

## Michael Reactions of Arylidenesulfonylacetonitriles. A New Route to Polyfunctional Benzo[*a*]quinolizines

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**Abstract:** Arylidenesulfonylacetonitriles react in acetonitrile with 1-methylisoquinoline and isoquinolin-1-yl-acetonitrile in the presence of piperidine to give benzo[*a*]quinolizines **6,9** and **7,10**, respectively. The structures of the products were established on the basis of elemental and spectral analyses and their chemical reactivity.

**Keywords:** Arylidenesulfonylacetonitriles, 1-methylisoquinoline, isoquinolin-1-yl-acetonitrile, benzo[*a*]quinolizines.

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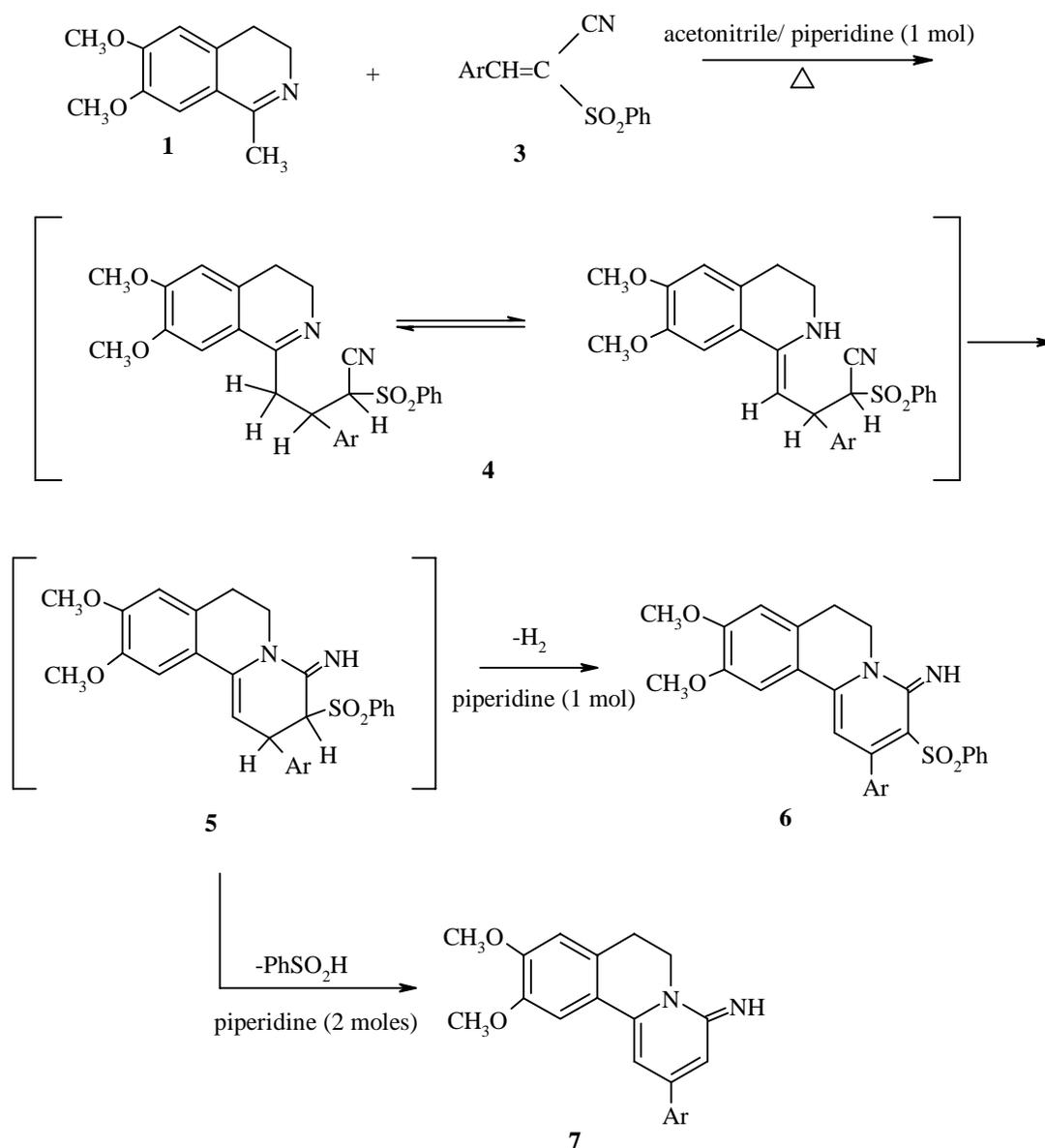
### Introduction

