proceedings

MDPI

Proceedings

Multicomponet Synthesis of Pyrrolo [3,4-*a*] Carbazole-1,3-Diones †

Ana Bornadiego, Ana G. Neo, Jesús Díaz * and Carlos F. Marcos *

Departamento de Química Orgánica e Inorgánica, Facultad de Veterinaria, Universidad de Extremadura, Avda, Universidad, s/n, 10003 Cáceres, Spain; bornadiego_a@hotmail.com (A.B.); aneo@unex.es (A.G.N.)

* Correspondence: jdal@unex.es (J.D.); cfernan@unex.es (C.F.M.); Tel.: +34-9-2725-7158 (C.F.M.)

† Presented at the 23rd International Electronic Conference on Synthetic Organic Chemistry, 15 November–15 December 2019; Available online: https://ecsoc-23.sciforum.net/.

Published: 14 November 2019

Abstract: Pyrrolocarbazoles are important structural motives present in many natural products and pharmaceuticals. Particularly, pyrrolo [3,4-*a*] carbazole-1,3-diones have attracted much attention as analogues of bioactive compounds, such as anticancer agent granulatimide. Surprisingly, only a few methods for the synthesis of these compounds have been reported in the literature, and they are almost limited to the Diel–Alder cycloaddition of 3-vinylindoles. We have recently developed a multicomponent synthesis of polysubstituted anilines starting from α,β-unsaturated carbonyls, isocyanides and dienophiles. Here we report the application of this tandem [4 + 1]–[4 + 2] cycloaddition procedure for the synthesis of 4-amino-5-arylisoindoline-1,3-diones, which are then cyclized by means of a metal catalyzed intramolecular C-N coupling, affording structurally diverse, natural product-like pyrrolo [3,4-*a*] carbazole-1,3-diones with high yields and selectivities.

Keywords: isocyanides; multicomponent reaction; pyrrolocarbazoles; cycloaddition

1. Introduction

Carbazole is a privileged heterocyclic structure, present in a wide range of naturally occurring alkaloids [1,2] and pharmacologically active compounds [3–6]. Carbazoles have also found important applications as photoactive organic functional materials, such as organic light-emitting diodes (OLEDs) [7,8] and organic photovoltaic devices [9,10].

Particularly, indolocarbazoles and the related pyrrolocarbazoles have attracted much interest for their biological properties [11]. For example, naturally occurring Staurosporin (1), Rebeccamycin (2) and Granulatimide (3) are lead structures in the development of novel anticancer agents due to their potent kinase inhibitor activities [12] (Figure 1). Furthermore, some pyrrolo [3,4-*a*] carbazoles have been developed as checkpoint kinase 1 inhibitors structurally related to granulatimide [13], and topoisomerase II poisons [14].

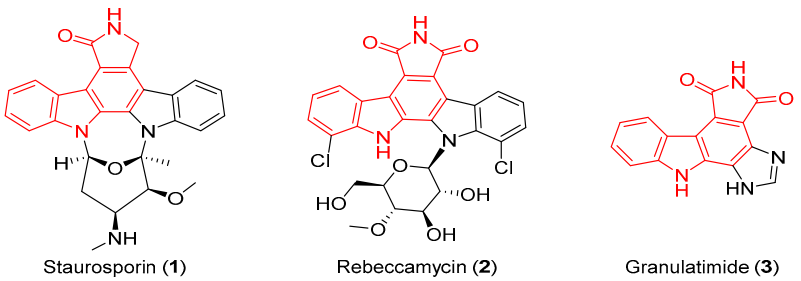


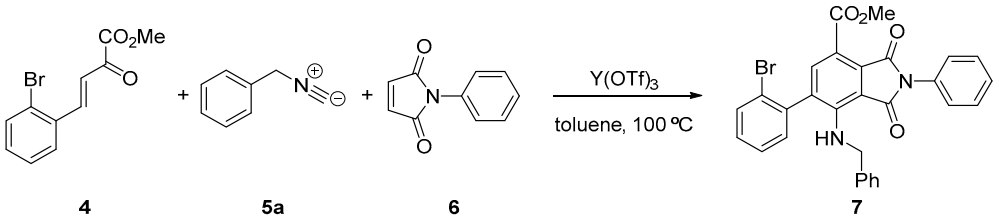
Figure 1. Bioactive isoindolopyrroles.

