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Copper Catalyzed Inverse Electron Demand [4+2] Cycloaddition for the Synthesis of Oxazines

Weiguang Yang [1,2,*], Zitong Zhou [1], Yu Zhao [1], Danyang Luo [1], Xiai Luo [3], Hui Luo [2], Liao Cui [1,*] and Li Li [1,*]

[1] Guangdong Key Laboratory for Research and Development of Natural Drugs, The Marine Biomedical Research Institute, Guangdong Medical University, Zhanjiang 524023, China; zzt15766229745@163.com (Z.Z.); gdmuzy@163.com (Y.Z.); huluodanyang@163.com (D.L.)
[2] Southern Marine Science and Engineering Guangdong Laboratory (Zhanjiang), Zhanjiang 524023, China; luohui@gdmu.edu.cn
[3] The Marine Biomedical Research Institute of Guangdong Zhanjiang, Zhanjiang 524023, China; luoxiai83@163.com
* Correspondence: yangwg@gdmu.edu.cn (W.Y.); cuiliao@163.com (L.C.); ll0661@163.com (L.L.)

Abstract: A copper catalyzed tandem CuAAC/ring cleavage/[4+2] annulation reaction of terminal ynones, sulfonyl azides, and imines has been developed to synthesize the functionalized oxazines under mild conditions. Particularly, the intermediate *N*-sulfonyl acylketenimines undergo cycloaddition of an inverse electron demand Diels–Alder reaction with imines and a series of 1,3-oxazine derivatives were obtained successfully in good yields.

Keywords: copper catalyzed; CuAAC/ring cleavage; [4+2] annulation reaction; inverse electrons; oxazine; ketenimine

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1. Introduction

Oxazines, a six-membered ring containing one nitrogen and one oxygen atom, are important functionalized skeletons and play a crucial role in medicinal chemistry [1]. Its derivatives are widely used as therapeutic agents, such as analgesic (1) [2], anticancer (2) [3], antioxidant (3) [4], anti-inflammatory (4) [5], BACE1 inhibitors (5) [6], and anti-HIV (6) [7] (Figure 1). Owing to pharmacological activity, these types of oxazine derivatives have numerous applications in drug discovery and medicinal chemistry [1,8–11]. Consequently, there is an attendant interest in the development of novel, concise, and flexible routes to construct such oxazine rings.

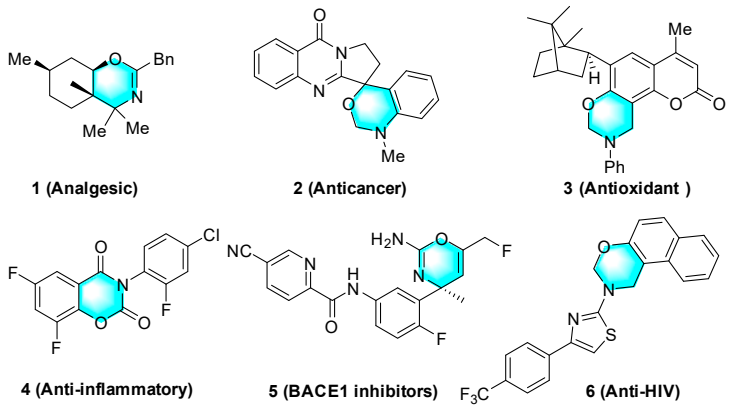
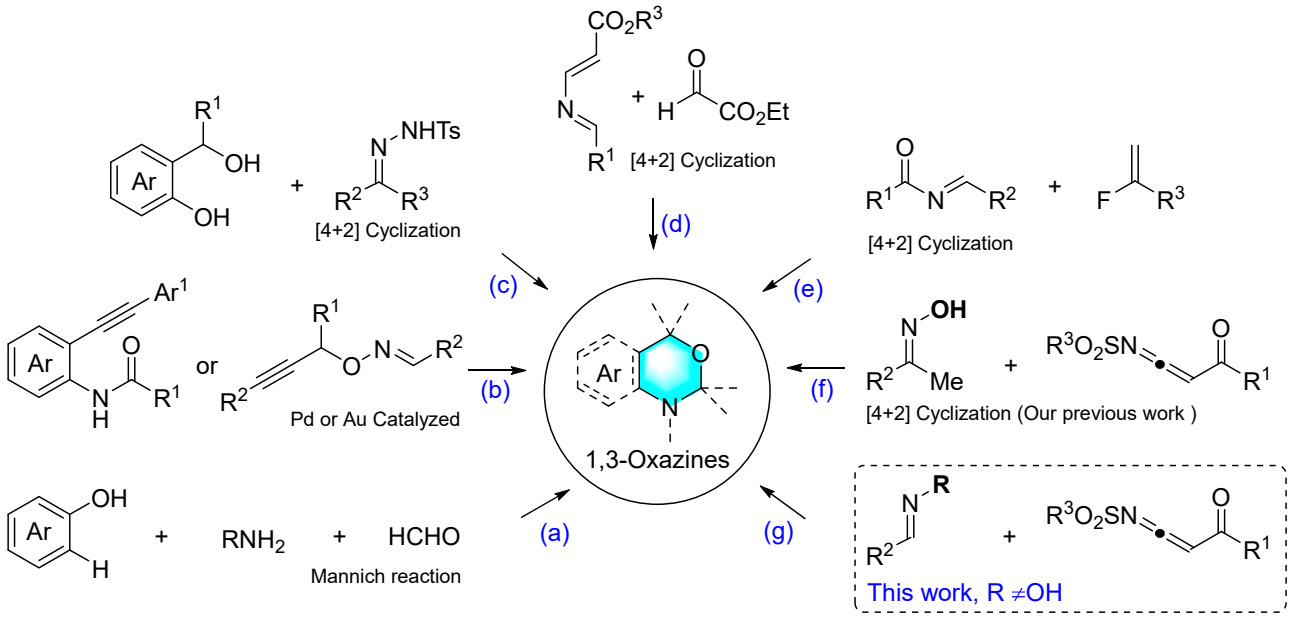


Figure 1. Examples of oxazine drug candidates.