High yielding syntheses of polyfunctional benzo[*a*]quinolizines are well documented [1-9]. As a continuation of our work on the use of isoquinoline and its derivatives for the synthesis of fused heterocyclic compounds [10,11], we now report a new and general one step route affording polyfunctional substituted benzo[*a*]quinolizines in good yield from readily available inexpensive starting materials, which competes favorably with the methods previously reported for the preparation of the title compounds.

## Results and Discussion

Treatment of 1-methylisoquinoline (**1**) [12] with arylidenesulfonylacetonitriles **3a-c** [13] in boiling acetonitrile in the presence of an equimolar amount of piperidine leads, in each case, to the formation of only one product **6a-c**, as indicated by TLC and  $^1\text{H-NMR}$  analyses (Scheme 1).

Scheme 1



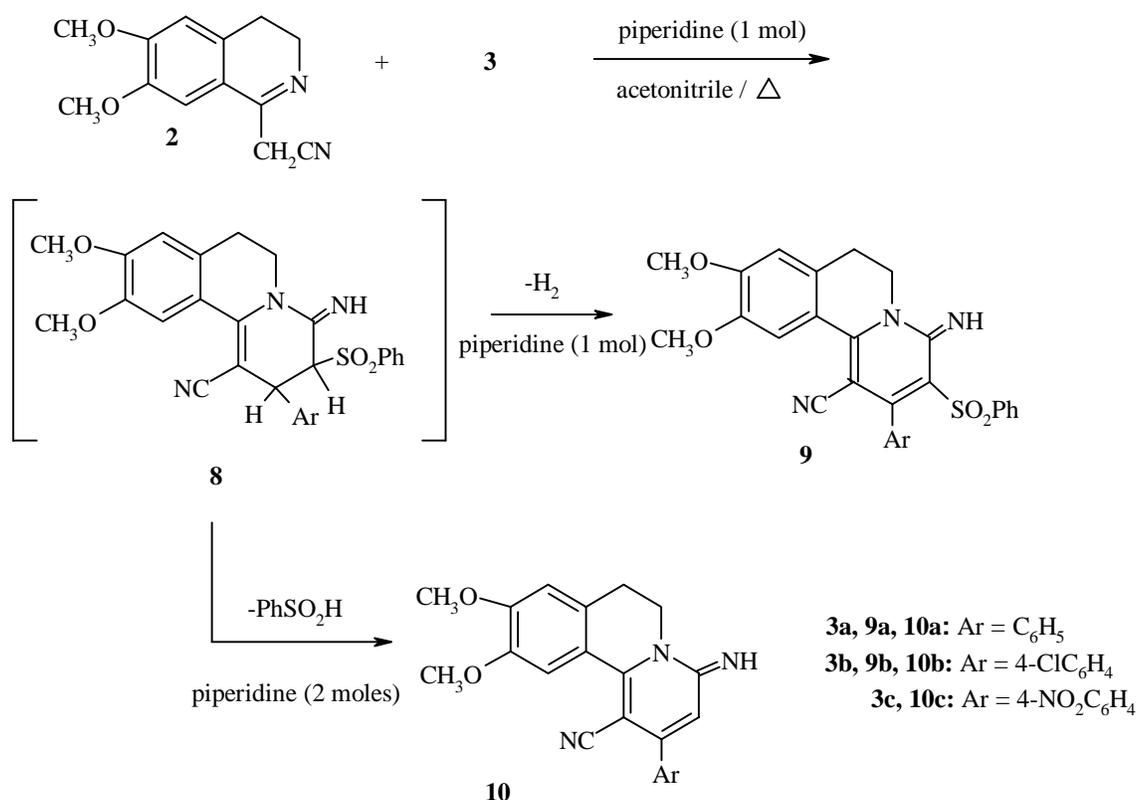
**3a, 6a, 7a:** Ar = C<sub>6</sub>H<sub>5</sub>

