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Synthesis of a 3,4-Dihydro-1,3-oxazin-2-ones Skeleton via an Intermolecular [4 + 2] Process of *N*-Acyliminium Ions with Ynamides/Terminal Alkynes

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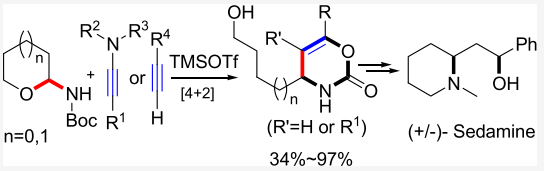
ABSTRACT: An approach to access functionalized 3,4-dihydro-1,3-oxazin-2-ones has been developed by reacting semicyclic *N*,*O*-acetals **5** and **6** with ynamides **7** or terminal alkynes **8** in a one-pot fashion. The reaction went through a formal [4 + 2] cycloaddition process to generate a number of functionalized 3,4-dihydro-1,3-oxazin-2-ones **9a**−**9ak** and **10a**−**10bc** in yields of 34−97%. In addition, the utility of this transformation was demonstrated by the synthesis of (±)-sedamine **13**.



INTRODUCTION

The discovery of an efficient methodology to access privileged azacycles and corresponding benzo heterocycles is one of the most important areas in current organic syntheses[1] due to their existence as unique scaffold in a large number of biologically active compounds and clinic drugs,[2] as well as important auxiliaries[3] and building blocks[4] in organic synthesis. As a prime instance (Figure 1), 1*H*-benzo[d][1,3]oxazin-2(4*H*)-one **1**[5] and 4*H*-benzo[d][1,3]oxazin-4-one **2**,[6] which are pharmacologically interesting molecules and the key framework of Efavirenz (a prescription medicine for the treatment of HIV), have received intensive attention in recent years.[7] Another example is 1,3-oxazinan-2-one **3**,[8] which is also an interesting scaffold within natural products and pharmaceuticals[9] including anti-HIV,[7b,10] antidiabetic,[9b,9c] anti-inflammatory[11] and anticancer,[9a,12] bioactive molecules. Although numerous synthetic approaches have been achieved to access skeleton **3** in past years, there are very few methods to obtain substituted 3,4-dihydro-1,3-oxazin-2-one **4**, which employed acid-catalyzed cyclization of Boc-protected aminals with alkynes.[13]

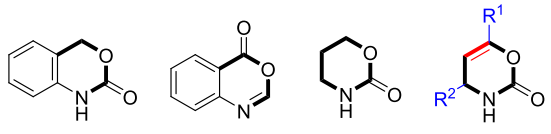


Figure 1. Several structures of privileged azacycles and corresponding benzo heterocycles.

N,*O*-acetals are widely utilized in organic synthesis.[14] In particular, semicyclic *N*,*O*-acetals **5** and **6** have been investigated in recent years. The first example came from Kobayashi's laboratory in which the nucleophilic addition was applied through the coupling with silyl enol ether to form linear 1,5-amino alcohol (**2a**, Figure 2).[15] Recently, we also achieved 1,4- and 1,5-amino alcohols through the reaction with organozinc reagents (**2b**, Figure 2).[16] In the past decade, alkynes and ynamides have undoubtedly gained significant attention in modern organic synthesis.[17,18] Many important acyclic and cyclic compounds including benzofurans,[19]

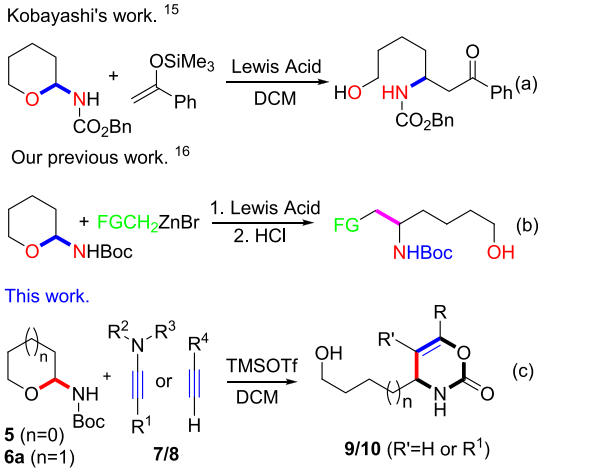


Figure 2. Lewis acid-promoted intermolecular reactions of semicyclic *N*,*O*-acetals.

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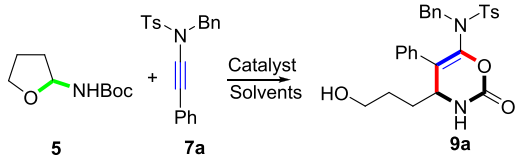
quinolines,[17a,18c] oxazoles,[20] pyridines,[17c,18a] carbolines,[21] enamides,[22] and amidines,[18b23] have been successfully synthesized from alkynes or ynamides. On the basis of our continuous efforts in exploring chemical transformations of semicyclic *N,O*-acetals,[16,24] alkynes,[17e] and ynamides,[18d25] we envisioned that the iminium ions derived from the semicyclic *N,O*-acetals **5** and **6** could undergo a formal [4 + 2] cycloaddition process to give substituted 3,4-dihydro-1,3-oxazin-2-one skeletons **9** and **10**, respectively (**2c**, Figure 2).

RESULTS AND DISCUSSION

Our investigation started with the reaction of semicyclic *N,O*-acetal **5** with ynamide **7a**. The reaction did not afford any desired product in the absent of Lewis acid (Table 1, entry 1).

Table 1. Optimization of Reaction Conditions



5 **7a** **9a**

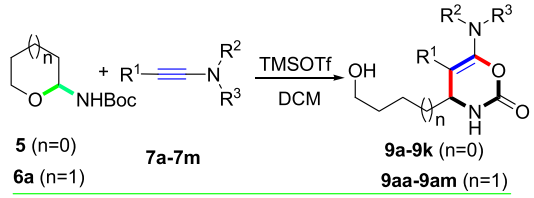
entry[a]	catalyst	solvent	T (°C)	Y (%)[b]
1		DCM	r.t.	NR
2	SIPrAuCl (0.1 equiv)	DCM	r.t.	NR
3	$AgNTf_2$ (0.1 equiv)	DCM	r.t.	NR
4	AgOTf (0.1 equiv)	DCM	r.t.	NR
5	$Zn(OTf)_2$ (0.1 equiv)	DCM	r.t.	NR
6	$Ni(OTf)_2$ (0.1 equiv)	DCM	r.t.	NR
7[c]	$Cu(OTf)_2$ (0.1 equiv)	DCM	r.t.	complex
8	$Sc(OTf)_3$ (0.1 equiv)	DCM	r.t.	NR
9	$ZnCl_2$ (1.0 equiv)	DCM	−78 ~ −45	NR
10	CuI (0.1 equiv)	DCM	r.t.	NR
11	$TiCl_4$ (1.0 equiv)	DCM	−78 ~ −45	35
12	$BF_3{\cdot}Et_2O$ (1.0 equiv)	DCM	−78 ~ −45	8
13	TMSOTf (1.0 equiv)	DCM	−78 ~ −45	94
14	TMSOTf (1.0 equiv)	DCM	r.t.	complex
15	TMSOTf (0.5 equiv)	DCM	−78 ~ −45	46
16	TMSOTf (2.0 equiv)	DCM	−78 ~ −45	83
17	TMSOTf (1.0 equiv)	DCE	−78 ~ −45	27
18	TMSOTf (1.0 equiv)	THF	−78 ~ −45	64
19	TMSOTf (1.0 equiv)	PhMe	−78 ~ −45	45

[a]The reactions were performed with **5** (0.5 mmol), **7a** (0.6 mmol), and catalyst in a dry solvent (2 mL) at specified temperature for 2 h. [b]Isolated yield. [c]When $Cu(OTf)_2$ was used, the amide enol carbamate was obtained in 38%.[18d]

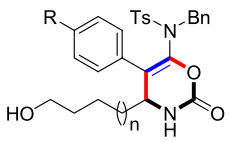
The screening of various Lewis acids, including catalytic amounts of SIPrAuCl, $AgNTf_2$, and $Sc(OTf)_3$, turned out to be fruitless (Table 1, entries 2−10). When $TiCl_4$ was investigated, the desired product **9a** was obtained in 35% yield (Table 1, entry 11). $BF_3{\cdot}Et_2O$ could also afford a small amount of desired product **9a** (8% yield, Table 1, entry 12). Delightfully, stoichiometric TMSOTf could significantly increase the yield of **9a** up to 94% (Table 1, entry 13). It was worth noting that the complex result was obtained when the reaction was treated at room temperature (Table 1, entry 14). However, the use of 0.5 equiv of TMSOTf led to erosion of yield to 46% (Table 1, entry 15). When 2.0 equiv of TMSOTf was applied, the yield of **9a** slightly decreased to 83% (Table 1, entry 16). Different solvents were also examined, and the results are summarized in Table 1 (entries 17−19). Among them, THF led to the moderate yield of **9a** (64%, Table 1, entry 18), while both DCE and PhMe gave much lower yields of **9a**, in 27% and 45%, respectively (Table 1, entries 17 and 19).

Next, we turned to investigate the scope and limitation of such cyclization of semicyclic *N,O*-acetal (**5** or **6a**) with ynamides **7a**−**7m** (Scheme 1). TsNBn-type ynamides with

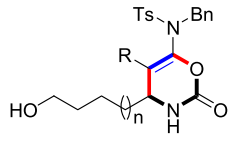
Scheme 1. Reactions of Semicyclic *N,O*-Acetals 5/6a with Ynamides 7a−7m[a,b]



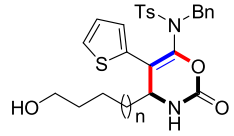
5 (n=0) **6a** (n=1) **7a-7m** **9a-9k** (n=0) **9aa-9am** (n=1)



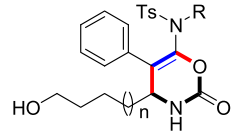
9a, R=H, n = 0, 94%
9b, R=Me, n = 0, 89%
9c, R=F, n = 0, 82%
9d, R=*n*-C_4H_9, n = 0, 87%
9aa, R=H, n = 1, 94%
9ab, R=Me, n = 1, 95%
9ac, R=F,n = 1, 87%
9ad, R=*n*-C_4H_9, n = 1, 93%
9al, R=OMe, n = 1, 86%



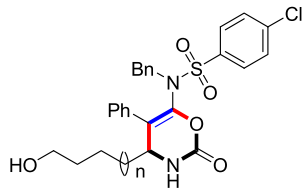
9e, R=*n*-C_5H_{11}, n = 0, 90%
9ae, R=*n*-C_5H_{11}, n = 1, 96%
9am, R=Cyclopropyl, n=1, 63%



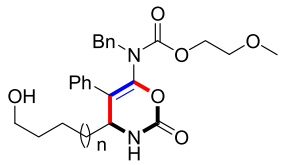
9f, n = 0, 45%
9af, n = 1, 53%



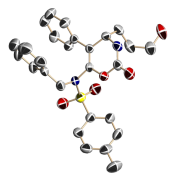
9g, R=Ph, n = 0, 67%
9ag, R=Ph, n = 1, 57%
9h, R=Me, n = 0, 85%
9ah, R=Me, n = 1, 91%
9i, R=*n*-C_4H_9, n = 0, 92%
9ai, R=*n*-C_4H_9, n = 1, 97%



9j, n = 0, 61%
9aj, n = 1, 51%



9k, n = 0, 58%
9ak, n = 1, 70%



9a

[a]The reactions were performed with *N,O*-acetal **5**/**6a** (0.5 mmol), ynamide **7** (0.6 mmol), and TMSOTf (0.5 mmol) in dry DCM (2 mL) at −78 to −45 °C for 2 h. [b]Isolated yield.

different *para*-substituted (methyl, methoxyl, *n*-butyl, and fluoro) aryls were surveyed under the optimized condition, as summarized in Scheme 1. In general, all these substituted aryl TsNBn ynamides (**7b**−**7d**, **7l**) could smoothly react with semicyclic *N,O*-acetals **5** and **6a**, affording the desired products in excellent yields. Aliphatic alkyl-substituted TsNBn ynamides were also suitable substrates for this cyclization reaction. When cyclopropyl-substituted TsNBn ynamide **7m** and semicyclic *N,O*-acetal **6a** were treated under the optimized condition, the desired product **9am** was obtained in 63% yield. *n*-Pentyl-

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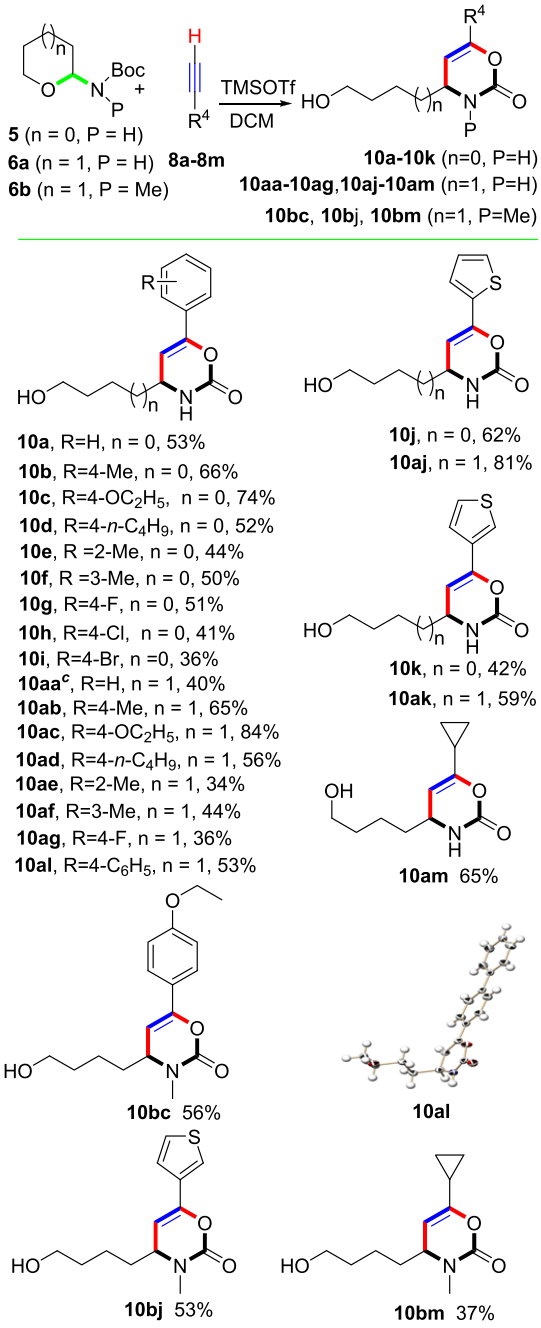
substituted TsNBn ynamide **7e** could also react with **5** and **6a**, affording the corresponding cyclization products **9e** and **9ae** in excellent yields. Heteroaryl-substituted TsNBn ynamide **7f** (with 2-thienyl) was also investigated, the desired products **9f** and **9af** were produced in moderate yields. When a Bn group in ynamides was replaced with different aryl and alkyl groups, the corresponding derivatives **7g**−**7i** were also proved to be appropriate substrates for this cyclization, affording the desired **products 9g**−**9i** and **9ag**−**9ai** in excellent yields. In addition, the replacement of the Ts group in ynamides with *p*-chlorobenzenesulfonyl and carbamate also gave positive results under the optimized condition, and the desired products **9j**, **9k**, **9aj**, and **9ak** were obtained from **7j** and **7k** in moderate yields. The chemical structures of **9a**−**9k** and **9aa**−**9am** were unambiguously confirmed based on the X-ray crystallographic analysis of compound **9a** (see the Supporting Information).

