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Synthesis of nicotinimidamides *via* a tandem CuAAC/ring-cleavage /cyclization/oxidation four-component reaction and their cytotoxicity†

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Nicotinamide and its derivatives, recognized as crucial drug intermediates, have been a focal point of extensive chemical modifications and rigorous pharmacological studies. Herein, a series of novel nicotinamide derivatives, nicotinimidamides, were synthesized *via* a tandem CuAAC/ring-cleavage/cyclization/oxidation four-component reaction procedure from *O*-acetyl oximes, terminal ynones, sulfonyl azides, and NH_4OAc. This strategy is significantly more efficient than previously reported, and the cytotoxicity of the nicotinimidamides is also tested. This project not only exhibits a sustainable and eco-friendly domino methodology for the creation of nicotinimidamides but also presents a promising candidate for liver cancer treatment.

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Introduction

Pyridines represent privileged motifs in both organometallic[1] and medicinal chemistry[2] with series of them having considerable therapeutic potential in particular. One subset of such compounds is the nicotinamides and these have been explored in clinical practice for anti-influenza virus and anti-tubercular activities (Fig. 1, **I**),[3] as effective agents against bacterial wilt (Fig. 1, **II**),[4] potential gyrase B inhibitors (Fig. 1, **III**),[5] novel inhibitors of bacterial DNA gyrase (Fig. 1, **IV**),[6] or treat pellagra and some neurodegenerative diseases.[7] Therefore, the synthesis of novel pyridine derivatives has received intense attention and encouraged the development of more valuable synthetic strategies.

Among the various synthetic approaches, multicomponent reactions (MCRs) stand out for their efficiency and simplicity,[8] making them highly appealing to pharmaceutical companies that seek to expedite the discovery of new medicinal agents.[9] To date, the predominant method for the synthesis of nicotinamide has been through the Hantzsch-type reaction. As illustrated in Scheme 1a, this process typically involves the three-

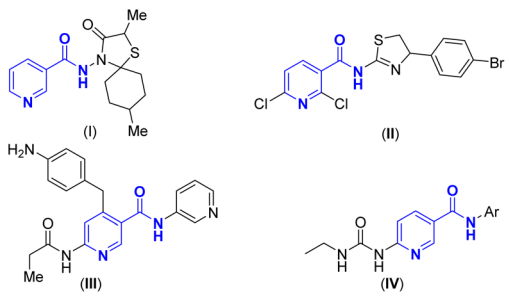
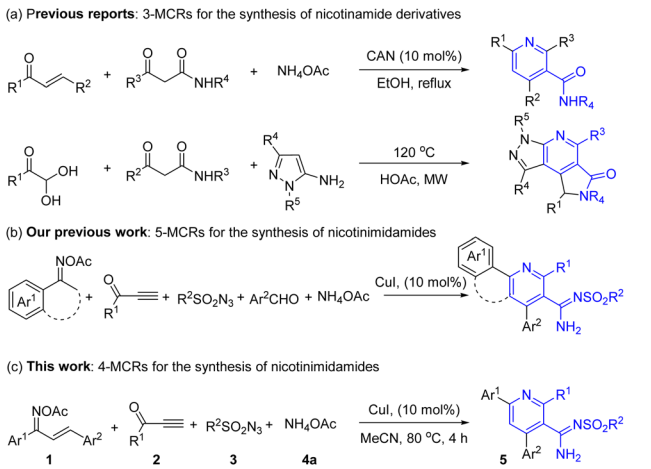


Fig. 1 Examples of nicotinamides, **I–IV**, that have been explored as drug candidates.



Scheme 1 Synthesis of nicotinamide derivatives.

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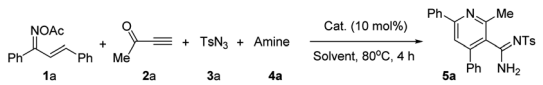
component [3 + 3] aza-annulation reaction of chalcones, β-ketoamides, and ammonium acetate, facilitated by CAN as a Lewis acid,[10] or alternatively, the reaction of phenylglyoxal, β-ketoamide, and 5-aminopyrazole through a Hantzsch-type 3-MCR.[11] However, these methods often yield suboptimal results, especially when less reactive β-ketoamides are utilized as substrates, requiring high temperatures and pressures for the reaction to proceed. Consequently, there is a pressing need for the development of innovative and modular synthetic methods that can effectively construct novel nicotinamide derivatives, indicating an important frontier in the field of medicinal chemistry.

Previous studies have documented the efficacy of Cu-catalyzed multicomponent reactions (MCRs) involving sulfonyl azides and terminal alkynes, which integrate with other components to form N-heterocycles and analogous compounds through a CuAAC/ring-cleavage process. Celebrated for their gentle reaction conditions and the rich tapestry of chemical transformations they enable, these MCRs have become a staple in the synthesis of N-containing compounds, featuring prominently in 3-MCRs[12] and, to a lesser extent, in 4-MCRs.[13] Although our group has previously reported a 5-MCRs for novel nicotinamide derivative nicotinimidamides (Scheme 1b),[14] it is characterized by low yields and the formation of numerous by-products. Moreover, no applications for these new products have been documented. Consequently, there is a clear necessity for the refinement and improvement of this method. Building on this foundation, we present a tandem CuAAC/ring-cleavage/cyclization/oxidation four-component reaction for the synthesis of nicotinimidamides as depicted in Scheme 1c. Our refined synthesis protocol entails the vigorous stirring of a mixture comprising *O*-acetyl oximes, terminal ynones, sulfonyl azides, and ammonium acetate (NH_4OAc) in conjunction with a copper(I) catalyst. Moreover, we preliminarily assessed the anti-tumor cell activity and cytotoxicity of these nicotinimidamides, considering the impact of various functional groups.