**3b, 6b, 7b:** Ar = 4-ClC<sub>6</sub>H<sub>4</sub>

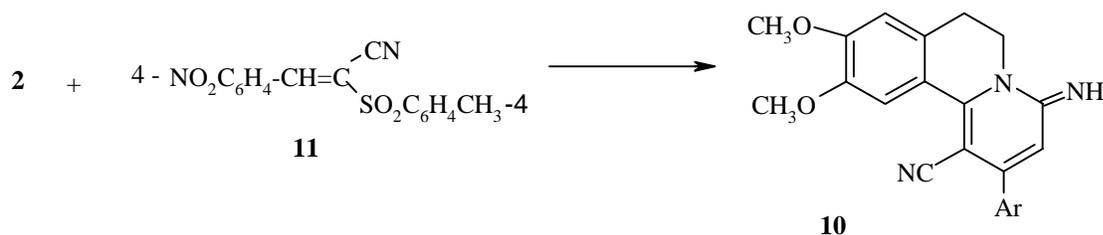
**3c, 6c, 7c:** Ar = 4-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>

The structures of the products **6a-c** were established on the basis of their elemental analyses and spectral data (IR,  $^1\text{H-NMR}$ , MS). For example, the IR spectrum of compound **6a** shows a stretching frequency at  $3350\text{ cm}^{-1}$  (NH) in addition to characteristic bands at  $1315$  and  $1155\text{ cm}^{-1}$  (asymmetric and symmetric stretching vibrations of a  $\text{SO}_2$  group). Its  $^1\text{H-NMR}$  spectrum reveals a singlet at  $\delta = 6.9$  assignable to the C-1 proton and a singlet at  $\delta = 8.8$ , which disappears upon deuterium exchange, assignable to the NH proton, in addition to the typical signals of the isoquinoline moiety. The formation of **6** may be explained by cyclization of the initially formed Michael addition product **4** to the unisolated product **5**. Subsequent autoxidation of the latter leads to the final product **6** (cf. Scheme 1). When the reaction of **1** with **3a-c** was carried out in the presence of excess piperidine (2 moles) then the products **7a-c** were formed directly. The structures of the products **7** were also inferred from their elemental analyses and spectral data. For example, the IR spectra show a characteristic peak near  $3320\text{ cm}^{-1}$  due to a NH group. The mass spectra of the products also show a molecular ion peak of high intensity, and the  $^1\text{H-NMR}$  and chemical reactivity also support the proposed structures of the products. In light of the previous results, it may be suggested that the unisolated products **5** afford the end products **7** via loss of benzenesulfonic acid (Scheme 1). Similarly, isoquinolin-1-yl-acetonitrile (**2**) [14] reacts with **3a,b** to give **9a,b** (cf. Scheme 2). The structures of the latter products were confirmed by elemental analysis and spectroscopic data. Upon treatment of p-nitrobenzylidene phenylsulfonfylacetonitrile **3c** in this fashion a product **10c** was formed directly due to elimination of benzenesulfonic acid from the intermediate **8** (Scheme 2). The structure of the product **10c** was confirmed by its independent synthesis via reaction of **2** with **11** (Scheme 3).

