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Polydentate ligands combining pirlinidole and piperazine fragments

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A series of polydentate ligands possessing pirlindole and piperazine fragments are synthesized. Their structures are assigned by 1D and 2D NMR spectra and confirmed by single crystal XRD of selected samples.

Keywords: pirlindole, piperazine, NMR, single crystal XRD.

INTRODUCTION

Heterocyclic compounds constitute the largest group of organic compounds with a wide range of applications, namely as ligands in coordination chemistry, catalysts, pharmaceuticals, agrochemicals, veterinary products, etc. [1–6]. In particular, nitrogen-containing heterocycles have shown remarkable coordination abilities and are widely found in natural products and pharmaceuticals [7–11]. Driven by the ubiquitous occurrence of *N*-heterocycles, their economic importance and academic significance, the preparation of libraries of novel molecules is still among the main goals of the synthetic organic chemistry [12, 13].

Pirlindole, known also as pyrazidole, is a tetracyclic compound with antidepressant properties [14–20], which is clinically used as a psychotropic drug nowadays [21]. From the other side, piperazine derivatives have shown remarkable variety of biological activity profiles [22–30]. In a search of novel bioactive compounds, arose the idea to combine both fascinating units in a common molecule. In the same time, the designed compounds **4**, shown on Fig. 1, possess four inequivalent nitrogens, which make them perspective candidates for coordination applications.

Herein, we report on the synthesis and solution and solid state characterization of a series of polydentate ligands, possessing bridged pirlindole and piperazine fragments.

EXPERIMENTAL

Synthesis

General: All reagents were purchased from Aldrich, Merck and Fluka and were used without any further purification. The deuterated solvents were purchased from Deutero GmbH. Fluka silica gel (TLC-cards 60778 with fluorescent indicator 254 nm) were used for TLC chromatography and R_f-values determination. Merck Silica gel 60 (0.040–0.063 mm) was used for flash chromatography purification of the products. The melting points were determined in capillary tubes on SRS MPA100 OptiMelt (Sunnyvale, CA, USA) automated melting point system. The NMR spectra were recorded on a Bruker Avance II+ 600 spectrometer (Rheinstetten, Germany) in $CDCl_3$; the chemical shifts were quoted in ppm in δ-values against tetramethylsilane (TMS) as an internal standard and the coupling constants were calculated in Hz. The spectra were processed with Topspin 3.5.5 program. The numeration schemes of the compounds are given on Fig. 1. The turbo spray mass spectra were taken on API 150EX (AB/MAS Sciex) mass-spectrometer. The yields, melting points and R_f-values are listed on Table 2.

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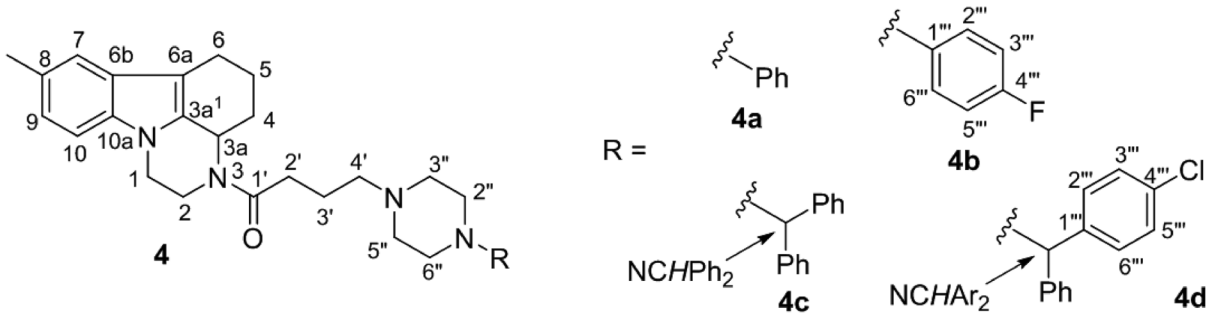


Fig. 1. Numeration schemes of compounds **4a**-**4d**. The numeration in chloride **2** follows the same scheme.

