Design, synthesis, characterization and biological studies of ruthenium and gold compounds with anticancer properties

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Appendix A

Novel Crystallographic Data of Compounds Developed in the Research Projects Described in this Thesis

This appendix contains additional crystallographic information about the crystal structures of some of the novel compounds briefly described in the previous chapters, but that were not the main focus of research.

A.1 Introduction

In the following lines and tables, novel crystallographic data of several monocrystal compounds obtained while developing the experimental part of the projects discussed in the previous chapters, is included.

A.2. Gold(III) Project

A.2.1 Introduction

It was repeatedly attempted to obtain transient species in solution of several gold(III)-2-(arylazo)pyridine derivatives. The addition of a counterion to stabilize the structures was tried and positively charged ligands were crystallized and diffraction studies performed in case of 3mazpy and 3mtazpy. This evidence could suggest that, Au(III) coordination is partially hampered by steric factors as the ligand prefers to be protonated at the pyridine ring instead of forming the coordination compounds. The crystal data is fully described in the coming section.

A.2.2 Experimental section

a) 3-methyl-2[(E)-phenyldiazenyl]pyridinium hexaflouridophosphate, 3mazpyH. The compound was synthesized according to the procedure described in Chapter 2 for the synthesis of Au-3mazpy. Once the solid was isolated and its composition confirmed, 0.01g (0.0180 mmol) of Au-3mazpy was dissolved in 2 mL of methanol and a solution of 0.0029 g (0.0180 mmol) of NH_4PF_6 in 1 mL of water was added as well. The slow evaporation of the solvent after 20 days at 278 K produced small yellow-orange crystals suitable for the diffraction studies.

b) 3-methyl-2[(E)-(2-methylphenyl)diazenyl]pyridinium hexaflouridophosphate, 3mtazpyH. The compound was synthesized according to the procedure described in Chapter 2 for the synthesis of Au-3mtazpy. Once the solid was isolated and its composition confirmed, 0.01g (0.0170 mmol) of Au-3mtazpy was dissolved in 2 mL of methanol and a solution of 0.0028 g (0.0170 mmol) of NH_4PF_6 in 1 mL of water was added as well. The slow evaporation of the solvent after 15 days at 278 K produced small dark orange crystals suitable for the diffraction studies.

A.2.3. X-ray crystallography

Crystals suitable for X-ray diffraction were obtained for 3mazpyH and 3mtazpyH when slow evaporation of the solvent took part at 278 K. All reflections intensities were measured at 150(2) K, using a Nonius KappaCCD diffractometer (fine-focus sealed tube) equipped with graphite-monochromated Mo $K\alpha$ radiation (λ = 0.71073 Å) under the program *COLLECT* [1] . The program *PEAKREF* [2] was used to determine the cell dimensions. The sets of data were integrated using the program *EVALCCD* [3]. The structures were solved with the program *DIRDIF99* [4]. All the structures were refined on F^2 with *SHELXL97* [5]. Multi-scan semi-empirical absorption corrections were applied to the sets of data using *SADABS* [6]. For 3-mazpyH, 3151 reflections were unique (R_{int} = 0.000), of which 2905 were observed (θ_{max} = 27.5°) with the criterion of $I > 2\sigma(I)$; while for 3mtazpyH, 3316 reflections were unique (R_{int} = 0.034), of which 2459 were observed (θ_{max} = 26.0°) with the criterion of $I > 2\sigma(I)$. The *PLATON* software [7] was used for molecular graphics, structure checking and calculations. The H atoms were placed at calculated positions (except as specified) with isotropic displacement parameters having values 1.2 or 1.5 times U_{eq} of the attached atom. Crystallographic data for 3-mazpyH and 3-mtazpyH are listed in table 1, while table 2 contains selected bond lengths and angles for each compound. The X-ray structures of the asymmetric units of 3mazpyH and 3mtazpyH, with the hexafluoridophosphate anion and used atomic numbering are shown in figures 1 and 3. Finally a PLATON projection of 3mazpyH showing the cooperative intra and inter hydrogen bonds in the unit cell, is presented in figure 2.

3-mazpyH and 3mtazpyH belong to the same space group and only one crystal structure of a closely related compound has been reported in the literature [8] by Panneerselvam et al., which presents a $C_{2/c}$ space group. In this crystallographic study, the authors conclude that the protonation of 2-(4-hydroxyphenylazo)pyridine takes part in the azo nitrogen instead of the pyridine nitrogen in the structure, which means that the formed nitrogen atom is more basic.

