Synthesis of Highly Functionalized Quinoline Derivatives via the Ring-Expansion Reaction of Indole Derivatives

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Abstract

Quinoline and it's most derivatives can be applied to synthetic drugs because of it's diverse chemical and pharmacological properties.Quinoline derivatives possess a variety of biological activities such as anti-malarial, anti-hypertensive, anti-depressant, anti-allergic, anti-bronchial asthma and other drugs，including fungicides and pesticides. In addition to it's application in medicine, quinoline derivatives are also applied in the fields of biological, organic and metal organic chemistry. Therefore, the study of synthesis about quinoline derivative has practical significance for drug research and chemical production.

The classical synthetic routes of quinoline have a great disadvantage that it is usually carried out under the high temperature or strong acid system, which existing the worry of high requirements on equipment and environmental pollution pressure in industrial production. Therefore, the study of new synthetic methods for atomic economic, green quinoline derivatives is of great significance.

In the work of this paper, we propose a novel synthesis method of quinoline derivatives:A diverse set of highly functionalized quinoline derivatives was synthesized via the ring-expansion reaction of 3-(1-arylsulfonylalkyl) indoles, and readily accessible starting materials in a mild one-step procedure.

The reagents used in all synthetic routes involved in this paper are basically non-toxic, comply with the requirements of green chemistry and environmental chemistry advocated by modern society, and provide experimental and theoretical basis for the research and development of quinoline derivatives.

Key words： ring-expansion reaction ，3-(1-arylsulfonylalkyl) indoles，one-step procedure

Statement of Originality

The research process and result of this team are conducted and derived under the guidance of the instructor. Other than the referenced content and the acknowledged sources, this paper does not include any published findings by this group or any other researchers. If there is any inaccuracy, this team is accountable for all liabilities.

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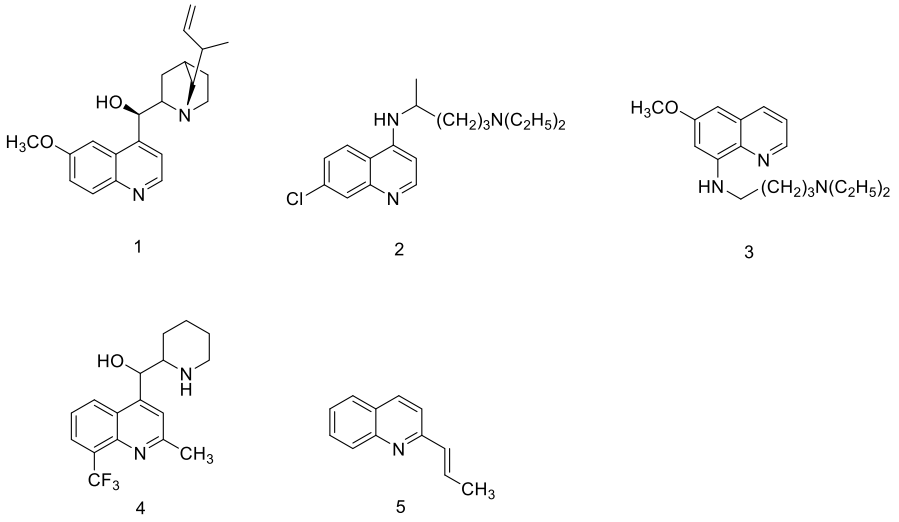
Date: 2018.9.7

Table of Contents

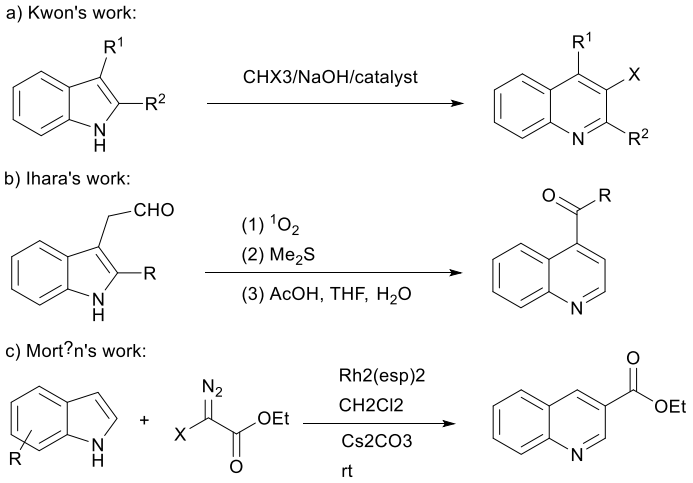
List of Figures

List of Tables

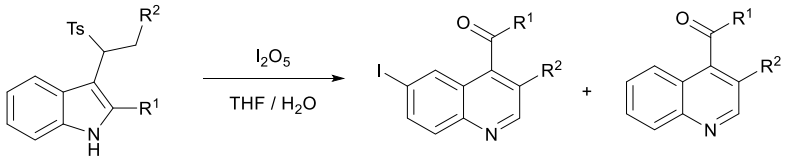
List of Schemes



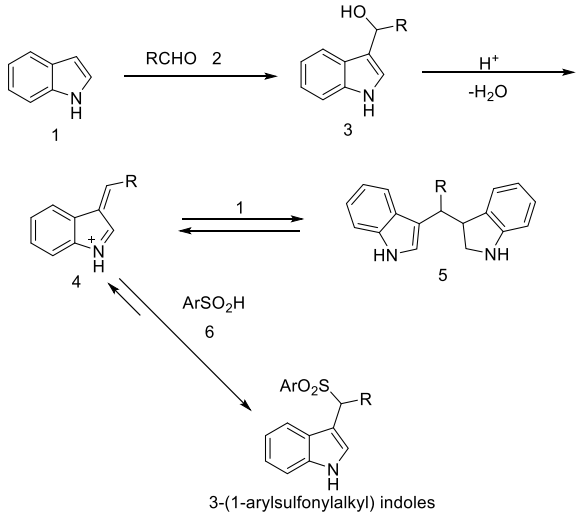
Scheme 2: Other's work



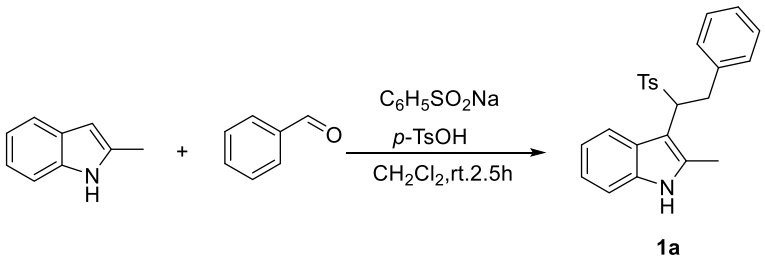
Scheme 3: new synthetic scheme



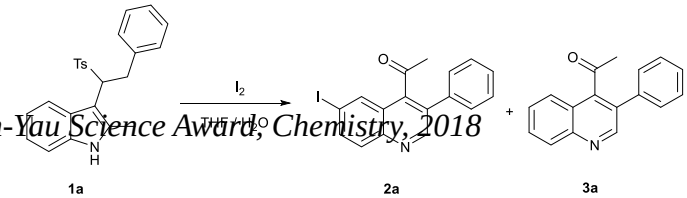
Scheme 4: The reaction mechanism of 3-(1-arylsulfonylalkyl) indoles



Scheme 5: Synthesis of compound **1a**



Scheme 6: The I_2-promoted ring-expansion reaction of indole derivatives



List of Abbreviations

Abbreviations	Name
CH_2Cl_2	dichloromethane
p-TsOH	p-toluenesulfonic acid
THF	Tetrahydrofuran
DMF	N,N-Dimethylformamide
NMR	Nuclear Magnetic Resonance
HR-MS	High resolution mass spectrometry
NOESY	nuclear overhauser effect spectroscopy
IR	Infrared Spectroscopy

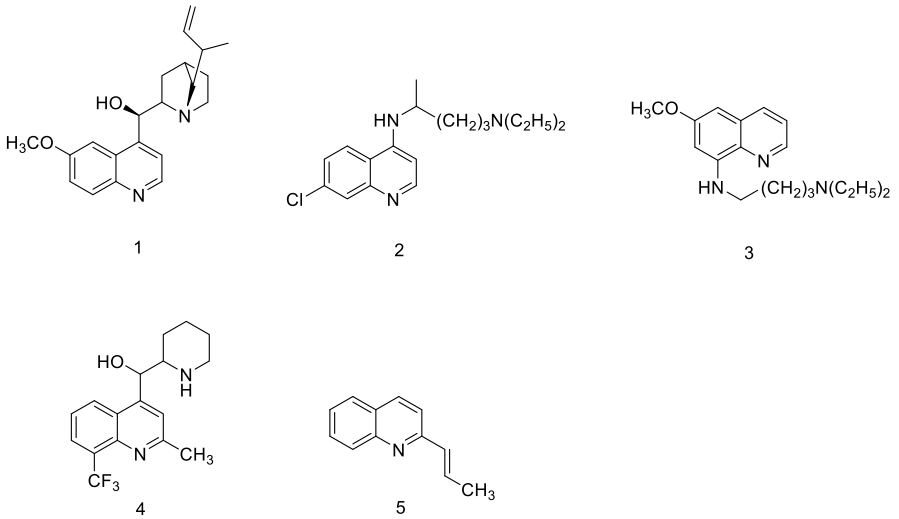
1 INTROUDUCTION

The structure of quinoline is the combination of pyridine and benzene, but the chemical properties are similar to pyridine and naphthalene.The electrophilic substitution reaction occurs almost exclusively in the benzene ring, however the nucleophilic substitution reaction occurs in the pyridine ring nitrogen-containing heterocyclic ring.

Nitrogen-containing heterocycles are prevalent in numerous natural products, and are extremely important in materials chemistry and medicinal chemistry.[1] Among these compounds, quinoline, a well-known heterocyclic compound, itself has few applications, but many of its derivatives are useful in diverse applications including pharmaceuticals and are available as drugs today.[2]

Quinolines are well known for their antimalarial properties.[3] For example, quinine **1** as the active ingredient has been isolated from the bark of Cinchona trees ,and has been found the function of the treatment of malaria. the structure determination and SAR studies resulted in emerging of newer antimalarial drugs such as chloroquine **2** , primaquine **3**, mefloquine **4**.(scheme 1).

Chimanine alkaloids **5** as the agents of leishmaniasis olated from the bark of Galipea longiflora trees of the Rutaceae family are effective against the parasites Leishmania sp. Cryptolepine as an indoloquinoline alkaloid was found in the west Africanc limbing shrub Cryptolepis sanguinolenta .DynemicinA and Streptonigrin are the members of the class of antitumor antibiotics.

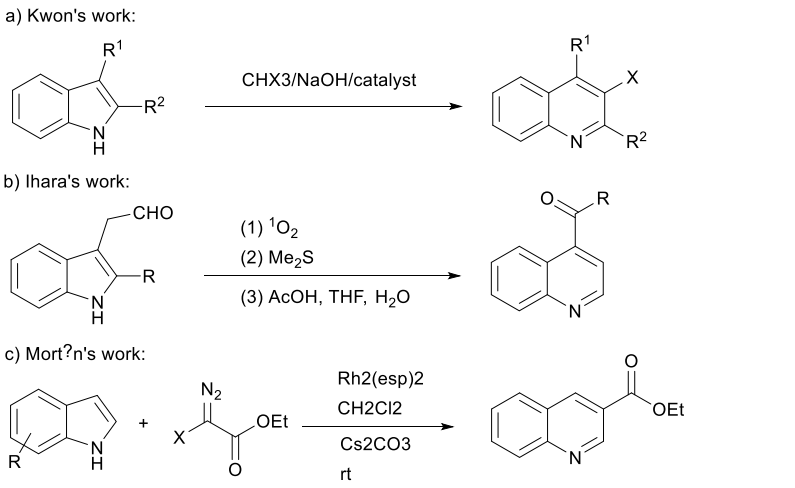


Scheme 2:Several derivatives of quinoline

1.1 Strategies for the synthesis of quinolone

Highly functionalized reactions are special types of synthetically useful organic reactions because they directly lead to a variety of many important products.[4]Among these reactions, the ring-expansion reactions have been widely used in organic synthesis.[5] To the best of our knowledge, however, there have been no reported examples concerning the ring-expansion reaction of 3-(1-arylsulfonylalkyl) indoles to quinoline derivatives.

