Unexpected Oxidative Ring Opening of Electron-Rich 3-Aminobenzofurans into α -Ketoimines Derivatives

Ilhem Khelifi, Guangkuan Zhao, Nour-Eddine Ghermani, Olivier Provot,
Mouad Alami

► To cite this version:

Ilhem Khelifi, Guangkuan Zhao, Nour-Eddine Ghermani, Olivier Provot, Mouad Alami. Unexpected Oxidative Ring Opening of Electron-Rich 3-Aminobenzofurans into α -Ketoimines Derivatives. *Journal of Organic Chemistry*, 2019, 84 (4), pp.1725-1733. 10.1021/acs.joc.8b01685 . hal-02394232

HAL Id: hal-02394232

<https://hal.science/hal-02394232>

Submitted on 4 Dec 2019

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Unexpected Oxidative Ring-Opening of Electron-Rich 3-Aminobenzofurans into α -Ketoimines Derivatives

Ilhem Khelifi,^a Guangkuan Zhao^a, Nour-Eddine Ghermani,^b Olivier Provot,^{a*} Mouad Alami^{a*}

^a Univ. Paris-Sud, BioCIS, CNRS, University Paris-Saclay, Equipe Labellisée Ligue Contre Le Cancer, F-92296 Châtenay-Malabry, France

^b Univ. Paris-Sud, Institut Galien Paris-Sud, CNRS, University Paris-Saclay, F-92296 Châtenay-Malabry, France
olivier.provot@u-psud.fr, mouad.alami@u-psud.fr

KEYWORDS: ketoimine, benzofuran, radical, ring-opening, NaOtBu.

RECEIVED DATE (to be automatically inserted after your manuscript is accepted if required according to the journal that you are submitting your paper to)

Abstract: An unexpected ring-opening of 3-aminobenzofurans promoted by NaOtBu in hot toluene, leading to a variety of α -ketoimines is described. In the presence of 3-iodobenzofurans, NaOtBu mediates the 3-aminobenzofurans ring-opening *via* a possible radical pathway without the help of any external radical sources.

INTRODUCTION

Combretastatin A-4 (CA-4, **Figure 1**) is a natural microtubule destabilizing drug, able to damage the vasculature cancer tumors causing central necrosis.¹ Recently, Food and Drug Administration (FDA) has granted orphan drug designation to its prodrug CA-4 phosphate (CA-4P) for the treatment of glioblastoma multiform and neuroendocrine tumors.²

FIGURE 1. Representative Vascular Disrupting Agents and Rational Drug Design from CA-4 to *isoCoQuin* Derivatives **1**

Although effective in antitumor therapy, CA-4 is not stable since its *Z*-double bond isomerizes during storage and administration leading to a 100-fold less active *E*-stilbene. This problem was solved in our group by the discovery of *isoCombretastatin* A-4 (*isoCA-4*), and other analogues³ including, *azaisoerianin* and various quinoline

derivatives as *isoCoQuin*. For instance, *isoCoQuin* in which a quinaldine replaced the 3,4,5-trimethoxyphenyl A-ring of *isoCA-4* has demonstrated low nanomolar potency against diverse tumor models and displayed antivasular properties identical to those of CA-4 and *isoCA-4*. Our studies around *isoCoQuins* were furthered to design, synthesize, and evaluate a novel panel of compounds of type **1** containing a benzofuran as B-ring encountered in BNC105,⁴ a potent tubulin polymerization inhibitor.

Initially, we applied efficient Buchwald-Hartwig coupling conditions,⁵ for the coupling reaction of 4-aminoquinoline **2a** with 3-iodobenzofuran **3a** (R = Ph) to provide **4a** using Pd₂dba₃ as the catalyst, XPhos as the ligand, NaOtBu as the base in hot toluene (**Scheme 1**). Surprisingly, the desired **4a** was not detected and, instead, (*Z*)- α -ketoimine **5a**, was obtained in 70% yield and evidenced by ¹H-NMR⁶ and mass spectrometry. However by replacing sodium *tert*-butoxide (NaOtBu) by cesium carbonate (Cs₂CO₃), we were pleased to observe the formation of **4a**, which turned out to be unstable⁷ and was rapidly *N*-methylated, using NaH and CH₃I providing **1a** in 47% yield (two steps). Using these experimental conditions, targeted compounds **1b** and **1c** were synthesized and their antiproliferative activity was investigated against HCT116 human colon tumor cell lines. However, biological results revealed that compounds **1a-c** exhibited a micromolar level of cytotoxicity, which was not sufficient to consider other structural modifications in this chemical series (see SI). 1

SCHEME 1. Formation of Ketoimine **5a** or *iso*CoQuins **1a-c** from the Coupling of **2a** with **3**

Next, we focused our attention on the intriguing formation of α -ketoimines of type **5**. Although being interesting intermediates in synthetic organic reactions, the synthesis of α -ketoimines is, however, poorly documented⁸ and in particular those of compounds **5**, which has never been reported. In this article we report the first 3-aminobenzofurans ring-opening⁹ leading to α -ketoimines **5** under Buchwald-Hartwig coupling conditions.

RESULTS AND DISCUSSION

We began our investigations to increase the chemical yield in α -ketoimine **5b** (Table 1) using *p*-anisidine **2b** and 3-iodobenzofuran **3b** as model substrates (47%, entry 1). A total conversion was observed and compound **5b** was isolated in 85% yield (entry 2) using an excess of NaOtBu (5 equiv), demonstrating that the base played a major role in the benzofuran ring-opening. We noted that replacing NaOtBu by LiOtBu and KOtBu (10 equiv) furnished **5b** but with lower yields (25 and 60%, resp., entries 6 and 7), probably because the Buchwald coupling reaction was less efficient using these bases. Subsequently, the screening reaction conditions with respect to the phosphine ligand was investigated and revealed that, on the contrary to BINAP (L3), Xphos (L2) gave a comparable result with the one obtained with the bulky bidentate phosphine Xantphos (L1) providing **5b** in 92% yield (entry 11). Finally, after screening other parameters (solvent, temperature and reaction time), our optimal conditions were found to require **2b** (1 equiv), **3b** (1.1 equiv), Pd₂dba₃ (5 mol %), Xphos (10 mol %), NaOtBu (5 equiv), in toluene in a sealed Schlenk tube at 140 °C for 16 h.

FIGURE 2. X-Ray Structure of **5b**

TABLE 1. Evaluation of Reaction Parameters^a

Entry	Ligand	Base ^b	Equiv of base	Solvent	T (°C)	Yield (%) ^c
1	L1	NaOtBu	2.2	Toluene	130	47
2	L1	NaOtBu	5	Toluene	130	85
3	L1	NaOtBu	10	Toluene	130	83
4	L1	NaOtBu	5	Toluene	140	89
5	L1	NaOtBu	5	Toluene	150	88
6	L1	LiOtBu	10	Toluene	140	25
7	L1	KOtBu	10	Toluene	140	60
8	L1	NaOtBu	5	Dioxane	140	32
9	L1	NaOtBu	5	DMAc	140	traces
10	L1	NaOtBu	5	NMP	140	traces
11	L2	NaOtBu	5	Toluene	140	92
12	L3	NaOtBu	5	Toluene	140	35

^aConditions: **2b** (1 equiv), **3b** (1.1 equiv), Pd₂dba₃ (5 mol %), L (10 mol %), base, solvent (3 mL), Schlenk tube, 16 h.

