XL Reunión del GEQO
Barcelona 2022

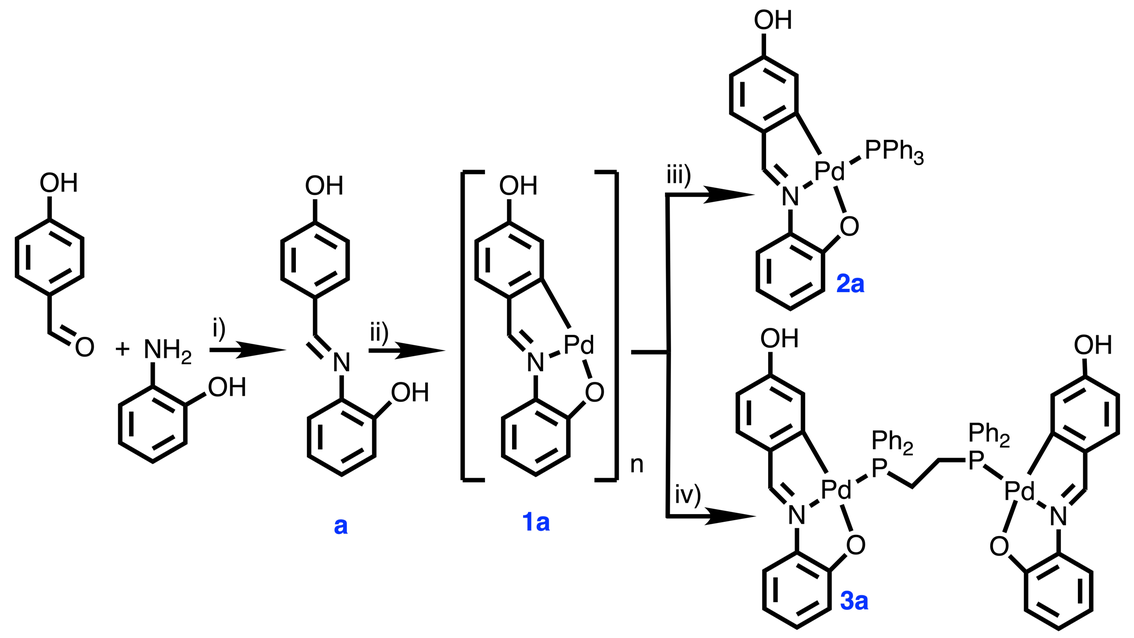
Synthesis and Biological Properties of Palladium(II) Cyclometallated compounds derived from (E)-2-((4-hydroxybenzylidene)amino)phenol

Joan Albert,[a] Basma Al Janabi,[a] Jaume Granell,[a] Mojdeh Sadat Hashemi,[a] Daniel Sainz,[a] M. Kaleem Khosa,[b] Laura Baldomà,[c] Josefa Badia,[c] Carme Calvis,[d] Ramon Messeguer,[d] Mercè Font-Bardia[e]

[a]Departament de Química Inorgànica i Orgànica, Facultat de Química, Universitat de Barcelona, Martí i Franquès 1, 08028 Barcelona, Spain.
[b]Department of Chemistry, Sir Syed Block, New Campus, Government College University, Jhang Road, Faisalabad, Pakistan.
[c]Departament de Bioquímica i Fisiologia, Facultat de Farmàcia, Av. Joan XXIII, 27-31, 08028-Barcelona, Spain.
[d]Biomed Division LEITAT Technological Center, Parc Científic, Edifici Hèlix, Baldiri Reixach 15-21, 08028 Barcelona, Spain.
[e]Unitat de Difracció de RX, Centre Científic i Tecnològic de la Universitat de Barcelona, Solé i Sabarís 1-3, 08028 Barcelona, Spain.

Palladium(II) compounds, containing chelating and good σ-donor or π-acceptor ligands and with steric hindrance around the palladium(II) centres, usually present good profiles as anticancer, antimicrobial and antiparasitic drugs [1, 2].

Therefore, compounds **a** were prepared by an adaptation of known procedures (**Scheme 1**) [3] and characterized by the usual techniques in the field, including the determination of the molecular structure of **2a** and **3a** by single crystal X-ray diffraction analysis (**Figure 1**). Furthermore, their cytotoxicity, antibacterial and antioxidant activities, and their ability to modify the electrophoretic mobility of the pBluescript SK+ plasmid DNA in agarose gel and to inhibit topoisomerases I and IIα were studied.



Scheme 1: i) EtOH, reflux, 4 h; ii) $Pd(OAc)_2$, acetic acid, 24 h, 60 °C; iii) PPh_3, acetone, 1 h, rt; iv) $PPh_2CH_2CH_2PPh_2$, acetone, 2 h, rt.

