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Multicomponent synthesis and anti-proliferative screening of biaryl triazole-containing cyclophanes

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ABSTRACT

We report a practical two-step approach involving a Ugi 4-CR/ azide-alkyne cycloaddition for the synthesis of biaryl-containing cyclophanes. The series represents an extension of our previously reported macrocycles as an effort to enhance the anti-proliferative activity of this scaffold. In this variant, we incorporate a biphenyl moiety in the framework, thus enhancing the macrocycle size, lipophilicity, and structural diversity. Macrocycles were tested against different cell lines, being more cytotoxic against prostate (PC-3 and DU-145) and breast (MCF-7) tumor cells. Gratifyingly, the most active compound showed a significative enhancement of PC-3 growth inhibition with respect to our previous series, reaffirming the potential anti-proliferative activity of this kind of cyclophanes.

Macrocycles, cyclic frameworks with at least twelve members,[1] are privileged scaffolds with numerous biological activities. Their unique physicochemical properties and their ability to interact with multiple residues inside of a pocket domain have made macrocycles promising leads in drug research programs.[2,3] Both natural and laboratory-made macrocyclic derivatives display antibiotic,[4] antitubercular,[5] anti-inflammatory,[6] and even anti-HIV activities.[7] In the battle against cancer, macrocycles have been identified as promising alternatives for its control (Fig. 1). The trichothecene roridin J (**1**),[8] isolated from *Myrothecium verrucaria* and *Calcarisporium arbuscula*, exhibits high activity against the hepatoma cell line BEL-7402 (IC_{50} 0.35 μg/mL)[9] Synthetic/semi-synthetic molecules are also currently studied for cancer treatment. In recent years, pacritinib (**2**) has been evaluated for the treatment of myelofibrosis. This macrocycle with a unique biaryl skeleton inhibits multiple kinases related to cancer development (such as Janus kinase 2).[10] Notably, acyclic derivatives of pacritinib (for example, momelotinib[11] and CEP-33779[12]) conserve the biaryl framework. Finally, the rapalog temsirolimus –a selective mTOR kinase inhibitor– is now prescribed for renal cell carcinoma treatment.[13]

Therefore, a macrocyclic-related medicinal chemistry program requires practical protocols that allow the rapid preparation of molecule collections for high-throughput screening. However, the iterative cycle of synthesis- biological evaluation-optimization can be slow and repetitive.[14] In this context, multicomponent approaches have become powerful techniques for accessing large collections of macrocyclic scaffolds. Additionally, enhanced molecular diversity may be achieved by combining a multicomponent process with several different chemical manifolds.[15] In general, for the construction of macrocyclic molecules, the use of a multicomponent reaction (MCR) directly at the macrocyclization stage is a common strategy, while another approach is the assembly –through the MCR– of a bifunctional linear intermediary, which in turn might be macrocyclized with an adequate post-condensation process.[16,17]

The Ugi reaction combined with azide/alkyne cycloaddition provides an excellent opportunity to assemble novel macrocyclic scaffolds and has been exploited elsewhere and by our group.[18,19] However, the synthesis and anti-proliferative activity of cyclophanes conjoining biaryl, 1,2,3-triazole and peptidic moieties has not been achieved. To further expand our macrocyclic-related program, we considered the possibility of preparing a series of cyclophanes (**4**, Fig. 2), and testing their preliminary anti-proliferative evaluation. In this design, we examined the overall effect of incorporating a biphenyl moiety into the macrocyclic framework preserving the peptoid and 1,2,3-triazole residues found in compound **3**.[20] Biaryl system is a common feature in JAK2 inhibitors –such as pacritinib– and we have also successfully prepared a series of biphenyl derivatives with remarkable cytotoxic activity.[21] Remarkably, in **4**, the presence of the biaryl frame increases not only the size of the macrocyclic structure but also its rigidity (compared with **3**), which represents an additional