Surprisingly, little attention has been paid to the synthesis of pyrrolo [3,4-*a*] carbazoles, in spite of the many reports on the synthesis of some of their isomers, such as 3,6-dihydropyrrolo [2,3-*c*] carbazoles [15]. Most of the methods to obtain [3,4-*a*] carbazoles are based on the Diels–Alder cycloaddition of 3-vinylindoles [13,14,16,17], which often requires harsh reaction conditions and non-readily available starting materials [12,13,15,16]. Thus, it is vital to develop new efficient and flexible syntheses of these important heterocyclic structures.

Here, we propose a two-step synthesis of pyrrolo [3,4-*a*] carbazoles by the succession of a tandem [4 + 1]–[4 + 2] cycloaddition of isocyanides, α,β-unsaturated carbonyls and maleimide dienophiles, followed by a metal catalyzed intramolecular C-N coupling of the resulting 4-amino-5-arylisoindoline-1,3-diones. Pyrrololo [3,4-*a*] carbazoles 11 [18] and 17a [19] and their isoindole precursors have been previously reported by us, while pyrrololo [3,4-*a*] carbazole 17b is a novel compound.

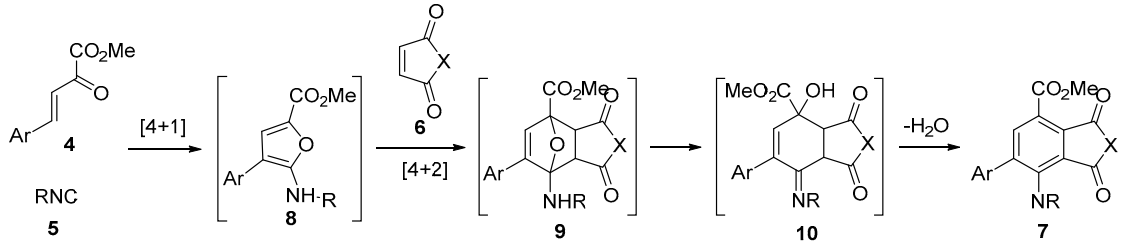
2. Results and Discussion

In a first approach, (*E*)-methyl 4-(2-bromophenyl)-2-oxobut-3-enoate (4), benzyl isocyanide (5a) and *N*-phenylmaleimide (6) were heated in toluene at 100 °C in the presence of a catalytic amount of yttrium trifluoromethanesulfonate (Scheme 1). In these conditions, methyl 7-(benzylamino)-6-(2-bromophenyl)-1,3-dioxo-2-phenylisoindoline-4-carboxylate (7) was obtained in 55% yield, as a yellow solid [18].



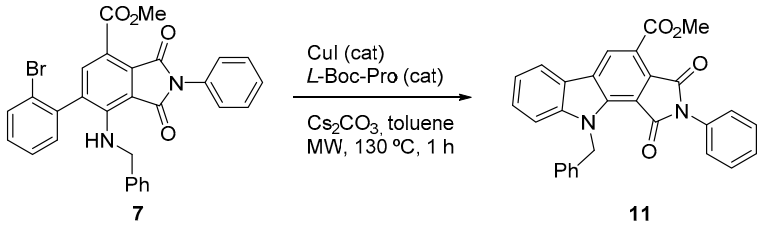
Scheme 1. Tandem [4 + 1]/[4 + 2] synthesis of isoindoline-1,3-dione (**7**).

The mechanism, outlined in Scheme 2, involves the [4 + 1] cycloaddition of α,β-unsaturated carbonyl (4) and isocyanide (5) to give unstable aminofuran (8). This is trapped in situ by maleimide (6) by means of a Diels–Alder reaction, leading to 7-oxabicyclo [2.2.1] heptene (9). Finally, oxygen ring opening and aromatization affords isoindole (7).



