Journal Pre-proofs

Ultrasound assisted one-pot synthesis of 1,2-diaryl azaindoles via Pd/C-Cu catalysis: identification of potential cytotoxic agents

Rapolu Venkateshwarlu, Shambhu Nath Singh, Vidavalur Siddaiah, Hindupur Ramamohan, Rambabu Dandela, Manojit Pal

PII: S0040-4039(19)31113-X
DOI: https://doi.org/10.1016/j.tetlet.2019.151326
Reference: TETL 151326

To appear in: *Tetrahedron Letters*

Received Date: 2 September 2019
Revised Date: 18 October 2019
Accepted Date: 24 October 2019

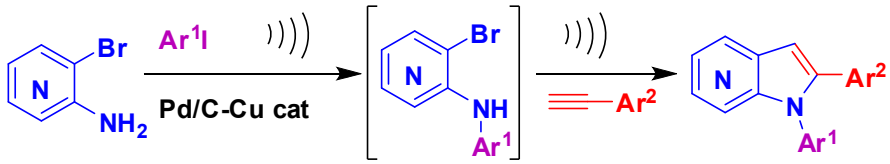
Please cite this article as: Venkateshwarlu, R., Nath Singh, S., Siddaiah, V., Ramamohan, H., Dandela, R., Pal, M., Ultrasound assisted one-pot synthesis of 1,2-diaryl azaindoles via Pd/C-Cu catalysis: identification of potential cytotoxic agents, *Tetrahedron Letters* (2019), doi: https://doi.org/10.1016/j.tetlet.2019.151326

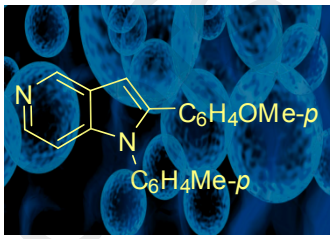
Graphical Abstract

Ultrasound assisted one-pot synthesis of 1,2-diaryl azaindoles via Pd/C-Cu catalysis: identification of potential cytotoxic agents

Leave this area blank for abstract info.

Rapolu Venkateshwarlu, Shambhu Nath Singh, Vidavalur Siddaiah, Hindupur Ramamohan, Rambabu Dandela,* and Manojit Pal*





The first ultrasound assisted azaindole synthesis was achieved under Pd/C-Cu catalysis. Some of the azaindoles were identified as promising cytotoxic agents.

ELSEVIER

Tetrahedron Letters

journal homepage: www.elsevier.com

Ultrasound assisted one-pot synthesis of 1,2-diaryl azaindoles via Pd/C-Cu catalysis: identification of potential cytotoxic agents

Rapolu Venkateshwarlu,[ab] Shambhu Nath Singh,[a] Vidavalur Siddaiah,[b] Hindupur Ramamohan,[a] Rambabu Dandela,[c]* and Manojit Pal[d,]*

[a]*Custom Pharmaceutical Services and Dr. Reddy's Laboratories Ltd., Bollaram Road, Miyapur, Hyderabad 500049, India.*
[b]*Department of Organic Chemistry & FDW, Andhra University, Visakhapatnam 530003, Andhra Pradesh, India.*
[c]*Department of Industrial and Engineering Chemistry, Institute of Chemical Technology, Indianoil Odisha Campus, Samantpuri, Bhubaneswar 751013, India.*
[d]*Dr. Reddy's Institute of Life Sciences, University of Hyderabad Campus, Hyderabad 500046, India.*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Azaindole
Ultrasound
Pd/C
Cytotoxicity

ABSTRACT

Ultrasound assisted one-pot and direct access to 1,2-diaryl substituted azaindole derivatives has been achieved *via* the sequential *N*-arylation followed by coupling-cyclization under Pd/C-Cu catalysis. The methodology involved initial C-N bond forming reaction (step 1) between an appropriate *o*-bromo substituted amino pyridine and iodoarene followed by C-C and C-N bond formation (step 2) between the resulting *N*-aryl substituted intermediate and a terminal alkyne in the same pot. A variety of azaindoles was prepared by using this method. These compounds were assessed for their cytotoxic properties against two different metastatic breast cancer cell lines. Compounds **4i, 4k** and **4o** showed promising growth inhibition of these cell lines and SIRT1 inhibition *in vitro*.

The azaindole framework, bioisostere of the indole scaffold, is prevalent in many molecules or agents of pharmacological interest. This is exemplified by inhibitors of several enzymes or proteins including mitotic kinase monopolar spindle 1 (MPS1) inhibitors,[1] e.g. **A** (Fig. 1) cyclooxygenase inhibitors[2] or cyclin-dependent kinase (CDK) inhibitors.[3,4] Indeed, variolins isolated from Antartic sponge Kirkpatrickia varialosa showed activities against P388 murine leukemia cells and Variolin B was the most active among them.[5,6] In our effort we have previously reported 2-substituted 7-azaindole derivatives **B** that showed sirtuin inhibiting properties in yeast without showing significant cell toxicities.[7] Notably, sirtuins the class III NAD-dependent deacetylases are shown to be up-regulated in various types of cancer and hence are considered as promising targets for cancer therapeutics.[8,9] Indeed, inhibition of sirtuins allows re- expression of silenced tumor suppressor genes, leading to reduced growth of cancer cells. Nevertheless, in order to identify more effective inhibitors of sirtuins we focused on various types of azaindoles **C** (including 7-azaindoles) possessing aryl groups at both 1- and 2-positions (Fig. 1). Our previous study indicated that the ''N–7'' of the azaindole moiety of **B** played a key role in the interaction with sirtuin *in silico* via forming the H-bond with the Asn484