Over the past decades, various reaction routes have been reported for the synthesis of 1,3-oxazine in the literature, involving the following six methods: (a) Mannich reaction by

using an aromatic amines reaction with phenol and formaldehyde [12–15]. (b) Au catalyzed rearrangement of *ortho*-propargylic oximes via N-O Bond cleavage or Pd catalyzed cascade arene/alkyne annulation [16,17]. (c) [4+2] Cycloaddition of *N*-tosylhydrazones with *ortho*-quinone methides [18]. (d) Cycloaddition reaction of 2-azadienes derived and carbonyl compounds [19]. (e) [4+2] Cycloaddition reaction of α-fluorostyrenes with imines [20]. (f) Our previous study has disclosed that a semblable strategy about tandem CuAAC/ring cleavage/[4+2] annulation reaction from sulfonyl azides, terminal ynones, and oximes [21] (Scheme 1a–f). However, a majority of these reactions have been reported to need expensive metal catalysts and have poor regioselectivity, a long reaction time, and a high temperature while having low yields. Thus, an efficient and new route for the synthesis of multi-substituted 1,3-oxazine derivatives is still required.



Scheme 1. Synthesis of 1,3-oxazines: (**a**) mannich reaction; (**b**) rearrangement; (**c**–**f**) [4+2] cycloaddition reaction; (**g**) this work, CuAAC/ring cleavage/[4+2] annulation reaction.

On the other side, the [4+2] cycloaddition has become a venerable strategy in synthetic routes to create sophisticated frameworks, especially the inverse-electron-demand Diels–Alder reactions (IEDDA). These reactions between easily available chemicals enable the concise construction of six-membered rings under mild conditions [22–26]. During the past decade, a series of substrates or intermediates, such as alkenes, enol ethers, indoles, enamines, and enolates, have been successfully exploited to undergo such types of annulation reactions, enriched the toolbox of organic chemists for further studies, and delivered various chiral cyclohexenes or six-membered heterocycles [27–36]. The IEDDA has been a central initial reaction in domino sequences, especially with azadienes toward complex heterocycles.

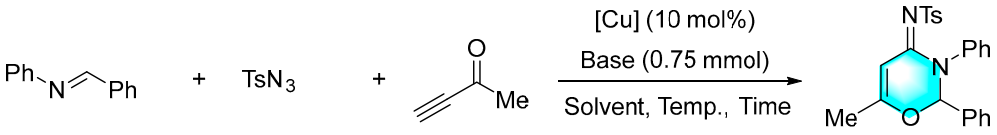
Herein, we report a high-efficiency copper catalyzed inverse-electron-demand oxa-Diels–Alder reaction using terminal ynones, sulfonyl azides, and imines, and a series of novel 1,3-oxazine derivatives were obtained (Scheme 1g).

2. Results and Discussion

We began the study on a multicomponent reaction by choosing *N*-Benzylideneaniline **1a**, with sulfonyl azides **2a** and but-3-yn-2-one **3a** as the model substrates to synthesize 2,3-dihydro-4*H*-1,3-oxazin-4-ylidene **4a**. The reaction was carried out in the presence of CuCl in acetone at room temperature for 4 h, and **4a** was isolated in a 21% yield (Table 1, entry 1). Based on this finding, the reaction conditions were screened. First, the solvents were screened, and a lower or comparable yield was obtained when THF, DMF, DCM, and DMSO were used as solvents, while MeCN gave **4a** the highest yield of 84% (Table 1,

entry 2–6). Then, the effects of catalysts were screened, and most Cu^{I}-catalysts exhibited a higher catalytic reactivity than Cu^{II}-catalysts in this reaction (Table 1, entries 7–13). Other catalysts such as AgTFA failed to produce the desired product (Table 1, entries 14). The effects of different additives were also evaluated, and the screening results revealed that additive-free achieved a superior result compared to an added base or acid (Table 1, entries 15–19). The reason maybe is that the terminal ynones will take a self-condensation under the base conditions according to previous reports [37–39]. Ultimately, we investigated the effect of reaction time and temperature and get the optimized conditions (Table 1, entries 20–24).

Table 1. Optimization of conditions [a].

