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Synthesis of chiral nopinane annelated 3-methyl-1-aryl-1*H*-pyrazolo[3,4-*b*]-pyridines by condensation of pinocarvone oxime with 1-aryl-1*H*-pyrazol-5-amines

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Chemical Experiments

Starting compounds

All the solvent used were freshly distilled.

The following commercially available reagent grade compounds were used: (−)-α-pinene (Kosher, W290203), 25% aq. ammonia (ReaChem), potassium hydroxide (ReaChem), conc. aq. HCl (ReaChem), 2-chloropyridine (Fluka AG, 26280), sodium (ReaChem), hydrazine hydrate (ReaChem), triethylamine (ReaChem), sodium tartrate dihydrate (ReaChem), anhydrous sodium sulphate (ReaChem), phosphorus pentoxide (ReaChem), $FeCl_3 \times 6H_2O$ (ReaChem), phenylhydrazine (**2a**, ReaChem), (2,6-dimethylphenyl)hydrazine (**2b**, ReaChem), bis(4-hydrazinylphenyl)methane (**2e**, ReaChem), naphthalen-1-ylhydrazine (**2c**, ReaChem).

(+)-Pinocarvone (E)-oxime (**4**) of 90% *e.e.* with m.p. 124 °C (from light petroleum) and $[\alpha]_D^{23}$ +14 (c 0.85, $CHCl_3$)* was prepared according to nitrosochlorination-dehydrochlorination by addition of a solution of NOCl in CH_2Cl_2 to (−)-α-pinene (94 % *e.e.*) followed by treatment with Et_3N.†

3-Aminocrotonitrile (**1**) (ca. 1:1 mixture of *E*- and *Z*-isomers) was prepared as light-yellow crystals in 84% yield in a mixture of acetonitrile and light petroleum as described in ref.‡ NMR spectra of the product fit the published data.§

2-Hydrazinylpyridine 2d. A stirred mixture of 2-chloropyridine (20 ml, 0.212 mol) and hydrazine hydrate (80 ml) was heated at reflux for 6 h. The mixture was cooled down to room temperature followed by addition of ethanol (50 ml). The volatiles were distilled off in vacuum. New portion of ethanol (50 ml) was added followed by removal of the volatiles. Removing of the volatiles with ethanol was repeated additionally twice. The residue was dissolved in diethyl ether (50 ml), and the solution was stored at –18 °C for 24. Light violet crystals were filtered off, washed with cold (–18 °C) diethyl ether (20 ml) and dried in an desiccator over P_2O_5 to afford the title compound in 76% yield. NMR ^{1}H spectrum of the product fits the published data.**

Microwave assisted experiments

Microwave assisted syntheses were carried out in a Single-Mode Microwave reactor Discover™ System S-Class (CEM corp., USA) using a special 10 ml reaction vessel.

Compounds analysis

Analytical TLC was carried out using ready-to-use commercially plates SORBFIL (TLC-AF-A-UF, 0.005-0.017 mm silica gel on aluminum foil), Dragendorff's solution being the visualization reagent. Silicagel SORBFILE (50-160 mm) was used for preparative column chromatography.

Optical rotation was measured with a PolAAr 3005 polarimeter at 589 nm, *c* is given in g/100 cm^3. Melting points were determined by differential scanning calorimetry using a NETZSCH STA

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* E. S. Vasilyev, A. M. Agafontsev and A. V. Tkachev, *Synth Commun*., 2014, **44**, 1817.

† A. V. Tkachev, *Ross. Khim. Zh*. (*Zh. Ross. Khim. Ob-va im. D. I. Mendeleeva*) (in Russian).

‡ J. Moir, *J. Chem. Soc. Trans*., 1902, **81**, 100.

§ K. L. Gallaher, D. Lukco and J. G. Grasselli, *Can. J. Chem*., 1985, **63**, 1960.

** V. S. Padalkar, V. S. Patil, K. R. Phatangare, P. G. Umape and N. Sekar, *Synth. Commun*., 2011, **41**, 925.

409 instrument.

Spectroscopic study

NMR spectra were recorded at 25–28 °C for solutions (*c* 10–40 mg/mL) on a Bruker AV-300 spectrometer (400.13 MHz for ^{1}H, 75.47 MHz for ^{13}C), a Bruker AV-400 spectrometer (400.13 MHz for ^{1}H, 100.62 MHz for ^{13}C), a Bruker DRX-500 spectrometer (500.13 MHz for ^{1}H, 125.75 MHz for ^{13}C) locked to the deuterium resonance of the solvent. The chemical shifts were calculated relative to the solvent signals used as the internal standard: δ_C 76.90 ppm and δ_H 7.24 ppm for $CDCl_3$, and δ_C 1.39 ppm and δ_H 1.94 ppm for CD_3CN. Signal assignment was made using *J* modulated ^{13}C NMR spectra (proton-noise-decoupling, the opposite phases for the signals of the atoms with the odd and even numbers of the attached protons, tuning to the constant J = 135 Hz) and 2D NMR spectra: 1) homonuclear ^{1}H–^{1}H correlation, 2) heteronuclear ^{13}C–^{1}H correlation at the direct spin-spin coupling constants (J = 135 Hz), and 3) heteronuclear ^{13}C–^{1}H correlation at the long-range spin-spin coupling constants (J = 10 Hz). Carbon-proton spin-spin coupling constants were taken from proton-coupled ^{13}C NMR spectra. Sign of spin-spin couplings was not determined. Chemical shifts are given in ppm, spin-spin coupling constants are given in Hz.

IR spectra were recorded on a Vector 22 instrument (frequencies are drawn in cm^{-1}), UV-spectra were registered on a HP UV-Vis 8453A DAD spectrometer (wavelengths are given in nm). A Varian Cary Eclipse instrument was used to measure fluorescence. The precise molecular weights were determined by high-resolution mass spectrometry on a Thermo electron DFS (electron impact ionization, EI, 70 eV) spectrometer. The same instrument was used to register the standard EI mass spectra.

Syntheses

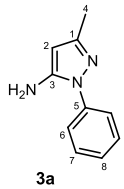
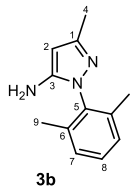
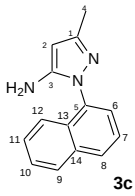
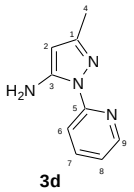
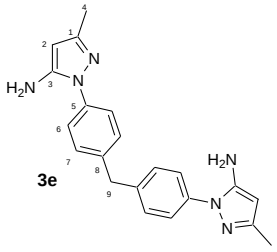
Syntheses of 1-aryl-1H-pyrazol-5-amines (3a-d) (general method)

A solution of 3-aminocrotonitrile (**1**) (1.15 g, 0.014 mol) in isopropyl alcohol (6 ml) was added dropwise to a boiling solution of the corresponding substituted hydrazine **2a-d** (0.014 mol) in a mixture of water (6 ml) and aq. conc. HCl (0.66 ml, 0.0154 mol). Additional portion of aq. conc. HCl (20 ml) was added, and the mixture was heated under reflux for 2 h. The mixture was concentrated under reduced pressure, the residue was treated with aq. 40% KOH (50 ml) and extracted with toluene (3×25 ml). The combined organic extract was dried over anhydrous Na_2SO_4 and concentrated in vacuo to leave the crude product which was then purified by column chromatography (SiO_2, light petroleum–ethyl acetate 3:1 v/v).