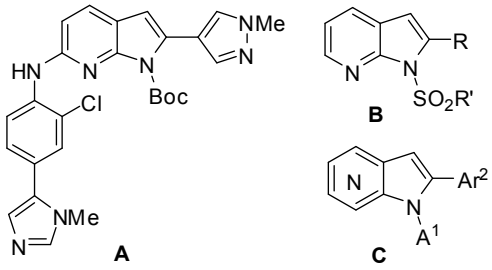


Fig. 1. Known bioactive azaindoles (**A** and **B**) and targeted analogues (**C**) of the current work

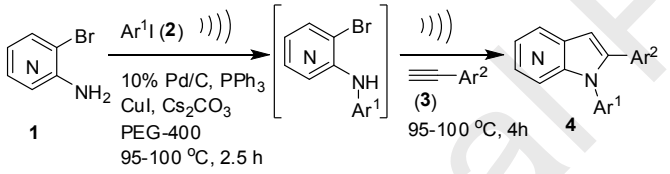
residue when docked into the active site of Sir2.[7] We anticipated that aryl group at position 1- (unlike the strong electron withdrawing sulfonyl moiety at the same position in case of **B**) would strengthened the H-bonding ability not only for ''N–7'' but also for this endocyclic nitrogen at other position like 4-, 5- and 6- position. Moreover, the H-bonding abilities thereby the potential sirtuin inhibitory properties could be (or expected to be) modulated by the nature of aryl group introduced at 1- position. Needless to say that the nature and type of aryl group at 2-position is expected to play a key role too. Hence it was essential to assess compounds derived from **C** possessing diverse set of aryl groups both at 1- and 2- position. Indeed, a small library of molecules could be generated for related SAR (Structure Activity Relationship) study and therefore we were in need of a direct as well as convenient access to target molecules based on the azaindole framework **C**.

---

*Corresponding author: Tel.: +91 40 6657; fax: +91 40 6657 1581

E-mail address: r.dandela@iocb.ictmumbai.edu.in (R. Dandela); manojitpal@rediffmail.com (M. Pal)

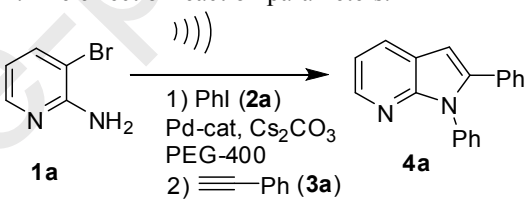
C our diaryl azaindoles appeared to be *N*-arylation of 2-aryl azaindoles. While this strategy worked for 2-substituted azaindoles (affording low yields of products)[10-12] the *N*-arylation of 2-aryl azaindoles was reported to be more challenging perhaps due to the steric hindrance.[12] Among the other methods for the synthesis of azaindoles the Pd-catalyzed construction of a pyrrole ring on a pyridine moiety is a common strategy.[13-26] These include Pd-catalyzed annulations of aryl halide with (i) terminal alkynes under Sonogashira conditions[14-24] or (ii) internal alkynes under Larock conditions.[25-26] While some of these methods afforded 1,2-disubstituted azaindoles only few of them were found to be effective for the synthesis of 1,2-diaryl azaindoles. Thus it was necessary to adopt an appropriate strategy for the synthesis of compounds represented by **C** (Fig. 1). The use of ultrasound as an alternative source of energy in organic reactions[27] has gained increasing interest particularly from the viewpoint of green chemistry. Indeed, a wide application of ultrasound has been found in many areas of organic chemistry such as heterocyclic chemistry, organic synthesis (e.g. condensation / substitution / addition reactions, protection / deprotection reactions, oxidation / reduction), photochemical processes, polymerization etc.[28] Its application in transition metal mediated coupling reactions has also been documented.[29,30] Notably, the use of ultrasound for the synthesis of azaindoles is not common in the literature. Herein we report the first use of ultrasound irradiation in synthesizing 1,2-diaryl azaindoles (**4**) *via* Pd/C-Cu catalyzed sequential C-N coupling followed by coupling-cyclization in a single pot (Scheme 1). The methodology involved initial C-N bond forming reaction (step 1) between an appropriate *o*-bromo substituted amino pyridine (**1**) and aryl iodide (**2**) followed by C-C and C-N bond formation (step 2) between the resulting *N*-aryl substituted intermediate and a terminal alkyne (**4**).