Most of compounds **a** were non-cytotoxic or poorly cytotoxic against the MDA-MB-231 and MCF-7 breast and HCT-117 colon human cancer cell lines. Nonetheless, **2a** was moderately cytotoxic against the MCF-7 breast (IC_{50} = 7.8 ± 1.7 µM) and HCT-116 colon (IC_{50} = 31 ± 5 µM) human cancer cell lines and presented a very low cytotoxicity towards normal human BJ cells (IC_{50} = 86 ± nd µM) (**Table 1**).

Compounds **a** showed moderate antibacterial activity against some Gram-positive (B. subtilis and S. aureus) and Gram-negative (E. coli) bacterial strains (**Table 2**), and moderate antioxidant activity in the DPPH free radical scavenging assay, having **3a** the best antioxidant activity of the series (IC_{50} = 0.08 mM) in relation to ascorbic acid (IC_{50} = 0.05 mM) (**Table 3**).

1a was the unique compound of the series that produced a change on the electrophoretic mobility of the pBluescript SK+ plasmid DNA in the agarose gel. This change followed the pattern of *cisplatin*, but started to take place at a concentration twenty times higher than with *cisplatin*. (**Figure 2**). In addition, compounds **a** were unable to inhibit topoisomerase I at a concentration of 100 µM, but **1a** – **3a** inhibited topoisomerase IIα at concentrations of 10, 50 and 25 µM (**Figure 3**), respectively.

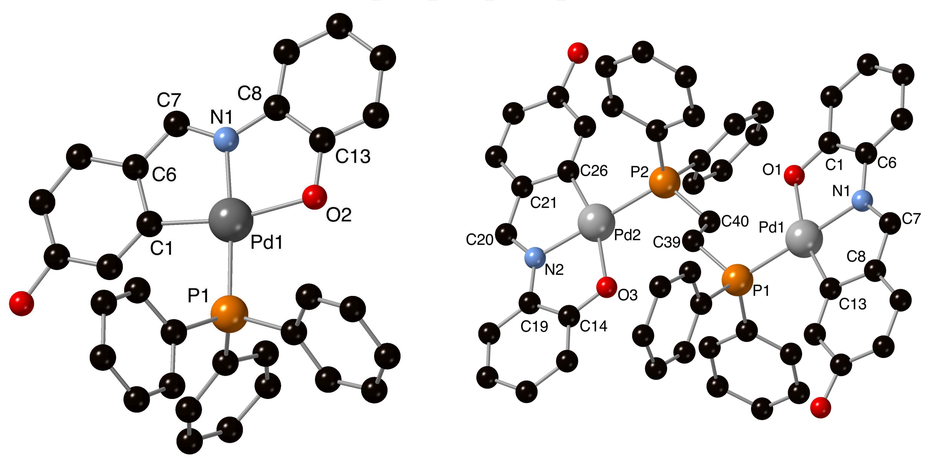


Figure 1: X-ray crystal molecular structure of **2a** (left) and **3a** (rigth)

	Trial	MDA-MB-231	MCF-7	HCT-116	BJ
a	1	> 100	64 ± nd	> 100	> 100
1a	1	> 100	> 100	> 100	> 100
2a	1	29 ± nd	7.8 ± 1.7	31 ± 5	86 ± nd
cisplatin	1	4.4 ± 0.5	3.6 ± 1.7	19 ± 2	3 ± nd
3a	2	> 100	> 100	22 ± 5	15 ± 6
cisplatin	2	13 ± 3	13 ± 2	3.6 ± 0.5	5.3 ± 0.7

Table 1: Cell viability [IC_{50} (µM)].

	B. subtilis[a]	S. aureus[a]	S. pyogenes[a]	E. coli[b]	P. aeruginosa[b]	S. typhi[b]
a	24 ± 1.5	26 ± 0.5	-	22 ± 0.5	-	20 ± 1
1a	22 ± 1	18 ± 1	-	19 ± 1	-	18 ± 1
2a	18 ± 0.5	20 ± 0.5	-	21 ± 1.5	-	-
3a	20 ± 0.5	16 ± 1.5	-	16 ± 1.25	-	-
cefixime	33 ± 1.5	31 ± 1	35 ± 1.5	29 ± 0.5	36 ± 1.25	31 ± 2

Table 2: Antibacterial activity [inhibition zone (mm). 5 - 10 = weak. 11 - 25 = moderate. 26 - 40 strong]. [a]Gram-positive. [b]Gram-negative.