Table 1 Crystallographic data for 3mazpyH and 3mtazpyH.

Abbreviation:	**3-mazpyH**	**3-mtazpyH**
empirical formula	$C_{12}H_{12}N_3PF_6$	$C_{13}H_{14}N_3PF_6 \cdot CH_4O$
Fw	343.22	389.28
crystal symmetry	triclinic	triclinic
Space group	P-$_1$ (No. 2)	P-$_1$ (No. 2)
a, Å	6.3793(4)	6.7416(3)
b, Å	7.7238(6)	11.3187(7)
c, Å	15.0110(8)	11.8820(11)
α (°)	89.405(3)	70.581(3)
β (°)	84.037(3)	80.120(4)
γ (°)	69.771(2)	86.080(3)
V, Å^3	689.99(8)	842.35(9)
Z	2	2
T, K	150(2)	150(2)
ρ_{calcd}, g/cm^3	1.652	1.535
μ, mm^{-1}	0.27	0.23
$R1^a$	0.038	0.039
$wR2^b$	0.107	0.098
GOF	1.22	1.05
$\Delta\rho_{max}$, e Å^{-3}	0.44	0.40
$\Delta\rho_{min}$, e Å^{-3}	-0.29	-0.27

^{a} $R1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$. ^{b} $wR2 = \{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$

Table 2 Selected geometric parameters (Angstroms, degrees) for 3-mazpyH and 3-mtazpyH.

Distances (Angstroms)			
3-mazpyH		**3-mtazpyH**	
N1-C2	1.352(3)	N1-C2	1.352(3)
N1- C6	1.338(3)	N1- C6	1.329(6)
N7-N8	1.257(3)	N7-N8	1.261(2)
N7-C2	1.415(3)	N7-C2	1.413(2)
N8-C9	1.416(3)	N8-C9	1.418(2)
C2-C3	1.385(3)	C2-C3	1.396(3)
C9-C10	1.386(4)	C9-C10	1.411(3)
P1-F1	1.596(15)	P1-F1	1.581(15)
P1-F2	1.586(15)	P1-F2	1.595(19)
N1-H1	0.88	N1-H1	0.88
N1-H1···N8	2.22	N1-H1···N8	2.27
N1-N8	2.551(3)	N1-N8	2.591(2)
N7···H14	2.49	N7···H14	2.43
N7···H15	2.81	N7···H15	2.50
		N8···H16	2.71

Angles (Degrees)			
3-mazpyH		**3-mtazpyH**	
C2-N1-C6	123.1(2)	C2-N1-C6	122.95(18)
N8-N7-C2	111.85(18)	N8-N7-C2	113.11(16)
N7-N8-C9	115.41(19)	N7-N8-C9	114.24(16)
N1-C2-N7	119.16(18)	N1-C2-N7	120.35(17)
C9-C10-C14	120.5(2)	C9-C10-C14	121.05(18)
N1-C2-N7-N8	-10.3(3)	N1-C2-N7-N8	1.5(2)
N7-N8-C9-C10	174.45(4)	N7-N8-C9-C10	178.81(16)
F1-P1- F2	90.80(8)	F1-P1- F2	91.12(8)
F1-P1-F6	178.62(8)	F1-P1-F6	179.91(9)

In opposition to these results, the difference-Fourier map of 3-mazpyH and 3-mtazpyH show bigger electron density near the nitrogen in the pyridine moiety (N1), this evidence probes that protonation occurs mainly at the pyridine nitrogen, which is more basic than the nitrogen atoms in the azo moiety. This discrepancy could be the result of the different substituents in the pyridine and phenyl rings, in the 2-(arylazo)pyridine derivatives. These results stress the importance of the substituents when talking about the basic and acidic properties of the donor nitrogen atoms, when considering coordination in this family of 2-(arylazo)pyridine ligands.

The N7-N8 distance of 1.257(3) and 1.261(2) angstroms for 3-mazpyH and 3mtazpyH, respectively are similar to the corresponding N-N bond distances for azobenzene (1.243 Å) [9] and for the protonated 2-(4-hydroxyphenylazo)pyridine tetrafluoridoborate (1.248(4) Å) [8].

