochlorides

Hydrazine	Time[a] (h)	Product		Yield (%)	Hydrochloride[b]	Yield (%)
$PhNHNH_2$	4	**5**		86	**2**	96
7	4	**15**		80	**23**	94
8	4	**16**		85	**24**	95
9	4	**17**		85	**25**	94
10	3.5	**18**		73	**26**	95
11	3	**19**		72	**27**	92
12	6	**20**		90	**28**	92
13	4	**21**		82	**29**	97
14	4	**22**		83	**30**	95

[a] Conditions: $(CH_2OH)_2$, 140 °C.
[b] For conditions see Scheme 3.

Thereafter, to show the applicability of the *N*-ethoxycarbonyl moiety in **4** as a 'pucker' for the regioselective synthesis of various pyrazoles, a set of diverse hydrazines **7**–**14** were tested (Figure 1).

Indeed, all the products were obtained as single regioisomers **5**, **15**–**22** in 72–90% yield (Table 1). Noteworthy, the reaction was equally efficient with all types of hydrazine used: aromatic, e.g., $PhNHNH_2$ and **7**–**9**, heteroaromatic **10**, and aliphatic **11**–**14**.

The structures of the obtained pyrazoles were confirmed by NOESY experiments (Figure 2).

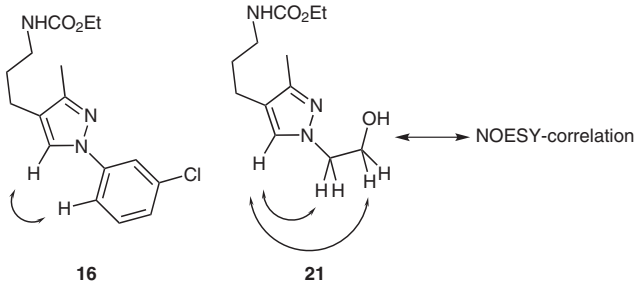
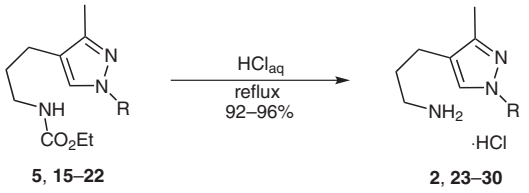


Figure 2 The key NOESY correlations of the selected representatives of pyrazoles with aromatic **16** and aliphatic **21** substituents

Finally, the protected pyrazoles **5**, **15**–**22** were easily converted into the corresponding amines **2**, **23**–**30** by heating at reflux in concentrated hydrochloric acid (Scheme 3, Table 1).



Scheme 3 Synthesis of amines **2**, **23**–**30**

In summary, we have shown, that the reaction of ethyl 5-acetyl-3,4-dihydropyridine-1(2*H*)-carboxylate (**4**) with diverse aliphatic and aromatic hydrazines occurs in a regioselective manner to provide N-substituted 3-methylpyrazoles.

Solvents were purified according to standard procedures. All other materials were purchased from Aldrich and Enamine. Melting points are uncorrected. Analytical TLC was performed using Polychrom SI F_{254} plates. ^1H and ^{13}C NMR spectra were recorded either on a Bruker Avance 500 spectrometer (at 499.9 MHz and 124.9 MHz) with TMS as internal standard. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument by chemical ionization (CI).

1-(1,4,5,6-Tetrahydropyridin-3-yl)ethanone (1)
Compound **1** was prepared following the method of Quin and Pinion.[3a] The product was purified by fractional distillation in vacuo; yield: 67%; bp 140–142 °C/1.33 mbar.

Ethyl 5-Acetyl-3,4-dihydropyridine-1(2*H*)-carboxylate (4)
Compound **4** was synthesized following the method of Wenkert and Hudlicky;[3e] yield: 89%; mp 47–49 °C.

Ethyl 5-[(*Z*)-1-(Phenylhydrazono)ethyl]-3,4-dihydropyridine-1(2*H*)-carboxylate (6)
A 50-mL reaction vessel equipped with a condenser was charged with a soln of phenylhydrazine (10 mmol) and **4** (10 mmol) in EtOH (30 mL); the soln was heated at reflux for 4 h. Thereafter, the soln was evaporated under reduced pressure to give the corresponding crude yellow hydrazone **6**. The product was washed with H_2O (30) and hexane (25 mL) and dried in vacuo; yield: 97%; mp 126–127 °C.