Synthesis of 1,1'-[methylenebis(4,1-phenylene)[bis(3-methyl-1H-pyrazol-5-amine) 3e.

A solution of 3-aminocrotonitrile (**1**) (0.984 g, 0.0120 mol) in isopropyl alcohol (6 ml) was added dropwise to a boiling solution of dihydrochloride of bis(4-hydrazinylphenyl)methane (**2e**) (1.37 g, 0.00455 mol). Additional portion of aq. conc. HCl (20 ml) was added, and the mixture was heated under reflux for 2 h. The mixture was concentrated under reduced pressure, the residue was treated with aq. 40% KOH (50 ml) and extracted with toluene (3×25 ml). The combined organic extract was dried over anhydrous Na_2SO_4 and concentrated in vacuum to leave the crude product which was then purified by column chromatography (SiO_2, ethyl acetate–light petroleum 1:1 v/v) to afford the title compound.

Spectral characteristics of 1-aryl-1H-pyrazol-5-amines 3a-e

 **3a**	**3-methyl-1-phenyl-1*H*-pyrazol-5-amine** Yield 86% (lit.[††] 70%). NMR spectra of the product fit the published data.[††]
 **3b**	**1-(2,6-dimethylphenyl)-3-methyl-1*H*-pyrazol-5-amine** Yield 61%. Light yellow crystals with m.p. 100-101 °C (light petroleum). HRMS (EI): calcd for $C_{12}H_{15}N_3$: ($M^{+\cdot}$) 201.1261; found: 201.1260. IR (KBr): 3405 and 3284 (ν_{N-H}). UV (*c* 9.95×10^{-5} M in EtOH): λ_{max} (lg ε) = 263 (2.94), 249 (3.95), 229 (4.29). NMR ^{1}H (400.13 MHz, $CDCl_3$–CCl_4 1:1 v/v): 2.02 *s* 6H (H-9), 2.16 *s* 3H (H-4), 3.36 *br.s* 2H (–NH_2) $^1J_{15N-H}$ = 78.7, 5.28 *s* 1H (H-2), 7.06 *m* 2H (H-7), 7.15 *m* H (H-8). NMR ^{13}C (75.47 MHz, $CDCl_3$–CCl_4 1:1 v/v): 14.12 $^1J_{C-H}$ = 126.6 (C-4), 17.47 $^1J_{C-H}$ = 127.5 (C-9), 88.21 $^1J_{C-H}$ = 172.9 (C-2), 128.15 (C-7), 129.07 (C-8), 135.64 C(5), 137.70 (C-6), 145.34 (C-3), 148.63 (C-1).
 **3c**	**3-methyl-1-(naphthalen-1-yl)-1*H*-pyrazol-5-amine 3c** Yield 93%. Viscous yellow oil. HRMS (EI): calcd for $C_{14}H_{13}N_3$: ($M^{+\cdot}$) 223.1104; found: 223.1098. IR (KBr): 3430 and 3300 (ν_{N-H}). UV (*c* 1.00×10^{-4} M in EtOH): λ_{max} (lg ε) = 282 (3.84), 222 (4.67). NMR ^{1}H (400.13 MHz, $CDCl_3$–CCl_4 1:1 v/v): 2.25 *s* 3H (H-4), 3.5 *br.* 2H (–NH_2), 5.42 *s* 1H (H-2), 7.44-7.58 *m* 5H (H-6, H-7, H-9, H-10, H-11), 7.84-7.92 *m* 2H (H-8 and H12). NMR ^{13}C (125.75 MHz, $CDCl_3$–CCl_4 1:1 v/v): 14.07 $^1J_{C-H}$ = 126.9 (C-4), 89.19 $^1J_{C-H}$ = 173.6 (C-2), 123.73, 125.18, 125.40, 126.54, 127.12, 127.98 and 129.14 (C-6, C-7, C-7, C-9, C-10, C-11 and C-12), 130.47 (C-13), 134.41 (C-14), 134.56 (C-5), 146.56 (C-3), 149.12 (C-1).
 **3d**	**3-methyl-1-(pyridin-2-yl)-1*H*-pyrazol-5-amine 3d** Yield 44%. NMR ^{1}H spectrum of the product fit the published data.[‡‡] NMR ^{13}C (75.47 MHz, $CDCl_3$–CCl_4 1:1 v/v): 14.07 $^1J_{C-H}$ = 127.0 (C-4), 89.72 $^1J_{C-H}$ = 173.6 (C-2), 113.38 (C-6), 118.85 (C-8), 138.23 (C-7), 146.18 (C-9), 149.07 (C-3), 150.53 (C-1), 154.74 (C-5).
 **3e**	**1,1'-[methylenebis(4,1-phenylene)]bis(3-methyl-1*H*-pyrazol-5-amine) 3e** Yield 30%. Light yellow crystals with m.p. 194-196 °C (light petroleum–ethyl acetate 1:1 v/v). HRMS (EI): calcd for $C_{21}H_{22}N_6$: ($M^{+\cdot}$) 358.1901; found: 358.1900. IR (KBr): 3446, 3396, 3346, 3299 (ν_{N-H}). UV (*c* 1.10×10^{-4} M in EtOH): λ_{max} (lg ε) = 251 (4.43). NMR ^{1}H (400.13 MHz, $CDCl_3$–CCl_4 1:1 v/v): 2.20 *s* 6H (H-4), 3.72 *br.s* 4H (–NH_2), 4.01 *s* 2H (H-9), 5.41 *s* 2H (H-2), 7.23 *m* 4H (H-7), 7.43 *m* 4H (H-6). NMR ^{1}H (500.13 MHz, CD_3CN): 2.10 *s* 6H (H-4), 4.05 *s* 2H (H-9), 4.2 *br.* 4H (–NH_2), 5.39 *s* 2H (H-2), 7.33 *m* 4H (H-7), 7.44 *m* 4H (H-6). NMR ^{13}C (125.75 MHz, CD_3CN): 14.08 $^1J_{C-H}$ = 127.2 (C-4), 41.36 $^1J_{C-H}$ = 128.4 (C-9), 91.24 $^1J_{C-H}$ = 173.5 (C-2), 124.42 (C-6), 130.67 (C-7), 138.69 (C-5), 140.70 (C-8), 147.66 (C-3), 149.74 (C-1).

[††] A. Ganesan and C. H. Heathcock, *J. Org. Chem.*, 1993, **58**, 6155.

