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Note

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Auxiliary-assisted palladium-catalyzed direct C(sp^3)-H sulfonamidation to afford 1,2-amino alcohol derivatives

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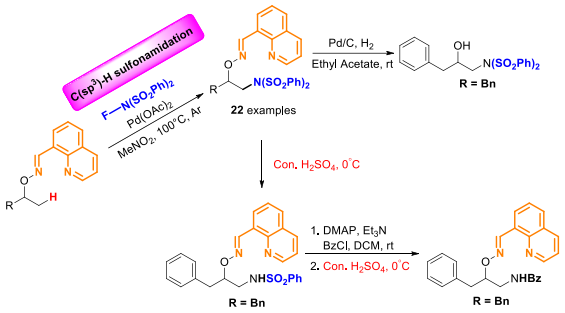
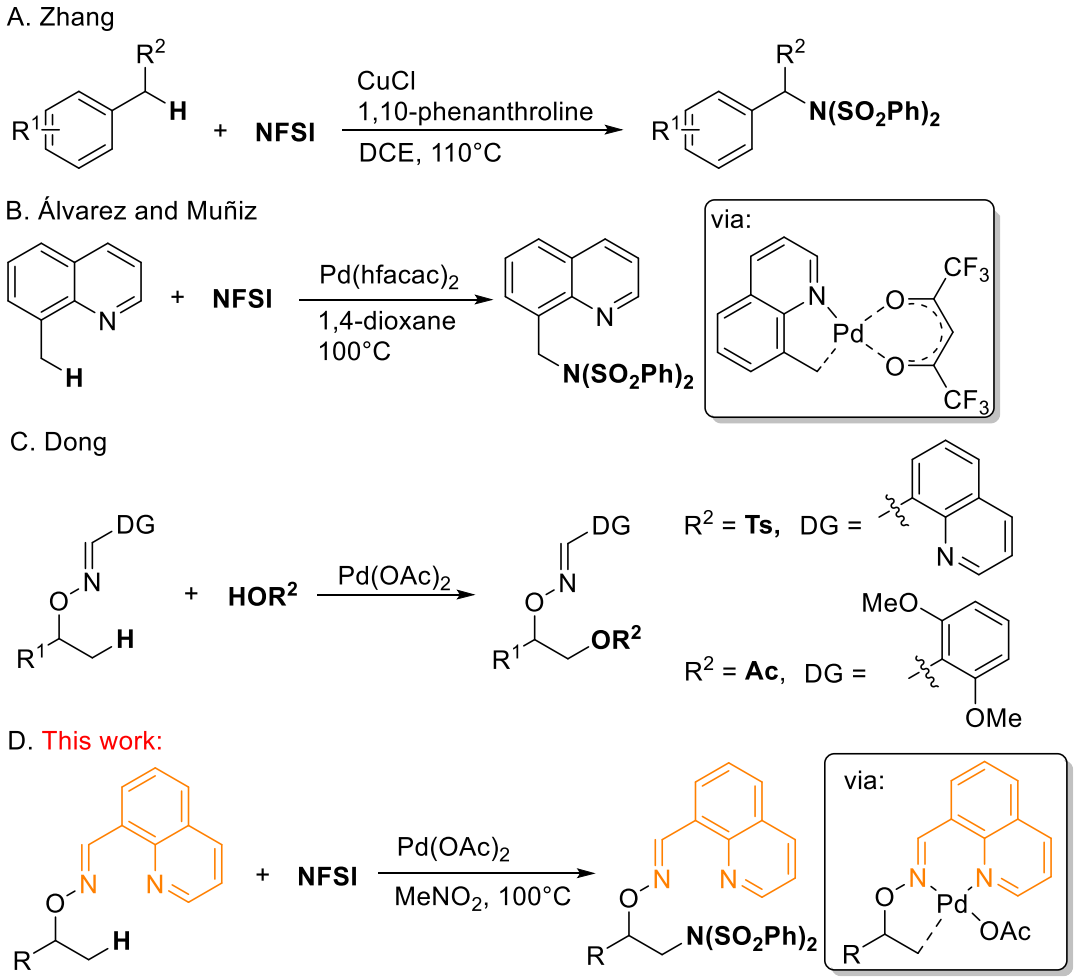


Abstract

An auxiliary-assisted Pd-catalyzed C(sp^3)-H sulfonamidation approach using NFSI as both nitrogen source and oxidant to afford 1,2-amino alcohol derivatives is described in this paper. This method is novel and attractive because of its high yields, wide range of substrate scopes and good tolerance for many functional groups. Oximido and sulfonyl group can be removed with this method.

Transition-metal-catalyzed direct C-H bond functionalization has emerged as a revolutionary synthetic technology to access target molecules during the process of organic synthesis due to its high atom and step economy. [1] Because of the significance of C-N bond formation in the synthetic progress of natural products and drug molecules, direct C-H amination or amidation catalyzed by transition metals, including Pd, Rh, Ir, Ru, Co, and Cu, has been well-established over the past several years. [2] In these typical procedures, C-H amination or amidation can work well to generate the new C-N bond through

two major strategies: one requiring amines/amides and external oxidants[3] and another requiring pre-activated amine sources under oxidant-free conditions, such as *N*-benzoate alkylamines,[4] *N*-chloroamines,[5] and nitrosobenzenes.[6] Recently, many excellent studies have shown that NFSI (*N*-Fluorobenzenesulfonimide), as both a nucleophilic nitrogen or nitrogen radical, is an effective nitrogen source for C-N bond formation, [7] and very recently, it was effectively applied in the benzylic C(sp^3)-H sulfonamidation catalyzed by palladium and copper catalysts to generate C-N bonds with high efficiency. (Scheme 1, A and B).[8]



Scheme 1. Transition-metal-catalyzed direct C(sp^3)-H sulfonamidation

In some classical examples of total synthetic procedures of natural products, the skillful application of directed C(sp^3)-H amination/amidation thoroughly demonstrated the art of total synthesis of complicated compounds,[2c, 9] causing

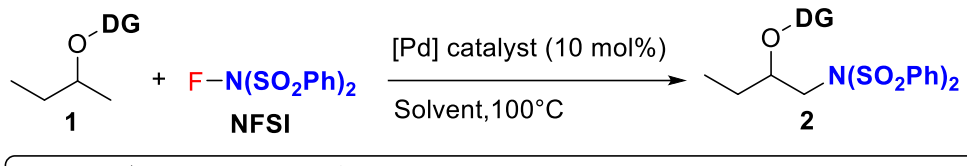
more researchers to take note and try to exploit novel methods of C(sp^3)-H amination/amidation with high efficiency and effective application. Previous studies of C(sp^3)-H amination mainly focused on intramolecular reactions, [2b, 10] but the method was generally limited because of the dependence on the substrate structure. Intermolecular C(sp^3)-H amination/amidation has often occurred on allylic and benzylic C(sp^3)-H bonds; however, activation on other unactivated groups, such as methyl, remains challenging. [11] Therefore, an efficient method with strong stability over a wide range of functional groups is an urgent need.

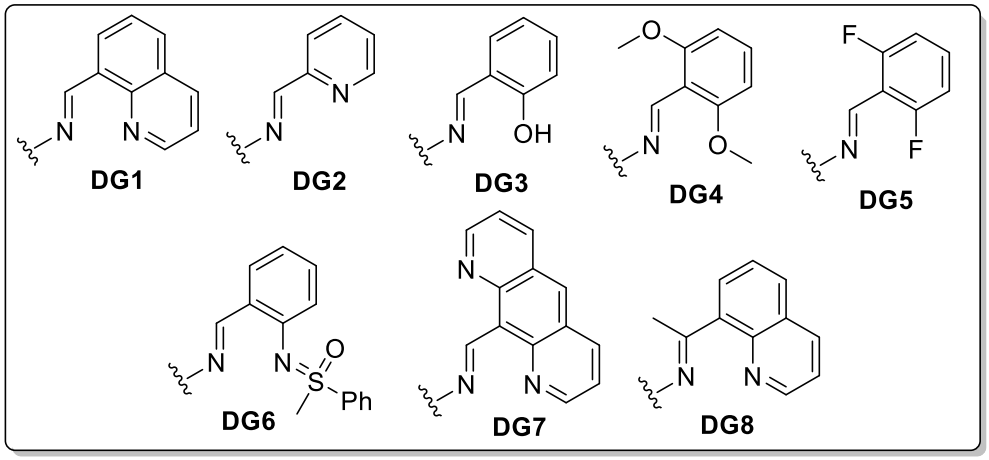
1,2-Amino alcohol is an important moiety in natural products and synthetic pharmacologically active molecules.[12] In the past few years, many small molecules containing the structural fragment of 1,2-amino alcohol have been successfully developed as drugs, such as a selective β2 acceptor agonist (Salbutamol), an α-adrenergicreceptor blocker (Tamsulosin), and a calcium channel blocker (Amlodipine), which shows that 1,2-amino alcohol is an important "privileged structure" for the biological activity of drug molecules. Recently, many intramolecular C-H amidation strategies have been developed to prepare amino alcohol derivatives. [10] Most recently, Chang et al reported a Cp*Ir(III)-catalyzed intermolecular C(sp^3)-H sulfonamidation approach to afford 1,2-amino alcohol by using sulfonyl azide as the nitrogen source via an exo-iridacycle formed through coordination with the ketoximenitrogen.[13] Given the general applicability of Pd-catalyzed coupling reactions in synthesis and the potent catalytic performance of Pd catalysts in the C(sp^3)-H bond activation process, [14] we propose to develop a Pd-catalyzed activation method to realize C-H amidation on the β-position of the hydroxyl group in the alcohol derivatives. In 2012, Álvarez and Muñiz et al (Scheme 1, B) reported that a chelation-assisted 5-member palladacycle intermediate could benefit C(sp^3)-H bond activation, which showed that Pd-catalyzed C-H sulfonamidation strongly relies on the stability of the palladium intermediate.[8a] In 2012 and 2015, Dong et al revealed that the C-H bond on the β-position of the alcohol could be

activated in a Pd-catalytic system by assembling an aldoxime group as an assisted directing group (Scheme 1, C). [15] Inspired by these results, we hypothesized that C-H sulfonamidation on the β-position of alcohol should be feasible by using a suitably auxiliary-assisted aldoxime group to form a stable exo-palladacycle intermediate (Scheme 1, D).