Scheme 1. Ultrasound assisted one-pot synthesis of 1,2-diaryl azaindoles under Pd/C-Cu catalysis

Initially, it was necessary to test the feasibility of our approach involving sequential C-N, C-C and C-N bond formation in a single pot. If successful then it was also essential to establish the reaction conditions that would afford the optimum yield of desired product **4**. Accordingly, the ultrasound assisted reaction sequence involving 2-amino-3-bromo pyridine (**1a**) and iodobenzene (**2a**) initially and then phenyl acetylene (**3a**) was studied under various conditions (Table 1). A laboratory ultrasonic bath SONOREX SUPER RK 510H model producing irradiation of 35 kHz was used for this purpose. The fact that Cs_2CO_3 is a commonly used base in N-arylation reaction[31] prompted us to use this particular base in our case too. Moreover, our earlier success on the use of 10%Pd/C-PPh_3-CuI as a catalyst system during tandam C-C/C-N bond forming reaction[32] at 95-100 ºC encouraged us to use the same catalyst / temperature in the current study. Thus, the coupling of **1a** with **2a** and subsequently with **3a** in the same pot was performed in the presence of 10%Pd/C-PPh_3-CuI in PEG-400 under ultrasound at 95-100 ºC. The reaction was performed for 1h for the initial step and for 4h for the next step (after addition of **3a**). The desired product **4a** was isolated in this case albeit in low yield (entry 1, Table 1). The reason for low yield of **4a** was found to be due to the poor conversion in the first step i.e. coupling of **1a** with **2a** as indicated by TLC. To address this issue the duration of the reaction (first step) was increased to double i.e. 2h satisfaction the yield of **4a** was increased significantly (entry 2, Table 1) but not up to the desired level yet. Hence the reaction time (first step) was increased further to 2.5 h when **4a** was isolated in 57% yield (entry 3, Table 1). Notably, further increase of reaction time in the first step as well as in the second step did not improve the product yield (entry 4 and 5, Table 1). We then evaluated the need as well as role of each component of the catalyst system used and hence reactions were performed under varying conditions accordingly (entries 6-8, Table 1). It was evident that the omission of any component of the catalyst 10%Pd/C-PPh_3-CuI decreased the reaction efficiency drastically thereby the product yield. The use of other Pd catalyst e.g. $Pd(OAc)_2$ (in combination with PPh_3) (entry 9, Table 1) or $(PPh_3)_2PdCl_2$ (entry 10, Table 1) or $(PPh_3)_4Pd$ (entry 11, Table 1) was tested but the product yield was lower in these cases. While the reaction proceeded in the absence of ultrasound affording **4a** in acceptable yield (entry 12, Table 1) however longer duration was required for both steps. Thus ultrasound appeared to play a key role in accelerating the current one-pot reaction leading to the desired azaindole **4a**. Overall, the conditions of entry 3 (Table 1) was chosen as the optimal condition and was used not only for the synthesis of other analoges of **4a** but also to expand the scope and generality of this ultrasound assisted methodology.

Table 1: The effect of reaction parameters.[a]



Entry	Catalysts	Time (h)		% Yield[b]
		Step 1	Step 2	
1.	10%Pd/C-PPh_3-CuI	1	4	21
2.	10%Pd/C-PPh_3-CuI	2	4	45
3.	10%Pd/C-PPh_3-CuI	2.5	4	57
4.	10%Pd/C-PPh_3-CuI	3	4	55
5.	10%Pd/C-PPh_3-CuI	3	6	58
6.	10%Pd/C-CuI	2.5	4	9
7.	PPh_3-CuI	2.5	4	0
8.	10%Pd/C-PPh_3	2.5	4	0
9.	$Pd(OAc)_2$-PPh_3-CuI	2.5	4	38
10.	$(PPh_3)_2PdCl_2$-CuI	2.5	4	33
11.	$(PPh_3)_4$Pd-CuI	2.5	4	32
12.	10%Pd/C-PPh_3-CuI	12	24	52[c]

[a]All the reactions were carried out using **1a** (1.0 mmol), **2a** (1.0 mmol), Pd catalyst (0.010 mmol), CuI (0.010 mmol), PPh_3 (0.022 mmol) and Cs_2CO_3 (3 mmol) in PEG-400 (3 mL) (step 1) followed by addition of **3a** (1.2 mmol) under nitrogen atmosphere.

[b]Isolated yield.

[c]The reaction was performed in the absence of ultrasound.

A range of 1,2-diaryl substituted azaindoles (**4a-p**) were prepared using the established optimized conditions and results are presented in Table 2. We have varied all three reactants e.g. bromopyridine (**1a-d**), iodoarene (**2a-c**) and terminal alkyne (**3a-e**).[33,34] The iodoarenes containing groups like Me, Cl were employed whereas terminal alkynes containing electron donating

(e.g. the reaction proceeded in all these cases affording the desired products in acceptable to good yield.

All the azaindole derivatives synthesized were characterized by spectral (NMR, MS) data. While the C-3 proton could not be detected for all the compounds (due to the overlapping of the corresponding signal with other signals) in their ^{1}HNMR spectra a singlet in the range δ 7.0-6.5 (depending on the position of endocyclic nitrogen atom in the bicyclic ring) could be assigned to this proton. The corresponding C-3 carbon appeared near 100 ppm in the ^{13}CNMR spectra. The partial ^{1}H and ^{13}C NMR data of a representative compound i.e. **4n** is shown in Fig 2. The -OMe group appeared near δ 3.7 and 55.4 ppm in the ^{1}H and ^{13}C NMR spectra, respectively. Similarly, the proton and carbon at 4-position appeared near δ 8.8 and 143.6 ppm in the ^{1}H and ^{13}C NMR spectra, respectively. Moreover, the ^{13}C NMR spectra showed that the carbon at 6-position and that attached to N-1 carbon bearing -OMe group appeared near 159.7 ppm.

