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Comparison between Conventional and Nonconventional Methods for the Synthesis of Some 2-Oxazolidinone Derivatives and Preliminary Investigation of Their Inhibitory Activity Against Certain Protein Kinases

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Abstract—A series of propargyl and allyl carbamates were prepared directly from propargyl and allyl alcohols and phenyl or cyclohexyl isocyanate or indirectly by generating the isocyanates *in situ* from the corresponding Cbz-protected amines. The obtained carbamates underwent intramolecular nucleophilic cyclization in presence of cesium hydroxide monohydrate as a base catalyst under conventional and ultrasonic irradiation conditions to give the corresponding substituted 4-(benzylidene)methylidene-2-oxazolidinones in good to excellent yields. The use of ultrasonic irradiation provided remarkably improved yield of the cyclization products and significant shortening of the reaction time. In some cases the reaction was highly stereoselective, and (*Z*)-4-benzylideneoxazolidinones were formed as a single stereoisomer. A series of biological tests were performed to evaluate the inhibitory potential of all synthesized compounds against some protein kinases.

Keywords: Propargyl carbamates, allyl carbamates, isocyanates, intramolecular cyclization, 3-phenyl-1,3-oxazolidin-2-ones, ultrasonic activation, protein kinase inhibition.

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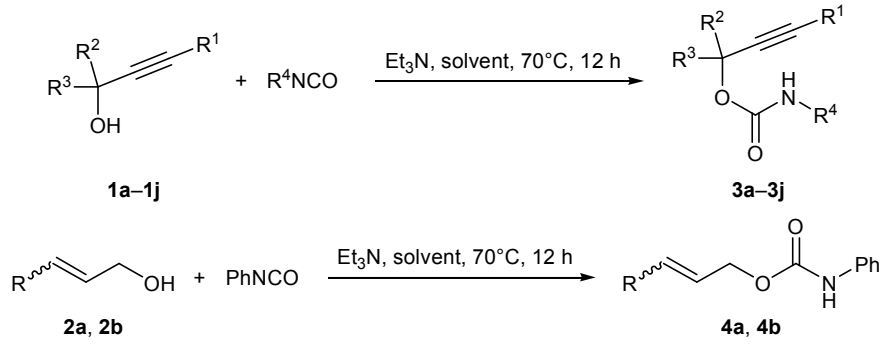
Oxazolidinones represent an important class of widely used organic compounds with a wide variety of applications in many fields, including agriculture [1, 2], organic synthesis [3–5], and medicinal chemistry [6]. Oxazolidinone derivatives have received significant attention due to their broad spectrum of biological activities like antimicrobial [7], anti-inflammatory [8], antifungal [9], anticonvulsant [10], antitubercular [11], and anticancer [12]. Various methods are available for the synthesis of methylidene-1,3-oxazolidin-2-ones, such as base-catalyzed cyclization of vinyl or propargyl carbamates, and only a limited number of publications on the synthesis of 4-methylideneoxazolidinones have been reported. In recent years, the use of ultrasound has become more widespread and has been used more and more frequently in organic synthesis. The use of ultrasound allows good dispersion of the reactants into the reaction solution, thus ensuring optimal interaction between them [13]. In fact, reactions carried out under ultrasonic irradiation often ensure higher yields, better selectivity, and shorter reaction times in comparison with traditional stirring methods [14, 15]. In order to extend the application scope of ultrasound irradiation in the synthesis of heterocyclic compounds, herein we report the synthesis of 4-methylidene(benzylidene)oxazolidinones from the corresponding carbamates starting from internal acetylenic alcohols as potential substrates in presence of cesium hydroxide monohydrate as a base catalyst under conventional and ultrasonic irradiation conditions. A series of biological tests were performed to evaluate the inhibitory potential of all synthesized compounds against some protein kinases.

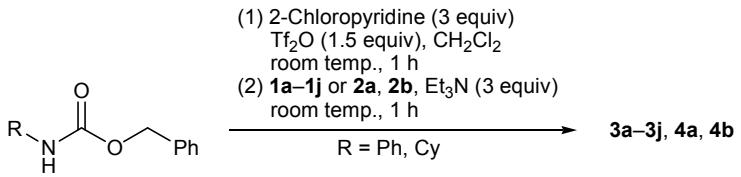
Initially, a number of propargyl and allyl carbamates were synthesized according to reported procedures [16–18]. Propargyl alcohols **1a**–**1j** and allyl alcohols **2a** and **2b** reacted with commercially available phenyl or cyclohexyl isocyanate in THF containing

Scheme 1.



1, **3**, R^1 = H (**a**, **b**, **j**), Ph (**c**), 4-ClC_6H_4 (**d**), 4-$O_2NC_6H_4$ (**e**), 4-FC_6H_4 (**f**), 4-CNC_6H_4 (**g**), 2,4-$(MeO)_2C_6H_3$ (**h**), 2-$MeOC(O)C_6H_4$ (**i**); $R^2 = R^3$ = H (**a**, **c**–**j**), Me (**b**); **3**, R^4 = Ph (**a**–**i**), Cy (**j**); **2**, **4**, R = H (**a**), Me (**b**).

Scheme 2.



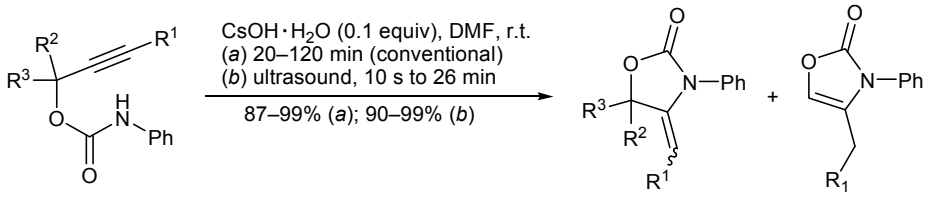
one or two drops of triethylamine under reflux for 12 h (Scheme 1) to give the corresponding carbamates in good to excellent yields (76–99%; Table 1). Alternatively, the synthesis of carbamates from propargyl alcohols and Cbz-protected amines at room temperature with *in situ* generation of intermediate isocyanates (Scheme 2) afforded moderate yields, in most cases due to incomplete conversion of the alcohol. Furthermore, the products required additional purification; the only exception was the reaction with 3-phenylprop-2-yn-1-ol (**1c**) in which the yield was fairly good. The reaction proceeded quite rapidly (2 h) as compared to the first procedure.