To verify the hypothesis of Pd-catalyzed C(sp^3)-H sulfonamidation of alcohol derivatives, aldoxime-assembling quinolyl (DG1) on butan-2-ol was chosen as a model substrate to test this reaction. By treating with 3.0 equivalent of NFSI in the presence of 10 mol% $Pd(OAc)_2$ in DCE at 100°C, this reaction was completed and the desired C-H sulfonamidated product **2a** was isolated in 52% yield (Table 1, entry 1). We then investigated the solvent effect on this reaction and found that no desired compound was detected by LC-MS when the reaction was performed in toluene or 1,4-dioxane (Table 1, entries 2 and 4). Other solvents such as acetonitrile gave low conversion rate (50%) and isolated yield (31%) at 100°C (Table 1, entry 3), whereas $MeNO_2$ granted a slightly raised yield of 67% (Table 1, entry 5). $Pd(dba)_2$ was effective for this C(sp^3)-H sulfonamidation with 58% yield in $MeNO_2$ (Table 1, entry 6), but $Pd(acac)_2$ had no catalytic performance under the same condition (Table 1, entry 7). Subsequent directing group (DG) screening revealed that only DG1 was effective for this Pd-catalyzed C(sp^3)-H sulfonamidation (Table 1, entries 5 and 8~14). When the reaction of **1a** was carried out in $MeNO_2$ under Ar atmosphere, the isolated yield further increased to 72% (Table 1, entry 15).

Table 1. Optimization of reaction condition[a]





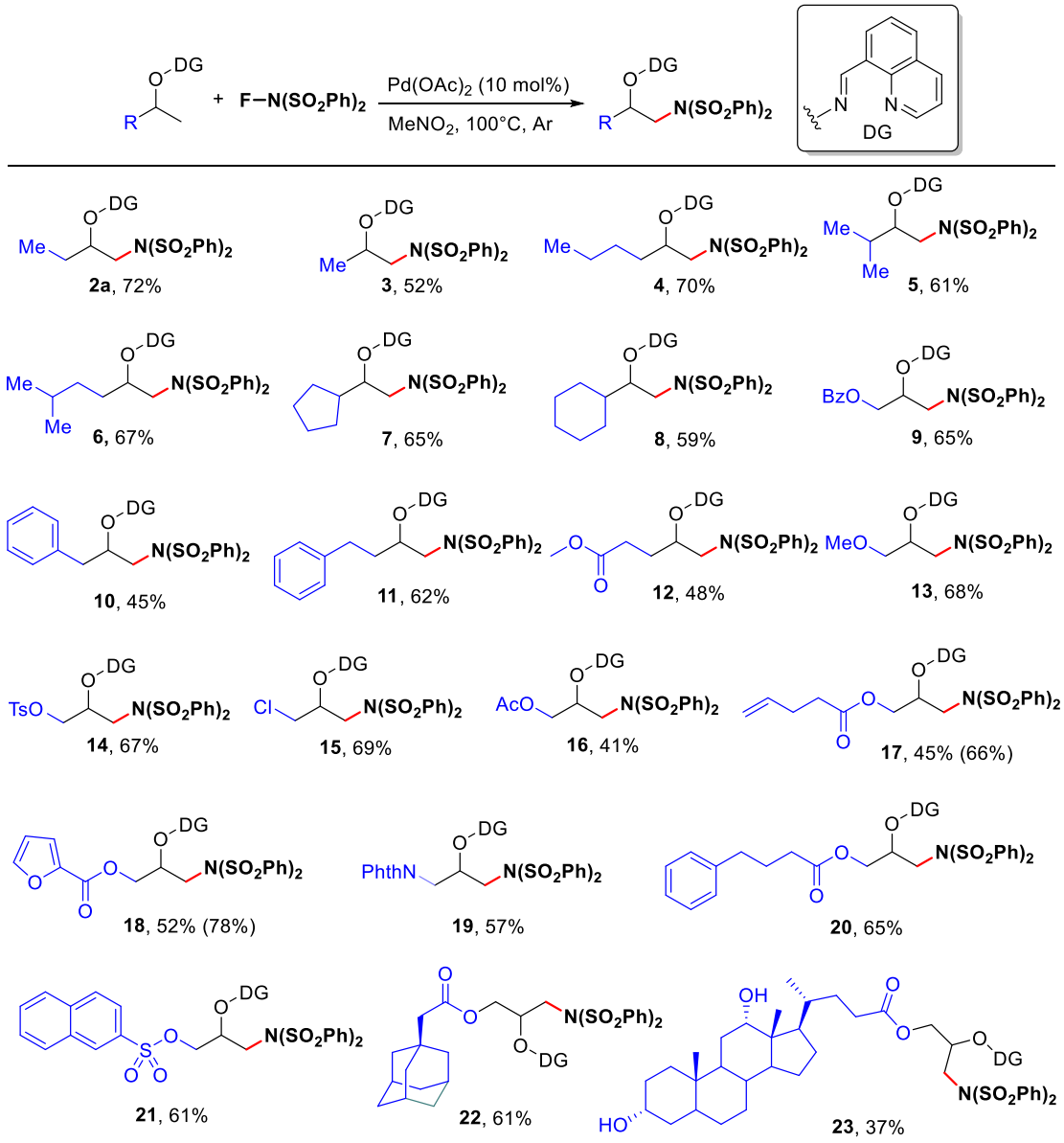
Entry	DG/substrate**1**	Pd catalyst	Solvent	Yield/%[b]
1	DG1/**1a**	$Pd(OAc)_2$	DCE	52
2	DG1/**1a**	$Pd(OAc)_2$	toluene	0
3	DG1/**1a**	$Pd(OAc)_2$	MeCN	31
4	DG1/**1a**	$Pd(OAc)_2$	1,4-dioxane	0
5	DG1/**1a**	$Pd(OAc)_2$	$MeNO_2$	67
6	DG1/**1a**	$Pd(dba)_2$	$MeNO_2$	58
7	DG1/**1a**	$Pd(acac)_2$	$MeNO_2$	0
8	DG2/**1b**	$Pd(OAc)_2$	$MeNO_2$	0
9	DG3/**1c**	$Pd(OAc)_2$	$MeNO_2$	0
10	DG4/**1d**	$Pd(OAc)_2$	$MeNO_2$	0
11	DG5/**1e**	$Pd(OAc)_2$	$MeNO_2$	0
12	DG6/**1f**	$Pd(OAc)_2$	$MeNO_2$	0
13	DG7/**1g**	$Pd(OAc)_2$	$MeNO_2$	0
14	DG8/**1h**	$Pd(OAc)_2$	$MeNO_2$	0
15[c]	DG1/**1a**	$Pd(OAc)_2$	$MeNO_2$	72

[a] Pd catalyst: 10 mo%, **1a**~**1h**: 0.2 mmol, NFSI: 3.0 equiv, solvent: 1.0 mL, under air. [b] Isolated yield. [c] Under Ar. DCE = Dichloroethane

Then, the substrate scope was investigated under the optimal conditions, and the

representative results are summarized in Table 2. A variety of aliphatic aldoxime derivatives can be utilized to afford the corresponding sulfonamides in good yields via this C(sp^3)-H activation, including different lengths of aliphatic chain substitution (**2a**, **3**~**6**), sterically demanding substitutions on the β-position (**5, 7** and **8**) and aromatic groups substituted on different positions (**10** and **11**). Additionally, a range of functional groups are stable in these reaction conditions, such as ester (**9**, **12**, **16**~**18**, **20**, **22** and **23**), chloride (**15**), sulfonate ester (**14** and**21**), amide (**19**), methoxyl (**13**), furyl (**18**), alkenyl (**17**) and hydroxyl (**23**). It is notable that when alkenyl- and furyl-containing substrates were applied in this method, the corresponding desired sulfonamidated products could be obtained with an incomplete conversion in 45% and 52% isolated yields, respectively, and the yields based on the recovered starting material could reach 66% and 78% (**17** and **18**). When the β-position was pre-activated by Cl and OTs, this C(sp^3)-H sulfonamidation also occurred well, and Cl and OTs groups were tolerated under this palladium catalytic condition.

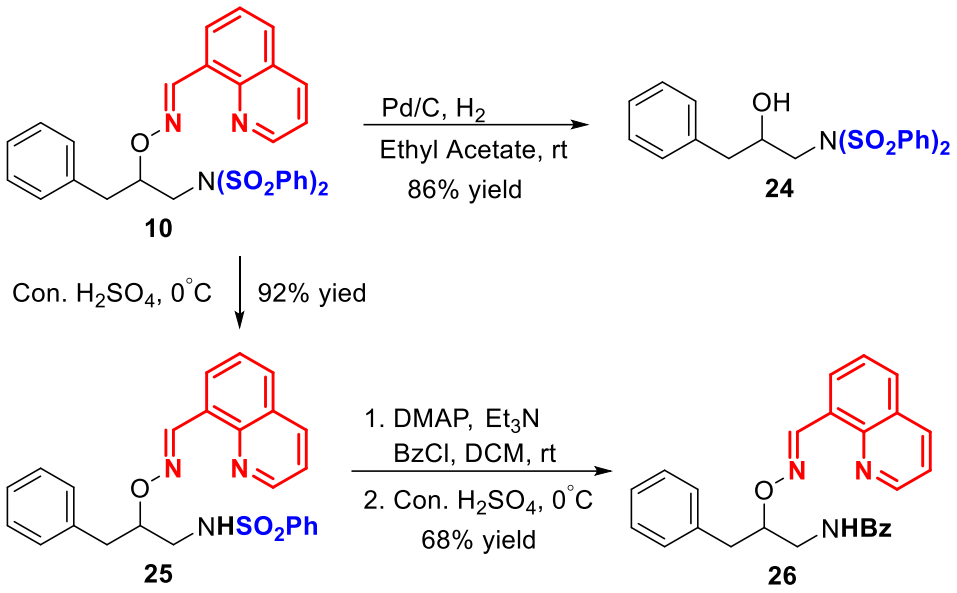
Table 2. Palladium-catalyzed C(sp^3)-H sulfonamidation to afford 1,2-amino alcohol derivatives [a]



[a] $Pd(OAc)_2$: 10 mol%, oxime: 0.2 mmol, NFSI: 3.0 equiv, $MeNO_2$: 1.0 mL, under Ar. Isolated yield (brsm yield in the parentheses), brsm, based on the recovered starting material.

Oximido and sulfonyl group can be removed with this method (Scheme 2). For the product **10**, the N-O bond of oximido is cleaved to give free hydroxyl group compound (**24**) in 86% yield under Pd/C-catalyzed hydrogenation conditions. Alternatively, treatment by con. H_2SO_4 at 0°C takes away one sulfonyl group to afford

compound **25** in excellent yield. Further benzoylation and acidification by con. H_2SO_4 remove the last sulfonyl group to give benzoylated product (**26**).