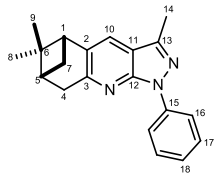
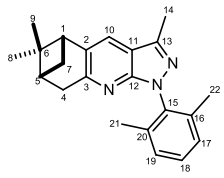
[‡‡] D. M. Volochnyuk, S. V. Ryabukhin, A. S. Plaskon, Y. V. Dmytriv, O. O. Grygorenko, P. K. Mykhailiuk, D. G. Krotko, A. Pushechnikov and A. A. Tolmachev, *J. Comb. Chem.*, 2010, **12**, 510.

Syntheses of fused 3-methyl-1-aryl-1H-pyrazolo[3,4-b]pyridines 5a-e

Method 1. A mixture of $FeCl_3 \times 6H_2O$ (0.108 g, 0.0004 mol), pinocarvone oxime (**4**) (0.330 g, 0.002 mol), 1-aryl-5-aminopyrazol **3a-e** (0.002 mol), and acetonitrile (10 ml) was stirred at room temperature for 30 min. The solvent was distilled off and the residue was kept at 120 °C for 1 h. The mixture was cooled down to room temperature and treated with 1 *M* aq. HCl (10 ml) and ethyl acetate (10 ml) upon complete dissolution. The aqueous phase was separated, and the organic solution was extracted with 1 *M* aq. HCl (2×10 ml). The combined aqueous extract was treated with conc. aq. NH_3 to pH 9 (3-5 ml) and sodium tartrate (0.5 g). The mixture was extracted with ethyl acetate (2×20 ml), the combined extract was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to leave the crude product which was purified by column chromatography on a silca gel column (10→40% of ethyl acetate in light petroleum).

Method 2. A mixture of pinocarvone oxime (**4**) and 1-aryl-5-aminopyrazol **3a-e** (2:1 mol/mol) was heated at stirring in the microwave reactor (1 h at 180 °C). The crude product was dissolved in benzene and the resulting solution was injected into a chromatographic column (SiO_2) followed by gradient elution with 15→40% of ethyl acetate in light petroleum to afford the desired compound.

Spectral characteristics of 3-methyl-1-aryl-1H-pyrazolo[3,4-b]pyridines 5a-e

 **5a**	**(5*R*,7*R*)-3,6,6-trimethyl-1-phenyl-5,6,7,8-tetrahydro-1*H*-5,7-methanopyrazolo[3,4-*b*]quinolone 5a** Yield 35% (Method 1), 20% (Method 2). Yellowish crystals with 130-131 °C (from acetonitrile). $[\alpha]_{589}^{25}$ –30, $[\alpha]_{546}^{25}$ –34 (c 0.29, $CHCl_3$). HRMS (EI): calcd for $C_{20}H_{21}N_3$: ($M^{+\cdot}$) 303.17300; found: 303.1728. IR (KBr): 3030 (C_{Ar}-H); UV (*c* 1.10×10^{-4} M in EtOH): λ_{max} (lg ε) = 323 (3.74), 262 (4.40), 205 (4.41). NMR ^{1}H (400.13 MHz, $CDCl_3$–CCl_4 1:1 v/v): 0.64 *s* 3H (H-8), 1.29 *d* (*J* = 9.7) 1H (*pro*-*R*-H-7), 1.41 *s* 3H (H-9), 2.38 *ddt* (*J* = 6.0, 6.0, and 3.0) 1H (H-5), 2.57 *s* 3H (H-14), 2.72 *ddd* (*J* = 9.7, 5.8, and 5.8) 1H (*pro*-*S*-H-7), 2.87 *dd* (*J* = 5.8 and 5.8) 1H (H-1), 3.24 *d* (*J* = 3.0) 2H (H-4), 7.22 *m* 1H (H-18), 7.47 *s* 1H (H-10), 7.48 *m* 2H (H-17), 8.29 *m* 2H (H-16). NMR ^{13}C data are given in Table S-1 below.
 **5b**	**(5*R*,7*R*)-1-(2,6-dimethylphenyl)-3,6,6-trimethyl-5,6,7,8-tetrahydro-1*H*-5,7-methanopyrazolo[3,4-*b*]quinoline 5b** Yield 13% (Method 1), 35% (Method 2). Pale yellow oil. $[\alpha]_{589}^{29}$ –31; $[\alpha]_{546}^{29}$ –33, $[\alpha]_{436}^{29}$ –22, $[\alpha]_{405}^{29}$ –1 (c 0.546 g/ml, $CHCl_3$) . HRMS (EI): calcd for $C_{22}H_{25}N_3$: ($M^{+\cdot}$) 331.2043; found: 331.2038. IR (KBr): 3030 (C_{Ar}-H). UV (*c* 8.42×10^{-5} M in EtOH): λ_{max} (lg ε) = 316 (3.74), 273 (3.72), 216 (4.33). NMR ^{1}H (400.13 MHz, $CDCl_3$–CCl_4 1:1 v/v): 0.63 *s* 3H (H-8), 1.32 *d* (*J* = 9.7) 1H (*pro*-*R*-H-7), 1.42 *s* 3H (H-9), 1.958 *s* 3H (H-21), 1.965 *s* 3H (H-22), 2.35 *ddt* (*J* = 6.0, 6.0, and 3.0) 1H (H-5), 2.57 *s* 3H (H-14), 2.71 *ddd* (*J* = 9.7, 5.8, and 5.8) 1H (*pro*-*S*-H-7), 2.86 *dd* (*J* = 5.8 and 5.8) 1H (H-1), 3.10 *d* (*J* = 3.0) 2H (H-4), 7.13 *m* 2H (H-17 and H-19), 7.22 *m* 1H (H-18), 7.44 *s* 1H (H-10). NMR ^{13}C data are given in Table S-1 below.