The above cyclization of semicyclic *N*,*O*-acetals (**5** and **6a**) with ynamides **7a**−**7m** could smoothly produce the 3,4-dihydro-1,3-oxazin-2-one skeleton, with different 6-amino substitutions. Next, we turn our attention to investigate the reaction of semicyclic *N*,*O*-acetal **5** or **6** with terminal alkynes, aiming at constructing the 3,4-dihydro-1,3-oxazin-2-one skeleton with different 6-alkyl or 6-aryl substitutions. First, various Lewis acids were investigated for the reaction of **6a** and **8c**, and the reactivity of terminal alkynes was shown to be much lower than that of ynamides (see the Supporting Information). In addition, TMSOTf still proved to be an excellent Lewis acid for this cyclization process. Then, a variety of terminal alkynes (**8a**−**8m**) with different substituted aryl groups were screened under the optimized condition, as summarized in Scheme 2. In general, the *para*-, *meta*-, and *ortho*-substituted phenylacetylenes **8b**-**8f** could react with five- and six-membered semicyclic *N*,*O*-acetals **5** and **6a**, giving the desired [4 + 2] cycloaddition products **10b**−**10f** and **10ab**−**10af** in moderate yields (34%−84%). Halogen-substituted phenylacetylenes (**8g**−**8i**) could also provide comparable yields (36%−51%). 2- and 3-Thienylacetylenes **8j** and **8k** were also suitable substrates for this reaction, affording the corresponding products in moderate yields (42%−81%). To our delight, when ethynylcyclopropane **8m** was examined, the desired **product 10am** was obtained in 65% yield. *N*-Methyl semicyclic *N*,*O*-acetal **6b** was also investigated, and the desired products **10bc**, **10bj**, and **10bm** were accordingly produced in moderate yields (37%−56%). The structures of **10a**−**10k**, **10aa**−**10ag**, **10aj**−**10am**, **10bc**, **10bj**, and **10bm** were unambiguously confirmed based on the X-ray crystallographic analysis of compound **10al** (see the Supporting Information).

A proposed mechanism for the TMSOTf-mediated [4 + 2] process was illustrated in Figure 3. First, TMSOTf activates semicyclic *N*,*O*-acetal **5** or **6** to form a diene-type *N*-acyliminium ion **int-2** through the ring-opening of intermediate **int-1**. Then, the [4 + 2] cycloaddition with the triple bond in ynamides **7** or terminal alkynes **8** would take place regioselectively from the less steric side of **int-2** to give a six-membered intermediate **int-3** via the transition state **TS-1**, which undergoes the cleavage of the *t*-butyl group to afford the desired product **9** or **10**, along with the generation of 2-methylprop-1-ene.

Finally, we focused on the utility of this intermolecular [4 + 2] process of *N*-acyliminium ions with ynamides/alkynes in the synthesis of biologically active molecules. Scheme 3 shows a facile synthesis of sedamine **13**, which was isolated from Sedum species[26] and attracted great interest in synthetic

Scheme 2. Reactions of Semicyclic *N*,*O*-Acetals 5/6 with Substituted Acetylenes 8a−8m[a,b]



[a]The reactions were performed with *N*,*O*-acetal **5**/**6** (0.5 mmol), terminal alkynes (1.0 mmol), and TMSOTf (0.5 mmol) in dry DCM (2 mL) at −78 to −45 °C for 6 h. [b]Isolated yield. [c]**10aa** (1.04 g, 42% yield) was obtained with **6a** (10 mmol), **8a** (20 mmol), and TMSOTf (10 mmol) in dry DCM (40 mL) at −78 to −45 °C for 6 h.

chemistry.[27] Dess−Martin oxidation (DMP) of alcohol **10aa** and subsequent reductive amination (Et_3SiH/TMSOTf) gave bicyclic lactone **11** in 75% overall yield. Hydrolysis (KOH) of **11** following protection of the secondary amine (Boc_2O/TEA) afforded *N*-Boc ketone **12a** in 78% overall yield. After the ketone reduction ($Li(^tBuO)_3AlH$) of **12a**, the crude secondary alcohol, without further purification, was treated with lithium aluminum hydride ($LiAlH_4$) to give (+/−)-sedamine (**13**) in 93% overall yield. The spectroscopic and physical data of the

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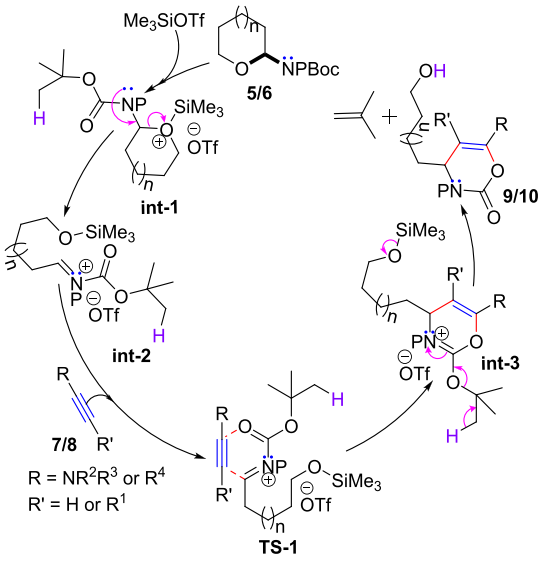
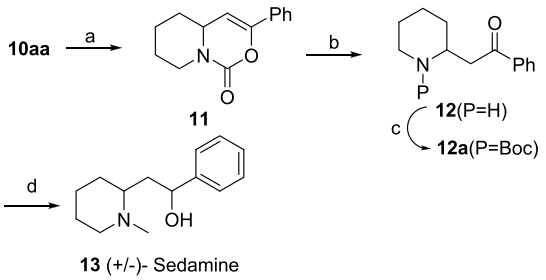


Figure 3. Proposed mechanism for the TMSOTf-catalyzed [4 + 2] process (P═H or Me).

Scheme 3. Synthesis of (+/−)-Sedamine 13[a]



[a]Reagents and conditions: (a) (1) DMP, DCM, r.t., 3 h; (2) Et_3SiH/TMSOTf, ACN, 0 °C to r.t., 40 min, 75% (2 steps); (b) *t*-BuOH/toluene (v/v = 1/1), KOH, 85 °C, 30 min, 85%; (c) Boc_2O/TEA, H_2O, r.t., 6 h, 92%; (d) (1) $Li(^tBuO)_3AlH$, THF, reflux, 4 h; (2) $LiAlH_4$, reflux, 4 h, 93% (2 steps).

synthetic (+/−)-sedamine (**13**) were identical to the reported data.[27c]

CONCLUSIONS

In summary, we established a novel and efficient approach for the synthesis of functionalized 3,4-dihydro-1,3-oxazin-2-ones **9a**−**9am** and **10a**−**10bm**. This TMSOTf-mediated one-pot process underwent a [4 + 2] cycloaddition from semicyclic *N,O*-acetals (**5** and **6**) with ynamides **7** or terminal alkynes **8**. In addition, the utility of this methodology was demonstrated by the facile synthesis of natural product (+/−)-sedamine **13**.

EXPERIMENTAL SECTION

General Considerations. THF was distilled from sodium/benzophenone, and DCM was distilled from phosphorus pentoxide. Reactions were monitored by thin-layer chromatography (TLC) on glass plates coated with silica gel with a fluorescent indicator. Flash chromatography was performed on silica gel (300−400) with petroleum/EtOAc or EtOAc/MeOH as the eluent. HRMS was measured on an LTQ-Orbitrap-XL apparatus. IR spectra were recorded using a film on a Fourier transform infrared spectrometer. NMR spectra were recorded at 400 or 600 MHz, and chemical shifts are reported in δ (ppm) referenced to an internal TMS standard for ^1H NMR and $CDCl_3$ (77.16 ppm) for $^{13}C\{^1H\}$ NMR. The heat source was an oil bath.

General Procedure for the Synthesis of 7.[28] To a mixture of an amide (2 mmol), K_3PO_4 (4 mmol), $CuSO_4{\cdot}5H_2O$ (0.2 mmol), and 1,10-phenanthroline (0.4 mmol) in toluene under an N_2 atmosphere was added a solution 1-bromoalkyne (2.2 mmol) in toluene. The reaction was stirred at 75 °C for 24 h under an N_2 atmosphere. The reaction mixture was cooled to room temperature, diluted with EtOAc, and filtered through Celite, and the filtrate was concentrated in vacuo. The crude products were purified by flash chromatography on silica gel to afford the desired ynamide **7**. Data for new compounds of ynamides as following:

2-Methoxyethyl Benzyl(phenylethynyl)carbamate (7k). Colorless oil (421 mg, 68%); purified by flash chromatography on silica gel (PE/EtOAc = 20:1); IR (film): ν_{max} 2888, 2241, 1727, 1598, 1400, 1294, 1114, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44−7.40 (m, 2H), 7.39−7.32 (m, 3H), 7.32−7.26 (m, 3H), 7.25−7.22 (m, 2H), 4.72 (s, 2H), 4.38−4.35 (m, 2H), 3.68−3.63 (m, 2H), 3.40 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 155.2, 136.0, 131.1, 128.7, 128.3, 128.2, 127.6, 123.4, 70.5, 66.6, 59.3, 54.1 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{20}NO_3^+$, 310.1438, found 310.1441.

General Procedure for the Syntheses of 9 and 10. To a solution of **5** or **6** (0.5 mmol) and **7** (0.6 mmol) or **8** (1.0 mmol) in dry DCM (2 mL) was added dropwise TMSOTf (91 μL, 0.5 mmol) at −78 °C. The reaction was allowed to warm to −45 °C slowly and stirred 2 h for compound **9** or 6 h for compound **10** at −45 °C. Saturated aqueous $NaHCO_3$ (2 mL) was added to quench the reaction. The mixture was extracted with DCM (5 mL × 3), and the combined organic layers were washed with brine. The organic phase was dried over anhydrous $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel to obtain **9** or **10**.

***N*-Benzyl-*N*-(4-(3-hydroxypropyl)-2-oxo-5-phenyl-3,4-dihydro-2*H*-1,3-oxazin-6-yl)-4-methylbenzenesulfonamide (9a).** White solid (232 mg, 94%); mp 149−151 °C; purified by flash chromatography on silica gel (PE/EtOAc = 1:2); IR (film): ν_{max} 3280, 2929, 1741, 1447, 1351, 1161, 914, 812 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78−7.70 (m, 2H), 7.33−7.27 (m, 3H), 7.25−7.20 (m, 3H), 7.17−7.10 (m, 2H), 6.97−6.84 (m, 4H), 6.70 (brs, 1H), 4.22−4.16 (m, 2H), 4.10−3.98 (m, 1H), 3.62−3.51 (m, 2H), 2.43 (s, 3H), 2.07 (brs, 1H), 1.62−1.43 (m, 4H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 151.6, 144.5, 137.1, 135.5, 133.7, 132.9, 129.8 (2C), 129.7, 128.8 (2C), 128.6 (2C), 128.4 (2C), 128.3 (2C), 128.2, 128.1 (2C), 119.0, 62.3, 55.3, 51.6, 32.0, 26.8, 21.8 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{27}H_{29}N_2O_5S^+$, 493.1792, found 493.1791.

***N*-Benzyl-*N*-(4-(3-hydroxypropyl)-2-oxo-5-(*p*-tolyl)-3,4-dihydro-2*H*-1,3-oxazin-6-yl)-4-methylbenzenesulfonamide (9b).** White solid (225 mg, 89%); mp 150−152 °C; purified by flash chromatography on silica gel (PE/EtOAc = 1:2); IR (film): ν_{max} 3261, 2918, 1739, 1594, 1400, 1341, 1137, 814 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.83−7.69 (m, 2H), 7.33−7.30 (m, 2H), 7.25−7.20 (m, 1H), 7.18−7.09 (m, 2H), 7.07−7.04 (m, 2H), 6.98−6.78 (m, 4H), 6.57 (brs, 1H), 4.23−4.15 (m, 2H), 4.14−4.01 (m, 1H), 3.62−3.52 (m, 2H), 2.44 (s, 3H), 2.35 (s, 3H), 2.07 (brs, 1H), 1.66−1.41 (m, 4H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 151.4, 144.4, 137.9, 137.1, 135.7, 133.8, 129.9, 129.8 (2C), 129.7, 129.0 (2C), 128.7 (4C), 128.4 (2C), 128.2 (2C), 118.8, 62.5, 55.4, 51.7, 32.2, 26.9, 21.8 21.4 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{28}H_{31}N_2O_5S^+$, 507.1948, found 507.1947.

***N*-Benzyl-*N*-(5-(4-fluorophenyl)-4-(3-hydroxypropyl)-2-oxo-3,4-dihydro-2*H*-1,3-oxazin-6-yl)-4-methylbenzenesulfonamide (9c).** White solid (209 mg, 82%); mp 149−150 °C; purified by flash chromatography on silica gel (PE/EtOAc = 1:2); IR (film): ν_{max} 3261, 2931, 2359, 1730, 1508, 1353, 1163, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.83−7.71 (m, 2H), 7.35−7.32 (m, 2H), 7.26−7.21 (m, 1H), 7.19−7.11 (m, 2H), 6.95−6.83 (m, 6H), 6.73 (brs, 1H), 4.27−4.21 (m, 1H), 4.20−3.87 (m, 2H), 3.64−3.54 (m, 2H), 2.44 (s, 3H), 2.24 (brs, 1H), 1.68−1.42 (m, 4H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.5 (d, $^1J_{C-F}$ = 246.3 Hz), 151.3, 144.7, 137.3,

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135.4, 133.7, 130.7 (d, $^3J_{C-F}$ = 8.0 Hz), 129.9, 129.8, 128.8, 128.7, 128.5, 128.3, 118.4, 115.3 (d, $^2J_{C-F}$ = 21.3 Hz), 62.4, 55.4, 51.6, 32.2, 26.8, 21.8 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −113.6 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{27}H_{28}FN_2O_5S^+$, 511.1698, found 511.1697.