Scheme 2. Removal of oximido and sulfonyl group

The mechanism of the palladium-catalyzed C(sp^3)-H sulfonamidation is proposed (Scheme S1 in supporting information). Substrate **1a** and the palladium(II) salt coordinate to form palladacycle **I** via auxiliary-assisted C-H activation, which was then oxidized by NFSI to the fluorinated high-oxidation state intermediate **II**.[16] Anionic bis(sulfonyl)imide and cationic fluorinated Pd(IV) intermediate **II** engage in direct nucleophilic substitution to form a new C-N bond and afford the palladium(II) intermediate **III,** which then was cleaved by HOAc to release the sulfonamidated product **2a** and regenerate $Pd(OAc)_2$ for the next catalytic cycle.

In summary, a palladium-catalyzed C(sp^3)-H sulfonamidation was developed using NFSI as both nitrogen source and oxidant to afford 1,2-amino alcohol derivatives in good yields with a wide range of substrate scopes. Oximido and sulfonyl group are removed, respectively, in this method. Compared with previous synthetic methods, this method is attractive for its highly efficient catalytic performance and tolerance for many functional groups, which likely

provides a potential application in the study of 1,2-amino alcohol fragment drugs.

Experimental Section

General information

The automatic LC-MS analysis was also performed on a Thermo Finnigan LCQ Advantage mass spectrometer equipped with an Agilent HPLC system and an eluent splitter (5% eluent was split into the MS system).

High-resolution LC-MS was carried out by Agilent LC/MSD TOF using a column of Agilent ZORBAX SB-C18 (rapid resolution, 3.5 μm, 2.1 × 30 mm) at a flow of 0.40 mL/min. The solvent was MeOH/water (75:25 (v/v)), containing 5 mmol/L ammonium formate. The ion source is electrospray ionization (ESI).

Proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectroscopy were performed on Bruker Advance 400, spectrometer. Chemical shifts of ^{1}H NMR spectra are reported as in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-d (δ = 7.260, singlet) or dmso-*d6* (δ = 2.500, quintet). Multiplicities were given as: s (singlet); br s (broad singlet); d (doublet); t (triplet); q (quartet); dd (doublet of doublets); m (multiplets), etc. The number of protons (n) for a given resonance is indicated by nH. Carbon nuclear magnetic resonance spectra (^{13}C NMR) are reported as in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-d (δ = 77.160, triplet) or dmso-*d6* (δ = 39.510, septet).

Gerenal procedure for synthesis of oximes.[15b] Alcohol (20 mmol), *N*-hydroxyphthalimide (24 mmol) and PPh_3 (24 mmol) were dissolved in 30 mL THF. The mixture was cooled to 0°C, and DIAD (24 mmol) was added. Then the reaction mixture was warmed to room temperature and stirred

overnight. The reaction mixture was concentrated, and the residue was purified with flash column chromatography to afford the PhthN protected alcohols. 2 mmol PhthN protected alcohol was dissolved in 10 mL MeOH, and 120 μL hydrazine hydrate was added. The reaction mixture was stirred at room temperature for 1h, then 2 mmol aldehyde was added. The reaction mixture was stirred at room temperature for 30min and concentrated, and the residue was purified with flash column chromatography to afford oxime.

(E)-quinoline-8-carbaldehyde O-(sec-butyl) oxime. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.39 (s, 1H), 8.95 (d, *J* = 3.0 Hz, 1H), 8.29 (d, *J* = 7.3 Hz, 1H), 8.17 (d, *J* = 8.2 Hz, 1H), 7.84 (d, *J* = 8.1 Hz, 1H), 7.56 (t, *J* = 7.7 Hz, 1H), 7.43 (dd, *J* = 8.2, 4.1 Hz, 1H), 4.41 – 4.28 (m, 1H), 1.89 – 1.72 (m, 1H), 1.71 – 1.55 (m, 1H), 1.33 (d, *J* = 6.3 Hz, 3H), 1.00 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 145.9, 145.5, 136.5, 130.7, 129.2, 128.4, 126.6, 126.3, 121.5, 81.0, 28.7, 19.5, 9.9.

(E)-picolinaldehyde O-(sec-butyl) oxime. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, *J* = 3.5 Hz, 1H), 8.16 (s, 1H), 7.81 (d, *J* = 7.9 Hz, 1H), 7.68 (t, *J* = 7.3 Hz, 1H), 7.25 (d, *J* = 8.8 Hz, 1H), 4.37 – 4.26 (m, 1H), 1.86 – 1.69 (m, 1H), 1.65 – 1.53 (m, 1H), 1.30 (d, *J* = 6.3 Hz, 3H), 0.97 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 149.4, 148.3, 136.7, 123.8, 121.0, 81.8, 28.6, 19.4, 9.8.

(E)-2-hydroxybenzaldehyde O-(sec-butyl) oxime. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.06 (s, 1H), 8.16 (s, 1H), 7.26 (t, *J* = 7.7 Hz, 1H), 7.14 (d, *J* = 7.5 Hz, 1H), 6.98 (d, *J* = 8.2 Hz, 1H), 6.90 (t, *J* = 7.4 Hz, 1H), 4.30 – 4.16 (m, 1H), 1.82 – 1.67 (m, 1H), 1.68 – 1.53 (m, 1H), 1.30 (d, *J* = 6.3 Hz, 3H), 0.97 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 151.0, 131.0, 130.7, 119.7, 116.9, 116.8, 81.6, 28.4, 19.1, 9.7.

(E)-2,6-dimethoxybenzaldehyde O-(sec-butyl) oxime. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.25 (t, *J* = 6.8 Hz, 1H), 6.56 (d, *J* = 8.3 Hz, 2H), 4.41 –

4.26 (m, 1H), 3.84 (s, 6H), 1.82 – 1.72 (m, 1H), 1.64 – 1.50 (m, 1H), 1.29 (d, *J* = 6.3 Hz, 3H), 0.97 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 143.4, 130.7, 110.1, 104.3, 80.3, 56.2, 28.7, 19.3, 9.8.

(E)-2,6-difluorobenzaldehyde O-(sec-butyl) oxime. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.32 – 7.19 (m, 1H), 6.92 (t, *J* = 8.4 Hz, 2H), 4.35 – 4.25 (m, 1H), 1.81 –1.71 (m, 1H), 1.65 – 1.52 (m, 1H), 1.29 (d, *J* = 6.3 Hz, 3H), 0.96 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3(d, *J* = 6.8 Hz), 159.7 (d, *J* = 6.8 Hz), 138.8, 130.4 (t, *J* = 10.5 Hz), 111.9 (m), 81.5, 28.6, 19.3, 9.8.

(E)-2-((methyl(oxo)(phenyl)-l6-sulfanylidene)amino)benzaldehyde O-(sec-butyl) oxime. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (s, 1H), 7.92 (d, *J* = 8.0 Hz, 2H), 7.78 (d, *J* = 7.7 Hz, 1H), 7.59 (t, *J* = 7.2 Hz, 1H), 7.52 (t, *J* = 7.4 Hz, 2H), 7.05 – 6.95 (m, 2H), 6.86 (t, *J* = 7.3 Hz, 1H), 4.27 (q, *J* = 6.4 Hz, 1H), 3.26 (s, 3H), 1.84 – 1.74 (m, 1H), 1.70 – 1.52 (m, 1H), 1.35 – 1.29 (m, 3H), 1.04 – 0.95 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.2, 143.8, 139.3, 133.5, 130.2, 129.7, 128.6, 126.3, 126.2, 122.4, 121.9, 80.7, 46.4, 28.7, 19.4, 9.9.

(E)-pyrido[3,2-g]quinoline-10-carbaldehyde O-(sec-butyl) oxime. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.54 (s, 1H), 9.08 (d, *J* = 1.8 Hz, 2H), 8.33 (s, 1H), 8.28 (d, *J* = 8.4 Hz, 2H), 7.41 (dd, *J* = 8.5, 3.7 Hz, 2H), 4.54 – 4.43 (m, 1H), 2.02 – 1.83 (m, 1H), 1.73 – 1.61 (m, 1H), 1.40 (d, *J* = 6.2 Hz, 3H), 1.02 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 145.8, 136.4, 134.3, 128.5, 126.6, 123.5, 121.2, 80.7, 28.8, 19.4, 9.9.

(E)-1-(quinolin-8-yl)ethan-1-one O-(sec-butyl) oxime. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (d, *J* = 2.5 Hz, 1H), 8.14 (d, *J* = 8.2 Hz, 1H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.73 (d, *J* = 7.0 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.39 (dd, *J* = 8.2, 4.2 Hz, 1H), 4.35 – 4.25 (m, 1H), 2.47 (s, 3H), 1.88 – 1.75 (m, 1H), 1.68 – 1.55 (m, 1H), 1.32 (d, *J* = 6.3 Hz, 3H), 0.99 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz,

$CDCl_3$) δ 157.2, 150.0, 146.7, 137.8, 136.2, 129.5, 128.8, 128.6, 126.4, 121.2, 80.4, 28.8, 19.5, 17.7, 9.9.

(E)-quinoline-8-carbaldehyde O-isopropyl oxime. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.39 (s, 1H), 8.92 (d, *J* = 1.8 Hz, 1H), 8.27 (d, *J* = 7.2 Hz, 1H), 8.14 (d, *J* = 8.2 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.55 (t, *J* = 7.7 Hz, 1H), 7.45 – 7.38 (m, 1H), 4.54 (dt, *J* = 12.4, 6.2 Hz, 1H), 1.36 (s, 3H), 1.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 146.0, 145.6, 136.3, 130.7, 129.3, 128.4, 126.5, 126.2, 121.4, 75.9, 21.9.

(E)-quinoline-8-carbaldehyde O-hexan-2-yl oxime. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.39 (s, 1H), 8.94 (s, 1H), 8.28 (d, *J* = 7.3 Hz, 1H), 8.16 (d, *J* = 8.3 Hz, 1H), 7.84 (d, *J* = 8.1 Hz, 1H), 7.56 (t, *J* = 7.7 Hz, 1H), 7.43 (dd, *J* = 8.0, 4.0 Hz, 1H), 4.52 – 4.27 (m, 1H), 1.96 – 1.69 (m, 1H), 1.61 – 1.51 (m, 1H), 1.52 – 1.27 (m, 7H), 0.92 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 145.9, 145.4, 136.4, 130.7, 129.2, 128.4, 126.6, 126.2, 121.4, 79.9, 35.7, 27.9, 23.0, 20.1, 14.2.

