Pterocarpanquinones, aza-pterocarpanquinone and derivatives: Synthesis, antineoplasic activity on human malignant cell lines and antileishmanial activity on *Leishmania amazonensis*

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ABSTRACT

Pterocarpanquinones (**1a–e**) and the aza-pterocarpanquinone (**2**) were synthesized through palladium catalyzed oxyarylation and azaarylation of conjugate olefins, and showed antineoplasic effect on leukemic cell lines (K562 and HL-60) as well as colon cancer (HCT-8), gliobastoma (SF-295) and melanoma (MDA-MB435) cell lines. Some derivatives were prepared (**3–8**) and evaluated, allowing establishing the structural requirements for the antineoplasic activity in each series. Compound **1a** showed the best selectivity index in special for leukemic cells while **2** showed to be more bioselective for HCT-8, SF-295 and MDA-MB435 cells. Pterocarpanquinones **1a** and **1c–e**, as well as **8** were the most active on amastigote form of *Leishmania amazonensis* in culture. Compounds **1a**, **1c** and **8** showed the best selectivity index.

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1. Introduction

The pterocarpanquinones of type **1** comprise a new group of antineoplasic and antiparasite prototypes. The first compounds of this series, bearing oxygenated substituents at the E-ring (not shown), were designed and synthesized in our laboratory some years ago.[1] These compounds and other further synthesized derivatives (Fig. 1), showed antineoplasic activity in cultured breast cancer,[1,2] leukemia,[3,4] and lung cancer cell lines,[4] some among them presenting MDR phenotype. These pterocarpanquinones also showed antileishmanial and antimalarial activities on *Leishmania amazonensis* and *Plasmodium falciparum* in culture.[2] Moreover, the mechanism of the antineoplasic action of **1a** on chronic myeloid leukemia was further studied and led to significant apoptosis rate in cells from patients with chronic myeloid leukemia in treatment in the National Institute of Cancer (INCA) in Rio de Janeiro.[5,6] These cells exhibit multifactorial drug resistance phenotype such as *P*-glycoprotein, MRP1 and p53 overexpression.[7–11]

In addition, **1a** and some derivatives showed low toxicity for PBMC human blood cells[3,4] and murine lymphocytes (high selectivity index).[2,3]

The compound **1a** was also effective by oral route in controlling lesion development in mice infected with *L. amazonensis*, without altering serological markers of toxicity.[6,12]

In order to further investigate the structural features required for the antineoplasic and antileishmanial activities in **1a**, new compounds were prepared and evaluated on *L. amazonensis*, promyelocytic leukemia (HL-60) and chronic myeloid leukemia (K562) cell lines as well as colon cancer (HCT-8), gliobastoma (SF-295) and melanoma (MDA-MB435) cell lines (Fig. 1).

Since the cleavage of the C–O bound at the D-ring in compounds type **1** could be involved in the molecular mechanism of action (reductive bioactivation),[4,13–18] we decided to introduce electron withdrawing groups at the E-ring, such as in **1c–e**, that could stabilize the phenoxide leaving group and facilitate this pathway.

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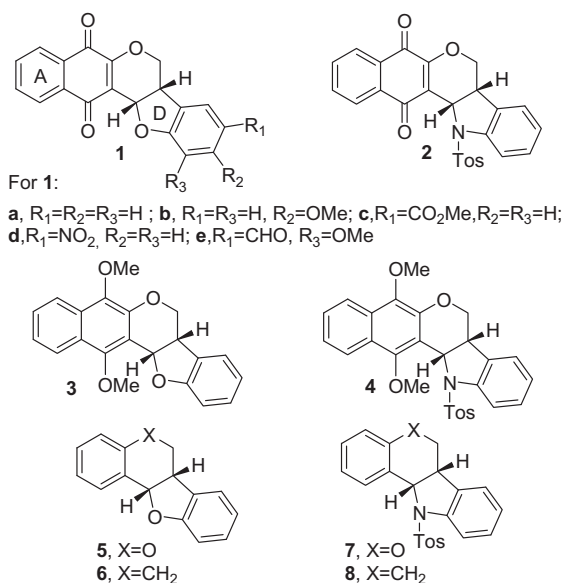E-mail address: prrcosta2011@gmail.com (P.R.R. Costa).

Figure 1. Compounds studied in this work.

Compound **1b**, bearing the electron-donor methoxy group, was prepared for comparative purposes. Excepted for **1b** and **1e**, these pterocarpanquinones were previously prepared in our laboratory.[4,19]

On the other hand, in aza-pterocarpanquinone **2** the oxygen at the D-ring was replaced by N–Ts group. Due to resonance stabilization provided by sulphone group, the C–N bond could also act as a reasonable leaving group, as the C–O bond in **1a**, and thus **2** would be expected to facilitate the reductive activation pathway.[20] Compounds **3** and **4** are the reduced form of **1a** and **2**, respectively, and could be eventually oxidized in the targeting cells, generating these quinones in situ (pro-drugs). Compounds **5** and **6**, and **7** and **8**, have similar molecular shapes when compared to **1a** and **2**, respectively, but do not have in their structure the quinone group and cannot participate in redox cycles, which are in general associated with the antineoplasic as well as the antiparasitic action
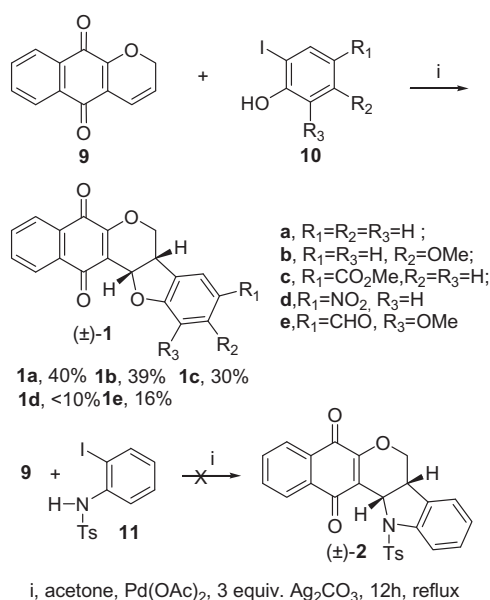
of quinones.[1–4,21–26] Compounds **2–8** are described for the first time in this work.

