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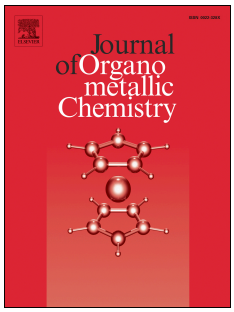

Pd(II) complexes with N-substituted pyrazoles as ligands. The influence of the R group [OMe *versus* NMe_2] of [1-{R-$(CH_2)_2$-}-3,5-Ph_2-(C_3HN_2)] on their cytotoxic activity on breast cancer cell lines

John U. Chukwu , Concepción López , Asensio González , Mercè Font-Bardía , M. Teresa Calvet , Ramon Messeguer , Carme Calvis

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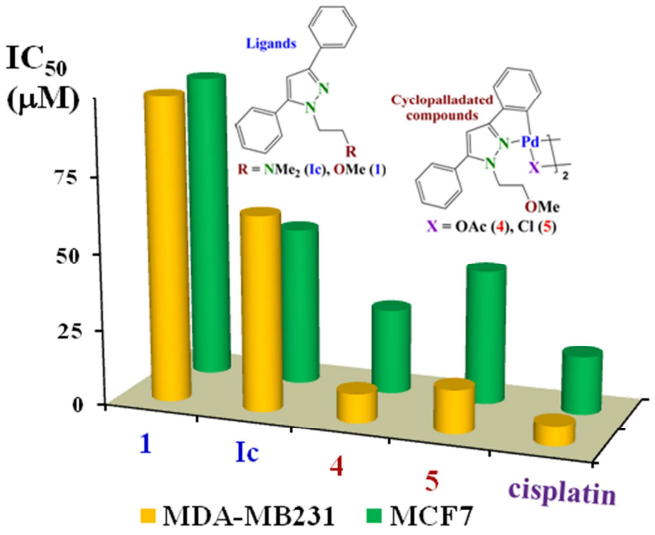
Several types of Pd(II) complexes containing the new pyrazole: [1(OMe-CH_2CH_2)-3,5Ph-(C_3HN_2)] acting as a monodentate (N-donor) or as a [C(phenyl), N(pyrazole)]$^-$ bidentate ligand have been prepared and characterized. Their antiproliferative activity in MCF7 and MDA-MB231 breast cell lines has also been evaluated and the results revealed that the cytotoxic activity of some of the cyclopalladated complexes was similar to that of cisplatin in the triple negative MDA-MB231 breast cancer cell line.



Pd(II) complexes with N-substituted pyrazoles as ligands. The influence of the R group [OMe *versus* NMe_2] of [1-{R-$(CH_2)_2$-}-3,5-Ph_2-(C_3HN_2)] on their cytotoxic activity on breast cancer cell lines.

John U. Chukwu,[a,b] Concepción López,[a,*] Asensio González,[c] Mercè Font-Bardía,[d] M. Teresa Calvet,[e] Ramon Messeguer[f] and Carme Calvis[f]

[a]*Departament de Química Inorgànica, Facultat de Química, Universitat de Barcelona, Martí i Franquès 1-11. E-08028-Barcelona, Spain. (C.López: E-mail: conchi.lopez@qi.ub.es).*

[b] *Current address: Department of Pure and Industrial Chemistry, University of Port-Hartcourt, P. M. B. 5323 Choba, Rivers State, Nigeria.*

[c] *Laboratori de Química Orgànica, Facultat de Farmàcia, Institut de Biomedicina (IBUB), Universitat de Barcelona, Av. Joan XIII. s/n, E-08028 Barcelona, Spain.*

[d] *Unitat de Difracció de Raigs-X, Centre Científic i Tecnològic de la Universitat de Barcelona, Solé i Sabarís 1-3, E-08028 Barcelona, Spain.*

[e] *Departament de Cristal·lografia, Mineralogia i Dipòsits Minerals, Facultat de Geologia, Universitat de Barcelona, Martí i Franquès s/n, E-08028 Barcelona, Spain.*

[f] *Biomed Division, Leitat Tecnological Center, Parc Científic de Barcelona, Edifici Hèlix, C/ Baldiri Reixach, 15–21, E-08028-Barcelona, Spain.*

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Abstract.

The study of the reactivity of the novel pyrazole derivative [1-{MeO-$(CH_2)_2$-}-3,5-Ph_2-(C_3HN_2)] (**1**) with $Na_2[PdCl_4]$ or $Pd(OAc)_2$ under different experimental conditions has allowed us to isolate and characterize the *trans*- isomers of [Pd{[1-{MeO-$(CH_2)_2$-}-3,5-Ph_2-(C_3HN_2)]}$_2(X)_2$] [X = Cl (**2**) or OAc (**3**)] and the di-μ-ligand bridged cyclopalladated complexes [Pd{κ^2,*C*,*N*)[1-{MeO-$(CH_2)_2$-}-3-(C_6H_4),5-Ph-(C_3HN_2)]}(μ-X)]$_2$ [X = OAc (**4**) or Cl (**5**)]. Further treatment of compounds **4** or **5** with PPh_3 in CH_2Cl_2 produced the bridge splitting and the formation of [Pd{κ^2,*C*,*N*)[1-{MeO-$(CH_2)_2$-}-3-(C_6H_4),5-Ph-(C_3HN_2)]}X(PPh_3)] [X = OAc (**6**) or Cl (**7**)]. The cytotoxic assessment of the free ligand (**1**) and the Pd(II) complexes on the two breast cancer cell lines MCF7 and MDA-MB231 reveals that: a) compound **1** is less active than its analogue [1-{Me_2N-$(CH_2)_2$-}-3,5-Ph_2-(C_3HN_2)] (**Ic**) and b) palladacycles **4-7** showed a remarkable cytotoxic activity in the MDA-MB231 cell line (with IC_{50} values in the range 9.1-14.4 μM).

1. Introduction

Pyrazoles are widely used as core motifs for a large number of compounds of significant relevancy and they have a variety of applications (i.e. as agrochemicals, dyes, food additives, catalysts and pharmaceuticals) [1-2]. Moreover, N-substituted derivatives are particularly attractive in view of their antiproliferative properties against cancer cells [3,4]. Furthermore, this type of heterocycles have a rich and versatile coordination ability with transition metals that affects their properties [5-6]. This fact, together with the increasing

interest in the design of novel antitumoral drugs with greater efficiency, lower toxicity and less undesirable side effects than the current Pt-based drugs [7], have triggered the development of novel Pd(II) and Pt(II)-pyrazole containing complexes [8-13]. Substituted pyrazoles in which there is a σ(C⁻H) bond with the proper orientation are valuable substrates to achieve cyclopallada- or platinated complexes [11-13]. This sort of metallacycles are relevant due to their chemical, physical or optical properties and their applications in different areas (i.e. as precursors in organic, organometallic synthesis, homogeneous catalysis and as building blocks in supramolecular chemistry) [14,15].

On the other hand, Bioorganometallic chemistry is a rapid developing area of increasing interest and the idea of using organometallic complexes in drug discovery is becoming more and more popular [16-17]. Antimalarials, antibacterials, neuroprotectors, based on organometallic compounds have been described [16-17]. Moreover, recent contributions suggest that cyclopallada- and cycloplatinated compounds are probably amongst the best candidates for the design of new anticancer drugs [18-20].

Despite the increasing interest in both Pd(II)-pyrazole complexes [21, 22] and cyclometallated compounds [14,15,18-20], only a few articles on cyclopalladated-pyrazole derivatives have been published [11, 13]. We have recently reported three N-substituted pyrazoles of general formulae 1-{Me_2N-$(CH_2)_2$-}-3,5-R_2-(C_3HN_2) (**I**) (Figure 1), their Pd(II) and Pt(II) complexes of general formulae [M{1-[Me_2N-$(CH_2)_2$-]-3,5-R_2-(C_3HN_2)}Cl_2] [(**II**) and (**III**), in Fig. 1) and the cyclometallated derivatives (**IV** and **V**) [11b]. The comparison of their antitumoral activity in three different cell lines (MDA-MB231, MCF7 and A549) revealed that: a) pyrazoles (**I**) with R = Ph were more potent than their analogues with R = H or Me, b) the binding of these ligands to Pd(II) or Pt(II)

produced an enhancement of their activity, and c) cyclometallated products (**IV** and **V**) were more potent than complexes **IIc** and **IIIc** in which the pyrazole **Ic** acts as a bidentate (N,N') ligand.