Results and discussion

Our investigation commenced with an examination of the synthesis of nicotinimidamide **5a** from *O*-acetyl oxime **1a**, but-3-yn-2-one **2a**, and tosyl azide **3a** (Table 1). The initial reactions were conducted at 80 °C, catalyzed by CuI, utilizing NH_4OAc as the amine source and MeCN as the solvent medium. After 4 h, and following chromatgraphic purification, target **5a** was obtained in 88% yield (Table 1, entry 1). In efforts to improve this outcome, various other amine sources were screened and so revealing that only NH_4OAc and NH_4O_2CH were effective (Table 1, entries 1–2), while $(NH_4)_2SO_4$, NH_4Cl, NH_4PF_6, $(NH_4)_2CO_3$, $PhNH_2$, and Et_2NH ones were not effective (Table 1, entries 3–8). The ammonium salt (Table 1, entries 3–8) with acidic property seemed to stabilize the triazole by protonating its copper complex, preventing ring-cleavage in the CuAAC reaction, which can inhibit the desired reaction or even stop it.[15] The organic base (Table 1, entries 7–8) with strong alkaline produce other side reactions that it cannot obtain the target product **5a**. Then, informed by earlier studies,[16] copper catalyst commonly used for CuAAC/ring-cleavage reactions, was also deployed in the present study. Among the copper catalysts used, Cu^I catalysts (Table 1, entries 9–10) exhibited higher catalytic reactivity than Cu^{II} catalysts (Table 1, entries 11–15). CuI catalyst generated product **5a** in the highest yield of 88%, while $Cu(OTf)_2$ (Table 1, entry 17) was the least efficient for this reaction. At last, comparable yields were obtained using DCE, DCM, toluene, THF, DMSO, DMF, dioxane or EtOH, as solvents but employing MeCN as the reaction medium gave target **5a** in the highest yield (Table 1, entries 16–23).

Table 1 Optimization of catalytic conditions[a]

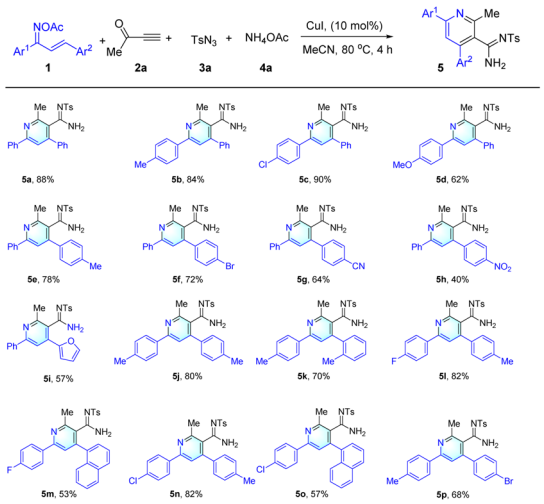


Entry	Amine (2 equiv.)	Cat. (10 mol%)	Solvent (3 mL)	Yield[b] (%)
1	NH_4OAc	CuI	MeCN	88
2	NH_4O_2CH	CuI	MeCN	42
3	$(NH_4)_2SO_4$	CuI	MeCN	0
4	NH_4Cl	CuI	MeCN	0
5	NH_4PF_6	CuI	MeCN	0
6	$(NH_4)_2CO_3$	CuI	MeCN	0
7	$PhNH_2$	CuI	MeCN	0
8	Et_2NH	CuI	MeCN	0
9	NH_4OAc	CuCl	MeCN	84
10	NH_4OAc	CuBr	MeCN	82
11	NH_4OAc	$CuBr_2$	MeCN	74
12	NH_4OAc	$CuCl_2 \cdot 2H_2O$	MeCN	60
13	NH_4OAc	$Cu(OAc)_2$	MeCN	72
14	NH_4OAc	$Cu(acac)_2$	MeCN	51
15	NH_4OAc	$Cu(OTf)_2$	MeCN	10
16	NH_4OAc	CuI	DCE	52
17	NH_4OAc	CuI	DCM	34
18	NH_4OAc	CuI	Toluene	67
19	NH_4OAc	CuI	THF	76
20	NH_4OAc	CuI	DMSO	56
21	NH_4OAc	CuI	DMF	12
22	NH_4OAc	CuI	Dioxane	40
23	NH_4OAc	CuI	EtOH	53

[a] Reaction conditions: **1a** (0.5 mmol), **3a** (0.75 mmol), **4a** (1.0 mmol), and the catalyst (10 mol%) in the solvent (3 mL) were added with **2a** (0.75 mmol) and stirred at 80 °C for 4 h. [b] Isolated yields.

Having defined optimized conditions for the "parent" reaction (Table 1, entry 1), these were then applied to a range of different substrates. Gratifyingly, and as shown in Table 2, the anticipated products were formed when various aryl groups including 4-MeC_6H_4, 4-ClC_6H_4, 4-$MeOC_6H_4$, 4-BrC_6H_4, 4-CNC_6H_4, 4-$NO_2C_6H_4$, or 2-furanyl were attached to the *O*-acetyl oximes **1** and so delivering compounds **5a–5i** in yields ranging from 40% to 90%, and with 4-$NO_2C_6H_4$ group resulting in poorer outcomes (see products **5h**) presumably as a result of strong electron-withdrawing effect of nitro. When *O*-acetyl oximes **1** carried either two aromatic substituents including 4-MeC_6H_4 & 4-MeC_6H_4, 4-FC_6H_4 & 4-MeC_6H_4, 4-FC_6H_4 & 1-naphthyl, 4-ClC_6H_4 & 4-MeC_6H_4, 4-ClC_6H_4 & 1-naphthyl or 4-MeC_6H_4 & 4-BrC_6H_4, then the anticipated products (**5j–5p**) were all obtained in acceptable yields from 53% to 82%. However, when