***N*-Benzyl-*N*-(5-(4-butylphenyl)-4-(3-hydroxypropyl)-2-oxo-3,4-dihydro-2*H*-1,3-oxazin-6-yl)-4-methylbenzenesulfonamide (9d).** White solid (239 mg, 87%); mp 151−153 °C; purified by flash chromatography on silica gel (PE/EtOAc = 1:2); IR (film): ν_{max} 3261, 2924, 1735, 1455, 1341, 1140, 812, 680 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82−7.69 (m, 2H), 7.33−7.30 (m, 2H), 7.23−7.19 (m, 1H), 7.16−7.08 (m, 2H), 7.06−7.04 (m, 2H), 6.93−6.80 (m, 4H), 6.58 (brs, 1H), 4.25−4.19 (m, 1H), 4.19−4.05 (m, 2H), 3.63−3.53 (m, 2H), 2.62−2.59 (m, 2H), 2.44 (s, 3H), 2.07 (brs, 1H), 1.67−1.57 (m, 5H), 1.44−1.35 (m, 3H), 0.99−0.95 (m, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 151.5, 144.4, 142.9, 137.0, 135.6, 133.8, 130.0, 129.8 (2C), 129.7, 128.7 (2C), 128.6 (2C), 128.4 (2C), 128.3 (2C), 128.1 (2C), 118.9, 62.5, 55.4, 51.7, 35.5, 33.7, 32.2, 26.9, 22.6, 21.8, 14.1 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{31}H_{37}N_2O_5S^+$, 549.2418, found 549.2415.

***N*-Benzyl-*N*-(4-(3-hydroxypropyl)-2-oxo-5-pentyl-3,4-dihydro-2*H*-1,3-oxazin-6-yl)-4-methylbenzenesulfonamide (9e).** White solid (219 mg, 90%); mp 121−123 °C; purified by flash chromatography on silica gel (PE/EtOAc = 1:2); IR (film): ν_{max} 3280, 2929, 1737, 1598, 1453, 1353, 1163, 816 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$,rotamers) δ 7.82−7.77 (m, 2H), 7.37−7.34 (m, 2H), 7.31−7.28 (m, 5H), 6.50 (brs, 1H), 4.72−4.64 (m, 1H), 4.03−3.93 (m, 1H), 3.93−3.83 (m, 1H), 3.72−3.65 (m, 1.45H), 3.49−3.39 (m, 0.55H), 2.44 (s, 3H), 2.34−2.22 (m, 2H), 1.93−1.86 (m, 1H), 1.89−1.67 (m, 4H), 1.85−1.79 (m, 0.55H), 1.78−1.70 (m, 1.45H), 1.68−1.62 (m, 1H), 1.43−1.21 (m, 3H), 1.14−0.98 (m, 2H), 0.94−0.88 (m, 2H), 0.83−0.77 (m, 2.55H), 0.20−0.08 (m, 0.45H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, rotamers) δ 151.7, 144.5, 135.8, 135.6, 135.4, 135.3, 134.6, 134.3, 130.0, 129.8, 128.7, 128.5, 128.4, 128.0, 118.8, 118.6, 62.5, 62.2, 51.9, 51.7, 50.7, 32.1, 31.8 31.7, 31.0, 27.7, 27.5, 26.8, 26.5, 26.3, 22.6, 21.8, 14.1 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{26}H_{35}N_2O_5S^+$, 487.2261, found 487.2268.

***N*-Benzyl-*N*-(4-(3-hydroxypropyl)-2-oxo-5-(thiophen-2-yl)-3,4-dihydro-2*H*-1,3-oxazin-6-yl)-4-methylbenzenesulfonamide (9f).** Pale yellow solid (112 mg, 45%); mp 133−135 °C; purified by flash chromatography on silica gel (PE/EtOAc = 1:2); IR (film): ν_{max} 3180, 2947, 2359, 1741, 1351, 1161, 1051, 814 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87−7.84 (m, 2H), 7.39−7.37 (m, 2H), 7.32−7.30 (m, 1H), 7.17−7.15 (m, 1H), 7.13−7.07 (m, 5H), 6.98−6.96 (m, 1H), 6.27 (brs, 1H), 4.62−3.87 (m, 3H), 3.65−3.57 (m, 2H), 2.47 (s, 3H), 1.78 (brs, 1H), 1.63−1.40 (m, 4H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 150.9, 144.8, 136.8, 135.1, 134.2, 133.0, 130.1, 129.9 (2C), 128.8 (2C), 128.4 (2C), 128.3 (2C), 126.9, 126.8 (2C), 114.6, 62.5, 54.3, 52.1, 33.2, 27.2, 21.8 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{25}H_{27}N_2O_5S_2^+$, 499.1356, found 499.1354.

***N*-(4-(3-Hydroxypropyl)-2-oxo-5-phenyl-3,4-dihydro-2*H*-1,3-oxazin-6-yl)-4-methyl-*N*-phenylbenzenesulfonamide (9g).** White solid (160 mg, 67%); mp 124−126 °C; purified by flash chromatography on silica gel (PE/EtOAc = 1:2); IR (film): ν_{max} 3355, 3153, 2941, 1731, 1492, 1357, 1133, 771 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.31 (brs, 1H), 7.48−7.43 (m, 2H), 7.42−7.36 (m, 3H), 7.36−7.29 (m, 4H), 7.24−7.18 (m, 3H), 6.83−6.68 (m, 2H), 4.44 (brs, 1H), 4.35−4.29 (m, 1H), 3.33−3.29 (m, 2H), 2.36 (s, 3H), 1.57−1.28 (m, 4H) ppm; ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 149.7, 144.4, 139.1, 138.4, 134.9, 133.0, 129.5 (2C), 129.2 (2C), 128.4 (4C), 128.2, 128.1 (3C), 126.0 (2C), 117.1, 60.4, 53.7, 31.2, 26.5, 21.0 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{26}H_{27}N_2O_5S^+$, 479.1635, found 479.1639.

***N*-(4-(3-Hydroxypropyl)-2-oxo-5-phenyl-3,4-dihydro-2*H*-1,3-oxazin-6-yl)-*N*,4-dimethylbenzenesulfonamide (9h).** White solid (177 mg, 85%); mp 137−139 °C; purified by flash chromatography on silica gel (PE/EtOAc = 1:2); IR (film): ν_{max} 3376, 2931, 1739, 1598, 1443, 1345, 1133, 765 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 (brs, 1H), 7.53−7.48 (m, 2H), 7.43−7.39 (m, 4H), 7.38−7.35 (m, 2H), 7.35−7.33 (m, 1H), 4.45 (t, *J* = 5.0 Hz, 1H), 4.33 (brs, 1H), 3.34−3.29 (m, 2H), 2.77 (s, 3H), 2.39 (s, 3H), 1.61−1.47 (m, 2H), 1.46−1.27 (m, 2H) ppm; ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 149.8, 144.0, 139.4, 134.7, 133.6, 129.6 (2C), 128.4 (2C), 128.3 (2C), 127.9, 127.7 (2C), 115.9, 60.4, 53.6, 35.7, 31.2, 26.4, 21.0 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{25}N_2O_5S^+$, 417.1479, found 417.1483.

***N*-Butyl-*N*-(4-(3-hydroxypropyl)-2-oxo-5-phenyl-3,4-dihydro-2*H*-1,3-oxazin-6-yl)-4-methylbenzenesulfonamide (9i).** White solid (211 mg, 92%); mp 135−137 °C; purified by flash chromatography on silica gel (PE/EtOAc = 1:2); IR (film): ν_{max} 3253, 2922, 1722, 1596, 1445, 1353, 1165, 767 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80−7.73 (m, 2H), 7.53−7.49 (m, 2H), 7.43−7.35 (m, 3H), 7.32−7.29 (m, 2H), 6.57 (brs, 1H), 4.45−4.41 (m, 1H), 3.72−3.61 (m, 2H), 2.97−2.92 (m, 2H), 2.42 (s, 3H), 2.02 (brs, 1H), 1.80−1.69 (m, 4H), 1.24−1.13 (m, 2H), 1.01−0.81 (m, 2H), 0.69−0.62 (m, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 151.3, 144.2, 138.0, 135.8, 133.3, 129.7 (2C), 128.9 (2C), 128.7 (2C), 128.6 (2C), 128.5, 118.4, 62.6, 55.6, 48.1, 32.7, 29.7, 27.1, 21.7, 19.9, 13.7 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{24}H_{31}N_2O_5S^+$, 459.1948, found 459.1953.

***N*-Benzyl-4-chloro-*N*-(4-(3-hydroxypropyl)-2-oxo-5-phenyl-3,4-dihydro-2*H*-1,3-oxazin-6-yl)benzenesulfonamide (9j).** White solid (156 mg, 61%); mp 135−137 °C; purified by flash chromatography on silica gel (PE/EtOAc = 1:2); IR (film): ν_{max} 3382, 1739, 1584, 1402, 1357, 1161, 1047, 751 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84−7.75 (m, 2H), 7.51−7.47 (m, 2H), 7.33−7.27 (m, 2H), 7.25−7.22 (m, 2H), 7.19−7.11 (m, 2H), 6.98−6.84 (m, 4H), 6.46 (brs, 1H), 4.25−4.17 (m, 2H), 4.13−3.97 (m, 1H), 3.65−3.55 (m, 2H), 1.90 (brs, 1H), 1.62−1.49 (m, 4H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 151.0, 140.2, 137.1, 137.0, 133.4, 132.7, 130.1 (2C), 129.7, 129.5 (2C), 128.8 (2C), 128.6 (2C), 128.44 (2C), 128.39, 128.3 (2C), 119.1, 62.5, 55.4, 52.0, 32.3, 26.9 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{26}H_{26}ClN_2O_5S^+$, 513.1246, found 513.1246.

2-Methoxyethylbenzyl(4-(3-hydroxypropyl)-2-oxo-5-phenyl-3,4-dihydro-2*H*-1,3-oxazin-6-yl)carbamate (9k). Colorless oil (128 mg, 58%); purified by flash chromatography on silica gel (PE/EtOAc = 1:2); IR (film): ν_{max} 3294, 2947, 1733, 1600, 1445, 1384, 1131, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$,rotamers) δ 7.34−7.28 (m, 1H), 7.26−7.24 (m, 2H), 7.19−7.11 (m, 3H), 7.09−7.07 (m, 0.64H), 7.06−6.90 (m, 4H), 6.80−6.75 (m, 0.36H), 4.58−4.51 (m, 1H), 4.43−4.40 (m, 0.36H), 4.40−4.35 (m, 0.64H), 4.30−4.27 (m, 1H), 4.27−4.23 (m, 1.36H), 4.22−4.19 (m, 0.64H), 3.78−3.64 (m, 1.64H), 3.55−3.50 (m, 2H), 3.44−3.41 (m, 2H), 3.37−3.35 (s, 0.36H), 3.32−3.29 (m, 0.36H), 3.10−2.95 (m, 0.64H), 2.18 (brs, 1H), 1.80−1.62 (m, 2H), 1.57−1.51 (m, 1H), 1.47−1.40 (m, 1H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, rotamers) δ 155.5, 152.2, 139.5, 139.3, 135.4, 133.4, 133.1, 129.7, 128.8, 128.6, 128.3, 128.2, 128.0, 127.7, 113.7, 70.8, 70.6, 65.4, 65.0, 62.4, 59.0, 58.6 54.7, 51.6, 51.2, 32.1, 31.3, 26.9, 26.5 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{24}H_{29}N_2O_6^+$, 441.2020, found 441.2024.

***N*-Benzyl-*N*-(4-(4-hydroxybutyl)-2-oxo-5-phenyl-3,4-dihydro-2*H*-1,3-oxazin-6-yl)-4-methylbenzenesulfonamide (9aa).** White solid (238 mg, 94%); mp 152−154 °C; purified by flash chromatography on silica gel (PE/EtOAc = 1:2); IR (film): ν_{max} 3257, 2943, 1737, 1496, 1349, 1163, 818, 759 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6, rotamers) δ 8.10 (brs, 1H), 7.67−7.61 (m, 2H), 7.41−7.38 (m, 2H), 7.31−7.27 (m, 2H), 7.25−7.23 (m, 2H), 7.22−7.18 (m, 2H), 6.91−6.82 (m, 4H), 4.33 (t, *J* = 5.0 Hz, 1H), 4.22−4.15 (m, 2H), 4.14−4.07 (m, 1H), 4.06 (brs, 1H), 2.42 (s, 3H), 1.40−1.24 (m, 6H) ppm; ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6, rotamers) δ 149.74, 149.69, 144.1, 136.8, 135.3, 133.8, 133.2, 129.7, 129.2, 128.3, 128.2, 128.0, 127.9, 127.6, 117.8, 60.5, 60.4, 54.1, 54.0, 51.0, 34.0, 32.2, 32.1, 21.0, 19.2 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{28}H_{31}N_2O_5S^+$, 507.1948, found 507.1948.

***N*-Benzyl-*N*-(4-(4-hydroxybutyl)-2-oxo-5-(*p*-tolyl)-3,4-dihydro-2*H*-1,3-oxazin-6-yl)-4-methylbenzenesulfonamide (9ab).** White solid (247 mg, 95%); mp 121−123 °C; purified by flash

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chromatography on silica gel (PE/EtOAc = 1:2); IR (film): ν_{max} 3271, 2924, 1737, 1355, 1161, 1047, 818, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84−7.65 (m, 2H), 7.32−7.29 (m, 2H), 7.25−7.20 (m, 1H), 7.18−7.10 (m, 2H), 7.07−7.04 (m, 2H), 6.94−6.75 (m, 5H), 4.21−4.16 (m, 1H), 4.15−3.97 (m, 2H), 3.59−3.55 (m, 2H), 2.43 (s, 3H), 2.35 (s, 3H), 2.12 (brs, 1H), 1.49−1.38 (m, 6H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 151.9, 144.4, 137.9, 137.0, 135.6, 133.8, 129.9, 129.8 (2C), 129.7, 129.0 (2C), 128.6 (4C), 128.4 (2C), 128.2 (2C), 118.8, 62.3, 55.4, 51.7, 34.4, 32.0, 21.7, 21.3, 19.7 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{29}H_{33}N_2O_5S^+$, 521.2105, found 521.2106.