Table 1. Crystal data and the most important structure refinement indicators for compounds **4a** and **4b**

	4a	4b
Chemical formula	$C_{29}H_{36}N_4O$	$C_{29}H_{34}FN_4O$
MW	456.62	473.60
Crystal system, space group	Triclinic, *P*-1	Triclinic, *P*-1
Temperature (K)	290	290
a, *b*, *c* (Å)	9.3374 (5), 12.0577 (5), 12.2983 (6)	9.4517(12). 12.1050(11), 12.6200(14)
α, β, γ (°)	110.962 (4), 104.727 (5), 90.867 (4)	69.079(18), 69.957(14), 89.335(14)
V (Å^3)	1241.86 (11)	1256.9(3)
Z	2	2
Radiation type	Mo *K*α, λ = 0.71073	Mo *K*α, λ = 0.71073
μ (mm^{-1})	0.08	0.082
Crystal size (mm^3)	0.3 × 0.25 × 0.12	0.32 × 0.3 × 0.28
Diffractometer	SuperNova, Dual, Cu at zero, Atlas, diffractometer	Enraf Nonius CAD4
Absorption correction	Multi-scan	none
T_{min}, T_{max}	0.775, 1.000	0.910, 1.000
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	11845, 5650, 3716	7594, 7198, 3168
R_{int}	0.032	0.025
$(\sin\theta/\lambda)_{max}$ (Å^{-1}),	0.685	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, *S*	0.064, 0.179, 1.03	0.0837, 0.207, 1.09
No. of reflections	5650	7198
No. of parameters	308	317
No. of restraints	0	0
H-atom treatment	constrained	constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.20, −0.22	0.38, -0.31
CCDC number	1875825	1875826

Compound 2: To a solution of pyrazidol (free base, 10 mmol) in dry DCM (25 ml), K_2CO_3 (30 mmol) and then 4-chlorobutyryl chloride (10 mmol) were added and the suspension was stirred at room temperature for 45 min. The products were partitioned between DCM and water. The organic phase was washed with water, dried over anhydrous Na_2SO_4, and evaporated to dryness to give the crude chloride **2**, which was pure enough (NMR) and was further used without purification: 75% yield; R_f 0.67 (5% MeOH/DCM); NMR (293K) ^{1}H 1.393 (bs, 1H, ½ CH_2-4), 1.988 (m, 1H, ½ CH_2-5), 2.154 (m, 1H, ½ CH_2-5), 2.213 (m, 3H, CH_2-3' + ½ CH_2-4), 2.452 (s, 3H, CH_3), 2.645 (m, 3H, CH_2-2' + ½ CH_2-4), 2.698 (bm, 1H ½ CH_2-6), 2.798 (bm, 1H, ½ CH_2-6), 3.135 (bs, 1H, ½ CH_2-2), 3.695 (t, 2H, J 5.7, CH_2-4'), 3.998 (bs, 1H, ½ CH_2-1), 4.132 (bs, 1H, ½ CH_2-1), 4.944 (bs, 1H, ½ CH_2-2), 5.225 (bs, 1H, C*H*-3a),

7.024(dd, 1H, J 1.0, 8.2, C*H*-9), 7.145 (d, 1H, J 8.2, C*H*-10), 7.288 (bs, 1H, C*H*-7); ^{13}C 20.24 (*C*H_2-6), 21.43 (*C*H_3), 21.99 (*C*H_2-5), 27.91 (*C*H_2-3'), 32.10 (*C*H_2-2'), 44.34 (*C*H_2-1), 44.89 (*C*H_2-4'), 51.47 (*C*H-3a), 108.74 (*C*H-10), 109.65 (C_q-6a), 118.57 (*C*H-7), 122.97 (*C*H-9), 128.07 (C_q-6b), 128.96 (C_q-8), 133.34 (C_q-3a^1), 136.48 (C_q-10a), 168.37 (C_q-1').

*Compounds **4**. General procedure:* A solution of crude chloride **2** (1 mmol), piperazine **3** (1 mmol), KI (1.5 mmol) and K_2CO_3 (2 mmol) in dry DMF (4 ml) was heated at 120 °C in a closed vessel for 12 h. The crude product was purified by flash chromatography on silica gel by using EtOAc:Et_3N 100:1 as a mobile phase and was then recrystallized from DCM-hexane.