^1H NMR (500 MHz, DMSO-d_6): δ = 9.02 (s, 1 H, NH), 7.18 (m, 5 H, Ph), 6.71 (s, 1 H, CH), 4.19 (q, ^3J = 6.5 Hz, 2 H, OCH_2), 3.57 (t, ^3J = 7 Hz, 2 H, NCH_2), 2.48 (t, ^3J = 7 Hz, 2 H, CH_2C), 1.99 (s, 3 H, CH_3), 1.81 (m, ^3J = 7 Hz, 2 H, CH_2), 1.27 (t, ^3J = 6.5 Hz, 3 H, CH_3CH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 153.22 (s, CO), 146.94 (s, *tert*-C, CN), 142.04 (s, *tert*-C, Ph), 129.20 (s, 2 C, Ph), 123.84 (s, CH), 119.72 (s, *tert*-C), 118.73 (s, Ph), 113.02 (s, 2 C, Ph), 62.20 (s, OCH_2), 42.54 (s, CH_2N), 21.60 (s, CCH_2), 21.31 (s, CH_2), 14.91 (s, CH_3CH_2), 11.58 (s, CH_3).

MS: m/z = 288.3 $(M + 1)^+$.

Pyrazoles 5, 15–22; General Procedure
A 25-mL reaction vessel equipped with a condenser was charged with a soln of the corresponding monosubstituted hydrazine (10 mmol), **7** (10.5 mmol) and concd HCl (0.25 mL) in aq ethylene glycol (10–15 mL). The soln was stirred under an inert atmosphere at 140 °C for 3–6 h followed by concentration in vacuo. The gummy residue was dissolved in $CHCl_3$ (50 mL), washed with 5% aq HCl (2 × 20 mL) and sat. aq $NaHCO_3$ (2 × 30 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the corresponding pyrazoles **5**, **15**–**22**. Scale of the synthesis: 1–5 g of **7**.

Ethyl 3-(3-Methyl-1-phenyl-1*H*-pyrazol-4-yl)propylcarbamate (5)
Pale brown oil; yield: 86%.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.67 (s, 1 H, CH), 7.67 (d, ^3J = 7.52 Hz, 2 H, Ph), 7.40 (t, ^3J = 7.5 Hz, 2 H, Ph), 7.21 (t, ^3J = 7.5 Hz, 1 H, Ph), 4.74 (br s, 1 H, NH), 4.12 (q, ^3J = 6.5 Hz, 2 H, OCH_2), 3.24 (m, ^3J = 6 Hz, 2 H, CH_2NH), 2.49 (t, ^3J = 7.5 Hz, 2 H, CCH_2), 2.28 (s, 3 H, CH_3), 1.79 (m, ^3J = 7 Hz, 2 H, CH_2), 1.24 (t, ^3J = 7 Hz, 3 H, CH_3CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.85 (s, CO), 149.06 (s, *tert*-C, CCH_3), 140.16 (s, *tert*-C, Ph), 129.32 (s, 2 C, Ph), 125.56 (s, CH), 125.32 (s, Ph), 120.73 (s, *tert*-C, CCH_2), 118.37 (s, 2 C, Ph), 60.72 (s, OCH_2), 40.47 (s, CH_2NH), 30.44 (s, CH_2), 20.97 (s, CCH_2), 14.70 (s, CH_3CH_2), 11.95 (s, CH_3).

MS: m/z = 288.2 $(M + 1)^+$.

