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Palladium-catalyzed intramolecular C–H amidation: synthesis and biological activities of indolobenzazocin-8-ones

Sasiwadee Boonya-udtayan [a], Meredith Eno [b], Somsak Ruchirawat [a,b,c], Chulabhorn Mahidol [a,b], Nopporn Thasana [a,b,c,*]

[a] Program on Chemical Biology, Chulabhorn Graduate Institute, Laksi, Bangkok 10210, Thailand
[b] Laboratory of Medicinal Chemistry, Chulabhorn Research Institute, Laksi, Bangkok 10210, Thailand
[c] Center of Excellence on Environmental Health and Toxicology, CHE, Ministry of Education, Bangkok, Thailand

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ABSTRACT

The synthesis of multi ring-fused indolobenzazocinone derivatives, an antimitotic agent, has been carried out using palladium-catalyzed C–H activation/intramolecular amidation of benzo[*d*]azocinones, which were synthesized by the ring annulations of dihydroisoquinolines and azlactone in refluxing acetonitrile. The target compounds, indolobenzazocin-8-one derivatives, were evaluated for their cytotoxicity against the cancer cell lines HUCCA-1, A549, HepG2, and MOLT-3. The results showed that an unsubstituted indolobenzazocin-8-one **1e** exhibited very good activities in the nanomolar IC_{50} value range (HepG2 and MOLT-3).

1. Introduction

Benzazocinone belongs to a class of alkaloid displaying a wide range of biological activities including hepatoprotective activity against chemical toxin and antiamnesia as well as acting as inhibitors of tubulin polymerization.[1] Recently our group reported a facile and convenient protocol based on ring annulations of dihydroisoquinoline with azlactone to synthesize benzo[*d*]azocin-4-ones **1**.[2] This protocol served as a useful template for the synthesis of eight-membered ring molecules. In our continuing interest concerning the application of this protocol, we focused our attention to the synthesis of indolobenzazocinone analogues from benzo[*d*]azocin-4-one derivatives. Indolobenzazocinone **2c** is closely related to some natural products and other biologically active compounds, such as indolobenzazepinones (with C5 substituted group) **3**, an antimitotic agent,[3] latonduine **4**, a cytotoxic agent,[4] and their regioisomers, paullones **5**, which act as cyclin-dependent kinase inhibitors (Fig. 1).[5]

In 2007, Joseph reported the synthesis of indolobenzazepinones **2b** using the intramolecular Heck reaction.[6] Similarly, Dodd revealed that the C5-alkylated indolobenzazepinones (**3a**) showed high cytotoxicity against various cancer cell lines and were categorized as antimitotic agents.[7] This methodology involved Suzuki coupling and lactamization steps. They also synthesized compounds with different substitution pattern **3b** at C5 position by using the application of an isocyanide-based multicomponent reactions (MCRs).[3]

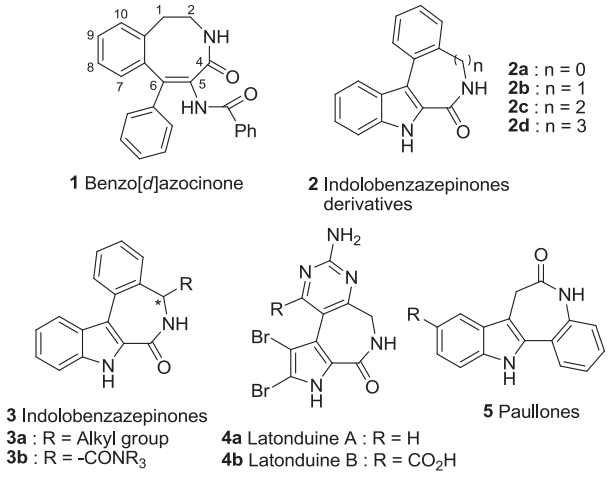

Fig. 1. Indolobenzazepinone derivatives and some related natural compounds.

* Corresponding author. E-mail address: nopporn@cri.or.th (N. Thasana).

