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Sonochemical synthesis of polyarylated oxazoles as potential cytotoxic agents

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ABSTRACT

The ultrasound assisted facile, rapid and one-pot synthesis of 2-aryl substituted 4,5-diphenyloxazoles was achieved *via* the reaction of commercially available benzoin (or 2-hydroxy-2-phenylacetophenone) with benzylamines in the presence of IBX under mild conditions. The methodology involved initial IBX mediated conversion of benzoin to benzil and then reaction with benzylamine followed by intramolecular cyclization (C—O bond formation) and finally aromatization in the presence of air in the same pot. The methodology afforded a variety of desired products that were assessed for their cytotoxic properties against a number of cancerous and a non-cancerous cell lines. Compounds **3h**, **3n** and **3o** showed promising growth inhibition of these cell lines except the non-cancerous one and interactions with SIRT1 *in silico* as well as *in vitro*.

The oxazole ring, frequently found in several natural products and bioactive molecules is considered as one of the privileged frameworks in the area of medicinal chemistry and drug discovery. It is not surprising that oxazole derivatives have shown various biological activities including anticancer properties [1–5]. While anticancer activities of di and tri substituted oxazole derivatives including the investigational agent PC-046 [4,5] have been reported earlier (Fig 1) the evaluation of cytotoxic effects of triaryl substituted oxazoles is rather uncommon in the literature. On the other hand, anticancer activities of triaryl substituted heterocycles such as imidazole [6] (**A**, Fig. 2) or 1,2,4-oxadiazole derivatives [7] (**B**, Fig. 2) is known. All these reports prompted us in exploring the cytotoxic potential of 2,4,5-triaryl substituted oxazole derivatives (**C**, Fig 2) leading to the identification of new cytotoxic agents. Notably, while chemotherapy plays an important role in the treatment of cancer however drug resistance [8] often cause a major hurdle resulting in failure of this approach. Since addition of novel drugs is considered as one of the key solutions to this multifaceted problem hence there is a great need in devoting continuing efforts towards the introduction of new and potent cytotoxic agents via Med Chem approaches. While the template **C**, as shown in Fig. 2, has three centers for the introduction of diversity into the oxazole molecule, we initially focused on the modification of C-2 aryl group maintaining C-4 and C-5 aryl moiety as benzene ring (e.g. **C** when Ar^1 = Ar^2 = Ph) in order to make a gradual but sequential progress. We aimed to examine the effect of variation of C-2 aryl group on biological activities of such derivatives at the initial stage. Therefore, we required a straightforward, convenient and rapid method for the synthesis of 2-aryl substituted 4,5-diphenyloxazole derivatives in order to access a focused library of molecules based on template **C**.

Due to their importance in pharmaceuticals and functional materials several approaches have been reported for the synthesis of arylated oxazoles. These include (i) C—H bond arylation of simple oxazoles leading to the di or tri arylated derivatives [9], (ii) the use of Cu-mediated aerobic oxidative dehydrogenation for the synthesis of 2,5-diaryl oxazoles [10], (iii) the synthesis of 2,4-diaryl oxazoles [11] via TBHP-I_2 mediated oxidative cyclization [12,13] etc. However, the triarylated oxazoles particularly were prepared via the oxidative cyclization of 1,2-diketones (benzils) with benzyl amine derivatives (Method A and B, Scheme 1) [14,15]. While these methods are handy for the preparation of a variety of triarylated oxazole derivatives however the requirement of relatively lengthy reaction time and transition metal based catalyst or reagent are

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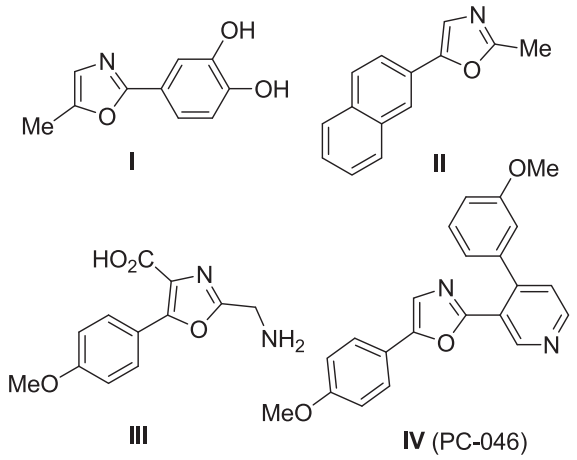


Fig. 1. Known oxazole derivatives possessing anticancer activities.