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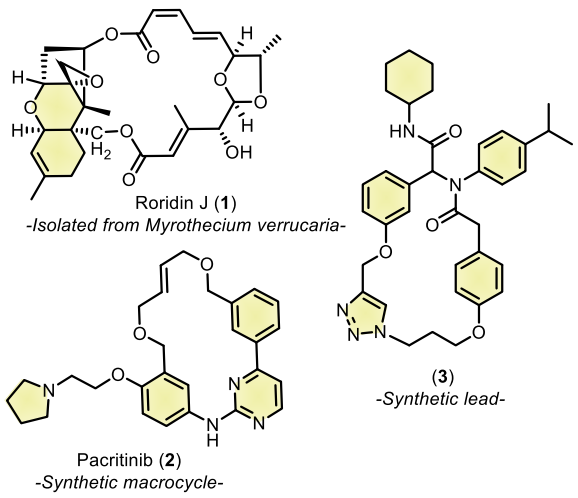


Fig. 1. Relevant cytotoxic macrocyclic structures.

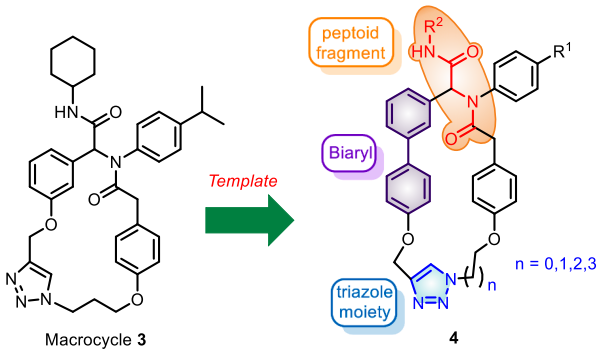


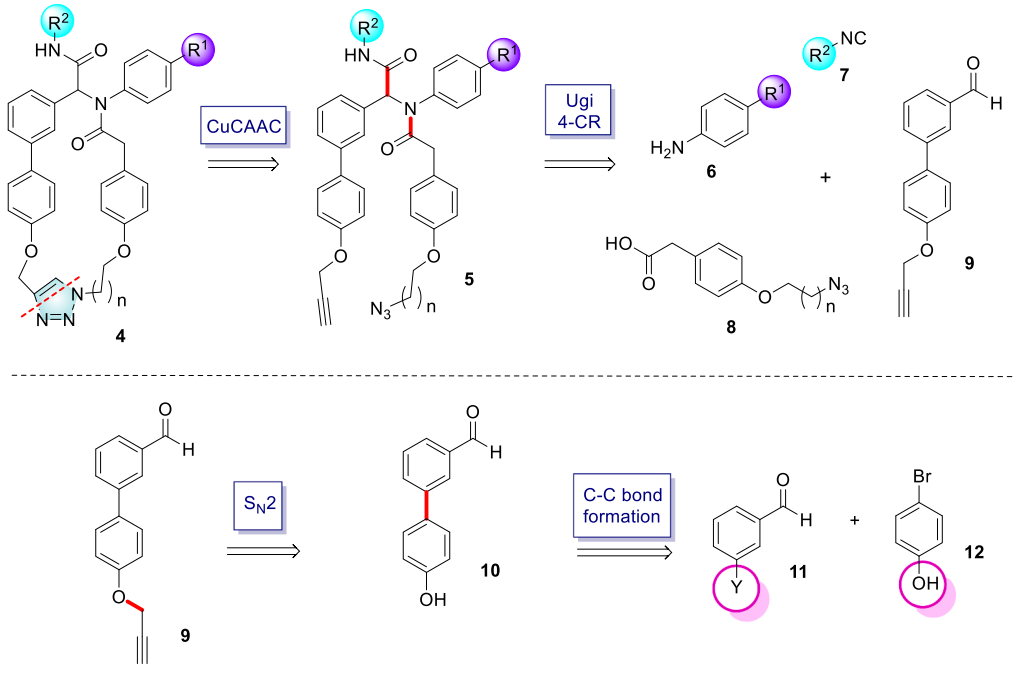
Fig. 2. Design of the biarylic cyclophanes **4**. The biaryl system is found in other cytotoxic compounds.

challenge for the copper-catalyzed azide-alkyne cycloaddition (CuAAC) during the macrocyclization process (Fig. 2).