^b Other bases as NaOMe, NaOEt, K₂CO₃, Na₂CO₃, K₃PO₄ and LiHMDS were evaluated under the condition of entry 4 but without any success as **2b** and **3b** were mainly found unchanged. ^cYield of isolated product.

As control experiments, when the reaction was achieved in the absence of NaOtBu (or Pd₂dba₃ or XPhos), no reaction occurred and starting materials **2b** and **3b** remained unchanged. One can note that after recrystallization of **5b** in dichloromethane/diethyl ether mixture (10:90), the structure of the ketoimine product (*Z*)-**5b** was confirmed by X-ray analysis (Figure 2). With these optimized conditions in hands, we then proceeded to investigate the scope of this transformation using various 3-iodobenzofurans **3** and aromatic amines **2**. As can be seen in Scheme 2, employing a variety of electron-rich anilines with 3-iodo-2-phenylbenzofurans **3a** and **3b**, α -ketoimines **5b-h** were obtained in good to excellent yields ranging from 62 to 98% yield. An acceptable yield of 50% was obtained using the less nucleophilic *p*-nitroaniline to give the expected α -ketoimine **5i**. Substituents on the aromatic ring on the C-2 position of the benzofuran nucleus were also permitted as it could be observed with α -ketoimines **5j,k** (75 and 86%, respectively). However, when mixing 4-methoxyaniline **2b** with benzofurans having an electron-withdrawing group on C5 (CO₂Me) or having an alkyl chain (*n*-Bu) on C2, starting materials were found unchanged suggesting that Buchwald coupling-reactions failed and were not optimized with these benzofurans. We further investigated the influence of various aromatic amines, and were pleased to observe that heterocyclic amines as 4-aminoquinoline, 9-methyl-9*H*-carbazol-3-amine and 1-methyl-1*H*-indol-5-amine reacted well under

SCHEME 2. Substrate Scope of α -Ketoimines **5b-o** Formation under Pd-Coupling Conditions in the Presence of NaOtBu

these conditions with 2-aryl-3-iodobenzofurans **3a**, **3b** and **3d** to furnish the expected ketoimines **5l-o** in good yields.

To gain some insight into the plausible mechanism of this unexpected ring-opening reaction, we next focused our attention on the role of NaOtBu, which seemed to be responsible of the benzofurans ring-opening. As depicted in Scheme 3, our current hypothesis favors a radical pathway. Beside the formation of 4-aminobenzofuran **4a** through Buchwald-Hartwig coupling, we hypothesized that catalytic amounts of the radical species **V[•]** and $t\text{BuO}^{\bullet}$ were formed together with NaI from the reaction between NaOtBu and 3-iodobenzofuran **3a**. This hypothesis was assumed with regard to a previous report of Cuthbertson,¹⁰ which showed that reaction of an aryl iodide with KOtBu alone in hot toluene generated $t\text{BuO}^{\bullet}$ radicals. Note that the formation of **V[•]** is supported by the presence in the crude reaction of small amounts of 2-phenylbenzofuran, which was detected by LC/MS at the end of the reaction. Then, a hydrogen abstraction from 3-aminobenzofuran **4a** by a $t\text{BuO}^{\bullet}$ radical would occur to give the resulting aminyl radical **W[•]**.¹¹ This hypothesis involving **W[•]** radicals is supported by the identification through LC/MS analysis of a dimeric hydrazine **W₂**¹² (m/z of 819.3082 ($[\text{M} + \text{H}]^+$) and 410.1577 ($[\text{M} + 2\text{H}]^{2+}$), see SI). In agreement with a recent report by Zhou et al.,¹³ radical **W[•]** would furnish a peroxy radical **X[•]** species by oxidation in the air. This latter, would then undergo oxidation of aminyl radical **W[•]** giving hemiketal radicals **Y[•]**. A subsequent monoelectronic ring-opening of **Y[•]** would furnish ketoimine **Z[•]**, which after hydrogen trapping from $t\text{BuOH}$

led to ketoimine **5a** and regenerated $t\text{BuO}^{\bullet}$ radical. This mechanistic hypothesis is also supported by Lavanya and Yamuna's works, which previously reported that 3-aminobenzofurans were excellent antioxidants agents able to trap free radicals.¹⁴

In order to determine the origin of the oxygen atom of ketoimine **5a**, we then carried out the Buchwald coupling reaction of **2a** with **3a** in an oxygen-free glove box (O_2 <0.2 ppm) using NaOtBu as the base. Under these conditions, the unstable diarylamine intermediate **4a** was detected (NMR and LC/MS) as the main product in the crude mixture, and no trace of the ketoimine **5a** was observed (absence of phenolic proton). This result demonstrated that the amount of O_2 (air atmosphere or dissolved in toluene) at the beginning of the Buchwald reaction in the Schlenk tube was enough to promote the benzofuran ring-opening of **4a**.

To get more insight into the radical-involving reaction pathway, control experiments were achieved in order to trap any radical species. To this end, **2a** and **3a** were reacted under standard conditions in the presence of radical traps (TEMPO or galvinoxyl, Scheme 4). Unfortunately, the presence of TEMPO or galvinoxyl shut down completely the Buchwald coupling reaction as starting materials were recovered unchanged. We then asked ourselves whether an external $t\text{BuO}^{\bullet}$ radical source could (i) accelerate the formation of **5a** when the reaction was conducted in the presence of NaOtBu or (ii) allow obtaining **5a** when the reaction was carried out in the presence of Cs_2CO_3 . As depicted in Scheme 4, by adding in the mixtures di-*t*-butylperoxide (DTBP, 5 equiv) again, the Buchwald coupling reaction did not occur as starting

SCHEME 3. Possible Mechanism Leading to Ketoimine **5a**

materials **2a** and **3a** were mainly found unchanged. All these experiments indicate that additives such as radical traps or external sources of *t*BuO• are not welcome in the Schlenk tube at the beginning of the coupling reaction.¹⁵ To demonstrate that **5a** was formed from **4a** in this novel process, a series of assays (reagents in blue, **Scheme 4**) were next performed from **4a**, previously prepared using Cs₂CO₃ as the base. First, to determine if molecular oxygen was able to promote the benzofuran ring-opening of **4a**, this latter was stirred under an O₂ atmosphere in hot toluene (TLC control). Accordingly, **4a** was slowly and totally consumed after 16 h of stirring in the Schlenk tube to furnish **5a** but with a low yield of 28% together with many unidentified by-products. This result shows

that molecular oxygen is not the only one responsible for the opening of benzofuran ring.

Since the source of bases played a crucial role in this process, diarylamine **4a** was mixed with NaOtBu (5 equiv) in hot toluene. After 16 h of reaction at 140 °C, no trace of **5a** was detected, clearly indicating that NaOtBu alone is not able to transform **4a** into **5a**. Next, we were interested to examine the behaviour of benzofuran **4a** in the presence of DTBPB. We were very pleased to observe, after only 3 h of reaction, the transformation of **4a** into **5a** in a good 65% yield by employing only 5 mol% of DTBPB. This last result clearly supports that the mechanism described in Scheme 3 involving *t*BuO• radicals (generated from NaOtBu and 3-iodobenzofurans) is plausible.