Table 1. Yields of propargyl and allyl carbamates **3a**–**3j**, **4a**, and **4b** and but-3-yn-1-yl phenylcarbamate directly from the corresponding isocyanates (method *a*) and from Cbz-protected amines (method *b*)

Compound no.	Yield, %	
	method *a*	method *b*
3a	99	91
3b	94	80
3c	93	70
3d	90	56
3e	94	63
3f	91	54
3g	93	61
3h	90	50
3i	94	62
3j	88	71
4a	82	66
4b	76	63
But-3-yn-1-yl phenylcarbamate	95	94

The yields of carbamates **3a**, **3b**, and **3j** (Table 1) were slightly higher due to the high reactivities of terminal propargylic alcohols compared to internal ones [19]. The required internal propargylic alcohols **1c**–**1i** were prepared by the Sonogashira coupling with the corresponding aryl iodides in the presence of triethylamine [20, 21]. It may be inferred that the presence of an electron-donating group in the benzene ring led to a slight decrease of the yield of carbamates (**3d**, **3f**, **3h**). Propargylic alcohols containing an electron-withdrawing substituent on the benzene were converted into carbamates **5e**, **5g**, and **5i** with relatively higher yields. Allyl carbamates **4a** and **4b** were obtained in good yields (82 and 76%, respectively) by refluxing phenyl isocyanate with allylic alcohols **2a** and **2b** for 12 h (Scheme 1). The reaction of Cbz-protected amines with allylic alcohols in anhydrous methylene chloride (Scheme 2) provided 66% of **4a** and 63% of **4b**. But-3-yn-1-yl phenylcarbamate derived from homopropargylic alcohol was synthesized with an excellent yield (95%).

Scheme 3.



3, **5**, **6**, R^1 = H (**a**, **b**), Ph (**c**), 4-ClC_6H_4 (**d**), 4-$O_2NC_6H_4$ (**e**), 4-FC_6H_4 (**f**), 4-CNC_6H_4 (**g**), 2,4-$(MeO)_2C_6H_4$ (**h**); 2-MeOC(O)C_6H_4 (**i**); $R^2 = R^3$ = H (**a**, **c**–**i**), Me (**b**).

Intramolecular cyclization of carbamates is a well-documented method for the synthesis of oxazolidin-2-one derivatives. Initially, the cyclization of 3-phenylprop-2-yn-1-yl phenylcarbamate (**3c**) was chosen as a model reaction (Scheme 3). The effect of various bases like pyridine, 4-dimethylaminopyrdine (DMAP), cesium carbonate, lithium hydroxide monohydrate, and cesium hydroxide monohydrate was thoroughly investigated, and various solvents were screened. A solution of carbamate **3c** in an appropriate solvent was treated with 0.1 equiv of a base, and the progress of the reaction was monitored by TLC. It was found that inorganic bases such as Cs_2CO_3 provided the target product **5c** in a moderate yield (68%) as a mixture of *Z* and *E* isomers (reaction time 18 h). In the presence of $LiOH \cdot H_2O$, the yield of **5c** was 82%. Organic bases such as pyridine and DMAP were found to be ineffective. Cesium hydroxide monohydrate proved to be the most active base catalyst ensuring an excellent yield of 4-benzylidene-3-phenyloxazolidin-2-one (**5c**, up to 93%); the reaction was accompanied by the formation of isomeric 2,3-dihydrooxazole **6c** with the endocyclic double bond. Furthermore, the reaction time in the presence of $CsOH \cdot H_2O$ (2 h) was 9 times shorter than in the presence of Cs_2CO_3 (18 h), and 15 times shorter than in the presence of $LiOH \cdot H_2O$ (30 h). The solvent optimization studies showed that polar aprotic solvents were the most suitable for the cyclization. Having optimized the conditions for the synthesis of **5c**, we next investigated the synthesis of a variety of 4-methylene(benzylidene)oxazolidinones (Scheme 3, Table 2).

In general, propargyl carbamates **3a**–**3h** were smoothly converted to the corresponding oxazolidin-2-ones in very good to excellent yields (Table 2). However, the cyclization of **3i** was an exception, and no reaction occurred because of its steric hindrances even under severe conditions (DMF, 90°C, 72 h); the use of excess $CsOH \cdot H_2O$ resulted in the hydrolysis of **3i** to the corresponding amine. Carbamates derived from terminal propargylic alcohols **3a** and **3b** underwent complete cyclization within 30 min to provide the desired 4-methylidene-3-phenyloxazolidin-2-one (**5a**) and 5,5-dimethyl-4-methylidene-3-phenyloxazolidin-2-one (**5b**) in 99 and 87% yield, respectively. Carbamates **3d** and **3f** having an electron-donating group on

Table 2. Synthesis of 4-methylidne(benzylidene)oxazolidin-2-ones under conventional and ultrasound irradiation conditions

Compound no.	Reaction time, min		Yield,[a] % (ratio *E*-**5**/*Z*-**5**/**6**)	
	conventional method	ultrasonic irradiation	conventional method	ultrasonic irradiation
5a	30	10	99	99
5b	30	11	87	94
5c,[b] **6c**	120	26	93 (80:20)	94 (0:100:0)
E-**5d**, *Z*-**5d**	25	6	92 (58:42:0)	96 (60:40:0)
E-**5e**, *Z*-**5e**	20	10 s	90 (50:50:0)	92 (53:47:0)
E-**5f**, *Z*-**5f**	22	4	93 (53:47:0)	98 (58:42:0)
E-**5g**, *Z*-**5g**, **6g**	20	12 s	92 (41:41:18)	92 (42:38:20)
5h	28	12	88 (0:100:0)	90 (0:100:0)
5i	72 h	8 h	–	–

