


Cite this: *RSC Adv.*, 2024, **14**, 25844

Received 8th July 2024
Accepted 12th August 2024

DOI: 10.1039/d4ra04918g

rsc.li/rsc-advances

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

Xi Chen,^{‡a} Guanrong Li,^{‡b} Zixin Huang,^b Qiaoli Luo,^c Tao Chen^{*a} and Weiguang Yang^{ID *b}

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 yrones, 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.

Introduction

Pyridines represent privileged motifs in both organometallic¹ and medicinal chemistry² 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-

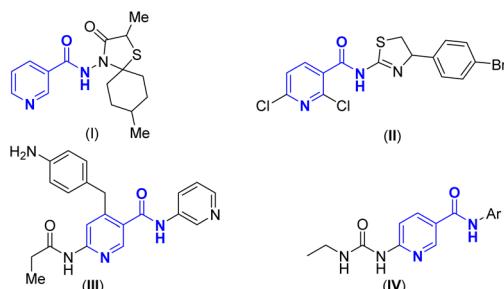


Fig. 1 Examples of nicotinamides, **I**–**IV**, that have been explored as drug candidates.

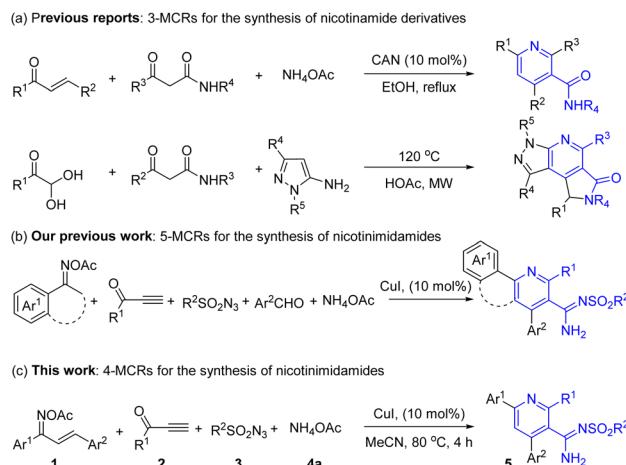
^aDepartment of Hepatobiliary Surgery, Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou 510120, China. E-mail: chentao@mail.sysu.edu.cn

^bSchool of Ocean and Tropical Medicine, Guangdong Medical University, Zhanjiang, Guangdong, 524023, China. E-mail: 09ywg@163.com

^cSchool of Chemistry and Chemical Engineering, Lingnan Normal University, Zhanjiang, 524048, P. R. China

† Electronic supplementary information (ESI) available. See DOI: <https://doi.org/10.1039/d4ra04918g>

‡ These authors contributed equally to this work.



Scheme 1 Synthesis of nicotinamide derivatives.



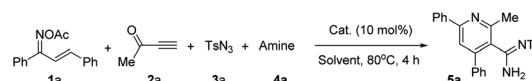
component [3 + 3] aza-annulation reaction of chalcones, β -ketoamides, and ammonium acetate, facilitated by CAN as a Lewis acid,¹⁰ or alternatively, the reaction of phenylglyoxal, β -ketoamide, and 5-aminopyrazole through a Hantzsch-type 3-MCR.¹¹ However, these methods often yield suboptimal results, 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-MCRs¹² 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 yrones, 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 chromatographic 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 $\text{NH}_4\text{O}_2\text{CH}$ were effective (Table 1, entries 1–2), while $(\text{NH}_4)_2\text{SO}_4$, NH_4Cl , NH_4PF_6 , $(\text{NH}_4)_2\text{CO}_3$, 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