The proposed retrosynthesis for the preparation of the biaryl cyclophanes **4** is shown in Scheme 1. The triazole ring would be constructed through a CuAAC during the macrocyclization event[22] from the biphenyl azido-alkyne **5**, which proceeded from an Ugi four-component reaction (Ugi 4-CR). The proposed design allows the introduction of at least three points of diversification in the multicomponent process, which encompass the use of various isocyanides and different amines (**6**), as well as azides with different aliphatic chains (**8**). The bifunctional carboxylic acids **8** might be prepared following a previously published protocol.[20] The required biphenyl alkyne-aldehyde **9**, in principle, could be prepared by a two-step strategy from 4-bromophenol (**12**) and a hypothetical organometallic aldehyde **11** through a palladium-catalyzed cross-coupling C(sp^2)-C(sp^2) bond formation, followed by an alkylation with propargyl bromide.

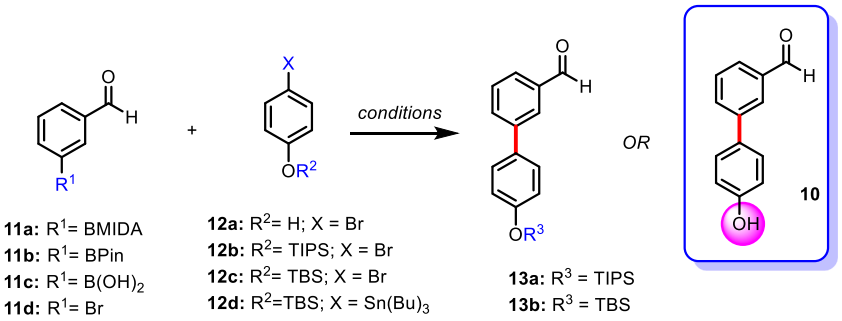
The synthetic journey commenced with the construction of aldehyde **9** (Table 1). In a first approach, we intended the direct coupling between 4-bromophenol (**12a**) and the 3-MIDA boronate ester of benzaldehyde (**11a**) to construct the biaryl system **10** in one step under typical Suzuki-Miyaura conditions ($Pd(PPh_3)_4$ and K_3PO_4), although the yield was low (37%; Table 1, entry 1). We observed similar results when the pinacol ester **11b** or the boronic acid **11c** were used (yield = 35% and 16%, respectively; entries 2 and 3). These outcomes emphasized the necessity of protecting the hydroxyl group, but the yield with the triisopropyl silyl ether **12b** drastically dropped to 12% (entry 4). The replacement of the TIPS-protected phenol by the *t*-butyldimethylsilyl (TBS)-protected **12c** resulted in the carbon–carbon bond formation in a reasonable yield (48%, entry 5). Surprisingly, when the phosphate equivalents increased to 7.5, the hydroxybiphenyl carbaldehyde **10** was directly formed in 62% yield from **12c**! (Table 1, entry 6). These findings are in accordance with preceding works, in which TBS ethers under basic treatment resulted in its cleavage.[23] Efforts to enhance the yield by replacing the Suzuki-Miyaura reaction by a Stille cross-coupling were futile (Table 1, entry 7), as well as the substitution of the palladium catalyst ($Pd(AcO)_2$/PPh_3; $PdCl_2$/PPh_3). Finally, the bimolecular substitution (S_N2) with propargyl bromide furnished the desired alkyne-aldehyde **9** without further complications and in a reasonable 85% yield.

Afterwards, we proceeded to establish the best conditions for the Ugi



Scheme 1. Retrosynthetic approach for the preparation of cyclophanes (**4**) and the synthesis of the biaryl aldehyde **9**.