To the best of our knowledge, however, there have been no reported examples concerning the ring-expansion reaction of 3-(1-arylsulfonylalkyl) indoles to quinoline derivatives. As for the synthesis of quinolones, in 1976, Kwon[6] reported a ring expansion of indoles into 3-haloquinolines by use of phase transfer catalysts (scheme 2-a). But the reaction were conducted under ice-cooling. Later on, Ihara[7] discovered a conversion of indoles into quinolones through the N-1-C-2 fission by singlet-oxygen (scheme 2-b). However, this method required low temperature and oxygen atmosphere. Very recently, Mortén[8] report a novel synthesis of ethyl quinoline-3-carboxylates from reactions between a series of indoles and halodiazoacetates (scheme 2-c). Although this reaction could be operated under mild conditions, this procedure suffered from expensive transition-metal catalyst.

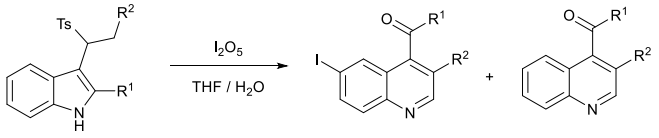


Scheme 2: Other's work

1.2 Proposal of the new synthetic scheme

It is important that the use of iodoquinoline skeletons is the crucial step of our synthetic strategy; this functional group can carry out a series of useful reactions.9 Therefore, the construction of

iodoquinoline skeletons has caught our attention. Herein, we present the synthesis of new, highly functionalized quinolines from 3-(1-arylsulfonylalkyl) indoles (scheme 3).



R^1 = CH_3, ph
R^2 = alkyl, benzyl

- **Ring-expansion**
- **Highly functionalized (3-phenyl/alkyl, 4-acyl, 6-iodo)**
- **Highly valuable products**
- **One-pot**
- **mild conditions**
- **transition metal-free conditions**

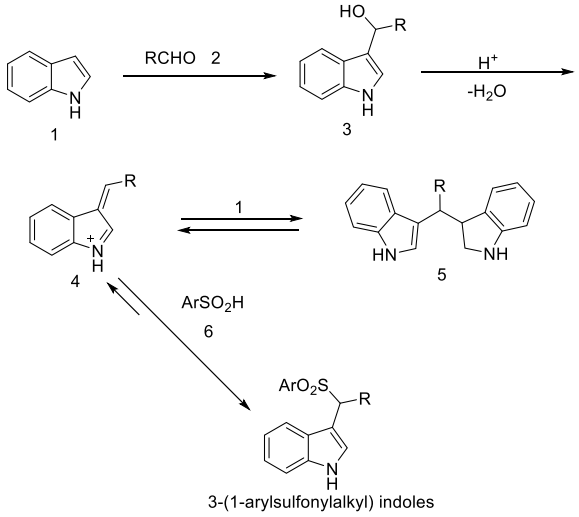
Scheme 3: new synthetic scheme

2 SYNTHESIS WORK

2.1 Synthesis of Product 1

2.1.1 The reaction mechanism of 3-(1-arylsulfonylalkyl) indoles

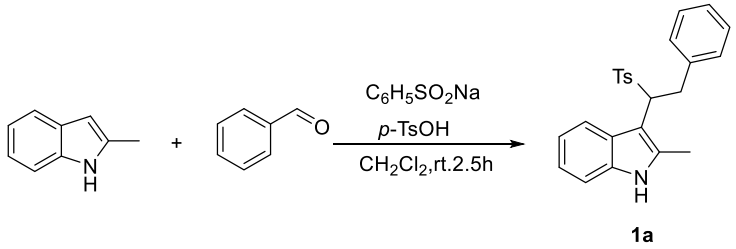
According to the reported literature, the reaction mechanism of 3-(1-arylsulfonylalkyl) indoles as follows：the aldehydes **2** reacts with indoles **1** under F-C conditions to form bisindoles **5** as mainproducts (Scheme 4).The Formation of bisindoles **5** is possible because the initiallyformed indolylalkanols **3** in acidic conditions suffer eliminationof water giving a vinylogous iminium ion **4** that reacts with a second molecule of indole **1**.arylsulfinic acids 6 act as promoters andeffective trapping nucleophiles of the intermediate iminium ions.



Scheme 4: The reaction mechanism of 3-(1-arylsulfonylalkyl) indoles

2.1.2 General Procedure for the Preparation of Sulfonyl Indoles

2-Methyl hydrazine (3 mmol), sodium p-toluenesulfinate (3 mmol), p-toluenesulfonic acid monohydrate (1.5 mmol) was added to 10 ml CH2Cl2. After dissolution, phenylacetaldehyde (3 mmol) was added. The resulting reaction mixture was stirred at rt or at reflux for 2.5 h（Scheme 5）. The reaction solution was then treated withsaturated $NaHCO_3$ (7 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic extracts were dried over Na_2SO_4 and treated with activated charcoal. The crude is separated by column chromatography.



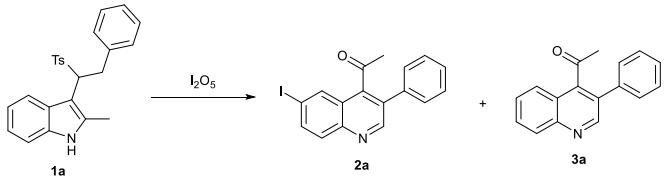
Scheme 5: Synthesis of compound **1a**

2.2 Second Experiment on Product 1

2.2.1 Optimization of reaction parameters

Initially, 2-methylsubstituted arenesulfonylindole 1a was selected as a model substrate for optimization of the conditions (Table 1). Our investigation was launched with 2-methylsubstituted arenesulfonylindole 1a (0.4 mmol, 1 equiv), I2O5 (1.2 mmol, 3 equiv), THF/H2O (5 mL/1 mL) as the solvent (entry 1). Delightfully, the product 2a was obtained with 28 % yield and a ratio of 2a and 3a was 1.7 : 1. Although the ratio of 2a and 3a increased sharply when the amount of I2O5 was increased to 9 equiv (entry 3), the yield of 2a made us feel disappointed. To further optimize the reaction, other parameters such the temperature and solvent were examined. Subsequently, several other temperatures were examined, and 69 % was obtained when the temperatue was 50 °C (entry 4). Unfortunately，other solvents including CH3CN, DMF and toluene were tested and they all proved to be less effective than THF (entry 6, 7 and 8). It is worth noting that no 2a was observed without H2O or THF (entry 9 and 10).

Table **1**. Optimization of reaction conditions for reaction of 2-methylsubstituted arenesulfonylindole **1a** with I_2O_5[a]



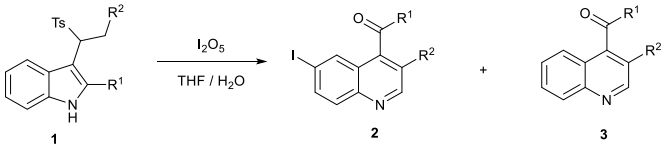
Entry	I_2O_5 (equiv)	Solvent	T (°C)	**2a**/**3a**[b]	**2**[c], **3**[d] Yield (%)
1	3	THF/H_2O	70	1.7/1	28,16
2	6	THF/H_2O	70	4.3/1	39,9
3	9	THF/H_2O	70	>95/1	26,<1
4	9	THF/H_2O	50	>95/1	69,<1
5	9	THF/H_2O	r.t.	11/1	46,4
6	9	CH_3CN/H_2O	50	7/1	35,5
7	9	DMF/H_2O	50	9.4/1	47,5
8	9	toluene/H_2O	50	—[e]	trace[e]/ trace
9	9	THF(6 mL)	50	—	0/trace
10	9	H_2O (6 mL)	50	—	0/0

[a]Reaction conditions: **1a** (0.4 mmol, 1 equiv), 12 h. [b]All of the ratios (**2a**/**3a**) were determined by ^{1}H NMR spectroscopy. [c]Isolated yields by silica gel column. [d]Yields of **3a** were determined by mixture qualitys and ratios of **2a** and **3a**. [e]Determined by TLC

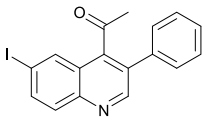
2.2.2 Substrate scope of 3-(1-arylsulfonylalkyl) indoles

Having identified the optimal reaction conditions, we next set out to examine the scope and limitations of this reaction, and the results are summarized in Table 2. As anticipated, the phenyl on the 2-position of the indole ring of the arenesulfonylindole 1 did not hamper the reaction process, but affected the reaction efficiency. It is worthy of note that when R1 was phenyl and R2 was ethyl, The yield of the compound 3b was more than that of the compound 2b. But it is regrettable that the specific reasons of the result are not very clear now.

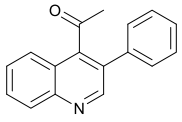
Table 2 Substrate scope[a,b,c,d]



A[e]



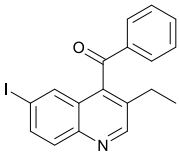
2a (69 %)



3a (< 1 %)

2a : **3a** > 95 : 1

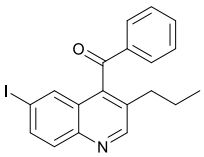
B[f]



2b (14 %)

2b : **3b** = 1 : 2.5 **3b** (35 %)

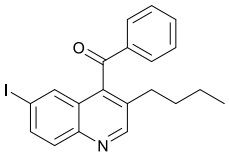
C[f]



2c (36 %)

2c : **3c** = 2.3 : 1 **3c** (16 %)

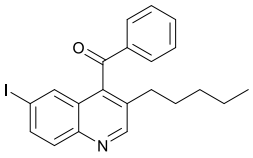
D[f]



2d (31 %)

2d : **3d** = 2.8 : 1 **3d** (11 %)

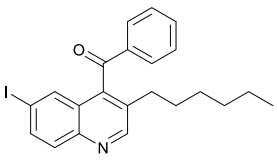
E[f]



2e (52 %)

2e : **3e** = 3.8 : 1 **3e** (14 %)

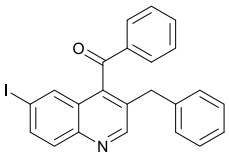
F[f]



2f (34 %)

2f : **3f** = 3 : 1 **3f** (11 %)

G[f]



2g (37 %)

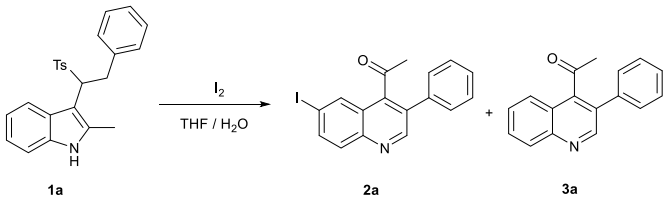
2g : **3g** = 1.7 : 1 **3g** (22 %)

[a]Reaction conditions: **1** (0.4 mmol, 1 equiv), I_2O_5 (3.6 mmol, 9 equiv), THF/H_2O (5/1, 6 mL), 12 h. [b]All of ratios were determined by ^1H NMR spectroscopy. [c]Yields of **2** was isolated yields by silica gel column. [d]Yields of **3** was determined by mixture qualitys and ratios of **2** and **3**. [e]50 °C. [f]90 °C.