< Figure 1, here >

In view of these findings and in order to elucidate the effect produced by the functional group on the pendant arm of the heterocyclic nitrogen, now we report a parallel study on the novel pyrazole: [1-{MeO-$(CH_2)_2$-}-3,5-Ph_2-(C_3HN_2)] (**1**), that has the OMe group attached at the end of the -$(CH_2)_2$- chain instead of the -NMe_2 of **Ic**.

2. Experimental

2.1. Materials and methods

All the reagents were obtained from commercial sources and used as received. Solvents were distilled and dried before use [23]. Elemental analyses were carried out at the *Serveis Científico-Tècnics* (Universitat Barcelona). Mass spectra (ESI^+) were performed at the *Servei d'Espectrometria de Masses* (Universitat de Barcelona). Infrared (IR) spectra were obtained with a Nicolet 400FTIR instrument using KBr pellets. A selection of the most relevant absorptions observed in the IR spectra are presented in the following sections. Ultraviolet-visible (UV-vis.) spectra of CH_2Cl_2 solutions of the free ligand **1** and the Pd(II) compounds (**5-7**) were recorded at 298 K with a Cary 100 scan 388 Varian UV spectrometer. The wavelengths (λ, in nm) and the extinction coefficients (ε, in M^{-1} cm^{-1}) of the bands observed in the UV-vis. spectra are specified in the characterization section of the corresponding product. The retention coefficients (R_f) were obtained using SiO_2 (Merck silica gel 60 F254) plates. High resolution ^1H NMR spectra and the two-dimensional [{^1H-

$^{1}H\}$ NOESY and COSY and $\{^{1}H$-$^{13}C\}$-heteronuclear single quantum coherence (HSQC), and heteronuclear multiple bond coherence (HMBC)] experiments were registered with a Varian VRX-500 or a Bruker Avance DMX-500 MHz instruments. $^{13}C\{^{1}H\}$-NMR spectra and $^{31}P\{^{1}H\}$ spectra of compounds **6** and **7** obtained with a Mercury-400 and a Varian 300 MHz instrument, respectively. NMR studies of **1-3** and **5-7** were carried out at 298 K, using $CDCl_3$ (99.9 %) as solvent and $SiMe_4$ [for ^{1}H and $^{13}C\{^{1}H\}$-NMR] and $P(OMe)_3$ [$\delta(^{31}P)$ = 140.17 ppm for ^{31}P NMR] as references. Due to the low solubility of complex **5** in $CDCl_3$ its NMR studies were performed in DMSO-d_6 (99.8%). In all cases, chemical shifts (δ) are given in ppm and the coupling constants (J) in Hz. In the characterization section of each product the assignment of signals detected in their NMR spectra refers to the labelling patterns presented in Scheme 1 (Abreviations for the multiplicities of the signals observed in the NMR spectra: s = singlet, d = doublet, t = triplet, m = multiplet and br = broad).

2.2. Synthesis

*2.2.1. Preparation of 1-{MeO-$(CH_2)_2$-}-3,5-Ph_2-(C_3HN_2) (**1**).*

Potassium hydroxide (0.800 g, 14×10^{-3} mol) was treated with 9.0 mL of DMSO and the resulting mixture was magnetically stirred at room temperature (ca. 298 K) for 30 min. After this period 3,5-diphenylpyrazole (0.788 g, 3.58×10^{-3} mol) was added and the stirring was maintained for 30 min at 298 K. Then, 1-chloro 2-methoxyethane (4.0 mL, 45×10^{-3} mol) was gradually added and the reaction mixture was left overnight under stirring at 298 K. After this period, 50 mL of iced cold water was added to eliminate the unreacted KOH; the organic phase was then extracted with diethylether and washed repeatedly with water,

dried over Na_2SO_4 and filtered. Then, the filtrate was concentrated to dryness on a rotary evaporator. The solid formed was collected and later on dried in vacuum for 3 days. [Yield: 0.880 g, (88 %)]. Characterization data: Anal (%). Calc. for $C_{18}H_{18}N_2O$ (MW = 278.35): C, 77.67; H, 6.52; N, 10.06 %; found: C, 77.8; H, 6.6 and N, 10.1. MS (ESI^+): *m/z* = 279.15 $\{[M] + H\}^+$. IR selected data: 3059-3015 [ν(C-H)] and 2987-2952 [ν(C-H)], 1481(m), 1462(s), 1441(m), 1363(m), 1300(m), 1115(s), 1012(m), 762(s), 691(s) cm^{-1}. UV-vis. data ($c = 5.74 \times 10^{-5}$ M in CH_2Cl_2): λ (ε) = 223 (1.5×10^4) and 253 (3.1×10^4). R_f (in $CHCl_3$) = 0.24. ^{1}H NMR data: δ = 3.32 (s, 3H, OMe); 3.91 [t, $^3J_{H,H}$ = 7.2, 2H, (-CH_2-^{d})]; 4.34 [t, $^3J_{H,H}$ = 7.2, 2H, (-CH_2-^{c})]; 6.65 (s, 1H, H^4); 7.35 (t, $^3J_{H,H}$ = 7.7, 1H, H^{4b}); 7.47-7.60 (m, 5H, H^{3a}, H^{4a}, H^{5a}, H^{3b} and H^{5b}); 7.70 (d, 2H, $^3J_{H,H}$ = 7.6, H^{2b} and H^{6b}), 7.92 (d, 2H, $^3J_{H,H}$ = 7.5, H^{2a} and H^{6a}). $^{13}C\{^1H\}$ NMR data: 49.1 (C^d); 58.9 (OMe); 71.4 (C^c); 103.4 (C^4); 125.3 (C^{2b} and C^{6b}); 125.7 (C^{2a} and C^{6a}); 126.0 (C^{4b}); 126.8 (C^{4a}); 128.7 (C^{3a} and C^{5a}); 129.2 (C^{3b} and C^{5b}); 130.7 (C^{1b}); 133.6 (C^{1a}); 145.9 (C^5) and 150.9 (C^3).

*2.2.2. Preparation of trans-[Pd{[1-{MeO-$(CH_2)_2$-}-3,5-Ph_2-(C_3HN_2)]$_2Cl_2$] (**2**).*

To a solution formed by $Na_2[PdCl_4]$ (100 mg, 3.4×10^{-4} mol) and methanol (10 mL), ligand **1** (189 mg, 6.8×10^{-4} mol) was added and the reaction mixture was stirred at 298 K for 2 h. The yellow solid formed was filtered and dried overnight. Afterwards, it was dissolved in the minimum amount of CH_2Cl_2 and passed through a SiO_2 (2.0 cm × 8.0 cm) column. Elution with CH_2Cl_2 produced a wide yellow band which was collected and concentrated to dryness on a rotary evaporator and the bright yellow solid formed was collected and finally dried in vacuum for 2 days. [Yield: 196 mg (78 %)]. Characterization data**:** Anal. (%) Calc for $C_{36}H_{36}Cl_2N_4O_2Pd$: (MW = 734.0): C, 58.91; H, 4.94; N, 7.63;