[a] Yields of isolated products after column chromatography
[b] Isomer mixture, *Z*/*E* ratio 60:40.

the aromatic ring were successfully converted into *Z*/*E*-isomeric oxazolidinones **5d** and **5f** with excellent yields (92 and 93%) in 25 and 22 min, respectively. The *Z* and *E* isomers of all compounds **5** were separated and isolated in the pure state; they were identified by the presence of the olefinic C=CH proton signal as a triplet at δ 4.04–5.70 ppm in the case of the *Z* isomers and as a singlet in the case of the *E* isomers. Protons of the two methyl protons on C^5 resonated as a doublet. Carbamates **3e** and **3g** bearing an electron-withdrawing group reacted slightly faster (in 20 min), but no stereoselectivity was observed, and the desired *Z*/*E*-oxazolidinones were obtained in excellent yields (90 and 92%, respectively) after column chromatography. In the cyclization of **3g**, we isolated isomer **6g** with the endocyclic double bond as a minor product in 18% yield. 3-(2,4-Dimethoxyphenyl)prop-2-yn-1-yl phenylcarbamate **3h** yielded the corresponding oxazolidinone **5h** with a very good conversion (88%) and exclusive formation of the *Z* isomer.

The cyclization of carbamates **3a**–**3i** was also accomplished under ultrasonic (US) irradiation, other conditions being equal. In all cases, the reaction was complete in a shorter time. For example, the cyclization time of **3c** was reduced significantly from 120 min under conventional method to 26 min under US irradiation conditions, and the *Z* isomer of **5c** was obtained as a single stereoisomer in 94% yield. The reaction time decreased down to 10 and 12 s for carbamates **3e** and **3g**, respectively. We also noticed a slight increase in selectivity toward the more stable *E* isomer. Our efforts to accomplish the cyclization of but-3-yn-1-yl phenylcarbamate were unsuccessful. All isolated compounds were characterized by physical and spectral data, as well as by comparison with authentic samples.

Tyrosine kinase inhibitors belong to a new therapeutic family called "targeted therapy" [22, 23]. Thus targeted therapies have a greater specificity of action toward tumor cells and allow obtaining broader therapeutic indexes and, consequently, less toxicity. Indeed, there are several approaches to targeted therapy, including monoclonal antibodies and tyrosine and serine–threonine kinase inhibitors. In this work, we have been particularly interested in the second approach (tyrosine kinase inhibitors). We conducted a series of biological tests to evaluate the inhibitory potential of all synthesized compounds toward CMGC group kinases like cyclin-dependent kinases Hs_CDK2/CyclinA, Hs_CDK5/p25, Hs_CDK9/CyclinT, Hs_PIM1, Hs_HASPIN, CDK-like kinases (Mm_CLK1), dual-specificity tyrosine phosphoryla-

Table 3. Inhibitory activity (% inhibition) of the synthesized compounds against some protein kinases at a concentration of 10 mM

Comp. no.	CDK2/ CyclinA	CDK5/p26	CDK9/ CyclinT	GSK3β	PIM1	HASPIN	CLK1	DYRK1A
3a	7	0	17	6	15	0	0	9
3c	0	0	44	75	0	31	58	61
3d	8	16	29	19	0	9	0	6
3e	0	0	28	24	0	23	2	0
3j	10	0	31	19	0	0	5	6
3i	0	0	23	49	40	13	43	43
3g	0	0	21	16	0	16	0	4
4b	0	5	22	41	0	22	0	2
***Z*-5c**	36	12	11	11	7	0	4	0
6c	0	1	29	35	0	18	5	1
***E*-5d**	2	0	40	38	15	36	18	5
***Z*-5d**	0	0	30	40	32	16	8	2
***E*-5e**	0	5	30	31	12	35	0	0
***Z*-5e**	37	40	20	36	18	27	0	0
***E*-5g**	0	9	31	3	0	13	0	0
***Z*-5g**	0	7	18	24	10	5	0	0
6g	3	9	30	69	21	46	12	7
***Z*-5h**	0	6	0	49	36	13	11	18

tion-regulated kinase 1A(Hs_ DYRK1A), and glycogen synthase kinase (GSK3β).

Initially, the synthesized compounds were tested at a final concentration of 10 μM, and those exhibiting less than 50% inhibition at 10 μM were considered to be inactive. The results given in Table 3 showed that only two compounds have an inhibitory activity greater than 50%, namely carbamate **3c** toward GSK3β, CLK1, and DYRK1A and dihydrooxazole **6g** toward GSK3β. Subsequently, the IC_{50} values of these two compounds were determined from the dose–response curves using Sigma Plot software (Table 4).

The IC_{50} values are in the micromolar range for 4-benzyl-3-phenyloxazol-2(3*H*)-one (**6g**, 3.3 μM) toward GSK3β and greater than 10 μM toward PIM1 which gives a selectivity coefficient of 0.463 (Gini coefficient [24] which allows objective ranking of compounds in terms of their overall selectivity at a pharmacologically relevant concentration). Carbamate **3c** is less active toward GSK3β (IC_{50} = 9.19) and almost inactive toward PIM1, and it has been shown to be a little more selective (Gini coefficient 0.473). We remind that nonselective inhibitors are characterized by Gini values close to zero and that highly selective compounds exhibit Gini values close to 1.

In conclusion, a number of propargyl and allyl carbamates have been synthesized and shown to readily undergo intramolecular nucleophilic cyclization in the presence of cesium hydroxide monohydrate as a base catalyst under conventional and ultrasonic irradiation conditions to give the corresponding substituted 4-methylene(benzylidene)oxazolidin-2-ones. Ultrasonic irradiation provides a remarkable improvement in the yield of the cyclization products and significant shortening of the reaction times in comparison to the conventional method. The reaction was highly stereoselective in some cases to afford *Z*-isomeric oxazolidinones as a single stereoisomer. Furthermore, the two Gini indices for carbamate **3c** and 4-benzyl-3-phenyloxazol-2(3*H*)-one (**6g**) indicated their moderate kinase selectivity representing an encouraging start-point for further optimization.