Table 1 Optimization of catalytic conditions^a



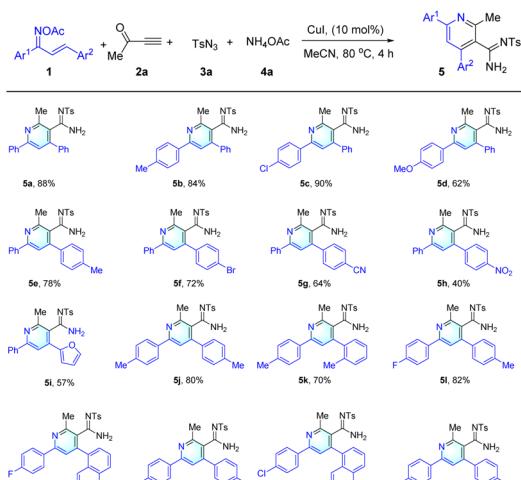
Entry	Amine (2 equiv.)	Cat. (10 mol%)	Solvent (3 mL)	Yield ^b (%)
1	NH_4OAc	CuI	MeCN	88
2	$\text{NH}_4\text{O}_2\text{CH}$	CuI	MeCN	42
3	$(\text{NH}_4)_2\text{SO}_4$	CuI	MeCN	0
4	NH_4Cl	CuI	MeCN	0
5	NH_4PF_6	CuI	MeCN	0
6	$(\text{NH}_4)_2\text{CO}_3$	CuI	MeCN	0
7	PhNH_2	CuI	MeCN	0
8	Et_2NH	CuI	MeCN	0
9	NH_4OAc	CuCl	MeCN	84
10	NH_4OAc	CuBr	MeCN	82
11	NH_4OAc	CuBr_2	MeCN	74
12	NH_4OAc	$\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$	MeCN	60
13	NH_4OAc	$\text{Cu}(\text{OAc})_2$	MeCN	72
14	NH_4OAc	$\text{Cu}(\text{acac})_2$	MeCN	51
15	NH_4OAc	$\text{Cu}(\text{OTf})_2$	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.

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).

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-MeC₆H₄, 4-ClC₆H₄, 4-MeOC₆H₄, 4-BrC₆H₄, 4-CNC₆H₄, 4-NO₂C₆H₄, 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-NO₂C₆H₄ 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-MeC₆H₄ & 4-MeC₆H₄, 4-FC₆H₄ & 4-MeC₆H₄, 4-FC₆H₄ & 1-naphthyl, 4-ClC₆H₄ & 4-MeC₆H₄, 4-ClC₆H₄ & 1-naphthyl or 4-MeC₆H₄ & 4-BrC₆H₄, then the anticipated products (**5j–5p**) were all obtained in acceptable yields from 53% to 82%. However, when



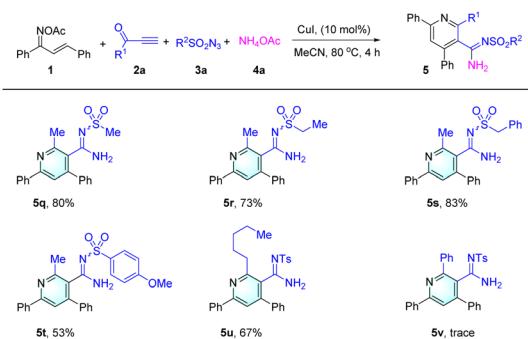
Table 2 Substrate scope of *O*-acetyl oximes 1^a

^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 yones 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 yones 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*-C₅H₁₁ were efficiently transformed into the desired pyridine derivatives 5a and 5u. However, terminal

Table 3 Substrate scope of terminal yones 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.

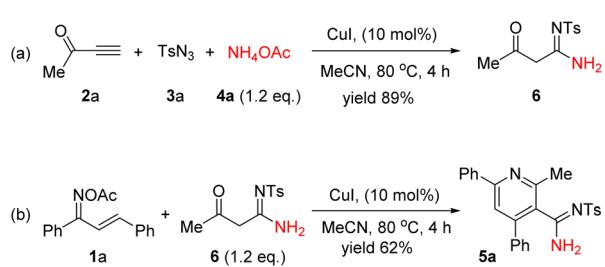
ynone substrates adorned with both aryl and ester groups, exemplified by 2c and 2d (as detailed in ESI Scheme S2†), did not yield the targeted products (e.g. 5v). The chemical structures of the synthesized compounds were meticulously elucidated using a suite of analytical techniques, including ¹H NMR, ¹³C 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 NH₄OAc (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.