Once some pterocarpanquinones also presented antiparasitic activity,[2,12] we decided to evaluate the antileishmanial activity of these compounds on promastigote and amastigote forms of *L. amazonensis*. Chromenquinone **9**, the synthetic precursor of pterocarpanquinones **1** and aza-pterocarpanquinone **2**, was also evaluated as antineoplasic and antileishmanial.

2. Results and discussion

2.1. Chemistry

As previously described, **1a** was prepared by oxyarylation of chromenquinone **9** with *ortho*-iodophenol **10a** in the presence of 10 mol % of Pd(OAc)$_2$, in acetone under reflux, using Ag$_2$CO$_3$ as a base (Scheme 1).[4,19] Under the same conditions, oxyarylation of **9** with *ortho*-iodophenols **10b–e** led to pterocarpanquinones **1b–e** in moderate chemical yield. However, we could not prepare the aza-pterocarpanquinone **2** by the azaarylation reaction of chromenquinone **9** with *ortho*-iodo-N-tosyl aniline (**11**). Since the oxyarylation reaction under the conditions used herein (cationic mechanism) goes better for electron-rich olefins,[18,27–29] we decided to use **12**, obtained by reduction of **9** followed by O-methylation of the resulting dihydroquinone, as starting material for the aza-Heck reaction with **11**. Fortunately, azaarylation of olefin **12** with **11** (Scheme 2) led to the aza-Heck adduct **4** in good yield. Similarly, **3a–c** were obtained by oxyarylation of **12** with **10a,c,d**. The oxidation of **3a–c** and **4** using cerium ammonium nitrate (CAN) in acetonitrile and water[30] furnished the target pterocarpanquinones **1a–c** and aza-pterocarpanquinone **2**, respectively, in good yields. This pathway is an alternative to prepare **1a**, **1b** and **1c**.

Finally, **5** and **6** were, respectively, obtained through the oxyarylation of olefins **13a** and **13b** with **10a**, in moderate chemical yields (Scheme 3). When these olefins were allowed to react with **11**, the corresponding aza-Heck adducts **7** and **8** were prepared in good chemical yields (Scheme 3).

Scheme 1. Synthesis of pterocarpanquinones **1a–e**.
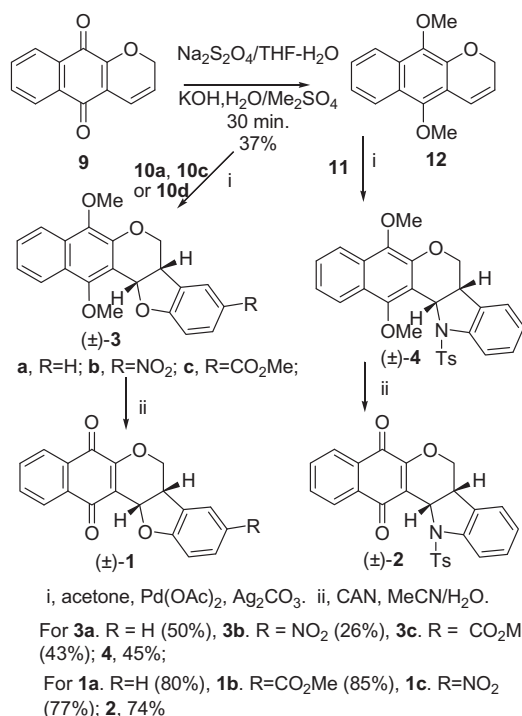
Scheme 2. Synthesis of compounds **1a**, **1c**, **1d**, **2**, **3** and **4**.
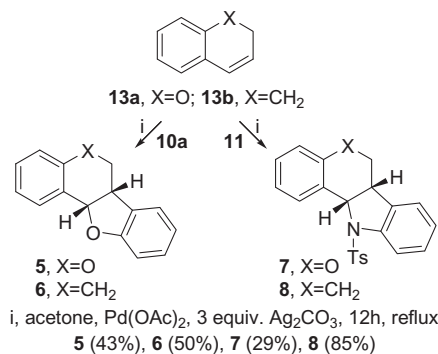
Scheme 3. Synthesis of compounds **5–8**.

Table 1
Antineoplasic activity of compounds **1–9** and doxorubicin (D*). IC_{50} values in µM

1–9	HL-60	K562	HCT-8	SF-295	MDA-MB435
1a	1.3	1.67	2.6	3.6	2.3
1b	3.5	3.3	10.4	17.7	11.4
1c	4.1	8.0	>13	>13	>13
1d	6.3	3.48	8.3	8.9	17.4
1e	3.0	13.5	6.0	7.4	10.7
3a	17.4	13.5	21.2	22.4	30.8
2	7.4	5.5	0.6	3.9	0.4
4	>51	46.7	>51	>51	>51
5	>112	>112	>112	>112	>112
6	>112	>112	>112	>112	>112
7	6.1	6.4	9.0	31.5	5.0
8	1.0	1.9	3.0	>62.5	0.5
9	0.5	ND	2.8	2.3	1.8
D*	0.04	1.67	0.02	ND	0.96

ND = Not determined.

2.2. Pharmacology

The antineoplasic activity of the compounds **1–8** was evaluated on five human cell lines: leukemia (HL-60 and K562), colon cancer (HCT-8), gliobastoma (SF-295) and melanoma (MDA-MB435). HL-60 cells, from a promyelocytic leukemia, present a low level of antioxidant defense and are sensible to oxidative stress[31] while K562 cells, from a chronic myeloid leukemia, contain high levels of intracellular glutathione (GSH) and are resistant to oxidative stress.[31] Cell viability greater than 90% was observed, even after treatment of these cells with H_2O_2 100 µM.[32] We did not find in the literature data about the phenotype of HCT-8, SF-295 and melanoma MDA-MB435 cell lines. In table 1 are presented the results obtained.