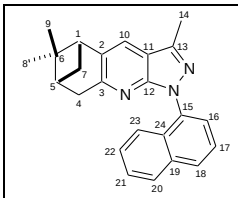
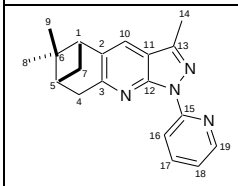
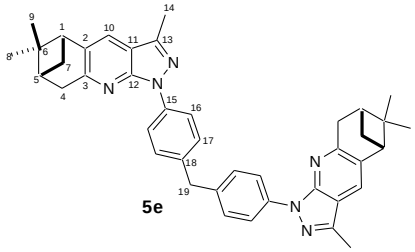
 **5c**	**(5*R*,7*R*)-3,6,6-trimethyl-1-(naphthalen-1-yl)-5,6,7,8-tetrahydro-1*H*-5,7-methanopyrazolo[3,4-*b*]quinolone 5c** Yield 30% (Method 2). Yellowish oil. $[\alpha]_{589}^{29}$ –34, $[\alpha]_{546}^{29}$ –39, $[\alpha]_{436}^{29}$ –61 (*c* 0.89, $CHCl_3$). HRMS (EI): calcd for $C_{24}H_{23}N_3$: ($M^{+\cdot}$) 353.1887; found: 353.1884. IR (KBr): 3050 (C_{Ar}-H). UV (*c* 1.00×10^{-4} M in EtOH): λ_{max} (lg ε) = 313 (3.83), 284 (3.99), 222 (4.65). NMR ^{1}H (500 MHz, $CDCl_3$): 0.65 *s* 3H (H-8), 1.30 *d* (*J* = 9.7) 1H (*pro*-*R*-H-7), 1.42 *s* 3H (H-9), 2.33 *dddd* (*J* = 6.0, 6.0, 2.9 and 2.9) 1H (H-5), 2.63 *s* 3H (H-14), 2.73 *dddd* (*J* = 9.7, 6.1, 5.3 and 0.6) 1H (*pro*-*S*-H-7), 2.91 *dd* (*J* = 6.1 and 5.4) 1H (H-1), 3.11 *m* 2H (H-4), 7.41 *ddd* (*J* = 8.7, 6.8, and 1.3) 1H (H-22), 7.48 *ddd* (*J* = 8.4, 6.8, and 1.3) 1H (H-21), 7.55 *s* 1H (H-10), 7.57 *dd* (*J* = 8.3 and 7.3) 1H (H-17), 7.69 *dd* (*J* = 7.3 and 1.2) 1H (H-16), 7.70 *dddd* (*J* = 8.3, 1.2, 0.8, and 0.8) 1H (H-18), 7.90 *dm* (*J* = 8.7, $W_{1/2}$ = 2.8 Hz) 1H (H-23). 7.91 *dm* (*J* = 8.4, $W_{1/2}$=2.6 Hz) 1H (H-20). NMR ^{13}C data are given in Table S-1 below.
 **5d**	**(5*R*,7*R*)-3,6,6-trimethyl-1-(pyridin-2-yl)-5,6,7,8-tetrahydro-1*H*-5,7-methanopyrazolo[3,4-*b*]quinoline 5d** Yield 11% (Method 1), 20% (Method 2). Light yellow crystals with M.p. 134-140 °C (from light petroleum). $[\alpha]_{589}^{29}$ –82, $[\alpha]_{546}^{29}$ –71 (*c* 0.57, $CHCl_3$). HRMS (EI): calcd for $C_{19}H_{20}N_4$: ($M^{+\cdot}$) 304.1683; found: 304.1682. IR (KBr): 3060 (C_{Ar}-H). UV (*c* 9.94×10^{-5} M in EtOH): λ_{max} (lg ε) = 315 (3.81), 284 (4.11), 257 (4.22). NMR ^{1}H (500 MHz, $CDCl_3$–CCl_4 1:1 v/v): 0.61 *s* 3H (H-8), 1.26 *d* (*J* = 9.8) 1H (*pro*-*R*-H-7), 1.39 *s* 3H (H-9), 2.36 *ddt* (*J* = 6.0, 6.0, and 2.9) 1H (H-5), 2.57 *s* 3H (H-14), 2.70 *ddd* (*J* = 9.8, 5.8, and 5.8) 1H (*pro*-*S*-H-7), 2.83 *dd* (*J* = 5.8 and 5.7) 1H (H-1), 3.23 *d* (*J* = 2.9) 2H (H-4), 7.09 *m* 1H (H-18), 7.43 *s* 1H (H-10), 7.78 *m* 1H (H-17), 8.56 *m* 2H (H-16 and H-19). NMR ^{13}C chemical shifts are given in Table S-1 below, whereas characteristic spin-spin couplings $^nJ_{C\text{-}H}$ are shown in Table S-4.
 **5e**	**bis{4-[(5*R*,7*R*)-3,6,6-trimethyl-5,6,7,8-tetrahydro-1*H*-5,7-methanopyrazolo[3,4-*b*]quinolin-1-yl]phenyl}methane 5e** Yield 15% (Method 1), 20% (Method 2). Light yellow oil. $[\alpha]_{589}^{28}$ –63, $[\alpha]_{546}^{28}$ –74, $[\alpha]_{436}^{28}$ –90, $[\alpha]_{405}^{28}$ –94 (*c* 0.29, $CHCl_3$) . HRMS (EI): calcd for $C_{41}H_{42}N_6$: (M^+) 618.3466; found: 618.3463. IR (KBr): 3037 (C_{Ar}-H); UV (*c* 1.00×10^{-4} M in EtOH): λ_{max} (lg ε) = 326 (2.96), 269 (3.61). NMR ^{1}H (400.13 MHz, $CDCl_3$–CCl_4 1:1 v/v): 0.65 *s* 3H (H-8), 1.30 *d* (*J* = 9.6) 1H (*pro*-*R*-H-7), 1.42 *s* 3H (H-9), 2.39 *ddd* (*J* = 5.8, 5.8, and 2.8) 1H (H-5), 2.56 *s* 3H (H-14), 2.72 *ddd* (*J* = 9.7, 5.8, and 5.8) 1H (*pro*-*S*-H-7), 2.85 *dd* (*J* = 5.6 and 5.6) 1H (H-1), 3.22 *m* 2H (H-4), 4.06 *s* 1H (H-19), 7.30 *m* 2H (H-17), 7.43 *s* 1H (H-10), 8.17 *d* (*J* = 8.5) 2H (H-16). NMR ^{13}C data are given in Table S-1 below.

Table S1. NMR ^{13}C spectral data for compounds 1-aryl substituted (5*R*,7*R*)-3,6,6-trimethyl-5,6,7,8-tetrahydro-1*H*-5,7-methanopyrazolo[3,4-*b*]quinolines **5a-e**

i[a]	δC*i*, ppm				
	5a[b]	**5b**[b]	**5c**[c]	**5d**[b]	**5e**[b]
1	47.19	47.12	47.05	46.98	47.12
2	135.04	136.79	135.30	135.80	134.96
3	157.47	157.89	158.34	157.88	157.50
4	37.29	37.07	37.10	37.18	37.23
5	40.18	40.02	39.91	39.98	40.10
6	39.94	39.93	39.71	39.74	41.10
7	32.70	32.53	32.39	32.42	32.66
8	21.57	21.90	21.35	21.42	21.57
9	26.24	26.17	25.94	26.04	26.22
10	124.75	124.62	124.84	124.96	124.70
11	114.56	112.15	113.01	115.12	114.37
12	150.30	150.86	151.74	150.41	150.12
13	141.37	140.87	141.80	143.35	141.23
14	12.46	12.57	12.43	12.47	12.48
15	140.14	137.14	134.91	151.45	137.64
16	120.39	134.32	125.00	114.98	120.68
17	128.71	128.26	125.19	137.65	129.37
18	124.70	128.79	123.90	120.09	138.19
19		128.26	134.65	148.71	39.91
20		134.32	128.60		
21		18.12	126.11		
22		18.16	126.47		
23			127.94		
24			130.28		

[a] the numbering schemes are given in the structures above; [b] in $CDCl_3$–CCl_4 1:1 v/v; [c] in $CDCl_3$

Quantum chemical calculations

Geometry optimization and NMR chemical shifts at the DFT level were obtained using ORCA program system[§§] by utilizing Gauge Including Atomic Orbitals (GIAOs, London orbitals) with the hybrid exchange-correlation functional PBE0 and basis set aug-cc-pVDZ. Solvent influence was taken into consideration using the Polarizable Continuum Model (PCM).[***] Chemical shifts were recomputed relative to $Si(CH_3)_4$, whose chemical shifts were calculated by the same method. Spin-spin couplings were calculated by Dalton[†††] (http://daltonprogram.org) using DFT (PBE0/aug-cc-pVDZ).