*Compound **4a**:* NMR (323K) ^{1}H 1.505 (bs, 1H, ½ CH_2-4), 1.965 (t, 2H, J 7.0, CH_2-3'), 2.005 (m, 1H, ½ CH_2-5), 2.154 (m, 1H, ½ CH_2-5), 2.440 (s, 3H, CH_3), 2.481 (t, 2H, J 6.8, CH_2-4'), 2.494 (t, 2H, J 7.2, CH_2-2'), 2.532 (m, 1H, ½ CH_2-4), 2.612 (m, 4H, CH_2-3"+ CH_2-5"), 2.683 (m, 1H ½ CH_2-6), 2.779 (ddt, 1H, J 1.4, 8.6, 16.0, ½ CH_2-6), 2.907 (bs, 1H, ½ CH_2-2), 3.180 (t, 4H, J 5.0, CH_2-2"+ CH_2-6"), 3.958 (td, 1H, J 2.4, 11.7, ½ CH_2-1), 4.088 (dt, 1H, J 2.2, 12.3, ½ CH_2-1), 4.415 (bs, 1H, ½ CH_2-2), 5.208 (d, 1H, J 9.8, C*H*-3a), 6.822 (tt, 1H, J 1.0, 7.3, p-Ph), 6.888 (dd, 2H, J 1.0, 8.8, o-Ph), 6.999 (dd, 1H, J 1.5, 8.3, C*H*-9), 7.109 (d, 1H, J 8.3, C*H*-10), 7.228 (dd, 2H, J 7.3, 8.8, m-Ph), 7.265 (bs, 1H, C*H*-7); ^{13}C 20.33 (*C*H_2-6), 21.41 (*C*H_3), 22.10 (*C*H_2-5), 22.62 (*C*H_2-3'), 29.40 (*C*H_2-4), 31.58 (*C*H_2-2'), 44.64 (*C*H_2-1), 49.21 (*C*H_2-2"+*C*H_2-6"), 51.87 (*C*H-3a), 53.26 (*C*H_2-3"+*C*H_2-5"), 57.60 (*C*H_2-4'), 108.77 (*C*H-10), 109.63 (C_q-6a), 116.07 (2x*C*H, o-Ph), 118.62 (*C*H-7), 119.67 (*C*H, p-Ph), 122.95 (*C*H-9), 128.34 (C_q-6b), 128.94 (C_q-8), 129.12 (2x*C*H, m-Ph), 133.40 (C_q-3a^1), 136.94 (C_q-10a), 151.42 (C_q, i-Ph), 172.74 (C_q-1'); ESI (TIS)-Q m/z 457.45 $[M+1]^+$, $C_{29}H_{36}N_4O$.

*Compound **4b**:* NMR ^{1}H (323K) 1.512 (bs, 1H, ½ CH_2-4), 1.982 (m, 3H, J 7.0, CH_2-3' + ½ CH_2-5), 2.161(bm, 1H, ½ CH_2-5), 2.443 (s, 3H, CH_3), 2.521 (m, 5H, CH_2-2' + CH_2-4' + ½ CH_2-4), 2.645 (m, 4H, CH_2-3"+ CH_2-5"), 2.690 (m, 1H ½ CH_2-6), 2.787 (ddt, 1H, J 1.4, 6.7, 15.8, ½ CH_2-6), 2.916 (bs, 1H, ½ CH_2-2), 3.119 (t, 4H, J 4.6, CH_2-2"+ CH_2-6"), 3.982 (td, 1H, J 2.3, 12.1, ½ CH_2-1), 4.109 (dt, 1H, J 2.2, 12.3, ½ CH_2-1), 4.412 (bs, 1H, ½ CH_2-2), 5.218 (d, 1H, J 9.8, C*H*-3a), 6.839 (dd, 2H, J 4.6, 9.2, CH_2-2"'+ CH_2-6"'), 6.930 (dd, 2H, J 8.3, 9.2, CH_2-3"'+ CH_2-5"'), 7.006 (dd, 1H, J 1.5, 8.3, C*H*-9), 7.118 (d, 1H, J 8.3, C*H*-10), 7.269 (bs, 1H, C*H*-7); ^{13}C (293K) 20.29 (*C*H_2-6), 21.45 (*C*H_3), 22.01 (*C*H_2-5), 22.12 (*C*H_2-3'), 32.09 (*C*H_2-2'), 44.55 (*C*H_2-1), 50.03 (*C*H_2-2"+*C*H_2-6"), 53.12 (*C*H_2-3"+*C*H_2-5"), 57.46 (*C*H_2-4'), 108.74 (*C*H-10), 109.59 (C_q-6a), 115.51 (*C*H_2-3"'+*C*H_2-5"', J 22.1), 117.82 (*C*H_2-2"'+*C*H_2-6"', J 7.5), 118.58 (*C*H-7), 122.87 (*C*H-9), 128.09 (C_q-6b), 128.91 (C_q-8), 134.61 (C_q-3a^1), 136.71 (C_q-10a), 147.84 (C_q,-1"'), 157.20 (C_q,-4"', J 238.5); ESI (TIS)-Q m/z 475.05 $[M+1]^+$, $C_{29}H_{35}FN_4O$.