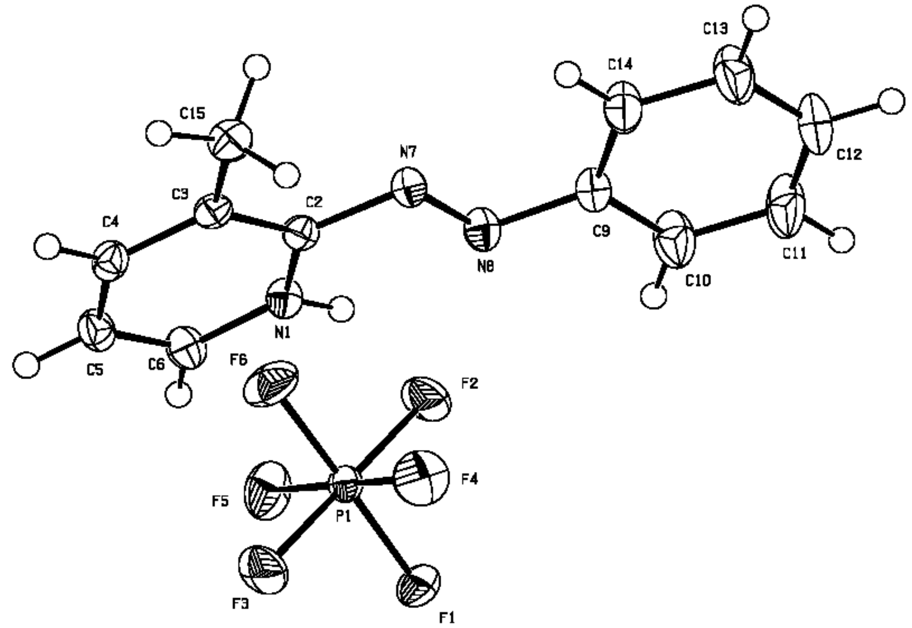

Figure 1 X-ray structure of the asymmetric unit of 3mazpyH with the hexafluoridophosphate anion and used atomic numbering.

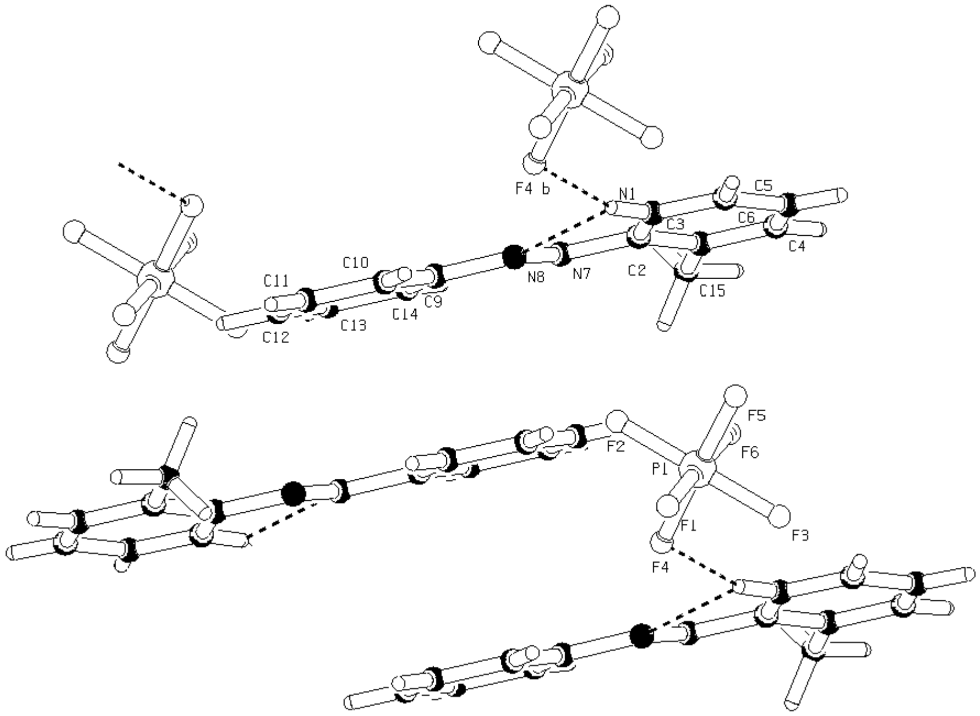

Figure 2 PLATON projection of 3mazpyH showing the cooperative intra and inter hydrogen bonds in the cell unit.