Ethyl 3-[1-(2-Fluorophenyl)-3-methyl-1*H*-pyrazol-4-yl]propylcarbamate (15)
Pale brown oil; yield: 80%.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.73 (s, 1 H, CH), 7.67 (t, $^3J_{H-F}$ = 8 Hz, 1 H, Ph), 7.20 (m, 3 H, Ph), 4.68 (br s, 1 H, NH), 4.12 (q, ^3J = 6.5 Hz, 2 H, OCH_2), 3.25 (m, ^3J = 6 Hz, 2 H, CH_2NH), 2.50 (t, ^3J = 7.5 Hz, 2 H, CCH_2), 2.29 (s, 3 H, CH_3), 1.80 (m, ^3J = 7 Hz, 2 H, CH_2), 1.24 (t, ^3J = 7 Hz, 3 H, CH_3CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.78 (s, CO), 153.19 (d, $^1J_{C,F}$ = 198.1 Hz, CF) 148.90 (s, *tert*-C, CCH_3), 129.33 (s, Ph), 126.73 (s, *tert*-C, Ph), 124.84 (s, CH), 125.32 (s, Ph), 123.74 (s, *tert*-C, CCH_2), 120.58 (s, Ph), 116.62 (s, Ph), 60.74 (s, OCH_2), 40.56 (s,

CH_2NH), 30.45 (s, CH_2), 20.99 (s, CCH_2), 14.66 (s, CH_3CH_2), 11.83 (s, CH_3).

MS: m/z = 306.2 $(M + 1)^+$.

Ethyl 3-[1-(3-Chlorophenyl)-3-methyl-1*H*-pyrazol-4-yl]propylcarbamate (16)
Pale brown oil; yield: 85%.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.66 (s, 1 H, CH), 7.48 (s, 1 H, Ph), 7.48 (d, ^3J = 8 Hz, 1 H, Ph), 7.31 (t, ^3J = 8 Hz, 1 H, Ph), 7.16 (d, ^3J = 8 Hz, 1 H, Ph), 4.81 (br s, 1 H, NH), 4.12 (q, ^3J = 6.5 Hz, 2 H, OCH_2), 3.23 (m, ^3J = 6 Hz, 2 H, CH_2NH), 2.46 (t, ^3J = 7.5 Hz, 2 H, CCH_2), 2.27 (s, 3 H, CH_3), 1.77 (m, ^3J = 7 Hz, 2 H, CH_2), 1.23 (t, ^3J = 7 Hz, 3 H, CH_3CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.80 (s, CO), 149.61 (s, *tert*-C, CCH_3), 140.88 (s, *tert*-C, Ph), 135.18 (s, Ph) 130.47 (s, Ph), 130.36 (s, Ph), 125.59 (s, CH), 121.37 (s, *tert*-C, CCH_2), 118.65 (s, Ph), 116.26 (s, Ph), 60.79 (s, OCH_2), 40.45 (s, CH_2NH), 30.37 (s, CH_2), 20.90 (s, CCH_2), 14.65 (s, CH_3CH_2), 11.82 (s, CH_3).

MS: m/z = 322.7 $(M + 1)^+$.

Ethyl 3-[1-(4-Chlorophenyl)-3-methyl-1*H*-pyrazol-4-yl]propylcarbamate (17)
Pale brown oil; yield: 85%.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.65 (s, 1 H, CH), 7.54 (d, ^3J = 8 Hz, 2 H, Ph), 7.36 (d, ^3J = 8 Hz, 1 H, Ph), 4.73 (br s, 1 H, NH), 4.11 (q, ^3J = 6.5 Hz, 2 H, OCH_2), 3.24 (m, ^3J = 6 Hz, 2 H, CH_2NH), 2.48 (t, ^3J = 7 Hz, 2 H, CCH_2), 2.27 (s, 3 H, CH_3), 1.78 (m, ^3J = 7 Hz, 2 H, CH_2), 1.24 (t, ^3J = 7 Hz, 3 H, CH_3CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.87 (s, CO), 149.43 (s, *tert*-C, CCH_3), 138.66 (s, *tert*-C, Ph), 130.76 (s, Ph), 129.32 (s, 2 C, Ph), 125.31 (s, CH), 121.17 (s, *tert*-C, CCH_2), 119.41 (s, 2 C, Ph), 60.70 (s, OCH_2), 40.38 (s, CH_2NH), 30.33 (s, CH_2), 20.87 (s, CCH_2), 14.66 (s, CH_3CH_2), 11.86 (s, CH_3).

MS: m/z = 322.9 $(M + 1)^+$.