*Compound **4c**:* NMR ^{1}H (323K) 1.492 (bs, 1H, ½ CH_2-4), 1.924 (t, 2H, J 7.0, CH_2-3'), 1.974 (m, 1H, ½ CH_2-5), 2.147 (m, 1H, ½ CH_2-5), 2.468 (m, 16H, CH_2-2', CH_2-4', CH_2-2", CH_2-3", CH_2-5", CH_2-6", ½ CH_2-4, CH_3; 2.446 – s, CH_3), 2.678 (m, 1H ½ CH_2-6), 2.788 (ddt, 1H, J 1.2, 6.7, 15.8, ½ CH_2-6), 2.896 (bs, 1H, ½ CH_2-2), 3.953 (td, 1H, J 1.9, 11.8, ½ CH_2-1), 4.088 (dt, 1H, J 2.2, 12.4, ½ CH_2-1), 4.209 (s, 1H, NC*H*Ph$_2$), 4.396 (bs, 1H, ½ CH_2-2), 5.201 (d, 1H, J 10.0, C*H*-3a), 7.005 (dd, 1H, J 1.3, 8.3, C*H*-9), 7.115 (d, 1H, J 8.3, C*H*-10), 7.154 (m, 2H, p-Ph), 7.231 (2t, 4H, m-Ph), 7.367 (2d, 4H, o-Ph), 7.273 (bs, 1H, C*H*-7); ^{13}C (293K) 20.33 (*C*H_2-6), 21.46 (*C*H_3), 22.03 (*C*H_2-5), 22.21 (*C*H_2-3'), 32.35 (*C*H_2-2'), 44.64 (*C*H_2-1), 51.09 (*C*H-3a), 53.26 (*C*H_2-3"+*C*H_2-5"), 57.48 (*C*H_2-2"+*C*H_2-6"), 76.18 (N*C*HPh$_2$), 108.71 (*C*H-10), 109.36 (C_q-6a), 118.56 (*C*H-7), 122.82 (*C*H-9), 126.93 (*C*H, p-Ph), 127.89 (2x*C*H, o-Ph), 128.10 (C_q-6b), 128.46 (2x*C*H, m-Ph), 128.88 (C_q-8), 142.61 (C_q, i-Ph); ESI (TIS)-Q m/z 547.65 $[M+1]^+$, $C_{36}H_{42}N_4O$.

*Compound **4d**:* NMR ^{1}H (293K) 1.631 (bs, 1H, ½ CH_2-4), 1.912 (bs, 2H, CH_2-3'), 1.955 (m, 1H, ½ CH_2-5), 2.134 (m, 1H, ½ CH_2-5), 2.25-2.60 (m, 16H, CH_2-2', CH_2-4', CH_2-2", CH_2-3", CH_2-5", CH_2-6", ½ CH_2-4, and s for CH_3 at 2.453 inside), 2.672 (m, 1H ½ CH_2-6), 2.789 (bdd, 1H, J 5.9, 15.9, ½ CH_2-6), 3.093 (bs, 1H, ½ CH_2-2), 3.959 (bs, 1H, ½ CH_2-1), 4.099 (bd, 1H, J 10.1, ½ CH_2-1), 4.164 (s, 1H, NC*H*Ar$_2$), 4.928 (bs, 1H, ½ CH_2-2), 5.211 (bs, 1H, C*H*-3a), 7.018 (bd, 1H, J 8.2, C*H*-9), 7.134 (d, 1H, J 8.3, C*H*-10), 7.178 (t, 1H, J 7.3, p-Ph), 7.239 (m, 4H, Ar) 7.289 (bs, 1H, C*H*-7), 7.338 (m, 4H, Ar); ESI (TIS)-Q m/z 581.35 $[M+1]^+$, $C_{36}H_{41}ClN_4O$.