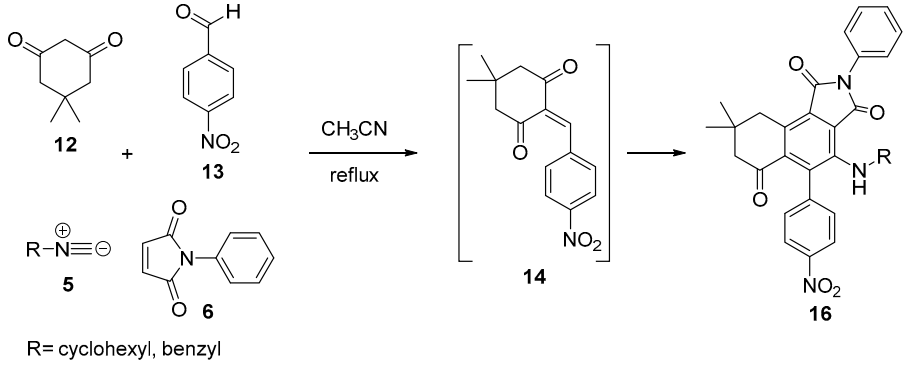
Scheme 2. Proposed mechanism for the tandem [4 + 1]/[4 + 2] cycloaddition.

Copper catalyzed intramolecular N–C coupling of isoindole 7 was efficiently achieved under microwave activation in toluene, in the presence of Cs_2CO_3 and 30% mol of *L*-Boc-proline. Thus, pyrrolocarbazole 11 was obtained in an excellent yield (Scheme 3) [18].



Scheme 3. Synthesis of pyrrolo [3,4-*a*] carbazole (**11**).

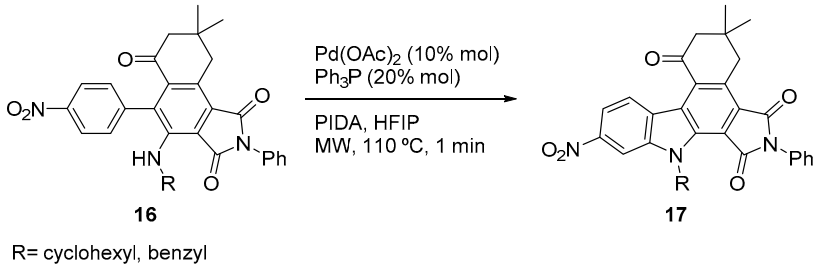
Structural diversity on final pyrrolocarbazoles could be increased by generating the starting α,β-unsaturated carbonyl compounds in situ. Notably, the Knoevenagel condensation of cyclic 1,3-dicarbonyls (12) and aldehydes (13) can readily generate α,β-unsaturated carbonyl compounds (14). Cycloaddition of these resulting heterodienes (14) with isocyanides (5) is known to afford 2-aminofuranes (15) [20,21], and subsequent Diels–Alder reaction with dienophiles (6) present in the reaction medium could purportedly afford tricyclic isoindoles (16) in the same pot (Scheme 4).



Scheme 4. Four-component synthesis of isoindoline-1,3-dione (**16**).

Thus, equimolar amounts of dimedone (12), *p*-nitrobenzaldehyde (13), cyclohexyl isocyanide (5b) and *N*-phenylmaleimide (6) were stirred in refluxing acetonitrile for 22 h, affording the expected. 4-(cyclohexylamino)-8,8-dimethyl-5-(4-nitrophenyl)-2-phenyl-8,9-dihydro-1*H*-benzo[*e*]isoindole-1,3,6(2*H*,7*H*)-trione (16a) with a 90% yield (Scheme 4) [19]. Interestingly, in contrast with our previous results, the addition of catalytic $Y(OTf)_3$ [18] did not improve the reaction. Analogously, the reaction with benzyl isocyanide (5c) affords the corresponding pentylaminoisoindole (16b).

In this case, dehydrogenative N-C bond forming cyclization of the cycloadducts (16a,b) yields straightforwardly natural product-like pyrrolocarbazoles (17a,b). Thus, isoindoline-1,3-dione (16a) was subjected to a palladium catalysed dehydrogenative cyclization, using phenyliodine (III) diacetate (PIDA) as an external oxidant [22–25]. The reaction is completed under microwave irradiation at 110 °C in hexafluoroisopropanol (HFIP) in just one minute, affording pyrrolocarbazole 17a in 58% yield (Scheme 5) [19]. Analogously, pyrrolocarbazole 17b was obtained in similar conditions from isoindoline 16b. Pyrrolo[3,4-*a*]carbazole-1,3-diones (17a,b) can be considered analogues of granulatimide (3) in which the position of the imidazole ring is occupied by a pyrrole-2,5-dione, while a cyclohexanone is the place of the pyrrole-2,5-dione [26]. Remarkably, these complex pentacyclic compounds are readily and efficiently synthesized from simple starting materials in a two-step reaction sequence.