***N*-Benzyl-*N*-(5-(4-fluorophenyl)-4-(4-hydroxybutyl)-2-oxo-3,4-dihydro-2*H*-1,3-oxazin-6-yl)-4-methylbenzenesulfonamide (9ac).** White solid (228 mg, 87%); mp 147−149 °C; purified by flash chromatography on silica gel (PE/EtOAc = 1:2); IR (film): ν_{max} 3259, 2934, 1729, 1600, 1508, 1355, 1163, 841 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84−7.71 (m, 2H), 7.37−7.33 (m, 2H), 7.26−7.21 (m, 1H), 7.20−7.11 (m, 2H), 6.97−6.81 (m, 6H), 6.38 (brs, 1H), 4.31−4.22 (m, 1H), 4.22−3.77 (m, 2H), 3.63−3.58 (m, 2H), 2.45 (s, 3H), 2.02 (brs, 1H), 1.51−1.38 (m, 6H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.5 (d, $^1J_{C-F}$ = 246.3 Hz), 151.3, 144.7, 137.4, 135.4, 133.7, 130.7 (d, $^3J_{C-F}$ = 8.0 Hz), 129.9, 129.8, 128.8, 128.7, 128.5, 128.3, 118.3, 115.3 (d, $^2J_{C-F}$ = 21.4 Hz), 62.4, 55.5, 51.6, 34.5, 32.0, 21.8, 19.7 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −113.5 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{28}H_{30}FN_2O_5S^+$, 525.1854, found 525.1853.

***N*-Benzyl-*N*-(5-(4-butylphenyl)-4-(4-hydroxybutyl)-2-oxo-3,4-dihydro-2*H*-1,3-oxazin-6-yl)-4-methylbenzenesulfonamide (9ad).** White solid (262 mg, 93%); mp 137−139 °C; purified by flash chromatography on silica gel (PE/EtOAc = 1:2); IR (film): ν_{max} 3392, 2931, 1731, 1594, 1351, 1163, 1084, 818 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.83−7.67 (m, 2H), 7.33−7.30 (m, 2H), 7.23−7.19 (m, 1H), 7.16−7.09 (m, 2H), 7.06−7.04 (m, 2H), 6.93−6.80 (m, 4H), 6.45 (brs, 1H), 4.23−4.19 (m, 1H), 4.13−3.98 (m, 2H), 3.60−3.57 (m, 2H), 2.63−2.59 (m, 2H), 2.44 (s, 3H), 1.94 (brs, 1H), 1.66−1.58 (m, 3H), 1.45−1.36 (m, 7H), 0.99−0.95 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 151.7, 144.4, 142.9, 137.0, 135.6, 133.8, 130.0, 129.8 (2C), 129.6, 128.7 (2C), 128.6 (2C), 128.4 (2C), 128.3 (2C), 128.2 (2C), 118.8, 62.4, 55.5, 51.7, 35.5, 34.6, 33.7, 32.0, 22.6, 21.8, 19.7, 14.1 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{32}H_{39}N_2O_5S^+$, 563.2574, found 563.2579.

***N*-Benzyl-*N*-(4-(4-hydroxybutyl)-2-oxo-5-pentyl-3,4-dihydro-2*H*-1,3-oxazin-6-yl)-4-methylbenzenesulfonamide (9ae).** White solid (240 mg, 96%); mp 105−107 °C; purified by flash chromatography on silica gel (PE/EtOAc = 1:2); IR (film): ν_{max} 3282, 2927, 1737, 1596, 1457, 1351, 1165, 814 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.81−7.77 (m, 2H), 7.37−7.34 (m, 2H), 7.31−7.28 (m, 5H), 6.09 (brs, 1H), 4.70−4.66 (m, 1H), 4.01−3.88 (m, 1.45H), 3.80−3.78 (m, 0.55H), 3.68−3.65 (m, 1.45H), 3.56−3.49 (m, 0.55H), 2.44 (s, 3H), 2.30−2.23 (m, 1H), 1.89 (brs, 1H), 1.86−1.77 (m, 1.45H), 1.57−1.52 (m, 1H), 1.50−1.46 (m, 0.55H), 1.43−1.35 (m, 1.45H), 1.32−1.22 (m, 2H), 1.15−1.07 (m, 2.45H), 1.03−0.98 (m, 0.55H), 0.95−0.87 (m, 3H), 0.83−0.78 (m, 3H), 0.20−0.08 (m, 0.55H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, rotamers) δ 151.8, 144.4, 135.8, 135.3, 134.6, 130.0, 129.8, 128.7, 128.5, 128.4, 128.3, 128.0, 118.7, 62.5, 62.3, 52.1, 51.8, 51.7, 50.7, 34.6, 32.2, 32.1, 31.7, 29.8, 27.8, 27.5, 26.5, 26.4, 22.6, 21.8, 19.8, 19.5, 14.1 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{27}H_{37}N_2O_5S^+$, 501.2418, found 501.2419.

***N*-Benzyl-*N*-(4-(4-hydroxybutyl)-2-oxo-5-(thiophen-2-yl)-3,4-dihydro-2*H*-1,3-oxazin-6-yl)-4-methylbenzenesulfonamide (9af).** Pale yellow solid (136 mg, 53%); mp 93−95 °C; purified by flash chromatography on silica gel (PE/EtOAc = 1:2); IR (film): ν_{max} 3347, 2937, 1743, 1592, 1351, 1161, 910, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87−7.83 (m, 2H), 7.39−7.34 (m, 2H), 7.31−7.29 (m, 1H), 7.18−7.03 (m, 6H), 6.98−6.94 (m, 1H), 6.48 (brs, 1H), 4.51−4.10 (m, 3H), 3.62−3.54 (m, 2H), 2.45 (s, 3H), 1.99 (brs, 1H), 1.56−1.37 (m, 6H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 151.2, 144.7, 136.9, 135.2, 134.1, 133.0, 130.0, 129.9 (2C), 128.8 (2C), 128.4 (2C), 128.3 (2C), 126.9, 126.8 (2C), 114.5, 62.4, 54.4, 52.1, 35.5, 31.9, 21.8, 20.2 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{26}H_{29}N_2O_5S_2^+$, 513.1512, found 513.1517.

***N*-(4-(4-Hydroxybutyl)-2-oxo-5-phenyl-3,4-dihydro-2*H*-1,3-oxazin-6-yl)-4-methyl-*N*-phenylbenzenesulfonamide (9ag).** White solid (140 mg, 57%); mp 127−129 °C; purified by flash chromatography on silica gel (PE/EtOAc = 1:2); IR (film): ν_{max} 3404, 2939, 1735, 1594, 1486, 1349, 1131, 763 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.30 (brs, 1H), 7.48−7.43 (m, 2H), 7.42−7.36 (m, 3H), 7.35−7.28 (m, 4H), 7.25−7.18 (m, 3H), 6.86−6.71 (m, 2H), 4.36 (brs, 1H), 4.32−4.27 (m, 1H), 3.33−3.28 (m, 2H), 2.35 (s, 3H), 1.50−1.24 (m, 6H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 149.7, 144.4, 139.2, 138.5, 134.9, 133.1, 129.5 (2C), 129.2 (2C), 128.4 (4C), 128.2, 128.1 (2C), 128.0, 125.9 (2C), 117.0, 60.6, 53.8, 34.2, 32.2, 21.1, 19.4 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{27}H_{29}N_2O_5S^+$, 493.1792, found 493.1793.

***N*-(4-(4-Hydroxybutyl)-2-oxo-5-phenyl-3,4-dihydro-2*H*-1,3-oxazin-6-yl)-*N*,4-dimethylbenzenesulfonamide (9ah).** White solid (196 mg, 91%); mp 137−139 °C; purified by flash chromatography on silica gel (PE/EtOAc = 1:2); IR (film): ν_{max} 3122, 2935, 2363, 1733, 1596, 1404, 1349, 843 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68−7.63 (m, 2H), 7.43−7.36 (m, 5H), 7.31−7.26 (m, 2H), 6.84 (brs, 1H), 4.41−4.35 (m, 1H), 3.64−3.58 (m, 2H), 2.78 (s, 3H), 2.41 (s, 3H), 2.33 (brs, 1H), 1.63−1.57 (m, 2H), 1.56−1.52 (m, 2H), 1.52−1.47 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 151.6, 144.3, 140.1, 135.0, 133.2, 129.7 (2C), 128.9 (2C), 128.52 (2C), 128.48, 128.4 (2C), 116.5, 62.3, 55.0, 35.9, 34.7, 32.0, 21.7, 19.9 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{22}H_{27}N_2O_5S^+$, 431.1635, found 431.1640.

***N*-Butyl-*N*-(4-(4-hydroxybutyl)-2-oxo-5-phenyl-3,4-dihydro-2*H*-1,3-oxazin-6-yl)-4-methylbenzenesulfonamide (9ai).** White solid (229 mg, 97%); mp 122−124 °C; purified by flash chromatography on silica gel (PE/EtOAc = 1:2); IR (film): ν_{max} 3237, 2933, 1737, 1594, 1355, 1165, 1071, 767 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80−7.73 (m, 2H), 7.52−7.48 (m, 2H), 7.44−7.36 (m, 3H), 7.32−7.29 (m, 2H), 6.36 (brs, 1H), 4.41−4.36 (m, 1H), 3.65−3.60 (m, 2H), 2.97−2.91 (m, 2H), 2.42 (s, 3H), 1.97 (brs, 1H), 1.65−1.50 (m, 6H), 1.23−1.12 (m, 2H), 1.01−0.80 (m, 2H), 0.68−0.62 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 151.5, 144.3, 138.1, 135.8, 133.2, 129.7 (2C), 128.9 (2C), 128.7 (2C), 128.6 (2C), 128.5, 118.2, 62.5, 55.7, 48.1, 34.9, 32.1, 29.7, 21.7, 19.9, 19.7, 13.7 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{25}H_{33}N_2O_5S^+$, 473.2105, found 473.2103.

***N*-Benzyl-4-chloro-*N*-(4-(4-hydroxybutyl)-2-oxo-5-phenyl-3,4-dihydro-2*H*-1,3-oxazin-6-yl)benzenesulfonamide (9aj).** White solid (134 mg, 51%); mp 140−142 °C; purified by flash chromatography on silica gel (PE/EtOAc = 1:2); IR (film): ν_{max} 3153, 2943, 2363, 1745, 1584, 1357, 1163, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88−7.67 (m, 2H), 7.51−7.46 (m, 2H), 7.31−7.28 (m, 1H), 7.26−7.21 (m, 3H), 7.19−7.11 (m, 2H), 6.99−6.83 (m, 4H), 6.80 (brs, 1H), 4.25−4.13 (m, 2H), 4.12−3.98 (m, 1H), 3.62−3.57 (m, 2H), 2.35 (brs, 1H), 1.50−1.41 (m, 6H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 151.5, 140.1, 137.1, 137.0, 133.4, 132.7, 130.1 (2C), 129.7, 129.5 (2C), 128.7 (2C), 128.5 (2C), 128.4 (3C), 128.2 (2C), 119.0, 62.3, 55.4, 52.0, 34.4, 31.9, 19.7 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{27}H_{28}ClN_2O_5S^+$, 527.1402, found 527.1405.

2-Methoxyethylbenzyl(4-(4-hydroxybutyl)-2-oxo-5-phenyl-3,4-dihydro-2*H*-1,3-oxazin-6-yl) Carbamate (9ak). Colorless oil (159 mg, 70%); purified by flash chromatography on silica gel (PE/EtOAc = 1:2); IR (film): ν_{max} 3302, 2933, 1737, 1602, 1441, 1380, 1131, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.34−7.30 (m, 1H), 7.26−7.23 (m, 2H), 7.18−7.11 (m, 3H), 7.06−6.97 (m, 3.5H), 6.94 (brs, 1H), 6.79−6.71 (m, 0.5H), 4.56−4.48 (m, 1H), 4.44−4.35 (m, 1H), 4.33−4.27 (m, 1H), 4.26−4.22 (m, 1.5H), 4.21−4.18 (m, 0.5H), 3.73−3.64 (m, 1.5H), 3.58−3.54 (m, 2H), 3.45−3.41 (m, 2H), 3.38−3.35 (m, 0.5H), 3.33−3.29 (m, 0.5H), 2.89−2.85 (m, 0.5H), 2.17 (brs, 1H), 1.66−1.56 (m, 1H), 1.47−1.37 (m, 5H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, rotamers) δ 155.6, 152.3, 139.4, 139.2, 135.9, 135.5, 133.3, 133.1, 129.7, 128.7, 128.6, 128.3, 128.2, 128.0, 127.6, 113.7, 70.9, 70.5, 65.3, 62.2, 58.9, 54.8, 51.6, 51.2, 34.5,

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32.3, 19.9, 19.4 ppm; HRMS (ESI-Orbitrap) *m/z*: [M + H]$^+$ Calcd for $C_{25}H_{31}N_2O_6^+$, 455.2177, found 455.2179.

***N*-Benzyl-*N*-(4-(4-hydroxybutyl)-5-(4-methoxyphenyl)-2-oxo-3,4-dihydro-2*H*-1,3-oxazin-6-yl)-4-methylbenzenesulfonamide (9al).** White solid (231 mg, 86%); mp 129−131 °C; purified by flash chromatography on silica gel (PE/EtOAc = 1:2); IR (film): ν_{max} 3261, 2933, 1735, 1608, 1510, 1349, 1161, 831 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85−7.72 (m, 2H), 7.34−7.31 (m, 2H), 7.25−7.20 (m, 1H), 7.19−7.10 (m, 2H), 6.94−6.83 (m, 3H), 6.81−6.75 (m, 3H), 6.71 (brs, 1H), 4.24−3.96 (m, 3H), 3.83 (s, 3H), 3.60−3.56 (m, 2H), 2.44 (s, 3H), 2.02 (brs, 1H), 1.49−1.38 (m, 6H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.4, 151.8, 144.5, 137.0, 135.6, 133.8, 130.0 (3C), 129.8 (2C), 129.6, 128.6 (2C), 128.4 (2C), 128.2, 125.0, 118.6, 113.7 (2C), 62.3, 55.4, 51.7, 34.5, 32.0, 21.8, 19.7 ppm; HRMS (ESI-Orbitrap) *m/z*: [M + H]$^+$ Calcd for $C_{29}H_{33}N_2O_6S^+$, 537.2054, found 537.2054.

***N*-Benzyl-*N*-(5-cyclopropyl-4-(4-hydroxybutyl)-2-oxo-3,4-dihydro-2*H*-1,3-oxazin-6-yl)-4-methylbenzenesulfonamide (9am).** White solid (148 mg, 63%); mp 146−147 °C; purified by flash chromatography on silica gel (PE/EtOAc = 1:2); IR (film): ν_{max} 3280, 2937, 1733, 1596, 1349, 1161, 1033, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.84−7.80 (m, 2H), 7.37−7.34 (m, 2H), 7.32−7.27 (m, 5H), 6.33 (brs, 1H), 4.77−4.58 (m, 1H), 4.15−3.96 (m, 1H), 3.70−3.53 (m, 2H), 3.44−3.33 (m, 0.4H), 3.27−3.16 (m, 0.6H), 2.45 (s, 3H), 2.13 (brs, 1H), 1.72−1.52 (m, 4H), 1.51−1.38 (m, 2H), 1.16−1.01 (m, 1H), 0.84−0.53 (m, 2H), 0.48−0.36 (m, 0.6H), 0.22−0.16 (m, 1H), −0.14 to −0.21 (m, 0.4H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, rotamers) δ 152.3, 144.4, 135.8, 134.3, 130.0, 128.5, 128.4, 128.3, 128.2, 119.3, 62.4, 51.4, 35.6, 32.0, 29.8, 21.8, 20.2, 9.3, 6.0, 4.9 ppm; HRMS (ESI-Orbitrap) *m/z*: [M + H]$^+$ Calcd for $C_{25}H_{31}N_2O_5S^+$, 471.1948, found 471.1952.