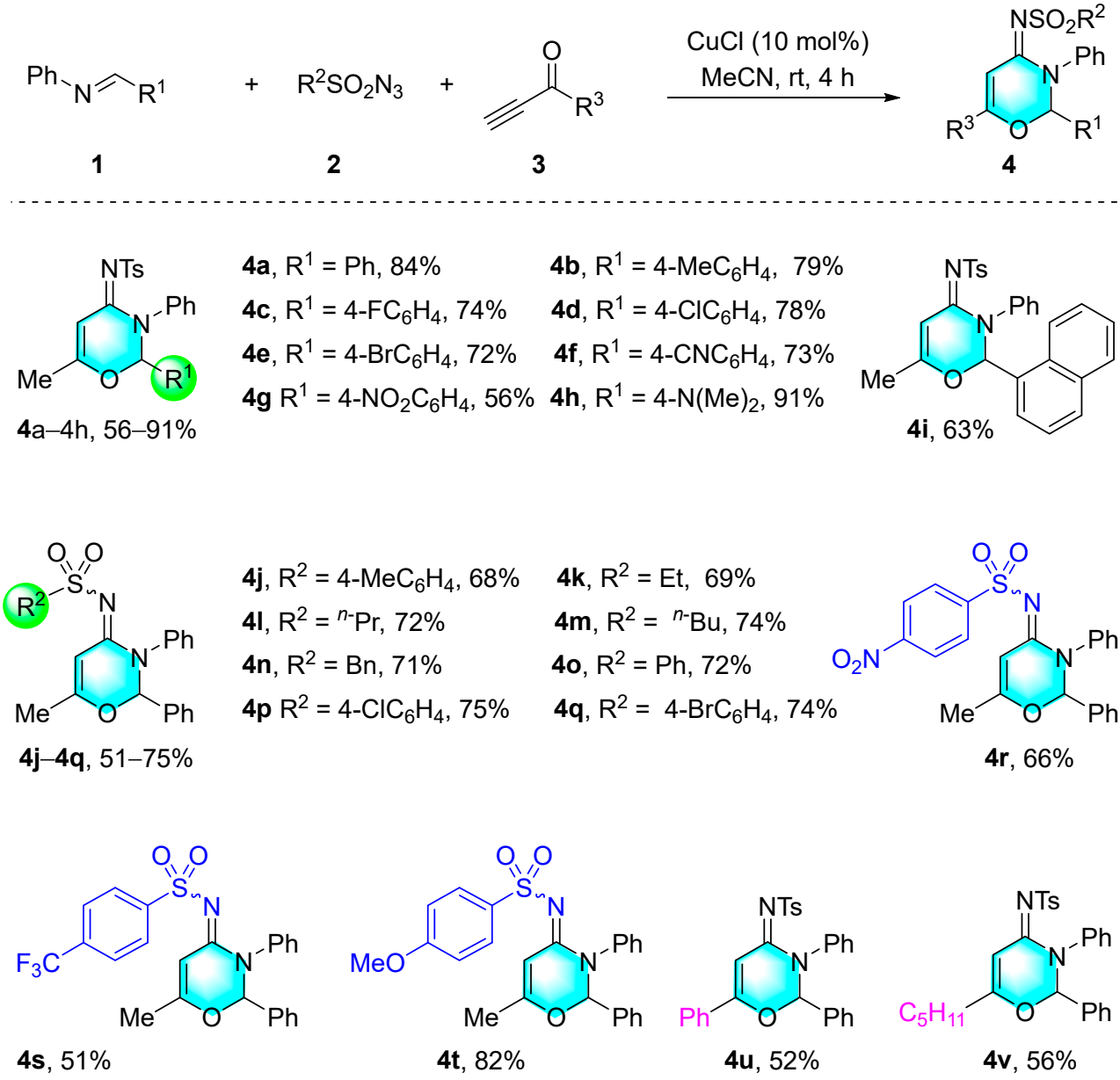


1a **2a** **3a** **4a**

Entry	Cat. (10 mol%)	Base (0.75 mmol)	Solvent (2 mL)	Temp. (°C)	Time (h)	Yield (%) [b]
1	CuCl	-	Acetone	rt	4.0	21
2	CuCl	-	THF	rt	4.0	65
3	CuCl	-	DMF	rt	4.0	12
4	CuCl	-	DCM	rt	4.0	21
5	CuCl	-	DMSO	rt	4.0	15
6	CuCl	-	MeCN	rt	4.0	84
7	CuI	-	MeCN	rt	4.0	78
8	$Cu(OAc)_2$	-	MeCN	rt	4.0	71
9	$Cu(acac)_2$	-	MeCN	rt	4.0	22
10	CuO	-	MeCN	rt	4.0	Trace
11	CuBr	-	MeCN	rt	4.0	65
12	$Cu(SO_4)_2$	-	MeCN	rt	4.0	Trace
13	$Cu(TFA)_2$	-	MeCN	rt	4.0	32
14	AgTFA	-	MeCN	rt	4.0	0
15	CuCl	DMAP	MeCN	rt	4.0	Trace
16	CuCl	TsOH	MeCN	rt	4.0	Trace
17	CuCl	K_2CO_3	MeCN	rt	4.0	12
18	CuCl	HOAc	MeCN	rt	4.0	24
19	CuCl	Et_3N	MeCN	rt	4.0	42
20	CuCl	-	MeCN	40	4.0	76
21	CuCl	-	MeCN	60	4.0	62
22	CuCl	-	MeCN	80	4.0	41
23	CuCl	-	MeCN	rt	3.0	77
24	CuCl	-	MeCN	rt	5.0	84

[a] Reaction conditions: To **1a** (0.5 mmol), Cat. 10 mol%, base 1.5 equivalent in the solvent (2 mL) was added **2a** (0.75 mmol) and **3a** (0.75 mmol), stirred at specified temperatures and times (monitored by TLC). [b] Isolated yields.

With this optimized condition in hand (Table 1, entries 6), the substrate diversity of the reaction was explored, as depicted in Scheme 2. Firstly, the scope of *N*-Benzylideneanilines were examined. It was found that the R^1 with the electron-donating group (including OMe, Me) was superior to the electron-withdrawing group (including CN, NO_2, Cl, etc). The 4-$N(Me)_2C_6H_4$ group (**4h**) presented the highest yield (91%) as well as 4-MeC_6H_4 (**4b**) in 79% yields. The R^1 with electron-withdrawing groups such as 4-nitrophenyl (**4g**) and 4-cyanobenzene (**4f**) were well-tolerated and showed a moderate reaction effect. In addition, 1-naphthyl was also tested in the reaction and afforded the desired products **4i** in 63%. Presumably, because of the steric hindrance effect and strong electronic effect, 2-Me, 3-Me, and 2-furan failed to generate the desired products.



Scheme 2. The synthesis of products **4a**–**4v**.

The scope of sulfonyl azides were further examined under optimized conditions. Surprisingly, Alkyl **4j**–**4m** then was screened to participate in the transformation and smoothly get the desired compound in a moderate yield (68–74%). With R^2 changed by aromatic substituents or aliphatic aryl groups, **4n**–**4t** were well-tolerated and gave satisfactory yields (51–82%). The 4-$OMeC_6H_4$ group (**4t**) as an electron-donating group provided excellent yields in 88% yields. Likewise, when R^3 was an *n*-pentyl or –Ph group, the terminal ynones afforded acceptable yields (**4u**, 52% and **4v**, 56%).

The structures of (**4a**–**4v**) 1,3-oxazine products are unreported, and their structures were confirmed by ^{1}HNMR, ^{13}CNMR, IR, and HRMS. The structure of **4a** unambiguously was confirmed by X-ray crystallography (Figure 2, CCDC deposition number 2164715).