2.3 Research on reaction mechanism

Enlightened by Patil' work[10], we designed a simple experiment (Scheme 6). The products **2a** and **3a** were obtained by the treatment of 2-methylsubstituted arenesulfonylindole **1a** with I_2 in THF/H_2O. But the yield of **2a** and ratio of **2a** and **3a** were significantly reduced by using I_2 instead of I_2O_5. This

experiment means that iodine may be generated in the reaction system. We proposed that the I_2 might come from I_2O_5 through multistep redox processes. The formation of I_2 has also been confirmed by observation of an obvious color change while starch was added into the system though the mechanistic details of the redox processes are not very clear at the present.[11] A detailed mechanistic investigation is currently under way in our laboratory.

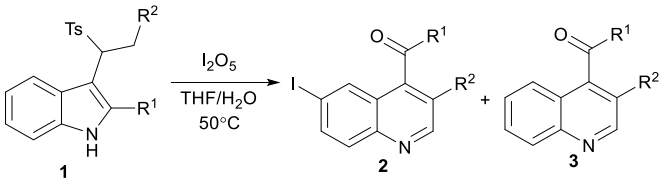


1a 2a 3a

Scheme 6: The I_2-promoted ring-expansion reaction of indole derivatives

3 CHARACTERIZATION AND ANALYSIS

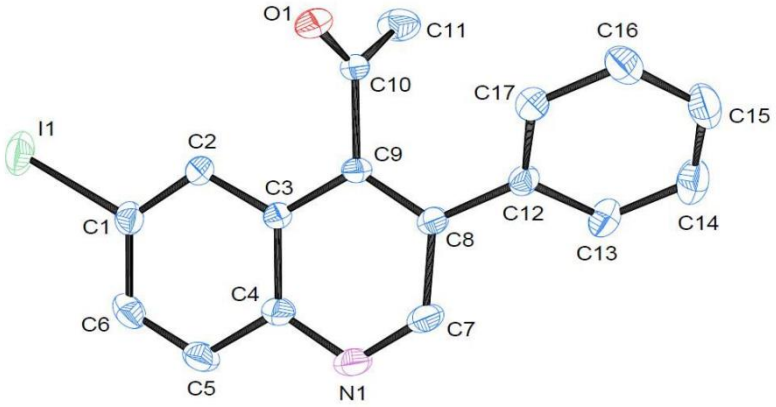
3.1 General Procedure for Synthesis of Products



An oven-dried screw cap reaction tube was charged with a magnetic stir-bar, 3-(1-arylsulfonylalkyl) indole **1a** (0.4 mmol, 0.156 g), I_2O_5 (3.6 mmol, 0.914 g), THF (5 mL) and H_2O (1 mL). The tube was placed at 50 °C or 90 °C for 12 h. After cooling to room temperature. Silica was added to the flask, and volatiles were evaporated under reduced pressure. Then it was passed through a short silica gel column, and eluted with petroleum ether and ethyl acetate, respectively. The filtrate was concentrated and the residue was purified by flash column chromatography to afford the desired products.

3.2 Crystallographic Data of Compound 2a

Besides the NMR and HR-MS spectroscopic analysis for these products, the X-ray diffraction for product **2a** has been performed as shown in Fig. 1.



Bond precision: C-C = 0.0059 A Wavelength=0.71073

Cell: a=9.816(3) b=21.393(6) c=7.139(2)
alpha=90 beta=108.640(4) gamma=90
Temperature: 296 K

	Calculated	Reported
Volume	1420.5(7)	1420.4(7)
Space group	P 21/c	P2(1)/c
Hall group	-P 2ybc	-P2ybc
Moiety formula	C17 H12 I N O	C17 H12 I N O
Sum formula	C17 H12 I N O	C17 H12 I N O
Mr	373.18	373.18
Dx,g cm-3	1.745	1.745
Z	4	4
Mu (mm-1)	2.249	2.249
F000	728.0	728.0
F000'	726.35	
h,k,lmax	12,28,9	12,27,9
Nref	3349	3288
Tmin,Tmax	0.602,0.638	0.626,0.662
Tmin'	0.590	

Correction method= # Reported T Limits: Tmin=0.626 Tmax=0.662
AbsCorr = MULTI-SCAN

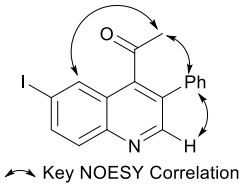
Data completeness= 0.982 Theta(max)= 27.750

R(reflections)= 0.0494(2963) wR2(reflections)= 0.1289(3288)

S = 1.076 Npar= 183

Figure 4: X-ray Structure of **2a**

3.3 NOESY Data of Compound 2a (500 MHz, $CDCl_3$)



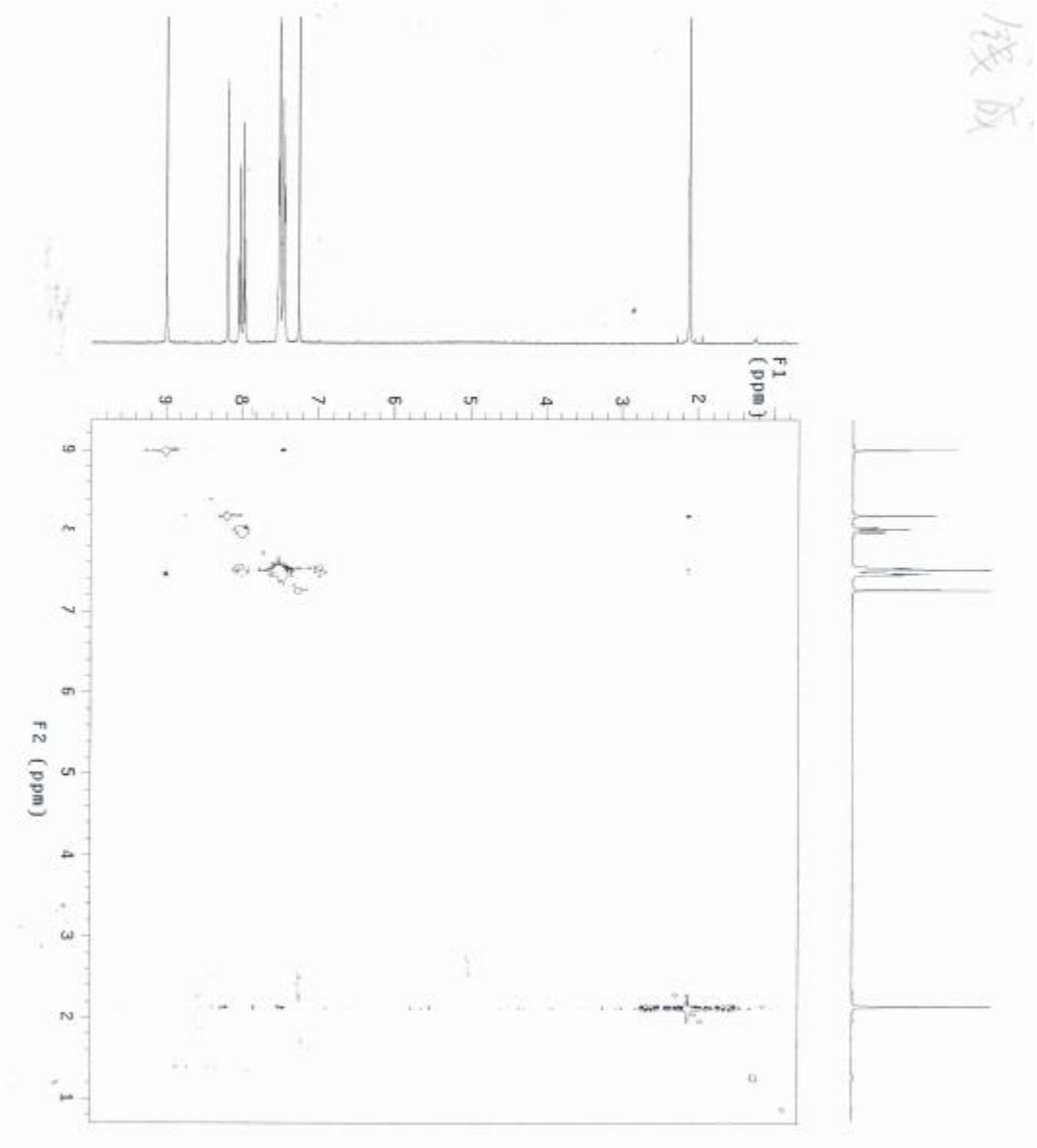
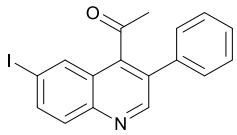


Figure 5: NOESY Data of Compound 2a

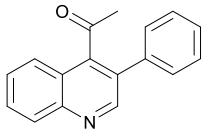
3.4 Characterization Data and Spectra of Products

3.4.1 1-(6-iodo-3-phenylquinolin-4-yl)ethan-1-one (2a)



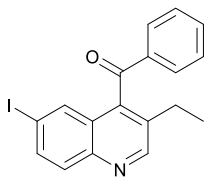
69% yield, unknown compound, yellow solid, mp = 154-155 °C. IR(KBr)/cm^{-1}: 3051, 2958, 2925, 2858, 1698, 1652, 1491, 1438, 1398, 1352, 1258, 1191, 1091, 1051, 1018, 805, 758, 698, 509; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.986 (s, 1H), 8.180 (d, *J* = 1.2 Hz, 1H), 8.002 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.899 (d, *J* = 8.8 Hz, 1H), 7.532-7.446 (m, 5H), 2.112 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.495, 151.928, 146.453, 143.559, 138.803, 136.252, 133.591, 131.542, 130.669, 129.492, 129.396, 129.170, 124.530, 94.394, 32.136. HRMS Calculated for [M^{+}] C17H12ONI 372.9958, found 372.9947.

3.4.2 1-(3-phenylquinolin-4-yl)ethan-1-one (3a)



< 1% yield, unknown compound, yellow oil. IR(KBr)/cm-1: 3058, 3031, 2958, 2925, 2858, 1698, 1652, 1498, 1458, 1258, 1198, 1091, 1025, 805, 765, 705; 1H NMR (400 MHz, CDCl3) δ 9.006 (s, 1H), 8.208 (d, J = 8.4 Hz, 1H), 7.820-7.763 (m, 2H), 7.629 (t, J = 7.2 Hz, 1H), 7.530-7.469 (m, 5H), 2.141 (s, 3H); 13C NMR (100 MHz, CDCl3) δ 205.090, 151.327, 147.303, 145.115, 136.583, 130.071, 129.951, 129.858, 129.542, 129.315, 128.939, 128.277, 124.776, 122.919, 32.170. HRMS Calculated for [M+] C17H13ON 247.0992, found 247.0991.