Table S2. Experimental and calculated carbon-13 chemical shifts in 3-methyl-1-(pyridin-2-yl)-1*H*-pyrazol-5-amine (**3d**)

	experimental	calculated by additive scheme		calculated by DFT[a]	
i	δ_{Ci}, ppm	δ_{Ci}, ppm	δ_{Ci}(calc.)–δ_{Ci}(exp.)	δ_{Ci}, ppm	δ_{Ci}(calc.)–δ_{Ci}(exp.)
1	150.53	140.6	–9.93	151.77	1.24
2	89.72	88.5	–1.22	87.72	–2.00
3	149.07	156.7	7.63	150.05	0.98
4	14.07	13.2	–0.87	16.00	1.93
5	154.74	154.1	–0.64	156.31	1.57
6	113.38	112.4	–0.98	112.34	–1.04
7	138.23	139.3	1.07	138.36	0.13
8	118.85	121.4	2.55	117.92	–0.93
9	146.18	148.0	1.82	147.42	1.24
mae			2.97		1.23

[a] PBE0/aug-cc-pVDZ–PCM ($CHCl_3$)

[§§] F. Neese, *WIREs Comput. Mol. Sci.*, 2012, **2**, 73.

[***] J. B. Foresman, T. A. Keith, K. B. Wiberg, J. Snoonian and M. J. Frisch, *J. Phys. Chem.*, 1996, **100**, 16098.

[†††] K. Aidas, C. Angeli, K. L. Bak, V. Bakken, R. Bast, L. Boman, O. Christiansen, R. Cimiraglia, S. Coriani, P. Dahle, E. K. Dalskov, U. Ekström, T. Enevoldsen, J. J. Eriksen, P. Ettenhuber, B. Fernández, L. Ferrighi, H. Fliegl, L. Frediani, K. Hald, A. Halkier, C. Hättig, H. Heiberg, T. Helgaker, A. C. Hennum, H. Hettema, E. Hjertenæs, S. Høst, I.-M. Høyvik, M. F. Iozzi, B. Jansík, H. J. A. Jensen, D. Jonsson, P. Jørgensen, J. Kauczor, S. Kirpekar, T. Kjærgaard, W. Klopper, S. Knecht, R. Kobayashi, H. Koch, J. Kongsted, A. Krapp, K. Kristensen, A. Ligabue, O. B. Lutnæs, J. I. Melo, K. V. Mikkelsen, R. H. Myhre, C. Neiss, C. B. Nielsen, P. Norman, J. Olsen, J. M. H. Olsen, A. Osted, M. J. Packer, F. Pawlowski, T. B. Pedersen, P. F. Provasi, S. Reine, Z. Rinkevicius, T. A. Ruden, K. Ruud, V. V. Rybkin, P. Sałek, C. C. M. Samson, A. S. de Merás, T. Saue, S. P. A. Sauer, B. Schimmelpfennig, K. Sneskov, A. H. Steindal, K. O. Sylvester-Hvid, P. R. Taylor, A. M. Teale, E. I. Tellgren, D. P. Tew, A. J. Thorvaldsen, L. Thøgersen, O. Vahtras, M. A. Watson, D. J. D. Wilson, M. Ziolkowski and H. Ågren, *WIREs Comput. Mol. Sci.*, 2014, **4**, 269.

Table S3. Experimental and calculated carbon-13 chemical shifts in (5*R*,7*R*)-3,6,6-trimethyl-1-(pyridin-2-yl)-5,6,7,8-tetrahydro-1*H*-5,7-methanopyrazolo[3,4-*b*]quinoline (**5d**).

	experimental	calculated by additive scheme		calculated by DFT[a]	
i	δ_{Ci}, ppm	δ_{Ci}, ppm	δ_{Ci}(calc.)–δ_{Ci}(exp.)	δ_{Ci}, ppm	δ_{Ci}, ppm
1	46.98	50.5	3.52	47.76	0.78
2	135.80	140.7	4.90	134.88	–0.92
3	157.88	156.5	–1.38	157.31	–0.57
4	37.18	37.1	–0.08	40.77	3.59
5	39.98	50.1	10.12	41.14	1.16
6	39.74	43.1	3.36	41.97	2.23
7	32.42	27.1	–5.32	34.37	1.95
8	21.42	22.2	0.78	21.04	–0.38
9	26.04	22.2	–3.84	26.16	0.12
10	124.96	133.9	8.94	125.02	0.06
11	115.12	123.9	8.78	116.80	1.68
12	150.41	157.6	7.19	148.16	–2.25
13	143.35	132.6	–10.75	145.91	2.56
14	12.47	14.0	1.53	15.35	2.88
15	151.45	151.5	0.05	155.23	3.78
16	114.98	112.4	–2.58	115.48	0.50
17	137.65	139.3	1.65	137.99	0.34
18	120.09	121.4	1.31	119.96	–0.13
19	148.71	148.0	–0.71	149.76	1.05
mae			4.04		1.42

[a] PBE0/aug-cc-pVDZ–PCM ($CHCl_3$)

Table S4. Selected characteristic experimental and calculated spin-spin couplings of the carbon atoms of the 1*H*-pyrazolo[3,4-*b*]pyridine moiety in (5*R*,7*R*)-3,6,6-trimethyl-1-(pyridin-2-yl)-5,6,7,8-tetrahydro-1*H*-5,7-methanopyrazolo[3,4-*b*]quinoline (**5d**).

	experimental[a] $J_{Ci\text{-}Hj}$ (calculated[b] $J_{Ci\text{-}Hj}$), Hz							
H*j* C*i*	H-1	H-4a	H-4b	H-5	H-7-*pro-R*	H-7-*pro-S*	H-10	3H-14
C-2	2.3 (–2.2)	3.2 (2.6)	3.2 (2.8)		4.7 (4.3)	6.2 (6.4)	<0.5 (–0.05)	
C-3	2.6 (5.0)	7.5 (–7.1)	7.5 (–7.6)	7.5 (8.2)			7.1 (6.6)	
C-10	4.8 (5.4)						160.9 (159.8)	
C-11							2.6 (2.1)	2.6 (3.3)
C-12							7.2 (6.9)	
C-13							2.2 (2.3)	6.9 (–7.1)