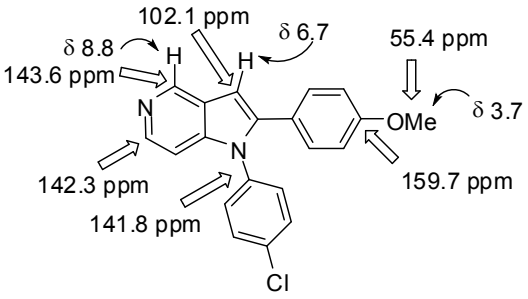
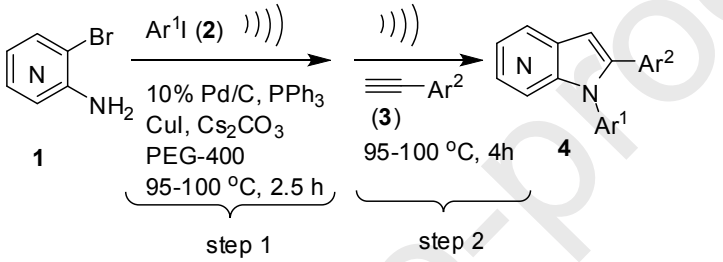
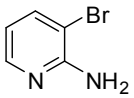
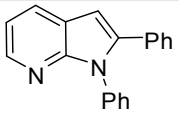
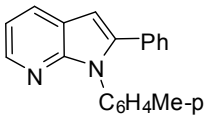
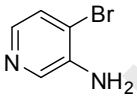
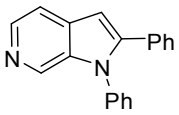
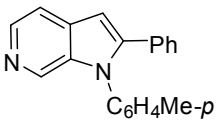
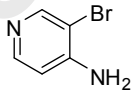
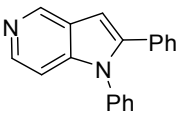
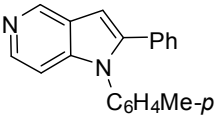
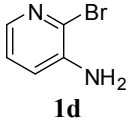
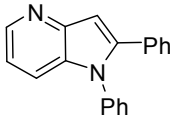
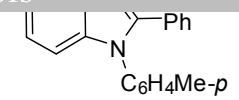
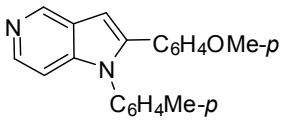
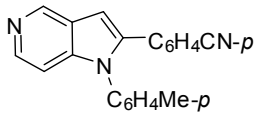
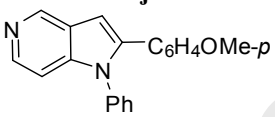
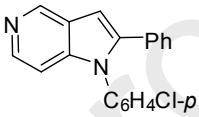
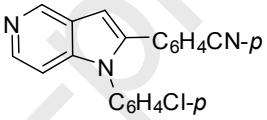
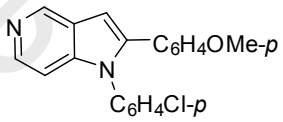
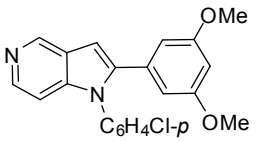
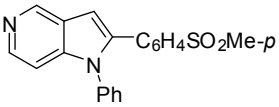


Fig. 2. Partial representation of ^{1}H and ^{13}C NMR spectral data of azaindole derivative **4n**

Table 2. Ultrasound assisted one-pot synthesis of azaindoles under Pd/C-Cu catalysis.[a]