Table 1
Preparation of the biphenyl carbaldehyde **10**.



Entry	Aldehyde	Phenol	Product	Conditions	Yield (%)
1	11a	12a	10	$Pd(PPh_3)_4$, 3.0 eq K_3PO_4 THF-H_2O (2:1), 80 °C, 12 h	37
2	11b	12a	10	$Pd(PPh_3)_4$, 3.0 eq K_3PO_4 THF-H_2O (2:1), 80 °C, 4 h	35
3	11c	12a	10	$Pd(PPh_3)_4$, 3.0 eq K_3PO_4, THF-H_2O (3:1), 80 °C, 4 h	16
4	11a	12b	13a	$Pd(PPh_3)_4$, 3.0 eq K_2CO_3, THF-H_2O (2:1), 80 °C, 4 h	12
5	11a	12c	13b	$Pd(PPh_3)_4$, 3.0 eq K_3PO_4 THF-H_2O (2:1), 80 °C, 17 h	48
6	11a	12c	10	$Pd(PPh_3)_4$, 7.5 eq K_3PO_4 THF-H_2O (2:1), 80 °C, 17 h	62
7	11d	12d	10	$Pd(PPh_3)_4$, PhMe, 80 °C, 3 h	32
8	11a	12c	10	$Pd(AcO)_2$, PPh_3, 7.5 eq K_3PO_4 THF-H_2O (2:1), 80 °C, 17 h	59
9	11a	12c	10	$PdCl_2$, PPh_3, 7.5 eq K_3PO_4 THF-H_2O (2:1), 80 °C, 17 h	37