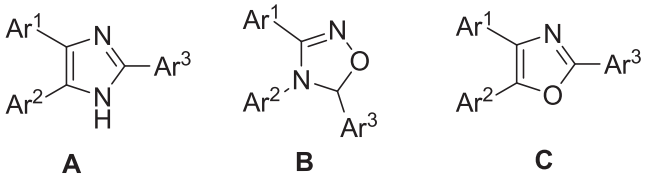
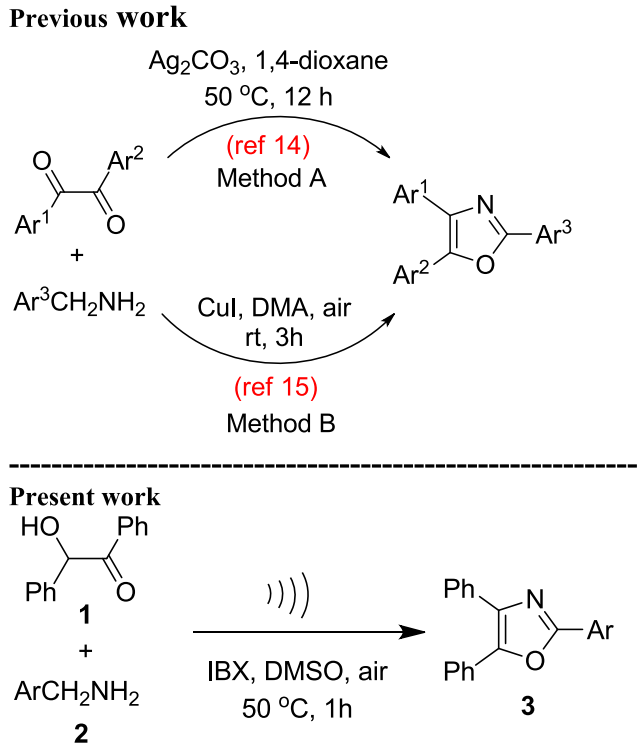


Fig. 2. Triaryl substituted heterocycles **A** and **B** possessing anticancer activities and the design of analogues oxazole derivatives **C**.



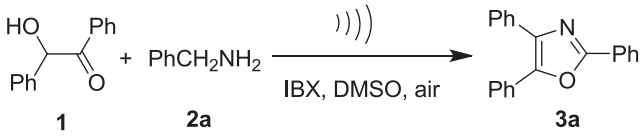
Scheme 1. Reported and current synthesis of 2,4,5-triaryl substituted oxazole derivatives.

somewhat problematic. Thus it was desirable to develop a rapid and efficient synthesis of polyarylated oxazoles to fulfil our Med Chem research goal.

Initially, the chemistry effort [16–23] was devoted to establish the optimized reaction conditions for the access of desired oxazole derivatives (**3**, Scheme 1). Accordingly, the domino reaction between benzoin (**1**) and benzylamine (**2a**) was performed using IBX [21–23] as an oxidant under a range of reaction conditions and the results are summarized in Table 1. The reaction proceeded well when carried out using 1.2 equiv of IBX in DMSO at 30 °C in the presence of air under ultrasound [16–20] using a laboratory ultrasonic bath SONOREX SUPER RK 510H model producing irradiation of 35 kHz (entry 1, Table 1). However, the desired coupled product **3a** was obtained in 49% yield after 3 h. The increase of reaction temperature from 30 to 50 °C improved the product yield significantly and the reaction was completed within 1 h (entry 2, Table 1). Encouraged by this observation we continued our study for possibility of further improvement in product yield. Thus the temperature was increased further from 50 to 70 °C but no significant increase in yield of **3a** was observed (entry 3, Table 1). Notably, the reaction did not proceed in the absence of IBX (entry 4, Table 1) whereas the use of lower quantity of IBX afforded **3a** in low or poor yield (entry 5 and 6, Table 1). The reaction was also found to be less efficient in terms of product yield when carried out in the absence of ultrasound even for 10 h (entry 7, Table 1). The use of other solvent e.g. MeCN (entry 8, Table 1) or THF (entry 9, Table 1) in place of DMSO though found to be effective but afforded **3a** in lower yield. Overall, the condition of entry 2 of Table 1 (i.e. the use of 1.2 equiv of IBX in DMSO at 50 °C under ultrasound) appeared to be optimum and was used for the preparation of analogues of **3a**.