[a] sign of spin-spin couplings was not determined; [b] DFT PBE0/aug-cc-pVDZ

X-ray crystallography

Single-crystal XRD data for **5d** were collected by a Bruker Apex DUO diffractometer equipped with a 4K CCD area detector at 200(2) K using radiation of microfocus CuKα X-ray tube (λ = 1.54178 Å). The φ- and ω-scan techniques were employed to measure intensities. Absorption corrections were applied with the use of the SADABS program in non-centrosimmetric diffraction class 2.[‡‡‡] The crystal structures were solved by direct methods and refined by full-matrix least squares techniques with the use of the SHELXTL package[§§§] and OLEX2 GUI.[****] Atomic thermal displacement parameters for non-hydrogen atoms were refined anisotropically. The positions of hydrogen atoms were calculated corresponding to their geometrical conditions and refined using the riding model. Investigation and visualization of intermolecular interactions were performed by CrystalExplorer v.17.5[††††] supported by Tonto v.17.04[‡‡‡‡] using promolecular Hirshfeld analysis and CE-HF/3-21G interaction energy models.[§§§§]

X-ray crystallographic data for (5*R*,7*R*)-3,6,6-trimethyl-1-(pyridin-2-yl)-5,6,7,8-tetrahydro-1*H*-5,7-methanopyrazolo[3,4-*b*]quinoline (5d)

Almost colorless plank crystal, size 0.31×0.28×0.09 mm. Monoclinic, $P12_11$, a = 6.4706(6) Å, b = 11.7781(11) Å, c = 10.4010(9) Å, β = 98.524(3)°, volume 783.92(12) Å^3 at T = 200 K. Empirical formula of moiety $C_{19}H_{20}N_4$; M_r = 304.39; Z = 2; Z′ = 1; F(000) = 324; ρ_{calc} = 1.290 g/cm^3; $\mu(CuK\alpha)_{calc}$ = 0.616 mm^{-1}. 2Θ range for data collection 8.596° to 135.968°; index ranges $-7 \le h \le 7$, $-14 \le k \le 13$, $-12 \le l \le 12$; reflections collected / independent 10835 / 2795, R_{int} = 0.0230, R_σ = 0.0232. Data / restraints / parameters 2795 / 1 / 212. Goodness-of-fit on F^2 1.032; final R indexes for I≥2σ(I): R_1 = 0.0256, wR_2 = 0.0645, for all data R_1 = 0.0257, wR_2 = 0.0646. Largest difference peak 0.14 e/Å^3, hole –0.13 e/Å^3. Flack parameter -0.06 (9).

Description of intermolecular interaction in the crystal structure of (5*R*,7*R*)-3,6,6-trimethyl-1-(pyridin-2-yl)-5,6,7,8-tetrahydro-1H-5,7-methanopyrazolo[3,4-b]quinoline (5d)

Flat pyrazolo[3,4-*b*]pyridine ring system and monosubstituted pyridine moiety are almost in the same plane (dihedral angle N3–N2–C15–C18 is 3.5(2)°), the planar conformation is being stabilized by the aromatic systems conjugation (N2–C15 distance is 1.42 Å). Anomalous dispersion effects confirm absolute configuration of the molecule and presence of two asymmetric carbons of *R* configuration (C-1, C-5).

According to promolecular Hirshfeld surface analysis, molecules of the title compound in the crystal structure have 16 neighbors (Table S5, Figure S1). The most strongly interacting six neighbors *n1*–*n6* with considerable contribution of dispersion component have shorter-than van der Waals intermolecular contacts (Figure S2). They may be associated with "parallel" π–π stacking (*n1*, *n2*, Figure S2a), ^{Ar}H–π interaction (*n3*, *n4*, Figure S2b), and "perpendicular" π–π stacking (*n5*, *n6*, Figure S2c). The fourth pair of strong interacting neighbors (*n7*, *n8*) has no shorter-than van der Waals contacts, however it has the greatest polarization component of pairwise interaction energy, which is apparently connected with extended ^{Ar}N–^{Aliph}H contacts (Figure S2d).

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‡‡‡ *APEX2 (Version 2.0), SAINT (Version 8.18c), and SADABS (Version 2.11)*, Bruker AXS Inc, Madison, Wisconsin, USA, 2000-2012.

§§§ G. M. Sheldrick, *Acta Crystallogr*., 2008, **A64**, 112.

**** O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann, *J. Appl. Crystallogr.*, 2009, **42**, 339.

†††† M. J. Turner, J. J. McKinnon, S. K. Wolff, D. J. Grimwood, P. R. Spackman, D. Jayatilaka and M. A. Spackman, *CrystalExplorer17*, University of Western Australia, 2017 (http://hirshfeldsurface.net).

‡‡‡‡ D. Jayatilaka and D. J. Grimwood, in *Computational Science - ICCS 2003: International Conference*, *Melbourne*, *Australia and St. Petersburg*, *Russia*, *June 2-4, 2003 Proceedings*, *Part IV*, eds. P. M. A. Sloot, D. Abramson, A. V. Bogdanov, Y. E. Gorbachev, J. J. Dongarra and A. Y. Zomaya, Springer, Berlin, 2003, pp. 142-151 (DOI: 10.1007/3-540-44864-0_15).

§§§§ M. J. Turner, S. Grabowsky, D. Jayatilaka and M. A. Spackman, *J. Phys. Chem. Lett.*, 2014, **5**, 4249.

There are layers of "strong-interacting" molecules, perpendicular to [001] direction, formed due to specific interactions (*n1–n6* contacts, Figure S3). Weaker intermolecular interaction in [001] direction is correlated with the experimentally determined crystal shape with stable facets of (001) Miller indices (Figure S4).