4-(3-Hydroxypropyl)-6-phenyl-3,4-dihydro-2*H*-1,3-oxazin-2-one (10a). Colorless oil (62 mg, 53%); purified by flash chromatography on silica gel (PE/EtOAc = 1:3 to EtOAc/MeOH = 19:1); IR (film): ν_{max} 3292, 2935, 1724, 1402, 1255, 1133, 1055, 753 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.69−7.65 (m, 2H), 7.43−7.38 (m, 3H), 5.80 (d, *J* = 4.0 Hz, 1H), 4.28−4.23 (m, 1H), 3.65−3.60 (m, 2H), 1.78−1.71 (m, 2H), 1.70−1.62 (m, 2H) ppm; ^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 153.5, 149.3, 133.2, 130.3, 129.6, 125.5, 100.4, 62.6, 52.0, 35.0, 28.2 ppm; HRMS (ESI-Orbitrap) *m/z*: [M + H]$^+$ Calcd for $C_{13}H_{16}NO_3^+$, 234.1125, found 234.1121.

4-(3-Hydroxypropyl)-6-(*p*-tolyl)-3,4-dihydro-2*H*-1,3-oxazin-2-one (10b). Colorless oil (82 mg, 66%); purified by flash chromatography on silica gel (PE/EtOAc = 1:3 to EtOAc/MeOH = 19:1); IR (film): ν_{max} 3280, 2922, 2861, 1722, 1402, 1259, 1057, 755 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50−7.46 (m, 2H), 7.23 (brs, 1H), 7.19−7.15 (m, 2H), 5.46−5.43 (m, 1H), 4.26−4.22 (m, 1H), 3.71−3.66 (m, 2H), 3.45−3.13 (brs, 1H), 2.34 (s, 3H), 1.79−1.64 (m, 4H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 152.2, 148.3, 139.4, 129.3, 129.0, 124.6, 98.2, 62.2, 51.1, 34.7, 27.5, 21.3 ppm; HRMS (ESI-Orbitrap) *m/z*: [M + H]$^+$ Calcd for $C_{14}H_{18}NO_3^+$, 248.1281, found 248.1281.

6-(4-Ethoxyphenyl)-4-(3-hydroxypropyl)-3,4-dihydro-2*H*-1,3-oxazin-2-one (10c). Foamed solid (103 mg, 74%); purified by flash chromatography on silica gel (PE/EtOAc = 1:3 to EtOAc/MeOH = 19:1); IR (film): ν_{max} 3298, 2941, 1722, 1604, 1512, 1247, 1176, 757 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.60−7.56 (m, 2H), 6.97−6.93 (m, 2H), 5.64 (d, *J* = 3.2 Hz, 1H), 4.26−4.20 (m, 1H), 4.10−4.05 (m, 2H), 3.65−3.60 (m, 2H), 1.75−1.64 (m, 4H), 1.44−1.40 (m, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 161.3, 153.7, 149.3, 127.0, 125.6, 115.5, 98.3, 64.6, 62.6, 52.0, 35.2, 28.2, 15.1 ppm; HRMS (ESI-Orbitrap) *m/z*: [M + H]$^+$ Calcd for $C_{15}H_{20}NO_4^+$, 278.1387, found 278.1385.

6-(4-Butylphenyl)-4-(3-hydroxypropyl)-3,4-dihydro-2*H*-1,3-oxazin-2-one (10d). Colorless oil (75 mg, 52%); purified by flash chromatography on silica gel (PE/EtOAc = 1:3 to EtOAc/MeOH = 19:1); IR (film): ν_{max} 3308, 2927, 1722, 1604, 1512, 1400, 1257, 755 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53−7.50 (m, 2H), 7.19−7.16 (m, 2H), 7.07 (brs, 1H), 5.47 (m, 1H), 4.28−4.24 (m, 1H), 3.72−3.68 (m, 2H), 2.63−2.58 (m, 2H), 1.80−1.68 (m, 4H), 1.61−1.56 (m, 2H), 1.37−1.31 (m, 2H), 0.99−0.95 (m, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 152.0, 148.3, 144.4, 129.1, 128.6, 124.6, 98.0, 62.2, 51.0, 35.4, 34.8, 33.4, 27.5, 22.3, 13.9 ppm; HRMS (ESI-Orbitrap) *m/z*: [M + H]$^+$ Calcd for $C_{17}H_{24}NO_3^+$, 290.1751, found 290.1752.

4-(3-Hydroxypropyl)-6-(*o*-tolyl)-3,4-dihydro-2*H*-1,3-oxazin-2-one (10e). Colorless oil (54 mg, 44%); purified by flash chromatography on silica gel (PE/EtOAc = 1:3 to EtOAc/MeOH = 19:1); IR (film): ν_{max} 3284, 2941, 1727, 1602, 1404, 1335, 1059, 757 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.31 (m, 1H), 7.30−7.28 (m, 1H), 7.27−7.23 (m, 1H), 7.20−7.18 (m, 1H), 7.18−7.14 (m, 1H), 5.11−5.08 (m, 1H), 4.25−4.21 (m, 1H), 3.68−3.64 (m, 2H), 3.30 (brs, 1H), 2.40 (s, 3H), 1.76−1.66 (m, 4H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 152.3, 149.6, 136.6, 132.7, 130.7, 129.5, 129.0, 125.8, 103.2, 62.1, 51.2, 34.6, 27.4, 20.4 ppm; HRMS (ESI-Orbitrap) *m/z*: [M + H]$^+$ Calcd for $C_{14}H_{18}NO_3^+$, 248.1281, found 248.1278.

4-(3-Hydroxypropyl)-6-(*m*-tolyl)-3,4-dihydro-2*H*-1,3-oxazin-2-one (10f). Colorless oil (62 mg, 50%); purified by flash chromatography on silica gel (PE/EtOAc = 1:3 to EtOAc/MeOH = 19:1); IR (film): ν_{max} 3276, 2933, 1724, 1402, 1259, 1186, 1061, 784 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.43 (m, 1H), 7.42−7.38 (m, 1H), 7.26−7.21 (m, 1H), 7.18−7.13 (m, 2H), 5.52−5.49 (m, 1H), 4.29−4.24 (m, 1H), 3.73−3.68 (m, 2H), 2.84 (brs, 1H) 2.36 (s, 3H), 1.83−1.67 (m, 4H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 152.1, 148.4, 138.3, 131.7, 130.2, 128.5, 125.4, 121.9, 98.9, 62.3, 51.1, 34.8, 27.6, 21.5 ppm; HRMS (ESI-Orbitrap) *m/z*: [M + H]$^+$ Calcd for $C_{14}H_{18}NO_3^+$, 248.1281, found 248.1279.

6-(4-Fluorophenyl)-4-(3-hydroxypropyl)-3,4-dihydro-2*H*-1,3-oxazin-2-one (10g). White solid (64 mg, 51%); mp 83−85 °C; purified by flash chromatography on silica gel (PE/EtOAc = 1:3 to EtOAc/MeOH = 19:1); IR (film): ν_{max} 3312, 2916, 1724, 1508, 1400, 1233, 1057, 753 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63−7.58 (m, 2H), 7.10−7.04 (m, 2H), 6.65 (brs, 1H), 5.48−5.45 (m, 1H), 4.30−4.25 (m, 1H), 3.76−3.71 (m, 2H), 2.17 (brs, 1H), 1.85−1.76 (m, 2H), 1.73−1.65 (m, 2H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 163.5 (d, $^1J_{C-F}$ = 247.9 Hz), 151.4, 147.7, 128.0 (d, $^4J_{C-F}$ = 1.2 Hz), 126.8 (d, $^3J_{C-F}$ = 8.2 Hz), 115.7 (d, $^2J_{C-F}$ = 21.7 Hz), 98.7, 62.5, 51.3, 35.1, 27.7 ppm; ^{19}F NMR (376 MHz, CD_3OD) δ −111.5 ppm; HRMS (ESI-Orbitrap) *m/z*: [M + H]$^+$ Calcd for $C_{13}H_{15}FNO_3^+$, 252.1031, found 252.1031.

6-(4-Chlorophenyl)-4-(3-hydroxypropyl)-3,4-dihydro-2*H*-1,3-oxazin-2-one (10h). Foamed solid (55 mg, 41%); purified by flash chromatography on silica gel (PE/EtOAc = 1:3 to EtOAc/MeOH = 19:1); IR (film): ν_{max} 3337, 2929, 1722, 1492, 1396, 1257, 1090, 755 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.68−7.64 (m, 2H), 7.45−7.41 (m, 2H), 5.85 (d, *J* = 4.0 Hz, 1H), 4.27−4.23 (m, 1H), 3.64−3.60 (m, 2H), 1.77−1.71 (m, 2H), 1.69−1.64 (m, 2H) ppm; ^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 153.2, 148.3, 136.1, 132.0, 129.8, 127.1, 101.1, 62.6, 52.1, 35.0, 28.2 ppm; HRMS (ESI-Orbitrap) *m/z*: [M + H]$^+$ Calcd for $C_{13}H_{15}ClNO_3^+$, 268.0735, found 268.0735.

6-(4-Bromophenyl)-4-(3-hydroxypropyl)-3,4-dihydro-2*H*-1,3-oxazin-2-one (10i). Pale yellow oil (56 mg, 36%); purified by flash chromatography on silica gel (PE/EtOAc = 1:3 to EtOAc/MeOH = 19:1); IR (film): ν_{max} 3288, 2927, 1729, 1396, 1257, 1006, 835, 755 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.59−7.55 (m, 4H), 5.84 (d, *J* = 4.0 Hz, 1H), 4.27−4.22 (m, 1H), 3.65−3.60 (m, 2H), 1.78−1.71 (m, 2H), 1.70−1.64 (m, 2H) ppm; ^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 153.1, 148.4, 132.8, 132.3, 127.3, 124.2, 101.2, 62.6, 52.1, 34.9, 28.2 ppm; HRMS (ESI-Orbitrap) *m/z*: [M + H]$^+$ Calcd for $C_{13}H_{15}BrNO_3^+$, 312.0230, found 312.0229.

4-(3-Hydroxypropyl)-6-(thiophen-2-yl)-3,4-dihydro-2*H*-1,3-oxazin-2-one (10j). Colorless oil (74 mg, 62%); purified by flash chromatography on silica gel (PE/EtOAc = 1:3 to EtOAc/MeOH = 19:1); IR (film): ν_{max} 3300, 2939, 1729, 1520, 1410, 1243, 1059, 753 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.30 (m, 1H), 7.28−7.26 (m, 1H), 7.14 (brs, 1H), 7.02−6.99 (m, 1H), 5.40 (dd, *J* = 3.6, 1.6 Hz, 1H), 4.26−4.23 (m, 1H), 3.71−3.68 (m, 2H), 2.95 (brs, 1H), 1.79−1.66 (m, 4H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 150.5,

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143.1, 134.2, 126.7, 125.1, 124.0, 97.1, 61.2, 50.1, 33.6, 26.5 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{11}H_{14}NO_3S^+$, 240.0689, found 240.0686.

4-(3-Hydroxypropyl)-6-(thiophen-3-yl)-3,4-dihydro-2*H*-1,3-oxazin-2-one (10k). White solid (50 mg, 42%); mp 130−132 °C; purified by flash chromatography on silica gel (PE/EtOAc = 1:3 to EtOAc/MeOH = 19:1); IR (film): ν_{max} 3290, 2935, 1722, 1398, 1261, 1184, 1061, 755 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.62−7.58 (m, 1H), 7.46−7.43 (m, 1H), 7.34−7.31 (m, 1H), 5.66 (d, J = 3.6 Hz, 1H), 4.21 (dd, J = 9.0, 4.6 Hz, 1H), 3.63−3.56 (m, 2H), 1.76−1.67 (m, 2H), 1.66−1.59 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, CD_3OD) δ 153.4, 146.4, 135.3, 127.7, 125.3, 123.1, 99.7, 62.6, 51.9, 35.0, 28.2 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{11}H_{14}NO_3S^+$, 240.0689, found 240.0686.

4-(4-Hydroxybutyl)-6-phenyl-3,4-dihydro-2*H*-1,3-oxazin-2-one (10aa). Colorless oil (49 mg, 40%); purified by flash chromatography on silica gel (PE/EtOAc = 1:3 to EtOAc/MeOH = 19:1); IR (film): ν_{max} 3278, 2939, 2861, 1729, 1400, 1257, 1022, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63−7.58 (m, 2H), 7.38−7.33 (m, 3H), 5.53−5.50 (m, 1H), 4.23−4.17 (m, 1H), 3.67−3.62 (m, 2H), 1.71−1.63 (m, 2H), 1.61−1.50 (m, 4H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 152.1, 148.2, 131.8, 129.4, 128.6, 124.7, 99.0, 62.3, 51.2, 37.5, 32.2, 20.7 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{18}NO_3^+$, 248.1281, found: 248.1278.

4-(4-Hydroxybutyl)-6-(*p*-tolyl)-3,4-dihydro-2*H*-1,3-oxazin-2-one (10ab). Colorless oil (85 mg, 65%); purified by flash chromatography on silica gel (PE/EtOAc = 1:3 to EtOAc/MeOH = 19:1); IR (film): ν_{max} 3324, 2937, 1730, 1606, 1404, 1261, 1130, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52−7.48 (m, 2H), 7.19−7.15 (m, 2H), 6.94 (brs, 1H), 5.48−5.45 (m, 1H), 4.23−4.17 (m, 1H), 3.69−3.63 (m, 2H), 2.35 (s, 3H), 1.72−1.64 (m, 2H), 1.63−1.58 (m, 2H), 1.56−1.49 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 152.2, 148.3, 139.5, 129.3, 129.0, 124.6, 98.1, 62.3, 51.2, 37.6, 32.2, 21.4, 20.7 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{20}NO_3^+$, 262.1438, found 262.1435.