Ethyl 3-[1-(1*H*-Benzimidazol-2-yl)-3-methyl-1*H*-pyrazol-4-yl]propylcarbamate (18)
Yellow solid; yield: 73%; mp 180 °C (subl.).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.68 (s, 1 H, CH), 7.60 (d, ^3J = 6.5 Hz, 2 H, $C_7H_6N_2$), 7.39 (t, ^3J = 6.5 Hz, 2 H, $C_7H_5N_2$), 7.17 (br s, 1 H, NH), 6.88 (br s, 1 H, NH), 3.94 (q, ^3J = 6 Hz, 2 H, OCH_2), 3.03 (m, 2 H, CH_2NH), 2.43 (t, ^3J = 6.5 Hz, 2 H, CCH_2), 2.27 (s, 3 H, CH_3), 1.68 (m, ^3J = 6.5 Hz, 2 H, CH_2), 1.12 (t, ^3J = 6 Hz, 3 H, CH_3CH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 156.86 (s, CO), 155.17 (s, *tert*-C, $C_7H_5N_2$), 131.34 (s, *tert*-C, $C_7H_5N_2$), 129.08 (s, *tert*-C, $C_7H_5N_2$), 142.98 (s, *tert*-C, CCH_3), 125.7 (s, CH), 125.26 (s, 2 C $C_7H_5N_2$), 120.88 (s, *tert*-C, CCH_2), 113.98 (s, $C_7H_5N_2$), 109.03 (s, $C_7H_5N_2$), 60.05 (s, OCH_2), 39.04 (s, CH_2NH), 29.56 (s, CH_2), 20.73 (s, CCH_2), 15.17 (s, CH_3CH_2), 12.19 (s, CH_3).

MS: m/z = 328.4 $(M + 1)^+$.

Ethyl 3-(1,3-Dimethyl-1*H*-pyrazol-4-yl)propylcarbamate (19)
Yellow oil; yield: 72%.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.05 (s, 1 H, CH), 4.83 (br s, 1 H, NH), 4.06 (q, ^3J = 6.5 Hz, 2 H, OCH_2), 3.73 (s, 3 H, NCH_3), 3.15 (m, ^3J = 6 Hz, 2 H, CH_2NH), 2.35 (t, ^3J = 7 Hz, 2 H, CCH_2), 2.13 (s, 3 H, CH_3), 1.67 (m, ^3J = 7 Hz, 2 H, CH_2), 1.19 (t, ^3J = 7 Hz, 3 H, CH_3CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.77 (s, CO), 146.32 (s, *tert*-C, CCH_3), 129.10 (s, CH), 118.23 (s, *tert*-C, CCH_2), 60.44 (s, OCH_2), 40.48 (s, CH_2NH), 38.53 (s, NCH_3), 30.54 (s, CH_2), 20.77 (s, CCH_2), 14.45 (s, CH_3CH_2), 11.50 (s, CH_3).

MS: m/z = 226.3 $(M + 1)^+$.

Ethyl 3-(1-Isobutyl-3-methyl-1*H*-pyrazol-4-yl)propylcarbamate (20)
Yellow oil; yield: 90%.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.84 (s, 1 H, CH), 5.56 (br s, 1 H, NH), 3.81 (q, ^3J = 6 Hz, 2 H, OCH_2), 3.48 (d, ^3J = 6.5 Hz, 2 H, NCH_2CH), 2.91 (m, 2 H, CH_2NH), 2.13 (t, ^3J = 6.5 Hz, 2 H, CCH_2), 1.88 (m, 4 H, CH_3, CH), 1.56 (m, ^3J = 6.5 Hz, 2 H, CH_2), 1.06 (t, ^3J = 6 Hz, 3 H, CH_3CH_2), 0.70 [d, ^3J = 6.5 Hz, 6 H, $CH(CH_3)_2$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.79 (s, CO), 145.82 (s, *tert*-C, CCH_3), 128.21 (s, CH), 117.40 (s, *tert*-C, CCH_2), 60.14 (s, NCH_2CH), 58.99 (s, OCH_2), 40.18 (s, CH_2NH), 30.44 [s, $CH(CH_3)_2$], 29.41 (s, CH_2), 20.67 (s, CCH_2), 19.68 [s, $CH(CH_3)_2$], 14.45 (s, CH_3CH_2), 11.40 (s, CH_3).