Pterocarpanquinone **1a** showed a potent antineoplasic activity on all cell lines studied, while the presence of the electron-releasing methoxy group in **1b** decreased the potency on HCT-8, SF-295 and MDA-MB435 cell lines but was still potent on the leukemia cell lines. The same trend was observed in **1c**, substituted by the electron-withdrawing carbomethoxy group. In **1d**, bearing the electron-withdrawing nitro group and in **1e**, substituted by one electron-withdrawing and one electron-releasing group, the activity decreases in all cell lines and this trend was more pronounced on MDA-MB435 cells. These data showed that HCT-8, SF-295 and MDA-MB435 were more sensitive to the substituent at the E-ring in compound type **1** than leukemic cells.

Pterocarpanquinone **1a** is the most promising compound of this series and, in addition, it is more easily synthesized than its derivatives. When the quinone group in **1a** is reduced, as in **3a**, the potency strongly decreased in all cell lines. These results show that **3a** is not oxidized to **1a** in those cells under the conditions of our assays and suggest that quinone group is involved in the molecular mechanism of action.

Aza-pterocarpanquinone **2** was less potent than pterocarpanquinone **1a** on leukemia cell lines (HL-60 and K562), equipotent in SF-295, but was more potent on HCT-8 and MDA-MB435 cell lines. Interestingly, these cells were the most resistant for pterocarpanquinones **1b–e**. We have previously demonstrated in the laboratory that **1a** could be activated by bioreduction, acting as alkylating agent and this mechanism could explain the citotoxic effect of this compound on cell lines resistant to oxidative stress, such as K562.[4] Compounds **5** and **6**, lacking the quinone moiety in their structure, were inactive, which corroborates this interpretation.
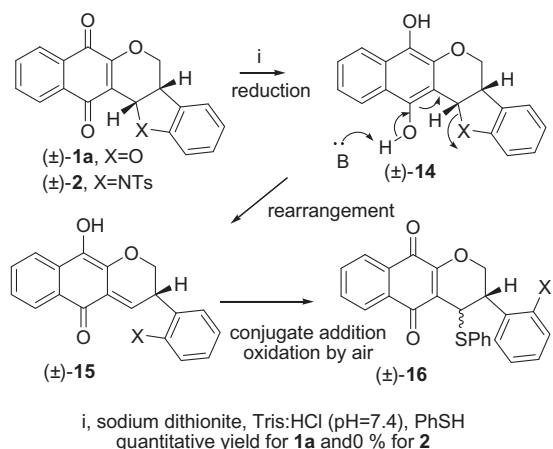
When the quinone group in **2** is reduced, as in **4**, the potency also strongly decreased in all cell lines. These results also show that **4** is not oxidized to **2** under the conditions of our assays and suggest that quinone group is also involved in the molecular mechanism of action of **2**. Surprisingly, however, except for SF-295, **7** and **8** showed potent antineoplasic effect on the other cell lines studied, suggesting that these compounds could act through a different mechanism.[33,34] We also decided to evaluate the antineoplasic effect of quinone **9** and found that this compound was potently active on the cell lines studied. Doxorubicin was used as a positive control. LQB-118 (**1a**), was 30 times less active than doxorubicin in HL-60, equipotent in K562, 100 times less potent on HCT-8, and twice more active in MDA-435. Compound **2**, on the other hand, was much less active in leukemic cells but only 3 times less active in HCT-8, and twice more active in MDA-435. Compounds **8** (excepted for SF-295) and **9** also presented a very favorable comparison with doxorubicin.

Next, we evaluated the bioselectivity of the more potent compounds by studying the toxic effect on human PMBC cells activated by mitogen phytohemagglutinin (PHA) (Table 2).

Pterocarpanquinone **1a** and aza-pterocarpanquine **2** showed the best selectivity index among the compounds tested. While **1a** was more bioselective for HL-60 (PBMC/HL-60, 15.4) and K562 (PBMC/K562, 12.0) cell lines, compound **2** showed the best selectivity index for the HCT-8 (PBMC/HCT-8, 38.5), SF-295 (PBMC/SF-295, 5.92) and MDA-MB435 (PBMC/MDA-MB435, 57.7) cell lines. Compound **8** has also shown a good selectivity index for the MDA-MB435 cell line (PBMC/MDA-MB435, 14.4). The N-tosyl group may be important for the cytotoxic activity since the compound **6** was inactive. Unfortunately, chromenquinone **9**, the simplest and easiest to synthesize derivative, showed a potent antineoplasic activity on all cell lines studied but presented very low selectivity index.

Table 2
Cytotoxic effect of compounds **1a**, **1d**, **2**, **7** and **8** on PBMC cells activated by PHA (IC_{50} in µM). Selectivity index

1–8	PBMC	PBMC/HL-60	PBMC/HCT-8	PBMC/SF-295	PBMC/MDA-MB435	PBMC/K562
1a	>20	15.4	7.7	5.5	8.7	12.0
1b	7.8	2.22	0.75	0.44	0.68	9.4
1d	8.6	1.36	1.06	0.96	0.49	ND
1e	6.0	2.0	1.0	0.8	0.56	ND
2	23.0	3.12	38.5	5.92	57.7	4.33
8	7.2	7.2	2.4	0.11	14.4	ND
9	<1.4	2.8	0.5	0.6	0.78	ND

i, sodium dithionite, Tris:HCl (pH=7.4), PhSH
quantitative yield for **1a** and 0 % for **2**

Scheme 4. Reductive activation of pterocarpanquinone **1a**.

Table 3
Antileishmanial activity of compounds **1**, **2**, **8** and pentamidine (P*) on promastigote and amastigote forms of *L. amazonensis* and toxicity for M J774 cells (IC$_{50}$ in μM)

1, 2, 8	Promastigote	Amastigote	MJ774	M J774/amastigote
1a	1.73	1.45	18.5	12.7
1b	2.85	>20	49.5	ND
1c	2.8	0.5	22.5	45
1d	1.07	1.85	12.1	6.5
1e	1.27	1.25	18	14.4
2	15	>20	>100	ND
8	4.85	2.15	23	10.7
P*	2.2	1.5	70	46

ND = Not determined.