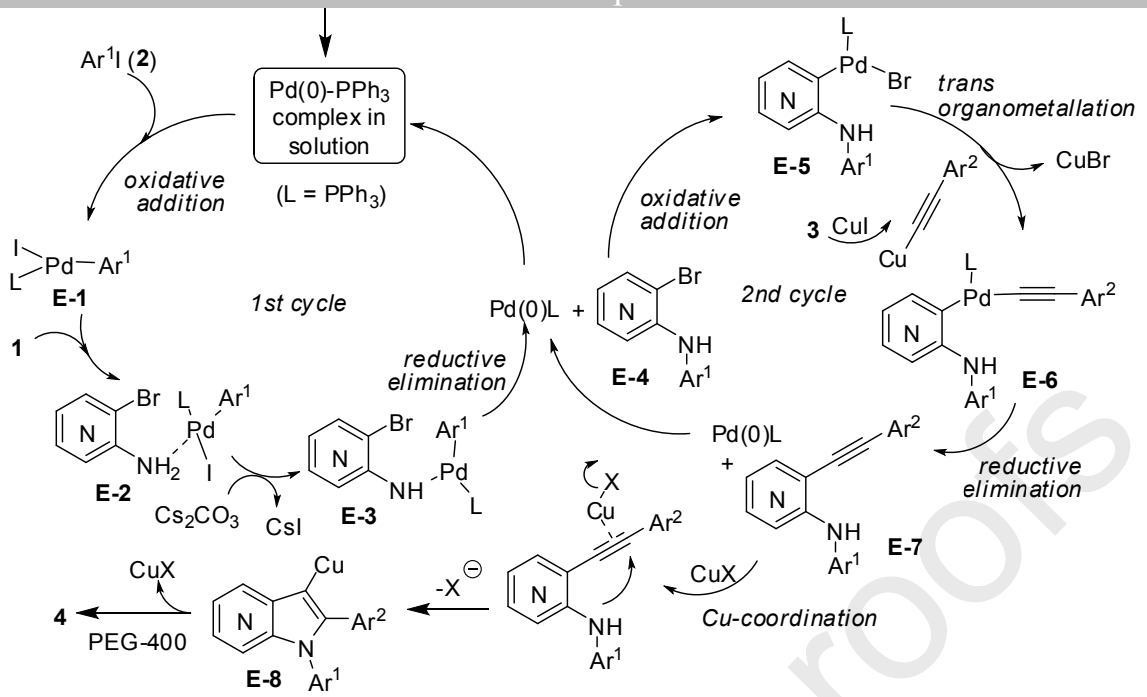


Entry	Bromopyridine **(1)**	**2**; Ar^1 =	**3**; Ar^2 =	Product **(4)**	%Yield[c]
1.	 **1a**	**2a**; Ph	**3a**; Ph	 **4a**	57
2.	**1a**	**2b**; C_6H_4Me-*p*	**3a**; Ph	 **4b**	61
3.	 **1b**	**2c**; Ph	**3a**; Ph	 **4c**	69
4.	**1b**	**2b**; C_6H_4Me-*p*	**3a**; Ph	 **4d**	60
5.	 **1c**	**2a**; Ph	**3a**; Ph	 **4e**	67
6.	**1c**	**2b**; C_6H_4Me-*p*	**3a**; Ph	 **4f**	68
7.	 **1d**	**2a**; Ph	**3a**; Ph	 **4g**	53

	1d	**2b**; C_6H_4Me-*p*	**3a**; Ph	 **4h**	55
9.	**1c**	**2b**; C_6H_4Me-*p*	**3b**; C_6H_4OMe-*p*	 **4i**	64
10.	**1c**	**2b**; C_6H_4Me-*p*	**3c**; C_6H_4CN-*p*	 **4j**	50
11.	**1c**	**2a**; Ph	**3b**; C_6H_4OMe-*p*	 **4k**	68
12.	**1c**	**2c**; C_6H_4Cl-*p*	**3a**; Ph	 **4l**	69
13.	**1c**	**2c**; C_6H_4Cl-*p*	**3c**; C_6H_4CN-*p*	 **4m**	50
14.	**1c**	**2c**; C_6H_4Cl-*p*	**3b**; C_6H_4OMe-*p*	 **4n**	72
15.	**1c**	**2c**; C_6H_4Cl-*p*	**3d**; $C_6H_3(OMe)_2$-*m,m*	 **4o**	62
16.	**1c**	**2a**; Ph	**3e**; $C_6H_4SO_2Me$-*p*	 **4p**	58

[a]All reactions were carried out using **1** (1.0 mmol), **2** (1.0 mmol), 10%Pd/C (0.010 mmol), CuI (0.010 mmol), PPh_3 (0.022 mmol) and Cs_2CO_3 (3 mmol) in PEG-400 (3 mL) for 2.5h (step 1) followed by addition of **3** (1.2 mmol) for 4h (step 2) under a nitrogen atmosphere.

[b]Isolated yield.



Scheme 2. The proposed reaction mechanism for the formation of azaindole derivatives (**4**)

Form the viewpoint of reaction mechanism (Scheme 2) the Pd/C-CuI-PPh_3 catalysed one-pot synthesis of azaindole **4** involved two catalytic cycles, e.g. (i) *N*-arylation *via* the C-N bond forming reaction[35,36] followed by (ii) coupling-cyclization *via* C-C and C-N bond formation.[7] While both the catalytic cycle was mainly catalyzed by the Pd-catalyst, the CuI played the role of a co-catalyst in the second catalytic cycle. Indeed, the cyclization step of the second catalytic cycle was aided by Cu-catalyst where the Pd-catalyst (being the Pd(0) species) appeared to have no role. Nevertheless, an active Pd(0) species[37] was generated *in situ* from the Pd/C as a result of the leaching process in the presence of PPh_3 (Scheme 3).[38] The reaction then followed the usual N-arylation steps[35,36] e.g. (i) oxidative addition of Pd(0) to the iodoarene **2** to generate **E-1**, (ii) interaction of amine **1** with **E-1** followed by deprotonation afforded the Pd-amide species **E-3** (via **E-2**) and (iii) reductive elimination of Pd(0) from **E-3** to complete the first catalytic cycle affording the N-arylated intermediate **E-4**. In the second catalytic cycle the reaction followed the usual Sonogashira steps[39] e.g. (i) oxidative addition of Pd(0) to **E-4** to generate **E-5**, (ii) *trans*-organometallation of **E-5** with Cu-acetylide generated *in situ* from **3** to give **E-6** and (iii) reductive elimination of Pd(0) from **E-6** to complete the cycle. The alkyne moiety of **E-6** was then activated *via* coordination with the Cu(I)-species that facilitated intramolecular cyclization followed by protodemetalation (aided by PEG-400) to give the desired azaindole derivative **4** (with the regeneration of Cu(I)-species). Though it is not clear if all steps or any particular step of this coupling-cyclization process was accelerated by ultrasound but the overall process appeared to be influenced by the ultrasound. Indeed, the higher efficiency of the reaction (entry 3 vs 12, Table 1) can be explained by faster Pd leaching process assisted by ultrasound thereby facilitating the subsequent steps.