SCHEME 4. Mechanistic Investigations

CONCLUSION

In summary, ring-opening of 3-aminobenzofuran derivatives **4** promoted by NaOtBu and O₂ has been described. 3-Aminobenzofurans were prepared from the *N*-arylation reaction between aromatic amines and 3-iodobenzofurans in the presence of Pd₂dba₃ and Cs₂CO₃ in toluene at 140 °C. When NaOtBu was used as the base, 3-aminobenzofuran derivatives **4** were not isolated because they rapidly reacted with *t*BuO[•] radicals and O₂ to give, after benzofurans ring-opening, a series of novel α -ketoimines **5** difficult to access by alternative routes. We believe that the ability of NaOtBu to promote in hot toluene, 3-aminobenzofuran ring-opening is of significant importance for the scientific community.

EXPERIMENTAL SECTION

General Information and Method. All reactions were carried out under an air atmosphere in dried glassware. When needed, non-aqueous reagents were transferred *via* syringe and dried prior to use. Toluene anhydrous (99.8%) from Sigma-Aldrich (244511) was used and sodium *tert*-butoxide was flame dried under high vacuum for 5 minutes prior to use and stored under argon. Other solvents and reagents were used as obtained from supplier, unless otherwise noted. Analytical TLC was performed using Merck silica gel F254 (230-400 mesh) plates and analyzed by UV light or by staining upon heating with vanillin solution. For silica gel chromatography on column, the chromatography technique was used, with Merck silica gel 60 (230-400 mesh) and p.a. grade solvents.

The ¹H NMR and ¹³C NMR spectra were recorded in either CDCl₃ on Bruker Avance 300 spectrometer. The chemical shifts of ¹H NMR spectra are reported in ppm relative to the solvent residual peak in CDCl₃ (δ 7.26) for ¹H NMR. For the ¹³C NMR spectra, the solvent signals of CDCl₃ (δ 77.16) were used as the internal standard. IR spectra were measured on a Bruker Vector 22 spectrophotometer. MS were recorded on a Micromass spectrometer. Analytical TLC was performed on Merck pre-coated silica gel 60F plates. Merck silica gel 60 (0.015–0.040 mm) was used for column chromatography. Melting points were recorded on a Büchi B-450 apparatus and were uncorrected. High resolution mass spectra (HR-MS) were recorded on a MicroMass LCT Premier Spectrometer, using ESI or APCI with methanol as the carrier solvent.

General Procedure for the synthesis of **3a-e** and characterization data

Suitable *o*-methoxydiarylalkyne (2 mmol, 1 equiv) was dissolved in dichloromethane (30 mL). To this solution was added iodine (3 mmol, 1.5 equiv), and the mixture was stirred at room temperature for 1 hour. The mixture was treated with saturated aqueous sodium thiosulfate (30 mL) and the product was extracted with dichloromethane (2×30 mL). The combined organic extracts were washed with water and dried over anhydrous sodium sulfate. The drying agent was removed by filtration, and the solvent was removed in vacuo leaving a crude solid. The solid was purified on silica gel chromatography (cyclohexane/ethyl acetate = 1/10) to afford the corresponding product **3**.

3-Iodo-6,7-dimethoxy-2-phenylbenzofuran (**3a**):

1.56 g, 88% yield, light brown solid; mp 92.7 - 93.5°C; ¹H NMR (300 MHz, CDCl₃) δ 8.17 (d, *J* = 7.3 Hz, 2H),

7.49 (t, *J* = 7.3 Hz, 2H), 7.41 (t, *J* = 7.3 Hz, 1H), 7.04 (d, *J* = 8.5 Hz, 1H), 6.98 (d, *J* = 8.6 Hz, 1H), 4.24 (s, 3H), 3.95 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 152.3, 149.7, 145.6, 134.1, 130.0 (2), 129.1, 128.5 (2), 127.2 (2), 114.9, 110.0, 61.2, 61.0, 57.3; HRMS (ESI-TOF) *m/z* [M + H]⁺ calcd for C₁₆H₁₄IO₃ 380.9988, found 380.9982; IR film ν_{max} /cm⁻¹ : 3057, 2998, 2932, 1622, 1591, 1503, 1485, 1463, 1485, 1446, 1304, 1292, 1253, 1090.

3-Iodo-6,7-dimethoxy-2-(4-methoxyphenyl)benzofuran (**3c**):

0.96 g, 62% yield, brown solid; mp 85.4 - 87.2 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.09 (d, *J* = 9.0 Hz, 2H), 7.02 (m, 4H), 4.22 (s, 3H), 3.94 (s, 3H), 3.87 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 160.2, 155.2, 153.0, 149.5, 145.4, 128.8 (2), 128.5, 122.6, 114.6, 113.9 (2), 109.9, 61.0, 59.4, 57.3, 55.4; HRMS (ESI-TOF) *m/z* [M + Na]⁺ calcd for C₁₇H₁₅INaO₄ 432.9913, found 432.9916; IR film ν_{max} /cm⁻¹ : 2999, 2961, 2932, 2904, 2835, 1612, 1580, 1506, 1495, 1439, 1418, 1277, 1257, 1231, 1160, 1101, 1088.

3-Iodo-6,7-dimethoxy-2-(*p*-tolyl)benzofuran (**3d**):

0.86 g, 62% yield, white solid; mp 112.5 - 112.9°C; ¹H NMR (300 MHz, CDCl₃) δ 8.06 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.05 (d, *J* = 8.5 Hz, 1H), 6.99 (d, *J* = 8.5 Hz, 1H), 4.25 (s, 3H), 3.97 (s, 3H), 2.44 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 153.1, 149.6, 139.2 (2), 134.1, 129.2 (2), 128.5, 127.2 (2), 122.6, 114.7, 109.9, 61.0, 60.4, 57.3, 21.5; HRMS (ESI-TOF) *m/z* [M + Na]⁺ calcd for C₁₇H₁₅INaO₃ 416.9964, found 416.9955; IR film ν_{max} /cm⁻¹ : 3000, 2950, 2927, 2899, 2832, 1595, 1495, 1458, 1439, 1423, 1272, 1255, 1236, 1163, 1093.

3-Iodo-6,7-dimethoxy-2-(thiophen-3-yl)benzofuran (**3e**):

0.22 g, 69% yield, white solid; mp 123.5 - 124.1 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.16 (d, *J* = 3.0 Hz, 1H), 7.92 (d, *J* = 5.0 Hz, 1H), 7.46 (dd, *J* = 5.0 Hz, *J* = 3.0 Hz, 1H), 7.04 (d, *J* = 8.5 Hz, 1H), 6.99 (d, *J* = 8.6 Hz, 1H), 4.23 (s, 3H), 3.96 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 150.6, 149.7, 145.2, 134.1, 131.1, 128.1, 126.2, 125.9, 124.1, 114.6, 110.0, 61.0, 60.5, 57.2; HRMS (ESI-TOF) *m/z* [M + H]⁺ calcd for C₁₄H₁₂IO₃S 386.9552, found 386.9545; IR film ν_{max} /cm⁻¹ : 2950, 2943, 2887, 2802, 1660, 1587, 1495, 1460, 1418, 1302, 1115, 1044.

General Procedure for the synthesis of **5a-o** and characterization data

Benzofuran **3** (0.550 mmol, 1.10 equiv), aniline **2** (0.500 mmol, 1.00 equiv), Pd₂(dba)₃ (0.025 mmol, 0.05 equiv), Xphos (0.050 mmol, 0.10 equiv), sodium *tert*-butoxide (2.50 mmol, 5.00 equiv) and toluene (5 mL) were added to a dried Sealed tube (30 mL) under air atmosphere. After the mixture was heated to 140°C and stirred for 16 hours, it was cooled to room temperature. The mixture was diluted with ethyl acetate (10 mL), filtered through a celite pad and concentrated. The solid was purified on silica gel chromatography (cyclohexane/ethyl acetate = 1/1) to afford the corresponding product **5**.