Table 2 Substrate scope of *O*-acetyl oximes **1**[a]



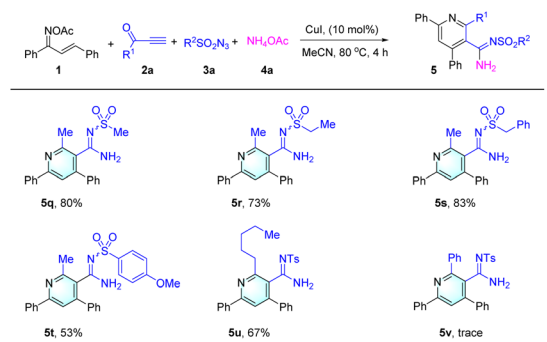
[a] Reaction conditions: **1** (0.5 mmol), **3a** (0.75 mmol), **4a** (1.0 mmol), and the CuI (10 mol%) in the MeCN (3 mL) were added with **2a** (0.75 mmol) and stirred at 80 °C for 4 h.

the alkyl groups instead of aryl groups were attached to the *O*-acetyl oximes **1** then the prospective products were not obtained.

The versatility of the reaction was further explored by evaluating the impact of varying the nature of terminal ynones **2** and sulfonyl azides **3**, as depicted in Table 3.

It was observed that alterations in the substituents on the sulfonyl azide moiety exerted minimal influence on the reaction's success, accommodating a diverse array of aryl and aliphatic groups. This led to the successful synthesis of products **5q** to **5t**, which bear –Me, –Et, benzyl, and –OMe groups, with yields ranging from 53% to 83%. In stark contrast, an examination of various terminal ynones **2** indicated that the functional groups attached to these substrates significantly dictate the reaction's outcome. For instance, alkyl groups such as –Me and $-^{n}C_5H_{11}$ were efficiently transformed into the desired pyridine derivatives **5a** and **5u**. However, terminal

Table 3 Substrate scope of terminal ynones **2** and sulfonyl azides **3**[a]



[a] Reaction conditions: **1a** (0.5 mmol), **3** (0.75 mmol), **4a** (1.0 mmol), and the CuI (10 mol%) in the MeCN (3 mL) were added with **2** (0.75 mmol) and stirred at 80 °C for 4 h.

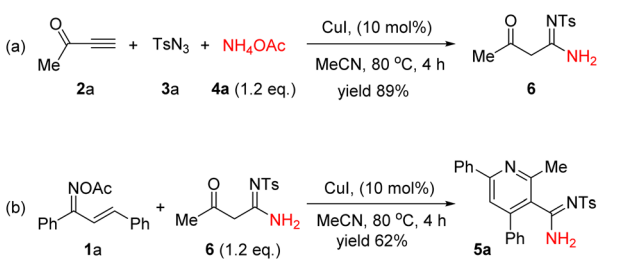
ynone substrates adorned with both aryl and ester groups, exemplified by **2c** and **2d** (as detailed in ESI Scheme S2†), did not yield the targeted products (*e.g.* **5v**). The chemical structures of the synthesized compounds were meticulously elucidated using a suite of analytical techniques, including ^{1}H NMR, ^{13}C NMR, IR spectroscopy, and high-resolution mass spectrometry (HRMS).

To elucidate the potential mechanism behind the observed transformations, a comprehensive series of experiments was meticulously conducted. Through the synthesis of the CuAAC/ring-cleavage reaction intermediate compound **6**, which was achieved by reacting **2a**, **3a**, and **4a** (as depicted in Scheme 2a). As expected, the compound **6** can be transformed to the final product **5a** under otherwise standard conditions (Scheme 2b). These experiments collectively suggest that compound **6** is a likely intermediate in the described chemical process.

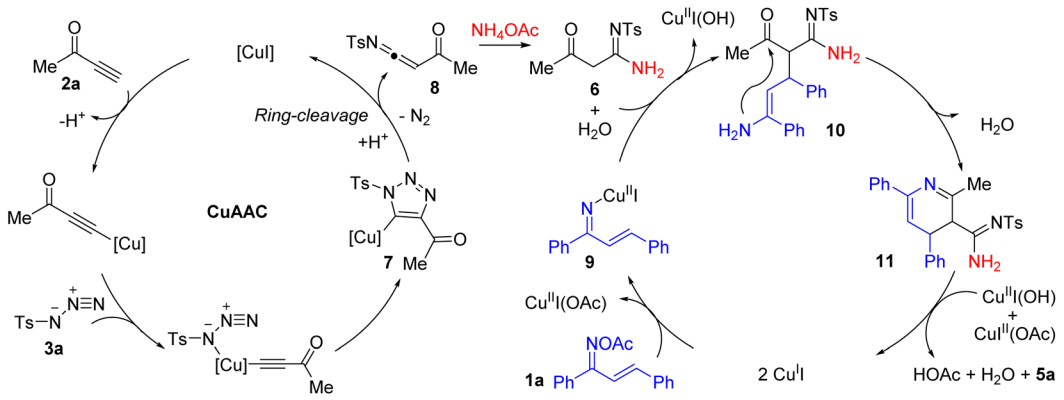
Consistent with prior hypotheses and the established reaction mechanism for oxime esters as detailed in references,[17] the likely cascade annulation reaction mechanism is illustrated in Scheme 3. As per the literature,[12] the interaction of substrates **2a** and **3a** in the presence of a copper(I) catalyst initiates the formation of the metallated triazole **7** *via* the CuAAC pathway. Subsequently, complex **7** experiences a ring-cleavage rearrangement, culminating in the generation of a highly reactive intermediate, the *N*-sulfonyl α-acylketenimine **8**. This intermediate is swiftly captured by NH_4OAc (**4a**) through a nucleophilic addition event, resulting in the formation of intermediate **6**. Intermediate **6** then participates in a Michael addition with precursor **9** to form intermediate **10**. An intramolecular nucleophilic attack subsequently forms the dihydropyridine intermediate **11**. The synthesis is concluded with the oxidation of intermediate **11** by Cu(II) species, accompanied by the regeneration of the Cu(I) catalyst, thereby producing the desired product **5a**. This domino sequence encompasses a CuAAC/ring-cleavage reaction, Michael addition, cyclization, and an oxidation step, showcasing the efficiency of this synthetic strategy.