Found: C, 59.0; H, 5.0; N, 7.5. MS (ESI^+): *m/z* = 697.16 {[M] - Cl}$^+$. IR selected data: 3047-3015 [ν(C-H)] and 2980-2925 [ν(C-H)], 1483(m), 1461(m), 1448(m), 1124(s), 765(s) and 700(s) cm^{-1}. UV-vis. data: ($c = 8.17 \times 10^{-6}$ M in CH_2Cl_2): λ (ε) = 238 (3.8×10^5), broad band. R_f (in $CHCl_3$) = 0.19. ^{1}H NMR data: δ = 3.20 [s, 6 H, 2 (OMe)]; 3.96 [t, $^3J_{H,H}$ = 6.9, 4H, 2 (–CH_2-^{d})]; 4.89 [t, $^3J_{H,H}$ = 6.9, 4H, 2 (–CH_2–^{c})]; 6.36 [s, 2H, 2 (H^4)]; 7.40-7.58 [br. m, 12H, 2(H^{3a}, H^{4a}, H^{5a} , H^{3b}, H^{4a} and H^{5b})]; 7.62 [d. $^3J_{H,H}$ = 7.6, 4H, 2 (H^{2b} and H^{6b})] and 8.20 [d, $^3J_{H,H}$ = 7.6, 4H, 2 (H^{2a} and H^{6a})]. $^{13}C\{^1H\}$ NMR data: 50.31 (2 C^d); 58.7 (2 OMe); 69.9 (2 C^c); 108.5 (2 C^4); 125.5 [2 (C^{2b} and C^{6b})]; 125.9 (2 C^{4b}); 126.4 (2 C^{4a}); 128.5 [2 (C^{2a} and C^{6a})]; 129.4 (2 C^{1b}), 129.8 [2 (C^{3b} and C^{5b})]; 130.1 [2 (C^{3a} and C^{5a})]; 132.7 (2 C^{1a}); 149.7 (2 C^5) and 154.7 (2 C^3).

*2.2.3. Preparation of trans-[Pd{[1-{MeO-$(CH_2)_2$-}-3,5-Ph_2-(C_3HN_2)]$_2$$(OAc)_2$] (**3**) and [Pd{$\kappa^2$,C,N)[1-{MeO-$(CH_2)_2$}-3-$(C_6H_4)$,5-Ph-$(C_3HN_2)$]}($\mu$-OAc)]$_2$ (**4**).*

76 mg (3.4×10^{-4} mol) of $Pd(OAc)_2$ was dissolved in 15 mL of toluene at 298 K, then ligand **1** (95 mg, 3.4×10^{-4} mol) was added. The reaction flask was protected from the light with aluminium foil and refluxed for 12 h. After this period the black solution was concentrated to dryness on a rotary evaporator and left overnight in a dessicator. The residue was then treated with CH_2Cl_2 (15 mL) and passed through a Celite pad to remove the metallic palladium. This was repeated until colourless mother liquors were obtained. The solution was dried with Na_2SO_4 and the filtrate was concentrated to dryness on a rotary evaporator. The brownish solid formed consisted on a mixture of compounds **3** and **4** in a molar ratio (**3**:**4** = 1:10). These products were isolated by SiO_2 column chromatography. Elution with $CHCl_3$ produced a pale yellow band that gave after concentration 11 mg of the

minor product (**3**). Afterwards the use of a $CHCl_3$: MeOH (100:0.4) mixture released another band that was collected and concentrated to dryness on a rotary evaporator. The yellowish solid formed (**4**) was collected, air-dried and dried in vacuum for 2 days (yield: 112 mg). Characterization data for **3**: Anal. (%) Calc. for $C_{40}H_{42}N_4O_6Pd$ (MW = 780.21): C, 61.59; H, 5.4; N, 7.17; Found: C, 61.4; H, 5.5; N, 7.0. MS (ESI^+): *m/z* = 721.2 {[M]-(OAc)}$^+$}. IR selected data: 3067-3023 [ν(C-H)] and 2984-2940 [ν(C-H)], 1566 [ν_{as}(COO)] and 1386 [ν_s (COO)] cm^{-1}. UV-vis. data: ($c = 1.43 \times 10^{-5}$ M in CH_2Cl_2): λ (ε) = 234 (4.1×10^5) broad band. R_f (in $CHCl_3$) = 0.21. ^{1}H NMR data: δ = 1.83 [br.s, 6H, 2 (OAc)]; 3.15 (s, 6H, 2 OMe); 3.95 [t, $^3J_{H,H}$ = 7.1, 4H, 2 (–CH_2–^{d})]; 4.75 [t, $^3J_{H,H}$ = 7.1, 4H, 2 (–CH_2–^{c})]; 6.40 (s, 2H, 2 H^4); 7.37-7.58 [m, 16H, 2(H^{3a}, H^{4a}, H^{5a}, H^{2b}, H^{3b}, H^{4b}, H^{5b} and H^{6b})] and 8.16 [d, $^3J_{H,H}$ = 7.6, 4H, 2 (H^{2a} and H^{6a})]. $^{13}C\{^1H\}$ NMR data: 23.3 [2 Me(OAc)]; 50.2 (2 C^d); 58.4 (2 OMe); 70.1 (2 C^c); 108.7 (2 C^4); 125.7 [2 (C^{2b} and C^{6b})]; 126.1 (2 C^{4b}); 126.4 (2 C^{4a}); 128.6 [2 (C^{2a} and C^{6a})]; 129.5 [2 (C^{3b} and C^{5b})]; 130.0 [2 (C^{3a} and C^{5a})]; 130.4 (2 C^{1b}); 132.6 (2 C^{1a}); 149.5 (2 C^5);154.3 (2 C^3) and 180.9 [2 >COO (OAc)]. For **4**: Anal. (%) Calc. for $C_{40}H_{40}N_4O_6Pd_2$ (MW = 886.1): C, 54.25; H, 4.55; N, 6.32; Found: C, 54.1; H, 4.5; N, 6.0. MS (ESI^+): *m/z* = 425.06 {[M]-2(OAc) + 2(CH_3CN)}$^{2+}$/2. IR selected data: 3060-3018 [ν(C-H)] and 2984-2940 [ν(C-H)], 1560 [ν_{as}(COO)] and 1413 [ν_s(COO)] cm^{-1}. UV-vis. data: ($c = 1.91 \times 10^{-5}$ M in CH_2Cl_2): λ (ε) = 223 (3.2×10^5), 247 (2.5×10^5) and 341(broad, ≈ 1.9×10^3). R_f (in $CHCl_3$) = 0.14. ^{1}H NMR data: δ = 2.01 [br. s, 6H, 2 (OAc)]; 3.17 [s, 6H, 2 (OMe)]; 3.30-3.40 [(br. m, 4H, 2 (–CH_2–^{d})]; 3.67 [m, 2 H, 2 (one of the two protons of the –CH_2–^{c} unit)]; 3.93 [m, 2 H, 2 (the other proton of the –CH_2–^{c} unit)]; 6.04 [s, 2H, 2 (H^4)]; 6.74 [m, 2H, 2 (H^{3a})]; 6.81 [m, 2H, 2 (H^{4a})]; 7.31-7.80 [m, 10H, 2 (H^{5a},

H^{6a}, H^{3b}, H^{4b} and H^{5b})] and 8.51 [br., 4H, 2 (H^{2b} and H^{6b})]. $^{13}C\{^1H\}$ NMR data: 23.9 [2 Me(OAc)]; 49.7 (2 C^d); 58.2 (2 OMe); 70.6 (2 C^c); 109.3 (2 C^4); 125.5 [2 (C^{2b} and C^{6b})]; 125.9 (2 C^{4b}); 126.3 (2 C^{4a}); 127.6 (2 C^{5a}); 128.3 (2 C^{6a}); 129.0 [2 (C^{3b} and C^{5b})]; 129.7 (2 C^{3a}); 130.2 (2 C^{1b}); 132.3 (2 C^{1a}); 148.9 (2 C^{2a}), 150.6 (2 C^5); 153.9 (2 C^3) and 178.9 [2 >COO (OAc)].