The current ultrasound assisted one-pot method afforded a series of 1,2-diaryl substituted azaindole derivatives. These compounds were initially assessed for their cytotoxic properties against two different metastatic breast cancer cell lines e.g. MDA-MB-231 and MCF-7. An MTT [(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay[40] was used to test these compounds at a concentration of 10 µM. Suramin was used as a reference standard in this assay. Notably suramin is not only known to inhibit the cell proliferation in ovarian and cervical cancer[41] but also an inhibitor of human sirtuin 1 (SIRT1). Nevertheless, the assay results are presented in Table 3. The compound **4f**, **4i**, **4k** and **4o** showed comparable anti proliferative properties to suramin. Indeed the compound **4i** was found to be better than suramin. Among the rest of azaindole derivatives some compounds showed moderate to weak cytotoxic properties. Though presenting a precise Structure-Activity-Relationship (SAR) within this series of azaindole derivatives was not straightforward the position of endocyclic "N" atom and the nature as well as type of aryl substituents at 1- and 2- position appeared to play a key role in activities (Fig. 3). In general 5-azaindole framework was found to be the most effective among all azaindoles tested. Among the substitutents of aryl rings present at 1- and 2- position the groups that are electron donating in nature were preferred over the electron withdrawing groups. Particularly compounds containing a methoxy group (e.g. **4f**, **4i** and **4o**) showed superior activities over those (e.g. **4j**, **4m** and **4p**) containing CN or SO_2Me substituents. Notably, "OMe" at *m*-position decreased the activity (e.g. **4o**). The 1-aryl ring containing a "Me" substituent at *p*- position was favored over the "Cl" substituent at the same place (e.g. **4i** vs **4n**). Nevertheless, having screened in the MTT assay we focused on assessing SIRT1 inhibitory properties of these molecules. Accordingly, all these compounds were tested at 10 µM using the Fluor-de-Lys peptide as a substrate following a reported biochemical enzymatic assay method.[42] Notably, over expression of SIRT1 has been observed in several types of cancer and inhibition of SIRT1 by small molecules demonstrated inhibition of cancer cell proliferation. The compounds that were found to be active in this assay (>50% inhibition, Table 3) include **4i, 4k** and **4o**. The compound **4i** and **4k** appeared to possess SIRT1 inhibitory properties comparable to suramin. This was further supported by the concentration dependent study of compound **4i** and suramin against SIRT1 enzyme. Indeed, **4i** was found to be a potent inhibitor of SIRT1 with an IC_{50} of 3.13±0.27 µM compared to the IC_{50} of suramin as 2.25±0.16 µM. Thus the current series of 5-azaindole derivatives are of further medicinal interest.

Tab and azaindole derivatives **4**.

Compounds	% inhibition @ 10 μM[a]		
	Cell based assay		Enzymatic assay
	MDA-MB-231	MCF-7	SIRT1
Control	0.39	0.45	0
Suramin	38.0	45.0	80.3
4a	25.3	31.2	43.1
4b	29.3	22.6	39.4
4c	19.8	27.5	35.1
4d	35.1	38.5	48.3
4e	34.7	41.3	47.0
4f	38.3	46.7	48.9
4g	23.6	20.4	21.8
4h	24.3	39.6	32.5
4i	53.5	59.3	78.5
4j	35.4	46.5	44.3
4k	45.5	42.1	76.8
4l	38.9	32.6	39.9
4m	36.0	34.1	38.4
4n	23.7	20.1	19.8
4o	47.0	34.1	68.4
4p	19.8	10.9	16.8

[a]Data represent the mean values of three independent determinations**.**

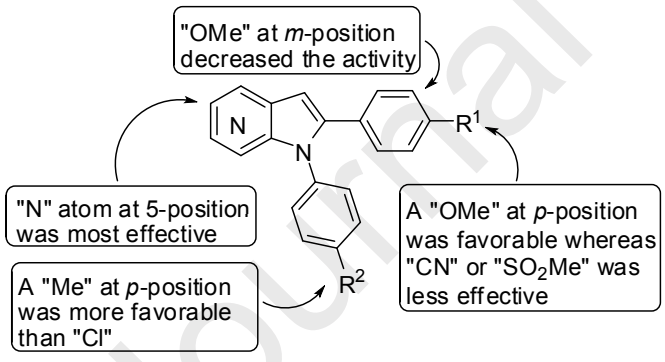


Fig. 3. Summary of SAR for cytotoxic activities of azaindole **4**

In conclusion we have reported the first ultrasound assisted one-pot and direct access to 1,2-diaryl substituted azaindole derivatives *via* the sequential *N*-arylation followed by coupling-cyclization under Pd/C-Cu catalysis. The methodology involved initial C-N bond forming reaction (step 1) between an appropriate *o*-bromo substituted amino pyridine and iodoarene followed by C-C and C-N bond formation (step 2) between the resulting *N*-aryl substituted intermediate and a terminal alkyne in the same pot. The advantages associated with the use of Pd/C include that it is an inexpensive, stable and widely used catalyst. Moreover, the solvent used here i.e. PEG-400 is known to be an environmentally friendly solvent. A variety of azaindoles was prepared by using this methodology. These compounds were assessed for their cytotoxic properties against two different metastatic breast cancer cell lines e.g. MDAMB-231 and MCF-7 **4o** showed promising growth inhibition of these cell lines and SIRT1 inhibition *in vitro*. Indeed, **4i** was found to be a potent inhibitor of SIRT1. Overall, the current research demonstrated the utility of ultrasound in combination with Pd/C-Cu catalysis for the direct synthesis of 1,2-diaryl substituted azaindoles some of which showed promising anticancer properties.