The phenyl and pyridyl moieties are almost planar, although the azo bond is not in the same plane than the pyridyl ring with a torsion angle of -10.3(3) degrees, in case of 3-mazpyH, and smaller in case of 3-mtazpyH (1.5(2) degrees). This data indicate that the pyridine present a slight distortion, which could be generated by repulsion forces between N1 and N8, even though a hydrogen bond interaction is observed between, N1-H1···N8. The reduced distortion detected in 3-mtazpyH might be result of a combination of repulsion- and steric-effects between N1 and N8, and the methyl groups in both, the phenyl and pyridine units, respectively.

Clearly in both cases, the crystal structure is stabilized by hydrogen bonds and van der Waals interactions.

In the particular case of 3-mtazpyH a molecule of solvent is providing with extra stabilization as hydrogen bonds are detected (structure not shown).

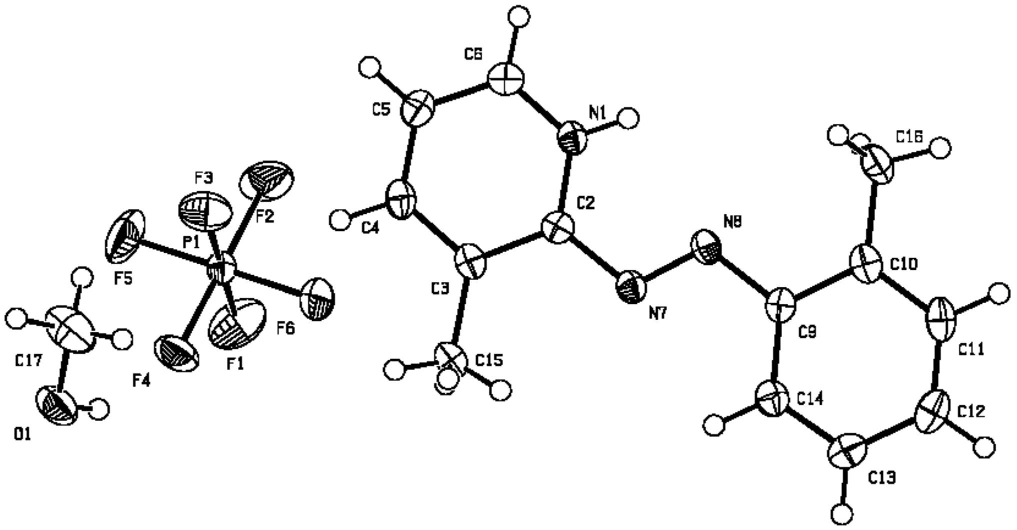

Figure 3 X-ray structure of the asymmetric unit of 3mtazpyH with the hexafluoridophosphate anion and used atom numbering.

A.3. Ruthenium(II,III) Project

A.3.1 Introduction

There is a limited number of crystallographic studies of tridentate bis(arylimino)pyridine molecules, mainly because the interest in this kind of compound just started in recent years [10].

These kind of compounds are readily accessible from the condensation reaction of either 2,6-pyridinedicarboxaldehyde or 2,6-diacetylpyridine with two equivalents of the corresponding aniline in an alcohol (for instance, ethanol, propanol or methanol).

In general, the X-ray structures of related bis(arylimino)pyridine compounds, reveals that the imino nitrogen atoms prefer to be disposed trans with respect to the central pyridine nitrogen [11-14].

The crystallographic data for the ligands L1, L2 and L3 will be described and briefly discussed in the coming section.

A.3.2 Experimental section

a) Synthesis of 2,6-bis(2,4,6-trimethylphenyliminomethyl)pyridine, L1; 2,6-bis(2,6-diisopropylphenyliminomethyl)pyridine, L2; and 2,6-bis(4-methylphenyliminomethyl) pyridine, L3. A detailed procedure for the synthesis of the titled compounds has been described in the experimental section in chapter 4. The relevant characterization information of each ligand can also be consulted in this section and was confirmed by the X-ray diffractions studies.