An in-depth evaluation of the synthesized nicotinimidamide derivatives **5a–5u** was conducted to determine their *in vitro* inhibitory effects on HepG2 cells, utilizing the MTT assay as a measure of cell viability. The outcomes, depicted as half-maximal inhibitory concentration (IC_{50}) values in Table 4, represent the mean of no fewer than three separate experiments, ensuring the reliability of the results.

As illustrated in Table 4, the majority of the nicotinimidamides demonstrated a notable anticancer potency,



Scheme 2 Investigation of the reaction mechanism. (a) Synthesis of intermediate **6**. (b) Synthesis of product **5a** from intermediate **6**.



Scheme 3 Plausible reaction mechanism.

Table 4 The *in vitro* anti-proliferative activities (IC_{50}, μM)[a] of compounds **5a–5u**

Compounds	HepG2 IC_{50}(μM)	Compounds	HepG2 IC_{50}(μM)
5a	>100	**5l**	56
5b	>100	**5m**	>100
5c	73	**5n**	46
5d	>100	**5o**	>100
5e	>100	**5p**	8.6
5f	23	**5q**	64
5g	55	**5r**	78
5h	>100	**5s**	>100
5i	32	**5t**	>100
5j	>100	**5u**	26
5k	>100	Nicotinamide	>100

[a] MTT method.

irrespective of their electron-donating or electron-withdrawing characteristics. Specifically, those bearing a –Me group (*e.g.*, **5a**, **5b**, **5e**, **5j**, **5k**), a –OMe group (*e.g.*, **5d**, **5t**), or identified as insoluble products (*e.g.*, **5h**, **5m**, **5o**), displayed moderate anticancer activity, with IC_{50} values surpassing 100 μM. In contrast, the introduction of halogen groups (*e.g.*, **5c**, **5f**, **5l**, **5n**, **5p**), alkyl substituents (*e.g.*, **5q**, **5r**, **5u**), a –CN group (**5g**), or a furyl group (**5i**), engendered a pronounced apoptotic effect, with IC_{50} values within a range from 8.6 to 78.0 μM. Notably, the derivatives featuring a –Br group (*e.g.*, **5p** and **5f**), showcased the most remarkable apoptotic activity, with IC_{50} values of 8.6 μM and 23 μM, respectively. This performance is significantly superior to that of nicotinamide, which showed an IC_{50} greater than 100 μM against HepG2 cells. This result is consistent with the literature reports that most halogens against antiproliferative activities.[18] Furthermore, an assessment of the most active compounds—**5p** and **5f**—on a healthy cell line (LO2 cells) revealed IC_{50} values above 100 μM, indicating their low toxicity towards non-cancerous cells.

Conclusions

A novel copper-catalyzed four-component domino reaction has been developed for the synthesis of nicotinimidamides. This innovative method utilizes a mixture of *O*-acetyl oximes, terminal ynones, sulfonyl azides, and NH_4OAc, proceeding *via* a CuAAC/ring-cleavage mechanism. The process not only streamlines the synthesis of nicotinimidamides but also enhances the production efficiency. In addition to the synthetic advancements, an in-depth evaluation of all synthesized nicotinimidamides was conducted to assess their *in vitro* cytotoxic activity against a panel of human hepatoma (HepG2) cell lines. Among the derivatives, the one featuring a bromine substituent (**5p**) demonstrated exceptional potency, with an IC_{50} value of 8.6 μM. The findings of this study underscore the potential of nicotinimidamides as antineoplastic agents, highlighting their significance and warranting further investigation.

Experimental

General

All melting points were determined on a Yanaco melting point apparatus (Kyoto, Japan) and were uncorrected. IR spectra were recorded as KBr pellets on a Nicolet FT-IR 5DX spectrometer (Waltham, MA, USA). All spectra of ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded on a Bruker AVANCE NEO 400 MHz spectrometer (Berne, Switzerland) in DMSO-d_6 or $CDCl_3$ (unless otherwise indicated), with TMS used as an internal reference and the *J* values given in Hz. HRMS were obtained on a Thermo Scientific Q Exactive Focus Orbitrap LC-MS/MS spectrometer (Waltham, MA, USA). Optical rotations are measured on a *P*–2000, serial number: B209161232, JASCO corporation (Tokyo, Japan). *O*-acetyl oximes (**1a–1p**, see ESI Scheme S2†) were prepared by using reported methods.[19] All terminal ynones (**2a–2d**, see ESI Scheme S2†) were prepared by the manufacturer and sulfonyl azides (**3a–3e**, see ESI Scheme S3†) were prepared using methods in the literature.[20]

General procedure for the synthesis of nicotinimidamides 5a–5u

We added *O*-acetyl oximes (**1**) (0.5 mmol), terminal ynones (**2**) (0.75 mmol), sulfonyl azides (**3**) (0.12 mmol), CuI (0.05 mmol), NH_4OAc (**4a**, 77.1 mg, 1.0 mmol) and MeCN (3 mL) to an oven-dried Schlenk tube, equipped with a magnetic stirring bar. After

the reaction was stirred at 80 °C for 4 h, and cooled to room temperature, the solvent was removed by evaporation in vacuum. The residue was directly purified by flash column chromatography (silica gel, using hexanes/EtOAc as eluent) to afford the corresponding products nicotinimidamides **5**. Details of the compound characterizations are provided in the following subsections.