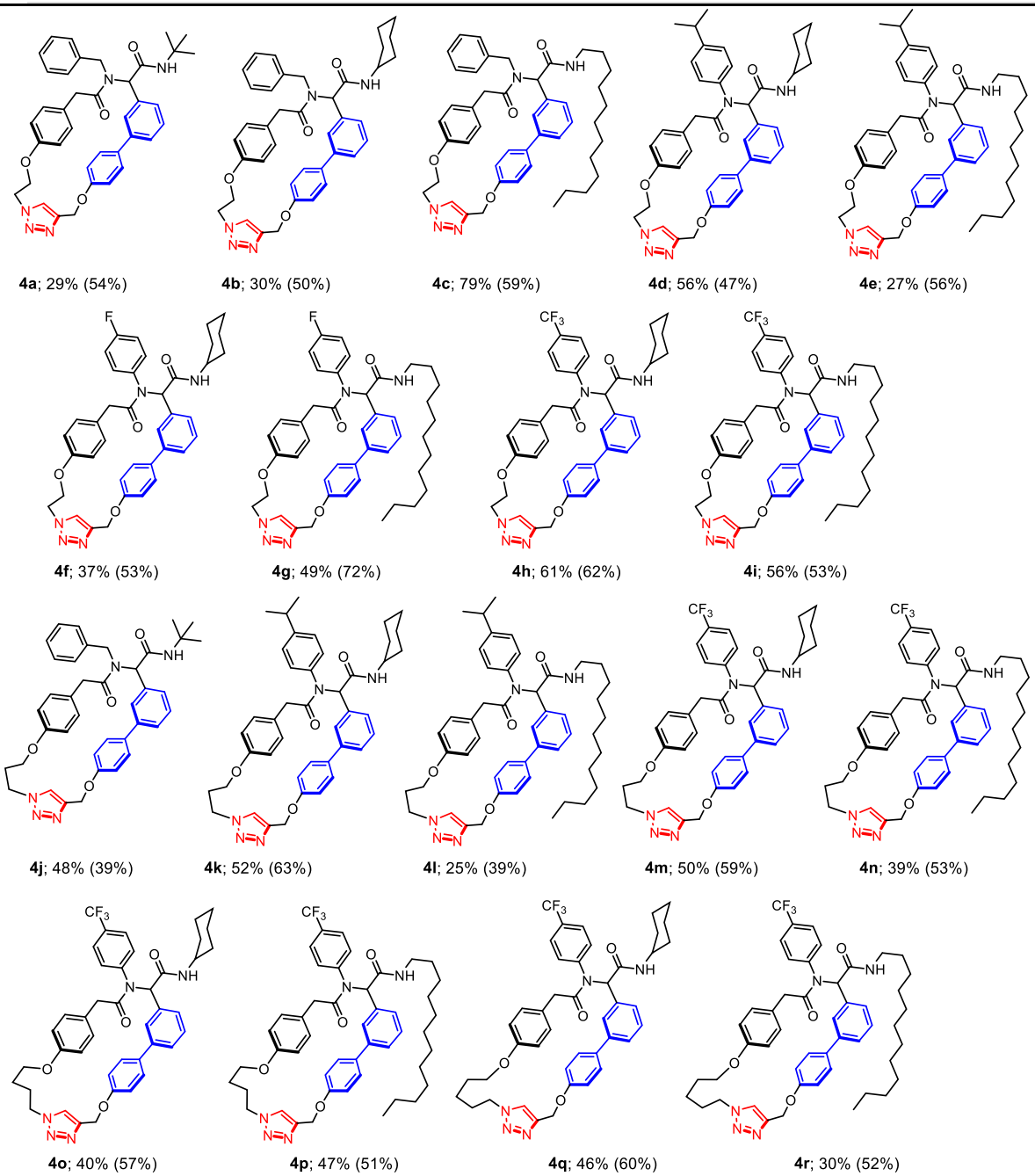
4-CR. Due to the complexity of the starting materials, our previous research as well as other works have corroborated that the use of $InCl_3$ as Lewis acid is an excellent option to carry out the transformation.[24,25] Thus, stirring at room temperature allowed the preparation of several α-acylamino-carboxamides **5a–5r** in moderate to good yields (Table 2). Then, the copper-catalyzed azide-alkyne cycloaddition was set up by using the binary system consisting of cuprous bromide as catalyst and 1,8-diazabicyclo[5.4.0]undec-7-ene as base (CuBr/DBU system).[26] Unfortunately, the treatment of **5a** under these conditions at room temperature did not achieve the expected transformation (Scheme 2). When the reaction was heated to reflux, the macrocycle **4a** was isolated, but only in trace amounts; on the contrary, a reasonable 29% yield was achieved when the reaction was heated under microwave-assisted irradiation (in an open vessel system) after 2.5 h of reflux (Scheme 2). Microwave irradiation provides a rapid and homogeneous heating during a chemical reaction,[27] thus increasing the energy efficiency (a principle of Green Chemistry proposed by Anastas and Warner).[28] However, toluene has a low dielectric constant and is a poor absorber of microwave radiation; the use of microwave susceptors –an inert compound that efficiently absorbs microwave radiation and transfers the thermal energy to other compounds–[29] may overcome this issue. Therefore, it is possible that microwave irradiation heated the solid CuBr particles to a temperature higher than the bulk toluene and the reaction occurred on "localized hot spots" on the surface of CuBr particles, acting as a catalyst and a microwave susceptor. Efforts to increase the yield were futile, which included: increasing the heating time to 3 or 5 h (yield = 25% and 20%, respectively); modificating the copper catalyst for CuI (10%); or replacing toluene for acetonitrile (no conversion). The low yield may be attributed to the degradation of the α-acylamino-carboxamide since we did not identify any by-product nor the formation of dimeric structures (through the analysis of the crude reaction by mass spectrometry). However, due to the complexity and diversity of the final products together with the accessibility of the starting materials, this protocol is considered as a suitable tool for the synthesis of related cyclophanes.