Scheme 5. Synthesis of pyrrolo [3,4-*a*]carbazole (**17**).

3. Conclusions

In conclusion, we have effectively designed a straightforward and versatile synthesis of natural product-like pyrrolo [3,4-*a*] carbazole-1,3-diones. This two-step method involves a multicomponent tandem succession of [4 + 1] and [4 + 2] cycloadditions, ring opening and aromatization, followed by an intramolecular metal catalysed N-C coupling. Moreover, the first step can be combined in the same pot with a Knoevenagel condensation, substantially increasing the structural diversity attainable by this procedure.

Initially, intermediate 4-amino-5-(2-bromoaryl) isoindoline-1,3-diones were cyclized in the presence of catalytic CuI to give the corresponding pyrrolocarbazoles. Successfully, we developed a significantly improved procedure that does not require a halogen on the aryl group. Conversely, an aryl C-H is efficiently coupled with an amino N, in the presence of catalytic $Pd(OAc)_2$ under the oxidative action of PIDA, in just one minute under microwave irradiation.

In this way, biologically important pyrrolocarbazoles, which would otherwise require long and complex syntheses, can be easily obtained in a high yielding, convergent and atom economic process involving readily available starting materials.

4. Experimental Section

Synthesis of methyl 7-(benzylamino)-6-(2-bromophenyl)-1,3-dioxo-2-phenylisoindoline-4-carboxylate (7): To a solution of (*E*)-methyl 4-(2-bromophenyl)-2-oxobut-3-enoate 4 (81 mg, 0.3 mmol) in dry toluene (1.2 mL), yttrium trifluoromethanesulfonate (8 mg, 5% mol), benzyl isocyanide 5a (66 µL, 0.54 mmol, 1.8 equivalent) and *N*-phenylmaleimide 6 (62 mg, 0.36 mmol, 1.2 equivalent) were added under a nitrogen atmosphere. The resulting mixture was heated 3 h at 100 °C. The reaction was cooled to rt, 10% HCl (5 mL) was added and the organic phase was extracted with CH_2Cl_2, dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (silica gel, hexane–EtOAc gradient), and isoindoline 7 (55%) was obtained as a yellow solid; mp: 175–177 °C; IR (cm^{-1}) 3428, 2962, 1766, 1696, 1620; ^1H NMR (500 MHz, $CDCl_3$) δ 8.31 (s, NH), 7.62 (s, 1H), 6.95–6.94 (m, 2H), 6.81–6.69 (m, 5H), 3.96 (s, 3H), 3.22 (s, 3H), 2.08 (s, 3H), 2.06 (s, 3H), 2.05 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 169.50 (C), 165.60 (C), 164.56 (C), 147.55 (C), 140.89 (CH), 140.03 (C), 137.97 (C), 132.69 (CH), 131.80 (CH), 131.62 (C), 131.49 (C), 130.87 (C), 130.23 (CH), 129.21 (CH), 128.86 (CH), 128.24 (CH), 127.82 (CH), 127.44 (CH), 127.39 (CH), 126.86 (CH), 124.65 (C), 117.12 (C), 113.32 (C), 52.61 (CH_2), 49.03 (CH_3); MS (EI) m/z (%) 542 (M^+, 15), 540 (M^+, 16), 461 (27), 429 (43), 383 (10), 91 (100); HRMS (EI) calculated for $C_{29}H_{21}N_2O_4Br$: 540.0685; found: 540.0681.