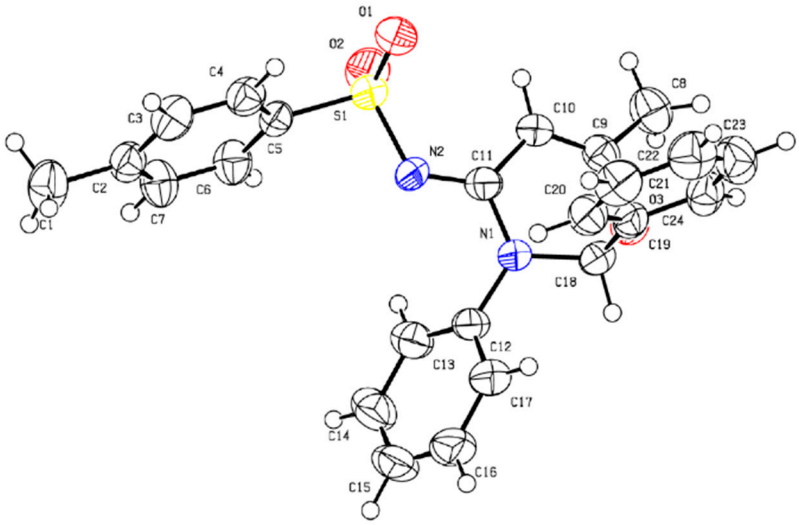
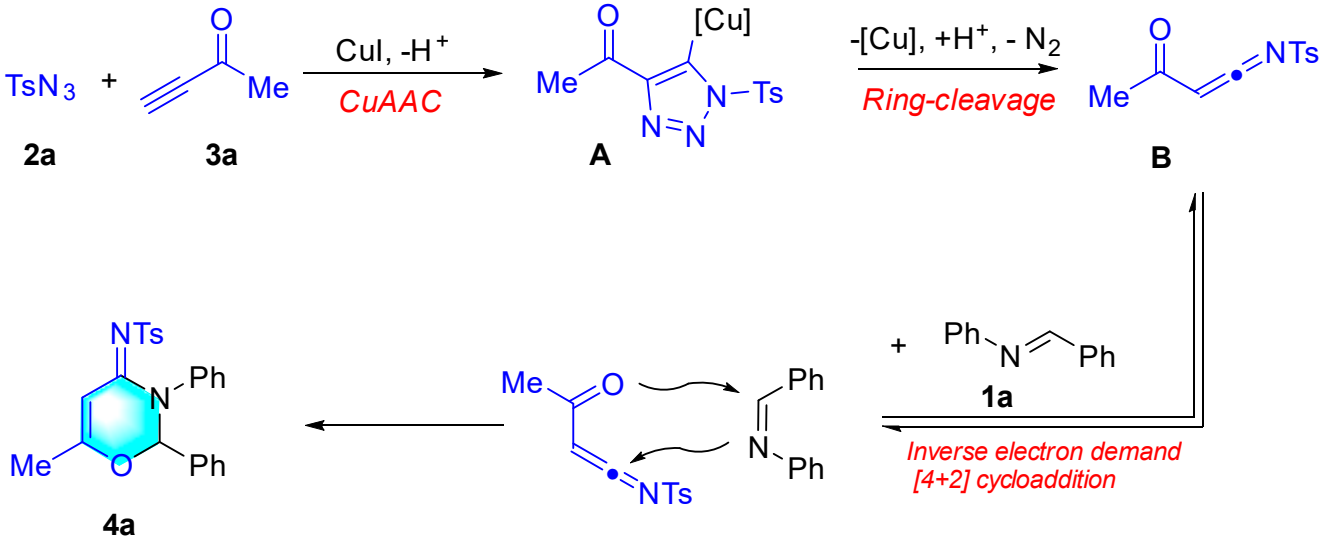


Figure 2. X-ray crystal structure of compound **4a**.

A possible reaction pathway for the formation of 2,3-dihydro-4*H*-1,3-oxazin-4-ylidene (**4a**) from precursors **1a**, **2a**, and **3a** is shown in Scheme 3. Thus, in keeping with earlier proposals, the substrates **2a** and **3a** are expected to react, in the presence of the copper (I) catalyst, so as to form the metallated triazole **A** that fragments with accompanying loss of nitrogen to form a highly active intermediate α-acyl-*N*-sulfonyl ketenimine **B**. This last species is captured by **1a** via inverse electron demand [4+2] cycloaddition to deliver the observed product **4a**.



Scheme 3. Plausible reaction mechanism.

3. Materials and Methods

3.1. General Methods

All melting points were determined on a Yanaco melting point apparatus and were uncorrected. IR spectra were recorded as KBr pellets on a Nicolet FT-IR 5DX spectrometer. All spectra of ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded on a Bruker AVANCE NEO 400 MHz spectrometer in DMSO-d_6 or $CDCl_3$ (otherwise as 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. All imines (**1a**–**2i**, see Supplementary Materials Section S1), sulfonyl azides (**2a**–**2l**, see Supplementary

Materials Section S1), and terminal alkynes (**2a**–**2b**, see Supplementary Materials Section S1) were prepared by literature methods [40–42].

3.2. General Procedure for the Synthesis of 2,3-Dihydro-4H-1,3-Oxazin-4-Ylidenes (**4a**–**4v**)

The solution of (*E*)-*N*,1-diphenylmethanimine (**1**, 91 mg, 0.5 mmol), CuI (95 mg, 0.05 mmol) in MeCN (1.0 mL) was added. Then, the mixture of TsN_3 (**2**, 147.8 mg, 0.75 mmol) and But-3-yn-2-one (**3**, 51.0 mg, 0.75 mmol) was added in MeCN (2 mL). After the reaction mixture was stirred at room temperature for 4 h (monitored by TLC), the solvent was removed. The residue was purified by flash chromatography (silica gel, 33% EtOAc in petroleum ether (60–90 °C)) to give the corresponding products **4a**–**4v**. Details of the compound characterizations:

4-Methyl-*N*-(6-methyl-2,3-diphenyl-2,3-dihydro-4H-1,3-oxazin-4-ylidene) benzenesulfonamide (**4a**) (176 mg, 84%), a white solid, m.p. = 164.9–166.4 °C (Rf = 0.30 in 1:3 *v*/*v* ethyl acetate/60–90 petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.0 Hz, 2H), 7.44–7.36 (m, 5H), 7.26–7.12 (m, 7H), 6.60 (s, 1H), 6.51 (s, 1H), 2.38 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 156.9, 142.0, 140.5, 139.9, 135.4, 129.8, 129.0 (2C), 128.9 (2C), 128.7 (2C), 127.3 (3C), 126.5 (2C), 126.3 (2C), 97.4, 89.7, 21.5, 20.4; IR ν_{max} (KBr) 3063, 3036, 2920, 1639, 1545, 1366, 1084 cm^{-1}; HRMS (ESI-TOF) *m*/*z*: Calculated for $C_{24}H_{22}N_2O_3S$, $[M+H]^+$ 419.1427, Found 419.1427.

4-Methyl-*N*-(6-methyl-3-phenyl-2-(p-tolyl)-2,3-dihydro-4H-1,3-oxazin-4-ylidene) benzenesulfonamide (**4b**) (171 mg, 79%), a white solid, m.p. = 158.1–160.0 °C (Rf = 0.30 in 1:3 *v*/*v* ethyl acetate/60–90 petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.6 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.24 (t, *J* = 7.8 Hz, 2H), 7.17 (t, *J* = 8.6 Hz, 5H), 7.12 (t, *J* = 8.0 Hz, 2H), 6.59 (s, 1H), 6.47 (s, 1H), 2.37 (s, 3H), 2.34 (s, 3H), 1.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 157.1, 142.1, 140.6, 140.0, 139.9, 132.5, 129.5 (2C), 129.1 (2C), 128.9 (2C), 127.3 (2C), 127.2, 126.6 (2C), 126.3 (2C), 97.3, 89.8, 21.5, 21.4, 20.5; IR ν_{max} (KBr) 3117, 3059, 2920, 1640, 1546, 1303, 1084 cm^{-1}; HRMS (ESI-TOF) *m*/*z*: Calculated for $C_{25}H_{24}N_2O_3S$, $[M+H]^+$ 433.1581, Found 433.1582.