2-Methyl-4,6-diphenyl-*N*′-tosylnicotinimidamide (5a). Yield 88%, white solid, mp 226–228 °C (lit.[14] 230–231 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.94 (s, 1H), 8.39 (s, 1H), 8.15 (d, J = 6.7 Hz, 2H), 7.74 (s, 1H), 7.55 (d, J = 8.0 Hz, 2H), 7.52–7.44 (m, 5H), 7.39 (t, J = 7.4 Hz, 1H), 7.31–7.27 (m, 4H), 2.47 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.6, 155.6, 154.4, 147.7, 142.2, 137.9, 137.6, 129.4, 129.2 (3C), 128.7 (2C), 128.3 (2C), 128.2 (4C), 126.8 (2C), 126.2 (2C), 118.2, 22.2, 21.0.

2-Methyl-4-phenyl-6-(*p*-tolyl)-*N*′-tosylnicotinimidamide (5b). Yield 84%, white solid, mp 192–194 °C (lit.[14] 188–190 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.98 (s, 1H), 8.44 (s, 1H), 8.06–8.04 (m, 2H), 7.68 (s, 1H), 7.54 (s, 2H), 7.43 (s, 2H), 7.30–7.29 (m, 5H), 7.06 (s, 2H), 2.48 (s, 3H), 2.40 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.7, 163.5, 161.0, 155.7, 154.3, 146.8, 142.4, 139.2, 135.2, 134.0, 130.3, 130.2, 129.4 (2C), 129.3 (2C), 128.2, 126.8 (2C), 126.3 (2C), 117.9, 115.2, 115.0, 22.3, 21.0, 20.9.

6-(4-Chlorophenyl)-2-methyl-4-phenyl-*N*′-tosylnicotinimidamide (5c). Yield 90%, white solid, mp 233–234 °C (lit.[14] 229–231 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.93 (s, 1H), 8.40 (s, 1H), 8.20 (d, J = 8.4 Hz, 2H), 7.78 (s, 1H), 7.56–7.54 (m, 4H), 7.47 (d, J = 7.4 Hz, 2H), 7.40–7.34 (m, 1H), 7.31–7.26 (m, 4H), 2.47 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.6, 154.6, 154.4, 147.9, 142.4, 137.6, 136.8, 134.4, 129.4, 129.3 (2C), 128.9 (2C), 128.7 (3C), 128.5, 128 (3C), 126.3 (2C), 125.7, 118.4, 22.3, 21.1.

6-(4-Methoxyphenyl)-2-methyl-4-phenyl-*N*′-tosylnicotinimidamide (5d). Yield 62%, white solid, mp 224–226 °C (lit.[14] 226–228 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.92 (s, 1H), 8.36 (s, 1H), 8.11 (d, J = 8.6 Hz, 2H), 7.66 (s, 1H), 7.54 (d, J = 7.8 Hz, 2H), 7.45 (d, J = 7.2 Hz, 2H), 7.38 (t, J = 7.2 Hz, 1H), 7.30 (d, J = 7.7 Hz, 4H), 7.03 (d, J = 8.6 Hz, 2H), 3.81 (s, 3H), 2.44 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.0, 160.6, 155.5, 154.3, 147.7, 142.4, 137.9, 130.5, 129.3 (3C), 128.4 (3C), 128.3 (4C), 127.7, 126.3 (2C), 117.4, 114.2 (2C), 55.4, 22.4, 21.1.

2-Methyl-6-phenyl-4-(*p*-tolyl)-*N*′-tosylnicotinimidamide (5e). Yield 85%, white solid, mp 221–223 °C (lit.[14] 223–224 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.94 (s, 1H), 8.38 (s, 1H), 8.13 (d, J = 6.7 Hz, 2H), 7.70 (s, 1H), 7.56 (d, J = 8.0 Hz, 2H), 7.51–7.43 (m, 3H), 7.34 (t, J = 8.4 Hz, 4H), 7.05 (t, J = 7.8 Hz, 2H), 2.46 (s, 3H), 2.41 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.9, 155.7, 154.5, 147.8, 142.3, 138.1, 137.9, 134.8, 129.5, 129.3 (2C), 128.9 (3C), 128.8 (2C), 128.4, 128.1 (2C), 126.9 (2C), 126.4 (2C), 118.2, 22.3, 21.1, 21.0.

4-(4-Bromophenyl)-2-methyl-6-phenyl-*N*′-tosylnicotinimidamide (5f). Yield 72%, white solid, mp 237–239 °C (lit.[14] 241–243 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.96 (s, 1H), 8.30 (s, 1H), 8.10 (d, J = 6.6 Hz, 2H), 7.66 (s, 1H), 7.55 (d, J = 8.5 Hz, 1H), 7.50–7.43 (m, 5H), 7.29–7.19 (m, 5H), 2.53 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.0, 155.5, 155.0, 147.4, 142.6, 139.2, 138.2, 138.0, 133.0, 130.8, 130.5, 130.0, 129.6 (2C), 129.3 (3C), 127.3, 127.2 (2C), 126.4 (2C), 122.3, 119.3, 22.7, 21.5.

4-(4-Cyanophenyl)-2-methyl-6-phenyl-*N*′-tosylnicotinimidamide (5g). Yield 64%, white solid, mp 228–230 °C (lit.[14] 226–227 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.12 (s, 1H), 8.52 (s, 1H), 8.14, (d, J = 7.0 Hz, 2H), 7.76 (s, 1H), 7.62 (s, 2H), 7.53–7.46 (m, 7H), 7.29, (d, J = 7.7 Hz, 2H), 2.55 (s, 3H), 2.44 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.2, 156.1, 154.8, 146.5, 142.7, 142.3, 137.9, 132.1 (2C), 129.8, 129.4 (3C), 129.1, 129.0 (3C), 128.3, 127.1 (2C), 126.5 (2C), 118.8, 118.1, 111.2, 22.5, 21.2.