18 cyclophanes containing the biaryl framework were prepared. Our previous investigation concluded that hydrophobicity may play a key role in the anti-proliferative effect for this kind of cyclophanes;[15] therefore, the design conserved bulky (for example isopropyl) or highly electronegative (fluoro and trifluoromethyl) groups attached at the 4-position. Neither the substitution of the isocyanide nor the replacement of benzylamine had negative influence on the transformation. The homologation to a propylene spacer in **4a** afforded cyclotetradecaphane **4j** with a slightly higher yield (Table 2, 48%). The methodology led to the synthesis of macrocycles bearing isopropyl (**4k** and **4l**) and trifluoromethyl (**4m** and **4n**) substituents in moderate yields. We also prepared higher macrocycles, namely cyclopentadecaphanes (**4o** and **4p**) and cyclohexadecaphanes (**4q** and **4r**). It is worth noting that the smallest yields corresponded to those macrocycles bearing both 4-isopropylaniline and dodecyl isocyanide **4e** and **4l** (yield = 27% and 25%, respectively).

Cancer is a growing world health problem and the urgency of new chemical entities for its control becomes a necessity. Our research interest focuses on prostate and breast cancer, so the biaryl cyclophanes **4a–4r** were tested against PC-3 and DU-145 (prostate) and MCF-7. Both PC-3 and DU-145 do not express the androgen receptor (AR) and are, among LNCaP –AR positive from a metastatic human prostate cancer–,[30] the most used prostate cancer cell lines.[31] MCF-7 is a breast cancer cell line which expresses both estrogen and progesterone receptors.[32] The preliminary screening for cyclophanes **4a**–**4r** at 50 μM is shown in Table 3. Clearly, almost all the compounds showed an inhibitory activity against the tested lines. Derivatives with benzylamine **4a–4c** and **4j** had low activity in the three tumors, but comparable toxicity against the healthy COS-7 (*Cercopithecus aethiops* fibroblast-like cells, a frequently used assay for evaluating toxicity)[33] which points out their lack of pharmacological relevance. We want to highlight compound **4d**, a close analogue of **3** with a biphenyl instead of a phenyl ring, displayed the best activity among the series in both prostate and breast cancer (Table 3). Moreover, **4d** exhibited low growth inhibition in the healthy cells COS-7. The activity drastically dropped when the cyclohexyl was replaced by a lipophilic dodecyl chain (**4e**). This outcome was also observed in other derivatives; compound **4k** had higher effect than its dodecyl analogue **4l** and the same for the pairs **4o**/**4p** and **4q**/**4r**. The only exception was the fluorinated cyclotridecaphane **4g**, which not only was more active than its cyclohexyl analogue **4f**, but also had the best inhibitory effect against breast cancer MCF-7.

Besides the cyclohexyl motif, we confirmed the necessity of an isopropyl chain attached at the exocyclic phenyl ring: **4d** and **4k** share this substituent and, in addition to **4g**, are the most active cyclophanes. Finally, the influence of the macrocycle size in the overall biological activity was also examined. In general terms, the best tumor cell growth inhibition corresponded to the cyclotridecaphanes while the homologation to the corresponding cyclotetradecaphanes caused a reduction in