(E)-quinoline-8-carbaldehyde O-(3-methylbutan-2-yl) oxime. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.40 (s, 1H), 8.95 (s, 1H), 8.29 (d, *J* = 7.3 Hz, 1H), 8.17 (d, *J* = 8.2 Hz, 1H), 7.84 (d, *J* = 8.1 Hz, 1H), 7.56 (t, *J* = 7.7 Hz, 1H), 7.43 (dd, *J* = 7.8, 3.8 Hz, 1H), 4.21 (p, *J* = 6.1 Hz, 1H), 2.06 – 1.97 (m, 1H), 1.28 (t, *J* = 6.8 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.9, 145.8, 145.2, 136.5, 130.7, 129.2, 128.4, 126.6, 126.2, 121.4, 84.3, 32.4, 18.8, 17.7, 16.2.

(E)-quinoline-8-carbaldehyde O-(5-methylhexan-2-yl) oxime. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.39 (s, 1H), 8.97 – 8.90 (m, 1H), 8.28 (d, *J* = 6.8 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.84 (d, *J* = 7.5 Hz, 1H), 7.56 (t, *J* = 7.7 Hz, 1H), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1H), 4.48 – 4.24 (m, 1H), 1.88 – 1.69 (m, 1H), 1.64 – 1.47

(m, 2H), 1.44 – 1.23 (m, 5H), 0.92 (s, 3H), 0.90 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 145.9, 145.4, 136.4, 130.7, 129.2, 128.4, 126.5, 126.2, 121.5, 80.1, 34.8, 33.8, 28.3, 22.8, 22.7, 20.1.

(E)-quinoline-8-carbaldehyde O-(1-cyclopentylethyl) oxime. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.38 (s, 1H), 8.94 (d, *J* = 2.6 Hz, 1H), 8.29 (d, *J* = 7.3 Hz, 1H), 8.16 (d, *J* = 8.3 Hz, 1H), 7.83 (d, *J* = 8.1 Hz, 1H), 7.56 (t, *J* = 7.7 Hz, 1H), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1H), 4.28 – 4.17 (m, 1H), 2.11 (dd, *J* = 16.5, 8.2 Hz, 1H), 1.90 – 1.82 (m, 1H), 1.79 – 1.71 (m, 1H), 1.68 – 1.60 (m, 2H), 1.58 – 1.50 (m, 2H), 1.35 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (100MHz, $CDCl_3$) δ 149.9, 145.8, 145.1, 136.5, 130.7, 129.2, 128.4, 126.6, 126.2, 121.4, 83.9, 45.3, 29.4, 29.2, 25.8(×2), 19.1.

(E)-quinoline-8-carbaldehyde O-(1-cyclohexylethyl) oxime. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.39 (s, 1H), 8.99 – 8.89 (m, 1H), 8.29 (d, *J* = 7.2 Hz, 1H), 8.20 – 8.11 (m, 1H), 7.83 (d, *J* = 8.1 Hz, 1H), 7.56 (t, *J* = 7.7 Hz, 1H), 7.42 (dd, *J* = 8.3, 4.2 Hz, 1H), 4.20 (p, *J* = 6.3 Hz, 1H), 1.91 (d, *J* = 12.7 Hz, 1H), 1.80 – 1.60 (m, 5H), 1.37 – 1.05 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.9, 145.8, 145.2, 136.4, 130.7, 129.2, 128.4, 126.6, 126.2, 121.4, 83.9, 42.6, 29.2, 28.4, 26.8, 26.5, 26.4, 17.0.

(E)-2-(((quinolin-8-ylmethylene)amino)oxy)propyl benzoate. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.44 (s, 1H), 8.94 (dd, *J* = 4.1, 1.6 Hz, 1H), 8.25 (dd, *J* = 7.3, 1.3 Hz, 1H), 8.17 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.12 – 8.04 (m, 2H), 7.85 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.56 –7.51 (m, 2H), 7.46 – 7.36 (m, 3H), 4.90 – 4.73 (m, 1H), 4.55 (d, *J* = 5.0 Hz, 2H), 1.47 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 150.1, 146.6, 145.9, 136.6, 133.1, 130.4, 130.2, 130.0, 129.6, 128.5 (×2), 126.6, 126.5, 121.6, 77.4, 67.2, 16.9.

(E)-quinoline-8-carbaldehyde O-(1-phenylpropan-2-yl) oxime. ^{1}H NMR (400

MHz, $CDCl_3$) δ 9.41 (s, 1H), 8.95 (s, 1H), 8.28 (d, *J* = 7.2 Hz, 1H), 8.16 (d, *J* = 8.2 Hz, 1H), 7.84 (d, *J* = 8.1 Hz, 1H), 7.56 (t, *J* = 7.7 Hz, 1H), 7.43 (dd, *J* = 8.1, 4.0 Hz, 1H), 7.35 – 7.16 (m, 5H), 4.74 – 4.53 (m, 1H), 3.19 (dd, *J* = 13.6, 5.7 Hz, 1H), 2.85 (dd, *J* = 13.6, 7.0 Hz, 1H), 1.31 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 145.9 (×2), 138.8, 136.5, 130.5, 129.8, 129.4, 128.4, 128.3, 126.6, 126.3, 126.2, 121.5, 80.4, 42.3, 19.4.

(E)-quinoline-8-carbaldehyde O-(4-phenylbutan-2-yl) oxime. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.43 (s, 1H), 8.95 (d, *J* = 2.3 Hz, 1H), 8.29 (d, *J* = 7.2 Hz, 1H), 8.16 (d, *J* = 8.2 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.56 (t, *J* = 7.7 Hz, 1H), 7.43 (dd, *J* = 8.1, 4.1 Hz, 1H), 7.31 – 7.21 (m, 4H), 7.18 (t, *J* = 7.0 Hz, 1H), 4.49 – 4.38 (m, 1H), 2.98 – 2.65 (m, 2H), 2.16 – 2.05 (m, 1H), 1.95 – 1.84 (m, 1H), 1.38 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 145.8, 145.6, 142.5, 136.5, 130.6, 129.3, 128.6, 128.5, 128.4, 126.6, 126.3, 125.8, 121.5, 79.0, 37.7, 31.9, 20.2.

methyl (E)-4-(((quinolin-8-ylmethylene)amino)oxy)pentanoate. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.37 (s, 1H), 8.94 (d, *J* = 2.6 Hz, 1H), 8.27 (d, *J* = 7.2 Hz, 1H), 8.16 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.56 (t, *J* = 7.7 Hz, 1H), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1H), 4.49 – 4.38 (m, 1H), 3.68 (s, 3H), 2.58 – 2.43 (m, 2H), 2.10 – 1.95 (m, 2H), 1.36 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 150.0, 145.8 (×2), 136.5, 130.4, 129.4, 128.4, 126.5, 126.3, 121.5, 78.6, 51.7, 31.0, 30.3, 20.0.

(E)-quinoline-8-carbaldehyde O-(1-methoxypropan-2-yl) oxime. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.43 (s, 1H), 8.94 (dd, *J* = 4.1, 1.6 Hz, 1H), 8.27 (dd, *J* = 7.3, 1.3 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.85 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.56 (t, *J* = 7.7 Hz, 1H), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1H), 4.64 – 4.54 (m, 1H), 3.65 (dd, *J* = 10.4, 5.7 Hz, 1H), 3.55 (dd, *J* = 10.4, 4.4 Hz, 1H), 3.43 (s, 3H), 1.37 (d, *J* =

6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 146.4, 145.8, 136.5, 130.3, 129.5, 128.4, 126.5, 126.5, 121.5, 78.6, 75.3, 59.5, 16.9.

(E)-quinoline-8-carbaldehyde O-(1-chloropropan-2-yl) oxime. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.44 (s, 1H), 8.93 (d, *J* = 2.3 Hz, 1H), 8.26 (d, *J* = 7.3 Hz, 1H), 8.16 (d, *J* = 8.2 Hz, 1H), 7.86 (d, *J* = 8.1 Hz, 1H), 7.56 (t, *J* = 7.7 Hz, 1H), 7.43 (dd, *J* = 8.2, 4.1 Hz, 1H), 4.65 –4.55 (m, 1H), 3.83 (dd, *J* = 11.0, 3.9 Hz, 1H), 3.70 (dd, *J* = 10.9, 6.2 Hz, 1H), 1.46 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 147.0, 145.9, 136.4, 130.0, 129.7, 128.4, 126.5, 126.4, 121.5, 78.7, 47.2, 17.4.

(E)-2-(((quinolin-8-ylmethylene)amino)oxy)propyl 4-phenylbutanoate. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.46 (s, 1H), 8.94 (dd, *J* = 4.1, 1.7 Hz, 1H), 8.29 (dd, *J* = 7.3, 1.1 Hz, 1H), 8.18 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.88 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.58 (t, *J* = 7.7 Hz, 1H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.30 – 7.25 (m, 2H), 7.22 – 7.16 (m, 3H), 4.69 – 4.615 (m, 1H), 4.33 (dd, *J* = 5.0, 1.8 Hz, 2H), 2.68 (t, *J* = 7.4 Hz, 2H), 2.41 (t, *J* = 7.4 Hz, 2H), 2.05 – 1.95 (m, 2H), 1.41 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 150.1, 146.6, 146.0, 141.5, 136.4, 130.2, 129.6, 128.6, 128.5, 128.4, 126.5, 126.3, 126.0, 121.5, 77.2, 66.4, 35.3, 33.7, 26.7, 16.7.

(E)-2-(((quinolin-8-ylmethylene)amino)oxy)propyl acetate. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.42 (s, 1H), 8.97 (d, *J* = 2.7 Hz, 1H), 8.27 (dd, *J* = 7.3, 1.3 Hz, 1H), 8.19 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.87 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.58 (t, *J* = 7.7 Hz, 1H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 4.72 – 4.58 (m, 1H), 4.30 (dd, *J* = 5.0, 1.5 Hz, 2H), 2.10 (s, 3H), 1.38 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 150.1, 146.6, 145.7, 136.8, 130.1, 129.7, 128.5, 126.7 (×2), 121.6, 77.3, 66.6, 21.1, 16.8.