A range of benzylamines (**2**) were employed to react with the benzoin (**1**) under the optimized conditions. The benzylamine may contain various substituents on the benzene ring including halogen (e.g. F, Cl and Br) or electron donating (e.g. Me and OMe) or electron withdrawing group (e.g. CN, NO_2 and CF_3) etc. Some of these group may present at *o*- or *m* or *p*-position of the benzene ring. The amine may contains 3,4-dimethoxyphenyl or benzo[*d*][1,3]dioxol-5-yl moiety as the aromatic ring or heteroaryl moiety such as pyridyl, furyl and thienyl ring. The amine may contain a polynuclear aromatic ring such as naphthalene moiety. The IBX

Table 1
Effect of conditions on the reaction of benzoin (**1**) and benzylamine (**2a**).[a]

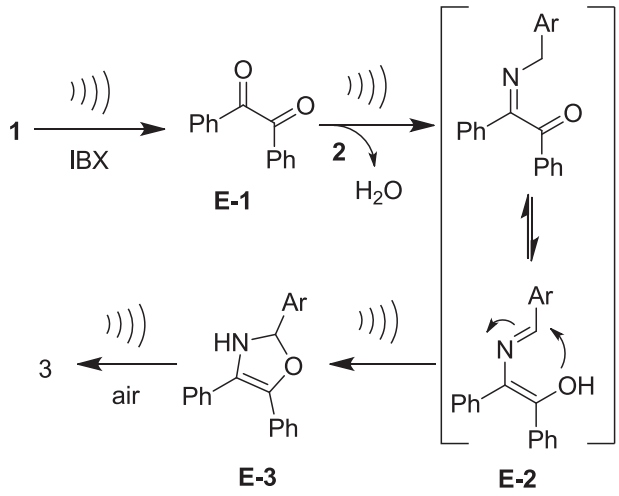


Entry	Temp (°C)	Time (h)	Yield[b] (%)
1	30	3	49
2	50	1	85
3	70	1	84
4	50	3	0[c]
5	50	1	10[d]
6	50	1	51[e]
7	70	10	50[f]
8	50	2	63[g]
9	50	2	69[h]

[a] All reactions were performed using the benzoin **1** (1.2 mmol), benzylamine **2a** (1 mmol) and IBX (1.2 equiv.) in DMSO (5 mL) under ultrasound and open air.
[b] Isolated yields.
[c] The reaction was performed in the absence of IBX.
[d] 0.05 equiv. IBX was used.
[e] 0.5 equiv. of IBX was used.
[f] The reaction was performed in the absence of ultrasound.
[g] MeCN was used in place of DMSO.
[h] THF was used in place of DMSO.

mediated sonochemical reaction proceeded smoothly in all these cases affording the desired coupled product in good to acceptable yield (Table 2). It is worthy to mention that the reaction was not successful when benzyl amine was replaced by other amines such as *n*-butyl amine or allyl amine or propargyl amine etc. This appeared to be the limitation of this methodology. Nevertheless, all the products were characterized by using common spectral (^{1}H and ^{13}C NMR and Mass) data (See Fig S-1 in ESI).