MS: m/z = 268.4 $(M + 1)^+$.

Ethyl 3-[1-(2-Hydroxyethyl)-3-methyl-1*H*-pyrazol-4-yl]propylcarbamate (21)
Yellow oil; yield: 82%.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.12 (s, 1 H, CH), 5.56 (br s, 1 H, NH), 4.03 (t, ^3J = 7.5 Hz, 2 H, NCH_2CH_2), 3.82 (m, 4 H, OCH_2, CH_2OH), 2.75 (br s, 1 H, OH), 2.62 (t, ^3J = 7.5 Hz, 2 H, CH_2NH_2), 2.33 (t, ^3J = 7.5 Hz, 2 H, CCH_2), 2.12 (s, 3 H, CH_3), 1.58 (m, ^3J = 7.5 Hz, 2 H, CH_2), 1.06 (t, ^3J = 6.5 Hz, 3 H, CH_3CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.66 (s, CO), 146.75 (s, *tert*-C, CCH_3), 128.94 (s, CH), 118.31 (s, *tert*-C, CCH_2), 61.15 (s, CH_2OH), 59.37 (s, OCH_2), 53.81 (s, NCH_2), 41.53 (s, CH_2NH_2), 34.13 (s, CH_2), 20.96 (s, CCH_2), 14.50 (s, CH_3CH_2), 11.62 (s, CH_3).

MS: m/z = 256.5 $(M + 1)^+$.

Ethyl 3-[3-Methyl-1-(pyridin-2-ylmethyl)-1*H*-pyrazol-4-yl]propylcarbamate (22)
The product was obtained as a hydrochloride from the aqueous phase as a yellow solid; yield: 83%; mp 169 °C (subl.).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.81 (d, ^3J = 5 Hz, 1 H, Py), 8.36 (t, ^3J = 7 Hz, 1 H, Py), 7.83 (t, ^3J = 6.5 Hz, 1 H, Py), 7.72 (s, 1 H, CH), 7.45 (d, ^3J = 7.5 Hz, 1 H, Py), 7.11 (br s, 1 H, NH), 5.62 (s, 2 H, NCH_2Py), 3.95 (q, ^3J = 7 Hz, 2 H, OCH_2), 2.97 (m, 2 H, CH_2NH), 2.32 (t, ^3J = 7 Hz, 2 H, CCH_2), 2.06 (s, 3 H, CH_3), 1.59 (m, ^3J = 7.5 Hz, 2 H, CH_2), 1.12 (t, ^3J = 7 Hz, 3 H, CH_3CH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 156.79 (s, CO), 153.25 (s, *tert*-C, Py), 147.41 (s, *tert*-C, CCH_3), 144.97 (s, Py), 143.8 (s, Py), 130.88 (s, CH), 125.91 (s, Py), 125.45 (s, Py), 119.38 (s, *tert*-C, CCH_2), 59.91 (s, OCH_2), 52.5 (s, NCH_2Py), 31.18 (s, CH_2NH), 30.47 (s, CH_2), 20.76 (s, CCH_2), 14.19 (s, CH_3CH_2), 11.78 (s, CH_3).

MS: m/z = 303.3 $(M + 1)^+$.

Aminopyrazoles 2, 23–30; General Procedure
A 1-necked 50-mL round-bottomed flask equipped with a reflux condenser was charged with a soln of the corresponding ethyl carbamate **5**, **15**–**22** (10 mmol) and concd HCl (25 mL). The soln was heated at reflux for 16 h. Thereafter, the soln was evaporated under reduced pressure to the corresponding crude aminopyrazole **2**, **23**–**30**. The product was washed with $CHCl_3$ (25 mL) and dried in vacuo.

Scale of the synthesis: 1–5 g of the corresponding pyrazole.