N-(2-(4-Fluorophenyl)-6-methyl-3-phenyl-2,3-dihydro-4H-1,3-oxazin-4-ylidene)-4-methylbenzenesulfonamide (**4c**) (161 mg, 74%), a white solid, m.p. = 162.4–163.2 °C (Rf = 0.20 in 1:4 *v*/*v* ethyl acetate/60–90 petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.0 Hz, 2H), 7.43–7.39 (m, 2H), 7.27–7.17 (m, 5H), 7.10–7.02 (m, 4H), 6.62 (s, 1H), 6.48 (s, 1H), 2.37 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 163.4 (d, *J* = 248.4 Hz, 1C), 156.9, 142.1, 140.4, 139.7, 131.2 (d, *J* = 3.2 Hz, 1C), 129.2 (d, *J* = 8.6 Hz, 2C), 129.0 (2C) 128.9 (2C), 127.4, 126.6 (2C), 126.2 (2C), 115.8 (d, *J* = 21.8 Hz, 2C), 97.3, 89.1, 21.4, 20.3; IR ν_{max} (KBr) 3109, 3067, 2970, 1639, 1546, 1431, 1084 cm^{-1}; HRMS (ESI-TOF) *m*/*z*: Calculated for $C_{24}H_{21}FN_2O_3S$, $[M+H]^+$ 437.1330, Found 437.1333.

N-(2-(4-Chlorophenyl)-6-methyl-3-phenyl-2,3-dihydro-4*H*-1,3-oxazin-4-ylidene)-4-methylbenzenesulfonamide (**4d**) (176 mg, 78%), a white solid, m.p. = 191.2–191.3 °C (Rf = 0.20 in 1:4 *v*/*v* ethyl acetate/60–90 petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.0 Hz, 2H), 7.39–7.32 (m, 4H), 7.26 (t, *J* = 7.6 Hz, 2H), 7.20 (t, *J* = 7.4 Hz, 3H), 7.10 (t, *J* = 7.2 Hz, 2H), 6.61 (s, 1H), 6.48 (s, 1H), 2.37 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 156.9, 142.4, 140.4, 139.8, 136.0, 134.1, 129.2 (2C), 129.1 (2C), 129.0 (2C), 128.8 (2C), 127.5, 126.6 (2C), 126.4 (2C), 97.5, 89.2, 21.6, 20.5; IR ν_{max} (KBr) 2971, 2919, 2839, 1720, 1496, 1366, 1088 cm^{-1}; HRMS (ESI-TOF) *m*/*z*: Calculated for $C_{24}H_{21}ClN_2O_3S$, $[M+H]^+$ 453.1034, Found 453.1038.

N-(2-(4-Bromophenyl)-6-methyl-3-phenyl-2,3-dihydro-4H-1,3-oxazin-4-ylidene)-4-methylbenzenesulfonamide (**4e**) (179 mg, 72%), a white solid, m.p. = 207.4–209.2 °C (Rf = 0.22 in 1:4 *v*/*v* ethyl acetate/60–90 petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.0 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.32–7.24 (m, 4H), 7.21 (d, *J* = 7.8 Hz, 3H), 7.10 (d, *J* = 7.6 Hz, 2H), 6.61 (s, 1H), 6.46 (s, 1H), 2.38 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 156.7, 142.1, 140.3, 139.7, 134.6, 132.0 (2C), 129.1 (2C), 129.0 (2C) 128.9 (2C), 127.4, 126.4 (2C), 126.3 (2C), 124.2, 97.4, 89.1, 21.5, 20.4; IR ν_{max} (KBr) 3117, 3059,

2920, 1500, 1496, 1304, 1084 cm^{-1}; HRMS (ESI-TOF) *m*/*z*: Calculated for $C_{24}H_{21}BrN_2O_3S$, $[M+H]^+$ 497.0529, Found 497.0521.

N-(2-(4-Cyanophenyl)-6-methyl-3-phenyl-2,3-dihydro-4H-1,3-oxazin-4-ylidene)-4-methylbenzenesulfonamide (**4f**) (162 mg, 73%), a white solid, m.p. = 163.5–165.2 °C (Rf = 0.10 in 1:4 *v*/*v* ethyl acetate/60–90 petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69–7.65 (m, 4H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.30–7.19 (m, 5H), 7.10 (d, *J* = 8.4 Hz, 2H), 6.63 (s, 1H), 6.54 (s, 1H), 2.38 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 156.4, 142.3, 140.6, 140.1, 139.6, 132.6 (2C), 129.1 (2C), 129.0 (2C), 128.0 (2C), 127.6, 126.4 (2C), 126.3 (2C), 117.9, 113.9, 97.7, 88.7, 21.5, 20.3; IR ν_{max} (KBr) 3117, 3059, 2920, 1497, 1412, 1304, 1084 cm^{-1}; HRMS (ESI-TOF) *m*/*z*: Calculated for $C_{25}H_{21}N_3O_3S$, $[M+H]^+$ 444.1107, Found 444.1146.

4-Methyl-*N*-(6-methyl-2-(4-nitrophenyl)-3-phenyl-2,3-dihydro-4H-1,3-oxazin-4-ylidene) benzenesulfonamide (**4g**) (130 mg, 56%), a white solid, m.p. = 221.3–223.2 °C (Rf = 0.20 in 1:3 *v*/*v* ethyl acetate/60–90 petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.4 Hz, 2H), 7.68–7.63 (m, 4H), 7.30–7.19 (m, 5H), 7.12 (d, *J* = 7.6 Hz, 2H), 6.65 (s, 1H), 6.59 (s, 1H), 2.38 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 165.6, 148.8, 142.5, 142.4, 140.2, 139.6, 129.3 (2C), 129.2 (2C), 128.4 (2C), 127.8, 126.5 (2C), 126.4 (2C), 124.1 (2C), 97.8, 88.7, 21.6, 20.4; IR ν_{max} (KBr) 3113, 2994, 2924, 1620, 1497, 1304, 1087 cm^{-1}; HRMS (ESI-TOF) *m*/*z*: Calculated for $C_{24}H_{21}N_3O_5S$, $[M+H]^+$ 464.1275, Found 464.1279.