A.3.3. X-ray crystallography

Crystals suitable for X-ray diffraction were obtained when slow diffusion of water in concentrated dmf solutions of L1, L2 and L3, took part at room temperature. Pale yellow block crystals were mounted on a glass fibre. All reflections intensities were measured at 150(2) K, using a Nonius KappaCCD diffractometer (fine-focus sealed tube) equipped with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å) under the program *COLLECT* [1] . The program *PEAKREF* [2] was used to determine the cell dimensions. The sets of data were integrated using the program *EVALCCD* [3]. The structures were solved with the program *SHELXS86 [15].* All the structures were refined on F^2 with *SHELXL97* [5]. Multi-scan semi-empirical absorption corrections were applied to the sets of data using *SADABS* [6]. For L1, 2026 reflections were unique (R_{int} = 0.037), of which 1637 were observed ($\theta_{\max}$ = 26°) with the criterion of $I > 2\sigma(I)$; for L2, 6182 reflections were unique (R_{int} = 0.051), of which 4401 were observed ($\theta_{\max}$ = 27.5°) with the criterion of $I > 2\sigma(I)$; for L3, 1576 reflections were unique (R_{int} = 0.071), of which 1051 were observed ($\theta_{\max}$ = 25.6°) with the criterion of $I > 2\sigma(I)$. The *PLATON* software [7] was used for molecular graphics, structure checking and calculations. The H atoms were placed at calculated positions (except as specified) with isotropic displacement parameters having values 1.2 or 1.5 times U_{eq} of the attached atom. For L1, the H-atoms of the two methyl groups C11 (*ortho* position) and C12 (*para* position) were found to be disordered by a rotation of 60° and were treated using the *AFIX 123* instruction. The occupation factors for the two major components of the disorder refined to 0.73(2) and 0.77(3). For L2, the H-atom of C16 and the two methyl groups C17 and C18 were found to be disordered by a rotation of 18° and were treated using the *AFIX 123* instruction. Crystallographic data for L1, L2 and L3 are listed in table 3, while table 4 contains selected bond lengths and angles of each compound.

The X-ray structures of the asymmetric units of L1, L2 and L3 along with the used atomic numbering are shown in figures 4, 5 and 6.

Table 3 Crystallographic data for L1, L2 and L3.

Abbreviation:	**L1**	**L2**	**L3**
empirical formula	$C_{25}H_{27}N_3$	$C_{31}H_{39}N_3$	$C_{21}H_{19}N_3$
Fw	369.50	453.65	313.39
crystal symmetry	monoclinic	triclinic	monoclinic
Space group	$C_{2/c}$ (No. 15)	P_{-1} (No. 2)	$P_{2/c}$ (No. 13)
a, Å	12.5220(7)	8.4651(1)	4.6864(2)
b, Å	9.9495(8)	10.3167(1)	6.2335(3)
c, Å	16.9423(13)	16.5315(2)	28.6998(15)
α (°)	90	106.860(1)	90
β (°)	102.382(4)	94.853(1)	93.586(3)
γ (°)	90	98.843(1)	90
V, Å^3	2061.7(3)	1352.44(3)	836.76(7)
Z	4	2	2
T, K	150(2)	150(2)	150(2)
ρ_{calcd}, g/cm^3	1.190	1.114	1.244
μ, mm^{-1}	0.07	0.065	0.075
$R1^a$	0.041	0.045	0.057
$wR2^b$	0.103	0.123	0.148
GOF	1.04	1.08	1.05
$\Delta\rho_{max}$, e Å^{-3}	0.17	0.17	0.19
$\Delta\rho_{min}$, e Å^{-3}	-0.16	-0.22	-0.20

^{a} $R1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$. ^{b} $wR2 = \{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$

Table 4 Selected geometric parameters (Angstroms, degrees) for 3-mazpy and 3-mtazpy.