Crystallography

The crystals of **4a** and **4b** were mounted on a glass capillary and all geometric and intensity data were taken from these crystals. Diffraction data for **4a** were taken on an Agilent SupernovaDual diffractometer equipped with an Atlas CCD detector using micro-focus Mo Kα radiation (λ = 0.71073 Å) at room temperature. **For 4b** data was collected on a CAD4, Enrafnonius diffractometer, using graphite monochromatized Mo Kα radiation using *ω/2θ* methode. The determination of the unit cell parameters, data collection and reduction were performed with Crysalispro software [31]. The structures were solved by direct methods and refined by the full-matrix least-squares method on F^2 with ShelxS and ShelxL 2018/1 programs [32]. All non-hydrogen at-

oms, were located successfully from Fourier maps and were refined anisotropically. The H atoms were placed in idealized positions (C—H = 0.86 to 0.93 Å) and were constrained to ride on their parent atoms, with $U_{iso}(H) = 1.2U_{eq}(C)$ or $1.5U_{eq}(C_{methyl})$. The most important crystallographic and refinement indicators are listed on Table 1.

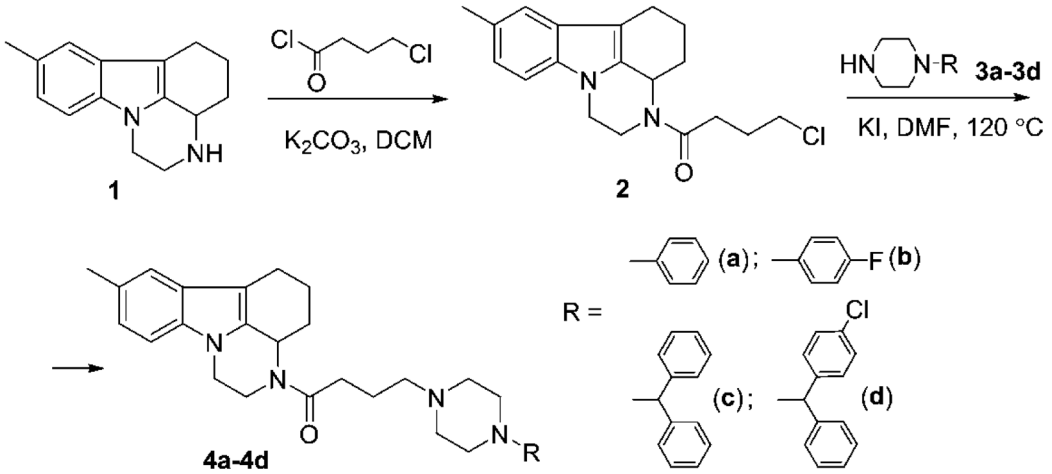
RESULTS AND DISCUSSION

The idea of the current study is to build novel polydentate ligands possessing pirlindole and piperazine fragments connected *via* a flexible four-carbon aliphatic linker. The later was designed in an attempt to ensure steric freedom of both units to occupy different mutual orientations. Piperazines with aryl or benzyl type substituents were chosen due to the observed remarkable biological activities of compounds possessing analogues structural element.

The target compounds were obtained *via* two step protocol; classical N-acylation by chlorobutyryl chloride followed by nucleophilic substitution of a series of mono-substituted piperazines without preliminary purification of chloride **2** (Scheme 1). The second reaction was performed by heating the reaction mixture in a closed vessel in halogen metathesis conditions, e. g. in the presence of potassium iodide, in order to override the low reactivity of terminal chlorine. The products **4** were isolated by column chromatography and subsequent recrystallization in moderate overall yields as listed on Table 2.

The structures of the products were assigned by 1D and 2D NMR experiments. The spectra at room temperature show broad signals due to exchange between two sides; e. g. hindered rotations around tertiary amide bond. Contrary, at 323K almost all signals are sharp and well defined. This pattern is valid for all compounds instead of **4d** where partial decomposition was detected at elevated temperature. The signals in the proton spectrum of **4d** at room temperature were assigned by comparison with those of the other products. The latter is possible as the aliphatic protons possess similar signals (Fig. 2), while the only difference is in the aromatic area, which is much better resolved.

The structures of the products were confirmed by singe crystal XRD of selected samples [33]. Compounds **4a** and **4b** (Figs. 3 and 4) crystalize in *P*–1 space group with a single molecule in the asym-



Scheme 1. Synthesis of target compounds **4**.

Table 2. Yields and analytical data of compounds **4a**-**4d**

Compd.	Yield, %[a]	m. p., °C	R_f[b]
4a	54	184.9–185.1	0.18
4b	46	179.3–179.6	0.13
4c	62	169.4–169.6	0.21
4d	48	154.4–154.9	0.23

[a] Overall from two steps; [b] Mobile phase: ethyl acetate:triethylamine 100:1.