(*Z*)-2-(2-Hydroxy-3,4-dimethoxyphenyl)-2-((2-methylquinolin-4-yl)imino)-1-phenylethanone (**5a**):

175 mg, 82% yield, yellow solid; mp 153.7 - 154.9 °C; ¹H NMR (300 MHz, CDCl₃) δ 13.31 (s, 1H), 8.07 (d, *J* = 8.3 Hz, 1H), 7.88 (d, *J* = 7.7 Hz, 1H), 7.72 (d, *J* = 7.3 Hz, 2H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.41 (t, *J* = 7.7 Hz, 1H), 7.23 (t, *J* = 7.7 Hz, 2H), 7.01 (d, *J* = 9.0 Hz, 1H), 6.72 (s, 1H), 6.49 (d, *J* = 9.0 Hz, 1H),

4.02 (s, 3H), 3.94 (s, 3H), 2.57 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 192.9, 171.54, 159.2, 157.8, 156.6, 150.3, 148.4, 137.2, 135.0, 134.1, 130.0, 129.2 (2), 129.0 (2), 128.7, 127.5, 125.9, 123.2, 120.9, 112.7, 112.2, 103.8, 60.9, 56.3, 25.5; HRMS (ESI-TOF) m/z [M + H]⁺ calcd for C₂₆H₂₃N₂O₄ 427.1658, found 427.1662; IR film ν_{max}/cm⁻¹ : 3332, 2934, 2840, 1735, 1669, 1601, 1512, 1467, 1290, 1234, 1125, 1085.

(Z)-2-(2-Hydroxyphenyl)-2-((4-methoxyphenyl)imino)-1-phenylethanone (**5b**):

152 mg, 92% yield, yellow solid; mp 157.2 - 158.4 °C; ¹H NMR (300 MHz, CDCl₃) δ 13.73 (s, 1H), 7.81 (d, *J* = 7.4 Hz, 2H), 7.54 (t, *J* = 8.4 Hz, 1H), 7.39 (m, 3H), 7.16 (d, *J* = 8.4 Hz, 1H), 7.10 (d, *J* = 8.4 Hz, 1H), 6.98 (d, *J* = 8.9 Hz, 2H), 6.80 (t, *J* = 8.4 Hz, 1H), 6.72 (d, *J* = 8.9 Hz, 2H), 3.72 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 195.3, 169.4, 161.8, 157.8, 138.9, 134.7, 134.2, 133.5, 130.3, 129.3 (2), 129.0 (2), 123.4 (2), 118.9, 118.2, 117.2, 114.1 (2), 55.3; HRMS (ESI-TOF) m/z [M + H]⁺ calcd for C₂₁H₁₈NO₃ 332.1287, found 332.1290; IR film ν_{max}/cm⁻¹ : 3372, 2928, 2851, 1669, 1575, 1504, 1433, 1407, 1125.

(Z)-2-((3,5-Dimethoxyphenyl)imino)-2-(2-hydroxyphenyl)-1-phenylethanone (**5c**):

125 mg, 69% yield, yellow solid; mp 153.3 - 153.9 °C; ¹H NMR (300 MHz, CDCl₃) δ 13.37 (s, 1H), 7.84 (d, *J* = 7.5 Hz, 2H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.42 (m, 3H), 7.28 (s, 1H), 7.19 (d, *J* = 8.4 Hz, 1H), 7.12 (d, *J* = 8.4 Hz, 1H), 6.82 (t, *J* = 7.5 Hz, 1H), 6.15 (s, 2H), 3.66 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 194.3, 170.6, 161.83, 160.9, 147.7, 142.1, 134.8, 134.6, 134.0, 130.7, 129.4 (2), 129.0 (2), 119.0, 118.3, 117.0, 100.3 (2), 98.5, 55.3 (2); HRMS (ESI-TOF) m/z [M + H]⁺ calcd for C₂₂H₂₀NO₄ 362.1392, found 362.1394; IR film ν_{max}/cm⁻¹ : 3061, 2960, 2936, 1678, 1592, 1425, 1259, 1140.

(Z)-2-((3,4-Dimethoxyphenyl)imino)-2-(2-hydroxyphenyl)-1-phenylethanone (**5d**):

112 mg, 62% yield, brown solid; mp 147.8 - 148.5 °C; ¹H NMR (300 MHz, CDCl₃) δ 13.68 (s, 1H), 7.83 (d, *J* = 7.3 Hz, 2H), 7.55 (t, *J* = 7.3 Hz, 1H), 7.40 (m, 3H), 7.16 (dd, *J* = 8.2 Hz, *J* = 1.3 Hz, 1H), 7.11 (dd, *J* = 8.2 Hz, *J* = 1.3 Hz, 1H), 6.80 (t, *J* = 7.6 Hz, 1H), 6.68 (d, *J* = 9.1 Hz, 1H), 6.60 (m, 2H), 3.79 (s, 3H), 3.74 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 195.3, 169.6, 161.8, 148.9, 147.3, 139.2, 134.8, 134.4, 133.6, 130.4, 129.3 (2), 129.0 (2), 118.9, 118.3, 117.2, 114.3, 111.1, 106.3, 55.9 (2); HRMS (ESI-TOF) m/z [M + H]⁺ calcd for C₂₂H₂₀NO₄ 362.1392, found 362.1387; IR film ν_{max}/cm⁻¹ : 3060, 2957, 2933, 1678, 1673, 1594, 1466, 1305, 1263.

(Z)-2-(2-Hydroxyphenyl)-1-phenyl-2-((3,4,5-trimethoxyphenyl)imino)ethanone (**5e**):

149 mg, 76% yield, yellow solid; mp 168.4 - 169.8 °C; ¹H NMR (300 MHz, CDCl₃) δ 13.38 (s, 1H), 7.73 (d, *J* = 7.6 Hz, 2H), 7.45 (t, *J* = 7.7 Hz, 1H), 7.31 (m, 3H), 7.08 (d, *J* = 7.7 Hz, 1H), 7.01 (d, *J* = 7.7 Hz, 1H), 6.71 (t, *J* = 7.7 Hz, 1H), 6.13 (s, 2H), 3.64 (s, 3H), 3.58 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 195.1, 170.5, 161.8, 153.3 (2), 141.9, 136.0, 134.9, 134.8, 134.0, 130.64, 129.4 (2), 129.1 (2), 119.1, 118.4, 117.1, 99.8 (2), 61.0, 56.1 (2); HRMS (ESI-TOF) m/z [M + H]⁺ calcd for C₂₃H₂₂NO₅ 392.1498, found 392.1497; IR film ν_{max}/cm⁻¹ : 3402, 2939, 2837, 1736, 1677, 1589, 1504, 1466, 1233, 1127.