We have previously demonstrated in the laboratory (Scheme 4) that **1a** and **1d** (not shown) can be activated by two electrons reduction of the quinone group, followed by rearrangement of the resulting hydroquinone **14**, leading to a Michael acceptor **15** which was trapped as adduct of thiophenol (**16**).[4] This mechanism could explain the cytotoxic effect of this compound on cell lines resistant to oxidative stress, as K562. This cell line overexpresses NQO1, the enzyme which promotes a two electrons reduction of quinones, step required to start the mechanism of bioactivation.

In contrast, when **2** was submitted to the same reaction conditions, the expected Michael adduct type **16** (X = NHTs) could not be detected in the crude product. In fact, the ^{1}H NMR shows the presence of a complex mixture of products.

Compounds **1a**–**e**, **2** and **8** were also evaluated on *L. amazonensis* in culture (promastigote and amastigote forms, Table 3). Except for **2**, these compounds were potent on promastigote form of the parasite. Except for **2** and **1b**, these compounds presented potent antileishmanial effect on macrophages infected with amastigotes, the form present in the human disease. The selectivity index was calculated for amastigote form using M J7744 cells (murine macrophages) as reference and these data are also shown in Table 3. The best selectivity index for pterocarpanquinones was obtained for **1a**, **1c** and **1e**.

In contrast with the low potency of the aza-ptarocarpanquinone **2**, compound **8** presented good antiamastigote and antipromastigote activity and good selectivity index (10.7). These results suggest that different mechanism of action may be contributing for the observed effects.

3. Conclusions

New bioactive pterocarpanquinones, an aza-pterocarpanquinone and analogues were prepared through palladium catalyzed oxa-Heck and aza-Heck reactions. Based on in vitro assays it was possible to discover new compounds with both antitumoral and antileishmanial activity. In particular, compound **8**, a N-tosyl aza-pterocarpan, represents an interesting model for the development of new antineoplasic and antiparasite compounds.

4. Experimental

4.1. Pharmacology

4.1.1. Cell lines and cell culture

The tumor cell lines used in this work were HL-60 (promyelocytic leukemia), K562 (chronic myelogenous leukemia), HCT-8 (colon carcinoma), MDA-MB 435 (melanoma) and SF-295 (gliobastoma) kindly provided by the National Cancer Institute (Bethesda, MD, USA). Also, peripheral blood mononuclear cells (PBMC) were tested, for chosen compounds. All cancer cells were maintained in RPMI 1640 medium supplemented with 10% fetal bovine serum, 2 mM glutamine, 100 U/mL penicillin, 100 μg/mL streptomycin at 37 °C with 5% CO$_2$. Heparinized blood (from healthy, non-smoker donors who had not taken any drug at least 15 days prior to sampling) was collected and PBMC were isolated by a standard method of density-gradient centrifugation over Ficoll-Hypaque. PBMC were washed and resuspended at a concentration of 3×10^5 cells/mL and plated in a 96-well plate with RPMI 1640 medium supplemented with 20% fetal bovine serum, 2 mM glutamine, 100 U/mL penicillin, 100 μg/mL streptomycin at 37 °C with 5% CO$_2$. Phytohemagglutinin (3%) was added at the beginning of culture. After 24 h, tested compounds (0.1–25 μg/mL) dissolved in DMSO 1% were added to each well and incubated for 72 h.

4.1.2. Cytotoxicity assay

The cytotoxicity of all compounds was tested against five tumor cell lines and PBMC using the 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H tetrazolium bromide (MTT) (Sigma Aldrich Co., St. Louis, MO, USA) reduction assay. For all experiments, tumor cells were plated in 96-well plates (10^5 cells/mL for adherent cells or 3×10^5 cells/mL for Leukemia). Tested Compounds (0.1–25 μg/mL) dissolved in DMSO 1% were added to each well and incubated for 72 h. Control groups received the same amount of DMSO. After 72 h of incubation, the supernatant was replaced by fresh medium containing MTT (0.5 mg/mL). Three hours later, the MTT formazan product was dissolved in 150 μL of DMSO, and absorbance was measured at 595 nm (DTX 880 Multimode Detector, Beckman Coulter, Inc. Fullerton, CA, USA). Doxorubicin (0.01–5 μg/mL) was used as positive control.

4.1.3. Antileishmanial activity

To evaluate the antileishmanial activity of pterocarpanquinones, aza-pterocarpanquinones and analogues, *L. amazonensis* promastigotes were maintained in flasks at 26 °C in Schneider's medium (Sigma–Aldrich Corp., St. Louis, MO, USA) supplemented with 10% fetal bovine serum. Tests were performed in 96-well plates for 72 h at 26 °C with initial inoculums of 1.0×10^6/ml and compound concentrations ranging from 0 to 20 μM. Parasite viability was assessed by a dye-reduction assay employing 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT). After incubation, 22 μL of MTT solution (5 mg/mL) was added per well, and then, the samples were incubated for an additional 2 h. Next, 80 μL of DMSO was added to each well and their optical densities were measured at 570 nm in spectrometer.