Synthesis of methyl 10-benzyl-1,3-dioxo-2-phenyl-1,2,3,10-tetrahydropyrrolo [3,4-a] carbazole-4-carboxylate (11): A solution of isoindoline **7** (16 mg, 0.03 mmol), CuI (2 mg, 0.010 mmol, 35% mol), Cs_2CO_3 (19 mg, 0.06 mmol, 2 equivalent) and *L*-Boc-proline (2 mg, 0.009 mmol, 31% mol) in toluene (1 mL) was heated for 1 h at 130 °C in a microwave oven. The crude product was filtered through a short pad of SiO_2 and washed with CH_2Cl_2. The solvents were removed in the rotary evaporator to give pyrrolocarbazole 11 (94%), obtained as a yellow solid; mp: 226–228 °C; IR (cm^{-1}) 2923, 1762, 1702, 1493, 1269, 1170, 804; ^1H NMR (500 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.18 (d, J = 7.8 Hz, 1H), 7.59–7.53 (m, 1H), 7.51–7.46 (m, 2H), 7.45–7.41 (m, 3H), 7.41–7.36 (m, 2H), 7.25–7.17 (m, 3H), 7.05 (d, J = 6.7 Hz, 2H), 6.40 (s, 2H), 4.05 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 167.56 (C), 166.57 (C), 165.80 (C), 143.34 (C), 137.65 (C), 137.48 (C), 131.75 (C), 130.15 (C), 129.19 (CH), 128.87 (CH), 128.29 (CH), 127.96 (C),

127.49 (CH), 127.13 (CH), 126.27 (CH), 126.22 (CH), 122.55 (C), 121.90 (CH), 121.40 (C), 121.21 (CH), 113.92 (C), 111.31 (CH), 53.17 (CH_3), 50.48 (CH_2); MS (CI) m/z (%) 461 (M^+ + 1, 21), 429 (21), 339 (3), 199 (17), 91 (100); HRMS (EI) calculated for $C_{29}H_{20}N_2O_4$: 460.1423; found: 460.1423.

Synthesis of 4-(Cyclohexylamino)-8,8-dimethyl-5-(4-nitrophenyl)-2-phenyl-8,9-dihydro-1*H*-benzo[*e*]isoindole-1,3,6(2*H*,7*H*)-trione (16a): To a solution of dimedone 12 (140 mg, 1 mmol) in dry acetonitrile (2 mL), *p*-nitrobenzalaldehyde 13 (151 mg, 1 mmol), *N*-phenylmaleimide 6 (173 mg, 1 mmol) and cyclohexyl isocyanide 5b (137 μL, 1.1 mmol) were successively added. The resulting mixture was stirred and heated to reflux under a nitrogen atmosphere until the starting materials were consumed, as judged by tlc. The precipitate was then filtered and washed with a mixture of cyclohexane and ethyl acetate. To the resulting washed mixture, a 1 N HCl solution was added and extracted with ethyl acetate. The organic layer was evaporated and then subjected to column chromatography (silica gel, gradient from cyclohexane to cyclohexane-EtOAc 70:30). The fractions obtained by filtration and chromatography were combined, giving the desired product 16a (28 h, 398 –mg, 73%); mp: 197–206 °C; IR (cm^{-1}): 3433, 2956, 1751, 1702, 1596; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.24 (d, *J* = 8.3 Hz, 2H), 7.52 (t, *J* = 7.5 Hz, 2H), 7.43 (d, *J* = 7.6 Hz, 3H), 7.33 (t, *J* = 9.9 Hz, 2H), 7.22 (d, *J* = 6.9 Hz, 3H), 6.98 (d, *J* = 6.3 Hz, 2H), 6.85 (s, 1H), 3.81 (s, 2H), 3.37 (s, 2H), 2.46 (s, 2H), 1.11 (s, 6H) ppm; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): 198.2 (C), 168.2 (C), 166.9 (C), 147.4 (C), 145.7 (C), 145.4 (C), 138.5 (C), 137.5 (C), 134.7 (C), 134.3 (CH), 132.5 (C), 131.5 (C), 130.4 (CH), 129.3 (CH), 129.2 (C), 128.8 (CH), 128.4 (CH), 127.8 (CH), 127.3 (CH), 126.7 (CH), 126.2 (CH), 123.7 (CH), 117.8 (C), 54.5 (CH_2), 51.0 (CH_2), 38.8 (CH_2), 33.6 (C), 28.4 (CH_3) ppm; HRMS (ESI-Q-TOF) m/z: $[M + H]^+$ calculated for $C_{33}H_{28}N_3O_5$ 546.2023; found: 546.2031.