(E)-quinoline-8-carbaldehyde O-(1-(1,3-dioxoisoindolin-2-yl)propan-2-yl) oxime. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.29 (s, 1H), 8.90 (d, *J* = 3.9 Hz, 1H), 8.12 (d, *J* = 8.3 Hz, 1H), 7.92 (d, *J* = 7.3 Hz, 1H), 7.89 – 7.85 (m, 1H), 7.80 – 7.73 (m, 2H), 7.65 – 7.60 (m, 2H), 7.44 – 7.33 (m, 2H), 4.88 – 4.76 (m, 1H), 4.09 (dd, *J* = 14.0, 8.3 Hz, 1H), 3.82 (dd, *J* = 14.0, 4.1 Hz, 1H), 1.41 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 150.0, 146.4, 136.5, 134.5, 133.9, 132.9, 132.5, 129.4, 128.4, 126.4, 123.8, 123.4, 121.5, 76.6, 42.9, 17.9.

(E)-2-(((quinolin-8-ylmethylene)amino)oxy)propyl pent-4-enoate. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.42 (s, 1H), 8.95 (dd, *J* = 4.1, 1.6 Hz, 1H), 8.27 (dd, *J* = 7.3, 1.3 Hz, 1H), 8.17 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.86 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.57 (t, *J* = 7.7 Hz, 1H), 7.44 (dd, *J* = 8.3, 4.2 Hz, 1H), 5.88 – 5.76 (m, 1H), 5.02 (ddq, *J* = 22.3, 10.2, 1.4 Hz, 2H), 4.72 – 4.56 (m, 1H), 4.31 (d, *J* = 2.7 Hz, 2H), 2.54 – 2.44 (m, 2H), 2.44 – 2.35 (m, 2H), 1.38 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 150.1, 146.6, 145.9, 136.9, 136.6, 130.2, 129.7, 128.5, 126.6, 126.6, 121.6, 115.7, 77.3, 66.5, 33.7, 29.1, 16.8.

(E)-2-(((quinolin-8-ylmethylene)amino)oxy)propyl furan-2-carboxylate. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.42 (s, 1H), 8.93 (dd, *J* = 4.1, 1.7 Hz, 1H), 8.24 (dd, *J* = 7.3, 1.2 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.85 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.59 – 7.52 (m, 2H), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.21 (dd, *J* = 3.5, 0.7 Hz, 1H), 6.48 (dd, *J* = 3.5, 1.7 Hz, 1H), 4.79 – 4.69 (m, 1H), 4.52 (dd, *J* = 5.0, 2.0 Hz, 2H), 1.44 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 150.1, 146.7, 146.5, 146.0, 144.8, 136.5, 130.3, 129.6, 128.5, 126.6, 126.5, 121.6, 118.3, 112.0, 77.2, 66.9, 16.8.

2-((((E)-quinolin-8-ylmethylene)amino)oxy)propyl 2-((3r,5r,7r)-adamantan-1-yl)acetate. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.41 (s, 1H), 8.93 (dd, *J* = 4.1, 1.7 Hz, 1H), 8.27 (dd, *J* = 7.3, 1.3 Hz, 1H), 8.17 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.85 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.56 (t, *J* = 7.7 Hz, 1H), 7.43

(dd, *J* = 8.3, 4.2 Hz, 1H), 4.68 – 4.57 (m, 1H), 4.28 (d, *J* = 5.0 Hz, 2H), 2.12 (s, 2H), 2.00 – 1.90 (m, 3H), 1.68 – 1.56 (m, 12H), 1.39 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 150.1, 146.6, 146.0, 136.5, 130.3, 129.6, 128.5, 126.6, 126.5, 121.6, 77.3, 66.1, 49.2, 42.6, 36.9, 33.0, 28.8, 16.9.

2-((E)-(quinolin-8-ylimino)methoxy)propyl (4R)-4-((3R,10S,12S,13R,17R)-3,12-dihydroxy-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)pentanoate. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.43 (s, 1H), 8.98 (d, *J* = 2.7 Hz, 1H), 8.30 (dd, *J* = 7.3, 1.1 Hz, 1H), 8.25 – 8.19 (m, 1H), 7.89 (d, *J* = 7.5 Hz, 1H), 7.78 – 7.66 (m, 1H), 7.66 – 7.57 (m, 1H), 7.52 – 7.44 (m, 2H), 4.70 –4.62 (m, 1H), 4.35 – 4.27 (m, 2H), 3.97 –3.93 (m, 1H), 3.69 – 3.57 (m, 1H), 2.48 – 2.38 (m, 1H), 2.35 –2.26 (m, 1H), 1.92 – 1.72 (m, 8H), 1.72 – 1.61 (m, 2H), 1.55 –1.45 (m, 3H), 1.45 –1.35 (m, 8H), 1.31 – 1.24 (m, 2H), 1.15 – 1.05 (m, 2H), 1.03 – 0.95 (m, 4H), 0.90 (s, 3H), 0.65 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 150.1, 146.5, 145.8, 136.7, 130.2, 129.7, 128.6, 126.7, 121.6, 73.3, 72.0, 66.4, 48.4, 47.6, 46.7, 42.3, 36.7, 36.2, 35.4, 35.3, 34.3, 33.9, 31.6, 31.1, 30.7, 28.8, 27.6, 27.3, 26.3, 23.8, 23.4, 17.5, 16.8, 12.9.

C-H sulfonamidation procedure for synthesis of 2a:

A 5 mL round-bottom flask was charged with $Pd(OAc)_2$ (10 mol%, 4.6 mg), NFSI (3.0 equiv, 189.2 mg), oxime **1a** (0.2 mmol, 45.6 mg) and 1.0 mL $MeNO_2$. The mixture was stirred at 100ºC under Ar atmosphere, and the reaction was monitored by UPLC-MS. When the starting material was consumed completely, the reaction mixture was cooled to room temperature, then 1,10-phenanthroline (8 mg) and Na_2CO_3 (180 mg) were added to quench the reaction, and the mixture was further stirred at room temperature for 24h. Then the mixture was filtered through a pad of Celite and washed with DCM. The filtrate was concentrated, and the residue was purified with flash column chromatography (Petroleum ether/ethyl acetate/DCM =

20:1:5) to afford the amidated product **2a** as a colorless oil (75 mg, 72% yield), R_f = 0.4 (Petroleum ether/EtOAc/DCM = 20:1:5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (s, 1H), 8.91 (d, *J* = 22.6 Hz, 1H), 8.18 (d, *J* = 7.2 Hz, 1H), 8.12 (d, *J* = 6.5 Hz, 5H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.56 – 7.38 (m, 8H), 4.70 –4.62 (m, 1H), 4.28 (dd, *J* = 15.6, 8.2 Hz, 1H), 3.79 (dd, *J* = 15.5, 2.6 Hz, 1H), 1.83 – 1.64 (m, 2H), 1.00 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.9, 146.2, 145.7, 139.8, 136.3, 133.7, 130.0, 129.5, 129.0, 128.5, 128.2, 126.4, 126.2, 121.5, 83.3, 51.5, 25.2, 9.5. HRMS (ESI): m/z (M + H^+) calcd for $C_{26}H_{26}O_5N_3S_2$, 524.1308, found: 524.1300.

*(E)-N-(phenylsulfonyl)-N-(2-(((quinolin-8-ylmethylene)amino)oxy)propyl) benzenesulfonamide (**3**)*, a colorless oil (53 mg, 52% yield). R_f = 0.4 (Petroleum ether/EtOAc/DCM = 20:1:5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (d, *J* = 26.9 Hz, 1H), 8.97 – 8.94 (m, 1H), 8.27 – 8.07 (m, 6H), 7.86 (d, *J* = 8.1 Hz, 1H), 7.65 – 7.40 (m, 8H), 4.94 – 4.75 (m, 1H), 4.24 (dd, *J* = 15.6, 8.1 Hz, 1H), 3.74 (dd, *J* = 15.6, 3.9 Hz, 1H), 1.33 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 146.5, 145.9, 139.9, 136.3, 133.8, 130.1, 129.6, 129.1, 128.6, 128.3, 126.5, 126.3, 121.5, 78.5, 52.8, 18.0. HRMS (ESI): m/z (M + H^+) calcd for $C_{25}H_{24}O_5N_3S_2$, 510.1152, found: 510.1143.

*(E)-N-(phenylsulfonyl)-N-(2-(((quinolin-8-ylmethylene)amino)oxy)hexyl) benzenesulfonamide (**4**)*, a colorless oil (77 mg, 70% yield). R_f = 0.4 (Petroleum ether/EtOAc/DCM = 20:1:5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (s, 1H), 8.96 (d, *J* = 2.1 Hz, 1H), 8.18 (d, *J* = 6.7 Hz, 2H), 8.11 (d, *J* = 6.9 Hz, 4H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.62 – 7.41 (m, 8H), 4.72 – 4.63 (m, 1H), 4.26 (dd, *J* = 15.6, 8.2 Hz, 1H), 3.77 (dd, *J* = 15.5, 3.2 Hz, 1H), 1.78 – 1.67 (m 1H), 1.65 – 1.55 (m, 1H), 1.52 – 1.41 (m, 1H), 1.38 – 1.27 (m, 3H), 0.88 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 146.1, 145.8, 140.0, 136.5, 133.8, 130.2, 129.5, 129.1, 128.6, 128.4, 126.5, 126.4, 121.5, 82.3, 51.9, 31.9, 27.4, 22.8, 14.1. HRMS (ESI): m/z (M + H^+) calcd for $C_{28}H_{30}O_5N_3S_2$, 552.1621, found: 552.1610.

*(E)-N-(3-methyl-2-(((quinolin-8-ylmethylene)amino)oxy)butyl)-N-(phenylsulfonyl) benzenesulfonamide (**5**)*, a colorless oil (65 mg, 61% yield). R_f = 0.4 (Petroleum ether/EtOAc/DCM = 20:1:5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (s, 1H), 8.98 (s, 1H), 8.20 (d, *J* = 7.0 Hz, 1H), 8.19 – 8.04 (m, 5H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.51 – 7.44 (m, 1H), 7.47 (d, *J* = 1.6 Hz, 7H), 4.63 – 4.57 (m, 1H), 4.24 (dd, *J* = 15.8, 9.2 Hz, 1H), 3.76 (d, *J* = 15.8 Hz, 1H), 2.16 – 2.05 (m, 1H), 1.04 (d, *J* = 6.9 Hz, 3H), 0.99 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.8, 145.7, 145.3, 139.9, 136.9, 133.7, 129.9, 129.5, 129.0, 128.6, 128.4, 126.7 (×2), 121.5, 86.8, 49.71, 30.6, 18.0, 17.9. HRMS (ESI): m/z (M + H^+) calcd for $C_{27}H_{28}O_5N_3S_2$, 538.1465, found: 538.1455.