	200[a]	100[a]	40[a]	20[a]	10[a]	5[a]	IC_{50}[a]	IC_{50}[b]
a	79 ± 1	67 ± 1	58 ± 1	39 ± 2	25 ± 1	16 ± 1	32 ± 1	0.15
1a	73 ± 1	60 ± 1	48 ± 1	36 ± 1	23 ±1	10 ± 1	50 ± 1	0.16
2a	66 ± 1	52 ± 2	41 ± 2	30 ± 2	20 ± 1	05 ± 1	87 ± 1	0.15
3a	81 ± 1	73 ± 2	64 ± 1	50 ± 1	33 ± 1	20 ± 1	82 ± 1	0.08
ascorbic acid	87 ± 0.5	84 ± 1	80 ± 0.25	70 ± 0.5	56 ± 1	35 ± 1	8.75 ± 0.5	0.05

Table 3: Antioxidant activity [% of DPPH free radical scavenging]. [a]µg/mL. [b]mM.

[1] Scattolin, T.; Voloshkin, V. A.; Visentin, F.; Nolan, S. P. *Cell Reports Physical Science* **2021**, *2(6)*, 100446.
[2] Garoufis, A.; Hadjikakou, S. K.; Hadjiliadis, N. *Coord. Chem. Rev*. **2009**, *253*, 1384 – 1397.
[3] Fernández, A.; Vázquez-García, D.; Fernández, J. J.; López-Torres, M.; Suárez, A.; Castro-Juiz, S.; Vila, J. M. *New. J. Chem*. **2002**, *26*, 398 – 404.

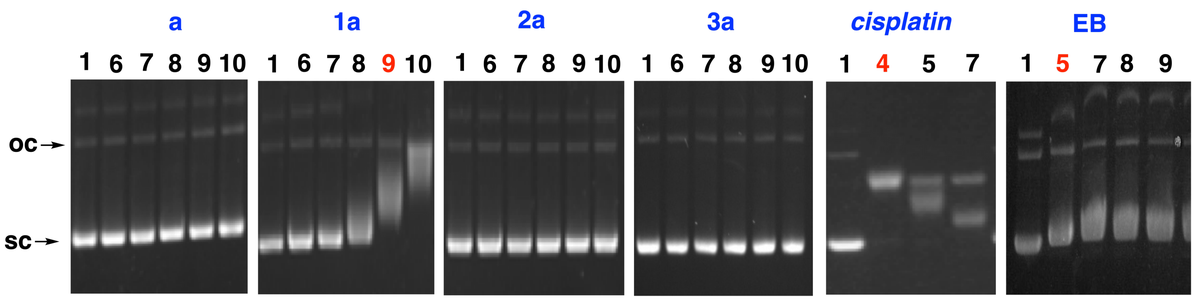


Figure 2: Electrophoretic mobility of pBluescript SK+ plasmid DNA. **1:** DNA (0.8 µg). **4**: 1 + 2.5 µM tested compound. **5**: 1 + 5 µM tested compound. **6**: 1 + 10 µM tested compound. **7**: 1 + 25 µM tested compound. **8**: 1 + 50 µM tested compound. **9**: 1 + 100 µM tested compound. **10**: 1 + 200 µM tested compound. sc = supercoiled closed circular DNA; oc = open circular DNA.

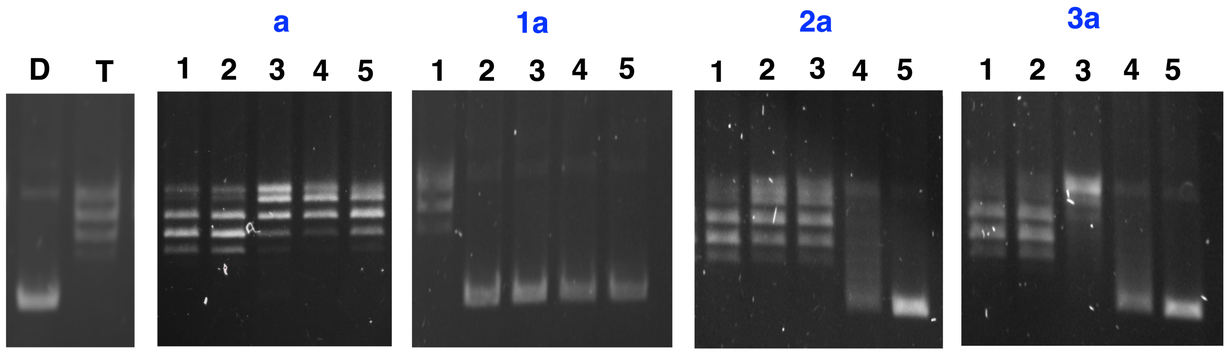


Figure 3: Topoisomerase IIα inhibition. **D**: supercoiled pBluescript DNA (0.3 µg). **T**: D + Topoisomerase IIα (4 units). **1**: T + 5 µM tested compound. **2**: T + 10 µM tested compound. **3**: T + 25 µM tested compound. **4**: T + 50 µM tested compound. **5**: T + 100 µM tested compound.

Acknowledgements: The authors are grateful to CCiTUB for the facilities given for the structural characterization of compounds **a**.