*2.2.4. Preparation of [Pd{κ²,C,N)[1-{MeO-(CH₂)₂}-3-(C₆H₄),5-Ph-(C₃HN₂)]}(μ-Cl)]₂ (**5**).*

Compound [Pd{κ^2,*C*,*N*)[1-{MeO-$(CH_2)_2$}-3-(C_6H_4),5-Ph-(C_3HN_2)]}(μ-OAc)]$_2$ (**4**) (40 mg, 4.37×10^{-5} mol) was suspended in acetone (20 mL), then LiCl (5 mg, 1.1×10^{-4} mol) was added. The resulting mixture was stirred overnight at 298 K. The solid formed was collected by filtration and dried in vacuum for 2 days. [Yield: 32 mg, (81%)]. Characterization data: Anal. (%) Calc. for $C_{36}H_{34}Cl_2N_4O_2Pd_2$ (MW = 838.43): C, 51.7; H, 4.09; N, 6.68; Found: C, 51.6; H, 4.2; N, 6.8. MS (ESI^+): *m/z* = 383.761 $\{[M]\text{-}2Cl\}^{2+}/2$. IR selected data: 3055-3022 [ν(C–H)] and 2988-2924 [ν(C–H)]. UV-vis. data: ($c = 1.91 \times 10^{-5}$ M in CH_2Cl_2): λ (ε) = 240 (br. 2.5×10^5) and 338 ($\approx 3.6 \times 10^3$). ^{1}H-NMR data (in DMSO-d_6): δ = 3.22 [s, 6H, 2 (OMe)]; 3.30 [br. m, 2H, {one of the protons of the ($–CH_2–^d$) unit}], 4.03 [m, 2 H, 2 {one of the protons of the ($–CH_2–^c$) moiety]; the signals due the remaining protons the ($–CH_2–$)$^{c \text{ and } d}$ moieties were masked by the broad signal (at δ = 3.50 ppm) of the residual water present in the DMSO-d_6, their chemical shifts [ca. 3.45 ($–CH_2–^d$) and 3.85 for that of the $–CH_2–^c$ unit] were obtained from the HSQC experiment; 6.07 [s, 2H, 2 (H^4)]; 6.74 [m, 2H, 2 (H^{3a})]; 6.81 [m, 2H, 2 (H^{4a})] and 7.18-8.10 [br.m, 14H, 2 (H^{5a}, H^{6a}, H^{2b}, H^{3b}, H^{4b}, H^{5b} and H^{6b})]. $^{13}C\{^1H\}$ NMR data (in DMSO-d_6): 50.1 (2 C^d); 58.0 (2 OMe); 70.3 (2 C^c); 109.1 (2 C^4); 125.0 [2 (C^{2b} and C^{6b})]; 125.7 (2 C^{4b}); 126.0 (2 C^{4a}); 127.9 (2

C^{5a}); 128.4 (2 C^{6a}); 128.9 [2 (C^{3b} and C^{5b})]; 129.6 (2 C^{3a}); 130.4 (2 C^{1b}); 131.8 (2 C^{1a}); 151.2 (2 C^{5}); 152.0 (2 C^{2a}) and 153.7 (2 C^{3})].

*2.2.5. Preparation of [Pd{κ²,C,N)[1-{MeO-$(CH_2)_2$-}-3-(C_6H_4),5-Ph-(C_3HN_2)]}(X)(PPh_3)] {X = OAc (**6**) or Cl (**7**)}.*

To a mixture containing 3.8×10^{-5} mol of the corresponding dimeric complex **4** (35 mg) {or **5** (34 mg)} and 20 mL of CH_2Cl_2, PPh_3 (20 mg, 7.6×10^{-5} mol) was added. The resulting mixture was kept under stirring for 20 min and then filtered. The pale yellowish filtrate was concentrated to dryness on a rotary evaporator and the solid formed was collected, air-dried and recrystallized in a CH_2Cl_2:n-hexane (1:1) mixture. [Yields: 38 mg (70 %) and 40 mg (77%) for **6** and **7**, respectively]. Characterization data for **6**: Anal. Calc for $C_{38}H_{35}N_2O_3PPd$ (MW= 705.9): C, 64.73; H, 5.00; N, 3.97%; Found: C, 64.6; H, 5.1 and N, 4.0; MS (ESI^+): *m/z* = 645.14{[M] – (OAc)}$^+$. IR selected data: 3050-3018 [ν(C-H)] and 2985-2925 [ν(C-H)]; 1590 [ν_{as}(COO)] and 1381 [ν_s(COO)] and 1094 (PPh_3, X-sensitive), cm^{-1}. UV-vis. (*c* = 1.42×10^{-5} M in CH_2Cl_2): λ (ε) = 229 (4.0×10^{-5}), 246 (3.0×10^{-4}) and 348 (3.5×10^{-3}). R_f (in $CHCl_3$) = 0.20. ^{1}H NMR data: δ =1.85 (s, 3H, OAc); 3.12 (s, 3H, OMe); 3.67 (t, $^3J_{H,H}$ = 7.3, 2H, –CH_2–^{d}); 4.37 (t, 2H, $^3J_{H,H}$ = 7.0, –CH_2–^{c}); 6.07 (s, 1H, H^4); 6.44 (br. 1H, H^{3a}); 6.96 (m, 1H, H^{4a}); 7.28-7.96 [br.m, 22H, (H^{5a}, H^{6a}, H^{2b}-H^{6b}, and aromatic protons of the PPh_3 ligand)]. $^{13}C\{^1H\}$ NMR data: 23.3 [Me(OAc)], 51.4 (C^d); 58.5 (OMe); 70.2 (C^c); 110.2 (C^4); 125.3 (C^{4b}); 126.5 (C^{4a}); 127.4 (C^{2b} and C^{6b}); 128.0 (C^{6a}); 128.4 (C^{5a}); 129.1 (C^{3b} and C^{5b}); 129.5 (C^{3a}); 129.8 (C^{1b}); 132.5 (C^{1a}); 150.2 (C^5); 151.2 (C^{2a}); 154.7 (C^3), 180.4 [>COO (OAc)] and four additional doublets due to four types of carbon-13 nuclei (ipso, ortho, meta and para) of the PPh_3 ligand. $^{31}P\{^1H\}$ NMR data: δ = 40.3. For

7: Anal. Calc. for $C_{36}H_{32}ClN_2OPPd$ (MW = 680.1): C, 63.45; H, 4.73; N, 4.11%; Found: C, 63.2; H, 4.8; N, 4.1; MS (ESI^+): *m/z* = 645.14 {[M] - Cl}$^+$. IR selected data: 3049-3018 [ν(C–H)] and 2982-2925 [ν(C–H)] and 1094 (X-sensitive of the phosphine ligand) cm^{-1}. UV-vis. data: ($c = 1.8 \times 10^{-5}$ M in CH_2Cl_2): λ (ε) = 242(2.0×10^{-5}); and 341(3.9×10^{-3}). ^1H NMR data: δ = 3.11 (s, 3H, OMe); 3.82 (br., 2H, -CH_2-^{d}); 4.50 (br., 2H, –CH_2-^{c}); 6.35 (s, 1H, H^4); 6.58 (m, 1H, H^{4a}); 6.84 (m, 1H, H^{3a}) and 7.30-8.10 [br.m, 22H, (H^{5a}, H^{6a}, H^{2b}-H^{6b} and aromatic protons of the PPh_3 ligand)]. $^{13}C\{^1H\}$ NMR data: 51.2 (C^d); 58.4 (OMe); 70.1 (C^c); 110.1 (C^4); 125.4 (C^{4b}); 126.3 (C^{4a}); 127.3 (C^{2b} and C^{6b}); 127.8 (C^{6a}); 128.6 (C^{5a}); 129.0 [(C^{3b} and C^{5b}); the $\{^1H$-$^{13}C\}$-HSQC spectra showed that the signal due to C^{3a} was overlapped by this one)]; 129.6 (C^{1b}); 132.8 (C^{1a}); 149.9 (C^5); 152.6 (C^{2a}); 153.8 (C^3), and four additional doublets due to the aromatic ^{13}C nuclei of the PPh_3. $^{31}P\{^1H\}$ NMR data: δ = 40.1.