EXPERIMENTAL

All chemicals were purchased commercially and were used without further purification. Anhydrous solvents were used for the reactions. Merck silica gel (60–120 and 100-200 mesh) was used for column chromatography. The ^1H and ^{13}C NMR spectra were recorded on a Jeol spectrometer at 400 and 100 MHz, respectively. The IR spectra were measured from thin films for liquids and from KBr pellets for solids. Ultrasound-assisted reactions were performed using a T660/H ultrasonic tank with a frequency of 35 kHz. The high-resolution mass spectra were obtained using a Waters Q/Tof Premier micro mass HAB 213 spectrometer with an ESI source. The melting points were measured on a Kofler hot stage.

Table 4. IC_{50} values (μM) of carbamate **3c** and 4-benzyl-3-phenyl-1,3-oxazol-2(3*H*)-one **6g** against GSK3β and PIM1 protein kinases

Comp. no.	IC_{50}, μM		Gini coefficient
	Hs_GSK3β	Hs_PIM1	
3c	9.19	>10	0.473
6g	3.30	>10	0.463

Initial benzyl phenylcarbamate and benzyl cyclohexylcarbamate were synthesized according to the procedure described in [25].

General procedures for the preparation of carbamates. *a*. Phenyl or cyclohexyl isocyanate (1.1 mmol) was added to a solution of alcohol **1a**–**1j**, **2a**, or **2b** (1 mmol) in anhydrous THF under a nitrogen atmosphere, and one or two drops of triethylamine were introduced via a syringe. The resulting homogeneous mixture was refluxed for 12 h. The mixture was cooled and extracted with methylene chloride (3 × 15 mL), the combined extracts were dried over Na_2SO_4 and evaporated under reduced pressure, and the residue was purified by flash column chromatography using ethyl acetate–hexane (2 : 8) as eluent.

b. Benzyl phenylcarbamate or benzyl cyclohexylcarbamate (1.0 mmol) and 2-chloropyridine (3.0 mmol) were dissolved in anhydrous methylene chloride (4 mL), and trifluoromethanesulfonic anhydride (1.5 mmol) was added dropwise over a period of 5 min. The mixture was stirred for 1 h at room temperature, alcohol **1a**–**1j**, **2a**, or **2b** (3.0 mmol) was added, and triethylamine (3.0 mmol) was then added. The mixture was stirred until the reaction was complete and diluted with methylene chloride, and the organic layer was washed with brine and water, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography using ethyl acetate–hexane (1 : 9) as eluent.

3-(4-Chlorophenyl)prop-2-yn-1-yl phenylcarbamate (3d). Yield 90 (*a*), 56% (*b*); yellow solid, mp 144–147°C. IR spectrum, ν, cm^{-1}: 3307 (N–H), 1696 (C=O). ^1H NMR spectrum, δ, ppm: 7.34–7.40 m

(4H, H_{arom}), 7.25–7.33 m (4H, H_{arom}), 7.05–7.12 t (1H, H_{arom}, J = 7.07 Hz), 6.82 s (1H, NH), 4.99 s (1H, CH_2). ^{13}C NMR spectrum, δ_C, ppm: 152.82, 137.68, 135.33, 133.36, 129.35, 128.92, 124.04, 120.81, 119.02, 85.85, 84.34, 53.69. Mass spectrum, m/z (I_{rel}, %): 303.0906 (100) $[M + NH_4]^+$, 308.0451 (18) $[M + Na]^+$.

3-(4-Nitrophenyl)prop-2-yn-1-yl phenylcarbamate (3e). Yield 94 (*a*), 63% (*b*); white solid, mp 153–155°C. IR spectrum, ν, cm^{-1}: 3339 (N–H), 1705 (C=O). ^1H NMR spectrum, δ, ppm: 8.20–8.16 m (2H, H_{arom}), 7.60–7.58 m (2H, H_{arom}), 7.42–7.40 d (2H, H_{arom}, J = 7.41 Hz), 7.34–7.30 t (2H, H_{arom}, J = 7.32 Hz), 7.12–7.08 t (1H, H_{arom}, J = 7.10 Hz), 6.80 s (1H, NH), 5.04 s (2H, CH_2). ^{13}C NMR spectrum, δ_C, ppm: 151.29, 146.25, 136.17, 131.45, 127.98, 127.76, 122.75, 122.39, 117.63, 87.30, 83.38, 51.96. Mass spectrum, m/z (I_{rel}, %): 297.0892 (45) $[M + H]^+$, 314.1142 (100) $[M + NH_4]^+$, 319.0713 (18) $[M + Na]^+$.

3-(4-Fluorophenyl)prop-2-yn-1-yl phenylcarbamate (3f). Yield 91 (*a*), 54% (*b*); yellow solid, mp 119–121°C. IR spectrum, ν, cm^{-1}: 3319 (N–H), 1698 (C=O). ^1H NMR spectrum, δ, ppm: 7.46–7.39 m (4H, H_{arom}), 7.33–7.29 m (2H, H_{arom}), 7.10–7.04 m (1H, H_{arom}), 7.03–6.97 m (2H, H_{arom}), 6.78 s (1H, NH), 5.00 s (2H, CH_2). ^{13}C NMR spectrum, δ_C, ppm: 164.23, 161.44, 152.68, 137.55, 133.93, 129.20, 123.87, 118.85, 116.00, 85.68, 82.84, 53.59. Mass spectrum, m/z (I_{rel} %): 241.1452 (100) $[M - CO]^+$, 287.1211 (12) $[M + NH_4]^+$, 292.0757 (72) $[M + Na]^+$.