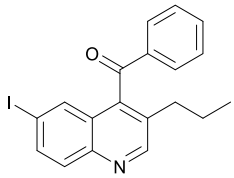
3.4.3 (3-ethyl-6-iodoquinolin-4-yl)(phenyl)methanone (2b)



14% yield, unknown compound, yellow solid, mp = 98-101 °C. IR(KBr)/cm-1: 3058, 2958, 2932, 2872, 1671, 1592, 1578, 1478, 1452, 1258, 1238, 1219, 1098, 1058, 1018, 905, 825, 798, 698; 1H NMR (400

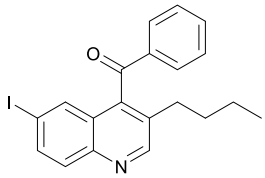
MHz, CDCl3) δ 8.893 (s, 1H), 7.917 (dd, J = 9.2, 1.2 Hz, 1H), 7.872-7.836 (m, 2H), 7.789 (d, J = 8 Hz, 2H), 7.653 (t, J = 7.2 Hz, 1H), 7.484 (t, J = 7.6 Hz, 2H), 2.623 (q, J = 7.2 Hz, 2H), 1.190 (t, J = 7.6 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ 196.963, 152.539, 145.617, 141.972, 138.109, 136.568, 134.920, 133.689, 133.504, 131.413, 129.905, 129.293, 126.640, 93.600, 24.596, 15.559. HRMS Calculated for [M+] C18H14ONI 387.0115, found 387.0112.

3.4.4 (6-iodo-3-propylquinolin-4-yl)(phenyl)methanone (2c)



36% yield, unknown compound, yellow solid, mp = 117-119 °C. IR(KBr)/cm-1: 3058, 3005, 2958, 2918, 2851, 1665, 1631, 1598, 1578, 1485, 1472, 1452, 1425, 1412, 1352, 1312, 1258, 1219, 1172, 1138, 1091, 1051, 1025, 918, 872, 818, 798, 751, 698, 632, ; 1H NMR (400 MHz, CDCl3) δ 8.869 (s, 1H), 7.913 (d, J = 8.8 Hz, 1H), 7.868-7.835 (m, 2H), 7.780 (d, J = 7.6 Hz, 2H), 7.651 (t, J = 7.2 Hz, 1H), 7.480 (t, J = 7.6 Hz, 2H), 2.558 (t, J = 7.6 Hz, 2H), 1.650-1.556 (m, 2H), 0.859 (t, J = 7.2 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ 196.974, 152.884, 145.639, 142.265, 138.095, 136.626, 134.876, 133.715, 132.135, 131.427, 129.871, 129.282, 126.697, 93.560, 33.323, 24.350, 14.042. HRMS Calculated for [M+] C19H16ONI 401.0271, found 401.0268.

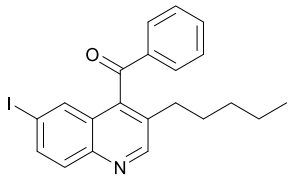
3.4.5 (3-butyl-6-iodoquinolin-4-yl)(phenyl)methanone (2d)



31% yield, unknown compound, brown oil. IR(KBr)/cm-1: 3058, 3038, 2958, 2925, 2865, 1671, 1592, 1491, 1452, 1258, 1212, 1098, 1051, 1025, 912, 832, 805, 705, 639; 1H NMR (400 MHz, CDCl3) δ 8.866 (s, 1H), 7.917 (dd, J = 8.8, 1.6 Hz, 1H), 7.870-7.841 (m, 2H), 7.782 (d, J = 7.6 Hz, 2H), 7.655 (t, J = 7,6 Hz, 1H), 7.484 (t, J = 8.0 Hz, 2H), 2.571 (t, J = 8.0 Hz, 2H), 1.575-1.507 (m, 2H), 1.298-1.206

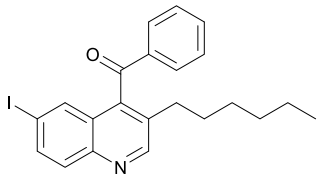
(m, 2H), 0.800 (t, J = 7.2 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ 197.019, 152.894, 145.584, 142.179, 138.087, 136.630, 134.892, 133.684, 132.358, 131.405, 129.877, 129.280, 126.702, 93.589, 33.205, 31.046, 22.568, 13.770. HRMS Calculated for [M+] C20H18ONI 415.0428, found 415.0420.

3.4.6 (6-iodo-3-pentylquinolin-4-yl)(phenyl)methanone (2e)



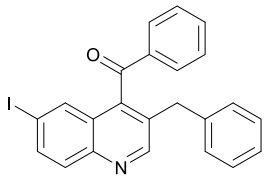
52% yield, unknown compound, yellow solid, mp = 77-80 °C. IR(KBr)/cm-1: 2958, 2932, 2858, 1659, 1592, 1478, 1452, 1258, 1219, 1098, 1051, 1018, 912, 805, 698, 632; 1H NMR (400 MHz, CDCl3) δ 8.864 (s, 1H), 7.910 (d, J = 8.8 Hz, 1H), 7.865-7.840 (m, 2H), 7.779 (d, J = 7.6 Hz, 2H), 7.647 (t, J = 7.6 Hz, 1H), 7.477(t, J = 7.6 Hz, 2H), 2.566 (t, J = 7.6 Hz, 2H), 1.635-1.481 (m, 2H), 1.235-1.128 (m, 4H), 0.785 (t, J = 6.4 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ 196.990, 152.903, 145.607, 142.158, 138.062, 136.657, 134.857, 133.691, 132.376, 131.424, 129.872, 129.261, 126.704, 93.559, 31.581, 31.277, 30.736, 22.326, 13.916. HRMS Calculated for [M+] C21H20ONI 429.0584, found 429.0584.

3.4.7 (3-hexyl-6-iodoquinolin-4-yl)(phenyl)methanone (2f)

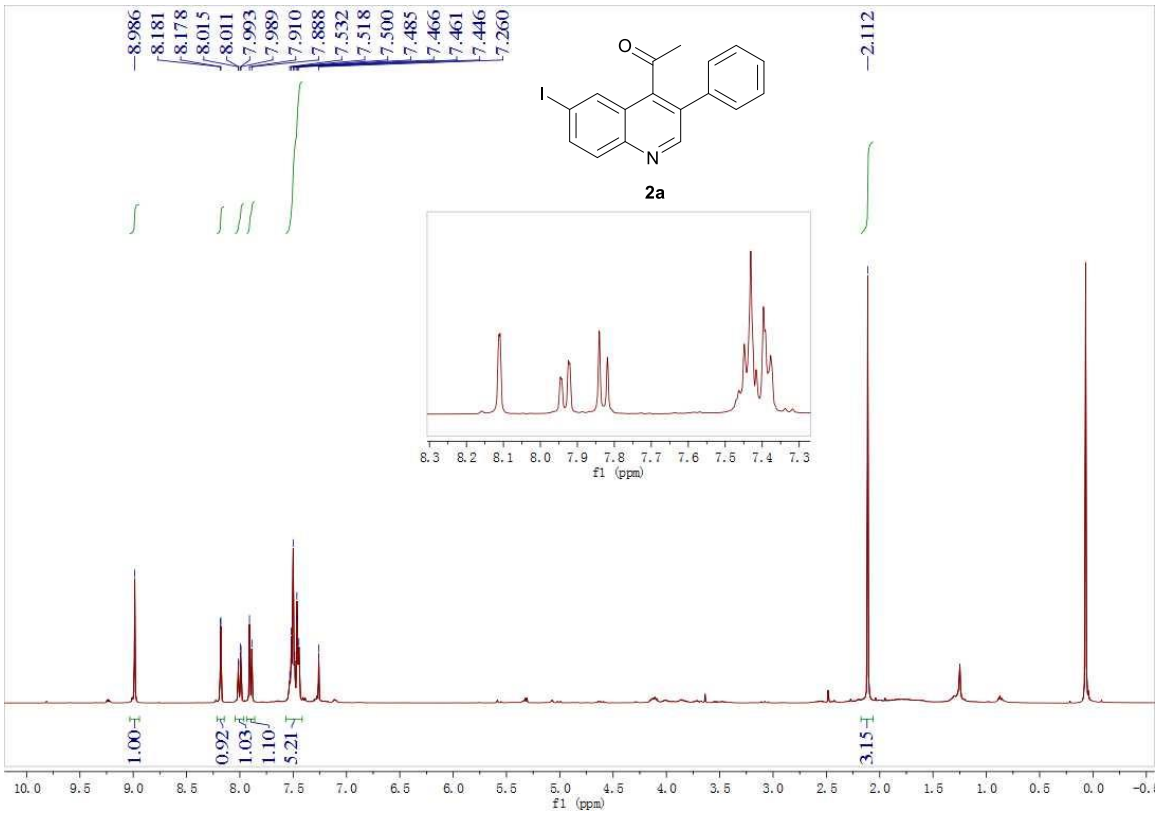


34% yield, unknown compound, white oil. IR(KBr)/cm-1: 3058, 2958, 2925, 2851, 1671, 1598, 1578, 1485, 1452, 1312, 1258, 1219, 1172,1098, 1051, 1025, 912, 818, 798, 698, 632; 1H NMR (400 MHz, CDCl3) δ 8.863 (s, 1H), 7.911 (dd, J = 8.8, 1.6 Hz, 1H), 7.865-7.836 (m, 2H), 7.779 (d, J = 7.6 Hz, 2H), 7.648 (t, J = 7.2 Hz, 1H), 7.477 (t, J = 8.0 Hz, 2H), 2.566 (t, J = 7.6 Hz, 2H), 1.621-1.475 (m, 2H), 1.235-1.133 (m, 6H), 0.803 (t, J = 6.4 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ 196.991, 152.900, 145.601, 142.158, 138.062, 136.657, 134.857, 133.691, 132.382, 131.420, 129.875, 129.260, 126.706, 93.560, 31.442, 31.307, 31.017, 29.108, 22.504, 14.100. HRMS Calculated for [M+] C22H22ONI 443.0741, found 443.0729.

3.4.8 (3-benzyl-6-iodoquinolin-4-yl)(phenyl)methanone (2g)



37% yield, unknown compound, yellow solid, mp = 133-140 °C. IR(KBr)/cm-1: 3058, 3031, 2958, 2918, 2851, 1652, 1592, 1491, 1452, 1312, 1265, 1219, 1172, 1098, 1058, 1025, 885, 818, 805, 732, 705, 632; 1H NMR (400 MHz, CDCl3) δ 8.832 (s, 1H), 7.934 (dd, J = 8.8, 1.2 Hz, 1H), 7.870-7.848 (m, 3H), 7.739(d, J = 7.6 Hz, 2H), 7.626 (t, J = 7.2 Hz, 1H), 7.440 (t, J = 7.6 Hz, 2H), 7.197-7.110 (m, 3H), 7.045 (d, J = 6.8 Hz, 2H), 3.962 (s, 2H); 13C NMR (100 MHz, CDCl3) δ 196.876, 153.126, 145.726, 142.637, 138.427, 138.330, 136.518, 134.910, 133.865, 131.445, 130.664, 129.949, 129.243, 129.123, 128.789, 126.887, 126.675, 93.747, 36.960. HRMS Calculated for [M+] C23H16ONI 449.0271, found 449.0274.