N-(2-(4-(Dimethylamino)phenyl)-6-methyl-3-phenyl-2,3-dihydro-4H-1,3-oxazin-4-ylidene)-4-methylbenzenesulfonamide (**4h**) (210 mg, 91%), a white solid, m.p. = 188.3–189.6 °C (Rf = 0.25 in 1:3 *v*/*v* ethyl acetate/60–90 petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.0 Hz, 2H), 7.27–7.17 (m, 7H), 7.11 (d, *J* = 7.6 Hz, 2H), 6.63 (d, *J* = 8.4 Hz, 2H), 6.58 (s, 1H), 6.41 (s, 1H), 2.95 (s, 6H), 2.36 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 157.4, 151.2, 141.9, 140.7, 140.0, 129.0 (2C), 128.7 (2C), 128.5 (2C), 127.1, 126.7 (2C), 126.3 (2C), 122.0, 111.7 (2C), 96.9, 90.1, 40.2 (2C), 21.5, 20.4; IR ν_{max} (KBr) 3043, 2955, 2808, 1539, 1450, 1277, 1084 cm^{-1}; HRMS (ESI-TOF) *m*/*z*: Calculated for $C_{26}H_{27}N_3O_3S$, $[M+H]^+$ 462.1846, Found 462.1848.

4-Methyl-*N*-(6-methyl-2-(naphthalen-2-yl)-3-phenyl-2,3-dihydro-4H-1,3-oxazin-4-ylidene)benzenesulfonamide (**4i**) (147 mg, 63%), a white solid, m.p. = 142.9–144.3 °C (Rf = 0.20 in 1:4 *v*/*v* ethyl acetate/60–90 petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87–7.81 (m, 4H), 7.72 (t, *J* = 8.0 Hz, 2H), 7.54–7.51 (m, 3H), 7.26–7.17 (m, 7H), 6.66 (s, 1H), 6.63 (s, 1H), 2.38 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 157.1, 142.1, 140.5, 140.0, 133.7, 132.6, 132.5, 129.1 (2C), 128.9 (3C), 128.5, 127.7, 127.3 (3C), 126.8 (2C), 126.4 (2C), 126.3 (2C), 97.3, 89.9, 21.5, 20.4; IR ν_{max} (KBr) 3113, 3059, 1632, 1501, 1308, 1150, 1084 cm^{-1}; HRMS (ESI-TOF) *m*/*z*: Calculated for $C_{28}H_{24}N_2O_3S$, $[M+H]^+$ 469.1581, Found 469.1584.

N-(6-Methyl-2,3-diphenyl-2,3-dihydro-4H-1,3-oxazin-4-ylidene) methane sulfonamide (**4j**) (116 mg, 68%), a white solid, m.p. = 175.4–176.0 °C (Rf = 0.30 in 1:3 *v*/*v* ethyl acetate/60–90 petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.41 (m, 2H), 7.39–7.36 (m, 3H), 7.32–7.26 (m, 2H), 7.22 (t, *J* = 8.4 Hz, 3H), 6.50 (s, 1H), 6.45 (s, 1H), 2.90 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 157.0, 139.8, 135.4, 129.8, 128.9 (2C), 128.7 (2C), 127.3 (3C), 126.7 (2C), 97.5, 89.7, 43.0, 20.3; IR ν_{max} (KBr) 3109, 3059, 2936, 1632, 1551, 1493, 1119 cm^{-1}; HRMS (ESI-TOF) *m*/*z*: Calculated for $C_{18}H_{18}N_2O_3S$, $[M+H]^+$ 343.1111, Found 343.1111.

N-(6-Methyl-2,3-diphenyl-2,3-dihydro-4H-1,3-oxazin-4-ylidene) ethane sulfonamide (**4k**) (123 mg, 69%), a white solid, m.p. = 140.7–142.2 °C (Rf = 0.25 in 1:3 *v*/*v* ethyl acetate/60–90 petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.41 (m, 2H), 7.38–7.36 (m, 3H), 7.28 (t, *J* = 7.2 Hz, 2H), 7.20 (t, *J* = 8.0 Hz, 3H), 6.50 (s, 1H), 6.46 (s, 1H), 2.99–2.89 (m, 2H), 2.01 (s, 3H), 1.23 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 157.3, 139.8, 135.4, 129.8, 128.8 (2C), 128.7 (2C), 127.3 (2C), 127.2, 126.9 (2C), 97.6, 89.7, 49.3, 20.3, 8.3; IR ν_{max} (KBr) 3063, 2986, 2940, 1647, 1497, 1431, 1115 cm^{-1}; HRMS (ESI-TOF) *m*/*z*: Calculated for $C_{19}H_{20}N_2O_3S$, $[M+H]^+$ 357.1268, Found 357.1273.

N-(6-Methyl-2,3-diphenyl-2,3-dihydro-4H-1,3-oxazin-4-ylidene)propane-1-sulfonamide (**4l**) (133 mg, 72%), a white solid, m.p. = 140.7–142.4 °C (Rf = 0.28 in 1:3 *v*/*v* ethyl acetate/60–90 petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.41 (m, 2H), 7.38–7.36 (m, 3H),

7.28 (t, *J* = 7.6 Hz, 2H), 7.20 (t, *J* = 7.6 Hz, 3H), 6.49 (s, 1H), 6.46 (s, 1H), 2.96–2.84 (m, 2H), 2.00 (s, 3H), 1.78–1.68 (m, 2H), 0.91 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 157.2, 139.8, 135.4, 129.8, 128.8 (2C), 128.7 (2C), 127.3 (2C), 127.2, 126.9 (2C), 97.6, 89.7, 56.7, 20.3, 17.3, 12.9; IR ν_{max} (KBr) 3109, 2971, 2874, 1639, 1555, 1369, 1115 cm^{-1}; HRMS (ESI-TOF) *m*/*z*: Calculated for $C_{20}H_{22}N_2O_3S$, $[M+H]^+$ 371.1424, Found 371.1424.