3-(4-Cyanophenyl)prop-2-yn-1-yl phenylcarbamate (3g). Yield 93 (*a*), 61% (*b*); white solid, mp 138–140°C. IR spectrum, ν, cm^{-1}: 3325 (N–H), 1705 (C=O). ^1H NMR spectrum, δ, ppm: 7.53–7.51 m (2H, H_{arom}), 7.45–7.43 m (2H, H_{arom}), 7.34–7.32 d (2H, H_{arom}, J = 7.93 Hz), 7.33–7.25 t (1H, H_{arom}, J = 7.35 Hz), 6.82 s (1H, NH), 4.96 s (1H, CH_2). ^{13}C NMR spectrum, δ_C, ppm: 151.45, 136.35, 131.34, 131.01, 128.12, 125.99, 122.88, 117.78, 117.27, 111.17, 86.62, 83.77, 52.14. Mass spectrum, m/z (I_{rel}, %): 294.1244 (64) $[M + NH_4]^+$, 299.0798 (88) $[M + Na]^+$, 575.1694 (100) $[2M + Na]^+$.

3-(2,4-Dimethoxyphenyl)prop-2-yn-1-yl phenylcarbamate (3h). Yield 90 (*a*), 50% (*b*); pale yellow solid, mp 163–165°C. IR spectrum, ν, cm^{-1}: 3301 (N–H), 1699 (C=O). ^1H NMR spectrum, δ, ppm: 7.40–7.26 m (5H, H_{arom}), 7.09–7.05 t (1H, H_{arom}, J = 7.02 Hz), 6.74 s (1H, NH), 6.45–6.43 d (2H, H_{arom}, J = 10.43 Hz), 5.05 s (2H, CH_2), 3.85–3.81 (6H, OCH_3). ^{13}C NMR spectrum, δ_C, ppm: 161.86, 161.79, 152.19, 137.68, 134.98, 129.31, 123.86, 118.94, 105.04, 104.02, 98.59, 85.78, 83.32, 56.03, 55.68, 54.13. Mass spectrum, m/z: 329.1502 $[M + NH_4]^+$, 334.1059 $[M + Na]^+$. Calculated: $M + NH_4$ 329.1358, M + Na 334.1156.

Methyl 2-[3-(phenylcarbamoyloxy)prop-2-yn-1-yl]benzoate (3i). Yield 94 (*a*), 62% (*b*); pale greenish solid, mp 60–62°C. IR spectrum, ν, cm^{-1}: 3331 (N–H), 1716 (C=O). ^1H NMR spectrum, δ, ppm: 7.95–7.93 d.d (1H, H_{arom}, J = 7.83, 1.29 Hz), 7.57–7.55 d.d (1H, H_{arom}, J = 7.65, 0.96 Hz), 7.46–7.35 m (4H, H_{arom}), 7.32–7.28 t (2H, H_{arom}, J = 8.47 Hz), 7.08–7.05 t (1H, H_{arom}, J = 7.55 Hz), 6.98 s (1H, NH), 5.06 s (2H, CH_2), 3.90 s (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 167.08, 152.82 ,137.73, 134.07, 132.08, 131.74, 130.46, 129.14, 128.48, 123.73, 122.78, 118.87, 88.26, 85.30, 53.78, 52.31. Mass spectrum, m/z (I_{rel}, %): 310.1087 (100) $[M + H]^+$, 332.0902 (79.5) $[M + Na]^+$.

Prop-2-yn-1-yl cyclohexylcarbamate (3j). Yield 88 (*a*), 71% (*b*); yellow solid, mp 69–61°C. IR spectrum, ν, cm^{-1}: 3284 (N–H), 1704 (C=O). ^1H NMR spectrum, δ, ppm: 4.71 s (1H), 4.67 d (1H, J = 2.25 Hz), 3.56–3.45 m (1H), 2.48–2.63 t (1H, J = 2.27 Hz), 1.96–1.91 m (2H), 1.73–1.57 m (3H), 1.42–1.11 m (5H). ^{13}C NMR spectrum, δ_C, ppm: 154.53, 78.36, 74.49, 52.05, 50.02, 33.31, 25.58, 24.74.

But-2-en-1-yl phenylcarbamate (4a). Yield 76 (*a*), 63% (*b*); white solid, mp 78–80°C. IR spectrum, ν, cm^{-1}: 3301 (N–H), 1721 (C=O). ^1H NMR spectrum, δ, ppm: 7.42–7.39 d (2H, H_{arom}, J = 8.52 Hz), 7.11–7.05 m (1H, H_{arom}), 6.72 s (1H, NH), 5.93–5.82 m and 5.72–5.61 m (1H each, CH=CH), 4.64–4.61 d.t (2H, CH_2, J = 6.46, 1.00 Hz), 1.78–1.75 m (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 153.45, 137.93, 131.59, 125.22, 123.42, 118.74, 66.00, 17.89. Mass spectrum: m/z 192.0946 $[M + NH_4]^+$. $C_{11}H_{17}N_2O_2$. Calculated: $M + NH_4$ 192.0988.

General procedure for the cyclization of carbamates 3a–3h. *a. Conventional method*. Cesium hydroxide monohydrate (0.1 mmol) was added to a solution of carbamate **3a**–**3h** (1 mmol) in DMF (2 mL), and the mixture was stirred at room temperature until the initial compound disappeared. The mixture was diluted with water (20 mL) and extracted with methylene chloride (3 × 10 mL), the combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated, and the residue was purified by column chromatography.

b. Ultrasonic irradiation method. Carbamate **3a**–**3h** (1 mmol) was dissolved in DMF (2 mL), $CsOH \cdot H_2O$ (0.1 mmol) was added to the solution, and the resulting

mixture was irradiated for an appropriate time (TLC). The mixture was diluted with water (20 mL) and extracted with methylene chloride (3×10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and filtered, the filtrate was rotary evaporated, and the crude product was purified by column chromatography using ethyl acetate–hexane (1:9 for **5a**–**5g** and 2:8 for **5h**).