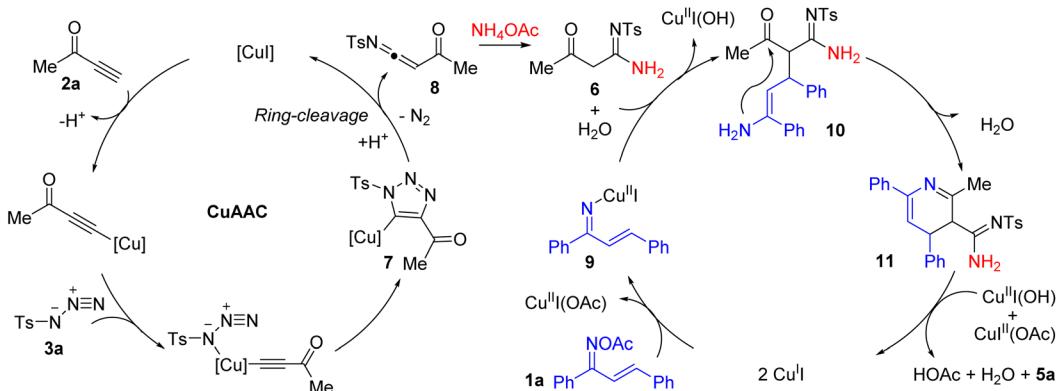
An in-depth evaluation of the synthesized nicotinimidamide derivatives 5a-5u was conducted to determine their *in vitro* inhibitory effects on HepG2 cells, utilizing the MTT assay as a measure of cell viability. The outcomes, depicted as half-maximal inhibitory concentration (IC₅₀) values in Table 4, 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 anti-cancer 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 ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded on a Bruker AVANCE NEO 400 MHz spectrometer (Berne, Switzerland) in $\text{DMSO}-d_6$ 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). ¹H 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); ¹³C 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). ¹H 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); ¹³C 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). ¹H 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); ¹³C 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). ¹H 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); ¹³C 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). ¹H 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); ¹³C 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). ¹H 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); ¹³C 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). ¹H 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). ¹³C 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). ¹H 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); ¹³C 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). ¹H 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); ¹³C 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). ¹H 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); ¹³C 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. ¹H 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); ¹³C 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 C₂₈H₂₇N₃O₂S, [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. ¹H 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); ¹³C 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 C₂₇H₂₄FN₃O₂S, [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); ¹³C 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 C₃₀H₂₄FN₃O₂S, [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); ¹³C 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 C₂₇H₂₄ClN₃O₂S, [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); ¹³C 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); ¹³C 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); ¹³C 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); ¹³C 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); ¹³C 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-diphenylnicotinimidamide (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); ¹³C 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); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 163.6, 158.1, 155.7, 147.8, 142.4, 138.2, 137.8, 129.5, 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 NH₄OAc (0.77 g, 10 mmol), CuI (0.19 g, 1.0 mmol), TsN₃ (**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); ¹³C 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% CO₂ 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 μ L 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.

Acknowledgements

This research was funded by the Scientific Research Project of General Universities in Guang-dong Province (2023KTSCX036).