2-Methyl-4-(4-nitrophenyl)-6-phenyl-*N*′-tosylnicotinimidamide (5h). Yield 40%, white solid, mp 236–238 °C (lit.[14] 233–234 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.14 (s, 1H), 8.54 (s, 1H), 8.16 (d, J = 6.9 Hz, 2H), 7.98 (d, J = 6.2 Hz, 2H), 7.80 (s, 1H), 7.58 (d, J = 6.6 Hz, 2H), 7.53–7.46 (m, 5H), 7.23 (d, J = 7.6 Hz, 2H), 2.58 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.0, 156.0, 154.7, 147.1, 146.0, 144.2, 142.5, 137.7, 129.7, 129.5 (2C), 129.2 (3C), 128.9 (2C), 128.2, 127.0 (2C), 126.4 (2C), 123.2 (2C), 118.0, 22.4, 20.9.

4-(Furan-2-yl)-2-methyl-6-phenyl-*N*′-tosylnicotinimidamide (5i). Yield 57%, white solid, mp 138–140 °C (lit.[14] 135–137 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.99 (s, 1H), 8.62 (s, 1H), 8.14 (d, J = 7.2 Hz, 2H), 8.04 (s, 1H), 7.71–7.64 (m, 3H), 7.54–7.46 (m, 3H), 7.32 (d, J = 7.0 Hz, 2H), 7.03 (s, 1H), 6.59–6.58 (m, 1H), 2.40 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.9, 155.1, 148.9, 144.8, 142.4, 138.0, 135.2, 129.6, 129.3 (2C), 128.9 (3C), 126.8 (3C), 126.5 (2C), 112.8, 112.5, 112.0, 22.2, 21.1.

2-Methyl-4,6-di-*p*-tolyl-*N*′-tosylnicotinimidamide (5j). Yield 80%, white solid, mp 140–142 °C (lit.[14] 144–146 °C). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.92 (s, 1H), 8.37 (s, 1H), 8.04 (d, J = 8.1 Hz, 2H), 7.66 (s, 1H), 7.56 (d, J = 7.8 Hz, 2H), 7.34–7.28 (m, 6H), 7.05 (d, J = 7.7 Hz, 2H), 2.45 (s, 3H), 2.41 (s, 3H), 2.36 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (DMSO-d_6, 400 MHz) δ 164.0, 155.7, 154.3, 147.6, 142.3, 139.1, 137.8, 135.3, 134.8, 129.4 (2C), 129.2 (3C), 128.8 (3C), 128.1 (2C), 126.8 (2C), 126.4 (2C), 117.8, 22.3, 21.1, 20.9, 20.8.

2-Methyl-4-(*o*-tolyl)-6-(*p*-tolyl)-*N*′-tosylnicotinimidamide (5k). Yield 70%, white solid, mp 140–142 °C. IR (KBr) ν 3371.6, 3051.9, 1631.8, 1546.9, 1446.6, 1149.6, 1083.9 cm^{-1}. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.90 (s, 1H), 8.36 (s, 1H), 8.05 (d, J = 8.0 Hz, 2H), 7.68 (s, 1H), 7.53 (d, J = 8.0 Hz, 2H), 7.32–7.28 (m, 5H), 7.25 (d, J = 6.9 Hz, 1H), 7.20–7.14 (m, 2H), 2.45 (s, 3H), 2.39 (s, 3H),2.36 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (DMSO-d_6, 400 MHz) δ 163.8, 155.6, 154.3, 147.8, 142.3, 139.1, 137.8, 137.5, 135.3, 129.4 (2C), 129.2 (3C), 129.0 (2C), 128.1, 126.8 (2C), 126.1 (3C), 125.3, 117.8, 22.3, 21.1. 21.0, 20.9. Calcd for $C_{28}H_{27}N_3O_2S$, $[M + H]^+$ 470.1897; found 470.1899.

6-(4-Fluorophenyl)-2-methyl-4-(*p*-tolyl)-*N*′-tosylnicotinimidamide (5l). Yield 82%, white solid, mp 210–212 °C. IR (KBr) ν 3440.2, 3263.5, 1624.1, 1550.2, 1161.2, 1087.9 cm^{-1}. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.94 (s, 1H), 8.39 (s, 1H), 8.22–8.19 (m,2H), 7.72 (s, 1H), 7.57 (d, J = 7.7 Hz, 2H), 7.35–7.29 (m, 6H), 7.06 (t, J = 7.5 Hz, 2H), 2.46 (s, 3H), 2.41 (s, 3H),2.32 (s, 3H); ^{13}C NMR (DMSO-d_6, 400 MHz) δ 163.1 (d, J = 245.4 Hz), 163.8, 154.7, 154.5, 147.8, 142.3, 137.9, 134.7, 134.6 (d, J = 2.8 Hz), 129.3 (4C), 129.2 (d, J = 8.5 Hz), 128.9 (3C), 128.4, 128.2 (2C), 126.4 (2C), 118.1, 115.7 (d, J = 21.2 Hz), 25.4, 22.3, 20.8. Calcd for $C_{27}H_{24}FN_3O_2S$, $[M + H]^+$ 474.1646; found 474.1650.