2.3. Crystallography

A plaque-like specimen of compound **2** (dimensions in Table 1), was used for the X-ray crystallographic analysis. The X-ray intensity data were measured and integration of the data using a triclinic unit cell yielded a total of 11383 reflections to a maximum θ angle of 28.34° (0.75 Å resolution), of which 4182 were independent (average redundancy 2.722, completeness = 99.7%, R_{int} = 2.43 %, R_{sig} = 2.81 %) and 3912 (93.54 %) were greater than $2\sigma(F^2)$. The final cell constants (Table 1) are based upon the refinement of the XYZ-centroids of reflections above 20 σ(I).

< Table 1, here >

The structure was solved and refined using the Bruker SHELXTL Software Package, [24] using the space group P-1, with $Z = 1$ for the formula unit, $C_{36}H_{36}Cl_2N_4O_2Pd$. The final anisotropic full-matrix least-squares refinement on F^2 with 205 variables converged at R_1 = 3.10%, for the observed data and wR_2 = 8.03% for all data. The goodness-of-fit was 1.055. The largest peak in the final difference electron density synthesis was 0.562 $e^-/Å^3$ and the largest hole was -0.269 $e^-/Å^3$ with an RMS deviation of 0.065 $e^-/Å^3$. Final details concerning the resolution and refinement of the crystal structure are presented in Table 1.

CCDC 951054 contains the crystallographic information file for compound **2**.

2.4. Biological studies.

2.4.1. Cell culture.

Breast cancer MCF7 and MDA-MB231 cells (from *European Collection of Cell Cultures, ECACC*) were grown as a monolayer culture in minimum essential medium (DMEM with L-glutamine, without glucose and without sodium pyruvate) in the presence of 10 % heat-inactivated fetal calf serum, 10 mM of D-glucose and 0.1% streptomycin/penicillin in standard culture conditions.

2.4.2. Cell viability assays.

For these studies, compounds were dissolved in 100% DMSO at 50 mM as stock solution; then, serial dilutions have been done in DMSO (1:1) (in this way DMSO concentration in cell media was always the same); finally, 1:500 dilutions of the serial dilutions of compounds on cell media were done. The assay was performed as described by

Givens et al. [25]. In brief, MDA-MB231 and MCF7 cells were plated at 5000 cells/well or 10000 cells/well respectively, in 100 µL media in tissue culture 96 well plates (Cultek). After 24 h, media was replaced by 100 µL/well of serial dilution of drugs. Each point concentration was run in triplicate. Reagent blanks, containing media plus colorimetric reagent without cells were run on each plate. Blank values were subtracted from test values and were routinely 5-10 % of uninhibited control values. Plates were incubated for 72 h. Hexosamidase activity was measured according to the following protocol: the media containing the cells was removed and cells were washed once with PBS 60 µL of substrate solution (p-nitrophenol-N-acetyl-β-D-glucosamide 7.5 mM [Sigma N-9376], sodium citrate 0.1 M, pH = 5.0, 0.25 % Triton X-100) was added to each well and incubated at 37 °C for 1-2 hours; after this incubation time, a bright yellow color appeared; then, plates could be developed by adding 90 µL of developer solution (Glycine 50 mM, pH = 10.4; EDTA 5 mM), and absorbance was recorded at 410 nm.

3. Results and discussion

3.1. Synthesis.

Compound 1-{MeO-$(CH_2)_2$-}-3,5-Ph_2-(C_3HN_2) (**1**) was obtained in a fairly good yield (88%) by alkylation of 3,5-diphenylpyrazole with a three-fold excess of 1-chloro 2-methoxyethane [Scheme 1, step i)] [26].

< Scheme 1, here >

Treatment of 1-{MeO-$(CH_2)_2$-}-3,5-Ph_2-(C_3HN_2) (**1**) with $Na_2[PdCl_4]$ (in a 1:1 or 2:1 molar ratio) in methanol at 298 K produced a yellow solid that was identified as [Pd{[1-{MeO-$(CH_2)_2$-}-3,5-Ph_2-(C_3HN_2)]}$_2Cl_2$] (**2**) [Scheme 2, step ii)]. Its X- ray crystal structure (see below) confirmed that it was the *trans* isomer.

When ligand **1** was reacted with $Pd(OAc)_2$ in toluene under reflux for 12 h a black solution was obtained. The subsequent chromatography on silica gel gave two products **3** and **4** [Scheme 1, step iii)] in a molar ratio **4**:**3** =10:1. The minor component (**3**) was identified as *trans*-[Pd{[1-{MeO-$(CH_2)_2$-}-3,5-Ph_2-(C_3HN_2)]}$_2(OAc)_2$] and characterization data of the major product (**4**) were consistent with those expected for the di-μ-acetato-bridged cyclopalladated complex [Pd{κ^2,*C*,*N*)[1-{MeO-$(CH_2)_2$-}-3-(C_6H_4),5-Ph-(C_3HN_2)]}(μ-OAc)]$_2$ that arises form the activation of the σ(C-H) bond of the phenyl ring in position 3 of the pyrazole.

The reaction of **4** with an excess of LiCl in acetone at 298 K gave the dinuclear compound [Pd{κ^2,*C*,*N*)[1-{MeO-$(CH_2)_2$-}-3-(C_6H_4),5-Ph-(C_3HN_2)]}(μ-Cl)]$_2$ (**5**) as a pale brownish solid [Scheme 1, step iv)]. Further treatment of di-μ-ligand bridged cyclopalladated products (**4** or **5**) with PPh_3 (in a 1:2 molar ratio) in CH_2Cl_2 produced the splitting of the "Pd(μ-X)$_2$Pd" units and the formation of the monomeric derivatives [Pd{κ^2,*C*,*N*)[1-{MeO-$(CH_2)_2$-}-3-(C_6H_4),5-Ph-(C_3HN_2)]}(X)(PPh_3)] with X = OAc (**6**) or Cl (**7**) [Scheme 1, step v)] respectively.

3.2. Characterization.

The new ligand (**1**) and its palladium(II) derivatives (**2-7**) were characterized by elemental analyses, mass spectra and infrared spectroscopy. In all cases the elemental analyses were consistent with the proposed formulae.

The IR spectra of the complexes **3**, **4** and **6** showed the typical bands due to the symmetric and asymmetric stretchings of the $–COO^-$ unit [27] and the separation between them was consistent with the values reported for related Pd(II)-compounds containing OAc^- ligands acting as monodentate group (in **3** and **6**) or as a bridging ligand (in **4**) [27]. For compounds **6** and **7**, with the PPh_3 ligand, X-sensitive bands were also detected in their IR spectra.

Compound **2** was also characterized by X-ray difraction. Its molecular structure and the atom labelling scheme is presented in Figure 2. The crystal contains molecules of [Pd{[1-{MeO-$(CH_2)_2$-}-3,5-Ph_2-(C_3HN_2)]$_2Cl_2$] in which, the Pd(II) atom is bound to two nitrogen atoms of two units of **2** and two chlorido ligands. Bond lengths and angles around the palladium(II) are similar to those reported for related *trans*-[Pd$(L)_2Cl_2$] complexes (with L = N-substituted pyrazoles) [28-30].

< Figure 2, here >

The Pd(II) atom is located on a inversion centre and as a consequence of this: a) the two Cl^- ligands are in a *trans*- arrangement and b) the "$(CH_2)_2$OMe" pendant arms are on opposite sides of the coordination plane. In addition, "$PdCl_2$" moiety is nearly orthogonal to the heterocycle and the phenyl rings are not coplanar with the pyrazolyl ring (angles between their main planes = 64.4 and. 36.0°). As a consequence of these arrangements the distance between the Cl^- ligands and one of the protons of the "$–CH_2$-O" unit [2.787 Å] is

smaller than the sum or the van der Waals radii of these atoms [31]; thus suggesting an intramolecular C-H···Cl interaction [32].