Synthesis of 4-(Benzylamino)-8,8-dimethyl-5-(4-nitrophenyl)-2-phenyl-8,9-dihydro-1*H*-benzo[*e*]isoindole-1,3,6(2*H*,7*H*)-trione (16b): Following the above described procedure for 16a, the compound 16b was obtained from dimedone (12), 1-benzylisocyanide (5a), *N*-phenylmaleimide (6) and 4-nitrobenzaldehyde (13) as an orange solid (13 h, 226 mg, 43%); mp: 68–74 °C; IR (cm^{-1}): 3397, 2956, 1755, 1702, 1598; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.30 (d, *J* = 8.7 Hz, 2H), 7.55–7.50 (m, 2H), 7.43 (d, *J* = 7.7 Hz, 3H), 7.41–7.38 (m, 2H), 3.35 (s, 2H), 2.47 (t, *J* = 7 Hz, 2H), 2.47 (s, 2H), 1.30 (quin, 2H), 1.19–1.04 (m, 5H), 1.11 (s, 6H), 0.80 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): 198.4 (C), 168.5 (C), 167.0 (C), 147,3 (C), 146.4 (C), 146.1 (C), 137.4 (C), 134.0 (C), 131.6 (C), 131.5 (C), 130.4 (CH), 129.3 (CH), 129.0 (C), 128.4 (CH), 126.7 (CH), 123.6 (CH), 116.8 (C), 54.5 (CH_2), 46.9 (CH_2), 38.7 (CH_2), 33.6 (C), 30.3 (CH_2), 28.7 (CH_2), 28.4 (CH_3), 22.3 (CH_2), 14.00 (CH_3) ppm; HRMS (ESI-Q-TOF) m/z: $[M + H]^+$ calculated for $C_{31}H_{32}N_3O_5$: 526.2336; found: 526.2334.

Synthesis of 12-Cyclohexyl-5,5-dimethyl-10-nitro-2-phenyl-4,5,6,12-tetrahydrobenzo[*c*]pyrrolo [3,4-*a*] carbazole-1,3,7(2*H*)-trione (17a): A solution of isoindole 16a (92 mg, 0.17 mmol), PIDA (203 mg, 3.7 equivalent) and $Pd(OAc)_2$ (4 mg, 10% mol) and Ph_3P (10 mg, 22% mol) in HFIP (1 mL) was heated to 110 °C under microwave irradiation for 1 minute. The crude mixture was evaporated to dryness and then subjected to column chromatography (silica gel, gradient from cyclohexane to cyclohexane-EtOAc 70:30) to give the indolocarbazole 17a, obtained as an orange solid (53 mg, 58% yield).; mp: 287–302 °C; IR (cm^{-1}): 3449, 2939, 2858, 1760, 1708, 1523; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.16 (d, *J* = 9.2 Hz, 1H), 8.71 (d, *J* = 2.0 Hz, 1H), 8.12 (dd, *J* = 9.2, 2.1 Hz, 1H), 7.59–7.54 (m, 2H), 7.48 (m, 3H), 6.12 (tt, *J* = 12.4, 3.8 Hz, 1H), 3.62 (s, 2H), 2.83 (s, 2H), 2.44 (dq, *J* = 12.4, 3.4 Hz, 2H), 2.11–1.95 (m, 4H), 1.84 (d, *J* = 13.1 Hz, 1H), 1.67 (ddd, *J* = 16.1, 13.1, 3.3 Hz, 3H), 1.51–1.38 (m, 1H), 1.21 (s, 6H) ppm; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): 199.8 (C), 167.6 (C), 166.1 (C), 146.8 (C), 141.8 (C), 139.3 (C), 134.9 (C), 134.4 (C), 131.6 (C), 129.4 (CH), 128.7 (CH), 128.3 (C), 128.2 (CH), 127.4 (CH), 127.3 (C), 127.0 (C), 117.8 (C), 114.8 (CH), 109.0 (CH), 59.6 (CH), 54.4 (CH_2), 39.5 (CH_2), 34.1 (C), 31.5 (CH_2), 28.6 (CH_3), 26.1 (CH_2), 25.5 (CH_2) ppm; HRMS (ESI-Q-TOF) m/z: $[M + H]^+$ calculated for $C_{32}H_{30}N_3O_5$: 536.2180; found: 536.2168.