(Z)-2-((2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)imino)-2-(2-hydroxyphenyl)-1-phenylethanone (**5f**):

131 mg, 73% yield, yellow solid; mp 196.2 - 197.4 °C; ¹H NMR (300 MHz, CDCl₃) δ 13.03 (s, 1H), 7.21 (d, *J* = 7.3 Hz, 2H), 6.92 (t, *J* = 7.6 Hz, 1H), 6.80-6.73 (m, 3H), 6.53 (d, *J* = 7.6 Hz, 1H), 6.48 (d, *J* = 7.6 Hz, 1H), 6.16 (t, *J* = 7.6 Hz, 1H), 6.05 (d, *J* = 8.6 Hz, 1H), 5.99 (d, *J* = 3.2 Hz, 1H), 5.91 (dd, *J* = 8.6 Hz, *J* = 3.2 Hz, 1H), 3.52 (s, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 194.9, 169.6, 161.8, 143.5, 141.9, 139.5, 134.7, 134.3, 133.6, 130.4, 129.4 (2), 129.1 (2), 118.9, 118.3, 117.3, 117.2, 115.4, 111.4, 64.2 (2); HRMS (ESI-TOF) m/z [M + H]⁺ calcd for C₂₂H₁₈NO₄ 360.1236, found 360.1240; IR film ν_{max}/cm⁻¹ : 3359, 2981, 2934, 2874, 1674, 1595, 1503, 1450, 1306, 1240, 1199, 1149, 1000.

(Z)-2-(2-Hydroxy-3,4-dimethoxyphenyl)-2-((4-methoxyphenyl)imino)-1-phenylethanone (**5g**):

192 mg, 98% yield, yellow solid; mp 168.4 - 169.7 °C; ¹H NMR (300 MHz, CDCl₃) δ 14.15 (s, 1H), 7.79 (d, *J* = 7.4 Hz, 2H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.36 (t, *J* = 7.4 Hz, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 9.0 Hz, 1H), 6.68 (d, *J* = 8.8 Hz, 2H), 6.38 (d, *J* = 9.0 Hz, 1H), 3.96 (s, 3H), 3.87 (s, 3H), 3.68 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 195.2, 169.0, 157.8, 156.8, 156.6, 139.0, 137.2, 134.8, 134.4, 129.5 (2), 129.1 (2), 126.4, 123.6 (2), 114.3 (2), 112.6, 103.1, 60.8, 56.1, 55.4; HRMS (ESI-TOF) m/z [M + H]⁺ calcd for C₂₃H₂₂NO₅ 392.1498, found 392.1482; IR film ν_{max}/cm⁻¹ : 3452, 2984, 2360, 1737, 1514, 1336, 1236, 1045.

(Z)-2-((3-(Benzyloxy)-4-methoxyphenyl)imino)-2-(2-hydroxy-3,4-dimethoxyphenyl)-1-phenyl ethanone (**5h**):

216 mg, 87% yield, yellow solid; mp 135.6 - 136.6 °C; ¹H NMR (300 MHz, CDCl₃) δ 14.10 (s, 1H), 7.76 (d, *J* = 7.7 Hz, 2H), 7.53 (t, *J* = 7.2 Hz, 1H), 7.37 (m, 7H), 6.88 (d, *J* = 8.9 Hz, 1H), 6.69 (d, *J* = 8.3 Hz, 1H), 6.60 (m, 2H), 6.40 (d, *J* = 9.0 Hz, 1H), 4.98 (s, 2H), 3.98 (s, 3H), 3.90 (s, 3H), 3.79 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 195.1, 168.9, 156.4, 147.7, 139.0, 134.6, 134.3, 129.3 (2), 129.0 (2), 128.6 (2), 127.9, 127.2 (2), 126.3, 118.6, 115.0, 112.4, 111.6, 110.3, 110.2, 108.5, 107.7, 103.0, 70.8, 60.7, 56.0 (2); HRMS (ESI-TOF) m/z [M + H]⁺ calcd for C₃₀H₂₈NO₆ 498.1917, found 498.1909; IR film ν_{max}/cm⁻¹ : 3320, 2934, 2840, 1671, 1564, 1513, 1443, 1416, 1399, 1225, 1159.

(Z)-2-(2-Hydroxy-3,4-dimethoxyphenyl)-2-((4-nitrophenyl)imino)-1-phenylethanone (**5i**):

102 mg, 50% yield; yellow cristal, mp 162.3 - 162.9 °C; ¹H NMR (300 MHz, CDCl₃) δ 12.95 (s, 1H), 8.06 (d, *J* = 8.9 Hz, 2H), 7.79 (d, *J* = 7.3 Hz, 2H), 7.60 (d, *J* = 7.3 Hz, 2H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.07 (d, *J* = 8.9 Hz, 2H), 6.95 (d, *J* = 9.0 Hz, 1H), 6.47 (d, *J* = 9.0 Hz, 1H), 3.99 (s, 3H), 3.93 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 193.5, 172.0, 158.4, 156.9, 152.6, 145.6, 137.7, 135.9, 134.6, 130.0 (2), 129.8 (2), 127.9, 125.2 (2), 123.0 (2), 112.4, 104.3, 61.3, 56.7; HRMS (ESI-TOF) m/z [M + H]⁺ calcd for C₂₂H₁₉N₂O₆ 407.1243, found 407.1240; IR film ν_{max}/cm⁻¹ : 3394, 2936, 2849, 1624, 1513, 1448, 1340, 1292, 1247, 1217, 1197, 1171.

(Z)-2-(2-Hydroxy-3,4-dimethoxyphenyl)-1-(4-methoxyphenyl)-2-((4-methoxyphenyl)imino) ethanone (**5j**):

181 mg, 86% yield, yellow solid; mp 210.4 - 211.9 °C; ¹H NMR (300 MHz, CDCl₃) δ 14.29 (s, 1H), 7.79 (d, *J* = 8.7 Hz, 2H), 6.99 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 9.0 Hz, 1H), 6.84 (d, *J* = 8.7 Hz, 2H), 6.72 (d, *J* = 8.7 Hz, 2H), 6.39 (d, *J* = 9.0 Hz, 1H), 3.97 (s, 3H), 3.89 (s, 3H), 3.82

(s, 3H), 3.71 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 193.2, 169.1, 164.7, 157.6, 156.5, 147.9, 138.9 (2), 131.9 (2), 127.4, 126.3, 123.4 (2), 114.3 (2), 114.1 (2), 112.6, 102.8, 60.7, 56.0, 55.5, 55.3; HRMS (ESI-TOF) m/z [M + H]⁺ calcd for C₂₄H₂₄N₂O₆ 422.1604, found 422.1625; IR film ν_{max}/cm⁻¹ : 3422, 2934, 2838, 2360, 1666, 1659, 1593, 1512, 1291, 1198, 1163, 1030.

(Z)-2-(2-Hydroxy-3,4-dimethoxyphenyl)-2-((3-methoxyphenyl)imino)-1-(p-tolyl)ethanone (**5k**):

158 mg, 75% yield, yellow solid; mp 187.6 - 187.9 °C; ¹H NMR (300 MHz, CDCl₃) δ 14.29 (s, 1H), 7.79 (d, J = 8.7 Hz, 2H), 6.99 (d, J = 8.7 Hz, 2H), 6.90 (t, J = 9.0 Hz, 1H), 6.84 (d, J = 8.7 Hz, 2H), 6.72 (d, J = 8.7 Hz, 2H), 6.39 (d, J = 9.0 Hz, 1H), 3.97 (s, 3H), 3.89 (s, 3H), 3.82 (s, 3H), 3.71 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 193.2, 169.1, 164.7, 157.6, 156.5, 147.9, 138.9 (2), 131.9 (2), 127.4, 126.3, 123.4 (2), 114.3 (2), 114.1 (2), 112.6, 102.8, 60.7, 56.0, 55.5, 55.3; HRMS (ESI-TOF) m/z [M + H]⁺ calcd for C₂₄H₂₄N₂O₅ 406.1654, found 406.1657; IR film ν_{max}/cm⁻¹ : 3280, 3003, 2936, 2837, 2358, 1670, 1602, 1584, 1564, 1512, 1290, 1249, 1236, 1145, 1127, 1085.