To evaluate the effect of compounds on intracellular amastigotes, resident peritoneal macrophages of BALB/c were plated in RPMI (Sigma–Aldrich, St. Louis, USA) at 2×10^6/mL (0.4 mL/well) in Lab-Tek 8-chamber slides (Nunc, Roskilde, Denmark) and

incubated at 37 °C in 5% CO_2 for 1 h. Stationary-phase *L. amazonensis* promastigotes were added at a 3:1 parasite/macrophage ratio, and the cultures were incubated for an additional 3 h. The resulting monolayers were washed three times with pre-warmed phosphate-buffered saline (PBS) to remove free parasites and non-adherent cells, then 0.4 mL of compounds (at concentrations ranging from 0 to 20 μM, each run in duplicate) was added, prior to incubation for an additional 72 h. Next, the slides were stained using an Instant Prov hematological dye system (Newprov, Curitiba, Brazil) and then examined under light microscopy. The number of intracellular amastigotes was determined by counting at least 100 macrophages per sample. To evaluate the toxicity of compounds, cell line macrophages J774 (2×10^6 in 200 μL) were incubated with various concentrations of compounds for 72 h at 37 °C/5% CO_2. The effect on macrophage viability was quantified using a MTT assay. Pentamidine isethionate was used as reference in these experiments. All experiments were repeated at least three times. Values of $p < 0.05$ produced by Student's t-test were considered statistically significant. The IC_{50} and ED_{50} values were obtained with Graphpad Prism 4 software.

4.2. Chemistry

Melting points were determined with a Thomas–Hoover apparatus and are uncorrected. Column chromatography was performed on silica gel 230–400 mesh (Aldrich). ^{1}H NMR spectrum was recorded on a Bruker Avance 400 (400.013 MHz) spectrometer at room temperature. All J values are given in Hz. Chemical shifts are expressed in parts per million downfield shift from tetramethylsilane as an internal standard, and reported as position (δ_H) (relative integral, multiplicity (s = singlet, d = doublet, dd = double doublet, dt = double triplet, m = multiplet), coupling constant (J Hz) and assignment. ^{13}C NMR spectrum was recorded on a Bruker Avance 400 (100.003 MHz) spectrometer at room temperature with complete proton decoupling. Data are expressed in parts per million downfield shift from tetramethylsilane as an internal standard and reported as position (δ_C).

4.2.1. General procedure for the oxyarylation synthesis of compounds type 1, compound 5 and 6

To a stirred solution of **9** (0.5 mmol), **13a** (0,5 mmol) or **13b** (0.5 mmol) in acetone (10 mL), 2-iodophenols **10** (0.6 mmol), silver carbonate (1.5 mmol) and Pd(OAc)$_2$ (10 mol%) were added. This experimental procedure was accomplished in presence (20 mol %) or in absence of PPh$_3$. The reaction mixture was refluxed for 8 h and filtered in celite with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na$_2$SO$_4$ and concentrated. The crude product was washed in *n*-hexane and purified by flash chromatography on silica.

4.2.1.1. Compound 1a. After column chromatography using *n*-hexane/ethyl acetate (95:5) as eluant, this compound was obtained as a yellow solid in 41% yield in presence of PPh$_3$, and in 40% in absence of PPh$_3$, mp 145 °C. ^{1}H NMR (CDCl$_3$) δ (ppm) 8.21–8.10 (2H, m); 7.78–7.68 (2H, m); 7.30–7.18 (2H, m); 6.98–6.91 (2H, m); 5.66 (1H, d, J = 6.7 Hz); 4.59 (1H, dd, J = 11.1 and 5.0 Hz); 3.81 (1H, t, J = 11.1 Hz); 3.64–3.53 (m, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ (ppm) 183.25 (C); 179.28 (C); 158.73 (C); 157.01 (C); 134.54 (CH); 133.38 (CH); 130.58 (C); 130.57 (C); 129.58 (CH); 126.49 (CH); 126.42 (CH); 125.11 (C); 124.51 (CH); 121.23 (CH); 118.16 (C); 110.80 (CH); 72.32 (CH); 67.09 (CH$_2$); 38.37 (CH); HRMS: [M+H]+ m/z calcd for C$_{21}$H$_{20}$O$_4$, 305.0814 [M+H]+ m/z found: 305.0890.

4.2.1.2. Compound 1b. After column chromatography using *n*-hexane/ethyl acetate (10:90) as eluant, this compound was

obtained as a yellow solid in 39% yield in absence of PPh$_3$; mp 230–235 °C; ^{1}H NMR (400 MHz, CDCl$_3$), δ (ppm): ^{1}H NMR (CDCl$_3$) δ (ppm): 8.20 (1H, d, J = 7.5 Hz); 8.14 (1H, d, J = 7.4 Hz); 7.80–7.72 (1H, m); 7.15 (1H, d, J = 8.1 Hz); 6.54 (1H, d, J = 2.0 Hz); 6.48 (1H, dd, J = 8.2 and 2.0 Hz); 5.66 (1H, d, J = 6.6 Hz); 4.55 (1H, dd, J = 11.3 and 5.2 Hz); 3.78–3.73 (1H, m); 3.77 (3H, s); 3.53–3.47 (1H, m) ^{13}C NMR (100 MHz, CDCl$_3$) δ (ppm): 183.4 (C); 179.5 (C); 161.5 (C); 160.3 (C); 157.2 (C); 134.7 (CH); 133.5 (CH); 132.1 (C); 130.8 (C); 126.7 (CH); 126.6 (CH); 124.8 (CH); 118.1 (C); 116.9 (C); 107.1 (CH); 97.5 (CH); 73.3 (CH); 67.5 (CH$_2$); 55.5 (CH$_3$); 37.9 (CH) LRMS (EI) m/z 334.

4.2.1.3. Compound 1c. After column chromatography using *n*-hexane/ethyl acetate (10:90) as eluant, this compound was obtained as a yellow solid in 22% yield in presence of PPh$_3$ and 30% yield in absence of PPh$_3$; mp 250–252 °C; ^{1}H NMR (400 MHz, CDCl$_3$), δ (ppm): 8.21–8.13 (2H, m); 7.99 (1H, s); 7.97 (1H, d, J = 8.6 Hz); 7.82–7.73 (2H, m); 6.95 (1H, d, J = 8.3 Hz); 5.77 (1H, d, J = 6.8 Hz); 4.61 (1H, dd, J = 5.1 and 11.3 Hz); 3.89 (3H, s); 3.82 (1H, t, J = 11.0 Hz); 3.68–3.63 (1H, m); ^{13}C NMR (75 MHz, CDCl$_3$) δ (ppm): 183.2 (C); 179.1 (C); 166.4 (C); 162.7 (C); 157.2 (C); 134.7 (CH); 133.6 (CH); 132.5 (CH); 131.8 (C); 130.6 (C); 126.6 (CH); 126.6 (CH); 126.6 (CH); 126.4 (CH); 125.6 (C); 123.6 (C); 117.6 (C); 110.5 (CH); 73.5 (CH); 66.8 (CH$_2$); 51.9 (CH$_3$); 37.9 (CH); LRMS (EI) m/z 362.