Synthesis of 12-Benzyl-5,5-dimethyl-10-nitro-2-phenyl-4,5,6,12-tetrahydrobenzo[*c*]pyrrolo [3,4-a] carbazole-1,3,7(2*H*)-trione (17b): Following the above described procedure for 17a, the compound 17b was obtained from 16b as an orange solid (11 mg, 12 % yield); mp: 249–257 °C; IR (cm^{-1}): 3444, 2957, 1762, 1711, 1516; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.29 (d, *J* = 9.1 Hz, 2H), 8.19 (dd, *J* = 9.1 Hz, *J* = 2.1, 2H), 7.55 (t, *J* = 7.7 Hz, 2H), 7.47–7.44 (m, 3H), 7.26–7.24 (m, 3H), 7.04 (d, *J* = 7.7 Hz, 2H), 6.54 (s, 2H), 3.66 (s, 2H), 2.89 (s, 2H), 1.26 (s, 6H) ppm; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): 199.5 (C), 163.7 (C),

165.8 (C), 147.8 (C), 143.4 (C), 138.5 (C), 136.7 (C), 135.2 (C), 134.1 (C), 131.3 (C), 129.2 (CH), 128.9 (CH), 128.5 (CH), 128.4 (CH), 128.2 (C), 127.7 (CH), 127.2 (C), 127.0 (CH). 126.1 (C), 125.9 (CH), 117.7 (C), 115.5 (CH), 106.0 (CH), 54.3 (CH_2), 50.5 (CH_2), 39.4 (CH_2), 33.9 (C), 28.5 (CH_3) ppm; HRMS (ESI-Q-TOF) m/z: $[M + H]^+$ calculated for $C_{33}H_{26}N_3O_5$: 544.1872; found: 544.1867.

Acknowledgments: We thank the financial support from Junta de Extremadura and FEDER (IB16095).

References

1. Greger, H. Phytocarbazoles: Alkaloids with great structural diversity and pronounced biological activities. *Phytochem. Rev.* **2017**, *16*, 1095–1153.
2. Schmidt, A.W.; Reddy, K.R.; Knolker, H.J. Occurrence, biogenesis, and synthesis of biologically active carbazole alkaloids. *Chem. Rev.* **2012**, *112*, 3193–3328.
3. Issa, S.; Prandina, A.; Bedel, N.; Rongved, P.; Yous, S.; Le Borgne, M.; Bouaziz, Z. Carbazole scaffolds in cancer therapy: A review from 2012 to 2018. *J. Enzym. Inhib. Med. Chem.* **2019**, *34*, 1321–1346.
4. Caruso, A.; Ceramella, J.; Iacopetta, D.; Saturnino, C.; Mauro, M.V.; Bruno, R.; Aquaro, S.; Sinicropi, M.S. Carbazole Derivatives as Antiviral Agents: An Overview. *Molecules* **2019**, *24*, 1912–1936.
5. Sherer, C.; Snape, T.J. Heterocyclic scaffolds as promising anticancer agents against tumours of the central nervous system: Exploring the scope of indole and carbazole derivatives. *Eur. J. Med. Chem.* **2015**, *97*, 552–560.
6. Głuszyńska, A. Biological potential of carbazole derivatives. *Eur. J. Med. Chem.* **2015**, *94*, 405–426.
7. Krucaite, G.; Grigalevicius, S. A review on low-molar-mass carbazole- based derivatives for organic light emitting diodes. *Synth. Met.* **2019**, *247*, 90–108.
8. Tao, Y.; Yang, C.; Qin, J. Organic host materials for phosphorescent organic light-emitting diodes. *Chem. Soc. Rev.* **2011**, *40*, 2943–2970.
9. Sathiyan, G.; Sivakumar, E.K.T.; Ganesamoorthy, R.; Thangamuthu, R.; Sakthivel, P. Review of carbazole based conjugated molecules for highly efficient organic solar cell application. *Tetrahedron Lett.* **2016**, *57*, 243–252.
10. Li, J.; Grimsdale, A.C. Carbazole-based polymers for organic photovoltaic devices. *Chem. Soc. Rev.* **2010**, *39*, 2399–2410.
11. Janosik, T.; Rannug, A.; Rannug, U.; Wahlström, N.; Slätt, J.; Bergman, J. Chemistry and Properties of Indolocarbazoles. *Chem. Rev.* **2018**, *118*, 9058–9128.
12. Sanchez, C.; Mendez, C.; Salas, J.A. Indolocarbazole natural products: Occurrence, biosynthesis, and biological activity. *Nat. Prod. Rep.* **2006**, *23*, 1007–1045.
13. Conchon, E.; Anizon, F.; Aboab, B.; Golsteyn, R.M.; Léonce, S.; Pfeiffer, B.; Prudhomme, M. Synthesis, in vitro antiproliferative activities, and Chk1 inhibitory properties of pyrrolo [3,4-a] carbazole-1,3-diones, pyrrolo[3,4-c]carbazole-1,3-diones, and 2-aminopyridazino[3,4-a]pyrrolo[3,4-c]carbazole-1,3,4,7-tetraone. *Eur. J. Med. Chem.* **2008**, *43*, 282–292.
14. Joseph, B.T.; Facompré, M.; Da Costa, H.; Routier, S.; Mérour, J.Y.; Colson, P.; Houssier, C.; Bailly, C. Synthesis, cytotoxicity, DNA interaction and topoisomerase II inhibition properties of tetrahydropyrrolo [3,4-a] carbazole-1,3-dione and tetrahydropyrido-[3,2-b]pyrrolo[3,4-g]indole-1,3-dione derivatives. *Biorg. Med. Chem.* **2001**, *9*, 1533–1541.
15. Giraud, F.; Pereira, E.; Anizon, F.; Moreau, P. Synthesis and applications of dihydropyrrolocarbazoles. *Eur. J. Org. Chem.* **2019**, *2019*, 5025–5042.
16. Pindur, U.; Otto, C. A new access to 2′-amino-substituted vinylindoles as donor-activated heterocyclic dienes and their first diels-alder reactions. *Tetrahedron* **1992**, *48*, 3515–3526.
17. Alonso, M.Á.; López-Alvarado, P.; Avendaño, C.; Menéndez, J.C. Regioselective Diels–Alder reactions of 3-indolylquinones. *Tetrahedron* **2003**, *59*, 2821–2830.
18. Neo, A.G.; Bornadiego, A.; Díaz, J.; Marcaccini, S.; Marcos, C.F. Elusive 2-aminofuran Diels-Alder substrates for a straightforward synthesis of polysubstituted anilines. *Org. Biomol. Chem.* **2013**, *11*, 6546–6555.
19. Bornadiego, A.; Díaz, J.; Marcos, C.F. Tandem synthesis of polycyclic isoindoles. *J. Org. Chem.* **2019**, *84*, 7426–7433.
20. Kaur, T.; Wadhwa, P.; Bagchi, S.; Sharma, A. Isocyanide based [4+1] cycloaddition reactions: An indispensable tool in multi-component reactions (MCRs). *Chem. Commun.* **2016**, *52*, 6958–6976.