6-(4-Ethoxyphenyl)-4-(4-hydroxybutyl)-3,4-dihydro-2*H*-1,3-oxazin-2-one (10ac). White solid (122 mg, 84%); mp 130−132 °C; purified by flash chromatography on silica gel (PE/EtOAc = 1:3 to EtOAc/MeOH = 19:1); IR (film): ν_{max} 2939, 1731, 1606, 1510, 1404, 1269, 1043, 755 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.56−7.53 (m, 2H), 6.92−6.89 (m, 2H), 5.59 (d, J = 3.6 Hz, 1H), 4.18−4.13 (m, 1H), 4.06−4.00 (m, 2H), 3.58−3.54 (m, 2H), 1.67−1.61 (m, 2H), 1.59−1.53 (m, 2H), 1.51−1.44 (m, 2H), 1.40−1.36 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, CD_3OD) δ 161.2, 153.7, 149.1, 126.9, 125.5, 115.4, 98.3, 64.6, 62.7, 52.1, 38.5, 33.4, 21.5, 15.1 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{22}NO_4^+$, 292.1543, found 292.1544.

6-(4-Butylphenyl)-4-(4-hydroxybutyl)-3,4-dihydro-2*H*-1,3-oxazin-2-one (10ad). Colorless oil (85 mg, 56%); purified by flash chromatography on silica gel (PE/EtOAc = 1:3 to EtOAc/MeOH = 19:1); IR (film): ν_{max} 3304, 2929, 2859, 1733, 1661, 1514, 1257, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54−7.51 (m, 2H), 7.19−7.16 (m, 2H), 7.04 (brs, 1H), 5.48−5.46 (m, 1H), 4.23−4.18 (m, 1H), 3.68−3.63 (m, 2H), 2.84 (brs, 1H), 2.63−2.58 (m, 2H), 1.72−1.64 (m, 2H), 1.63−1.59 (m, 2H), 1.58−1.47 (m, 4H), 1.37−1.31 (m, 2H), 0.94−0.90 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 152.3, 148.3, 144.5, 129.2, 128.6, 124.6, 98.1, 62.3, 51.1, 37.6, 35.5, 33.5, 32.2, 22.4, 20.7, 14.0 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{26}NO_3^+$, 304.1907, found 304.1906.

4-(4-Hydroxybutyl)-6-(*o*-tolyl)-3,4-dihydro-2*H*-1,3-oxazin-2-one (10ae). Colorless oil (44 mg, 34%); purified by flash chromatography on silica gel (PE/EtOAc = 1:3 to EtOAc/MeOH = 19:1); IR (film): ν_{max} 3280, 2933, 1727, 1663, 1400, 1249, 1022, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.32 (m, 1H), 7.30−7.25 (m, 1H), 7.22−7.20 (m, 1H), 7.19−7.16 (m, 1H), 6.97 (brs, 1H), 5.13−5.11 (m, 1H), 4.23−4.19 (m, 1H), 3.67−3.62 (m, 2H), 2.42 (s, 3H), 2.14 (brs, 1H), 1.71−1.65 (m, 2H), 1.61−1.52 (m, 4H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 152.2, 149.8, 136.7, 132.7, 130.7, 129.5, 129.0, 125.8, 103.1, 62.3, 51.3, 37.5, 32.1, 20.6, 20.5 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{20}NO_3^+$, 262.1438, found 262.1436.

4-(4-Hydroxybutyl)-6-(*m*-tolyl)-3,4-dihydro-2*H*-1,3-oxazin-2-one (10af). Colorless oil (57 mg, 44%); purified by flash chromatography on silica gel (PE/EtOAc = 1:3 to EtOAc/MeOH = 19:1); IR (film): ν_{max} 3280, 2933, 1729, 1657, 1400, 1265, 1073, 784 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46−7.43 (m, 1H), 7.42−7.39 (m, 1H), 7.26−7.23 (m, 1H), 7.17−7.14 (m, 1H), 5.52−5.49 (m, 1H), 4.23−4.17 (m, 1H), 3.68−3.63 (m, 2H), 2.36 (s, 3H), 1.71−1.64 (m, 2H), 1.63−1.57 (m, 2H), 1.56−1.49 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 152.2, 148.2, 138.2, 131.6, 130.1, 128.4, 125.2, 121.8, 98.8, 62.2, 51.0, 37.4, 32.1, 21.4, 20.6 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{20}NO_3^+$, 262.1438, found 262.1436.

6-(4-Fluorophenyl)-4-(4-hydroxybutyl)-3,4-dihydro-2*H*-1,3-oxazin-2-one (10ag). White solid (48 mg, 36%); mp 88−90 °C; purified by flash chromatography on silica gel (PE/EtOAc = 1:3 to EtOAc/MeOH = 19:1); IR (film): ν_{max} 3284, 2935, 1727, 1600, 1506, 1406, 1069, 755 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.71−7.66 (m, 2H), 7.17−7.11 (m, 2H), 5.75 (d, J = 3.6 Hz, 1H), 4.23−4.18 (m, 1H), 3.61−3.57 (m, 2H), 1.72−1.65 (m, 2H), 1.63−1.57 (m, 2H), 1.55−1.48 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, CD_3OD) δ 163.2 (d, $^1J_{C-F}$ = 246.2 Hz), 151.9, 147.0, 128.2 (d, $^4J_{C-F}$ = 2.9 Hz), 126.3 (d, $^3J_{C-F}$ = 8.7 Hz), 115.0 (d, $^2J_{C-F}$ = 22.0 Hz), 98.9, 61.3, 50.8, 36.9, 32.0, 20.2 ppm; ^{19}F NMR (376 MHz, CD_3OD) δ −114.0 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{17}FNO_3^+$, 266.1187, found 266.1185.

4-(4-Hydroxybutyl)-6-(thiophen-2-yl)-3,4-dihydro-2*H*-1,3-oxazin-2-one (10aj). Colorless oil (103 mg, 81%); purified by flash chromatography on silica gel (PE/EtOAc = 1:3 to EtOAc/MeOH = 19:1); IR (film): ν_{max} 3280, 2937, 1733, 1402, 1237, 1059, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33−7.30 (m, 1H), 7.29−7.25 (m, 1H), 7.21 (brs, 1H), 7.02−6.98 (m, 1H), 5.41−5.38 (m, 1H), 4.21−4.16 (m, 1H), 3.67−3.62 (m, 2H), 2.96 (brs, 1H), 1.70−1.62 (m, 2H), 1.61−1.55 (m, 2H), 1.54−1.47 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 151.6, 144.0, 135.2, 127.6, 126.0, 125.0, 98.1, 62.2, 51.1, 37.4, 32.1, 20.6 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{16}NO_3S^+$, 254.0845, found 254.0843.

4-(4-Hydroxybutyl)-6-(thiophen-3-yl)-3,4-dihydro-2*H*-1,3-oxazin-2-one (10ak). White solid (75 mg, 59%); mp 89−91 °C; purified by flash chromatography on silica gel (PE/EtOAc = 1:3 to EtOAc/MeOH = 19:1); IR (film): ν_{max} 3306, 2935, 1729, 1655, 1414, 1259, 1051, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60−7.57 (m, 1H), 7.32−7.29 (m, 1H), 7.22−7.19 (m, 1H), 7.00 (brs, 1H), 5.39 (dd, J = 3.2, 1.6 Hz, 1H), 4.22−4.18 (m, 1H), 3.68−3.63 (m, 2H), 2.63 (brs, 1H), 1.71−1.63 (m, 2H), 1.62−1.57 (m, 2H), 1.55−1.48 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 151.9, 145.1, 133.8, 126.6, 124.1, 122.7, 98.4, 62.3, 51.0, 37.5, 32.1, 20.7 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{16}NO_3S^+$, 254.0845, found 254.0843.

6-([1,1′-Biphenyl]-4-yl)-4-(4-hydroxybutyl)-3,4-dihydro-2*H*-1,3-oxazin-2-one (10al). White solid (86 mg, 53%); mp 137−139 °C; purified by flash chromatography on silica gel (PE/EtOAc = 1:3 to EtOAc/MeOH = 19:1); IR (film): ν_{max} 3147, 2933, 1714, 1486, 1400, 1276, 1067, 765 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.77−7.74 (m, 2H), 7.71−7.65 (m, 4H), 7.49−7.44 (m, 2H), 7.40−7.35 (m, 1H), 5.86 (d, J = 4.0 Hz, 1H), 4.25 (dd, J = 9.2, 5.2 Hz, 1H), 3.63−3.59 (m, 2H), 1.75−1.69 (m, 2H), 1.66−1.60 (m, 2H), 1.57−1.51 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, CD_3OD) δ 153.5, 149.0, 143.2, 141.5, 132.1, 130.0, 128.7, 128.1, 127.9, 126.0, 100.5, 62.7, 52.2, 38.4, 33.4, 21.6 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{22}NO_3^+$, 324.1594, found 324.1591.

6-Cyclopropyl-4-(4-hydroxybutyl)-3,4-dihydro-2*H*-1,3-oxazin-2-one (10am). Colorless oil (69 mg, 65%); purified by flash chromatography on silica gel (PE/EtOAc = 1:3 to EtOAc/MeOH = 19:1); IR (film): ν_{max} 3285, 2934, 2863, 1729, 1410, 1263, 1069, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.11 (brs, 1H), 4.81 (dd, J = 3.0, 1.4 Hz, 1H), 4.02−3.96 (m, 1H), 3.65−3.60 (m, 2H), 3.22 (brs, 1H), 1.60−1.51 (m, 4H), 1.49−1.41 (m, 3H), 0.79−0.73 (m, 2H), 0.71−0.65 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 152.2,

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150.9, 97.1, 62.1, 50.8, 37.6, 32.1, 20.5, 12.4, 4.5, 4.4 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{11}H_{18}NO_3^+$, 212.1281, found 212.1281.

6-(4-Ethoxyphenyl)-4-(4-hydroxybutyl)-3-methyl-3,4-dihydro-2*H*-1,3-oxazin-2-one (10bc). White solid (86 mg, 56%); mp 110−112 °C; purified by flash chromatography on silica gel (PE/EtOAc = 1:2 to EtOAc/MeOH = 49:1); IR (film): ν_{max} 3449, 2933, 1712, 1604, 1512, 1239, 1176, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55−7.52 (m, 2H), 6.88−6.85 (m, 2H), 5.40 (d, J = 4.4 Hz, 1H), 4.06−4.02 (m, 2H), 4.01−3.98 (m, 1H), 3.64−3.60 (m, 2H), 3.02 (s, 3H), 2.19 (brs, 1H), 1.79−1.71 (m, 1H), 1.69−1.62 (m, 1H), 1.61−1.56 (m, 2H), 1.46−1.42 (m, 1H), 1.41−1.39 (m, 3H), 1.38−1.36 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.8, 151.4, 148.4, 126.1, 124.1, 114.4, 96.5, 63.6, 62.4, 57.5, 34.2, 33.9, 32.5, 19.8, 14.8 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{24}NO_4^+$, 306.1700, found 306.1700.

4-(4-Hydroxybutyl)-3-methyl-6-(thiophen-3-yl)-3,4-dihydro-2*H*-1,3-oxazin-2-One (10bj). Pale yellow solid (71 mg, 53%); mp 90−92 °C; purified by flash chromatography on silica gel (PE/EtOAc = 1:2 to EtOAc/MeOH = 49:1); IR (film): ν_{max} 3133, 2935, 1712, 1404, 1231, 1192, 1112, 790 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62−7.59 (m, 1H), 7.33−7.29 (m, 1H), 7.21−7.18 (m, 1H), 5.40 (d, J = 4.8 Hz, 1H), 4.05−4.01 (m, 1H), 3.67−3.63 (m, 2H), 3.04 (s, 3H), 1.83−1.77 (m, 1H), 1.71−1.62 (m, 3H), 1.46−1.41 (m, 2H), ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 151.1, 145.7, 133.8, 126.6, 124.2, 122.8, 97.9, 62.7, 57.4, 34.4, 33.9, 32.6, 19.9 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_{18}NO_3S^+$, 268.1002, found 268.1001.

6-Cyclopropyl-4-(4-hydroxybutyl)-3-methyl-3,4-dihydro-2*H*-1,3-oxazin-2-one (10bm). Colorless oil (42 mg, 37%); purified by flash chromatography on silica gel (PE/EtOAc = 1/2 to EtOAc/MeOH = 49/1); IR (film): ν_{max} 3424, 2939, 1720, 1602, 1453, 1237, 1067, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.83 (d, J = 4.4 Hz, 1H), 3.85−3.81 (m, 1H), 3.66−3.62 (m, 2H), 2.96 (s, 3H), 2.13 (brs, 1H), 1.71−1.64 (m, 1H), 1.64−1.57 (m, 2H), 1.56−1.50 (m, 1H), 1.48−1.41 (m, 1H), 1.39−1.30 (m, 2H), 0.82−0.73 (m, 2H), 0.72−0.66 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 151.6, 151.4, 96.7, 62.5, 57.3, 34.2, 33.9, 32.5, 19.6, 12.3, 4.7, 4.5 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{20}NO_3^+$, 226.1438, found 226.1434.

3-Phenyl-4a,5,7,8-tetrahydro-1*H*,6*H*-pyrido[1,2-c][1,3]-oxazin-1-one (11).[17b] Colorless oil (344 mg, 75%, 2 steps); purified by flash chromatography on silica gel (PE/EtOAc = 5/1); IR (film): ν_{max} 2937, 2853, 1720, 1496, 1447, 1222, 765 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64−7.58 (m, 2H), 7.38−7.32 (m, 3H), 5.43−5.40 (m, 1H), 4.50 (d, J = 13.6 Hz, 1H), 4.02−3.96 (m, 1H), 2.79−2.71 (m, 1H), 1.96−1.91 (m, 1H), 1.84−1.80 (m, 1H), 1.75−1.70 (m, 1H), 1.60−1.46 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 149.7, 147.3, 131.9, 129.3, 128.5, 124.7, 98.9, 55.4, 45.3, 34.0, 25.1, 24.3 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{16}NO_2^+$, 230.1176, found 230.1174.

1-Phenyl-2-(piperidin-2-yl)ethan1-one (12).[17b] Colorless oil (864 mg, 85%); purified by flash chromatography on silica gel (EtOAc/MeOH = 2/1, 0.2% TEA); IR (film): ν_{max} 3335, 2931, 1682, 1596, 1447, 1290, 1008, 749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98−7.92 (m, 2H), 7.58−7.52 (m, 1H), 7.49−7.41 (m, 2H), 3.15−3.10 (m, 1H), 3.06−3.01 (m, 3H), 2.75−2.67 (m, 1H), 2.46 (brs, 1H), 1.83−1.77 (m, 1H), 1.69−1.60 (m, 2H), 1.50−1.38 (m, 2H), 1.34−1.24 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 199.6, 137.1, 133.2, 128.6, 128.1, 52.9, 46.9, 45.7, 32.8, 26.1, 24.8 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_{18}NO^+$, 204.1383, found 204.1381.