N-(6-Methyl-2,3-diphenyl-2,3-dihydro-4H-1,3-oxazin-4-ylidene)butane-1-sulfonamide (**4m**) (142 mg, 74%), a white solid, m.p. = 127.6–129.9 °C (Rf = 0.35 in 1:3 *v*/*v* ethyl acetate/60–90 petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.42 (m, 2H), 7.38–7.36 (m, 3H), 7.28 (t, *J* = 7.2 Hz, 2H), 7.18 (t, *J* = 8.0 Hz, 3H), 6.49 (s, 1H), 6.46 (s, 1H), 2.98–2.86 (m, 2H), 2.00 (s, 3H), 1.72–1.64 (m, 2H), 1.35–1.25 (m, 2H), 0.83 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 157.2, 139.8, 135.4, 129.8, 128.8 (2C), 128.7 (2C), 127.3 (2C), 127.2, 127.0 (2C), 97.6, 89.7, 54.7, 25.7, 21.4, 20.3, 13.6; IR ν_{max} (KBr) 3109, 2971, 2932, 1636, 1547, 1288, 1111 cm^{-1}; HRMS (ESI-TOF) *m*/*z*: Calculated for $C_{21}H_{24}N_2O_3S$, $[M+H]^+$ 385.1581, Found 385.1579.

N-(6-Methyl-2,3-diphenyl-2,3-dihydro-4H-1,3-oxazin-4-ylidene)-1-phenyl methanesulfonamide (**4n**) (148 mg, 71%), a white solid, m.p. = 154.1–155.6 °C (Rf = 0.30 in 1:3 *v*/*v* ethyl acetate/60–90 petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.25 (m, 9H), 7.20 (t, *J* = 8.0 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 4H), 6.40 (s, 1H), 6.33 (s, 1H), 4.12 (q, 2H), 1.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 157.6, 139.5, 135.0, 131.1 (2C), 130.3, 129.7, 128.9 (2C), 128.6 (2C), 128.1 (2C), 127.8, 127.5 (2C), 127.4 (3C), 97.4, 89.8, 60.7, 20.1; IR ν_{max} (KBr) 3040, 2970, 2870, 1647, 1493, 1354, 1107 cm^{-1}; HRMS (ESI-TOF) *m*/*z*: Calculated for $C_{24}H_{22}N_2O_3S$, $[M+H]^+$ 419.1424, Found 418.1351.

N-(6-Methyl-2,3-diphenyl-2,3-dihydro-4H-1,3-oxazin-4-ylidene) benzene sulfonamide (**4o**) (145 mg, 72%), a white solid, m.p. = 153.1–154.7 °C (Rf = 0.30 in 1:3 *v*/*v* ethyl acetate/60–90 petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.6 Hz, 2H), 7.48–7.35 (m, 7H), 7.28–7.17 (m, 4H), 7.13 (d, *J* = 8.4 Hz, 2H), 6.61 (s, 1H), 6.52 (s, 1H), 2.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 157.0, 143.3, 139.8, 135.4, 131.5, 129.8, 128.9 (2C), 128.7 (2C), 128.4 (2C), 127.3, 127.2 (2C), 126.6 (2C), 126.2 (2C), 97.4, 89.7, 20.4; IR ν_{max} (KBr) 3059, 1636, 1501, 1454, 1362, 1308, 1157, 1088 cm^{-1}; HRMS (ESI-TOF) *m*/*z*: Calculated for $C_{23}H_{20}N_2O_3S$, $[M+H]^+$ 405.1268, Found 405.1271.

4-Chloro-*N*-(6-methyl-2,3-diphenyl-2,3-dihydro-4H-1,3-oxazin-4-ylidene) benzene sulfonamide (**4p**) (164 mg, 75%), a white solid, m.p. = 141.9–143.1 °C (Rf = 0.40 in 1:3 *v*/*v* ethyl acetate/60–90 petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.4 Hz, 2H), 7.44–7.41 (m, 2H), 7.39–7.33 (m, 5H), 7.28–7.18 (m, 3H), 7.12 (d, *J* = 8.0 Hz, 2H), 6.57 (s, 1H), 6.52 (s, 1H), 2.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 157.1, 141.9, 139.6, 137.7, 135.1, 129.9, 128.9 (2C), 128.8 (2C), 128.6 (2C), 127.7 (2C), 127.5, 127.3 (2C), 126.6 (2C), 97.3, 89.7, 20.4; IR ν_{max} (KBr) 3098, 3067, 2974, 1543, 1393, 1431, 1084 cm^{-1}; HRMS (ESI-TOF) *m*/*z*: Calculated for $C_{23}H_{19}ClN_2O_3S$, $[M+H]^+$ 439.0878, Found 439.0879.

4-Bromo-*N*-(6-methyl-2,3-diphenyl-2,3-dihydro-4H-1,3-oxazin-4-ylidene) benzene sulfonamide (**4q**) (178 mg, 74%), a white solid, m.p. = 160.6–161.9 °C (Rf = 0.35 in 1:3 *v*/*v* ethyl acetate/60–90 petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.44–7.36 (m, 5H), 7.28–7.18 (m, 3H), 7.11 (d, *J* = 7.6 Hz, 2H), 6.57 (s, 1H). 6.52 (s, 1H), 2.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 157.2, 142.4, 139.6, 135.1, 131.6 (2C), 129.9, 128.9 (2C), 128.8 (2C), 127.9 (2C), 127.5, 127.3 (2C), 126.7 (2C), 126.2, 97.3, 89.7, 20.4; IR ν_{max} (KBr) 3117, 3086, 1639, 1510, 1458, 1393, 1138, 1084 cm^{-1}; HRMS (ESI-TOF) *m*/*z*: Calculated for $C_{23}H_{19}BrN_2O_3S$, $[M+H]^+$ 483.0373, Found 483.0376.

N-(6-Methyl-2,3-diphenyl-2,3-dihydro-4H-1,3-oxazin-4-ylidene)-4-nitro benzenesulfonamide (**4r**) (148 mg, 66%), a white solid, m.p. = 176.3–177.7 °C (Rf = 0.30 in 1:3 *v*/*v* ethyl acetate/60–90 petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.8 Hz, 2H), 7.92 (d, *J* = 8.8 Hz, 2H), 7.45–7.36 (m, 5H), 7.30–7.21 (m, 3H), 7.12 (d, *J* = 7.2 Hz, 2H), 6.54 (d, *J* = 7.2 Hz, 2H), 2.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 157.5, 149.3, 149.0, 139.3, 134.8, 130.1, 129.1 (2C), 128.8 (2C), 127.8, 127.5 (2C), 127.3 (2C), 126.8 (2C), 123.7 (2C), 97.3, 89.8, 20.4; IR ν_{max} (KBr) 3105, 1624, 1435, 1300, 1169, 1142, 1084 cm^{-1}; HRMS (ESI-TOF) *m*/*z*: Calculated for $C_{23}H_{19}N_3O_5S$, $[M+H]^+$ 450.1118, Found 450.1122.