21. Nair, V.; Menon, R.S.; Vinod, A.U.; Viji, S., A facile three-component reaction involving [4+1] cycloaddition leading to furan annulated heterocycles. *Tetrahedron Lett.* **2002**, *43*, 2293–2295.
22. Kim, B.S.; Lee, S.Y.; Youn, S.W. Pd-catalyzed sequential C-C and C-N bond formations for the synthesis of N-heterocycles: Exploiting protecting group-directed C-H activation under modified reaction conditions. *Chem. Asian J.* **2011**, *6*, 1952–1957.
23. Antonchick, A.P.; Samanta, R.; Kulikov, K.; Lategahn, J. Organocatalytic, oxidative, intramolecular C-H bond amination and metal-free cross-amination of unactivated arenes at ambient temperature. *Angew. Chem. Int. Ed.* **2011**, *50*, 8605–8608.
24. Jordan-Hore, J.A.; Johansson, C.C.; Beck, E.M.; Gaunt, M.J.,Oxidative Pd (II)-catalyzed C-H bond amination to carbazole at ambient temperature. *J. Am. Chem. Soc.* **2008**, *130*, 16184–16186.
25. Tsang, W.C.; Zheng, N.; Buchwald, S.L. Combined C-H functionalization/C-N bond formation route to carbazoles. *J. Am. Chem. Soc.* **2005**, *127*, 14560–14561.
26. Conchon, E.; Anizon, F.; Aboab, B.; Prudhomme, M. Synthesis and Biological Activities of New Checkpoint Kinase 1 Inhibitors Structurally Related to Granulatimide. *J. Med. Chem.* **2007**, *50*, 4669–4680.