(Z)-2-(2-Hydroxy-3,4-dimethoxyphenyl)-2-((2-methylquinolin-4-yl)imino)-1-(p-tolyl)ethanone (**5l**):

158 mg, 72% yield, off white solid; mp 237.5 - 238.5 °C; ¹H NMR (300 MHz, CDCl₃) δ 13.38 (s, 1H), 8.09 (d, J = 8.3 Hz, 1H), 7.88 (d, J = 8.3 Hz, 1H), 7.66 - 7.61 (m, 3H), 7.48 (t, J = 7.9 Hz, 1H), 7.05 - 6.97 (m, 3H), 6.74 (s, 1H), 6.45 (d, J = 7.7 Hz, 1H), 4.01 (s, 3H), 3.92 (s, 3H), 2.57 (s, 3H), 2.24 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 192.2, 171.6, 159.1, 157.7, 156.5, 150.2, 148.3, 146.4, 137.2, 131.5, 129.9, 129.7 (2), 129.2 (2), 128.5, 127.4, 125.8, 123.1, 120.9, 112.5, 112.2, 105.2, 103.6, 60.8, 56.1, 25.4, 21.8; HRMS (ESI-TOF) m/z [M + H]⁺ calcd for C₂₇H₂₅N₂O₄ 441.1814, found 441.1817; IR film ν_{max}/cm⁻¹ : 3402, 3059, 2945, 2843, 2359, 1678, 1669, 1583, 1500, 1465, 1448, 1321, 1304, 1241, 1104, 1069.

(Z)-2-(2-Hydroxy-3,4-dimethoxyphenyl)-2-((9-methyl-9H-carbazol-3-yl)imino)-1-(p-tolyl)ethanone (**5m**):

179 mg, 75% yield, yellow solid; mp 174.4 - 175.2 °C; ¹H NMR (300 MHz, CDCl₃) δ 14.61 (s, 1H), 7.98 (d, J = 7.7 Hz, 1H), 7.81 - 7.71 (m, 3H), 7.45 (t, J = 7.6 Hz, 1H), 7.33 - 7.24 (m, 2H), 7.19 (d, J = 6.9 Hz, 2H), 7.10 (d, J = 8.1 Hz, 2H), 6.93 (d, J = 9.0 Hz, 1H), 6.40 (d, J = 9.0 Hz, 1H), 4.02 (s, 3H), 3.89 (s, 3H), 3.70 (s, 3H), 2.26 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 195.1, 168.5, 156.6, 156.4, 145.9, 141.4, 139.1, 137.7, 137.1, 131.9, 129.7 (2), 129.5 (2), 126.2, 126.1, 122.9, 122.5, 120.9, 120.5, 119.0, 114.1, 112.8, 108.6 (2), 102.8, 60.7, 56.0, 29.1, 21.8; HRMS (ESI-TOF) m/z [M + H]⁺ calcd for C₃₀H₂₇N₂O₄ 479.1979, found 479.1974; IR film ν_{max}/cm⁻¹ : 3202, 2934, 2839, 2359, 1666, 1609, 1588, 1511, 1466, 1450, 1432, 1330, 1290, 1183, 1162, 981.

(Z)-2-(2-Hydroxyphenyl)-2-((9-methyl-9H-carbazol-3-yl)imino)-1-phenylethanone (**5n**):

137 mg, 68% yield, yellow solid; mp 182.5 - 183.0 °C; ¹H NMR (300 MHz, CDCl₃) δ 14.08 (s, 1H), 8.00 (d, J = 7.7 Hz, 1H), 7.86 (d, J = 7.2 Hz, 2H), 7.80 (d, J = 1.8 Hz, 1H), 7.47 - 7.41 (m, 2H), 7.36 - 7.30 (m, 4H), 7.25 - 7.15 (m, 5H), 6.84 (t, J = 8.1 Hz, 1H), 3.73 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 196.0, 169.0, 162.0 (2), 141.6, 139.8, 137.9, 134.7, 134.4, 133.5, 130.4, 129.4 (2), 129.1 (2), 126.3, 123.0, 122.7, 121.0, 120.6, 119.2, 118.9, 118.4, 117.6, 114.4, 108.8 (2), 29.3; HRMS (ESI-

TOF) m/z [M + H]⁺ calcd for C₂₇H₂₁N₂O₂ 405.1603, found 405.1591; IR film ν_{max}/cm⁻¹ : 3264, 3002, 2856, 1675, 1580, 1492, 1442, 1354, 1256, 1207.

(Z)-2-(2-Hydroxy-3,4-dimethoxyphenyl)-2-((1-methyl-1H-indol-5-yl)imino)-1-phenylethanone (**5o**):

149 mg, 72% yield, yellow solid; mp 147.5 - 147.9 °C. ¹H NMR (300 MHz, CDCl₃) δ 14.58 (s, 1H), 7.83 (d, J = 8.0 Hz, 2H), 7.46 (t, J = 7.0 Hz, 1H), 7.33 (t, J = 7.7 Hz, 2H), 7.28 (d, J = 2.0 Hz, 1H), 7.12 (d, J = 8.7 Hz, 1H), 7.01 - 6.95 (m, 2H), 6.90 (d, J = 9.0 Hz, 1H), 6.40 (d, J = 9.1 Hz, 1H), 6.37 (d, J = 2.0 Hz, 1H), 4.00 (s, 3H), 3.90 (s, 3H), 3.69 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 195.3, 167.7, 156.3, 156.1, 137.8 (2), 134.7, 134.1, 134.0, 129.4, 129.0 (2), 128.6 (2), 128.1, 125.8, 117.0, 113.8, 112.4, 109.2, 102.5, 101.1, 60.4, 55.7, 32.6; HRMS (ESI-TOF) m/z [M + H]⁺ calcd for C₂₅H₂₃N₂O₄ 415.1658, found 415.1657; IR film ν_{max}/cm⁻¹ : 3445, 2936, 2840, 2360, 1670, 1614, 1592, 1484, 1292, 1222, 1125, 1085.

General Procedure for the synthesis of 1a-c and characterization data

Benzofuran **3** (0.750 mmol, 1.5 equiv), aniline **2a** (0.500 mmol, 1.00 equiv), Pd₂(dba)₃ (0.025 mmol, 0.05 equiv), Xphos (0.050 mmol, 0.10 equiv), cesium carbonate (1.1 mmol, 2.20 equiv) and toluene (5 mL) were added to a dried Schlenk tube (30 mL) under air atmosphere. After the mixture was heated to 130°C and stirred for 16 hours, it was cooled to room temperature. The mixture was diluted with ethyl acetate (10 mL), filtered through a celite pad and concentrated. Dry DMF (5 mL) was added to the resulting solid and the mixture was cooled to 0°C. Sodium hydride (2.5 mmol, 5 equiv) was added and the mixture was stirred at 0°C for 30 min. Methyl iodide was added slowly and the crude mixture was stirred at r.t. for 2h. Water (5 mL) was added slowly and the product was extracted with ethyl acetate (3x10 mL). The combined organic extracts were dried over anhydrous sodium sulfate. The drying agent was removed *in vacuo* leaving a crude solid. The solid was purified on silica gel chromatography (cyclohexane/ethyl acetate = 1/1) to afford the corresponding product **1**.