Based on the results of Table 1 and the earlier reports [14,15] a proposed reaction mechanism for the IBX mediated reaction of **1** with **2** under ultrasound irradiation is presented in Scheme 2. The reaction seems to proceed *via* (i) IBX mediated conversion [24] of benzoin (**1**) to the benzil (**E-1**) which on (ii) reaction with benzylamine (**2**) followed by (iii) intramolecular cyclization (C—O bond formation) of the resulting **E-2** gives **E-3** that (iv) aromatizes to **3** in the presence of air. While IBX mediated aromatization has been reported earlier [25a] a similar reaction is unlikely in the present case considering the fact that only 1.2 equivalent of IBX was used. Thus aromatization of **E-3** was aided by the aerial oxygen under ultrasound. It is worthy to mention that according to the results presented in Table 1, ultrasound not only accelerated the reaction rate but also facilitated the formation of the desired product. Indeed, the ultrasound is known to cause cavitation involving the growth, oscillation, and collapse of bubbles under the action of an acoustic field [26,27]. As a result, drastic conditions e.g. the temperature of 2000–5000 K and pressure up to 1800 atmosphere inside the medium within an extremely short period of time is created particularly by the cavitational collapse. Moreover, shear forces, jets, and shock waves are caused by this collapse outside the bubble. Therefore the overall effects induced by cavitation could be involved in the IBX-mediated oxidation of **1** followed by condensation with **2** in the crucial initial steps (Scheme 2). The ultrasound seemed to have played an important role in the aromatization of **E-3** also as the air (oxygen) alone might not be enough to facilitate this step under the normal condition within short duration of reaction time [25b]. Overall, the combined effect of ultrasound, IBX and air was essential for the successful preparation of **3**.



Scheme 2. Proposed reaction mechanism for the IBX-mediated reaction of **1** with **2** under ultrasound irradiation.

Table 2
IBX-mediated sonochemical synthesis of 2-aryl substituted 4,5-diphenyloxazoles (**3**) (Scheme 1).[a]

Entry	Amine Ar ; **2**	Product **3**	Yield (%)[b]
1	Phenyl, **2a**	**3a**	85
2	4-FC_6H_4, **2b**	**3b**	79
3	4-ClC_6H_4, **2c**	**3c**	74
4	4-BrC_6H_4, **2d**	**3d**	73
5	4-MeC_6H_4, **2e**	**3e**	82
6	3-MeC_6H_4, **2f**	**3f**	74
7	2-MeC_6H_4, **2g**	**3g**	67
8	4-$MeOC_6H_4$, **2h**	**3h**	68
9	4-CNC_6H_4, **2i**	**3i**	73
10	4-$NO_2C_6H_4$, **2j**	**3j**	87
11	4-$CF_3C_6H_4$, **2k**	**3k**	83
12	3-$CF_3C_6H_4$, **2l**	**3l**	78
13	2-$CF_3C_6H_4$, **2m**	**3m**	63
14	4-$CF_3OC_6H_4$, **2n**	**3n**	74
15	3,4-dimethoxyphenyl, **2o**	**3o**	80
16	benzo[*d*][1,3]dioxol-5-yl, **2p**	**3p**	69
17	4-pyridyl, **2q**	**3q**	81
18	3-pyridyl, **2r**	**3r**	79
19	2-pyridyl, **2s**	**3s**	73
20	2-furyl, **2t**	**3t**	72
21	2-thienyl, **2u**	**3u**	76
22	1-naphthyl, **2v**	**3v**	70
23	2-naphthyl, **2w**	**3w**	74

[a] All reactions were performed using **1** (1.2 mmol), **2** (1 mmol) and IBX (1.2 equiv.) in DMSO (5 mL) at 50 °C for 1 h under ultrasound and open air.
[b] Isolated yields.

With a range of synthesized compounds on hand we then decided to assess these oxazole derivatives **3** for their potential anti-cancer properties *in vitro*. A number of cancerous cell lines were used for this purpose that include MDA-MB 231 and MCF7 (human metastatic breast cancer), K562 (human chronic myeloid leukemia), Colo-205 (human colon carcinoma), and IMR-32 (human neuroblastoma) cell lines. A non-cancerous HEK293 (human embryonic kidney) cell line was also used to test the selectivity of active compounds towards cancerous cell lines. The colorimetric MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay [28] was used to measure the effect of test compounds on above mentioned cancerous/non-cancerous cell lines after 24 h of treatment in culture medium containing PBS. All the compounds were tested initially at a concentration of 10 μM and the % inhibition in growth of cancer cell lines caused by these compounds are shown in Table 3. Generally, compounds were considered as active when showed >50% inhibition in cell growth. As can be seen from Table 3 that compounds **3h**, **3n** and **3o** showed significant growth inhibition against K562 Leukemia cell lines whereas compounds **3t** and **3u** showed moderate effects against the same cell lines. Similarly compounds **3h**, **3n**, **3o**, **3r** and **3w** showed encouraging growth inhibition against MDA-MB 231 and MCF7 (human metastatic breast cancer) cell lines whereas **3b** and **3v** was found to be other compounds that showed some effects. While **3h**, **3n**, and **3o** showed moderate effects against IMR-32 Neuroblastoma cell lines the compound **3h** was the only one that showed effects against HepG2 Hepato-carcinoma cell lines. Notably, none of these compounds showed significant effects against Colo-205 Colon cell lines. All these observations suggested that this class of compounds is generally active against breast cancer cell lines and the activity was mainly affected by the absence/presence of the OMe/OCF_3 group at the C-2 benzene ring attached to the oxazole moiety. The 3-pyridyl or the 2-naphthyl moiety at the C-2 position was also found to be favorable whereas the 4-flourophenyl or benzo[*d*][1,3]-dioxol-5-yl or 1-naphthyl at the same position was moderately effective only against breast cancer cell lines.