L1		**L2**		**L3**	
		Distances (Angstroms)			
C1-N1	1.3419(15)	C1-N1	1.3442(16)	C2-N1	1.345(2)
C4-N2	1.2494(17)	C6-N2	1.2686(17)	C5-N6	1.270(3)
C5-N2	1.4225(17)	C7-N2	1.4325(16)	C7-N6	1.423(3)
		C19-N3	1.2676(16)		
		C20-N3	1.4240(17)		
C1-C4	1.4733(18)	C1-C6	1.4761(18)	C2-C5	1.467(3)
		C5-C19	1.4769(18)		
C1-C2	1.3840(2)	C1-C2	1.3914(19)	C2-C3	1.392(3)
		C4-C5	1.3965(19)		
C5-C10	1.4019(19)	C7-C8	1.4064(18)	C7-C8	1.387(3)
		C20-C21	1.4163(18)		
		Angles (Degrees)			
L1		**L2**		**L3**	
C1-N1-C1a	117.37(16)	C1-N1-C5	117.33(11)	C2-N1-C2a	117.9(2)
C4-N2-C5	119.25(12)	C6-N2-C7	117.88(12)	C5-N6-C7	120.21(18)
		C19-N3-C20	119.34(12)		
N1-C1-C2	123.22(13)	N1-C1-C2	123.25(11)	N1-C2-C3	122.45(19)
		N1-C5-C4	122.96(11)		
N1-C1-C4	115.26(12)	N1-C1-C6	114.74(11)	N1-C2-C5	115.74(17)
		N1-C5-C19	114.74(11)		
N2-C4-C1	122.54(13)	N2-C6-C1	122.19(13)	N6-C5-C2	121.99(18)
		N3-C19-C5	121.79(12)		
C6-C5-N2	123.30(12)	C8-C7-N2	117.47(11)	C8-C7-N6	117.21(18)
		C21-C20-N3	115.93(11)		
C6-C5-C11	121.75(12)				
C1-C4-N2-H4	179.98(12)	C1-C6-N2-H6	178.22(11)	C2-C5-N6-H5	179.94(18)
C6-C5-N2-C4	77.92(16)	C12-C7-N2-C6	70.98(12)	C12-C7-N6-C5	23.21(12)

The molecules L1 and L3 lie about a crystallographic mirror plane, which passes through the N1 and C3 atoms for L1 (figure 4) and N1 and C4 for L3 (figure 6).

Like observed in crystal structures of related systems [12-14, 16], the titled ligands (L1, L2 and L3) show, in the solid state, the imino nitrogen atoms in the *trans* conformation with respect to the central pyridine nitrogen. This spatial organization provides the least steric hindrance within the aryl moieties.

Also to be mention is the fact that the terminal aryl moieties, in the bis(arylimino)pyridine ligands, are slightly twisted, 77.92 (L1), 70.98 (L2) and 23.21 (L3) degrees, from the plane of the imino-pyridine system, reducing the hindrance between both aromatic rings. L3 that has the lowest torsion angle and it only contains a methyl group at C10 atom (figure 6), producing the lowest steric effect.

The bond lengths within the ligands are as expected. For L1, the double bond nature of the imino C4-N2 bond is shown by the bond length of 1.2494(17) Å and the C1-N1 length, slightly longer, with 1.3419(15) Å, typical value for an aromatic double bond. The sp^2 nature of C4 atom is confirmed by the planarity of the C1-C4-N2-H4 moiety.

In case of L2, the double bond nature of the imino bonds, C6-N2 and C19-N3, is shown by the bond lengths of 1.2686(17) Å and 1.2676(16) Å. The sp^2 nature of C6 and C19 atoms is confirmed by the planarity of the C1-C6-N2-H6 moiety (178.22(11) degrees).

Finally, the double bond nature of the two imino C5-N6 bonds in L3, is shown by the bond length of 1.270(3) Å. The sp^2 nature of the C5 atom is confirmed by the planarity of the C2-C5-N6-H5 moiety (179.94(18) degrees).

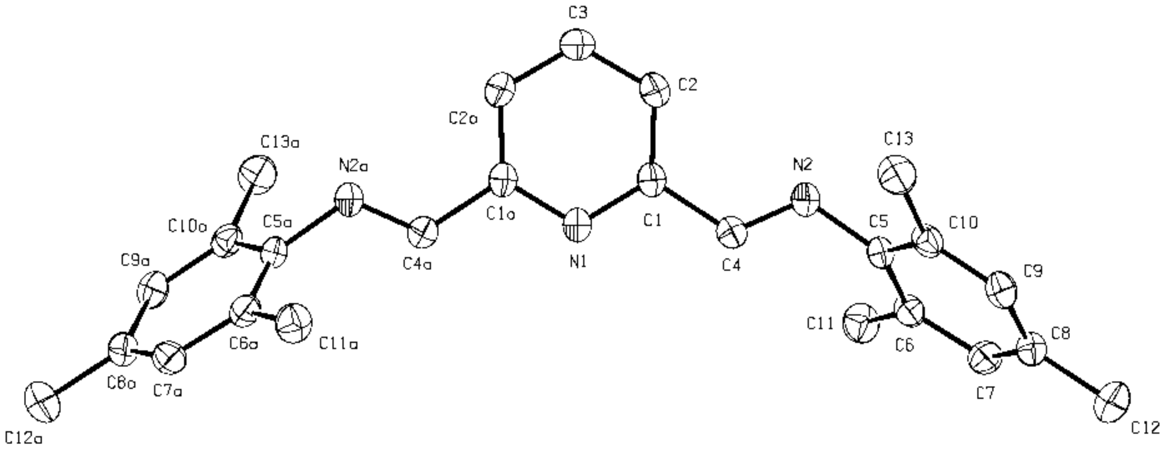

Figure 4 Molecular structure of the asymmetric unit of L1 and atom numbering.