Scheme 2

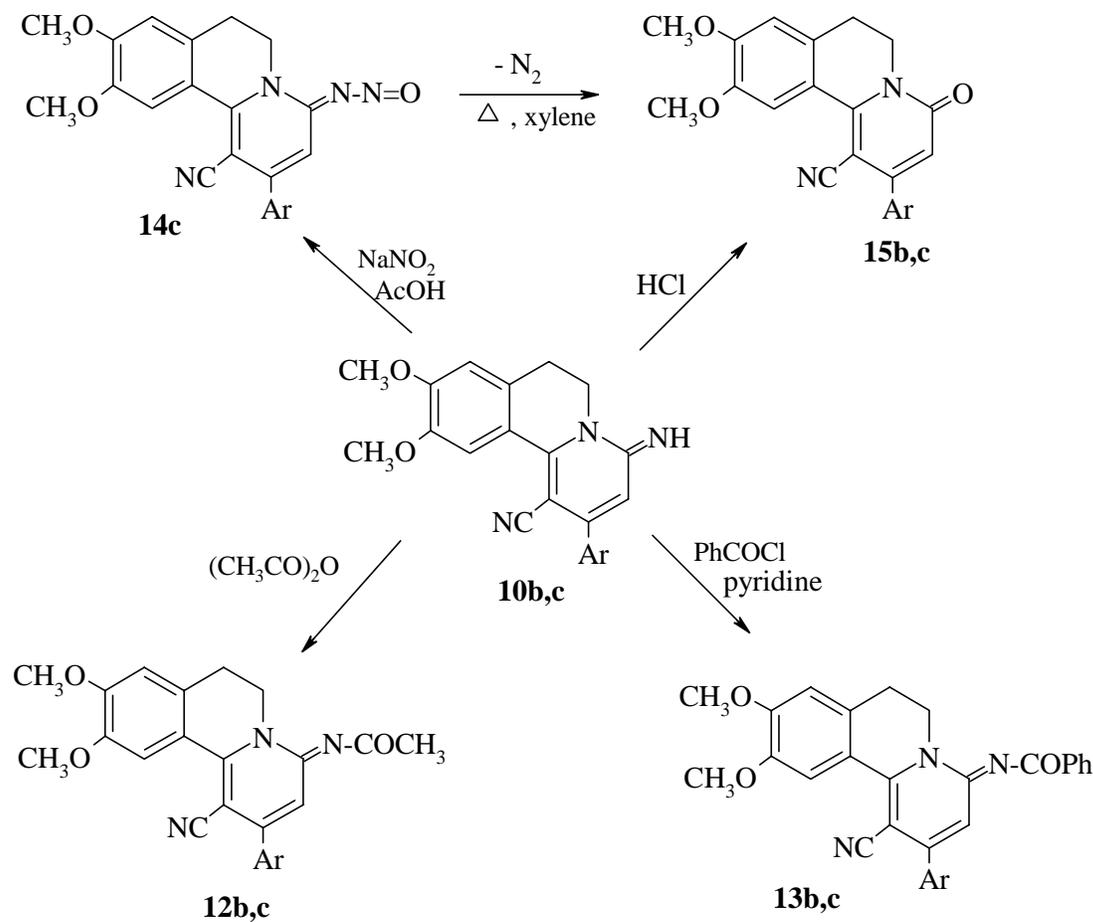


## Scheme 3



The structures of **10b,c** were also confirmed by their chemical reactions as described in Scheme 4. For example, acylation of **10b,c** with acetic anhydride or benzoylation with benzoyl chloride in pyridine affords the corresponding N-acetylimino or N-benzoylimino compounds **12b,c** and **13b,c**, respectively. Nitrosation of **10c** with sodium nitrite in acetic acid gives the corresponding N-nitroso compound **14c**. Thermolysis of **14c** in xylene gives the carbonyl compound **15c**. The structure of **15c** was confirmed by its alternative synthesis by hydrolysis of **10c** with dilute hydrochloric acid. Also, hydrolysis of **10b** with dilute hydrochloric acid leads to the formation of **15b**. Their elemental analyses and spectral data (cf. Table 1 and 2) confirmed the structures of **12**, **13**, **14** and **15**.