3-(3-Methyl-1-phenyl-1*H*-pyrazol-4-yl)propylamine Hydrochloride (2)
White solid; yield: 96%; mp >300 °C (dec.).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.24 (s, 1 H, CH), 8.01 (br s, 3 H, NH_3^+), 7.73 (d, ^3J = 7.5 Hz, 2 H, Ph), 7.43 (t, ^3J = 7.5 Hz, 2 H,

Ph), 7.21 (t, ^3J = 7.5 Hz, 1 H, Ph), 2.80 (m, ^3J = 6 Hz, 2 H, CH_2NH$_2$), 2.52 (t, ^3J = 7.5 Hz, 2 H, CCH$_2$), 2.19 (s, 3 H, CH$_3$), 1.84 (m, ^3J = 7.5 Hz, 2 H, CH$_2$).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 149.06 (s, *tert*-C, *C*CH$_3$), 137.70 (s, *tert*-C, Ph), 129.99 (s, 2 C, Ph), 129.79 (s, CH), 127.91 (s, Ph), 120.65 (s, *tert*-C, *C*CH$_2$), 119.90 (s, 2 C, Ph), 39.06 (s, CH$_2$NH$_2$), 27.16 (s, CH$_2$), 19.81 (s, C*C*H$_2$), 10.13 (s, CH$_3$).

MS: *m*/*z* = 216.3 (M + 1)$^+$.

3-[1-(2-Fluorophenyl)-3-methyl-1*H*-pyrazol-4-yl]propylamine Hydrochloride (23)

White solid; yield: 94%; mp 205–206 °C (subl.).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.18 (br s, 3 H, NH$_3^+$), 7.92 (t, $^3J_{H-F}$ = 8 Hz, 1 H, Ph), 7.73 (s, 1 H, CH), 7.37 (t, 1 H, Ph), 7.28 (m, 2 H, Ph), 3.41 (m, ^3J = 7 Hz, 2 H, CH_2NH$_2$), 2.76 (t, ^3J = 7.5 Hz, 2 H, CCH$_2$), 2.18 (s, 3 H, CH$_3$), 1.83 (m, ^3J = 7 Hz, 2 H, CH$_2$).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 153.23 (d, $^1J_{C,F}$ = 198.10 Hz, CF), 148.94 (s, *tert*-C, *C*CH$_3$), 129.38 (s, Ph), 126.70 (s, *tert*-C, Ph), 126.31 (s, Ph), 125.01 (s, CH), 123.64 (s, *tert*-C, *C*CH$_2$), 120.63 (s, Ph), 116.66 (s, Ph), 40.39 (s, CH$_2$NH$_2$), 30.49 (s, CH$_2$), 20.94 (s, C*C*H$_2$), 11.81 (s, CH$_3$).

MS: *m*/*z* = 234.4 (M + 1)$^+$.

3-[1-(3-Chlorophenyl)-3-methyl-1*H*-pyrazol-4-yl]propylamine Hydrochloride (24)

White solid; yield: 95%; mp 210–212 °C (subl.).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.37 (s, 1 H, CH), 8.19 (br s, 3 H, NH$_3^+$), 7.82 (s, 1 H, Ph), 7.72 (d, ^3J = 7.5 Hz, 1 H, Ph), 7.44 (t, ^3J = 7.5 Hz, 1 H, Ph), 7.24 (d, ^3J = 7.5 Hz, 1 H, Ph), 2.79 (m, 2 H, CH_2NH$_2$), 2.52 (t, ^3J = 7.5 Hz, 2 H, CCH$_2$), 2.18 (s, 3 H, CH$_3$), 1.86 (m, ^3J = 7.5 Hz, 2 H, CH$_2$).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 149.60 (s, *tert*-C, *C*CH$_3$), 141.31 (s, *tert*-C, Ph), 134.41 (s, Ph), 131.63 (s, Ph), 126.89 (s, Ph), 125.32 (s, CH), 121.22 (s, *tert*-C, *C*CH$_2$), 117.49 (s, Ph), 116.29 (s, Ph), 38.71 (s, CH$_2$NH), 27.49 (s, CH$_2$), 20.65 (s, C*C*H$_2$), 12.22 (s, CH$_3$).

MS: *m*/*z* = 250.6 (M + 1)$^+$.