In the crystal the molecules are assembled by C-H ··π interactions (Figure 3) involving: the centroids of the phenyl rings (Cg_1 and Cg_2) {defined by the sets of atoms [C1-C6] and [C10-C15], respectively} and one of the hydrogen atoms of the OMe unit (H18C) and the H5 atom, [distances Cg_1···· H18C = 3.440 Å and Cg··· H5 = 3.477 Å].

< Figure 3, here >

The new products were also characterized in solution by UV-vis. spectroscopy and NMR. The absorption spectra of the new compounds were registered in CH_2Cl_2 at 298K. The UV-vis spectra of the Pd(II) complexes showed a band in the range 320 nm < λ_3 < 360 nm {not present in the spectrum of the free ligand (**1**)} with extinction coefficients between 2.0×10^3 and 4.0×10^3 M^{-1} cm^{-1}. This band that has also been observed for related Pd(II) complexes with pyrazole ligands [11] is assigned to a metal-to-ligand charge transfer (MLCT) transition from the *4d* orbitals of the Pd(II), to a π orbital of the ligand. The remaining bands detected at lower wavelengths (220 nm < λ < 370 nm) are attributed to metal perturbed intraligand transitions (MPILT).

In the ^{1}H NMR spectra of the Pd(II) complexes (**2**-**7**), the chemical shifts of the OMe protons were very similar to that of the free ligand, thus suggesting that the oxygen of the methoxy group was not bound to the Pd(II) centre. NMR spectra of **3**, **4** and **7** showed the typical resonances due to the OAc^- ligand bound to the Pd(II) atom. The low-field region of these ^{1}H NMR spectra was complex and the assignment of the signals detected was

achieved with the aid of 2D NMR experiments [NOESY, COSY, {^{1}H-^{13}C}-HSQC and HMBC].

For the palladacycles (**4-7**): a) the signal due to H^{2a} proton was not observed in their ^{1}H-NMR spectra and b) the resonances of the H^{3a} and H^{4a} nuclei, appeared at higher fields than for the free ligand (**1**). Carbon-13 NMR and the 2D {^{1}H-^{13}C}-HMBC spectra showed a downfield shift of the signal due to the metallated carbon (C^{2a}). All these findings are consistent with previous NMR studies of cyclopalladated complexes [11a,14b,19b].

The ^{31}P{^{1}H}-NMR spectra of **6** and **7** showed a singlet at around 40 ppm. According to the bibliography [11], this is indicative of a *cis*-arrangement of the PPh_3 ligand and the metallated carbon, in good agreement with the *transphobia effect* [33].

3.3. Study of the antitumor activity of the free ligand and the complexes.

The cytotoxic activity of the new ligand (**1**) and the palladium(II) complexes (**2**, **4-7**) against two human breast cancer cell lines (MCF7 and MDA-MB231) was tested using *cisplatin* as positive control. The effects of these products on the growth of two cell lines were assessed after 72 h and the results are displayed in Figure 4. The IC_{50} values corresponding to the inhibition of cancer cell growth at 50% level are listed in Table 2. For comparison purposes the IC_{50} parameters for the free ligand **Ic** and the palladacycle [Pd{κ^3, *C,N,N'*)[1-{Me_2N-$(CH_2)_2$-}-3,5-Ph_2-(C_3HN_2)]$_2$Cl] (**V** in Figure 1) are also included [11b].

< Figure 4, here >

< Table 2, here >

< Figure 5, here >

The comparison of the in vitro cytotoxic activities of the free ligands (**Ic** and **1**) against the MCF7 and MDA-MB231 cell lines shows (Table 2 and Figure 4) that the presence of the NMe_2 group on the pendant arm of the two 3,5-diphenyl pyrazole: [1-{R'-$(CH_2)_2$-}-3,5-Ph_2-(C_3HN_2)] produces a greater cytotoxic effect than the OMe. This could be related to several factors such as their different lipophilicity and their proclivity to protonate in biological media [18,20].

Complex **2** did not show any significant effect on the MCF7 cell line. This result is similar to those obtained for compound: [Pd{κ^2, *N*,*N*'[1-{Me_2N-$(CH_2)_2$-}-3,5-Ph_2-(C_3HN_2)]Cl_2] (**IIc** shown in Fig. 1). Except for **6**, the remaining cyclopalladated complexes were more active in the MCF7 cell line than the free ligand (**1**) and compound **2**. Among all these palladacycles, the di-μ-acetato-bridged complex **4** was the most potent. Its effect was ca. 1.4 times greater than the palladacycle **V** (shown in Figure 1) with a $(C,N,N')^-$ pincer ligand [11b]. Unfortunately, none of these products exhibited IC_{50} values smaller than cisplatin.

More encouraging were the results obtained for MDA-MB231 cell line. Compound **2** exhibited a moderate activity and for the remaining products, the IC_{50} values [in the range: 9.1 μM (for **6**) - 14.4 μM (for **5**)] were a bit smaller, if significant, than that of **V** [IC_{50} = 16.2 ± 4.6 μM] [11b] and closer to that of cisplatin [IC_{50}= 6.5 ± 2.4 μM]. Thus, suggesting that the new Pd(II) compounds were more effective in the triple negative MDA-MB231 cancer cell line than in the MCF7 line.

4. Conclusions.

The study of the reactivity of the novel N-substituted pyrazole derivative: [1-{MeO-$(CH_2)_2$-}-3,5-Ph_2-(C_3HN_2)] (**1**) with $Na_2[PdCl_4]$ or $Pd(OAc)_2$ has allowed us to isolate and characterize a family of palladium(II) complexes (**2-7**). In two of them (**2** and **3**) the Pd(II) atom is bound to the heterocyclic nitrogen. The remaining four complexes (**4-7**) contain one (in **6** and **7**) ot two (in **4** and **5**) five-membered palladacycles formed by the binding of the same nitrogen and the metallation of the phenyl ring on position 3 of the pyrazole. These findings indicate that ligand **1** may adopt two binding modes [(N) or $(C,N)^-$] in front of the Pd(II) atom. However, no evidences of the formation of complexes containing **1** as a $(C,N,O)^-$ ligand were detected.

The comparison of the results obtained from *in vitro* studies of their cytotoxic activity against the MCF7 cell line and the MDA-MB231 {triple negative (ER, PR and no HER2 over expression)} breast cancer cell line showed that the free ligand (**1**) was less active than its analogue **Ic** (Figure 1) with the NMe_2 unit at the end of the pendant arm. We have also proved that compounds (**4-7**) exhibit greater cytotoxic activity than the free ligand (**1**) and complex **2** (with two units of **1** acting as a monodentate N-donor ligand). The new cyclopalladated complexes (**4-7**) have an outstanding antiproliferative effect in the MDA-MB231 cell line. For all of them the IC_{50} values (Table 2) are a bit smaller than that reported for palladacycle **V** previously reported [11b]; but closer to that of cisplatin (under identical conditions). These results are especially outstanding because they open up new possibilities in the design of Pd(II)-pyrazole based complexes as promising alternatives to cisplatin and related Pt(II) drugs.

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Appendix A. Supplementary material

CCDC 951054 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the *Cambridge Crystallographic Data Centre* via: www. ccdc.cam.ac.uk/data_request/cif.

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Captions for Scheme 1 and Figures 1-5

Scheme 1. Key reagents and conditions: i) KOH, in DMSO, followed by treatment with 1-chloro 2-methoxyethane, 298 K; ii) $Na_2[PdCl_4]$ in MeOH at 298 K; iii) $Pd(OAc)_2$ in refluxing toluene, (12h), followed by SiO_2 column chromatography; iv) LiCl in acetone, at 298 K; v) PPh_3 in CH_2Cl_2 at 298 K

Figure 1. General formulae of three N-substituted pyrazoles (**I**) and their Pd(II) and Pt(II) complexes recently reported [11b]. {In compounds **I-III**, the R group represents H (**a**), Me (**b**) or Ph (**c**)}.