N-(6,7-Dimethoxy-2-phenylbenzofuran-3-yl)-N,2-dimethylquinolin-4-amine (**1a**):

100 mg, 47% yield, off white solid; mp 204.6 - 205.1 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.02 (d, J = 7.8 Hz, 2H), 7.82 (d, J = 8.8 Hz, 2H), 7.38 (m, 3H), 7.29 (t, J = 7.8 Hz, 1H), 6.97 (t, J = 7.8 Hz, 1H), 6.90 (s, 1H), 6.48 (d, J = 8.8 Hz, 1H), 6.22 (d, J = 8.8 Hz, 1H), 4.16 (s, 3H), 3.72 (s, 3H), 3.37 (s, 3H), 2.68 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 158.9, 152.8, 149.3, 146.2, 145.0, 134.6, 129.7, 129.0, 128.9 (3), 128.4, 127.4, 125.2 (2), 124.4, 123.3, 122.2, 121.1, 112.6, 110.0, 109.7, 107.5, 61.0, 57.0, 41.6, 25.7; HRMS (ESI-TOF) m/z [M + H]⁺ calcd for C₂₇H₂₅N₂O₃ 425.1865, found 425.1872; IR film ν_{max}/cm⁻¹ : 2932, 2837, 1736, 1619, 1562, 1507, 1296, 1267, 1091, 1069; HPLC [H₂O, 0.1% ac. form. / ACN - gr 5-100% - 20 min] r. t. : 12.52 min., purity : 100%.

N-(6,7-Dimethoxy-2-(p-tolyl)benzofuran-3-yl)-N,2-dimethylquinolin-4-amine (**1b**):

77 mg, 35% yield, off white solid; mp 254.7 - 254.9 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.76 (d, J = 8.6 Hz, 1H), 7.90 (d, J = 8.6 Hz, 1H), 7.68-7.62 (m, 3H), 7.25 (d, J = 8.1 Hz, 2H), 7.17 (t, J = 8.1 Hz, 1H), 6.95 (s, 1H), 6.81

(d, $J = 8.6$ Hz, 1H), 6.57 (d, $J = 8.6$ Hz, 1H), 4.28 (s, 3H), 3.90 (s, 3H), 3.72 (s, 3H), 3.11 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 157.2, 154.4, 149.9, 148.0, 140.1, 139.7, 135.7, 132.9, 131.4 (2), 130.0, 126.6, 125.3 (2), 124.1, 121.0, 120.3, 118.2, 111.4, 110.5, 108.5, 105.3, 89.9, 61.1, 57.1, 43.7, 21.5, 20.6; HRMS (ESI-TOF) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{28}\text{H}_{27}\text{N}_2\text{O}_3$ 439.2022, found 439.1989; IR film $\nu_{\text{max}}/\text{cm}^{-1}$: 2863, 2788, 1633, 1590, 1506, 1439, 1403, 1383, 1268, 1225, 1101, 1091; HPLC [H_2O , 0.1% ac. form. / ACN – gr 5-100% - 20 min.] r.t. : 13.22 min., purity: 100%.

N-(6,7-Dimethoxy-2-(thiophen-3-yl)benzofuran-3-yl)-*N*,2-dimethylquinolin-4-amine (**1c**):

84 mg, 39% yield, white solid; mp 248.2 - 248.6 °C; ^1H NMR (300 MHz, CDCl_3) δ 7.90 (d, $J = 8.4$ Hz, 1H), 7.74 (d, $J = 8.4$ Hz, 1H), 7.52 (d, $J = 4.0$ Hz, 1H), 7.41 (t, $J = 7.7$ Hz, 1H), 7.31 (d, $J = 4.0$ Hz, 1H), 7.05 (t, $J = 4.0$ Hz, 1H), 7.00 (t, $J = 7.7$ Hz, 1H), 6.88 (s, 1H), 6.54 (d, $J = 8.5$ Hz, 1H), 6.31 (d, $J = 8.5$ Hz, 1H), 4.15 (s, 3H), 3.74 (s, 3H), 3.42 (s, 3H), 2.70 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 158.3, 153.6, 149.5, 148.0, 145.0, 144.3, 134.6, 130.6, 129.6, 127.8 (2), 126.8, 125.3, 125.1, 124.7, 123.5, 121.7, 120.6, 112.1, 109.8, 107.4, 61.0, 57.0, 41.8, 25.1; HRMS (ESI-TOF) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{25}\text{H}_{23}\text{N}_2\text{O}_3\text{S}$ 431.1429, found 431.1432; IR film $\nu_{\text{max}}/\text{cm}^{-1}$: 2854, 2776, 1642, 1604, 1515, 1430, 1394, 1392, 1276, 1112, 1083; HPLC [H_2O , 0.1% ac. form. / ACN – gr 5-100% - 20 min] r. t.: 12.13 min., purity: 96%.

SUPPORTING INFORMATION AVAILABLE: ^1H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

ACKNOWLEDGMENT.

Authors gratefully acknowledge support of this project by CNRS, Univ. Paris-Saclay, and by La Ligue Nationale Contre le Cancer through an Equipe Labellisée 2014 grant. Ilhem Khelifi and Guangkuan Zhao thank respectively the MRES (Ministère de la Recherche et de l'Enseignement Supérieur) and the Chinese Scholarship Council (CSC) for Ph.D. fundings. Dr. Serge Turcaud, from Univ. Paris V, is warmly thanked for his help during experiments achieved in glove box. Our laboratory (BioCIS UMR 8076) is a member of the laboratory of excellence LERMIT supported by a grant from ANR (ANR-10-LABX-33).

REFERENCES

- (1) (a) Pettit, G. R.; Singh, S. B.; Hamel, E.; Lin, C. M.; Alberts, D. S.; Garcia-Kendall, D. Isolation and structure of the strong cell growth and tubulin inhibitor combretastatin A-4. *Experientia*, **1989**, *45*, 209-210. (b) Lin, C. M.; Ho, H. H.; Pettit, G. R.; Hamel, E., Antimitotic natural products combretastatin A-4 and combretastatin A-2: studies on the mechanism of their inhibition of the binding of colchicine to tubulin. *Biochemistry* **1989**, *28*, 6984-6991.
- (2) <http://www.mateon.com/>
- (3) (a) Messaoudi, S.; Tréguier, B.; Hamze, A.; Provot, O.; Peyrat, J. F.; De Losada, J.R.; Liu, J. M.; Bignon, J.; Wdziejczak-Bakala, J.; Thoret, S.; Dubois, J.; Brion, J. D.; Alami, M. *Isocombretastatins* A versus combretastatins A: The forgotten *iso*CA-4 isomer as a highly promising cytotoxic and antitubulin agent. *J. Med. Chem.* **2009**, *52*, 4538-4542. (b) Soussi, M. A.; Provot, O.; Bernadat, G.; Bignon, J.; Wdziejczak-Bakala, J.; Desravines, D.; Dubois, J.; Brion, J. D.;

Messaoudi, S.; Alami, M.; Discovery of azaisoerianin derivatives as potential antitumors agents. *Eur. J. Med. Chem.* **2014**, *78*, 178-189. (c) Khelifi, I.; Naret, T.; Renko, D.; Hamze, A.; Bernadat, G.; Bignon, J.; Lenoir, C.; Dubois, J.; Brion, J. D.; Provot, O.; Alami, M. Design, synthesis and anticancer properties of *isocombretaquinolines* as potent tubulin assembly inhibitors. *Eur. J. Med. Chem.* **2017**, *127*, 1025-1034. (d) Hamze, A.; Rasolofonjatovo, E.; Provot, O.; Mousset, C.; Veau, D.; Rodrigo, J.; Bignon, J.; Liu, J.M.; Wdziejczak-Bakala, J.; Thoret, S.; Dubois, J.; Brion, J.D.; Alami, M. B-Ring Modified *iso*Combretastatin A-4 Analogues Endowed with Interesting Anticancer Activities. *ChemMedChem* **2011**, *6*, 2179-2191.