3-[1-(4-Chlorophenyl)-3-methyl-1*H*-pyrazol-4-yl]propylamine Hydrochloride (25)

White solid; yield: 94%; mp 211 °C (subl.).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.28 (s, 1 H, CH), 8.16 (br s, 3 H, NH$_3^+$), 7.75 (d, ^3J = 8 Hz, 2 H, Ph), 7.45 (d, ^3J = 8 Hz, 2 H, Ph), 2.78 (m, ^3J = 6 Hz, 2 H, CH_2NH$_2$), 2.46 (t, ^3J = 7.5 Hz, 2 H, CCH$_2$), 2.17 (s, 3 H, CH$_3$), 1.85 (m, ^3J = 7.5 Hz, 2 H, CH$_2$).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 149.32 (s, *tert*-C, *C*CH$_3$), 138.96 (s, *tert*-C, Ph), 131.62 (s, Ph), 129.77 (m, 2 C, Ph), 126.7 (s, CH), 122.02 (s, *tert*-C, *C*CH$_2$), 119.48 (s, 2 C, Ph), 38.74 (s, CH$_2$NH$_2$), 27.53 (s, CH$_2$), 20.63 (s, C*C*H$_2$), 12.17 (s, CH$_3$).

MS: *m*/*z* = 250.7 (M + 1)$^+$.

3-[1-(1*H*-Benzimidazol-2-yl)-3-methyl-1*H*-pyrazol-4-yl]propylamine Hydrochloride (26)

White solid; yield: 95%; mp >300 °C (dec.).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.58 (s, 1 H, CH), 8.19 (br s, 4 H, NH, NH$_3^+$), 7.53 (d, ^3J = 6.5 Hz, 2 H, *H*-C$_7$H$_6$N$_2$), 7.28 (t, ^3J = 6.5 Hz, 2 H, *H*-C$_7$H$_5$N$_2$), 3.17 (m, 2 H, CH_2NH$_2$), 2.81 (t, ^3J = 6.5 Hz, 2 H, CCH$_2$), 2.28 (s, 3 H, CH$_3$), 1.87 (m, ^3J = 6.5 Hz, 2 H, CH$_2$).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 156.77 (s, *tert*-C, C$_7$H$_5$N$_2$), 141.32 (s, *tert*-C, *C*CH$_3$), 130.38 (s, *tert*-C, C$_7$H$_5$N$_2$), 129.45 (s, *tert*-C, C$_7$H$_5$N$_2$), 125.74 (s, CH), 125.36 (s, 2 C, C$_7$H$_5$N$_2$), 120.78 (s, *tert*-C, *C*CH$_2$), 113.59 (s, C$_7$H$_5$N$_2$), 109.11 (s, C$_7$H$_5$N$_2$), 39.12 (s, CH$_2$NH$_2$), 29.49 (s, CH$_2$), 20.68 (s, C*C*H$_2$), 12.21 (s, CH$_3$).

MS: *m*/*z* = 256.4 (M + 1)$^+$.

3-(1,3-Dimethyl-1*H*-pyrazol-4-yl)propylamine Hydrochloride (27)

White solid; yield: 92%; mp 243 °C (subl.).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.22 (br s, 3 H, NH$_3^+$), 7.67 (s, 1 H, CH), 3.78 (s, 3 H, NCH$_3$), 2.72 (m, 2 H, CH_2NH$_2$), 2.41 (t, ^3J = 7 Hz, 2 H, CCH$_2$), 2.14 (s, 3 H, CH$_3$), 1.76 (m, ^3J = 7 Hz, 2 H, CH$_2$).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 146.39 (s, *tert*-C, *C*CH$_3$), 129.32 (s, CH), 118.33 (s, *tert*-C, *C*CH$_2$), 40.67 (s, CH$_2$NH$_2$), 39.66 (s, NCH$_3$), 30.57 (s, CH$_2$), 20.87 (s, C*C*H$_2$), 11.73 (s, CH$_3$).

MS: *m*/*z* = 154.1 (M + 1)$^+$.