*(E)-N-(5-methyl-2-(((quinolin-8-ylmethylene)amino)oxy)hexyl)-N-(phenylsulfonyl) benzenesulfonamide (**6**)*, a colorless oil (76 mg, 67% yield). R_f = 0.4 (Petroleum ether/EtOAc/DCM = 20:1:5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19 (s, 1H), 9.02 – 8.90 (m, 1H), 8.18 (t, *J* = 7.6 Hz, 2H), 8.12 (d, *J* = 6.9 Hz, 4H), 7.85 (d, *J* = 8.1 Hz, 1H), 7.63 – 7.39 (m, 8H), 4.71 – 4.61 (m, 1H), 4.26 (dd, *J* = 15.6, 8.1 Hz, 1H), 3.78 (dd, *J* = 15.6, 3.6 Hz, 1H), 1.85 – 1.47 (m, 3H), 1.43 –1.33 (m, 1H), 1.28 – 1.18 (m, 1H), 0.88 (d, *J* = 1.6 Hz, 3H), 0.86 (d, *J* = 1.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 146.2, 145.8, 140.0, 136.3, 133.8, 130.2, 129.5, 129.0, 128.6, 128.4, 126.5, 126.3, 121.5, 82.4, 51.9, 34.2, 30.1, 28.1, 22.7, 22.6. HRMS (ESI): m/z (M + H^+) calcd for $C_{29}H_{32}O_5N_3S_2$, 566.1778, found: 566.1767.

*(E)-N-(2-cyclopentyl-2-(((quinolin-8-ylmethylene)amino)oxy)ethyl)-N-(phenylsulfonyl) benzenesulfonamide (**7**)*, a colorless oil (73 mg, 65% yield). R_f = 0.4 (Petroleum ether/EtOAc/DCM = 20:1:5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (s, 1H), 8.97 (d, *J* = 2.7 Hz, 1H), 8.18 (dd, *J* = 14.9, 7.7 Hz, 2H), 8.14 – 8.04 (m, 4H), 7.86 (d, *J* = 8.1 Hz, 1H), 7.55 (t, *J* = 7.7 Hz, 1H), 7.50 –7.44 (m, 7H), 4.64 (t, *J* = 7.4 Hz, 1H), 4.32 (dd, *J* = 15.7, 9.2 Hz, 1H), 3.75 (dd, *J* = 15.7, 2.0 Hz, 1H), 2.31 – 2.04 (m, 1H), 1.88 – 1.40 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.9, 145.5 (×2), 140.0, 136.7, 133.7, 130.2, 129.4, 129.0, 128.6, 128.4, 126.6, 126.6, 121.5, 86.2, 51.4, 42.6, 29.1, 28.7, 25.7, 25.6. HRMS (ESI): m/z (M + H^+) calcd for $C_{29}H_{30}O_5N_3S_2$, 564.1621, found: 564.1608.

*(E)-N-(2-cyclohexyl-2-(((quinolin-8-ylmethylene)amino)oxy)ethyl)-N-(phenylsulfonyl) benzenesulfonamide (**8**)*, a colorless oil (68 mg, 59% yield). R_f = 0.4 (Petroleum ether/EtOAc/DCM = 20:1:5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (s, 1H), 8.99 (s, 1H), 8.28 – 8.00 (m, 6H), 7.87 (s, 1H), 7.57 (t, *J* = 7.3 Hz, 1H), 7.47 (s, 7H), 4.59 (s, 1H), 4.36 – 4.19 (m, 1H), 3.81 (d, *J* = 15.6 Hz, 1H), 1.86 (d, *J* = 11.2 Hz, 1H), 1.81– 1.61 (d, *J* = 32.9 Hz, 5H), 1.19 (s, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 145.7 (×2), 140.1, 136.7, 133.8, 130.2, 129.5, 129.1, 128.7, 128.5, 128.5, 126.7, 126.5, 121.6, 86.5, 50.2, 40.8, 28.8, 28.4, 26.7, 26.5, 26.4. HRMS (ESI): m/z ($M + H^+$) calcd for $C_{30}H_{32}O_5N_3S_2$, 578.1778, found: 578.1766.

*(E)-3-(N-(phenylsulfonyl)phenylsulfonamido)-2-(((quinolin-8-ylmethylene)amino)oxy) propyl benzoate (**9**)*, a colorless oil (82 mg, 65% yield). R_f = 0.3 (Petroleum ether/EtOAc/DCM = 20:1:5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (s, 1H), 8.96 (dd, *J* = 4.1, 1.6 Hz, 1H), 8.21 –8.16 (m, 2H), 8.16 – 8.12 (m, 4H), 8.11 –8.07 (m, 2H), 7.88 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.59 – 7.41 (m, 11H), 5.09 –5.03 (m, 1H), 4.67 – 4.53 (m, 2H), 4.44 (dd, *J* = 16.0, 8.6 Hz, 1H), 3.94 (dd, *J* = 16.0, 3.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 150.1, 147.5, 145.8, 139.7, 136.5, 134.0, 133.3, 130.0, 129.9, 129.6, 129.1, 128.7, 128.5(×2), 128.4, 126.6, 126.5, 121.6, 80.6, 64.0, 49.2. HRMS (ESI): m/z ($M + H^+$) calcd for $C_{32}H_{28}O_7N_3S_2$, 630.1363, found: 630.1346.

*(E)-N-(3-phenyl-2-(((quinolin-8-ylmethylene)amino)oxy)propyl)-N-(phenylsulfonyl)be nzenesulfonamide (**10**)*, a colorless oil (53 mg, 45% yield). R_f = 0.3 (Petroleum ether/EtOAc/DCM = 20:1:5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.30 (s, 1H), 8.98 (d, *J* = 2.8 Hz, 1H), 8.22 (t, *J* = 8.9 Hz, 2H), 7.95 (d, *J* = 7.6 Hz, 4H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.58 (t, *J* = 7.7 Hz, 1H), 7.54 – 7.40 (m, 7H), 7.34 (t, *J* = 7.2 Hz, 2H), 7.26 (t, *J* = 6.5 Hz, 3H), 5.03 (td, *J* = 8.7, 2.7 Hz, 1H), 4.29 (dd, *J* = 16.0, 8.9 Hz, 1H), 3.57 (dd, *J* = 16.0, 2.7 Hz, 1H), 3.26 (dd, *J* = 14.0, 6.1 Hz, 1H), 2.85 (dd, *J* = 14.0, 7.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 146.8, 145.7, 139.6, 137.5, 136.7, 133.8, 130.0, 129.8, 129.7, 129.0, 129.0, 128.7, 128.6, 128.5, 128.4, 126.6, 126.6, 121.6, 83.2, 50.4,

38.9. HRMS (ESI): m/z (M + H^+) calcd for $C_{31}H_{28}O_5N_3S_2$, 586.1465, found: 586.1451.

(E)-N-(4-phenyl-2-(((quinolin-8-ylmethylene)amino)oxy)butyl)-N-(phenylsulfonyl)benzenesulfonamide ***(11)***, a colorless oil (74 mg, 62% yield). R_f = 0.3 (Petroleum ether/EtOAc/DCM = 20:1:5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.26 (s, 1H), 8.98 (d, *J* = 2.2 Hz, 1H), 8.20 (d, *J* = 7.4 Hz, 2H), 8.07 (d, *J* = 7.8 Hz, 4H), 7.88 (d, *J* = 8.1 Hz, 1H), 7.60 – 7.44 (m, 8H), 7.26 (d, *J* = 6.3 Hz, 2H), 7.18 (d, *J* = 7.5 Hz, 3H), 4.77 –4.69 (m, 1H), 4.29 (dd, *J* = 15.6, 7.7 Hz, 1H), 3.79 (dd, *J* = 15.5, 3.9 Hz, 1H), 2.94 – 2.76 (m, 1H), 2.75 – 2.63 (m, 1H), 2.16 – 2.00 (m, 1H), 1.99 – 1.89 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 146.5, 145.6, 141.9, 139.9, 136.7, 133.8, 130.0, 129.6, 129.1, 128.7 (×2), 128.6, 128.5 (×2), 126.6, 126.0, 121.5, 81.5, 51.8, 33.9, 31.5. HRMS (ESI): m/z (M + H^+) calcd for $C_{32}H_{30}O_5N_3S_2$, 600.1621, found: 600.1609.

methyl (E)-5-(N-(phenylsulfonyl)phenylsulfonamido)-4-(((quinolin-8-ylmethylene)amino)oxy)pentanoate ***(12)***, a colorless oil (56 mg, 48% yield). R_f = 0.3 (Petroleum ether/EtOAc/DCM = 20:1:5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19 (s, 1H), 8.98 (d, *J* = 2.4 Hz, 1H), 8.24 – 8.16 (m, 2H), 8.11 (d, *J* = 6.8 Hz, 4H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.64 – 7.42 (m, 8H), 4.77 – 4.69 (m, 1H), 4.28 (dd, *J* = 18.2, 10.5 Hz, 1H), 3.75 (dd, *J* = 15.7, 3.6 Hz, 1H), 3.66 (s, 3H), 2.61 – 2.40 (m, 2H), 2.08 – 2.00 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 149.5, 146.4, 144.3, 139.6, 137.8, 133.8, 130.9, 129.7, 129.0, 128.5, 128.4, 127.4, 126.9, 121.5, 81.4, 51.7, 51.4, 29.8, 27.5. HRMS (ESI): m/z (M + H^+) calcd for $C_{28}H_{28}O_7N_3S_2$, 582.1363, found: 582.1347.

(E)-N-(3-methoxy-2-(((quinolin-8-ylmethylene)amino)oxy)propyl)-N-(phenylsulfonyl)benzenesulfonamide ***(13)***, a colorless oil (73 mg, 68% yield). R_f = 0.4 (Petroleum ether/EtOAc/DCM = 20:1:5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.24 (s, 1H), 8.94 (dd, *J* = 4.1, 1.7 Hz, 1H), 8.20 – 8.10 (m, 6H), 7.86 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.58 – 7.46 (m, 7H), 7.44 (dd, *J* = 8.3, 4.2 Hz, 1H), 4.85 (td, *J* = 8.3, 4.5 Hz, 1H), 4.34 (dd, *J* = 16.0, 8.6 Hz, 1H), 3.93 (dd, *J* = 16.0, 3.4 Hz, 1H), 3.67 (qd, *J* = 10.8, 4.7 Hz, 2H), 3.39 (s,

3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 147.1, 145.9, 139.8, 136.3, 133.8, 129.8, 129.7, 129.0, 128.6, 128.3, 126.4, 126.3, 121.5, 81.3, 72.0, 59.5, 49.6. HRMS (ESI): m/z ($M + H^+$) calcd for $C_{26}H_{26}O_6N_3S_2$, 540.1257, found: 540.1245.