4-Benzylidene-3-phenyl-1,3-oxazolidin-2-one (5c, *E/Z*). Yield 80% (*a*), yellow solid, mp 114–116°C. IR spectrum, ν, cm^{-1}: 1771 (C=O), 1669 (C=C). ^1H NMR spectrum, δ, ppm: 7.55–7.38 m (6H, H_{arom}), 7.32–7.28 t (2H, H_{arom}, J = 7.71 Hz), 7.18–7.14 t (2H, H_{arom}, J = 7.41 Hz), 7.06–6.62 m (10H, H_{arom}), 5.69 s (*E*) and 5.64–5.62 t (*Z*, J = 2.49 Hz) (1H, =CH), 5.37 d (J = 2.49 Hz) and 5.14 d (J = 2.10 Hz) (2H, CH_2). ^{13}C NMR spectrum, δ_C, ppm: 157.20, 155.70, 137.11, 135.14, 134.82, 133.71, 132.51, 129.99, 128.94, 128.42, 128.37, 127.76, 127.22, 127.16, 126.25, 126.13, 125.93, 101.74, 100.07, 68.26, 67.46. Mass spectrum, m/z (I_{rel}, %): 252.1026 (100) $[M + H]^+$, 253.1026 (18) $[M + 2H]^+$.

(*Z*)-4-Benzylidene-3-phenyl-1,3-oxazolidin-2-one (*Z*-5c). Yield 94% (*b*), pale yellow solid, mp 169–161°C. IR spectrum, ν, cm^{-1}: 1770 (C=O), 1655 (C=C). ^1H NMR spectrum, δ, ppm: 7.58–7.53 m (2H, H_{arom}), 7.48–7.39 m (3H, H_{arom}), 7.34–7.29 t (2H, H_{arom}, J = 7.56 Hz), 7.20–7.15 t (1H, H_{arom}, J = 8.06 Hz), 7.00–6.97 m (2H, H_{arom}), 5.66–5.64 t (1H, =CH, J = 2.56 Hz), 5.39 d (2H, CH_2, J = 2.56 Hz). ^{13}C NMR spectrum, δ_C, ppm: 155.56, 136.83, 135.07, 133.53, 129.95, 128.89, 127.62, 127.12, 126.08, 101.71, 67.62. Mass spectrum, m/z (I_{rel}, %): 269.1303 (16.5) $[M + NH_4]^+$, 274.0864 (54) $[M + Na]^+$, 297.1624 (100) $[M + 2Na]^+$.

4-Benzyl-3-phenyl-1,3-oxazol-2(3*H*)-one (6c). Yield 20% (*a*), pale yellow solid, mp 64–66°C. IR spectrum, ν, cm^{-1}: 1750 (C=O), 1598 (C=C). ^1H NMR spectrum, δ, ppm: 7.41–7.39 m (3H, H_{arom}), 7.24–7.18 m (5H, H_{arom}), 7.02–7.00 m (2H, H_{arom}), 6.56 t (1H, 5-H, J = 1.36 Hz), 3.55 s (2H, 4-CH_2). ^{13}C NMR spectrum, δ_C, ppm: 155.20, 134.92, 134.02, 133.40, 129.56, 128.84, 128.73, 128.69, 128.58, 127.51, 127.24, 125.06, 30.48. Mass spectrum, m/z (I_{rel}, %): 252.1024 (100) $[M + H]^+$, 274.0862 (11) $[M + Na]^+$.

(*E*)-4-(4-Chlorobenzylidene)-3-phenyl-1,3-oxazolidin-2-one (*E*-5d). Yield 58 (*a*), 60% (*b*); white solid, mp 94–96°C. IR spectrum, ν, cm^{-1}: 1779 (C=O), 1681 (C=C). ^1H NMR spectrum, δ, ppm: 7.12–7.09 m (3H, H_{arom}), 7.01–6.97 m (2H, H_{arom}), 6.81–6.80 m (2H, H_{arom}), 6.55–6.53 m (2H, H_{arom}), 5.60 s (1H, =CH), 5.12 d (2H, CH_2, J = 1.96 Hz). ^{13}C NMR spectrum, δ_C, ppm: 155.57, 137.89, 133.88, 133.67, 131.91, 130.19, 129.22, 129.18, 128.43, 122.91, 100.53, 67.44. Mass spectrum, m/z (I_{rel}, %): 286.0635 (100) $[M + H]^+$, 308.0467 (49) $[M + Na]^+$.

(*Z*)-4-(4-Chlorobenzylidene)-3-phenyl-1,3-oxazolidin-2-one (*Z*-5d). Yield 42 (*a*), 40% (*b*); yellow solid, mp 131–133°C. IR spectrum, ν, cm^{-1}: 1770 (C=O), 1661 (C=C). ^1H NMR spectrum, δ, ppm: 7.57–7.54 m (2H, H_{arom}), 7.49–7.47 m (1H, H_{arom}), 7.41–7.38 d.t (2H, H_{arom}, J = 2.53, 8.59 Hz), 7.30–7.27 d.t (2H, H_{arom}, J = 2.54, 4.41 Hz), 6.93–6.89 t (2H, H_{arom}, J = 2.66 Hz), 5.60 t (1H, =CH, J = 2.55 Hz), 5.36 d (2H, CH_2, J = 2.42 Hz), ^{13}C NMR spectrum, δ_C, ppm: 157.01, 134.68, 133.30, 131.74, 131.58, 129.55, 128.63, 127.60, 127.30, 126.21, 98.72, 68.20. Mass spectrum, m/z (I_{rel}, %): 286.0638 (100) $[M + H]^+$, 287.0638 (18) $[M + 2H]^+$.