Figure 2. ORTEP plot of the molecular structure of *trans*-[Pd{[1-{MeO-$(CH_2)_2$-}-3,5-Ph_2-(C_3HN_2)]$_2$$Cl_2$] (**2**). Selected bond lengths (in Å) and angles (in deg.): Pd1-N1, 2.020(19); Pd1-Cl1, 2.3044(5), N1-C9, 1.339(2); N1-N2, 1.362(2); N2-C7, 1.535(4); N2-C16, 1.460(3); C9-C10, 1.472(3); C16-C17, 1.500(3); C17-O1, 1.404(3); O1-C18, 1.387(4); N1-Pd-Cl, 87.17(5); N1-N2-C16, 120.98(16); N1-N2-C7,110.24(16); N2-C7-C6,124.11(19); N2-C7-C8, 107.02(17); C7-C8-C9, 106.76(18) and N1-C9-C10, 124.11(17).

Figure 3. Schematic view of assembly of vicinal molecules of *trans*-[Pd{[1-{MeO-$(CH_2)_2$-}-3,5-Ph_2-(C_3HN_2)]$_2$$Cl_2$] (**2**) by C-H$\cdots\pi$ interactions. Red balls represent the centroids of the rings defined by the sets of atoms [C1-C6] and [C10-C15] (Cg_1 and Cg_2, respectively).

Figure 4. Inhibition of cell growth proliferation in MCF7 and MDA-MB231 human breast cancer cell lines, after 72 h of exposure to the free ligand **1** and compounds **2**, **4**-**7**.

Figure 5. Comparative plot of the IC_{50} values (in μM) of the free ligands [1-{R′-$(CH_2)_2$-}-3,5-Ph_2-(C_3HN_2)] {R′ = NMe_2 (**Ic**) or MeO (**1**)}, the Pd(II) complex *trans*-[Pd{[1-{MeO-$(CH_2)_2$-}-3,5-Ph_2-(C_3HN_2)]$_2Cl_2$] (**2**), the cyclopalladated compounds (**4**-**7** and **V**) and *cisplatin* in front of the MCF7 and MDA-MB231 cancer cell lines.

Table 1. Crystal data and structure refinement for *trans*-[Pd{[1-{MeO-$(CH_2)_2$-]-3,5-Ph_2-(C_3HN_2)}$_2$$Cl_2$] (**2**).

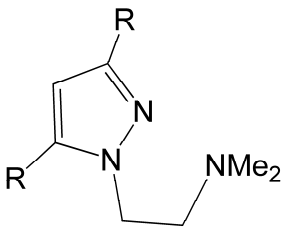
Crystal dimmensions / mm × mm × mm	0.2 × 0.08 × 0.08
Empirical formula	$C_{36}H_{36}Cl_2N_4O_2Pd$
Formula weight	733.99
T / K	293(2)
λ / Å	0.71073
Crystal system	Triclinic
Space group	$P\bar{1}$
a / Å	9.1567(5)
b / Å	9.5825(5)
c / Å	10.6315(5)
α / º	108.171(2)
β / º	104.895(2)
γ / º	95.986(2)
Volume / $Å^3$	839.09(7)
Z	1
Calculated density / $Mg×m^{-3}$	1.453
μ / mm^{-1}	0.750
F(000)	376
Θ range for data collection / º	2.12 to 28.34
Limiting indices	$-12 \le h \le 8$, $-12 \le k \le 12$, $-13 \le l \le 14$

Reflections collected / unique	11383 / 4182 [R(int) = 0.0243]
Completeness to Θ = 28.34°	99.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. Transmission	0.7457 and 0.6541
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4182 / 0 / 205
Goodness-of-fit on F^2	1.055
Final R indices [$I > 2\sigma(I)$]	R_1 = 0.0310, wR_2 = 0.0763
R indices (all data)	R_1 = 0.0349, wR_2 = 0.0803
Largest diff. peak and hole/ e $Å^{-3}$	0.562 and -0.269

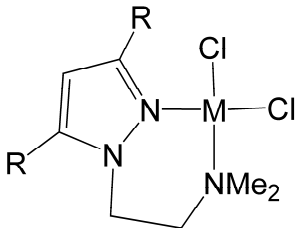
Table 2. Cytotoxic activities (IC_{50} values) on MCF7 and MDA-MB231 cancer cell lines for ligands 1-[R'-$(CH_2)_2$-]-3,5-Ph_2-(C_3HN_2) with R' = NMe_2 (**Ic**) or OMe (**1**), the palladium(II) complex (**2**), the cyclometallated products (**4-7** and **V**) and *cisplatin* under identical experimental conditions are also included.

			IC_{50} (μM) for the cell lines[a]		
Compound	R'	Mode of binding	MCF7	MDA-MB231	Reference
Free ligands					
Ic	NMe_2	——	52 ± 10	64 ± 24	[11b]
1	OMe	——	100	100	This work
Palladium(II) complexes					
2	OMe	(N)	>100	75 ± nd	This work
4	OMe	$(C,N)^-$	28 ± 5	9.5 ± 2.1	This work
5	OMe	$(C,N)^-$	44 ± nd	14.4 ± 4	This work
6	OMe	$(C,N)^-$	> 100	9.1 ± nd	This work
7	OMe	$(C,N)^-$	67 ± nd	13 ± nd	This work
V	NMe_2	$(C,N,N')^-$	38.4 ± 16.5	16.2 ± 4.6	[11b]
Cisplatin	——	(N)	19 ± 4.5	6.5 ± 2.4	This work

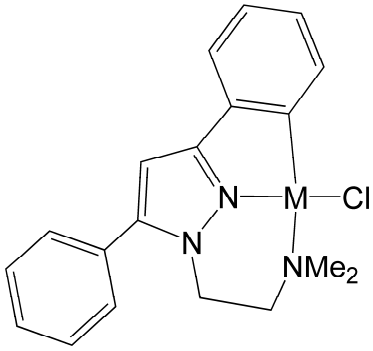
[a]Data are shown as the mean values obtained of two or more experiments performed in triplicate with the corresponding standard deviation.



I



M = Pd (**II**) or Pt (**III**)



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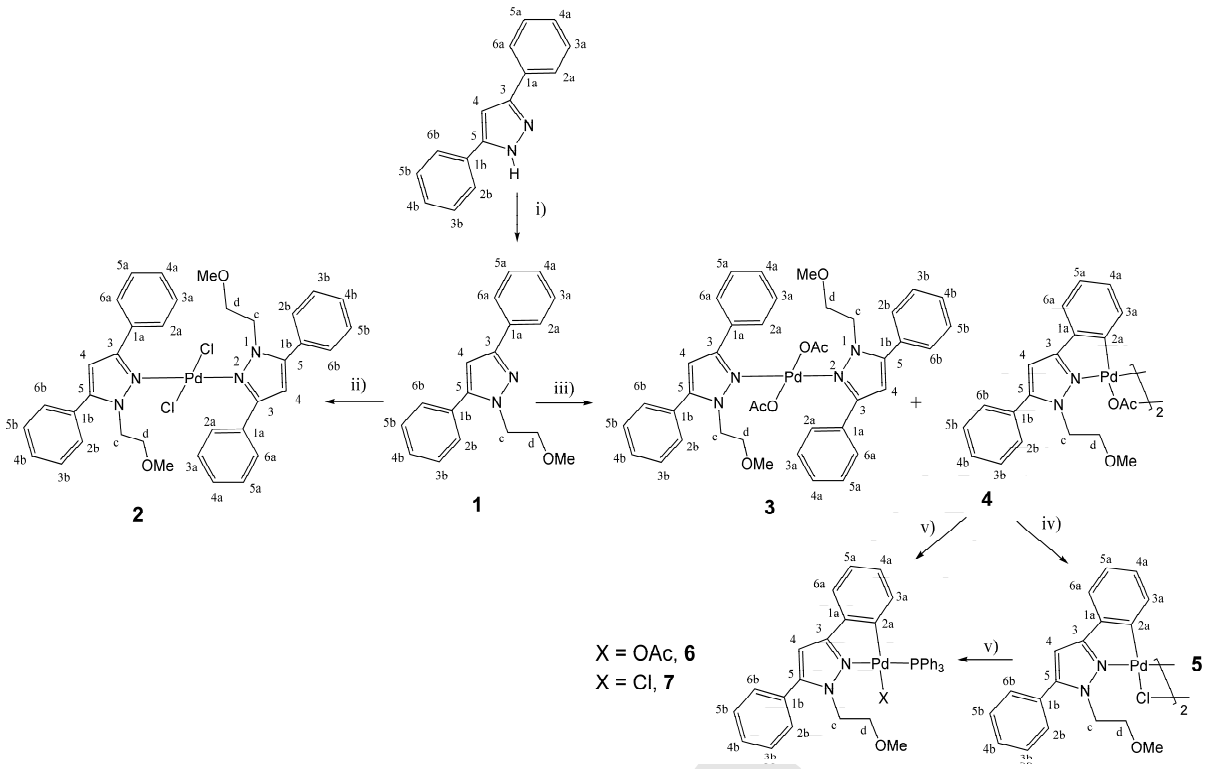