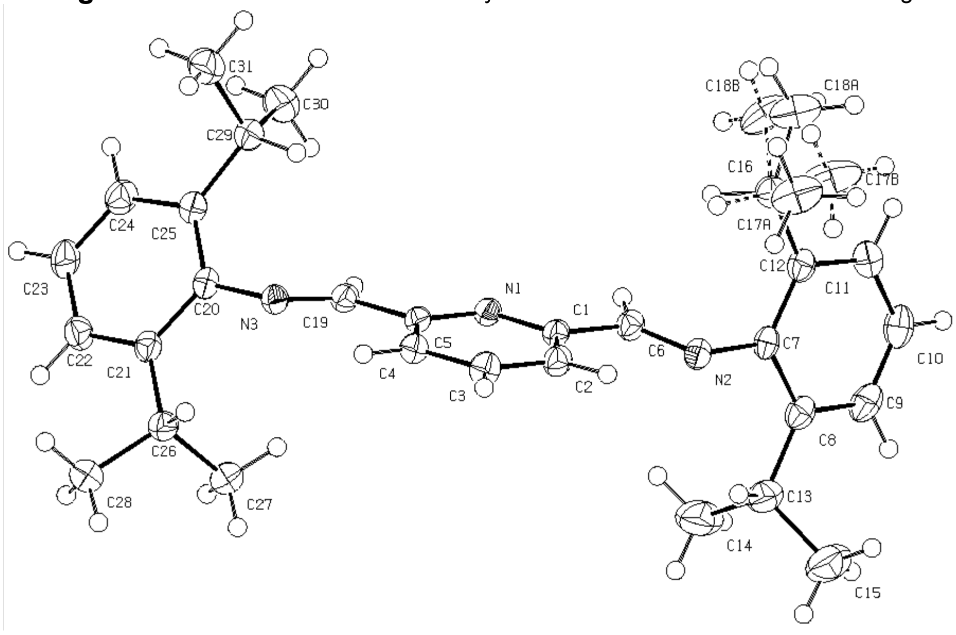

Figure 5 Molecular structure of the asymmetric unit of L2 and atom numbering.

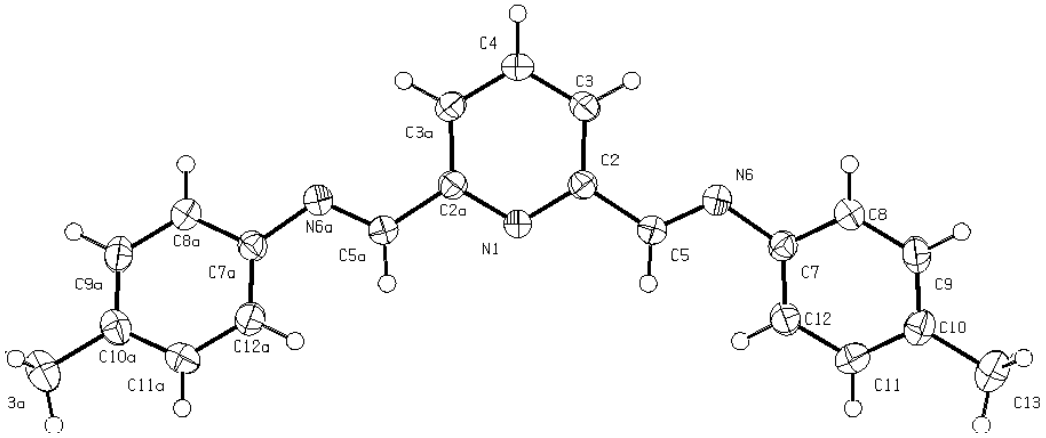

Figure 6 Molecular structure of the asymmetric unit of L3 and atom numbering.

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