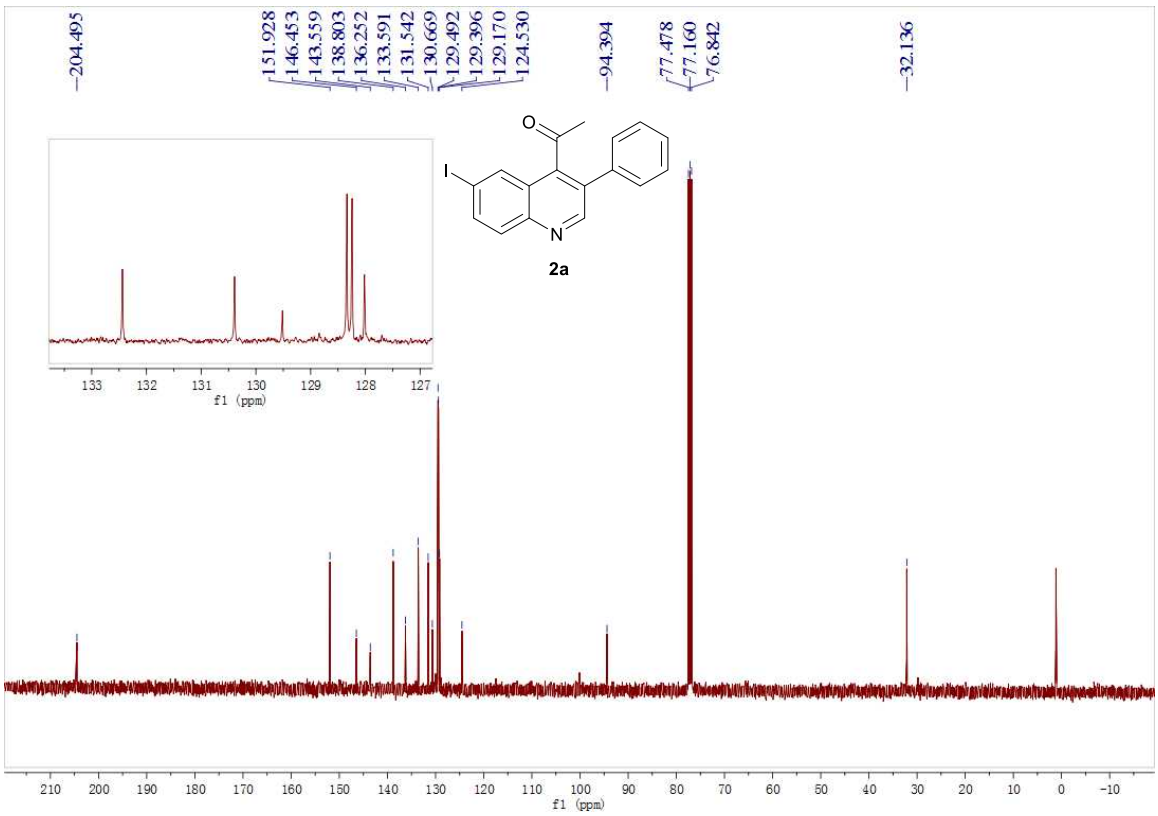
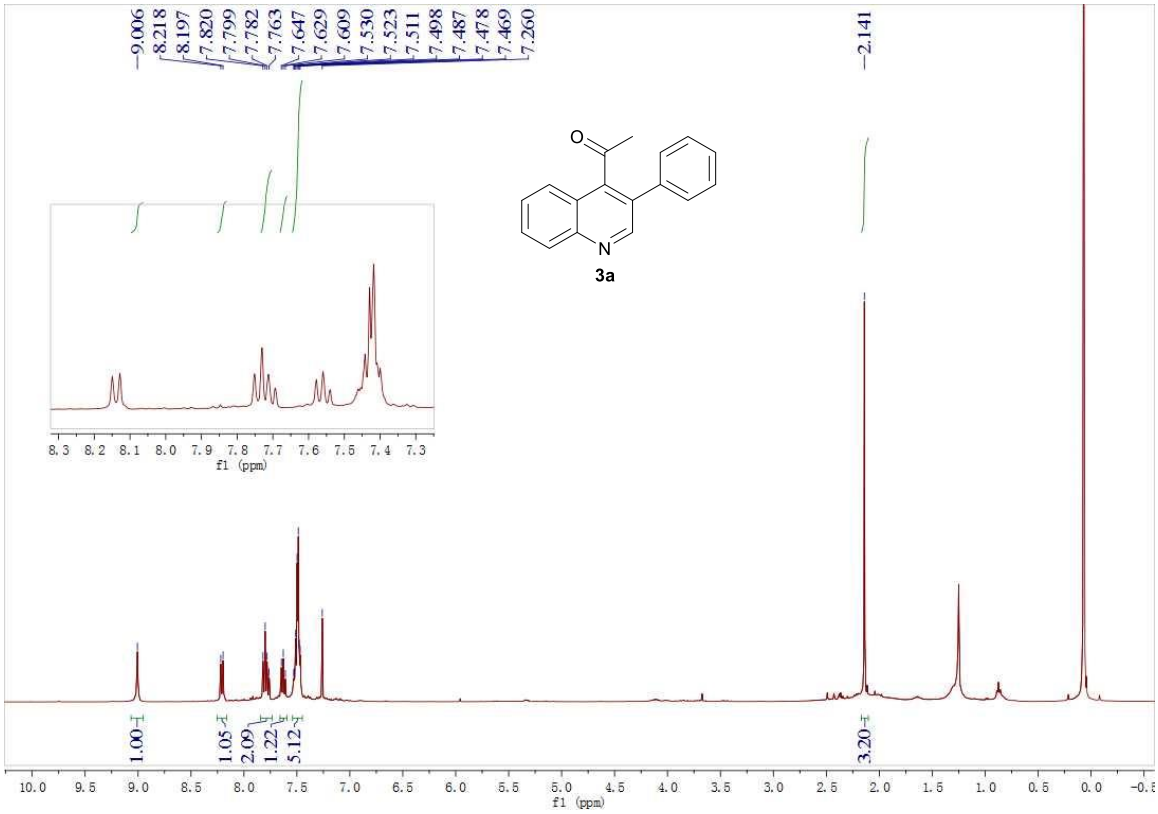


Figure 6: ^{1}H NMR and ^{13}C NMR spectra of 2a



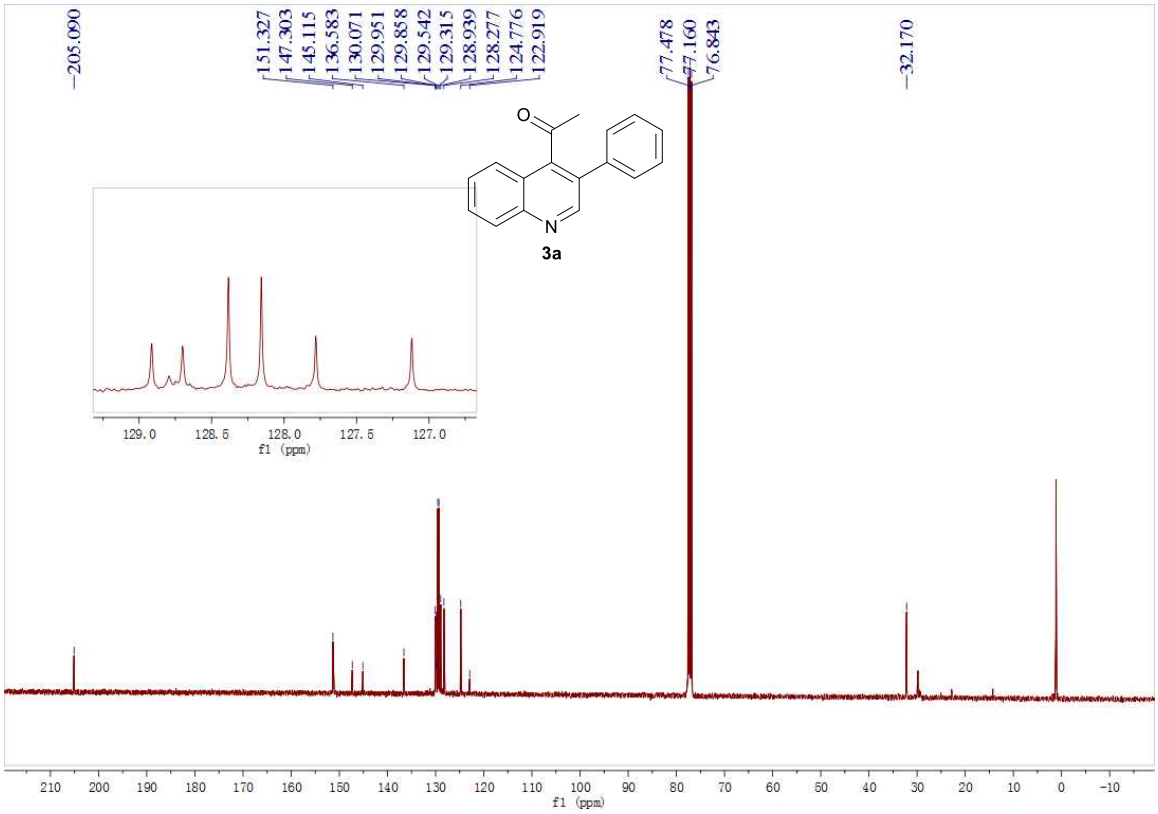
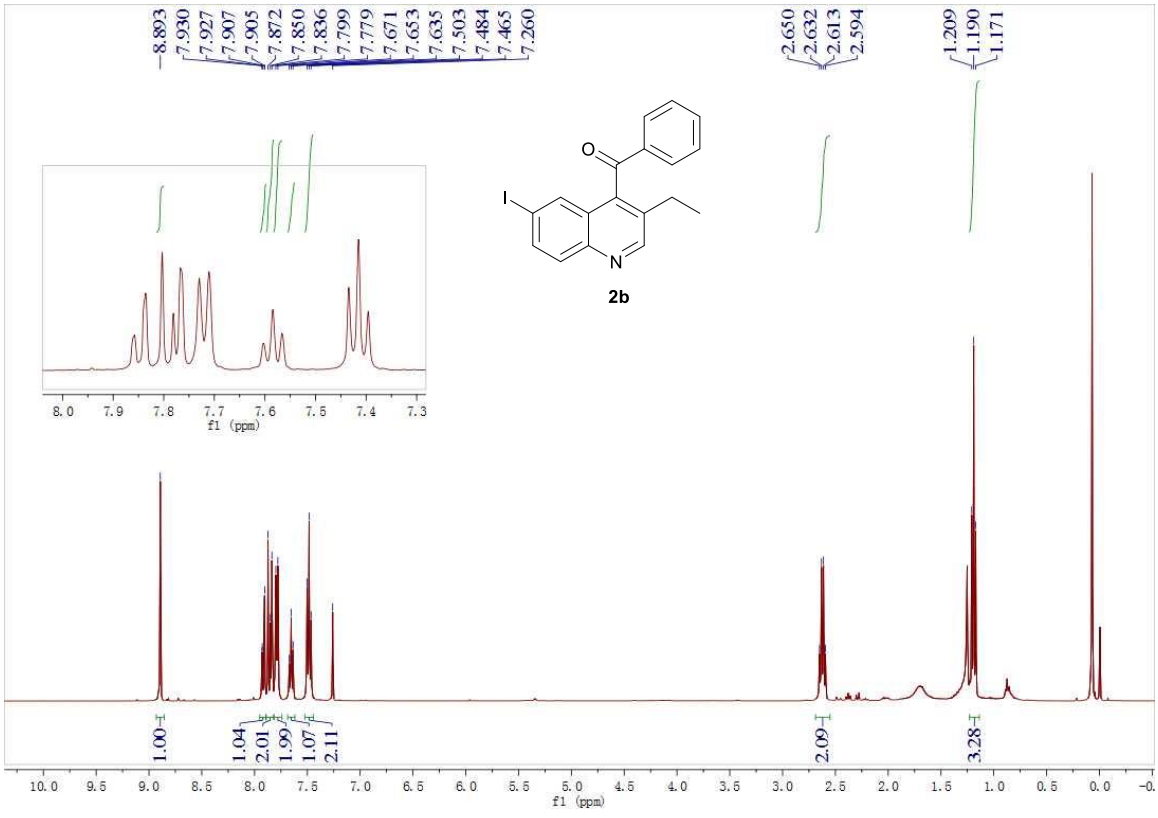