(*E*)-4-(4-Nitrobenzylidene)-3-phenyl-1,3-oxazolidin-2-one (*E*-5e). Yield 50 (*a*), 53% (*b*); yellow solid, mp 179–181°C. IR spectrum, ν, cm^{-1}: 1778 (C=O), 1674 (C=C). ^1H NMR spectrum, δ, ppm: 7.72–7.70 d (2H, H_{arom}, J = 8.7 Hz), 7.13–7.11 m (3H, H_{arom}), 7.04–7.01 m (2H, H_{arom}), 6.79–6.77 d (2H, H_{arom}, J = 8.62 Hz), 5.70 s (1H, =CH), 5.20 d (2H, CH_2, J = 1.91 Hz). ^{13}C NMR spectrum, δ_C, ppm: 156.66, 145.56, 140.23, 136.09, 134.62, 128.94, 128.83, 128.11, 126.21, 122.37, 97.48, 68.22. Mass spectrum, m/z (I_{rel}, %): 314.1144 (100) $[M + NH_4]^+$, 319.0706 (56) $[M + Na]^+$.

(*Z*)-4-(4-Nitrobenzylidene)-3-phenyl-1,3-oxazolidin-2-one (*Z*-5e). Yield 50 (*a*), 47% (*b*); yellow solid, mp 198–200°C. IR spectrum, ν, cm^{-1}: 1782 (C=O), 1656 (C=C). ^1H NMR spectrum, δ, ppm: 8.17–8.15 m (2H, H_{arom}), 7.59–7.55 m (2H, H_{arom}), 7.51–7.47 m (1H, H_{arom}), 7.39–7.37 m (2H, H_{arom}), 7.08–7.05 m (2H, H_{arom}), 5.68–5.66 t (1H, =CH, J = 2.55 Hz), 5.44 d (2H, CH_2, J = 2.40 Hz). ^{13}C NMR spectrum, δ_C, ppm: 155.37, 145.27, 142.44, 141.42, 133.08, 130.05, 129.50, 127.73, 127.51, 124.41, 99.91, 67.39. Mass spectrum, m/z (I_{rel}, %): 297.0895 (19) $[M + H]^+$, 314.1149 (100) $[M + NH_4]^+$.

(*E*)-4-(4-Fluorobenzylidene)-3-phenyl-1,3-oxazolidin-2-one (*E*-5f). Yield 53 (*a*), 58% (*b*); white solid, mp 109-111°C. IR spectrum, ν, cm^{-1}: 1779 (C=O), 1681 (C=C). ^1H NMR spectrum, δ, ppm: 7.11–7.08 m (3H, H_{arom}), 7.03–6.98 m (2H, H_{arom}), 6.63–6.53 m (4H, H_{arom}), 5.65 s (1H, =CH), 5.15 d (2H, CH_2, J = 2.17 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm:

162.36, 159.93, 155.63, 133.62, 130.02, 128.99, 128.67, 128.59, 127.72, 115.75, 100.81, 67.16. Mass spectrum, *m*/*z* (I_{rel}, %): 270.0935 (100) $[M + H]^+$, 271.0980 (23) $[M + 2H]^+$.

(*Z*)-4-(4-Fluorobenzylidene)-3-phenyl-1,3-oxazolidin-2-one (*Z*-5f). Yield 47 (*a*), 42% (*b*); white solid, mp 129–131°C. IR spectrum, ν, cm^{-1}: 1774 (C=O), 1674 (C=C). ^1H NMR spectrum, δ, ppm: 7.56–7.52 m (2H, H_{arom}), 7.48–7.45 m (1H, H_{arom}), 7.40–7.39 m (2H, H_{arom}), 7.04–6.95 m (4H, H_{arom}), 5.62–5.60 t (1H, =CH, *J* = 2.67 Hz), 5.35 d (2H, CH_2, *J* = 2.66). ^{13}C NMR spectrum, δ_C, ppm: 162.34, 159.83, 157.06, 132.72, 132.64, 129.84, 128.56, 127.57, 126.06, 114.07, 98.90, 68.28. Mass spectrum, *m*/*z* (I_{rel}, %): 241.1452 (100) $[M - CO]^+$, 292.0757 (72.5) $[M + Na]^+$.

(*E*)-4-[(2-Oxo-3-phenyl-1,3-oxazolidin-4-ylidene)methyl]benzonitrile (*E*-5g). Yield 41 (*a*), 42% (*b*); yellow solid, mp 128–130°C. IR spectrum, ν, cm^{-1}: 1781 (C=O), 1673 (C=C). ^1H NMR spectrum, δ, ppm: 7.15–7.09 m (5H, H_{arom}), 7.01–6.99 m (2H, H_{arom}), 6.74–6.72 d (2H, H_{arom}, *J* = 8.22 Hz), 5.67 s (1H, =CH), 5.18 d (2H, CH_2, *J* = 2.12 Hz). ^{13}C NMR spectrum, δ_C, ppm: 156.52, 138.11, 135.21, 134.45, 132.66, 130.68, 128.83, 128.00, 126.19, 119.21, 109.08, 97.89, 68.17. Mass spectrum, *m*/*z* (I_{rel}, %): 277.0977 (100) $[M + H]^+$, 294.1234 (24.8) $[M + NH_4]^+$, 299.0812 (13) $[M + Na]^+$.

(*Z*)-4-[(2-Oxo-3-phenyl-1,3-oxazolidin-4-ylidene)methyl]benzonitrile (*Z*-5g). Yield 41 (*a*), 38% (*b*); pale orange solid, mp 181–183°C. IR spectrum, ν, cm^{-1}: 1760 (C=O), 1655 (C=C). ^1H NMR spectrum, δ, ppm: 7.59–7.55 t (4H, H_{arom}, *J* = 8.06 Hz), 7.51–7.47 m (1H, H_{arom}), 7.39 d (2H, H_{arom}, *J* = 8.37 Hz), 5.63 t (1H, =CH, *J* = 2.38 Hz), 5.18 d (2H, CH_2, *J* = 2.41 Hz). ^{13}C NMR spectrum, δ_C, ppm: 155.02, 140.20, 139.89, 132.99, 132.51, 129.93, 127.49, 127.21, 118.68, 108.90, 99.92, 67.14, 68.17. Mass spectrum, *m*/*z* (I_{rel}, %): 277.0982 (74) $[M + H]^+$, 294.1255 (50) $[M + NH_4]^+$, 299.0799 (100) $[M + Na]^+$.