4.2.1.4. Compound 1d. After column chromatography using *n*-hexane/ethyl acetate (80:20) as eluant, this compound was obtained as a yellow solid in <10% yield in presence of PPh$_3$, an in <10% in absence of PPh$_3$, mp 250 °C. ^{1}H NMR (CDCl$_3$) δ 8.24–8.16 (m, 4H); 7.86–7.77 (m, 2H); 7.02 (d, 1H, J = 8.6 Hz); 5.90 (d, 1H, J = 6.3 Hz); 4.67 (d, 1H, J = 4.1 and 10.9 Hz); 3.90 (t, 1H, 10.8 Hz); 3.78–3.75 (m, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 179.0 (C); 164.2 (C); 157.4 (C); 142.6 (C); 134.9 (CH); 133.9 (CH); 131.8 (C); 130.7 (C); 127.2 (CH); 126.8 (CH); 126.8 (CH); 121.2 (CH); 117.3 (C); 110. 9 (CH); 74.8 (CH); 66.6 (CH$_2$); 38.1 (CH). LRMS (EI) m/z 349.

4.2.1.5. Compound 1e. After column chromatography using *n*-hexane/ethyl acetate (70:30) as eluant, this compound was obtained as a yellow solid in 12% yield in presence of PPh$_3$, and in 16% in absence of PPh$_3$, mp 160–165 °C. ^{1}H NMR (CDCl$_3$) δ (ppm): 9.82 (1H, s); 8.16 (1H, d, J = 7.6 Hz); 8.11 (1H, d, J = 7.4 Hz); 7.79–7.71 (2H, m); 7.47 (1H, s); 7.37 (1H, s); 5,85 (1H, d, J = 6.8 Hz); 4.64 (1H, dd, J = 11.1 and 5.1 Hz); 3.91 (3H, s); 3.84 (1H, t, J = 11.0 Hz); 3.75–3.70 (1H, m) ^{13}C NMR (100 MHz, CDCl$_3$) δ (ppm): 190.2 (CH); 190.1 (C); 182.8 (C); 179.1 (C); 157.2 (C); 153.0 (C); 145.7 (C); 134.8 (CH); 133.6 (CH); 131.9 (C); 130.6 (C); 127.3 (C); 126.7 (CH); 126.6 (CH); 120.3 (CH); 117.5 (C); 113.2 (CH); 74.4 (CH); 66.9 (CH$_2$); 56.1 (CH$_3$); 38.3 (CH). LRMS (EI) m/z 334.

4.2.1.6. Compound 5. After column chromatography using *n*-hexane/ethyl acetate (5:95) as eluant, this compound was obtained as a yellow solid 43% yield in absence of PPh$_3$; mp 125–127 °C; ^{1}H NMR (CDCl$_3$, 400 MHz): δ (ppm): 7.56 (1H, d, J = 7.4 Hz); 7,27 (2H, d, J = 8.3 Hz); 7.19 (1H, t, J = 7.6 Hz); 7,06 (1H, t, J = 7.3 Hz); 6.91–6.85 (1H, m); 5.54 (1H, d, J = 5.2 Hz); 4.31 (1H, d, J = 5.7 Hz); 3.71–3.62 (1H, m); ^{13}C NMR (CDCl$_3$, 100 MHz): 163.1 (C); 159.6 (C); 135.2 (CH); 134.2 (CH); 133.4 (CH); 131.3 (C); 128.8 (CH); 125.8 (CH); 124.9 (CH); 124.3 (C); 121.5 (CH); 114.4 (CH); 81.8 (CH); 70.6 (CH$_2$); 44.5 (CH).

4.2.1.7. Compound 6. After column chromatography using *n*-hexane/ethyl acetate (5:95) as eluant, this compound was obtained as a yellow solid in 50% in presence of PPh$_3$ and 45% yield in absence of PPh$_3$; mp 40 °C ^{1}H NMR (200 MHz, CDCl$_3$), δ (ppm): 7.56–7.52

(1H, m), 7.27–7.20 (2H, m), 7.14–7.08 (2H, m), 6.91–6.76 (3H, m), 5.63 (1H, d, *J* = 8.0 Hz), 3.71–3.70 (1H, m), 2.75–2.54 (2H, m), 2.96–2.11 (1H, m), 1.87–1.71 (1H, m); ^{13}C NMR (50 MHz, CDCl$_3$), δ (ppm): 159.3 (C), 138.8 (C), 133.3 (C), 131.2 (C), 130.1 (CH), 128.3 (CH), 128.2 (CH), 126.6 (CH), 124.3 (CH), 120.5 (CH), 110.7 (CH), 109.5 (CH), 81.7 (CH), 40.9 (CH), 27.9 (CH$_2$), 27.5 (CH$_2$); HRMS: [M+H]+ *m/z* calcd for C$_{16}$H$_{14}$O 222.1123, [M+H]+ *m/z* found: 222.1223.

4.2.2. General procedure for the oxyarylation: synthesis of compounds type 3

To a stirred solution of **12** (0.5 mmol) in acetone (10 ml), 2-iodophenols **10** (0.6 mmol), silver carbonate (1.5 mmol) and Pd(OAc)$_2$ (10 mol %) were added. This experimental procedure was accomplished in presence (20 mol %) or in absence of PPh$_3$. The reaction mixture was refluxed for 4 h and filtered in celite with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na$_2$SO$_4$ and concentrated. The crude product was washed in *n*-hexane and purified by flash chromatography on silica.