(4) Kremmidiotis, G.; Leske, A. F.; Lavranos, T. C.; Beaumont, D.; Gasic, J.; Hall, A.; O'Callaghan, M.; Matthews, C. A.; Flynn, B., BNC105: a novel tubulin polymerization inhibitor that selectively disrupts tumor vasculature and displays single-agent antitumor efficacy. *Mol. Cancer Ther.* **2010**, *9*, 1562-1573.

(5) (a) Ji, J.; Li, T.; Bunnelle, W. H., Selective Amination of Polyhalopyridines Catalyzed by a Palladium-Xantphos Complex. *Org. Lett.* **2003**, *5*, 4611-4614. (b) Yin, J.; Zhao, M. M.; Huffman, M. A.; McNamara, J. M., Pd-catalyzed N-arylation of heteroarylamines. *Org. Lett.* **2002**, *4*, 3481-4. (c) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Licandro, E.; Maiorana, S.; Perdicchia, D., Synthesis of *N,N*-Dialkyl-*N'*-arylhydrazines via Palladium-Catalyzed N-Arylation by Using *N,N*-Dialkylhydrazines/ 2LiCl Adducts. *Org. Lett.* **2005**, *7*, 1497-1500.

(6) For a NMR comparison with similar products, see: Zhou, Y.; Yan, W.; Cao, D.; Shao, M.; Li, D.; Wang, F.; Yang, Z.; Chen, Y.; He, L.; Wang, T.; Shen, M.; Chen, L., Design, synthesis and biological evaluation of 4-anilinoquinoline derivatives as novel potent tubulin depolymerization agents. *Eur. J. Med. Chem.* **2017**, *138*, 1114-1125.

(7) All secondary diarylamines **4** turn out to be unstable in air and during purification on silica gel leading to ketoimines **5** in small amount together with many unidentified by-products (TLC multi-spots). For example, after 50 h under air, diarylamine **4a** was totally transformed; ketoimine **5a** was isolated in 20 % yield, the mass balance being constituted by unidentified by-products. Therefore, it is necessary to rapidly filter the diarylamines **4** on a pad of celite and engage them immediately in the *N*-methylation step, leading to *iso*Coquin derivatives **1**.

(8) (a) Wheatley, W.B.; Fitzgibbon, W.E.; Cheney, L.C., 1,2-Diphenyl-2-Aminoethanols. I. Synthesis of some erythro-1,2-Diphenyl-2-Alkylaminoethanols. *J. Org. Chem.*, **1953**, *18*, 1564-1571. (b) Jousseume, B.; Vilot, N.; Ricci, A.; Tiekink, E.R.T., Imidoystannanes, improved preparation and uses as acylation equivalents. *J. Chem. Soc., Perkin Trans. I*, **1994**, 2283-2288. (c) Miyashita, A.; Matsuda, H.; Higashino, T., Catalytic Action of Azolium Salts. III. Aroylation of *N*-Phenylbenzimidoyl Chlorides with Aromatic Aldehydes in the Presence of 1, 3-Dimethylimidazolium Iodide. *Chem. Pharm. Bull.* **1992**, *40*, 2627-2631. (d) Barluenga, J.; Aznar, F.; Liz, R., Oxidative alkyl- and aryl-aminomercuriation of prop-2-ynyl alcohols. Synthesis of *N*-substituted α -iminoketones, α -di-imines, and α -amino propionamides. *J. Chem. Soc. Perkin Trans. I*, **1983**,

1093-1098. (e) Farcas, S.; Namy, J.-M., *Tetrahedron*, **2001**, *57*, 4881-4888.

(9) For benzofuran ring-opening under basic or oxidative conditions, see: (a) Stoermer, R.; Kahlert, B., Ueber das 1-und 2-Brom-cumaron *Ber., Dtsch. Chem. Ges.*, **1902**, *35*, 1633-1640. (b) Ishii, H.; Ishikawa, Y., Mizukami, K.; Mitsui, H.; Ikeda, N., Oxidation of 6-Methyl-2-phenylbenzofuran with Chromic Acid under Various Conditions. An Abnormal Dimeric Oxidation Product of the Benzofuran Derivative. Studies on the Heterocyclic Quinones. *Chem. Pharm. Bull.* **1971**, *19*, 970-997. (c) Srinivas, K.; Sharma, R.; Ramana, C.V., Interrupting Base-Mediated Benzofuran Ring Transformation with Michael Acceptors *J. Org. Chem.* **2017**, *82*, 9816-9823.

(10) (a) Cuthbertson, J.; Gray, V.J.; Wilden, J.D., Observations on transition metal free biaryl coupling: potassium *tert*-butoxide alone promotes the reaction without diamine or phenanthroline catalysts *Chem. Commun.* **2014**, *50*, 2575-2578. (b) see also: Yanagisawa, S.; Ueda, K.; Tanigushi, T.; Itami, K., Potassium *t*-Butoxide Alone Can Promote the Biaryl Coupling of Electron-Deficient Nitrogen Heterocycles and Haloarenes *Org. Lett.* **2008**, *10*, 4673-4676.

(11) (a) Encina, M.V.; Diaz, S.; Lissi, E., Reactivity of amines toward *tert*-butoxy radicals: Effect of solvent and amine structure *Int. J. Chem. Kinetics* **1981**, *13*, 119-123. (b) Nazran, A. S.; Griller, D., Hydrogen abstraction from amines: formation of aminyl vs. α -aminoalkyl radicals *J. Am. Chem. Soc.* **1983**, *105*, 1970-1971.

(12) When achieving the reaction of **2a** with **3a** under optimized conditions using Cs₂CO₃ instead of NaOtBu, dimer **W**₂ was not detected.

(13) Shen, H.-Q.; Gao, X.; Liu, C.; Hu, S.-B.; Zhou, Y.-G, A Hydrogenation/Oxidative Fragmentation Cascade for Synthesis of Chiral 4,5-Dihydro-1H-benzo[d]azepin-1-ones. *Org. Lett.* **2016**, *18*, 5920-5923.

(14) (a) Lavanya, A; Sribalan, R.; Padmini, V., Synthesis and biological evaluation of new benzofuran carboxamide derivatives *J. Saudi Chem. Soc.* **2017**, *21*, 277-285. (b) Yamuna, A.J.; Vaidya, V.P., Shruthi, E., Mahadevan, K.M., Synthesis, characterization and biological activities of some benzofuopyrimidine derivatives *Int. J. Pharm. Pharm. Sci.* **2013**, *5*, 450-455.

(15) Under an O₂ atmosphere, no Buchwald coupling reaction of **2a** and **3a** took place.

Table of contents

Ar = phenyl, quinolines, carbazoles, indoles
 R = H, OMe; R^1 = H, OMe, Me.

- Rapid "one pot" access to unsymmetrical α -keto-imines
- 15 exemples (50 to 98%)
- Possibility to prepare separately Buchwald amines using Cs_2CO_3 in place of $NaOtBu$