Nevertheless, none of these compounds showed any significant effects when tested against HEK293 cells indicating that they are selective towards the growth inhibition of cancer cells. Based on their encouraging growth inhibition data against K562, MDA-MB 231 and MCF7 cells compound **3h**, **3n**, **3o**, **3r** and **3w** were taken for the determination of IC_{50} values. A well- known anticancer

Table 3
In vitro antiproliferative properties of oxazole derivatives **3** against various cells.

Compounds	% Inhibition in growth of cancer cell lines by compounds **3** at 10 μM[a]						
	K562 Leukemia	Colo-205 Colon	MDA-MB 231 ER –ve breast cancer	MCF7 ER +ve breast cancer	IMR-32 Neuroblastoma	HepG2 Hepato-carcinoma	HEK293[b] Non-cancerous
3a	31.8	32.1	55.2	47.4	22.7	29.8	1.9
3b	36.3	39.8	59.6	52.3	27.0	31.2	1.1
3c	29.0	27.8	47.8	44.6	20.7	29.7	0.6
3d	13.8	17.8	23.3	49.3	46.4	36.2	3.8
3e	39.3	33.6	47.9	39.6	31.7	33.1	2.7
3f	33.7	29.7	35.9	31.8	27.6	29.9	0.7
3g	29.0	31.2	33.8	34.6	24.9	28.5	0.3
3h	72.2	49.0	88.0	75.6	60.0	52.4	9.1
3i	38.3	35.8	26.3	23.7	30.8	35.3	0.7
3j	31.1	37.0	41.3	40.7	36.8	33.6	2.6
3k	35.7	32.8	39.0	38.4	28.9	30.1	1.2
3l	17.9	31.0	33.6	35.4	21.9	23.4	2.3
3m	18.7	19.8	29.5	33.3	27.8	20.3	1.0
3n	67.7	35.8	70.8	87.6	54.4	46.3	11
3o	64.8	36.5	68.0	81.8	52.3	42.6	7.5
3p	36.6	31.4	50.1	55.8	30.7	43.9	6.1
3q	33.8	39.2	47.3	40.1	39.0	37.9	7.3
3r	37.9	25.0	64.1	69.0	25.2	21.9	1.6
3s	39.8	35.4	42.7	43.8	30.8	29.6	2.1
3t	56.2	49.3	42.3	41.9	48.4	44.8	0.8
3u	51.8	43.8	38.7	45.6	44.3	36.8	11
3v	29.7	30.4	56.9	66.2	40.1	37.5	5.9
3w	39.8	45.0	57.2	71.8	36.9	38.2	4.9

[a] Data represent the mean values of three independent determinations.
[b] HEK293 cell line was used as non-cancerous cell line.

agent i.e. doxorubicin (that is primarily used to treat breast cancer) was used as a reference compound in this assay [29,30]. The corresponding data are presented in Table 4. The compound **3h**, **3n** and **3o** were found to be potent against MDA-MB 231 and MCF7 cell lines as reflected by their IC_{50} values (~0.9–1.5 μM). However, their IC_{50} values were slightly higher (~3–5 μM) against K562 cells. The compound **3r** and **3w** also showed the same trend though they were relatively less potent as indicated by their IC_{50} values.