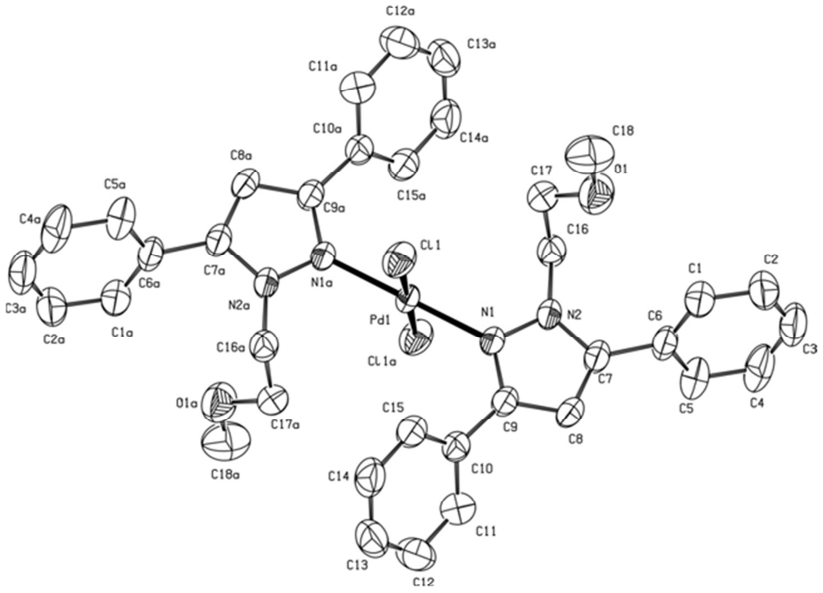

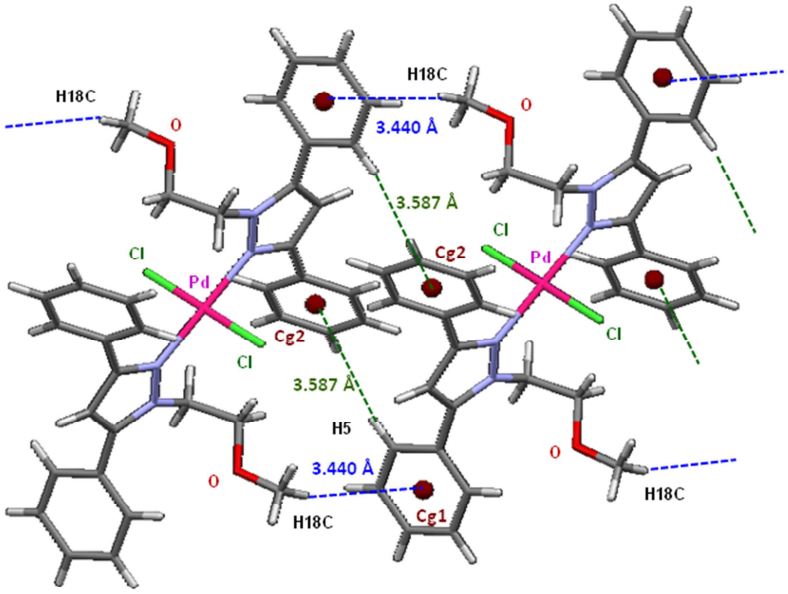

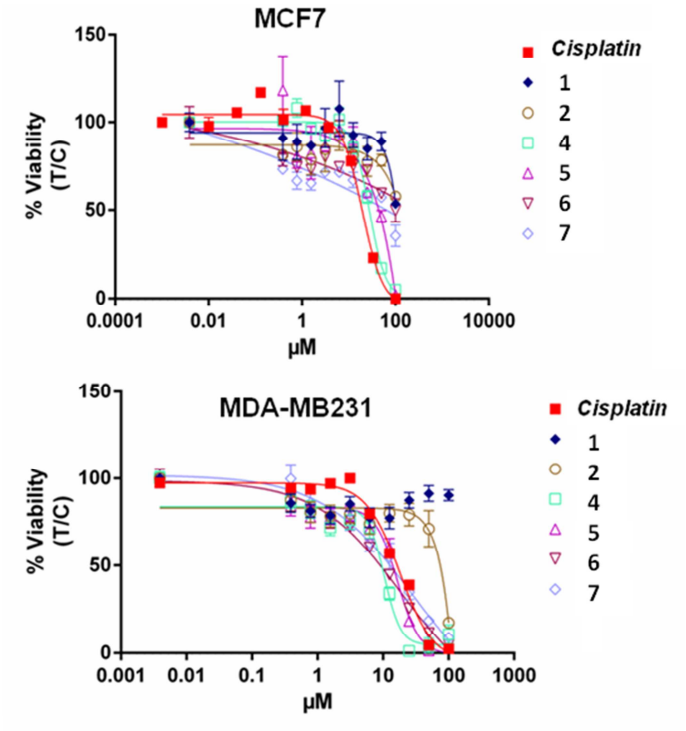

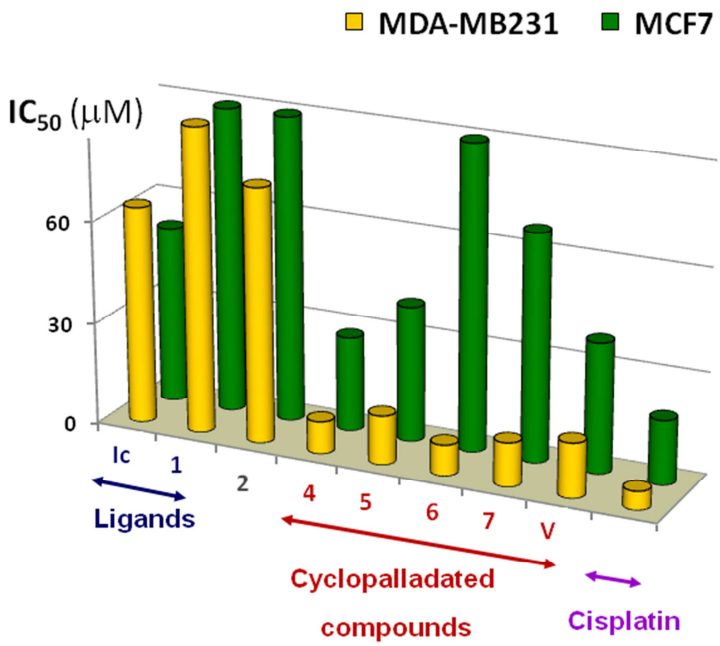

Highlights

♦ Mono and di Pd(II) complexes with N-{$(CH_2)_2$-R}-3,5-diphenylpyrazole (R = OMe) as ligands.

♦ The influence of the R groups (OMe vs NMe_2) on the reactivity, properties and activities.

♦ Pd(II) complexes are more potent than the free pyrazolyl ligand in MCF7 and MDA-MB231 breast cell lines

♦ Palladacycles with cytotoxic activity similar to cisplatin in the triple negative MDA-MB231 breast cancer cell lines.