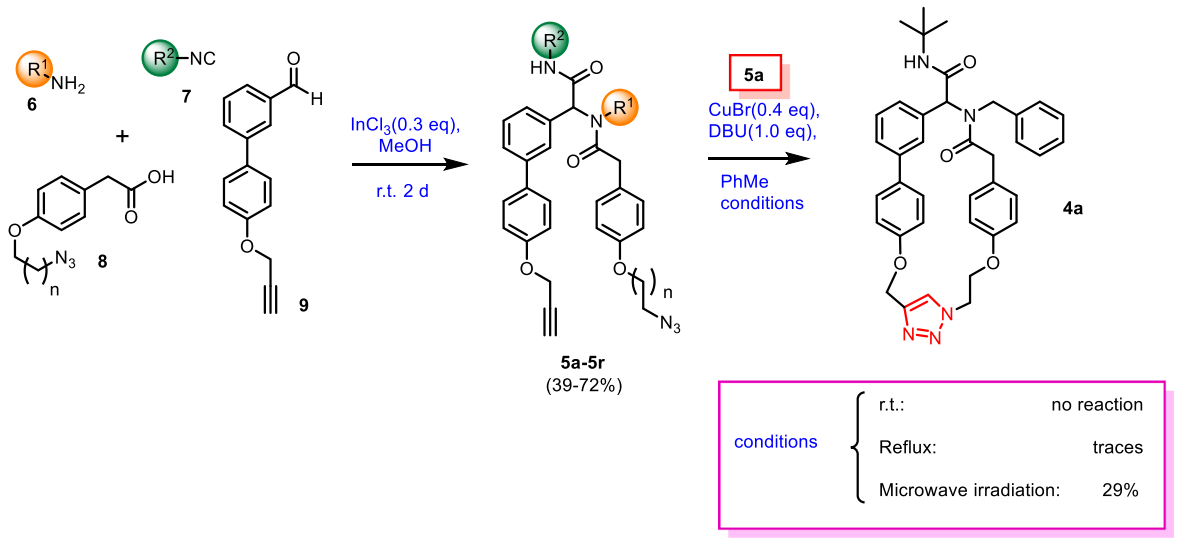
Table 2
Structures and yields of the biaryl cyclophanes.[a]



the activity. This trend is demonstrated by a comparison of the homologues **4d**/**4k** and in the pairs **4a**/**4j**, **4h**/**4m** and **4i**/**4n**. In the case of the larger macrocycles, cyclopentadecaphanes **4o** and **4p** were slightly more active than their corresponding cyclohexadecaphanes **4q** and **4r**.

We have previously demonstrated that cyclophane **3** is able of inducing apoptosis in PC-3;[20] since the derivatives herein reported are closely related to it, we decided to determine the IC_{50} only in this cell line. Fig. 3 shows the IC_{50} value of those compounds having inhibition levels higher than 60%. Compound **3** was used as reference as well as etoposide. All compounds displayed a higher PC-3 inhibition than etoposide (IC_{50} = 31.47 μM). Surprisingly, **4d** was two-fold more active than **3** and displayed minor toxicity in COS-7; therefore, it deserves more experimentation in terms of mechanism of action. Kinases become an attractive starting point for this search, such as JAK2[34] or mTOR kinase, the molecular target of rapamycin and temsirolimus.[35] The outcomes described in this work, along with our previous SAR, conclude that the cyclohexyl and 4-isopropylaniline (features found in the most active macrocycles **3**, **4d** and **4k**) play a vital role in the cytotoxicity over PC-3; therefore, future modifications may include reducing the macrocycle size, incorporating polar groups in the cyclic framework (for example, a peptide bond), and replacing the triazole with other linkers.

In summary, we reported the synthesis of 23-, 24-25 and 26-decaphanes containing a biphenyl aromatic portion and a 1,4-disubstituted 1,2,3-triazole. Due to the facile disposition of the starting materials, this synthetic route is an excellent and reliable proposal for the rapid generation of collections of structurally diverse macrocycles for



Scheme 2. Two-step methodology for the synthesis of the biaryl macrocycles **4a–r**.

Table 3
Percentage of inhibition at 50 μM for compounds **4a–4r**.