In order to understand the potential mechanism of action the *in silico* docking studies were carried out using compounds **3h**, **3n** and **3o** against the SIRT1 protein (PDB: 4I5I). Being considered as important targets for cancer therapeutics sirtuins (class III NAD-dependent deacetylases) are shown to up-regulated in various types of cancer [31]. Inhibition of sirtuins allows re-expression of silenced tumour suppressor genes, leading to the decreased growth of cancer cells. The compound **3h**, **3n** and **3o** interacted with the catalytic residues of ALA262, ILE347, HIS363, ILE411 and PHE273 through the Van der Waals, π-sigma and π-alkyl interactions in the catalytic domain of SIRT1 (see Table S-1 in ESI). Compound **3n** showed better binding free energy among them with its –OCF_3 substituent involving in a H-bonding interaction with the residue ALA262 and one of the fluorine atoms interacting with the GLN345 (see Fig S-3 in ESI). It also showed common interactions with PHE 273, ILE347 and ILE411 residues similar to **3h** and **3o** and interactions comparable to the reference compound [32,33] EX527a (see Table S-1, See also Fig S-2, 3, 4 and 5 in ESI). In order to gain further evidence, we focused on assessing SIRT1 inhibitory properties of these molecules. Accordingly, all these compounds were tested *in vitro* at 10 μM using a reported biochemical enzymatic assay [34] when **3h**, **3n** and **3o** showed 67, 79 and 64% inhibition (with 82% inhibition shown by the reference compound Suramin) respectively indicating SIRT1 as the potential pharmacological target of this class of compounds.

Table 4
IC_{50} values of selected oxazole derivatives.

Compound	IC_{50} (μM)[a]		
	K562	MDA-MB 231	MCF7
3h	3.43 ± 0.24	0.83 ± 0.71	1.32 ± 0.16
3n	4.85 ± 0.31	1.02 ± 0.32	0.98 ± 0.33
3o	4.87 ± 0.18	1.50 ± 0.41	1.09 ± 0.28
3r	>10	6.31 ± 0.81	5.22 ± 1.23
3w	>10	7.64 ± 0.99	5.01 ± 1.10
Doxorubicin	n.d.	0.67 ± 0.31	0.43 ± 0.24

n.d. = not done.
[a] IC_{50} represent the concentration of compound that causes a 50% growth inhibition to untreated cells using an MTT assay.

In conclusion, 2-aryl substituted 4,5-diphenyloxazoles were explored for the identification of potential cytotoxic agents. Accordingly, an ultrasound assisted facile, rapid and one-pot method was developed and employed for the synthesis of targeted 2-aryl substituted 4,5-diphenyloxazoles. The methodology involved the reaction of commercially available benzoin (or 2-hydroxy-2-phenylacetophenone that is less expensive than benzil) with benzylamines in the presence of IBX under mild conditions and afforded the desired products in good to acceptable yields. The methodology involved initial IBX mediated conversion of benzoin to benzil and then reaction with benzylamine followed by intramolecular cyclization (C—O bond formation) and finally aromatization in the presence of air in the same pot. Notably, the reaction was found to be less efficient when carried out in the absence of ultrasound whereas the combined effect of ultrasound, IBX and air was essential for the success of this reaction. All the synthesized compounds were assessed for their cytotoxic properties against a number of cancerous cell lines including MDA-MB 231 and MCF7 (human metastatic breast cancer), K562 (human chronic myeloid leukemia), Colo-205 (human colon carcinoma), and IMR-32 (human neuroblastoma) cell lines along with a non-cancerous HEK293 (human embryonic kidney) cell line using an MTT assay. Results suggested that this class of compounds are generally active against breast cancer cell lines and the activity was mainly affected by the absence/presence of the OMe/OCF_3 group at the C-2 benzene ring attached to the oxazole moiety. Moreover, none of these

compounds showed any significant effects against HEK293 cells indicating their selectivity towards the growth inhibition of cancer cells. Three compounds e.g. **3h**, **3n** and **3o** were identified as the most active agents against MDA-MB 231 and MCF7 cell lines (IC_{50} ~ 0.9–1.5 μM) and appeared to have medicinal value especially from the view point of developing potential agents against breast cancer. Overall, the current research demonstrated the utility of ultrasound in combination with IBX for the one-pot synthesis of 2-aryl substituted 4,5-diphenyloxazoles as potential anticancer agents.

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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153011.

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