4.2.2.1. Compound 3a.
After column chromatography using *n*-hexane/ethyl acetate (95:5) as eluant, this compound was obtained as a yellow oil in 50% yield in presence of PPh$_3$, and in 45% in absence of PPh$_3$ ^{1}H NMR (CDCl$_3$, 400 MHz) δ (ppm): 8.13–8.06 (2H, m); 7.54–7.39 (2H, m); 7.34–7.20 (2H, m); 6.97–6.87 (2H, m); 5.98 (1H, d, *J* = 6.9 Hz); 4.39 (1H, dd, *J* = 11.0 and 4.8 Hz), 4.17 (3H, s); 3.98–3.82 (4H, m); 3.74–3.63 (1H, m).
^{13}C NMR (CDCl$_3$, 100 MHz) δ (ppm): 159.6 (C); 153.4 (C); 144.4 (C); 138.8 (C); 129.7 (C); 129.2 (CH); 127.1 (C); 126.9 (CH); 124.5 (CH); 124.1 (CH); 123.5 (C); 122.5 (CH); 121.7 (CH); 120.9 (CH); 114.8 (C); 110.2 (CH); 75.0 (CH$_2$); 66.8 (CH$_2$); 61.2 (CH$_3$); 40.3 (CH).
HRMS: [M+H]+ *m/z* calcd for C$_{19}$H$_{12}$O$_4$: 335.1283, [M+H]+ *m/z* found: 335.0999.

4.2.2.2. Compound 3b.
After column chromatography using *n*-hexane/ethyl acetate (90:10) as eluant, this compound was obtained as a yellow solid in 26% yield in presence of PPh$_3$, and in 26% in absence of PPh$_3$; mp 210 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) = 8.30–8.06 (4H, m), 7.52 (1H, t, *J* = 7.7 Hz); 7.44 (1H, t, *J* = 8.1 Hz); 6.88 (1H, d, *J* = 8.8 Hz); 6.27 (1H, d, *J* = 7.8 Hz); 4.39 (1H, dd, *J* = 4.7 and 11.3 Hz); 4.16 (3H, s); 4.04 (1H, dd, *J* = 8.2 and 11.2 Hz); 3.95 (3H, s); 3.91–3.88 (1H, m); ^{13}C NMR (100 MHz, CDCl$_3$), δ (ppm): 164.7 (C); 153.1 (C); 144.0 (C); 142.1 (C); 138.8 (C) 129.7 (C); 128.4 (C); 127.3 (CH); 126.6 (CH); 124.5 (CH); 123.4 (C); 122.4 (CH); 121.7 (CH); 121.0 (CH); 113.4 (C); 109.8 (CH); 77.2 (CH); 66.6 (CH$_2$); 64.0 (CH$_3$); 61.9 (CH$_3$); 39.7 (CH); LRMS (EI) *m/z* 379.

4.2.2.3. Compound 3c.
After column chromatography using *n*-hexane/ethyl acetate (90:10) as eluant, this compound was obtained as a yellow solid in 39% yield in presence of PPh$_3$, and in 43% in absence of PPh$_3$; mp 145 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) = 8.12–8.01 (2H, m); 8.02 (1H, s); 7.96 (1H, d, *J* = 8.4 Hz); 7.51 (1H, t, *J* = 7.2 Hz); 7.42 (1H, t, *J* = 7.8 Hz); 6.88 (1H, d, *J* = 8.4 Hz); 4.39 (1H, dd, *J* = 11.2 and 4.8 Hz); 4.17 (3H, s); 3.95 (3H, s); 3.90–3.87 (4H, m); 3.81–3.76 (1H, m); ^{13}C NMR (100 MHz, CDCl$_3$), δ (ppm): 166.8 (C); 163.6 (C); 153.3 (C); 144.3 (C); 138.8 (C); 132.2 (CH); 129.7 (C); 127.5 (C); 127.3 (CH); 126.6 (CH); 124.4 (CH); 123.5 (C); 123.3 (C); 122.5 (CH); 121.7 (CH); 114.12 (C); 109.9 (CH); 76.2 (CH); 66.7 (CH$_2$); 64.1 (CH$_3$); 61.5 (CH$_3$); 52.0 (CH$_3$); 39.8 (CH); LRMS (EI) *m/z* 392.

4.2.3. Azaarylation reactions: synthesis of 4, 7 and 8

To a stirred solution of **12** (0.5 mmol), **13a** (0.5 mmol) or **13b** (0.5 mmol) in acetone (10 mL), tosyl-2-iodoaniline **12** (0.75 mmol), silver carbonate (1.5 mmol) and Pd(OAc)$_2$ (10 mol %) were added. This experimental procedure was accomplished in presence (20 mol %) or in absence of PPh$_3$. The reaction mixture was refluxed for 8 h and filtered in celite with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na$_2$SO$_4$ and concentrated. The crude product was washed in *n*-hexane and purified by flash chromatography on silica.

4.2.3.1. Compound 4.
After column chromatography using *n*-hexane/ethylacetate (5:95) as eluant, this compound was obtained as a yellow solid in 45% yield in absence of PPh$_3$; mp: 50–55 °C 1H NMR (CDCl$_3$, 400 MHz): δ (ppm): 8.08 (1H, d, *J* = 8.4 Hz); 7.95 (1H, d, *J* = 8.4 Hz); 7.51 (1H, d, *J* = 7.8 Hz); 7.51–7.46 (3H, m); 7.37–7.33 (1H, m); 7.24–7.10 (5H, m); 5.92 (1H, d, *J* = 7.9 Hz); 4.60 (1H, dd, *J* = 11.8 and 2.0 Hz); 4.21 (3H, s); 4.07 (1H, dd, *J* = 11.8 and 2.0 Hz); 3.0 (3H, s); 2.94 (1H, d, *J* = 7.9 Hz); 2.36 (3H, s); ^{13}C NMR (CDCl$_3$, 100 MHz): δ (ppm): 153.6 (C); 145.4 (C); 144.0 (C); 143.1 (C); 138.1 (C); 135.2 (C); 134.5 (C); 129.3 (CH); 129.3 (CH); 129.01 (C); 128.3 (CH); 127.7 (CH); 127.7 (CH); 126.8 (CH); 126.5 (CH); 123.9 (CH); 123.7 (CH); 123.6 (C); 122.8 (CH); 121.5 (CH); 121.2 (CH); 114.8 (C); 63.9 (CH$_2$); 63.1 (CH$_3$); 61.0 (CH); 59.4 (CH$_3$); 40.8 (CH); 21.5 (CH$_3$) LRMS (EI) *m/z* 332.