(E)-3-(N-(phenylsulfonyl)phenylsulfonamido)-2-(((quinolin-8-ylmethylene)amino)oxy) propyl 4-methylbenzenesulfonate ***(14)***, a colorless oil (91 mg, 67% yield). R_f = 0.4 (Petroleum ether/EtOAc/DCM = 4:1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (s, 2H), 8.22 (d, *J* = 8.0 Hz, 1H), 8.09 (dd, *J* = 8.0, 1.6 Hz, 4H), 7.98 (dd, *J* = 7.2, 1.1 Hz, 1H), 7.92 – 7.86 (m, 1H), 7.77 (d, *J* = 8.3 Hz, 2H), 7.60 – 7.48 (m, 8H), 7.16 (d, *J* = 8.0 Hz, 2H), 4.82 – 4.76 (m, 1H), 4.38 – 4.26 (m, 3H), 3.81 (dd, *J* = 16.2, 3.0 Hz, 1H), 2.08 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 147.7, 145.0, 139.6, 134.1, 134.1, 132.6, 130.2, 130.0, 129.3, 128.9, 128.7, 128.6, 128.5, 128.3, 126.9, 126.2, 121.9, 80.2, 68.8, 48.8, 21.5. HRMS (ESI): m/z ($M + H^+$) calcd for $C_{32}H_{30}O_8N_3S_3$, 680.1189, found: 680.1174.

(E)-N-(3-chloro-2-(((quinolin-8-ylmethylene)amino)oxy)propyl)-N-(phenylsulfonyl)be nzenesulfonamide ***(15)***, a colorless oil (75 mg, 69% yield). R_f = 0.4 (Petroleum ether/EtOAc/DCM = 20:1:5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.26 (s, 1H), 9.00 (d, *J* = 2.6 Hz, 1H), 8.27 – 8.06 (m, 6H), 7.90 (d, *J* = 8.1 Hz, 1H), 7.64 – 7.45 (m, 8H), 4.88 –4.92 (m, 1H), 4.37 (dd, *J* = 16.0, 8.5 Hz, 1H), 3.93 (dd, *J* = 16.1, 2.8 Hz, 1H), 3.84 (dd, *J* = 11.7, 3.9 Hz, 1H), 3.77 (dd, *J* = 11.8, 5.9 Hz, 1H). ^{13}C NMR (100MHz, $CDCl_3$) δ 150.2, 148.0, 145.6, 139.7, 136.8, 134.1, 130.2, 129.4, 129.2, 128.7, 128.5, 126.9, 126.6, 121.8, 81.6, 49.7, 44.0. HRMS (ESI): m/z ($M + H^+$) calcd for $C_{25}H_{23}ClO_5N_3S_2$, 544.0762, found: 544.0755.

(E)-3-(N-(phenylsulfonyl)phenylsulfonamido)-2-(((quinolin-8-ylmethylene)amino)oxy) propyl acetate ***(16)***, a colorless oil (47 mg, 41% yield). R_f = 0.3 (Petroleum ether/EtOAc/DCM = 20:1:5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (s, 1H), 9.00 (dd, *J* = 4.1, 1.5 Hz, 1H), 8.26 – 8.18 (m, 2H), 8.15 (dd, *J* = 7.8, 1.8 Hz, 4H), 7.91 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.63 – 7.47 (m, 8H), 4.91 (dd, *J* = 8.2, 3.7 Hz, 1H), 4.41 – 4.32 (m,

3H), 3.89 (dd, *J* = 16.0, 3.4 Hz, 1H), 2.12 (s, 3H). ^{13}C NMR (10 MHz, $CDCl_3$) δ 171.0, 150.2, 147.6, 145.8, 139.7, 136.6, 134.1, 130.0, 129.6, 129.2, 128.7, 128.5, 126.6 (×2), 121.7, 80.4, 63.6, 49.3, 21.1. HRMS (ESI): m/z ($M + H^+$) calcd for $C_{27}H_{26}O_7N_3S_2$, 568.1207, found: 568.1193.

*(E)-3-(N-(phenylsulfonyl)phenylsulfonamido)-2-(((quinolin-8-ylmethylene)amino)oxy) propyl pent-4-enoate (**17**)*, a colorless oil (55 mg, 45% yield). R_f = 0.4 (Petroleum ether/EtOAc/DCM = 20:1:5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (s, 1H), 8.98 – 8.93 (m, 1H), 8.21 – 8.10 (m, 6H), 7.88 (d, *J* = 8.1 Hz, 1H), 7.60 – 7.45 (m, 8H), 5.90 – 5.73 (m, 1H), 5.10 – 4.94 (m, 2H), 4.93 –4.86 (m, 1H), 4.40 – 4.36 (m, 2H), 4.35 – 4.30 (m, 1H), 3.86 (dd, *J* = 16.0, 3.2 Hz, 1H), 2.50 – 2.42 (m, 2H), 2.42 –2.36 (dd, *J* = 13.3, 6.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 150.5, 147.5, 145.8, 139.8, 136.8, 136.6, 134.0, 130.0, 129.6, 129.2, 128.7, 128.5, 126.6, 126.6, 121.7, 115.8, 80.4, 63.5, 49.3, 33.6, 29.0. HRMS (ESI): m/z ($M + H^+$) calcd for $C_{30}H_{30}O_7N_3S_2$, 608.1520, found: 608.1508.

*(E)-3-(N-(phenylsulfonyl)phenylsulfonamido)-2-(((quinolin-8-ylmethylene)amino)oxy) propyl furan-2-carboxylate (**18**)*, a colorless oil (64 mg, 52% yield). R_f = 0.3 (Petroleum ether/EtOAc/DCM = 20:1:5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.28 (s, 1H), 8.98 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.22 – 8.14 (m, 6H), 7.90 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.62 (dd, *J* = 1.6, 0.8 Hz, 1H), 7.59 – 7.46 (m, 8H), 7.27 (dd, *J* = 3.5, 0.7 Hz, 1H), 6.53 (dd, *J* = 3.5, 1.7 Hz, 1H), 5.03 (td, *J* = 8.1, 4.6 Hz, 1H), 4.66 – 4.57 (m, 2H), 4.43 (dd, *J* = 16.1, 8.5 Hz, 1H), 3.95 (dt, *J* = 8.5, 4.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 150.2, 147.7, 146.8, 145.9, 144.4, 139.6, 136.5, 134.1, 130.0, 129.6, 129.2, 128.9, 128.7, 128.4, 126.6, 121.7, 118.7, 112.1, 80.5, 63.8, 49.2. HRMS (ESI): m/z ($M + H^+$) calcd for $C_{30}H_{26}O_8N_3S_2$, 620.1156, found: 620.1139.

*(E)-N-(3-(1,3-dioxoisoindolin-2-yl)-2-(((quinolin-8-ylmethylene)amino)oxy)propyl)-N -(phenylsulfonyl)benzenesulfonamide (**19**)*, a colorless oil (75 mg, 57% yield). R_f = 0.4 (Petroleum ether/EtOAc/DCM = 20:2:5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (s,

1H), 8.94 (dd, *J* = 4.1, 1.5 Hz, 1H), 8.20 – 8.09 (m, 5H), 8.07 – 8.02 (m, 1H), 7.85 – 7.78 (m, 3H), 7.68 – 7.62 (m, 2H), 7.58 – 7.47 (m, 6H), 7.46 – 7.40 (m, 2H), 5.03 –4.95 (m, 1H), 4.35 (dd, *J* = 16.1, 7.9 Hz, 1H), 4.11 (dd, *J* = 14.2, 6.2 Hz, 1H), 4.01 (dd, *J* = 14.2, 6.1 Hz, 1H), 3.94 (dd, *J* = 16.1, 3.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 150.1, 147.5, 145.8, 139.7, 136.5, 134.1, 134.0, 132.2, 129.8, 129.6, 129.2, 128.7, 128.6, 128.3, 126.5, 123.5, 121.6, 80.5, 49.9, 39.6. HRMS (ESI): m/z ($M + H^+$) calcd for $C_{33}H_{27}O_7N_4S_2$, 655.1316, found: 655.1300.

*(E)-3-(N-(phenylsulfonyl)phenylsulfonamido)-2-(((quinolin-8-ylmethylene)amino)oxy) propyl 4-phenylbutanoate (**20**)*, a colorless oil (87 mg, 65% yield). R_f = 0.3 (Petroleum ether/EtOAc/DCM = 20:1:5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (s, 1H), 8.95 (dd, *J* = 4.0, 1.4 Hz, 1H), 8.21 – 8.15 (m, 2H), 8.12 (dd, *J* = 8.1, 1.5 Hz, 4H), 7.91 – 7.81 (m, 1H), 7.59 – 7.43 (m, 8H), 7.29 – 7.22 (m, 2H), 7.20 – 7.12 (m, 3H), 4.95 – 4.82 (m, 1H), 4.39 – 4.26 (m, 3H), 3.85 (dd, *J* = 16.0, 3.4 Hz, 1H), 2.65 (t, *J* = 7.5 Hz, 2H), 2.37 (t, *J* = 7.5 Hz, 2H), 2.02 – 1.90 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 150.1, 147.5, 145.8, 141.5, 139.7, 136.5, 134.0, 129.9, 129.6, 129.1, 128.6, 128.5, 128.4, 126.6, 126.5, 126.1, 121.6, 80.4, 63.3, 49.2, 35.2, 33.6, 26.5. HRMS (ESI): m/z ($M + H^+$) calcd for $C_{35}H_{33}O_7N_3S_2$, 672.1833, found: 672.1818.