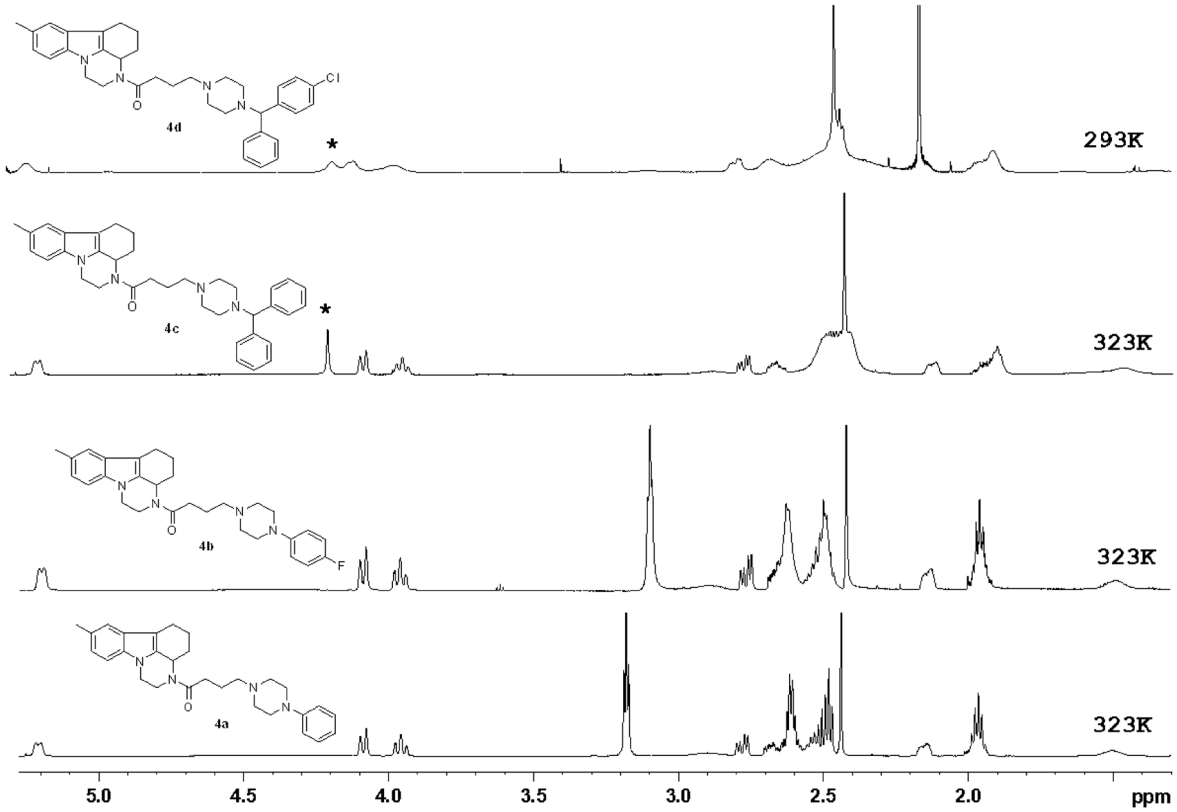


Fig. 2. Aliphatic area of the proton spectra of ligands **4a**-**4c** at 323K and **4d** at 293K. The asterisks indicate the signals for methyne NC*H*Ar$_2$ protons in **4c** and **4d**.

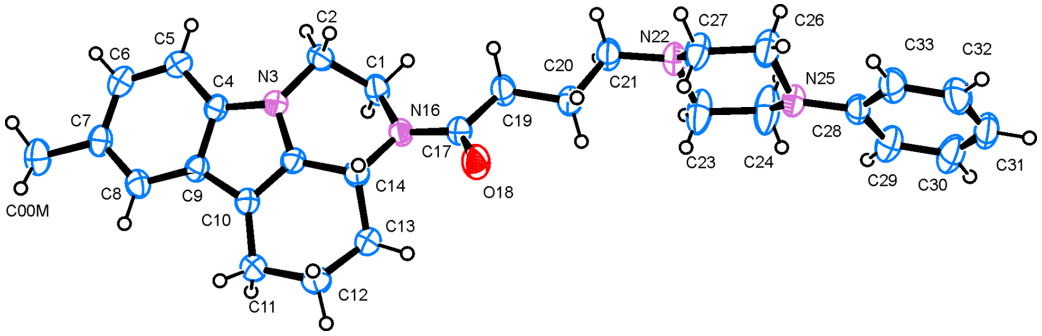


Fig. 3. ORTEP view of **4a** with the atomic numbering scheme; ellipsoids are drawn at 50% probability, hydrogen atoms are shown as small spheres with arbitrary radii.