4-[(2-Oxo-3-phenyl-2,3-dihydro-1,3-oxazol-4-yl)-methyl]benzonitrile (6g). Yield 18 (*a*), 20% (*b*); orange solid, mp 73–75°C. IR spectrum, ν, cm^{-1}: 1755 (C=O), 1597 (C=C). ^1H NMR spectrum, δ, ppm: 7.51–7.49 d (2H, H_{arom}, *J* = 8.25 Hz), 7.40 m (3H, H_{arom}), 7.13–7.10 m (2H, H_{arom}), 7.08 d (2H, H_{arom}, *J* = 8.08 Hz), 6.68 t (1H, 5-H, *J* = 1.34 Hz), 3.65 s (2H, 4-CH_2). ^{13}C NMR spectrum, δ_C, ppm: 154.97, 140.20, 132.42, 129.72, 129.45, 129.14, 127.44, 118.52, 111.32, 30.45. Mass spectrum, *m*/*z* (I_{rel}, %): 277.0982 (100) $[M + H]^+$, 299.0800 (32) $[M + Na]^+$.

(*Z*)-4-(2,4-Dimethoxybenzylidene)-3-phenyl-1,3-oxazolidin-2-one (5h). Yield 88 (*a*), 90% (*b*), white solid, mp 111–113°C. IR spectrum, ν, cm^{-1}: 1771 (C=O), 1685 (C=C). ^1H NMR spectrum, δ, ppm: 7.26–6.94 m (5H, H_{arom}), 6.37–6.34 d (1H, H_{arom}, *J* = 8.44 Hz), 6.09 d (1H, H_{arom}, *J* = 2.38 Hz), 5.95–5.91 d.d (2H, H_{arom}, *J* = 2.38, 8.44 Hz), 5.60 t (1H, =CH, *J* = 2.33 Hz), 5.17 d (2H, CH_2, *J* = 2.19 Hz), 3.66–3.64 (6H, OCH_3). ^{13}C NMR spectrum, δ_C, ppm: 159.77, 157.42, 156.92, 134.59, 132.13, 130.42, 127.89, 126.96, 125.85, 114.89, 103.43, 97.50, 95.49, 68.31, 55.41, 55.14. Mass spectrum, *m*/*z* (I_{rel}, %): 312.1239 (100) $[M + H]^+$, 234.1063 (13.5) $[M + Na]^+$.

Kinase preparations and assays. Kinase activities were assayed in buffer A (10 mM $MgCl_2$, 1 mM EGTA, 1 mM DTT, 25 mM Tris–HCl, pH 7.5, 50 μg/mL heparin, 30°C) at a final ATP concentration of 15 μM. Blank values were subtracted and the activities were expressed in percent of the maximal activity, i.e., in the absence of inhibitors. Controls were performed with appropriate dilutions of DMSO. The kinase peptide substrates were obtained from Proteogenix (Oberhausbergen, France).

The protein kinase DYRK1A (rat recombinant, expressed in *Escherichia coli* as a GST fusion proteins) was purified by affinity chromatography on glutathione-agarose and assayed in buffer A (+0.15 mg/mL BSA) using Woodtide synthetic protein (KKISGRLSPIMTEQ, 1.5 mg per assay) as a substrate in the presence of 15 mM [g-33P] ATP (3000 Ci× $mmol^{-1}$; 10 mCi/mL) in a final volume of 30 mL. After incubation for 30 min at 30°C, the reaction was stopped by harvesting onto P81 phosphocellulose paper (Whatman) using a Filter Mate harvester (Packard), and samples were washed with 1% phosphoric acid. Scintillation fluid was added, and the radioactivity was measured in a Packard counter. CLK1 kinase (mouse recombinant, expressed in *E. coli* as GST fusion proteins) was assayed in buffer A (+0.15 mg/mL BSA) with RS peptide (GRSRSRSRSRSR) (1 mg per assay). GSK-3α/β was prepared as described previously [26]. CDK5/p25 (human recombinant) was prepared as described in [27], and the kinase activity was assayed in buffer C [10 mM $MgCl_2$, 1 mM ethylene glycol bis(2-aminoethyl) ether-*N*,*N*,*N*′,*N*′-tetraacetic acid (EGTA), 1 mM dithiothreitol (DTT), 25 mM Tris–HCl pH 7.5, 50 μg/mL heparin), with 1 mg/mL histone H1. Haspin kinase domain (HsHaspin-kdaa 470 to 798) encoding cDNA obtained by RT-PCR was cloned into pGex-

6P-3. The fusion protein was expressed in *Escherichia coli* strain BL21-KRX (Promega, Madison, WI, USA) and purified by affinity chromatography on glutathione-agarose beads (Sigma). CDK2/CyclinA activity was assayed with 3 μM Histone H3 (1-21) peptide, a specific Haspin substrate, (ARTKQTARKS TGGKAPRKQLA), in buffer E (25 mM MOPS, pH 7.5, 10 mM $MgCl_2$). CDK9/CyclinT (human, recombinant) was prepared as described in [27]; its kinase activity was assayed in buffer B (50 mM $MgCl_2$, 90 mM NaCl, 30 mM Tris-HCl, pH 7.4) and buffer D (25 mM MOPS, pH 7.2, 12.5 mM β-glycerophosphate, 25 mM $MgCl_2$, 5 mM EGTA, 2 mM EDTA, 0.25 mM DTT) with 1 mg/mL histone H1. HsPIM1 (human proto-oncogene, recombinant, expressed in bacteria) was assayed in buffer B with 0.8 μg/μL of histone H1 (Sigma) as substrate.

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CONFLICT OF INTERESTS

No conflict of interests is declared by the authors.

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