N-(6-Methyl-2,3-diphenyl-2,3-dihydro-4H-1,3-oxazin-4-ylidene)-4-(trifluoromethyl) benzenesulfonamide (**4s**) (120 mg, 51%), a white solid, m.p. = 166.0–166.7 °C (Rf = 0.40 in 1:3 *v*/*v* ethyl acetate/60–90 petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.4 Hz, 2H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.45–7.36 (m, 5H), 7.29–7.21 (m, 3H), 7.13 (d, *J* = 7.6 Hz, 2H), 6.58 (s, 1H), 6.53 (s, 1H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 157.4, 146.7, 139.5, 135.0, 133.2 (q, *J* = 32.6 Hz, 1C), 130.0, 129.0 (2C), 128.8 (2C), 127.7, 127.3 (2C), 126.7 (4C), 125.6 (q, *J* = 3.7 Hz, 2C), 123.5 (q, *J* = 271.1 Hz, 1C), 97.3, 89.8, 20.4; IR ν_{max} (KBr) 3507, 3475, 2924, 1539, 1427, 1141, 1084 cm^{-1}; HRMS (ESI-TOF) *m*/*z*: Calculated for $C_{24}H_{19}F_3N_2O_3S$, $[M+H]^+$ 473.1141, Found 473.1145.

4-Methoxy-*N*-(6-methyl-2,3-diphenyl-2,3-dihydro-4H-1,3-oxazin-4-ylidene)benzenesul fonamide (**4t**) (178 mg, 82%), a white solid, m.p. = 135.5–136.5 °C (Rf = 0.20 in 1:3 *v*/*v* ethyl acetate/60–90 petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.8 Hz, 2H), 7.45–7.42 (m, 2H), 7.38–7.34 (m, 3H), 7.24 (d, *J* = 7.6 Hz, 2H), 7.18 (t, *J* = 7.4 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 6.60 (s, 1H), 6.51 (s, 1H), 3.82 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 162.0, 156.8, 139.9, 135.4, 129.8, 128.8 (2C), 128.8 (3C), 128.2 (2C), 127.3 (2C), 127.2, 126.5 (2C), 113.6 (2C), 97.3, 89.7, 55.5, 20.4; IR ν_{max} (KBr) 3102, 3067, 2947, 1647, 1593, 1498, 1258, 1084 cm^{-1}; HRMS (ESI-TOF) *m*/*z*: Calculated for $C_{24}H_{22}N_2O_4S$, $[M+H]^+$ 435.1373, Found 435.1376.

4-Methyl-*N*-(2,3,6-triphenyl-2,3-dihydro-4H-1,3-oxazin-4-ylidene) benzene sulfonamide (**4u**) (125 mg, 52%), a white solid, m.p. = 135.1–136.6 °C (Rf = 0.20 in 1:4 *v*/*v* ethyl acetate/ 60–90 petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.0 Hz, 4H), 7.54–7.46 (m, 3H), 7.43–7.35 (m, 5H), 7.28 (t, *J* = 7.2 Hz, 3H), 7.22–7.16 (m, 5H), 6.72 (s, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 157.5, 142.1, 140.5, 139.9, 135.1, 132.3, 131.0, 129.8, 129.1 (2C), 128.9 (2C), 128.8 (4C), 127.3, 127.2 (2C), 127.1 (2C), 126.4 (2C), 126.3 (2C), 94.8, 89.9, 21.5; IR ν_{max} (KBr) 3063, 2970, 1610, 1578, 1497, 1296, 1138, 1080 cm^{-1}; HRMS (ESI-TOF) *m*/*z*: Calculated for $C_{29}H_{24}N_2O_3S$, $[M+H]^+$ 481.1581, Found 481.1584.

4-Methyl-*N*-(6-pentyl-2,3-diphenyl-2,3-dihydro-4H-1,3-oxazin-4-ylidene) benzenesul-fonamide (**4v**) (133 mg, 56%), a white solid, m.p. = 159.3–160.9 °C (Rf = 0.42 in 1:3 *v*/*v* ethyl acetate/60–90 petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.0 Hz, 2H), 7.34–7.21 (m, 12H), 7.08 (t, *J* = 7.4 Hz, 1H), 5.70 (d, *J* = 6.0 Hz, 1H), 5.15 (d, *J* = 6.0 Hz, 1H), 2.42 (s, 3H), 2.05–1.97 (m, 1H), 1.27–1.20 (m, 2H), 1.13–1.05 (m, 2H), 0.88–0.80 (m, 2H), 0.75 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.2, 160.7, 143.1, 138.9, 136.7, 132.0, 129.3 (3C), 129.0 (2C), 128.9 (2C), 127.4 (2C), 127.1 (2C), 125.2, 118.6 (2C), 63.8, 61.0, 44.0, 30.7, 22.3, 22.0, 21.6, 13.8; IR ν_{max} (KBr) 2954, 2928, 2866, 1639, 1501, 1458, 1088 cm^{-1}; HRMS (ESI-TOF) *m*/*z*: Calculated for $C_{28}H_{30}N_2O_3S$, $[M+H]^+$ 475.2050, Found 475.2076.

4. Conclusions

In summary, we have developed an operationally simple and effective means for preparing 2,3-dihydro-4*H*-1,3-oxazin-4-ylidenes from a mixture of the corresponding imines, sulfonyl azides, and terminal ynones, through CuAAC/ring cleavage/[4+2] annulation process, base-free, and stirred at room temperatures. This methodology appears quite flexible and offers a capacity to generate forms of the title products that will be particularly useful in, for example, building more 1,3-oxazines block facility.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/catal12050526/s1, Scheme S1: Structures of the starting materials **1a**–**1b**, Scheme S2: Structures of the starting materials **2a–2l**, Scheme S3: Structures of the starting materials **3a**–**3b**, Scheme S4: X-ray Crystallographic Data for Compound **4a**, Figures S1–S44: 1H NMR and 13C NMR spectra of 2,3-dihydro-4*H*-1,3-oxazin-4-ylidenes (**4a**–**4v**).

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