Figure4: ^{1}H NMR and ^{13}C NMR spectra of 3a



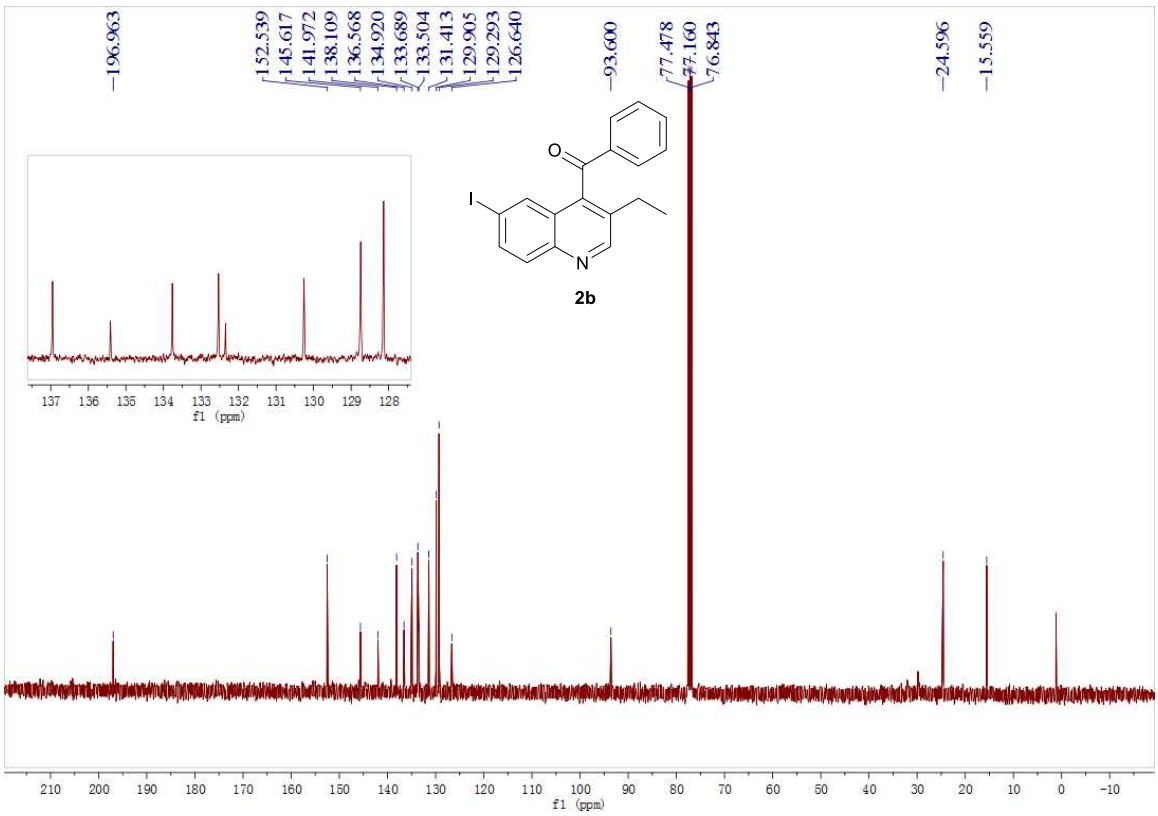
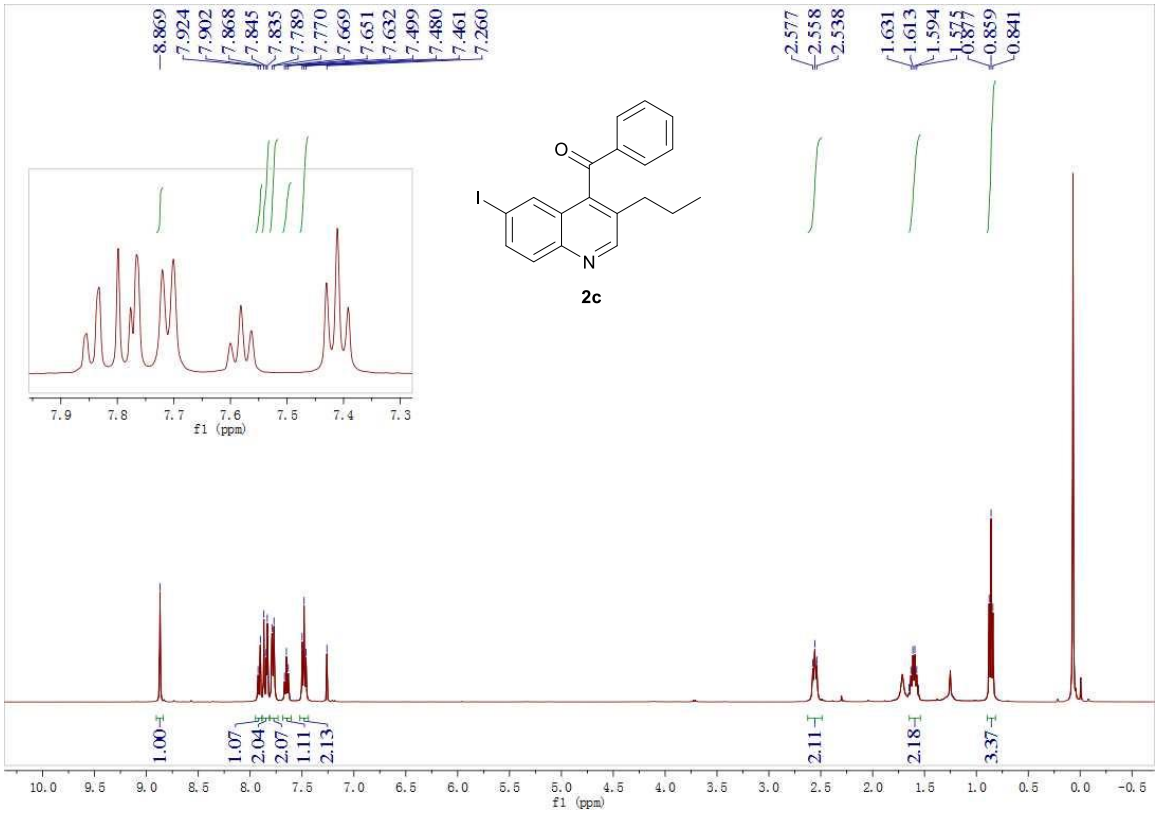


Figure 5: ^{1}H NMR and ^{13}C NMR spectra of 2b



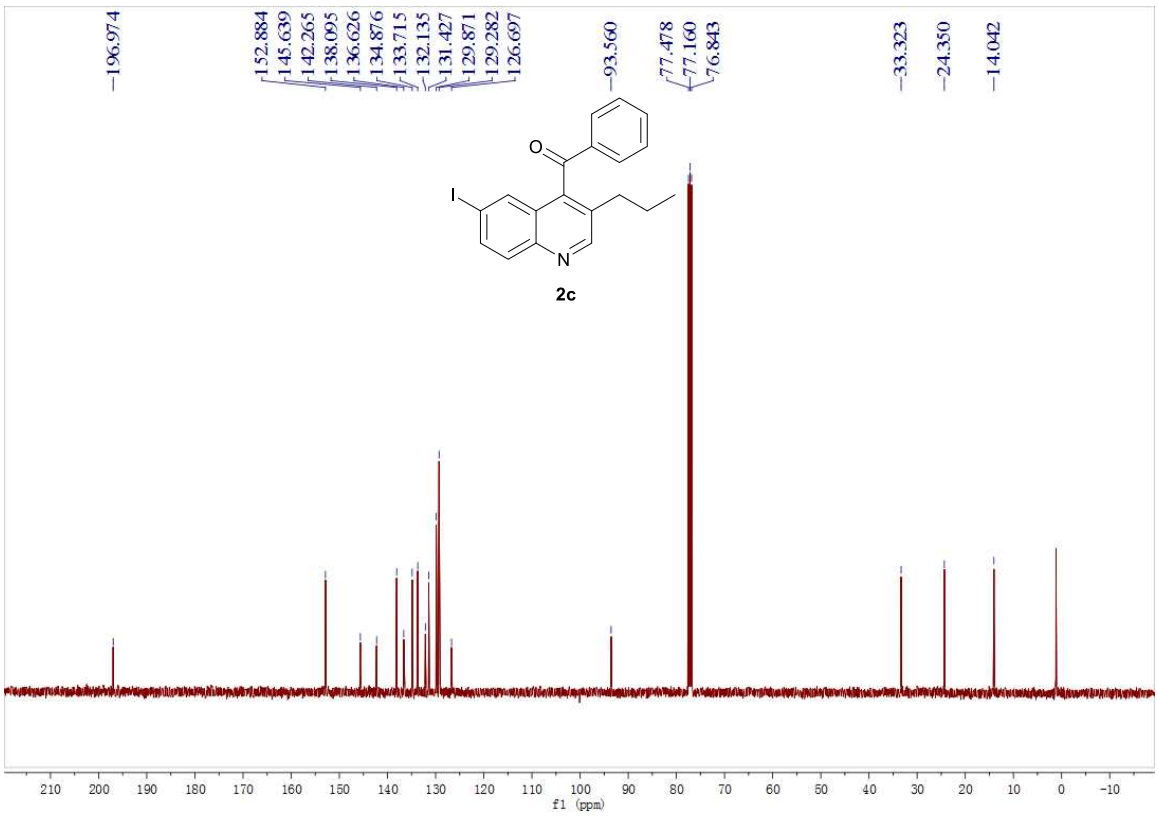
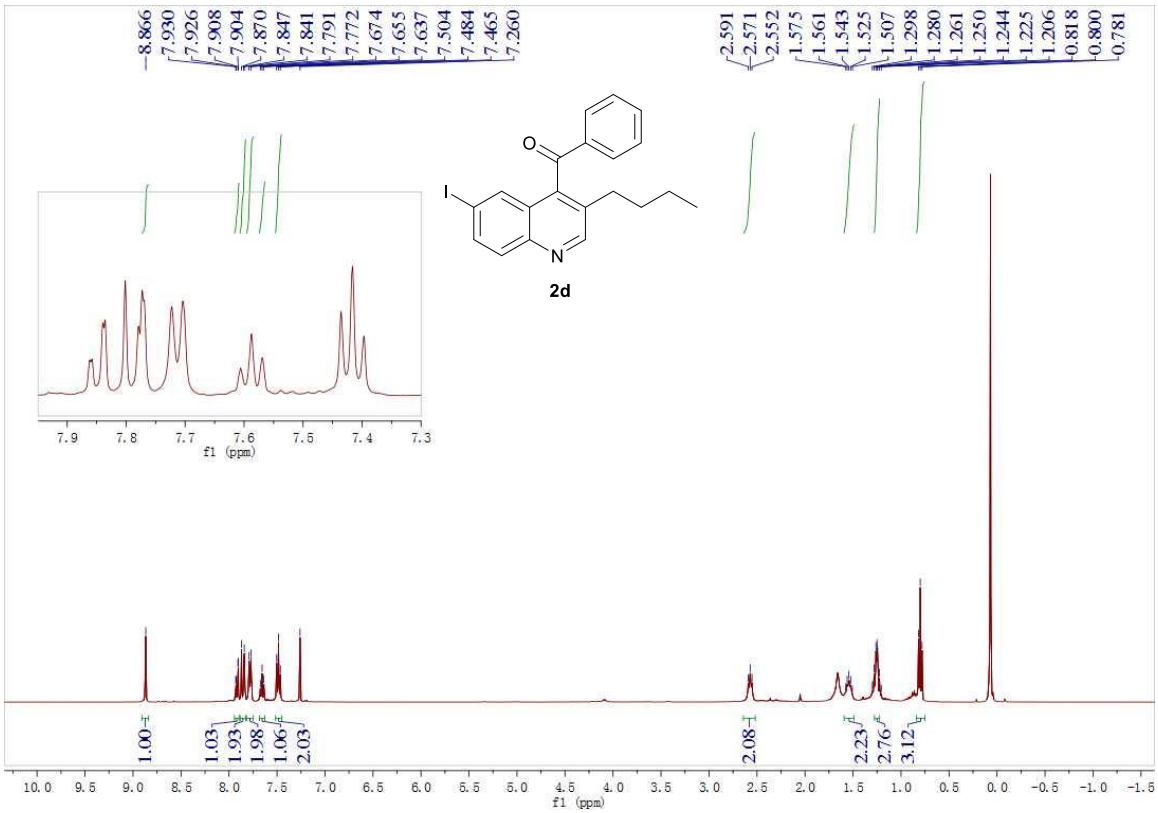