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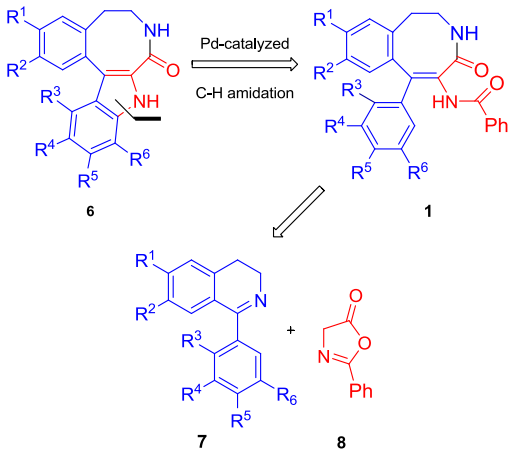
Recently, Joseph and colleagues reported the synthesis and SAR studies involving six-, seven-, eight- and nine-membered ring derivatives of indolobenzazepinones. The result showed that almost all of them exhibited good potency in both cell-based and target-based assays, especially, 5,6,7,9-tetrahydro-8*H*-indolo[2,3-*e*][3]benzazocin-8-one **2c**.[8] Moreover, the molecular modeling of indolobenzazepinones was also studied in comparison with tubulin polymerization inhibitor colchicine.[8] To accomplish these target indolobenzazocinones **6**, we have elaborated not only the condensation of various dihydroisoquinolines with azlactone but also investigated the C–N bond formation involving palladium-catalyzed intramolecular C–H amidation as depicted in Scheme 1.



Scheme 1. Retrosynthetic plan for the synthesis of indolobenzazocin-8-one derivatives.

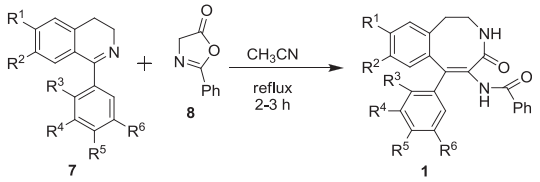
During the past decade, Pd-catalyzed C–H activation[9] has played a significant role in construction of the desired C–C, C–O, C–S, C–X bond formation and particularly the formation of C–N bond, as pioneered by Buchwald and co-workers.[10] The advantage of this approach is the support of green chemistry because reducing the number of steps as well as improving atom economy led to an increase in overall efficiency.[11] Accordingly, Pd-catalyzed C–N bond formation has attracted attention from many research groups.[9,10,12] Herein, this chemistry was used as the first time application to establish biologically active indolobenzazocinone derivatives.

2. Results and discussion

Ten analogues of dihydroisoquinolines **7a**–**j** were first investigated to expand our developed protocol.[2,13] Various dihydroisoquinolines **7** were prepared from different arylethylamines and various benzoic acids and nicotinic acid to generate amides followed by Bischler–Napieralski reaction.[2] Only dihydroisoquinoline **7e** was prepared using the Movassaghi's method.[14] Azlactone **8** was obtained from hippuric acid, as previously reported.[2,15] With both key starting materials in hand, we studied the ring annulations of dihydroisoquinolines **7a**–**j** with azlactone **8** in refluxing acetonitrile under dry conditions to afford compounds **1a**–**i** in moderate yields (30–74%) as shown in Table 1.

Notably, beta-lactam intermediate **9j** was isolated in 45% yield (Table 1, entry 10).[16] This supported our previously proposed mechanism that beta-lactams are intermediates in the formation of benzo[*d*]azocinones.[2] Furthermore, the isolation of beta-lactam **9j** shed some lights on the mechanism of ring expansion. Possible pathway might involve ring expansion via the carbocation **10** and the carbocation must be stabilized by both adjacent phenyl groups. In the case of beta-lactam **9j** ring expansion was not possible

Table 1
Synthesis of 5-amido-8,9-dimethoxy-6-aryl-2,3-dihydrobenzo[*d*]azocin-4-ones **1**[a]



Entry	Dihydroisoquinolines **7**	Products **1**	Yield [%]
1	**7a**		**1a**, 74[a]
2	**7b**		**1b**, 39[a]
3	**7c**		**1c**, 40[a]
4	**7d**		**1d**, 48[a]
5	**7e**		**1e**, 37[a]
6	**7f**		**1f**, 40[b]
7	**7g**		**1g**, 37[b]
8	**7h**		**1h**, 30[a]
9	**7i**		**1i**, 58[a]
10	**7j**		**9j**, 45[a]

[a] Products were purified by crystallization.
[b] Products were purified by column chromatography.