Acknowledgement

The authors thank the management of Dr. Reddy's Lab Ltd, Hyderabad, India, for continuous support and encouragement.

Supplementary data

Supplementary data associated with this article can be found, in the on line version, at xxxxxxxxx

References and notes

1. Naud, S., Westwood, I.M., Faisal, A., Sheldrake, P., Bavetsias, V., Atrash, B., Cheung, K.M.J., Liu, M., Hayes, A., Schmitt, J., Wood, A., Choi, V., Boxall, K., Mak, G., Gurden, M., Valenti, M., de Haven Brandon, A., Henley, A., Baker, R., McAndrew, C., Matijssen, B., Burke, R., Hoelder, S., Eccles, S. A., Raynaud, F. I., Linardopoulos, S., van Montfort, R. L., Blagg, J. *J. Med. Chem.* **2013**, *56*, 10045–10065.
2. Beswick, P., Gleave, R., Swarbrick, M., 7-Azaindole derivatives as COX_2 inhibitors. World patent application number WO 2005/016924 A1, 24 Feb 2005.
3. Echalier, A., Bettayeb, K., Ferandin, Y., Lozach, O., Clément, M., Valette, A., Liger, F., Marquet, B., Morris, J. C., Endicott, J. A., Joseph, B., Meijer, L., *J. Med. Chem.* **2008**, *51*, 737−751.
4. Walker, S. R., Carter, E. J., Huff, B. C., Morris, J. C., *Chem. Rev.* **2009**, *109*, 3080−3098.
5. Perry, N. B., Ettouatti, L., Litaudon, M., Blunt, J. W., Munro, M. H. G., Parkin, S., Hope, H., *Tetrahedron* **1994**, *50*, 3987-3992.
6. Trimurtulu, G., Faulkner, D. J., Perry, N. B., Ettouatti, L., Litaudon, M., Blunt, J. W., Munro, M. H. G., Jameson, G. B., *Tetrahedron* **1994**, *50*, 3993-4000.
7. Layek, M., Kumar, Y. S., Islam, A., Karavarapu, R., Sengupta, A., Halder, D., Mukkanti, K., Pal, M., *Med. Chem. Commun.* **2011**, *2*, 478-485.
8. Michan, S., Sinclair, D., *Biochem. J.,* **2007**, *404*, 1-13.
9. Bedalov, A., Gatbonton, T., Irvine, W.P., Gottschling, D.E., Simon, J.A., *Proc. Natl. Acad. Sci. U. S. A.,* **2001**, *98*, 15113-15118.
10. Mérour, J.-Y., Routier, S., Suzenet, F., Joseph, B., *Tetrahedron* **2013**, *69,* 4767−4834.
11. Cullen, M. H. S., Geng, B., Foley, M., Bastos, C. M., Munoz, B., Haeberlein, M. Proteasome activity enhancing compounds. World patent application number WO 2015/073528, 21 May 2015.
12. (a) Qian, G., Hong, X., Liu, B., Mao, H., Xu, B., *Org. Lett.* **2014**, *16*, 5294−5297; (b) Purificacao, S. I.; Pires, M. J. D.; Rippel, R.; Santos, A. S.; Marques, M. B. *Org. Lett.* **2017**, *19*, 5118-5121.
13. (a) Song, J. J., Reeves, J. T., Gallou, F., Tan, Z., Yeea, N. K., Senanayake, C. H. *Chem. Soc. Rev.* **2007**, *36*, 1120-1132; (b) For the synthesis of 2-unsubstituted azaindoles, see: Xu, Z.; Hu, W.; Zhang, F.; Li, Q.; Lu, Z.; Zhang, L.; Jia, Y. *Synthesis* **2008**, 3981-3987.
14. Koradin, C., Dohle, W., Rodriguez, A. L., Schmid, B., Knochel, P. *Tetrahedron* **2003**, *59*, 1571-1587.
15. Rodriguez, A. L., Koradin, C., Dohle, W., Knochel, P., *Angew. Chem. Int. Ed.* **2000**, *39*, 2488-2490.
16. Harcken, C., Ward, Y., Thomson, D., Riether, D. *Synlett* **2005**, 3121-3125.
17. Sun, L.-P., Huang, X.-H., Wang, J.-X. *J. Chinese Chem. Soc.* **2007**, *54*, 569-573.
18. Majumdar, K. C., Mondal, S. *Tetrahedron Lett.* **2007**, *48*, 6951-6953.
19. Majumdar, K. C., Samanta, S., Chattopadhyay, B., *Tetrahedron Lett.* **2008**, *49*, 7213-7216.
20. Kumar, V., Dority, J. A., Bacon, E. R., Singh, B., Lesher, G. Y., *J. Org. Chem.* **1992**, *57*, 6995-6998.
21. de Mattos, M. C., Alatorre-Santamaría, S., Gotor-Fernández, V., Gotor, V., *Synthesis* **2007**, 2149-2152.
22. Sakai, N., Annaka, K., Fujita, A., Sato, A., Konakahara, T., *J. Org. Chem.* **2008**, *73*, 4160-4165.