Figure 6: ^{1}H NMR and ^{13}C NMR spectra of 2c



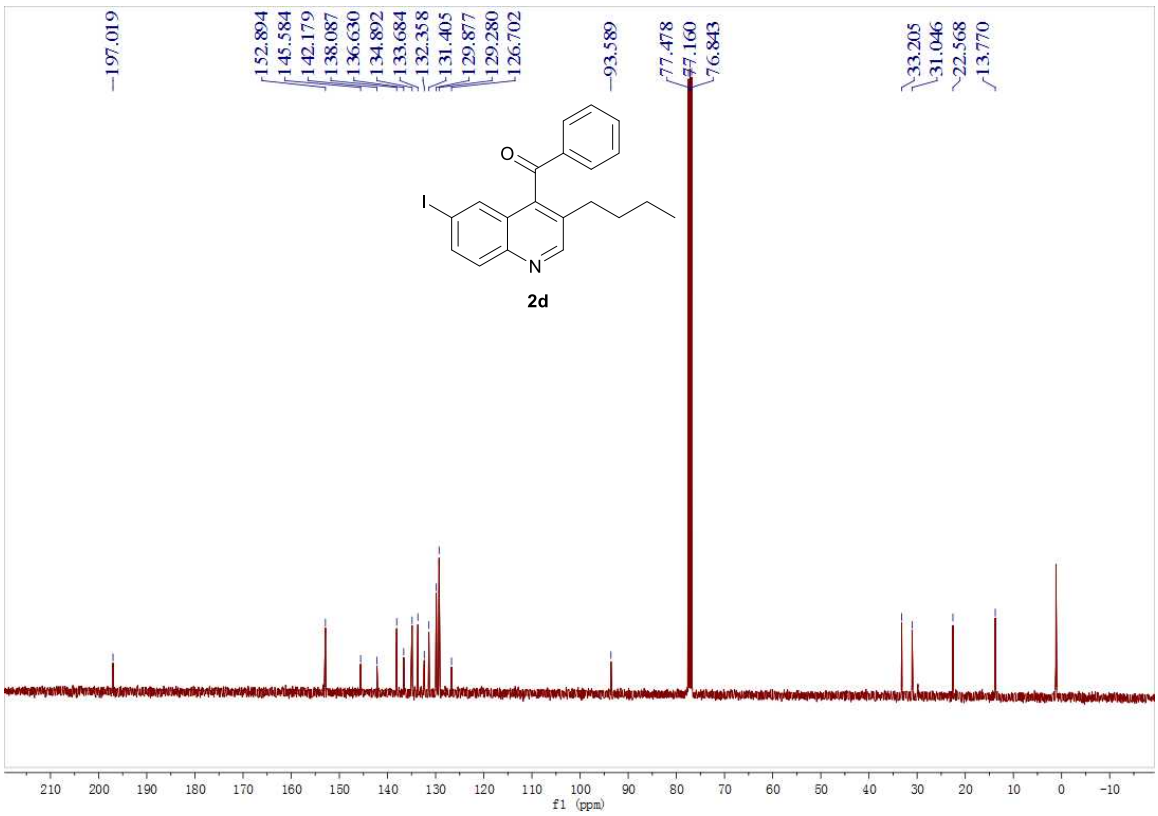
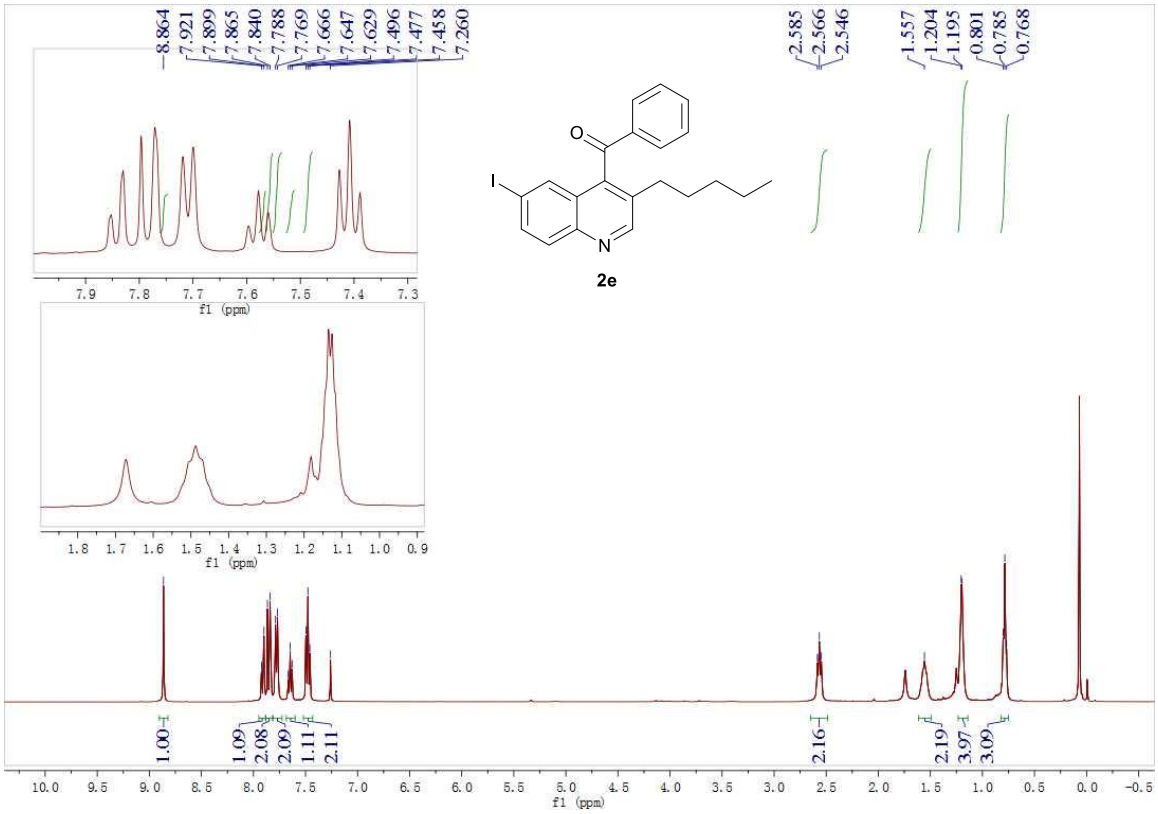


Figure 7: ^{1}H NMR and ^{13}C NMR spectra of 2d



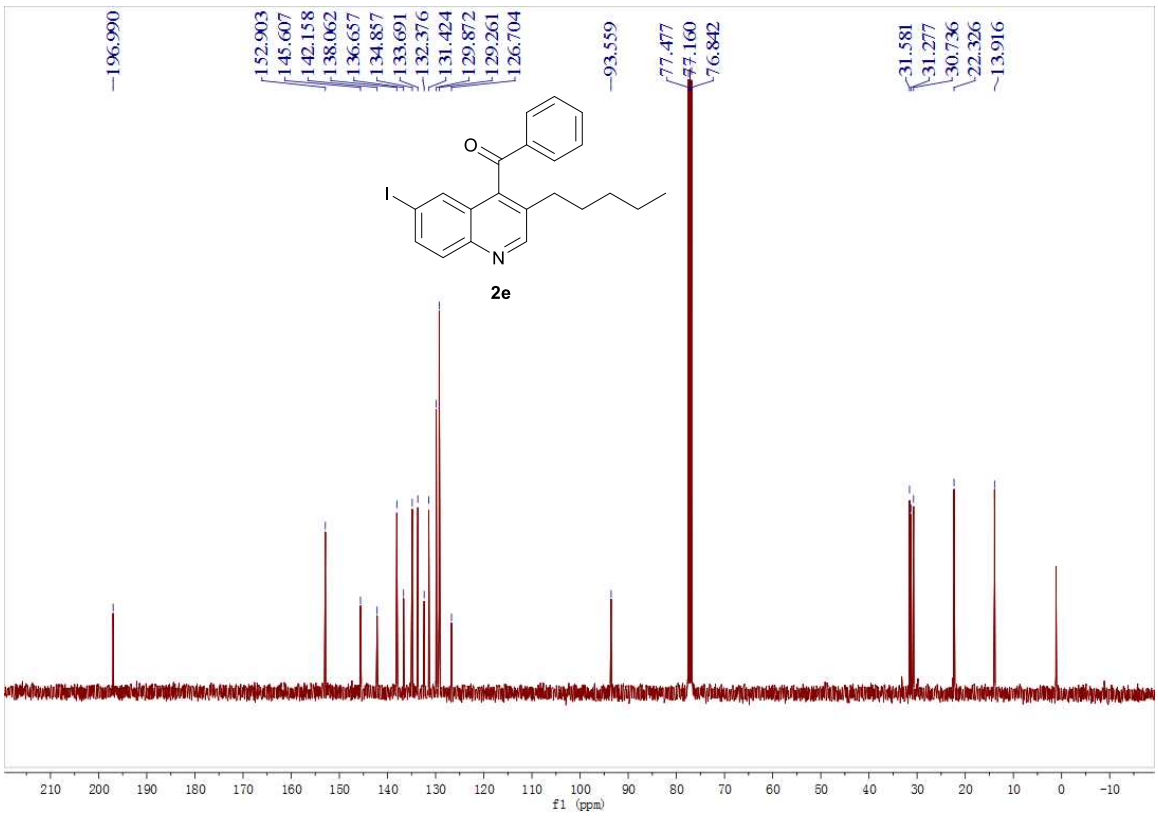
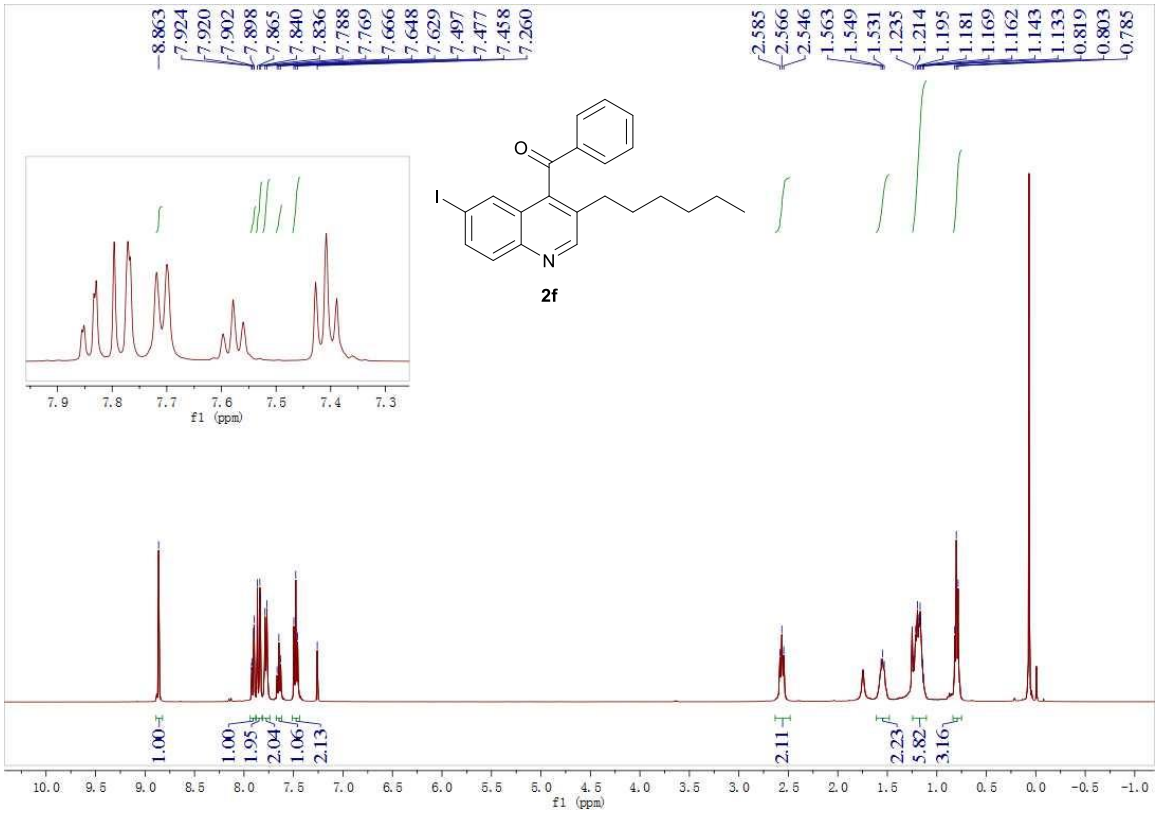