6-(4-Fluorophenyl)-2-methyl-4-(naphthalen-1-yl)-*N*′-tosylnicotinimidamide (5m). Yield 53%, white solid, mp 122–124 °C. IR (KBr) ν 3450.7, 3221.2, 1631.6, 1549.1, 1442.8, 1273.0, 1083.9 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.03 (s, 1H), 8.42 (s, 1H), 8.27–8.23 (m, 2H), 8.04 (s, 1H), 7.95 (d, J = 7.4 Hz, 1H), 7.88 (s, 1H), 7.79 (d, J = 7.9 Hz, 2H), 7.62–7.56 (m, 3H), 7.43 (d, J = 8.1 Hz, 2H), 7.33 (t, J = 8.8 Hz, 2H), 7.05 (d, J = 7.9 Hz, 2H), 2.52 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (DMSO-d_6, 400 MHz) δ 164.2, 163.8, 162.0, 154.7, 154.6, 147.9, 142.2, 135.2, 134.5 (d, J = 2.9 Hz), 132.7, 132.6, 129.3, 129.2 (d, J = 8.4 Hz), 129.1 (2C), 128.6, 128.3 (2C), 127.7 (d, J = 31.2 Hz), 127.6, 126.8, 126.6, 126.1 (3C), 118.5, 115.7 (d, J = 214.7 Hz), 22.4, 21.1 (2C). Calcd for $C_{30}H_{24}FN_3O_2S$, $[M + H]^+$ 510.1646; found 510.1641.

6-(4-Chlorophenyl)-2-methyl-4-(*p*-tolyl)-*N*′-tosylnicotinimidamide (5n). Yield 82%, white solid, mp 201–204 °C. IR (KBr) ν 3371.6, 3251.6, 1627.9, 1546.9, 1303.9, 1157.3, 1083.9 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ 8.94 (s, 1H), 8.39 (s, 1H), 8.18 (d, J = 6.3 Hz, 2H), 7.74 (s, 1H), 7.55–7.53 (m, 4H) 7.32 (d, J = 8.9 Hz, 4H), 7.05 (d, J = 6.6 Hz, 2H), 2.46 (s, 3H), 2.41 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (DMSO-d_6, 400 MHz) δ 164.2, 155.0, 154.8, 148.3, 142.7, 138.4, 137.3, 135.1, 134.7, 129.6 (3C), 129.2 (4C), 129.1 (3C), 128.5 (2C), 125.7 (2C), 118.7, 26.8, 22.7, 21.5. Calcd for $C_{27}H_{24}ClN_3O_2S$, $[M + H]^+$ 490.1354; found 490.1358.

6-(4-Chlorophenyl)-2-methyl-4-(naphthalen-1-yl)-*N*′-tosylnicotinimidamide (5o). Yield 57%, white solid, mp 126–128 °C (lit.[14] 128–130 °C). ^1H NMR (DMSO-d_6, 400 MHz) δ 9.03 (s, 1H), 8.42 (s, 1H), 8.23 (d, J = 7.5 Hz, 2H), 8.04 (s, 1H), 7.94 (d, J = 7.6 Hz, 1H), 7.91 (s, 1H), 7.79 (d, J = 7.5 Hz, 2H), 7.62–7.55 (m, 5H), 7.43 (t, J = 7.2 Hz, 2H), 7.04 (d, J = 7.6 Hz, 2H), 2.52 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (DMSO-d_6, 400 MHz) δ 163.7, 154.7, 154.4, 148.0, 124.2, 136.9, 135.2, 134.4, 132.7, 132.6, 129.1 (3C), 129.0 (2C), 128.8 (2C), 128.3, 127.8 (2C), 127.6, 126.8, 126.6, 126.1 (3C), 126.0, 118.6, 22.4, 22.1.

4-(4-Bromophenyl)-2-methyl-6-(*p*-tolyl)-*N*′-tosylnicotinimidamide (5p). Yield 68%, white solid, mp 164–166 °C (lit.[14] 162.3–165.2 °C). ^1H NMR (DMSO-d_6, 400 MHz) δ 8.98 (s, 1H), 8.42 (s, 1H), 8.05 (d, J = 8.2 Hz 2H), 7.69 (s, 1H), 7.55 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 7.7 Hz, 2H), 7.31 (t, J = 7.3 Hz, 6H), 2.50 (s, 3H), 2.43 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 163.7, 155.8, 154.5, 146.6, 142.4, 139.2, 136.9, 135.2, 131.1 (3C), 130.2, 129.5 (2C), 129.3 (3C), 127.9, 126.9 (2C), 126.4 (2C), 122.1, 117.7, 22.4, 21.2, 21.0.

2-Methyl-*N*′-(methylsulfonyl)-4,6-diphenylnicotinimidamide (5q). Yield 80%, white solid, mp 102–104 °C (lit.[14] 92 °C). ^1H NMR (400 MHz, DMSO-d_6) δ 8.88 (s, 1H), 8.24 (s, 1H), 8.15 (d, J = 7.7 Hz, 2H), 7.76 (s, 1H), 7.59 (d, J = 6.8 Hz, 2H), 7.52–7.44 (m, 6H), 2.62 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.9, 155.9, 154.6, 148.1, 138.2, 138.1, 129.6, 129.0 (2C), 128.7, 128.6 (4C), 127.1 (3C), 118.3, 22.6 (2C).