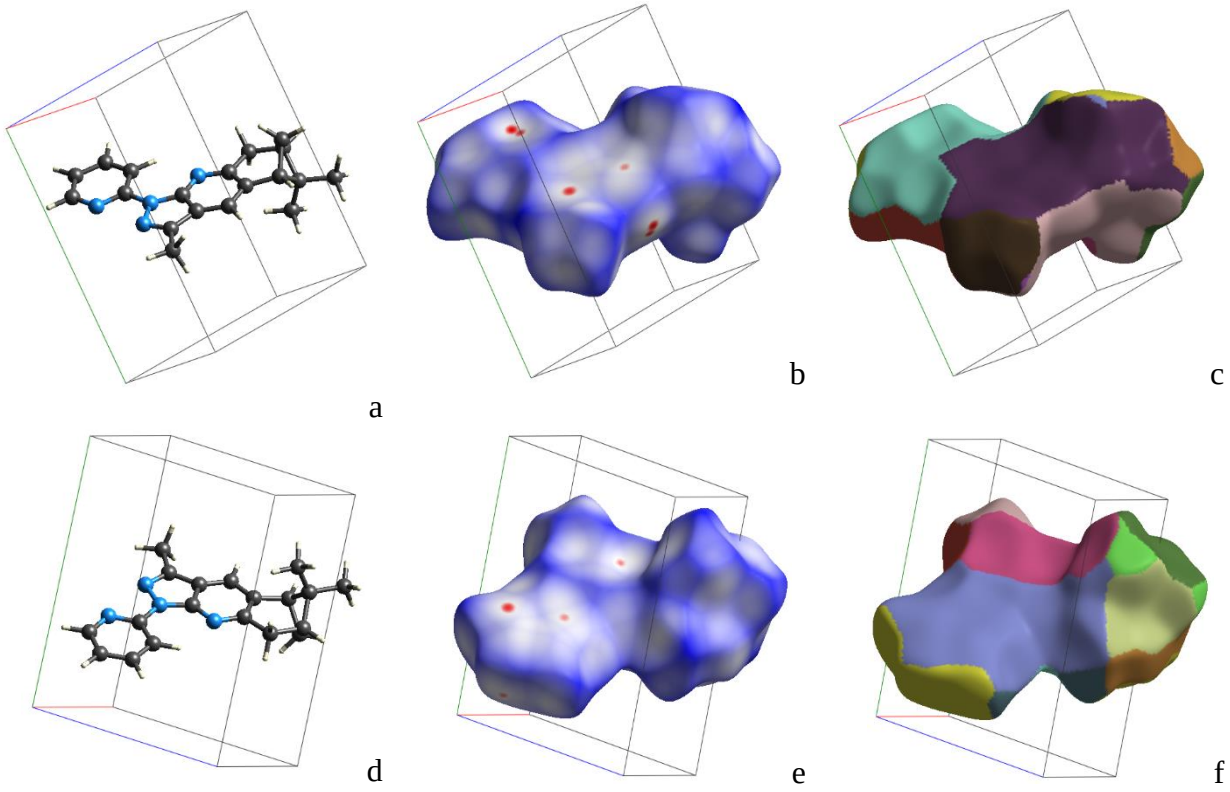


Figure S1. Ball-and-stick representation of a molecule (a, d), normalized contact distance (d_{norm}) (b, e) and fragment patch (c, f) mapping on promolecular Hirshfeld surface. Two orientations (a–c and d–f) of the same molecule are shown. Red areas of d_{norm} mapping correspond to shorter-than van der Waals contacts, blue ones – to longer-than van der Waals contacts. Hereinafter red, green and blue edges of unit cell correspond to ***a***, ***b*** and ***c*** translations.

Table S5. Nearest neighbors of the molecule in independent part of the crystal structure and CE-HF/3-21G estimation of pairwise intermolecular interaction energies. Both total interaction energy and its four key components (electrostatic, polarization, dispersion, and exchange-repulsion) are tabulated. Neighbor colors corresponds to fragment patch coloring in Figure S1.

neigh. color	neigh. ID	symmetry operation	contact area, Å²	E_{ele}, kJ/mol	E_{pol}, kJ/mol	E_{disp}, kJ/mol	E_{rep}, kJ/mol	E_{tot}, kJ/mol
	n1	–1+x, y, z	51.7	-9.0	-4.6	-64.4	31.7	-44.4
	n2	1+x, y, z	51.5	-9.0	-4.6	-64.4	31.7	-44.4
	n3	–x, ½+y, –z	41.2	-10.7	-4.3	-38.8	18.0	-34.0
	n4	–x, –½+y, –z	36.1	-10.7	-4.3	-38.8	18.0	-34.0
	n5	–1–x, ½+y, –z	28.0	-6.5	-1.7	-29.8	15.1	-22.4
	n6	–1–x, –½+y, –z	25.5	-6.5	-1.7	-29.8	15.1	-22.4
	n7	–1+x, y, –1+z	17.4	-5.4	-5.3	-16.5	7.0	-18.2
	n8	1+x, y, 1+z	17.0	-5.4	-5.3	-16.5	7.0	-18.2
	n9	1–x, ½+y, 1–z	18.4	-0.5	-0.2	-14.7	5.6	-9.4
	n10	1–x, –½+y, 1–z	18.1	-0.5	-0.2	-14.7	5.6	-9.4
	n11	x, y, –1+z	15.3	-0.1	-0.5	-12.8	5.0	-7.9
	n12	x, y, 1+z	15.2	-0.1	-0.5	-12.8	5.0	-7.9
	n13	–x, –½+y, 1–z	6.1	-0.2	-0.1	-6.1	0.6	-5.3
	n14	–x, ½+y, 1–z	6.0	-0.2	-0.1	-6.1	0.6	-5.3
	n15	1–x, –½+y, –z	0.3	-1.4	-0.2	-3.3	0.0	-4.6
	n16	1–x, ½+y, –z	0.2	-1.4	-0.2	-3.3	0.0	-4.6