*(E)-3-(N-(phenylsulfonyl)phenylsulfonamido)-2-(((quinolin-8-ylmethylene)amino)oxy) propyl naphthalene-2-sulfonate (**21**)*, a colorless oil (87 mg, 61% yield). R_f = 0.4 (Petroleum ether/EtOAc/DCM = 4:1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (s, 1H), 8.87 (s, 1H), 8.45 (s, 1H), 8.18 (d, *J* = 8.2 Hz, 1H), 8.07 (d, *J* = 7.7 Hz, 4H), 7.90 – 7.78 (m, 4H), 7.76 (d, *J* = 7.3 Hz, 1H), 7.56 – 7.44 (m, 8H), 7.34-7.40 (m, 3H), 4.82 – 4.73 (m, 1H), 4.44 (dd, *J* = 11.2, 3.7 Hz, 1H), 4.40 – 4.30 (m, 2H), 3.82 (dd, *J* = 16.2, 2.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.9, 147.8, 147.5, 139.5, 135.3, 134.0, 132.4, 131.8, 130.1, 123.0, 129.8, 129.3, 129.2, 129.1, 128.8, 128.7, 128.6, 128.4, 128.4, 127.7, 127.5, 126.5, 122.8, 121.7, 80.0, 69.0, 48.8. HRMS (ESI): m/z ($M + H^+$) calcd for $C_{35}H_{30}O_8N_3S_3$, 716.1189, found: 716.1179.

*3-(N-(phenylsulfonyl)phenylsulfonamido)-2-((((E)-quinolin-8-ylmethylene)amino)oxy) propyl 2-((3r,5r,7r)-adamantan-1-yl)acetate (**22**)*, a colorless oil (86 mg, 61% yield). R_f = 0.3 (Petroleum ether/EtOAc/DCM = 20:1:5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (s, 1H), 8.98 – 8.91 (m, 1H), 8.24 – 8.11 (m, 6H), 7.87 (d, *J* = 7.5 Hz, 1H), 7.62 – 7.41 (m, 8H), 4.94 – 4.86 (m, 1H), 4.53 – 4.24 (m, 3H), 3.86 (dd, *J* = 16.0, 3.1 Hz, 1H), 2.11 (s, 2H), 1.93 (s, 3H), 1.69 – 1.53 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 150.1, 147.5, 145.9, 139.8, 136.4, 134.0, 129.9, 129.7, 129.2, 128.7, 128.4, 126.5 (×2), 121.6, 80.4, 63.1, 49.5, 49.0, 42.6, 36.9, 33.0, 28.8. HRMS (ESI): m/z (M + H^+) calcd for $C_{37}H_{40}O_7N_3S_2$, 702.2302, found: 702.2294.

*3-(N-(phenylsulfonyl)phenylsulfonamido)-2-((((E)-quinolin-8-ylmethylene)amino)oxy) propyl (4R)-4-((3R,10S,12S,13R,17R)-3,12-dihydroxy-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)pentanoate (**23**)*, a colorless oil (67 mg, 37% yield). R_f = 0.3 (Petroleum ether/EtOAc/DCM = 20:2:5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (s, 1H), 9.00 (s, 1H), 8.27 – 8.17 (m, 2H), 8.13 (dd, *J* = 7.7, 1.7 Hz, 4H), 7.90 (d, *J* = 8.1 Hz, 1H), 7.66 – 7.49 (m, 9H), 4.90 (d, *J* = 4.5 Hz, 1H), 4.37 (dd, *J* = 21.6, 9.9 Hz, 3H), 3.93 (s, 1H), 3.86 (dd, *J* = 15.8, 3.1 Hz, 1H), 3.67 – 3.54 (m, 1H), 2.46 – 2.36 (m, 1H), 2.35 – 2.23 (m, 1H), 1.84 – 1.73 (m, 6H), 1.63 (d, *J* = 9.3 Hz, 8H), 1.54 – 1.42 (m, 7H), 1.37 (s, 8H), 1.22 (d, *J* = 23.9 Hz, 5H), 1.17 – 1.06 (m, 2H), 0.99 – 0.91 (m, 5H), 0.89 (s, 4H), 0.65 – 0.60 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 150.1, 147.4, 145.6, 139.8, 136.8, 134.1, 130.0, 129.6, 129.2, 128.8, 128.5, 126.8, 126.7, 121.7, 80.5, 73.3, 72.1, 63.4, 49.3, 48.4, 47.5, 47.5, 46.7, 42.3, 36.7, 36.2, 35.4, 35.2, 34.3, 33.9, 31.5, 31.4, 31.0, 30.7, 29.9, 28.8, 27.6, 27.3, 26.3, 23.8, 23.4, 17.5, 12.9. HRMS (ESI): m/z (M + H^+) calcd for $C_{49}H_{62}O_9N_3S_2$, 900.3922, found: 900.3893.

*N-(2-hydroxy-3-phenylpropyl)-N-(phenylsulfonyl)benzenesulfonamide (**24**).* Compound **10** (0.1mmol, 58.5 mg) was dissolved in 10 mL ethyl actetate, and 600 mg Pd/C (10%) was added. The reaction mixture was stirred under H_2 atmosphere at room temperature until the starting material was consumed completely. Then the

mixture was filtered through a pad of Celite and washed with ethyl acetate. The filtrate was concentrated, and the residue was purified with flash column chromatography (Petroleum ether/ethyl acetate/DCM = 20:2:5) to afford product **24** as a colorless oil (37 mg, 86% yield), R_f = 0.3 (Petroleum ether/EtOAc/DCM = 20:3:5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.9 Hz, 4H), 7.64 (t, *J* = 7.4 Hz, 2H), 7.52 (t, *J* = 7.8 Hz, 4H), 7.33 (t, *J* = 7.3 Hz, 2H), 7.28 (d, *J* = 7.1 Hz, 1H), 7.19 (d, *J* = 7.2 Hz, 2H), 4.31 – 4.22 (m, 1H), 3.80 (dd, *J* = 15.7, 8.8 Hz, 1H), 3.69 (dd, *J* = 15.6, 3.0 Hz, 1H), 2.84 – 2.73 (m, 2H). ^{13}C NMR (100 Hz, $CDCl_3$) δ 139.3, 137.1, 134.0, 129.5 129.1, 128.7, 128.5 126.8 71.3, 53.5, 41.6. HRMS (ESI): m/z (M + H^+) calcd for $C_{21}H_{22}O_5NS_2$, 432.0934, found: 432.0922.

(E)-N-(3-phenyl-2-(((quinolin-8-ylmethylene)amino)oxy)propyl)benzenesulfonamide ***(25)***. Compound **10** (0.2 mmol, 117 mg) was dissolved in 1 mL con. H_2SO_4 at 0°C, and the reaction mixture was stirred for 2 mins. Then the mixture was poured into 10 mL ice water, and extracted by ethyl acetate (2 × 15 mL). The combined organic layer was washed with brine (15 mL) and then dried over anhydrous sodium sulfate. The organic solvent was removed on a rotary evaporator in vacuo. The residue was purified by column chromatography on silica gel (Petroleum ether/ethyl acetate/DCM = 20:2:5) to afford product **25** as a colorless oil (82 mg, 92% yield), R_f = 0.3 (Petroleum ether/EtOAc/DCM = 20:3:5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (s, 1H), 9.08 (s, 1H), 8.22 (d, *J* = 8.0 Hz, 1H), 8.06 (d, *J* = 7.0 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.81 (d, *J* = 7.6 Hz, 2H), 7.59 (t, *J* = 7.7 Hz, 1H), 7.53 – 7.46 (m, 2H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.31 (t, *J* = 7.2 Hz, 2H), 7.26 (d, *J* = 7.0 Hz, 1H), 7.23 (t, *J* = 6.7 Hz, 2H), 5.71 (s, 1H), 4.51 (d, *J* = 4.8 Hz, 1H), 3.40 (ddd, *J* = 13.1, 7.0, 2.7 Hz, 1H), 3.29 – 3.17 (m, 1H), 3.13 (dd, *J* = 14.0, 6.5 Hz, 1H), 2.90 (dd, *J* = 14.0, 7.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.7, 147.8, 145.8, 140.0, 136.6, 132.6, 130.2, 129.6, 129.5, 129.2, 128.7, 128.6, 127.6, 127.2, 126.8, 126.5, 121.8, 82.0, 46.4, 38.0. HRMS (ESI): m/z (M + H^+) calcd for $C_{25}H_{24}O_3N_3S$, 446.1533, found: 446.1528.

*(E)-N-(3-phenyl-2-(((quinolin-8-ylmethylene)amino)oxy)propyl)benzamide (**26**).* 1 step: Compound **25** (0.1 mmol, 44.5 mg) was dissolved in 2 mL DCM, and DMAP (2 mg), Et_3N (28 μL), BzCl (14 μL) were added. The reaction mixture was stirred until the starting material was consumed completely. The solvent was removed on a rotary evaporator in vacuo, and the residue was purified by column chromatography on silica gel (Petroleum ether/ethyl acetate = 6:1) to afford benzoylated product as a colorless oil (53.8 mg, 98% yield), R_f = 0.3 (Petroleum ether/EtOAc = 4:1).

2 step: Benzoylated product (53.8 mg) was dissolved in 1 mL con. H_2SO_4 at 0°C, and the reaction mixture was stirred for 2 mins. Then the mixture was poured into 10 mL ice water, and extracted by ethyl acetate (2 × 15 mL). The combined organic layer was washed with brine (15 mL) and then dried over anhydrous sodium sulfate. The organic solvent was removed on a rotary evaporator in vacuo. The residue was purified by column chromatography on silica gel (Petroleum ether/ethyl acetate/DCM = 20:1:5) to afford product **26** as a colorless oil 27.2 mg, 69% yield), R_f = 0.2 (Petroleum ether/EtOAc/DCM = 20:2:5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.45 (s, 1H), 8.93 (s, 1H), 8.19 (dd, *J* = 14.0, 7.7 Hz, 2H), 7.87 (d, *J* = 8.1 Hz, 1H), 7.73 (d, *J* = 7.4 Hz, 2H), 7.54 (t, *J* = 7.7 Hz, 1H), 7.44 (dd, *J* = 12.5, 5.2 Hz, 2H), 7.40 – 7.27 (m, 6H), 7.22 – 7.15 (m, 1H), 6.85 (s, 1H), 4.71 (s, 1H), 4.02 – 3.92 (m, 1H), 3.68 – 3.58 (dd, *J* = 12.8, 6.1 Hz, 1H), 3.18 (dd, *J* = 14.1, 6.6 Hz, 1H), 3.01 (dd, *J* = 14.1, 6.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 150.3, 147.3, 146.0, 137.7, 136.6, 134.9, 131.5, 130.0, 129.8, 129.6, 128.7, 128.7, 128.6, 127.3, 127.2, 126.7, 126.6, 121.7, 82.9, 43.5, 38.5. HRMS (ESI): m/z ($M + H^+$) calcd for $C_{26}H_{24}O_2N_3$, 410.1863, found: 410.1860.

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Supporting information:

Copies of ^{1}H and ^{13}C NMR spectra of oxime substrates and compounds of **2a**, **3**~**26**;

Scheme of Proposed mechanism

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