Comp	Percentage of inhibition ± SEM[a]			
	PC-3	DU-145	MCF-7	COS-7
4a	48.3 ± 1.8	25.5 ± 8.6	44.6 ± 8.1	37.8 ± 5.8
4b	11.6 ± 2.0	11.0 ± 2.3	15.2 ± 2.7	9.9 ± 2.3
4c	25.8 ± 1.8	10.4 ± 3.6	26.4 ± 1.6	28.2 ± 3.8
4d	90.2 ± 9.8	93.8 ± 4.2	81.8 ± 7.5	37.5 ± 4.9
4e[b]	25.4 ± 2.9	51.0 ± 7.7	39.2 ± 9.8	25.6 ± 2.9
4f	50.3 ± 5.2	28.4 ± 1.3	43.2 ± 7.5	43.2 ± 3.4
4g	68.3 ± 1.6	93.1 ± 3.1	82.4 ± 11.7	35.0 ± 6.9
4h	46.9 ± 3.6	37.1 ± 14.4	45.8 ± 6.7	37.7 ± 1.5
4i	45.8 ± 0.8	19.7 ± 1.6	41.7 ± 2.7	33.6 ± 3.4
4j	5.5 ± 0.7	*NA*[c]	67.9 ± 1.4	33.1 ± 8.1
4k	60.8 ± 7.2	41.9 ± 14.3	58.2 ± 10.3	48.0 ± 6.5
4l[b]	30.1 ± 6.5	21.2 ± 3.8	31.8 ± 3.2	9.9 ± 1.5
4m	35.5 ± 3.9	20.1 ± 5.8	60.9 ± 16.2	30.9 ± 6.4
4n	15.3 ± 1.0	9.8 ± 3.7	45.6 ± 5.0	20.4 ± 9.4
4o	48.5 ± 12.2	39.0 ± 0.5	57.1 ± 3.0	38.1 ± 2.3
4p	36.4 ± 6.4	52.8 ± 28.6	42.9 ± 9.7	16.6 ± 0.1
4q	46.0 ± 3.3	48.8 ± 25.1	53.3 ± 7.3	45.4 ± 4.5
4r	22.0 ± 5.1	*NA*[c]	24.9 ± 11.1	10.2 ± 1.8

[a] The assay was performed by triplicate.
[b] These compounds had poor aqueous solubility.
[c] Non active.

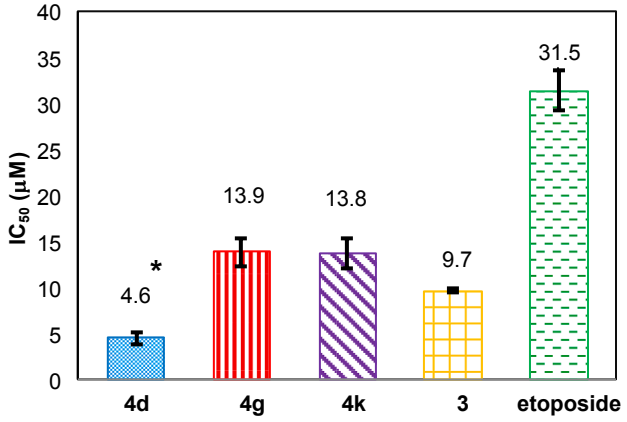


Fig. 3. IC_{50} values for PC-3 of the most active cyclophanes. The values represent the mean ± EEM. *p < 0.05 **4d** versus **3** and etoposide.

medicinal chemistry programs. Compounds showed a significant activity against prostate and breast cancer; the most active derivatives consisted in those having an ethylene spacer (i.e., cyclotridecaphanes), while the electron-donating 4-isopropylphenyl moiety seemed to be preferable over fluorinated aromatic rings. We want to highlight cyclotridecaphane **4d**: it was two-fold more active in PC-3 than macrocycle **3** and showed low toxicity towards the healthy line COS-7. Therefore, these findings delineate macrocycle **4d** as a suitable candidate for further optimization and investigation. For instance, due to the high lipophilicity of **4d**, an alternative to enhance the drug-likeness might be the reduction of logP value by incorporating more polar isocyanides or replacing the biphenyl with other heterocyclic moieties, such as the biaryl system observed in pacritinib.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data (Experimental procedures (synthesis of aldehyde **9** and biological test), and compound characterization data of cyclophanes and Ugi adducts, including full ^{1}H and ^{13}C NMR spectra) to this article can be found online at https://doi.org/10.1016/j.bmcl.2021.127899.

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