4.2.3.2. Compound 7.
After column chromatography using *n*-hexane/ethyl acetate (5:95) as eluant, this compound was obtained as a white solid in 29% yield in absence of PPh$_3$; mp 55–60 °C 1H NMR (CDCl$_3$, 400 MHz): δ (ppm): 7.86 (1H, d, *J* = 7.6 Hz); 7.59 (1H, m); 7.51 (2H, d, *J* = 8.1 Hz); 7.20–7.17 (2H, m); 7.14–7.11 (3H, m); 7.10 (1H, t, *J* = 7.7 Hz); 7.01 (1H, t, *J* = 7.4 Hz); 6.66 (1H, d, *J* = 8.2 Hz); 5.47 (1H, d, *J* = 8.6 Hz); 4.48 (1H, d, *J* = 12.0 Hz); 4.15 (1H, dt, *J* = 12.0 and 5.8 Hz); 3.04 (1H, d, *J* = 8.7 Hz); 2.37 (3H,s) ^{13}C NMR (CDCl$_3$, 100 MHz): δ (ppm: 155.6 (C); 144.0 (C); 141.9 (C); 135.4 (C); 133.2 (C); 131.3 (CH); 129.7 (CH); 129.1 (CH); 128.6 (CH); 127.0 (CH); 125.9 (CH); 123.4 (CH); 122.1 (CH); 121.3 (C); 120.1 (CH); 116.9 (CH); 64.1 (CH$_2$); 59.8 (CH); 40.5 (CH); 21.5 (CH$_3$). LRMS (EI) *m/z* 349.

4.2.3.3. Compound 8.
After column chromatography using *n*-hexane/ethylacetate (5:95) as eluant, this compound was obtained as a yellow solid in 45% yield in absence of PPh$_3$; mp: 160–165 °C ^{1}H NMR (CDCl$_3$, 400 MHz):δ (ppm): 8.0 (1H, d, *J* = 7.8 Hz); 7.61 (1H, d, *J* = 7.9 Hz); 7.51 (1H, d, *J* = 8.1 Hz); 7.29–7.09 (7H, m); 7.04 (1H, d, *J* = 7.0 Hz); 6.93 (1H, d, *J* = 7.5 Hz); 5.42 (1H, d, *J* = 8.5 Hz); 3.13–3.11 (1H, m); 2.54–2.45 (2H, m); 2.37 (3H, m); 2.13–2.09 (1H, m); 2.06–1.98(1H,m); 13C NMR (CDCl$_3$,100 MHz): δ (ppm): 143.8 (C);142.1(C); 137.6 (C);136.2 (C); 135.6 (C); 134.4 (C); 30.5 (CH); 129.6 (CH); 129.6 (CH); 127.9 (CH); 127.8 (CH); 127.3(CH); 127.1(CH); 127.1 (CH); 126.8 (CH); 125.7 (CH); 123.4 (CH); 119.9 (CH); 64.0 (CH); 39.5 (CH); 24.8 (CH$_2$); 23.6 (CH$_2$); 21.5 (CH$_3$). LRMS (EI) *m/z* 220.

4.2.4. Procedure for the reaction for substance 2 and alternative procedure for 1a, 1c and 1d

To a stirred solution of substances **3a**, **3c**, **3d** and **4** (0.12 mmol) in acetonitrile, cerium nitrate ammonium (CAN) (3 equiv; 0.036 mmol) in 0.25 mL of water was added slowly and the reaction mixture was stirred for 15 min at room temperature. After that, the reaction mixture was extracted with ethyl acetate and the organic layer was washed with 50% aq NaHCO$_3$ solution, dried over anhydrous Na$_2$SO$_4$ and concentrated to obtain the crude products in 77% yield (**1a**), 85% yield (**1c**), 75% yield (**1d**) and 74% yield (**2**).

4.2.4.1. Compound 2.
Crude product was obtained in pure form 74% yield. ^{1}H NMR (CDCl$_3$, 400 MHz): δ (ppm): 8.22 (1H, dd, *J* = 7.7 and 1.0 Hz); 8.06 (1H, dd, *J* = 7.7 and 1.0 Hz); 7.79–7.75

(1H, m); 7.70 (1H, dd, J = 7.6 and 1.3 Hz); 7.66 (1H, d, J = 8.3 Hz), 7.58 (1H, d, J = 8.1 Hz) 7.31–7.27 (2H, m); 7.22–7.14 (4H, m); 5.65 (1H, d, J = 7.1 Hz); 4.44 (1H, dd, J = 12.1 and 5.1 Hz); 4.25 (1H, dd, J = 12.1 and 3.3 Hz); 3.12–3.08 (1H, m); 2.40 (3H, s) ^{13}C NMR (CDCl$_3$, 400 MHz): δ (ppm): 182.7(C); 179.2(C); 156.5(C); 144.2 (C); 144.1 (C); 142.4 (C); 135.1 (C); 134.5 (CH); 133.1 (CH); 132.5 (C); 131.5(C); 130.5 (C); 129.5 (CH); 129.5 (CH); 128.9 (CH); 127.7 (CH); 127.7 (CH); 126.8 (CH); 126.2 (CH); 125.8 (CH); 123.9 (CH); 120.1 (CH); 65.5 (CH$_2$); 56.5 (CH); 39.0 (CH); 21.6 (CH$_3$). LRMS (EI) m/z 302.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2011.09.025.

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