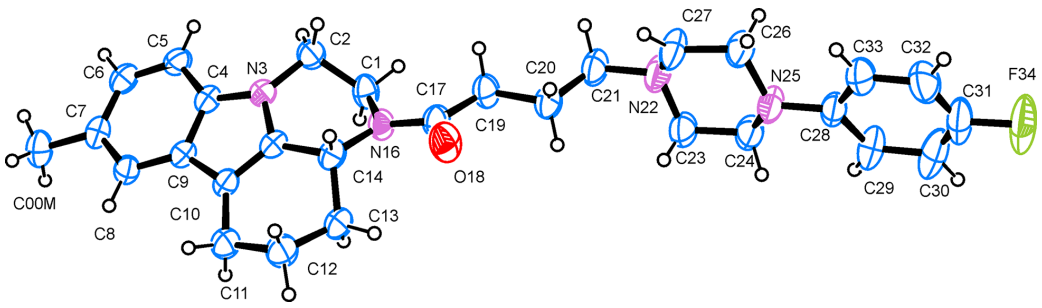


Fig. 4. ORTEP view of **4b** with the atomic numbering scheme; ellipsoids are drawn at 50% probability, hydrogen atoms are shown as small spheres with arbitrary radii.

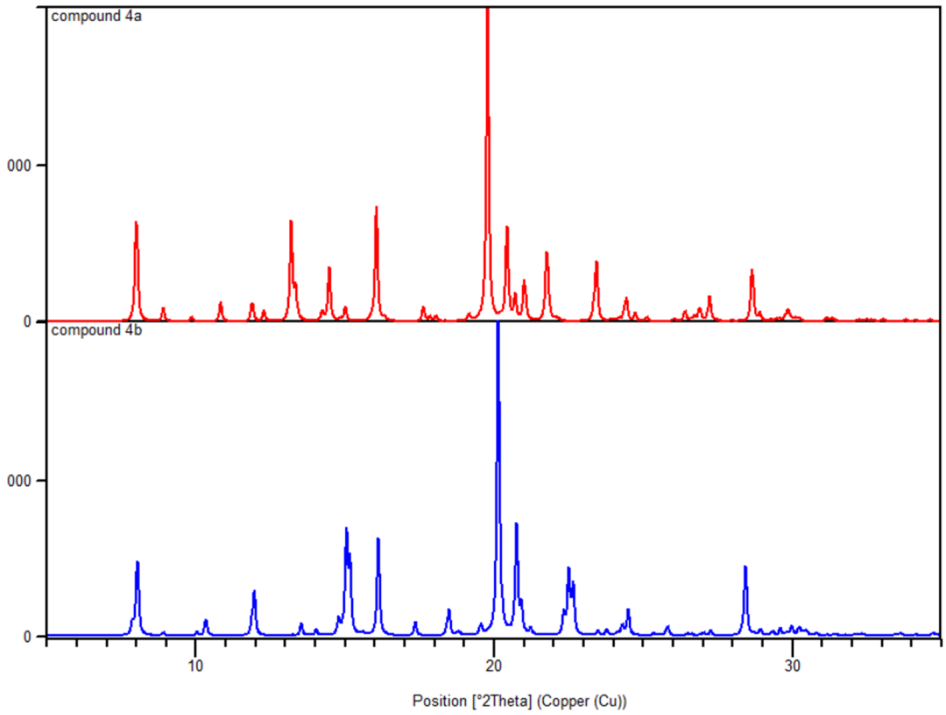


Fig. 5. Comparison of powder diffraction patterns of **4a** and **4b**.

metric unit and almost identical unit cell parameters (Table 1), e.g. they are nearly isostructural though there is an additional F atom in **4b**. It was found that piperazine substituent does not influenced significantly the reaction out-put and preferred geometry.

Even though the variations of the cell parameters and chemical composition of **4a** and **4b** are marginal (Table 1), the compounds may be differentiated from powder X-ray experiments (Fig. 5). In addition the presented powder diffraction data may serve as a basis for further investigations on compounds having almost similar crystal structures.