Figure 8: ^{1}H NMR and ^{13}C NMR spectra of 2e



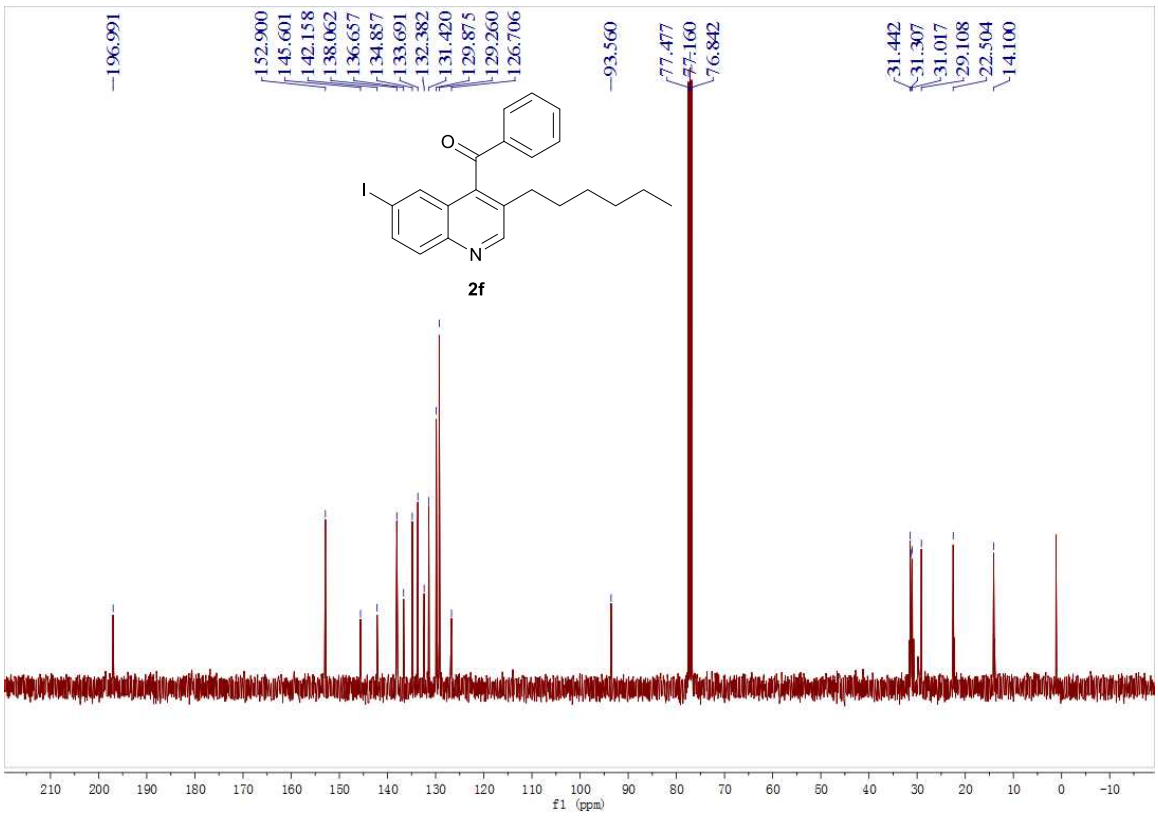
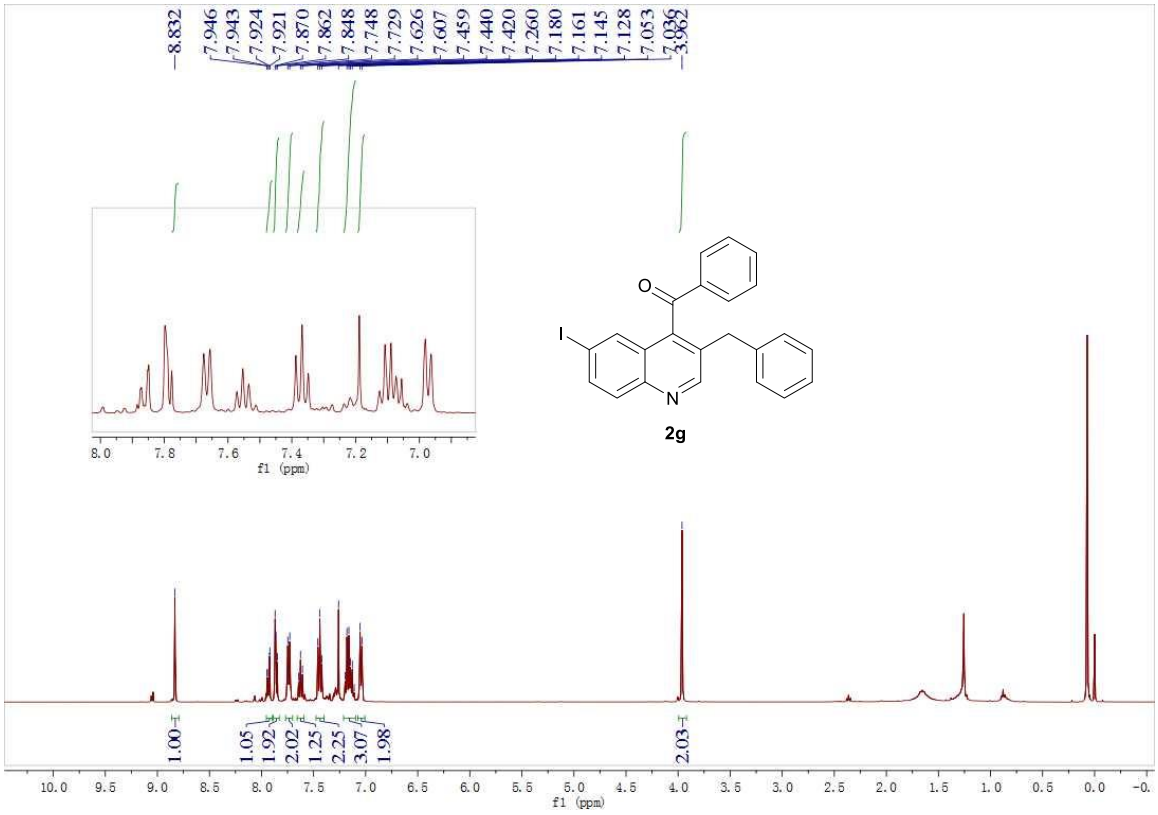


Figure 9: ^{1}H NMR and ^{13}C NMR spectra of 2f



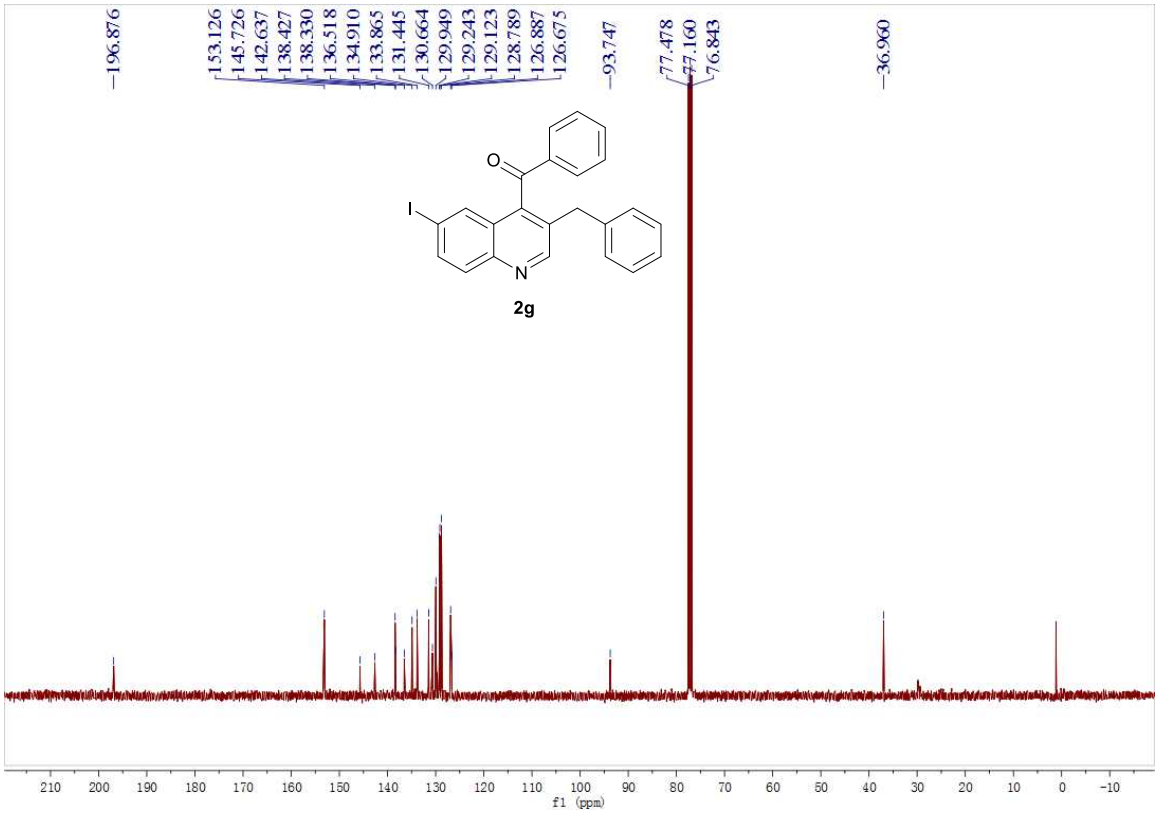


Figure 10: ^{1}H NMR and ^{13}C NMR spectra of 2g

4 BENEFITS OF THIS RESEARCH OUTCOME& CONCLUSION

In conclusion, we developed a new metal-free ring expansion reaction of indole derivatives into highly functionalized quinoline derivatives. This transformation represents an extremely simple way to afford highly functionalized quinoline derivatives. Moreover, the reaction can be conducted in one pot and readily accessible starting material. We believe that this new ring-expansion reaction could become a widely used transformation in organic synthesis.

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The Synthesis of Highly Functionalized Quinoline Derivatives via the Ring-Expansion Reaction of
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