***tert*-Butyl 2-(2-oxo-2-phenylethyl)piperidine-1-carboxylate (12a).**[17d] Colorless oil (1.1 g, 92%); purified by flash chromatography on silica gel (PE/EtOAc = 5/1); IR (film): ν_{max} 3341, 2939, 1684, 1596, 1410, 1276, 1161, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01−7.97 (m, 2H), 7.59−7.54 (m, 1H), 7.50−7.45 (m, 2H), 4.86−4.79 (m, 1H), 4.14−3.96 (m, 1H), 3.26−3.19 (m, 1H), 3.18−3.12 (m, 1H), 2.93−2.84 (m, 1H), 1.69−1.58 (m, 6H), 1.36 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 198.5, 154.8, 136.9, 133.2, 128.8, 128.4, 79.7, 48.3, 39.3, 28.4, 25.4, 19.0 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{26}NO_3^+$, 304.1907, found 304.1904.

2-(1-Methylpiperidin-2-yl)-1-phenylethan-1-ol (13).[27c] White solid (202 mg, 93%, 2 steps); mp 77−79 °C; IR (film): ν_{max} 2931, 2855, 2792, 1453, 1371, 1063, 751, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39−7.36 (m, 2H), 7.35−7.30 (m, 2H), 7.26−7.21 (m, 1H), 4.88 (dd, J = 10.4, 2.4 Hz, 1H), 3.10−3.02 (m, 1H), 2.88−2.80 (m, 1H), 2.58−2.50 (m, 1H), 2.48 (s, 3H), 2.16−2.03 (m, 1H), 1.79−1.71 (m, 1H), 1.69−1.56 (m, 2H), 1.55−1.48 (m, 1H), 1.48−1.45 (m, 1H), 1.44−1.41 (m, 1H), 1.36−1.30 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 145.8, 128.4, 127.1, 125.7, 74.7, 61.0, 51.5, 40.1, 39.9, 26.0, 22.5, 20.7 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{22}NO^+$, 220.1696, found 220.1691.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c01692.

Optimization of reaction conditions for the synthesis of compound **10**; copies of ^1H, $^{13}C\{^1H\}$, and ^{19}F NMR spectra; X-ray structural data (CIF) (**9a**; **10al**); and HPLC reports of **9aa**, **9e**, **9k**, and **9ak** (PDF)

Accession Codes

CCDC 2013028 (**9a**) and 2013029 (**10al**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +441223 336033.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Taylor, E. C.; Saxton, J. E., *The Chemistry of Heterocyclic Compounds*. vol.47, Wiley-Interscience, New York, 1994; (b) Deiters, A.; Martin, S. F. Synthesis of Oxygen- and Nitrogen-Containing Heterocycles by Ring-Closing Metathesis. *Chem. Rev.* **2004**, *104*, 2199−2238. (c) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. Recent advances in the transition metal-catalyzed twofold oxidative C-H bond activation strategy for C-C and C-N bond formation. *Chem. Soc. Rev.* **2011**, *40*, 5068−5083. (d) Godoi, B.; Schumacher, R. F.; Zeni, G. Synthesis of heterocycles via electrophilic cyclization of alkynes containing heteroatom. *Chem. Rev.* **2011**, *111*, 2937−2980. (e) Dhiman, A. K.; Thakur, A.; Kumar, I.; Kumar, R.; Sharma, U. Co(III)-Catalyzed C−H Amidation of Nitrogen-Containing Heterocycles with Dioxazolones under Mild Conditions. *J. Org. Chem.* **2020**, 9244. (f) Mehedi, M. S. A.; Tepe, J. J. $Sc(OTf)_3$-Mediated One-Pot Synthesis of 2,3-Disubstituted Quinolines from Anilines and Epoxides. *J. Org. Chem.* **2020**, *85*, 6741−6746.

(2) (a) Taylor, R. D.; MacCoss, M.; Lawson, A. D. G. Rings in drugs. *J. Med. Chem.* **2014**, *57*, 5845−5859. (b) Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. *J. Med. Chem.* **2014**, *57*, 10257−10274. (c) Afanasyev, O. I.; Podyacheva, E.; Rudenko, A.; Tsygankov, A. A.; Makarova, M.; Chusov, D. Redox Condensations of *o*-Nitrobenzaldehydes with Amines under Mild Conditions: Total Synthesis of the Vasicinone Family. *J. Org. Chem.* **2020**, 9347.

(3) For selected examples, see: (a) Lu, J.-T.; Meng, D.-D.; Meng, Q.-G. Assembly of Zn^{II} and Cd^{II} Coordination Polymers Based on a Flexible Multicarboxylate Ligand and Nitrogen-Containing Auxiliary Ligands Through a Mixed-Ligand Synthetic Strategy: Syntheses Structures and Fluorescence Properties. *Acta Cryst.* **2016**, *C72*, 99−104. (b) Lou, J.; Wang, Q.; He, Y.; Yu, Z. A Simple Aliphatic Diamine Auxiliary for Palladium-Catalyzed Arylation of Unactivated β-C(sp^3)-H Bonds. *Adv. Synth. Catal.* **2018**, *360*, 4571−4584. (c) Wang, X.-N.; Li, J.-L.; Zhao, Y.-M.; Pang, J.; Li, B.; Zhang, T.-L.; Zhou, H.-C. Structural Tuning of Zinc-Porphyrin Frameworks via Auxiliary Nitrogen-Containing Ligands towards Selective Adsorption of Cationic Dyes. *Chem. Commun.* **2019**, *55*, 6527−6530.

(4) (a) Dolfen, J.; De Kimpe, N.; D'hooghe, M. Deployment of Small-Ring Azaheterocycles as Building Blocks for the Synthesis of Organofluorine Compounds. *Synlett* **2016**, *27*, 1486−1510. (b) Gleede, T.; Reisman, L.; Rieger, E.; Mbarushimana, P. C.; Rupar, P. A.; Wurm, F. R. Aziridines and Azetidines: Building Blocks for Polyamines by Anionic and Cationic Ring-Opening Polymerization. *Polym. Chem.* **2019**, *10*, 3257−3283. (c) Hua, T.-B.; Xiao, C.; Yang, Q.-Q.; Chen, J.-R. Recent Advances in Asymmetric Synthesis of 2-Substituted Indoline Derivatives. *Chin. Chem. Lett.* **2020**, *31*, 311−323.

(5) For selected examples, see: (a) Zhang, X.; Wang, P.; Niu, X.; Li, Z.; Fan, X.; Zhang, G. Selenium-Catalyzed Oxidative Carbonylation of 2-Aminobenzyl Alcohol to give 1, 4-Dihydro-2H-3,1-Benzoxazin-2-one. *Chin. J. Catal.* **2016**, *37*, 2034−2038. (b) Xiong, H.; Wu, X.; Wang, H.; Sun, S.; Yu, J.-T.; Cheng, J. The Reaction of *o*-Aminoacetophenone *N*-Tosylhydrazone and CO_2 toward 1,4-Dihydro-2*H*-3,1-Benzoxazin-2-ones. *Adv. Synth. Catal.* **2019**, *361*, 3538−3542. (c) Fan, H.; Wan, Y.; Pan, P.; Cai, W.; Liu, S.; Liu, C.; Zhang, Y. A Cascade Approach to 3D Cyclic Carbamates via an Ionic Decarboxylative Functionalization of Olefinic Oxamic Acids. *Chem. Commun.* **2020**, *56*, 86−89.

(6) For selected examples, see: (a) Liu, Q.; Chen, P.; Liu, G. Palladium-Catalyzed C-C Triple Bond Cleavage: Efficient Synthesis of 4H-Benzo[d] [1,3]oxazin-4-ones. *ACS Catal.* **2013**, *3*, 178−181. (b) Tanimoto, I.; Kawai, K.; Sato, A.; Yoshino, T.; Matsunaga, S. One-Step Synthesis of 4H-3,1-Benzoxazin-4-ones from Weinreb Amides and 1,4,2-Dioxazol-5-ones via Cobalt-Catalyzed C-H Bond Activation. *Heterocycles* **2019**, *99*, 118−125. (c) Wang, L.; Xie, Y.-B.; Huang, N.-Y.; Yan, J.-Y.; Hu, W.-M.; Liu, M.-G.; Ding, M.-W. Catalytic aza-Wittig Reaction of Acid Anhydride for the Synthesis of 4H-Benzo[d][1,3]oxazin-4-ones and 4-Benzylidene-2-aryloxazol-5(4H)-one. *ACS Catal.* **2016**, *6*, 4010−4016. (d) Hao, W.; Xu, Z.; Zhou, Z.; Cai, M. Recyclable Heterogeneous Palladium-Catalyzed Cyclocarbonylation of 2-Iodoanilines with Acyl Chlorides in the Biomass-Derived Solvent 2-Methyltetrahydrofuran. *J. Org. Chem.* **2020**, *85*, 8522−8532.

(7) (a) Gholami, H. R.; Asghari, S.; Mohseni, M. Synthesis, Characterization, and Evaluation of Antibacterial and Antioxidant Activities of Novel Benzoxazinones and Benzoxathiinones. *J. Heterocyclic Chem.* **2019**, *56*, 1505−1513. (b) Watts, P.; Chada, S., Semi-continuous Flow Synthesis for the Manufacture of Efavirenz. [P]. PCT Int. Appl., WO2018154414 A1, 20180830; (c) Nardi, A.; Troelsen, K.; Erichsen, H. K., Novel Benzoxazinone Derivatives Useful for the Treatment of CNS Disorders. [P]. U.S. Pat. Appl. Publ., US 20,120,071,471 A1, 20120322; (d) Padwal, R. Cetilistat, a new Lipase Inhibitor for the Treatment of Obesity. *Curr. Opin. Investig. Drugs* **2008**, *9*, 414−421.

(8) For selected examples, see: (a) Boddy, A. J.; Cordier, C. J.; Goldberg, K.; Madin, A.; Spivey, A. C.; Bull, J. A. Acid-Mediated Ring Expansion of 2,2-Disubstituted Azetidine Carbamates to 6,6-Disubstituted 1,3-oxazinan-2-ones. *Org. Lett.* **2019**, *21*, 1818−1822. (b) Mei, C.; Zhao, Y.; Chen, Q.; Cao, C.; Pang, G.; Shi, Y. Synthesis of Oxazolidinones and Derivatives through Three-Component Fixation of Carbon Dioxide. *ChemCatChem* **2018**, *10*, 3057−3068. (c) Buyck, T.; Wang, Q.; Zhu, J. Triple Role of Phenylselenonyl Group Enabled a One-Pot Synthesis of 1,3-oxazinan-2-ones from α-Isocyanoacetates, Phenyl Vinyl Selenones, and Water. *J. Am. Chem. Soc.* **2014**, *136*, 11524−11528. (d) Rigoli, J. W.; Weatherly, C. D.; Vo, B. T.; Neale, S.; Meis, A. R.; Schomaker, J. M. Chemoselective Allene Aziridination via Ag(I) Catalysis. *Org. Lett.* **2013**, *15*, 290−293.

(9) (a) Taft, F.; Harmrolfs, K.; Nickeleit, I.; Heutling, A.; Kiene, M.; Malek, N.; Sasse, F.; Kirschning, A. Combined Muta- and Semisynthesis: A Powerful Synthetic Hybrid Approach to Access Target Specific Antitumor Agents Based on Ansamitocin P3. *Chem. − Eur. J.* **2012**, *18*, 880−886. (b) Xu, Z.; Tice, C. M.; Zhao, W.; Cacatian, S.; Ye, Y.-J.; Singh, S. B.; Lindblom, P.; McKeever, B. M.; Krosky, P. M.; Kruk, B. A.; Berbaum, J.; Harrison, R. K.; Johnson, J. A.; Bukhtiyarov, Y.; Panemangalore, R.; Scott, B. B.; Zhao, Y.; Bruno, J. G.; Togias, J.; Guo, J.; Guo, R.; Carroll, P. J.; McGeehan, G. M.; Zhuang, L.; He, W.; Claremon, D. A. Structure-Based Design and Synthesis of 1,3-Oxazinan-2-one Inhibitors of 11β-Hydroxysteroid Dehydro-genase Type 1. *J. Med. Chem.* **2011**, *54*, 6050−6062. (c) Zhuang, L.; Tice, C. M.; Xu, Z.; Zhao, W.; Cacatian, S.; Ye, Y.-J.; Singh, S. B.; Lindblom, P.; McKeever, B. M.; Krosky, P. M.; Zhao, Y.; Lala, D.; Kruk, B. A.; Meng, S.; Howard, L.; Johnson, J. A.; Bukhtiyarov, Y.; Panemangalore, R.; Guo, J.; Guo, R.; Himmelsbach, F.; Hamilton, B.; Schuler-Metz, A.; Schauerte, H.; Gregg, R.; McGeehan, G. M.; Leftheris, K.; Claremon, D. A. Discovery of BI 135585, an in vivo Efficacious Oxazinanone-based 11β Hydroxysteroid Dehydrogenase Type 1 inhibitor. *Bioorg. Med. Chem.* **2017**, *25*, 3649−3657. (d) Wang, Y. F.; Izawa, T.; Kobayashi, S.; Ohno, M. Stereocontrolled Synthesis of (+)-Negamycin from an Acyclic Homoallylamine by 1,3-Asymmetric Induction. *J. Am. Chem. Soc.* **1982**, *104*, 6466−6466.

(10) Young, S. D.; Britcher, S. F.; Tran, L. O.; Payne, L. S.; Lumma, W. C.; Lyle, T. A.; Huff, J. R.; Anderson, P. S.; Olsen, D. B.; Carroll, S. S. L-743,726 (DMP-266): a Novel, Highly Potent Nonnucleoside Inhibitor of the Human Immunodeficiency Virus Type 1 Reverse Transcriptase. *Antimicrob. Agents Chemother.* **1995**, *39*, 2602−2605.