Notes and references

- (a) M. Schlosser and F. Mongin, *Chem. Soc. Rev.*, 2007, **36**, 1161–1172; (b) M. R. Stentzel and D. A. Klumpp, *J. Org. Chem.*, 2020, **85**, 12740–12746; (c) D. C. Leary, Y. Zhang, J. G. Rodriguez, N. G. Akhmedov, J. L. Petersen, B. S. Dilinar and C. Milsmann, *Organometallics*, 2023, **42**, 1220–1231; (d) G. R. Peddiaghari Vasu, K. R. Motakatla Venkata, R. R. Kakarla, K. V. S. Ranganath and T. M. Aminabhavi, *Environ. Res.*, 2023, **225**, 115515.
- (a) R. Roman, L. Pintilie, D. C. Nuță, M. T. Căproiu, F. Dumitrascu, I. Zarafu, P. Ionită, I. C. Marinas, L. Mărutescu, E. Kapronczai, S. Ardelean and C. Limban, *Pharmaceutics*, 2023, **15**, 2501; (b) J. A. Tali, G. Kumar, B. K. Sharma, Y. Rasool, Y. Sharma and R. Shankar, *Org. Biomol. Chem.*, 2023, **21**, 7267–7289; (c) M. B. Islam, M. I. Islam, N. Nath, T. B. Emran, M. R. Rahman, R. Sharma and M. M. Matin, *Biomed Res. Int.*, 2023, **2023**, 9967591; (d) Y. Wu, T. Wu and Y. Huang, *Arch. Pharm.*, 2023, **356**, e2300067.
- G. Cihan-Üstündağ, Ç. Acar, L. Naesens, G. Erköse-Genç and D. Şatana, *Arch. Pharm.*, 2022, **355**, e2200224.
- Y. H. I. Mohammed, I. M. Shamkh, A. H. Shhtaif, M. Sufyan, M. T. Rehman, M. F. AlAjmi, M. Shahwan, S. Alghamdi, A. E. Abd El-Lateef, E. B. Khidir, A. S. Abouzied, N. E. Khalifa, W. M. A Khojali, B. Huwaimel, D. A. Al Farraj and S. M. Almutairi, *Sci. Rep.*, 2024, **14**, 11118.
- M. A. Azam and J. Thathan, *SAR QSAR Environ. Res.*, 2017, **28**, 275–296.
- I. A. Yule, L. G. Czaplewski, S. Pommier, D. T. Davies, S. K. Narramore and C. W. Fishwick, *Eur. J. Med. Chem.*, 2014, **86**, 31–38.
- (a) L. Fania, C. Mazzanti, E. Campione, E. Candi, D. Abeni and E. Dellambra, *Int. J. Mol. Sci.*, 2019, **3**, 5946; (b) M. A. Chiacchio, D. Iannazzo, S. Romeo, S. V. Giofre and L. Legnani, *Curr. Med. Chem.*, 2019, **26**, 7166–7195; (c) P. W. Ondachi, A. H. Castro, J. M. Bartkowiak, C. W. Luetje, M. I. Damaj, S. W. Mascarella, H. A. Navarro and F. I. Carroll, *J. Med. Chem.*, 2014, **57**, 836–848.
- (a) C. Allais, J. M. Grassot, J. Rodriguez and T. Constantieux, *Chem. Rev.*, 2014, **114**, 10829–10868; (b) N. Deibl, K. Ament and R. Kempe, *J. Am. Chem. Soc.*, 2015, **137**, 12804–12807; (c) J. Zhu and H. Bienaymé, *The Discovery of New Isocyanide-Based Multicomponent Reactions*, Wiley-VCH, Weinheim, Germany, 2005.
- (a) D. Insuasty, J. Castillo, D. Becerra, H. Rojas and R. Abonia, *Molecules*, 2020, **25**, 505; (b) C. S. Graebin, F. V. Ribeiro, K. R. Rogerio and A. E. Kummerle, *Curr. Org. Synth.*, 2019, **16**, 855–899; (c) A. E. van der Westhuyzen, L. V. Frolova, A. Kornienko and W. A. L. van Otterlo, *Alkaloids*, 2018, **79**, 191–220; (d) J.-P. Wan, L. Gan and Y. Liu, *Org. Biomol. Chem.*, 2017, **15**, 9031–9043; (e) S. Brauch, S. S. Berkel and B. van Westermann, *Chem. Soc. Rev.*, 2013, **42**, 4948–4962.
- G. Tenti, M. T. Ramos and J. C. Menéndez, *ACS Comb. Sci.*, 2012, **14**, 551–557.
- (a) X. Feng, J. Wang, D. Liu, H. Shi, W. Lu and D. Shi, *J. Org. Chem.*, 2023, **88**, 6682–6690; (b) H. Tan and Y. Wang, *ACS Comb. Sci.*, 2020, **22**, 468–474.
- (a) S. H. Kim, S. H. Park, J. H. Choi and S. Chang, *Chem.-Asian J.*, 2011, **6**, 2618–2634; (b) I. Bae, H. Han and S. Chang, *J. Am. Chem. Soc.*, 2005, **127**, 2038–2039; (c) S. H. Cho, E. J. Yoo, I. Bae and S. Chang, *J. Am. Chem. Soc.*, 2005, **127**, 16046–16047; (d) W. Yang, G. Li, D. Luo, Z. Huang, M. G. Banwell and X. Luo, *Adv. Synth. Catal.*, 2024, DOI: [10.1002/adsc.202400339](https://doi.org/10.1002/adsc.202400339); (e) C.-G. Wang, R. Wu, T.-P. Li, T. Jia, Y. Li, D. Fang, X. Chen, Y. Gao, H.-L. Ni, P. Hu, B.-Q. Wang and P. Cao, *Org. Lett.*, 2020, **22**, 3234–3238; (f) G. Li, D. Luo, Q. Luo, Z. Huang, W. Zhuang, H. Luo and W. Yang, *J. Org. Chem.*, 2024, **89**, 2190–2199; (g) L. Xu, T. Zhou, M. Liao, R. Hu and B. Z. Tang, *ACS Macro Lett.*, 2019, **8**, 101–106; (h) S. Guo, P. Dong, Y. Chen, X. Feng and X. Liu, Chiral Guanidine/Copper Catalyzed Asymmetric Azide-Alkyne Cycloaddition/[2+2] Cascade Reaction, *Angew. Chem. Int. Ed.*, 2018, **57**, 16852–16856.
- (a) M. Nematpour, H. F. Dastjerdi, S. M. I. M. Rabbani and S. A. Tabatabai, *J. Heterocycl. Chem.*, 2019, **56**, 2604–2611; (b) D. Cheng, F. Ling, C. Zheng and C. Ma, *Org. Lett.*, 2016, **18**, 2435–2438; (c) G. Murugavel and T. Punniyamurthy, *J. Org. Chem.*, 2015, **80**, 6291–6299; (d) R. Husmann, Y. S. Na, C. Bolm and S. Chang, *Chem. Commun.*, 2010, **46**, 5494–5496; (e) W. Song, W. Lu, J. Wang, P. Lu and Y. Wang, *J.*