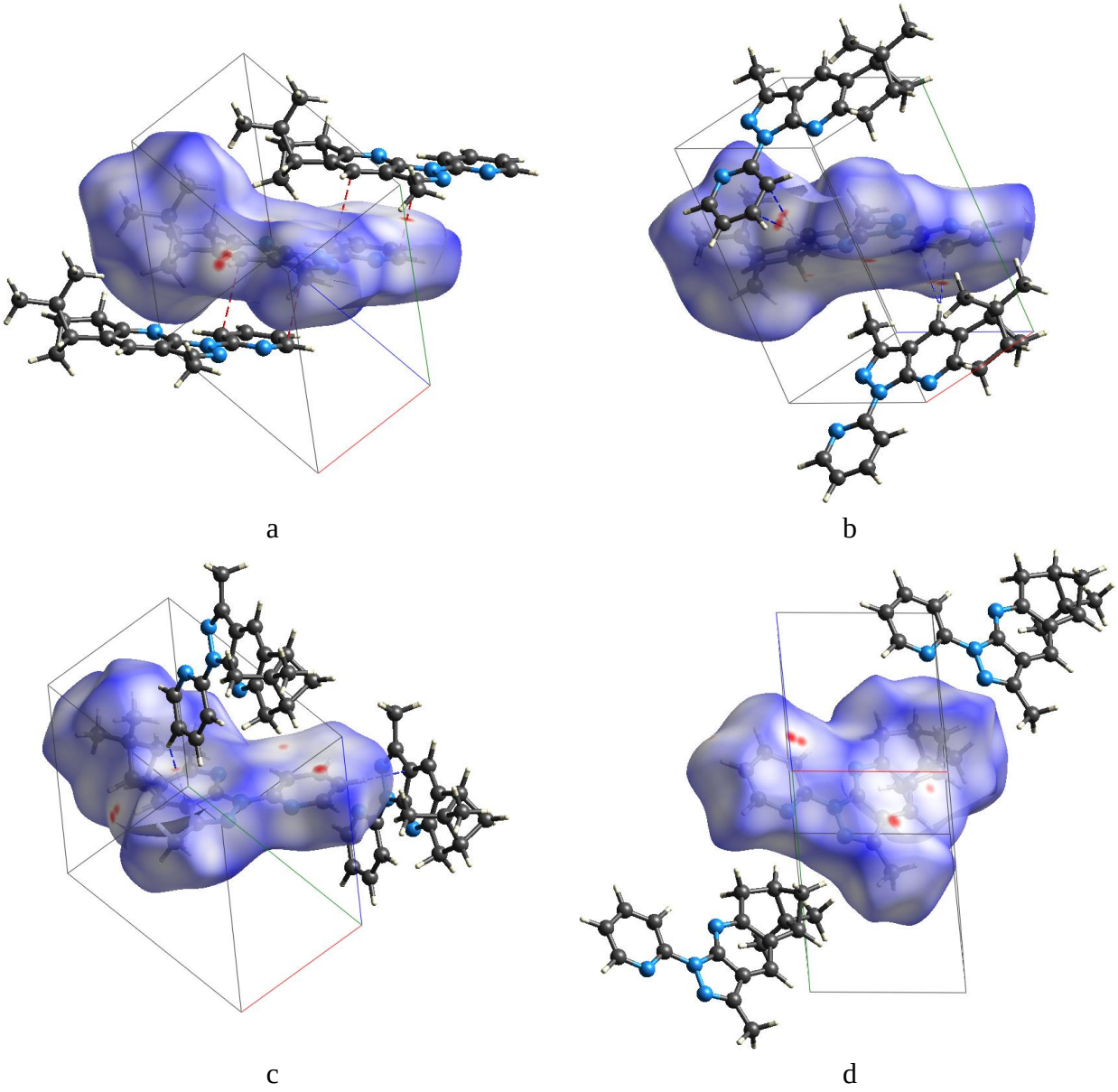
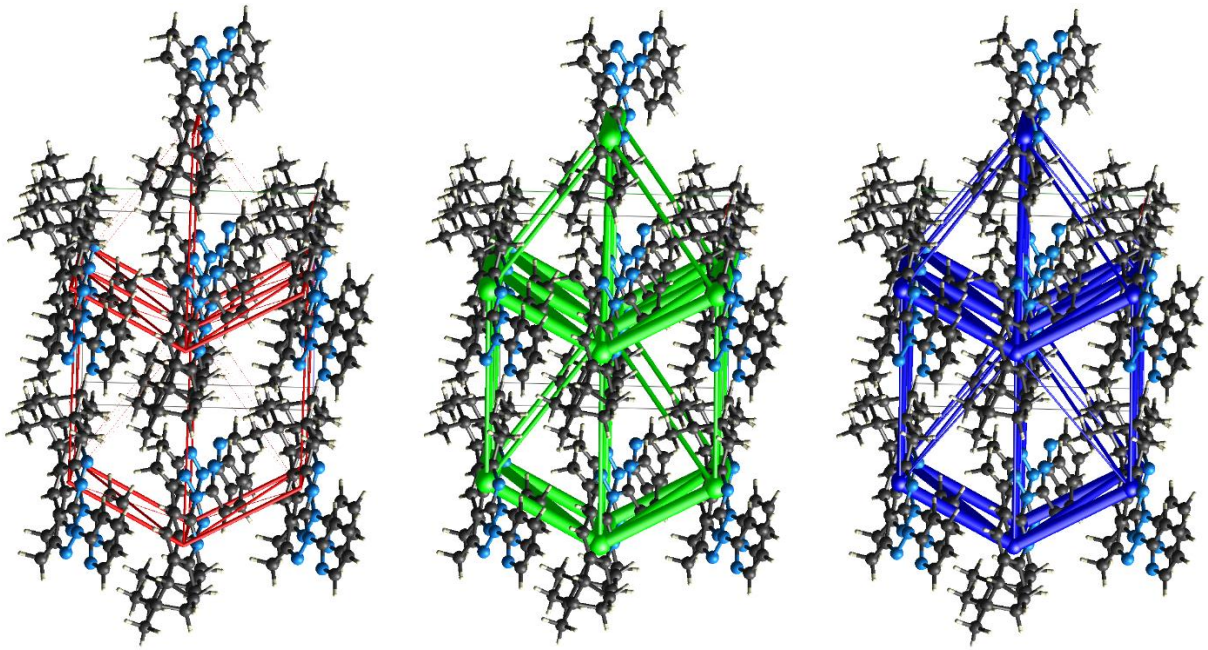


Figure S2. Short intermolecular contacts for the strongest interacting pairs: (a) *n1*, *n2*; (b) *n3*, *n4*; (c) *n5*, *n6*; (d) *n7*, *n8*. Short C–C (d_{C-C}<3.40Å) and C–H (d_{C-H}<2.79Å) are shown with red and blue dashes correspondingly.



a b c

Figure S3. "Energy framework" representation of pairwise Coulomb (a), dispersion (b) and total (c) intermolecular interactions. Diameters of sticks are proportional to energies of the interactions.

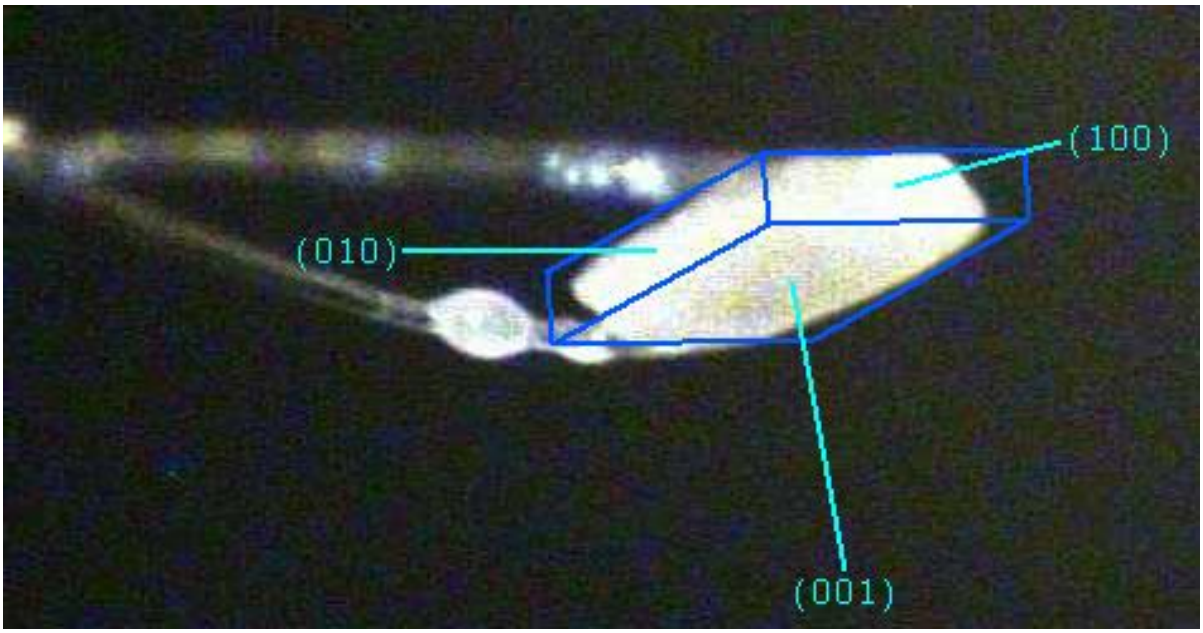


Figure S4. The **5d** crystal shape. Circumscribed cuboid with facets of the simplest Miller indices is shown in color.