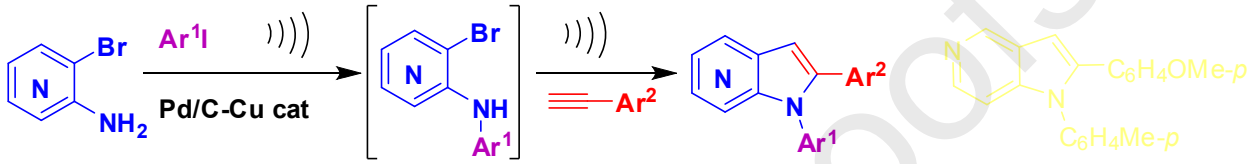
Lett. **1998**, *39*, 5159-5162.
25. Park, S. S., Choi, J.-K., Yum, E. K., *Tetrahedron Lett.* **1998**, *39*, 627-630.
26. Ujjainwalla, F., Walsh, T. F., *Tetrahedron Lett.* **2001**, *42*, 6441-6445.
27. Mason, T. J., *Chem. Soc. Rev.* **1997**, *26*, 443-451. DOI: 10.1039/CS9972600443
28. Puri, S., Kaur, B., Parmar, A., Kumar, H., *Curr. Org. Chem.* **2013**, *17*, 1790-1828

Xie, R., Disch, J.S., Ng, P. Y., Nunes, J.J., Lynch, A.V., Yang, H., Galonek, H., Israelian, K., Choy, W., Iffland, A., Lavu, S., Medvedik, O., Sinclair, D.A., Olefsky, J.M., Jirousek, M.R., Elliott, P.J., Westphal, C. H. *Nature* **2007**, *450*, 712-716.

Ultrasound assisted one-pot synthesis of 1,2-diaryl azaindoles via Pd/C-Cu catalysis: identification of potential cytotoxic agents

Leave this area blank for abstract info.

Rapolu Venkateshwarlu, Shambhu Nath Singh, Vidavalur Siddaiah, Hindupur Ramamohan, Rambabu Dandela,* and Manojit Pal*



The first ultrasound assisted azaindole synthesis was achieved under Pd/C-Cu catalysis. Some of the azaindoles were identified as promising cytotoxic agents.

29. Ghotbinejad, M., Khosropour, A. R., Mohammadpoor-Baltork, I., Moghadam, M., Tangestaninejad, S., Mirkhani, V., *RSC Adv.*, **2014**, *4*, 8590-8596.
30. Palimkar, S. S., More, V. S., Srinivasan, K. V., *Ultrason. Sonochem.*, **2008**, *15*, 853-862.
31. Riedmüller, S., Nachtsheim, B. J., *Beilstein J. Org. Chem.* **2013**, *9*, 1202–1209.
32. Prasad, B., Kumar, K. S., Babu, P. V., Anusha, K., Rambabu, D. Kandale, A., Vanaja, G. R., Kalle, A. M., Pal, M., *Tetrahedron Lett.* **2012**, *53*, 6059–6066.
33. Burroughs, L., Ritchie, J., Ngwenya, M., Khan, D., Lewis, W., Woodward, S., *Beilstein J. Org. Chem.* **2015**, *11*, 273-279.
34. Dell'Acqua, M., Ronda, L., Piano, R., Pellegrino, S., Clerici, F., Rossi, E., Mozzarelli, A., Gelmi, M. L., Abbiati, G., *J. Org. Chem.* **2015**, *50*, 10939-10954.
35. Driver, M.S., Hartwig, J.F., *J. Am. Chem. Soc.*, **1997**, *119*, 8232–8245.
36. Widenhoefer, R.A., Buchwald, S.L., *Organometallics* **1996**, *15*, 2755–2763.
37. Chen, J.-S., Vasiliev, A.N., Panarello, A.P., Khinast, J.G., *Appl. Catal. A: Gen.* **2007**, 325, 76-86.
38. Kohler, K., Heidenreich, R.G., Krauter, J.G., Pietsch, J., *Chem. A Eur. J.* **2002**, *8*, 622-631.
39. Sonogashira, K., Tohda, Y., Hagihara, N., *Tetrahedron Lett.*, **1975**, *16*, 4467–4470.
40. Plumb, J. A., *Methods Mol. Med.*, **2004**, 88, 165-169.
41. Li, H. P., Li, H. L., Qu, H. J., Zhao, M. Z., Yuan, B., Cao, M. H., Cui, J. Q., *Cancer Cell Int.* **2015**, *15*, 52. doi: 10.1186/s12935-015-0196-y

Declaration of interests

☒ 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.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Graphical Abstract

Highlights

- Reported the first ultrasound assisted one-pot and direct synthesis of 1,2-diaryl

- Synthesis involved sequential *N*-arylation / coupling-cyclization under Pd/C-Cu catalysis
- Three azaindoles showed cytotoxicities against MDAMB-231 / MCF-7 cell lines
- One of them was identified as a potent inhibitor of SIRT1.