***N*′-(Bthylsulfonyl)-2-methyl-4,6-diphenylnicotinimidamide (5r).** Yield 73%, white solid, mp 105–107 °C (lit.[14] 98–100 °C). ^1H NMR (400 MHz, DMSO-d_6) δ 8.87 (s, 1H), 8.25 (s, 1H), 8.16 (d, J = 7.0 Hz, 2H), 7.76 (s, 1H), 7.61 (d, J = 7.7 Hz, 2H), 7.53–7.44 (m, 6H), 2.74–2.64 (m, 2H), 2.69 (s, 3H), 0.96 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.0, 155.7, 154.5, 147.9, 138.1, 129.5, 128.9 (2C), 128.7, 128.6, 128.5 (2C), 128.4 (3C), 127.0 (2C), 118.3, 47.4, 22.6, 7.8. This structure has been identified by X-ray structure (CCDC deposition number 2043697).[14]

***N*′-(Benzylsulfonyl)-2-methyl-4,6-diphenylnicotinimidamide (5s).** Yield 83%, white solid, mp 150–152 °C (lit.[14] 148–150 °C). ^1H NMR (400 MHz, DMSO-d_6) δ 8.83 (s, 1H), 8.27 (s, 1H), 8.16 (d, J = 7.0 Hz, 2H), 7.77 (s, 1H), 7.58 (d, J = 8.8 Hz, 2H), 7.52–7.44 (m, 6H), 7.33–7.31 (m, 5H), 4.00 (s, 2H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.2, 155.7, 154.6, 147.9, 138.1, 138.0, 131.1 (2C), 130.2, 129.5, 128.9 (2C), 128.6 (3C), 128.5 (3C), 128.2 (2C), 127.9, 127.0 (2C), 118.2, 58.6, 22.5.

***N*′-((4-Methoxyphenyl)sulfonyl)-2-methyl-4,6-diphenylnicotinimid amide (5t).** Yield 53%, white solid, mp 164–166 °C (lit.[14] 160–162 °C). ^1H NMR (400 MHz, DMSO-d_6) δ 8.92 (s, 1H), 8.36 (s, 1H), 8.14 (d, J = 7.0 Hz, 2H), 7.73 (s, 1H), 7.61 (d, J = 8.0 Hz, 2H), 7.49 (d, J = 7.3 Hz, 5H), 7.38 (t, J = 7.0 Hz, 1H), 7.31 (d, J = 7.0 Hz, 2H), 7.00 (d, J = 8.5 Hz, 2H), 3.85 (3H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.5, 162.1, 155.8, 154.6, 147.8, 138.1, 137.7, 129.5, 128.9 (2C), 128.5 (2C), 128.4 (2C), 128.3 (4C), 127.8, 127.0 (3C), 118.3, 114.1, 55.8, 22.4.

2-Pentyl-4,6-diphenyl-*N*′-tosylnicotinimidamide (5u). Yield 67%, yellow oil (lit.[14] yellow oil). ^1H NMR (400 MHz, DMSO-d_6) δ 8.93 (s, 1H), 8.35 (s, 1H), 8.15 (d, J = 8.3 Hz, 2H), 7.72 (s, 1H), 7.62 (d, J = 7.8 Hz, 2H), 7.51–7.45 (m, 5H), 7.39 (d, J = 7.3 Hz, 1H), 7.34–7.32 (m, 4H), 2.61 (t, J = 8.0 Hz, 2H), 2.40 (s, 3H), 1.68 (t, J = 6.8 Hz, 2H), 1.30–1.23 (m, 3H), 0.87 (t, J = 7.0 Hz, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.6, 158.1, 155.7, 147.8, 142.4, 138.2, 137.8, 129.5, 129.3 (3C), 128.9 (2C), 128.5, 128.4 (2C), 128.3 (2C), 128.1, 126.9 (2C), 126.4 (2C), 118.2, 34.9, 31.4, 28.5, 22.1, 21.1, 14.0.

3-Oxo-*N*′-tosylbutanimidamide (6). To a solution of NH_4OAc (0.77 g, 10 mmol), CuI (0.19 g, 1.0 mmol), TsN_3 (**3a**, 2.37 g, 12 mmol) in MeCN (15 mL) was added. Then added the but-3-yn-2-one (**2a**, 0.82 g, 12 mmol) slowly within 30 min at 0 °C. After the reaction was stirred at 0 °C for 1 h, room temperature for 12 h, the mixture was evaporated in vacuum. The residue was purified by a flash chromatography [silica gel, 50% EtOAc in petroleum ether (60–90 °C)] to give 1.57 g (62%) of product **5** as a white solid, mp 130–134 °C (lit.[14] 128–129 °C). ^1H NMR (400 MHz, DMSO-d_6) δ 8.52 (s, 1H), 8.18 (s, 1H), 7.69 (d, J = 7.3 Hz, 2H), 7.33 (d, J = 7.3 Hz, 2H), 3.54 (s, 2H), 2.35 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 201.4, 163.7, 142.1, 140.0, 129.2 (2C), 126.0 (2C), 49.8, 29.8, 21.0.

All NMR spectra please see ESI Section 3.†

Biological assay

The HepG2 cells and LO2 cells were obtained from the American Type Culture Collection and cultured in an environment of 5% CO_2 at 37 °C in RPMI-1640 medium supplemented with 10% fetal bovine serum (FBS). Human liver (HepG2) cancer cell lines were seeded in 96-well plates at a density of 3000 cells/well in normoxia for 12 h. Then, measures of 100 μL drug-containing medium, with a series of concentrations, were dispensed into the wells to attain the final concentration as 100, 80, 20, 10, 5, and 2 μM. After 48 h incubated under normoxia or hypoxia, 20 μL MTT solution (Beyotime Biotechnology, Nantong, China, 5 mg mL^{-1} MTT dissolved in PBS) was added. Then, following

incubation for another 4 h, the medium was discarded, followed by the addition of 200 μL DMSO. The absorbance was measured at 570 nm with a microplate reader. Experiments were conducted in triplicate. The IC_{50} values are the average of at least three independent experiments.

Data availability

The data supporting this article have been included as part of the ESI.†

Author contributions

Xi Chen and Guanrong Li: main contributor in this manuscript who did experiment, data curation, formal analysis, investigation, and methodology. Zixin Huang: experiment, spectroscopic characterization. Qiaoli Luo: spectroscopic characterization. Tao Chen and Weiguang Yang: main contributor in this manuscript who did conceptualization, funding acquisition, project administration, resources, supervision, writing original draft, and review. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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