3-(1-Isobutyl-3-methyl-1*H*-pyrazol-4-yl)propylamine Hydrochloride (28)

White solid; yield: 92%; mp 164 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.79 (br s, 3 H, NH$_3^+$), 7.20 (s, 1 H, CH), 3.77 (d, ^3J = 6.5 Hz, 2 H, NCH_2CH), 2.73 (m, 2 H, CH_2NH$_2$), 2.52 [m, 1 H, C*H*(CH$_3$)$_2$], 2.38 (t, ^3J = 7 Hz, 2 H, CCH$_2$), 2.14 (s, 3 H, CH$_3$), 1.72 (m, ^3J = 7 Hz, 2 H, CH$_2$), 0.81 [d, ^3J = 6.5 Hz, 6 H, CH(CH_3)$_2$].

^{13}C NMR (100 MHz, DMSO-d_6): δ = 146.82 (s, *tert*-C, *C*CH$_3$), 127.21 (s, CH), 117.42 (s, *tert*-C, *C*CH$_2$), 60.34 (s, NCH$_2$CH), 40.48 (s, CH$_2$NH$_2$), 30.62 [s, *C*H(CH$_3$)$_2$], 30.10 (s, CH$_2$), 20.63 (s, C*C*H$_2$), 19.71 [s, CH(*C*H$_3$)$_2$], 11.40 (s, CH$_3$).

MS: *m*/*z* = 196.5 (M + 1)$^+$.

2-[4-(3-Aminopropyl)-3-methyl-1*H*-pyrazol-1-yl]ethanol Hydrochloride (29)

White solid; yield: 97%; mp 74 °C.

^{1}H NMR (500 MHz, CDCl$_3$): δ = 7.12 (s, 1 H, CH), 4.03 (t, ^3J = 7.5 Hz, 2 H, NCH_2CH$_2$), 3.83 (d, ^3J = 7.5 Hz, 2 H, CH_2OH), 2.75 (br s, 3 H, OH, NH$_3^+$), 2.61 (t, ^3J = 7.5 Hz, 2 H, CH_2NH$_2$), 2.33 (t, ^3J = 7.5 Hz, 2 H, CCH$_2$), 2.12 (s, 3 H, CH$_3$), 1.58 (m, ^3J = 7.5 Hz, 2 H, CH$_2$).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 146.72 (s, *tert*-C, *C*CH$_3$), 128.90 (s, CH), 118.29 (s, *tert*-C, *C*CH$_2$), 61.16 (s, CH$_2$OH), 53.84 (s, NCH$_2$), 41.51 (s, CH$_2$NH$_2$), 34.03 (s, CH$_2$), 20.97 (s, C*C*H$_2$), 11.62 (s, CH$_3$).

MS: *m*/*z* = 184.2 (M + 1)$^+$.

3-[3-Methyl-1-(pyridin-2-ylmethyl)-1*H*-pyrazol-4-yl]propylamine Hydrochloride (30)

White solid; yield: 95%; mp >300 °C (dec.).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.75 (d, ^3J = 5 Hz, 1 H, Py), 8.25 (t, ^3J = 7 Hz, 1 H, Py), 8.14 (br s, 3 H, NH$_3^+$), 7.72 (m, 2 H, Py, CH), 7.38 (d, ^3J = 6.5 Hz, 1 H, Py), 5.55 (s, 2 H, NCH_2Py), 2.75 (m, 2 H, CH_2NH$_2$), 2.41 (t, ^3J = 7 Hz, 2 H, CCH$_2$), 2.07 (s, 3 H, CH$_3$), 1.77 (m, ^3J = 7 Hz, 2 H, CH$_2$).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 154.25 (s, *tert*-C, Py), 147.56 (s, *tert*-C, *C*CH$_3$), 145.65 (s, Py), 142.91 (s, Py), 129.34 (s, CH), 125.37 (s, Py), 124.85 (s, Py), 119.44 (s, *tert*-C, *C*CH$_2$), 52.52 (s, NCH$_2$Py), 39.44 (s, CH$_2$NH$_2$), 30.89 (s, CH$_2$), 20.76 (s, C*C*H$_2$), 11.78 (s, CH$_3$).

MS: *m*/*z* = 231.2 (M + 1)$^+$.

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