Interestingly the supposedly "flexible" four-carbon aliphatic linker bridging the pirlindole and piperazine moieties has a "conserved" geometry. What is more, on both sides the four-carbon linker is connected to sp^3 N atom, thus the eventual rotation around the C–N bond is hampered. Consequently the molecular geometry of **4a** or **4b** is preserved as it can be acknowledged by the overlay of the two molecules (Fig. 6).

The three dimensional arrangement of the molecules in the crystal structure is governed by the closest packing and hence the in 4a and 4b no typical hydrogen bond acceptors are present the latest is ruled by weak C–H…O and C–H…π interactions (Fig. 7). Not unexpectedly, the observed weak intermolecular interactions are nearly identical. As a result of the conserved molecular geometry, the equal intermolecular interactions resulting in a comparable three-dimensional arrangement, the crystal structure is compelled to accommodate and additional F atom. This stringency is reflected by the lowering of melting point of **4b** by nearly 10 °C when compared to **4a**.

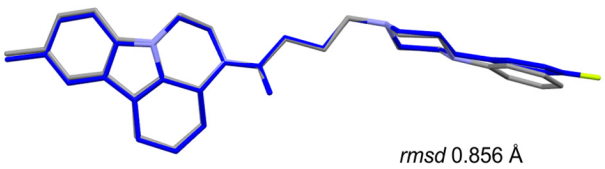


Fig. 6. Overlay of **4a** and **4b** (in blue/dark) based on the four-carbon linking the pirlindole and piperazine groups.

CONCLUSIONS

Novel polydentate ligands containing bridged pirlindole and piperazine fragments were obtained *via* a two-step protocol in moderate overall yields. The low reactivity of intermediate chloride was overridden by performing the reaction in halogen metathesis conditions under pressure. The products were characterized by NMR, mass spectra and single crystal XRD of selected samples.

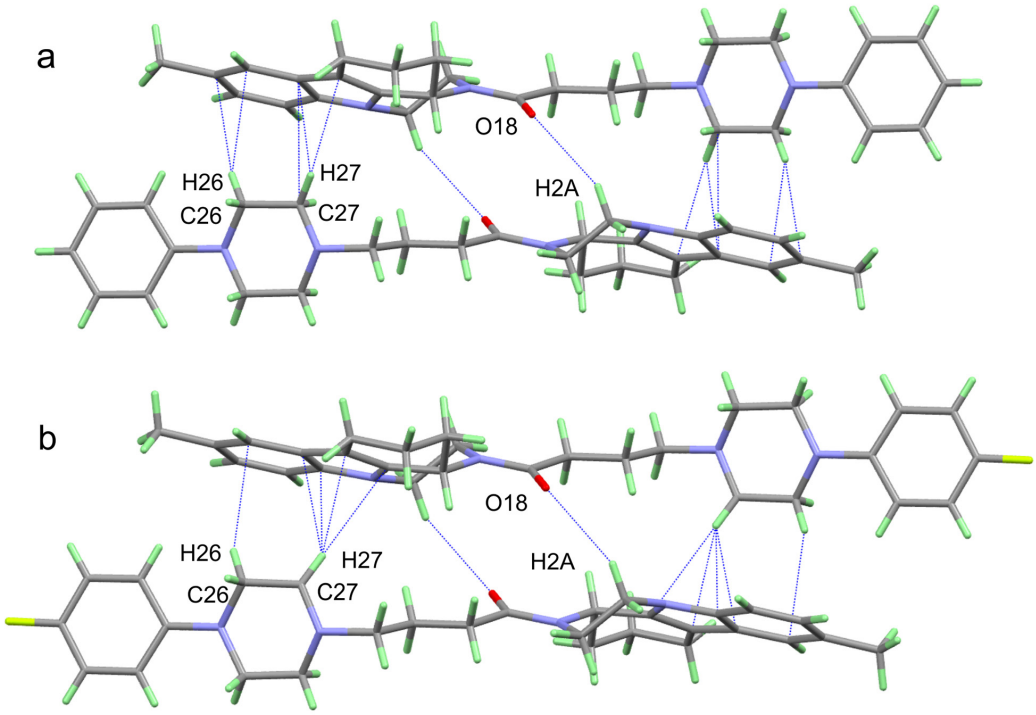


Fig. 7. Observed weak C–H…O and C–H…π interaction in a) **4a** and b) **4b**.

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