(11) (a) Ullrich, T.; Baumann, K.; Welzenbach, K.; Schmutz, S.; Camenisch, G.; Meingassner, J. G.; Weitz-Schmidt, G. Statin-derived 1,3-Oxazinan-2-ones as Submicromolar Inhibitors of LFA-1/ICAM-1 Interaction: Stabilization of the Metabolically Labile Vanillyl Side Chain. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2483−2487. (b) Ina, S.; Kenjirou, Y.; Kyoji, N., Preparation of 6-Phenyltetra-hydro-1,3-oxazin-2-one Derivatives as Phosphodiesterase IV Inhibitors. Nikken Chemicals Co., Ltd., 2001, US6,251,897 (B1).

https://dx.doi.org/10.1021/acs.joc.0c01692
J. Org. Chem. XXXX, XXX, XXX−XXX

(12) Cassady, J. M.; Chan, K. K.; Floss, H. G.; Leistner, E. Recent Developments in the Maytansinoid Antitumor Agents. *Chem. Pharm. Bull.* **2004**, *52*, 1−26.
(13) (a) Esch, P. M.; Hiemstra, H.; Speckamp, W. N. Intermolecular Reactions of *N*-Alkoxycarbonyliminium Ions with Propargyltrimethylsilane; Oxazinone versus Allene Formation. *Tetrahedron* **1992**, *48*, 3445−3462. (b) Kano, T.; Yasumoto, K.; Maruoka, K. BF_3-Catalyzed Synthesis of Cyclic Carbamates from Boc-Protected Aminals and Alkynes. *Asian J. Org. Chem.* **2018**, *7*, 1575−1578.
(14) For selected examples, see: (a) Esch, P. M.; Hiemstra, H.; Speckamp, W. N. Oxazinone versus Allene Formation in the Reaction of *N*-alkoxycarbonyliminium Ions with Propargyltrimethylsilane. *Tetrahedron Lett.* **1988**, *29*, 367−370. (b) Fisher, M. J.; Overman, L. E. Intramolecular *N*-(acyloxy)iminium Ion-alkyne Cycloadditions. A new Route to Bicyclic. alpha.-Amino Ketones. *J. Org. Chem.* **1990**, *55*, 1447−1459. (c) Suga, S.; Nagaki, A.; Tsutsui, Y.; Yoshida, J. "*N*-Acyliminium Ion Pool" as a Heterodiene in [4 + 2] Cycloaddition Reaction. *Org. Lett.* **2003**, *5*, 945−947. (d) Galván, A.; Calleja, J.; Fañanás, F. J.; Rodríguez, F. Synthesis of Pyrrolidine Derivatives by a Platinum/Brønsted Acid Relay Catalytic Cascade Reaction. *Chem. − Eur. J.* **2015**, *21*, 3409−3414. (e) Wu, P.; Nielsen, T. E. Scaffold Diversity from *N*-Acyliminium Ions. *Chem. Rev.* **2017**, *117*, 7856. (f) Chen, L.; Yu, J.; Tang, S.; Shao, Y.; Sun, J. Gold Catalyzed Highly Diastereoselective Oxy-Propargy-lamination of Allenamides with C-Alkynyl *N*-Boc *N*, O-Acetals. *Org. Lett.* **2019**, *21*, 9050−9054.
(15) Sugiura, M.; Hagio, H.; Hirabayashi, R.; Kobayashi, S. Lewis Acid Catalyzed Ring-Opening Reactions of Semicyclic *N, O*-Acetals Possessing an Exocyclic Nitrogen Atom: Mechanistic Aspect and Application to Piperidine Alkaloid Synthesis. *J. Am. Chem. Soc.* **2001**, *123*, 12510−12517.
(16) Wang, X.-M.; Liu, Y.-W.; Ma, R.-J.; Si, C.-M.; Wei, B.-G. Synthesis of 1,4- and 1,5-Amino Alcohols via Nucleophilic Addition of Semicyclic *N, O*-Acetal with Organozinc Reagents. *J. Org. Chem.* **2019**, *84*, 11261−11267.
(17) For selected examples about the application of alkyne, see: (a) Li, Y.; Zhang, Q.; Xu, X.; Zhang, X.; Yang, Y.; Yi, W. One-pot Synthesis of 2,4-Disubstituted Quinolines via Silver-Catalyzed Three-Component Cascade Annulation of Amines, Alkyne Esters and Terminal Alkynes. *Tetrahedron Lett.* **2019**, *60*, 965−970. (b) Scarpi, D.; Begliomini, S.; Prandi, C.; Oppedisano, A.; Deagostino, A.; Gómez-Bengoa, E.; Fiser, B.; Occhiato, E. G. Gold-Catalysed Synthesis of Exocyclic Vinylogous Amides and *β*-Amino Ketones: A Detailed Study on the 5-*exo*/6-*endo*-*dig* Selectivity, Methodology and Scope. *Eur. J. Org. Chem.* **2015**, 3251−3265. (c) Sujatha, C.; Bhatt, C. S.; Ravva, M. K.; Suresh, A. K.; Namitharan, K. Copper-Catalyzed Ring-Expansion Cascade of Azirines with Alkynes: Synthesis of Multisubstituted Pyridines at Room Temperature. *Org. Lett.* **2018**, *20*, 3241−3244. (d) Morita, N.; Tsunokake, T.; Narikiyo, Y.; Harada, M.; Tachibana, T.; Saito, Y.; Ban, S.; Hashimoto, Y.; Okamoto, I.; Tamura, O. Gold(I)/(III)-Catalyzed Synthesis of 2-Substituted Piperidines; Valency Controlled Cyclization Modes. *Tetrahedron Lett.* **2015**, *56*, 6269−6272. (e) Wang, C.; Mao, Z.-Y.; Liu, Y.-W.; Wang, Q.-E.; Si, C.-M.; Wei, B.-G.; Lin, G.-Q. Stereoselective Intermolecular [4+2] Process of *N, O*-acetals with Terminal Alkynes for Construction of Functional *cis*-Pyrido and Pyrrolo[1,2-c] [1,3] oxazin-1-ones. *Adv. Synth. Catal.* **2020**, *362*, 822−831.
(18) For selected examples about the application of ynamides, see: (a) Wang, Y.; Song, L.-J.; Zhang, X.; Sun, J. Metal-Free [2+2+2] Cycloaddition of Ynamides and Nitriles: Mild and Regioselective Synthesis of Fully Substituted Pyridines. *Angew. Chem., Int. Ed.* **2016**, *55*, 9704−9708. (b) Ruan, P.-P.; Li, H.-H.; Liu, X.; Zhang, T.; Zuo, S.-X.; Zhu, C.; Ye, L.-W. Synthesis of *α, β*-Unsaturated Amidines through Gold-Catalyzed Intermolecular Reaction of Azides with Ynamides. *J. Org. Chem.* **2017**, *82*, 9119−9125. (c) Rode, N. D.; Arcadi, A.; di Nicola, A.; Marinelli, F.; Michelet, V. Gold-Catalyzed Cascade Reaction of *β*-(2-Aminophenyl)-*α, β*-ynones with Ynamides: A Sequential Route to Polysubstituted 2-Aminoquinolines. *Org. Lett.* **2018**, *20*, 5103−5106. (d) Han, P.; Mao, Z.-Y.; Li, M.; Si, C.-M.; Wei, B.-G.; Lin, G.-Q. Synthesis of Amide Enol Carbamates and Carbonates through Cu$(OTf)_2$-Catalyzed Reactions of Ynamides with *t*-Butyl Carbamates/Carbonates. *J. Org. Chem.* **2020**, *85*, 4740−4752. (e) Im, J.; Shin, S. I.; Cho, C.-G.; Shin, S. Aminooxygenation of Ynamides with *N*-Hydroxybenzotriazoles: Synthesis of *α*-Benzotriazolyl Carbonyl Compounds. *J. Org. Chem.* **2020**, *85*, 6935−6950.
(19) For selected examples, see: (a) Iqbal, N.; Iqbal, N.; Maiti, D.; Cho, E. J. Access to Multifunctionalized Benzofurans by Aryl Nickelation of Alkynes: Efficient Synthesis of the Anti-Arrhythmic Drug Amiodarone. *Angew. Chem., Int. Ed.* **2019**, *58*, 15808−15812. (b) Zhang, D.; Man, J.; Chen, Y.; Yin, L.; Zhong, J.; Zhang, Q.-F. Synthesis of Poly-Functionalized Benzofurans via one-pot Domino Oxidation/[3+2] Cyclization Reactions of a Hydroquinone Ester and Ynamides. *RSC Adv.* **2019**, *9*, 12567−12571. (c) Rong, M.-G.; Qin, T.-Z.; Zi, W. Rhenium-Catalyzed Intramolecular Carboalkoxylation and Carboamination of Alkynes for the Synthesis of C3-Substituted Benzofurans and Indoles. *Org. Lett.* **2019**, *21*, 5421−5425. (d) Qiu, J.; Ohno, S.; Matsuzaki, T.; Suzuki, T.; Murai, K.; Arisawa, M. Iridium-Catalyzed Intramolecular Cycloisomerization between Functionalized Alkyne with Aryl Vinyl Ether: Synthesis of 2-Vinyl-3-Functionalized Methyl-Benzofurans. *J. Org. Chem.* **2020**, 10198.
(20) (a) Dong, J.-J.; Zhang, S.-L. Synthesis of 2,2,2-Trifluoroethyl Oxazoles, Oxazolines and Furans via Alkyne Oxytrifluoromethylation. *Adv. Synth. Catal.* **2020**, *362*, 795−800. (b) Tian, X.; Song, L.; Han, C.; Zhang, C.; Wu, Y.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. Gold (III)-Catalyzed Formal [3 + 2] Annulations of *N*-Acyl Sulfilimines with Ynamides for the Synthesis of 4-Aminooxazoles. *Org. Lett.* **2019**, *21*, 2937−2940. (c) Davies, P. W.; Cremonesi, A.; Dumitrescu, L. Intermolecular and Selective Synthesis of 2,4,5-Trisubstituted Oxazoles by a Gold-Catalyzed Formal [3+2] Cycloaddition. *Angew. Chem., Int. Ed.* **2011**, *50*, 8931−8935.
(21) (a) Chalotra, N.; Ahmed, A.; Rizvi, M. A.; Hussain, Z.; Ahmed, Q. N.; Shah, B. A. Photoredox Generated Vinyl Radicals: Synthesis of Bisindoles and *β*-Carbolines. *J. Org. Chem.* **2018**, *83*, 14443−14456. (b) Cao, J.; Xu, Y.; Kong, Y.; Cui, Y.; Hu, Z.; Wang, G.; Deng, Y.; Lai, G. Synthesis of *δ*-Carbolines via a Pd-Catalyzed Sequential Reaction from 2-Iodoanilines and *N*-Tosylenynamines. *Org. Lett.* **2012**, *14*, 38−41. (c) Wang, G.; You, X.; Gan, Y.; Liu, Y. Synthesis of *δ*- and *α*-Carbolines via Nickel-Catalyzed [2 + 2 + 2] Cycloaddition of Functionalized Alkyne-Nitriles with Alkynes. *Org. Lett.* **2017**, *19*, 110−113.
(22) (a) Yang, Y.; Wang, L.; Zhang, F.; Zhu, G. Preparation of (Z)-*α, β*-Disubstituted Enamides via Palladium Catalyzed Addition of Boronic Acids to Ynamides. *J. Org. Chem.* **2014**, *79*, 9319−9324. (b) Kuai, C.; Wang, L.; Cui, H.; Shen, J.; Feng, Y.; Cui, X. Efficient and Selective Synthesis of (*E*)-Enamides via Ru (II)-Catalyzed Hydroamidation of Internal Alkynes. *ACS Catal.* **2016**, *6*, 186−190. (c) Lin, L.; Zeng, X.; Xu, B. Synthesis of *Z*-Enamides through Heterogeneous Gold-Catalyzed Stereoselective Hydrogenation of Ynamides. *J. Org. Chem.* **2019**, *84*, 11240−11246.
(23) (a) Liu, B.; Ning, Y.; Virelli, M.; Zanoni, G.; Anderson, E. A.; Bi, X. Direct Transformation of Terminal Alkynes into Amidines by a Silver-Catalyzed Four-Component Reaction. *J. Am. Chem. Soc.* **2019**, *141*, 1593−1598. (b) Kim, J.; Stahl, S. S. Cu-Catalyzed Aerobic Oxidative Three-Component Coupling Route to *N*-Sulfonyl Amidines via an Ynamine Intermediate. *J. Org. Chem.* **2015**, *80*, 2448−2454.
(24) (a) Liu, R.-C.; Huang, W.; Ma, J.-Y.; Wei, B.-G.; Lin, G.-Q. $BF_3.Et_2O$ Catalyzed Diastereoselective Nucleophilic Reactions of 3-Silyloxypiperidine *N, O*-acetal with Silyl Enol Ether and Application to the Asymmetric Synthesis of (+)-Febrifugine. *Tetrahedron Lett.* **2009**, *50*, 4046−4049. (b) Liu, Y.-W.; Ma, R.-J.; Yan, J.-H.; Zhou, Z.; Wei, B.-G. Asymmetric Synthesis of (−)-Sedacryptine through a Diastereoselective Mannich Reaction of *N, O*-acetals with Ketones. *Org. Biomol. Chem.* **2018**, *16*, 771−779.
(25) (a) Han, P.; Mao, Z.-Y.; Si, C.-M.; Zhou, Z.; Wei, B.-G.; Lin, G.-Q. Stereoselective Synthesis of Pyrido- and Pyrrolo[1,2-c][1,3]-oxazin-1-ones via a Nucleophilic Addition-Cyclization Process of *N,O*-Acetal with Ynamides. *J. Org. Chem.* **2019**, *84*, 914−923. (b) Liu, Y.-W.; Mao, Z.-Y.; Nie, X.-D.; Si, C.-M.; Wei, B.-G.; Lin, G.-Q. Approach to Tertiary-Type *β*-Hydroxyl Carboxamides Through Sc$(OTf)_3$-

https://dx.doi.org/10.1021/acs.joc.0c01692
J. Org. Chem. XXXX, XXX, XXX−XXX

Catalyzed Addition of Ynamides and Ketones. *J. Org. Chem.* **2019**, *84*, 16254−16261.
(26) (a) Kim, J. H.; Hart, H. T.; Stevens, J. F. Alkaloids of some Asian Sedum Species. *Phytochemistry* **1996**, *41*, 1319−1324. (b) Marion, L.; Lavigne, R.; Lemay, L. the Structure of Sedamine. *Can. J. Chem.* **1951**, *29*, 347−351.
(27) (a) Spangenberg, T.; Breit, B.; Mann, A. Hydroformylation of Homoallylic Azides: A Rapid Approach toward Alkaloids. *Org. Lett.* **2009**, *11*, 262−264. (b) Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. Ag-Catalyzed Asymmetric Mannich Reactions of Enol Ethers with Aryl, Alkyl, Alkenyl, and Alkynyl Imines. *J. Am. Chem. Soc.* **2004**, *126*, 3734−3735. (c) Reddy, A. A.; Prasad, K. R. Synthesis of *β*-Amino Ketones by Addition of Aryl Methyl Ketones to Sulfinimines: Application to the Total Synthesis of HPA-12, Norsedamine, and Sedamine. *J. Org. Chem.* **2017**, *82*, 13488−13499.
(28) Zhang, X.; Zhang, Y.; Huang, J.; Hsung, R. P.; Kurtz, K. C. M.; Oppenheimer, J.; Petersen, M. E.; Sagamanova, I. K.; Shen, L.; Tracey, M. R. Copper (II)-Catalyzed Amidations of Alkynyl Bromides as a General Synthesis of Ynamides and *Z*-Enamides. An Intramolecular Amidation for the Synthesis of Macrocyclic Ynamides. *J. Org. Chem.* **2006**, *71*, 4170−4177.

https://dx.doi.org/10.1021/acs.joc.0c01692
J. Org. Chem. XXXX, XXX, XXX−XXX