Org. Chem., 2010, **75**, 3481–3483; (f) W. Song, M. Lei, Y. Shen, S. Cai, W. Lu, P. Lu and Y. Wang, *Adv. Synth. Catal.*, 2010, **352**, 2432–2436; (g) E. J. Yoo, S. H. Park, S. H. Lee and S. Chang, *Org. Lett.*, 2009, **11**, 1155–1158.

14 Y. Zhao, L. Li, Z. Zhou, M. Chen, W. Yang and H. Luo, *Org. Biomol. Chem.*, 2021, **19**, 3868–3872.

15 E. J. Yoo, M. Ahlquist, I. Bae, K. B. Sharpless and V. V. Fokin, *J. Org. Chem.*, 2008, **73**, 5520–5528.

16 (a) X. Luo, Z. Yang, J. Zheng, G. Liang, H. Luo and W. Yang, *Org. Lett.*, 2022, **24**, 7300–7304; (b) W. Yang, Y. Zhao, Q. Bu, L. Li, B. Zhou and Z. Huang, *Org. Lett.*, 2022, **24**, 457–461.

17 (a) H. Jiang, J. Yang, X. Tang, J. Li and W. Wu, *J. Org. Chem.*, 2015, **80**, 8763–8771; (b) H. Jiang, J. Yang, X. Tang, J. Li and W. Wu, *J. Org. Chem.*, 2016, **81**, 2053–2061.

18 (a) B. Muthu Ramalingam, N. Dhatchana Moorthy, S. R. Chowdhury, T. Mageshwaran, E. Vellaichamy, S. Saha, K. Ganesan, B. N. Rajesh, S. Iqbal, H. K. Majumder, K. Gunasekaran, R. Siva and A. K. Mohanakrishnan, *J. Med. Chem.*, 2018, **61**, 1285–1315; (b) D. E. Beck, M. Abdelmalak, W. Lv, P. V. Reddy, G. S. Tender, E. O'Neill, K. Agama, C. Marchand, Y. Pommier and M. Cushman, *J. Med. Chem.*, 2015, **58**, 3997–4015.

19 P. C. Too, Y. F. Wang and S. Chiba, *Org. Lett.*, 2010, **12**, 5688–5691.

20 D. Das and R. Samanta, *Adv. Synth. Catal.*, 2018, **360**, 379–384.