## Scheme 4



## Experimental

### General

All melting points were determined on an Electrothermal melting point apparatus and are uncorrected. IR spectra were recorded (KBr discs) on a Shimadzu FT-IR 8201 PC spectrophotometer.  $^1\text{H}$  NMR spectra were recorded in  $\text{CDCl}_3$  and  $(\text{CD}_3)_2\text{SO}$  solutions on a Varian Gemini 200 MHz spectrometer and chemical shifts are expressed in  $\delta$  units using TMS as internal reference. Mass spectra were recorded on a Shimadzu GCMS-QP1000 EX mass spectrometer, operating at 70 eV. Elemental analyses were carried out at the Microanalytical Center of the University of Cairo, Giza, Egypt. The analytical and spectral data of the compounds prepared is summarized in Tables 1 and 2.

### *Synthesis of 2-aryl-6,7-dihydro-9,10-dimethoxy-4-imino-2-phenylsulphonyl-benzo[a]quinolizines 6 and 9.*

Piperidine (0.5 mL, 0.005 mol) was added at room temperature to a solution of arylidene-sulfonylacetonitriles **3** (0.005 mol) and 1-methylisoquinoline (**1**) (1.02 g, 0.005 mol) or isoquinolin-1-yl-acetonitrile (**2**) (1.15 g, 0.005 mol) in acetonitrile (40 mL). The reaction mixture was refluxed for 8 h. The solvent was evaporated under reduced pressure and the residue was triturated with methanol (10 mL) whereupon it solidified. The crude product was collected and crystallized from DMF.

### *Synthesis of 2-aryl-6,7-dihydro-9,10-dimethoxy-4-iminobenzo[a]-quinolizines 7 and 10*

These compounds were prepared by the same procedure described for the synthesis of compounds **6** and **9** using (1mL, 0.01 mol) of piperidine. The precipitated compounds were crystallized from DMF.

### *Nitrosation of 10c.*

Cold sodium nitrite solution (0.7 g in 10 mL water) was added dropwise to a stirred solution of **10c** (2.01 g, 0.005 mol) in acetic acid (30 mL). The mixture was left in an ice bath for 4 h., then the reddish solid that precipitated was collected. Crystallization of the crude product from DMF gave the corresponding N-nitroso derivative **14c**.

### *Thermolysis of 14c.*

The N-nitroso compound **14c** (2.16 g, 0.005 mol) was refluxed in xylene (20 mL) until its red color disappeared (ca. 20 min). The reaction mixture was then cooled, the crude product was collected, washed with water and crystallized from DMF.

Acylation of **10b,c**.

A solution of **10b,c** (0.005 mol) in acetic anhydride (25 mL) was refluxed for 1 h. The solvent was removed under reduced pressure and the residue was triturated with water. The solid formed was collected, washed with water and crystallized from ethanol to give N-acetylimino derivatives **12b,c**.

Treatment of **10b,c** (0.005 mol) with benzoyl chloride (0.58 mL, 0.005 mol) in pyridine (30 mL) at reflux for 30 min. and workup of the reaction mixture in usual way gave the corresponding N-benzoylimino derivatives **13b,c**.

Hydrolysis of **10 b,c**.

A suspension of **10 b,c** (2.01g, 0.005 mol) in 10% hydrochloric acid (20 mL) was refluxed for 30 min. The reaction mixture was cooled and the solid that precipitated out was collected and crystallized from DMF to give **15b,c**.

**Table 1.** Analytical data of the synthesized compounds

Compd. no.	Color	Yield %	m.p.°C solvent	Mol. formula Mol. Wt.	% Analysis Calcd. (Found)			
					C	H	N	S
<b>6a</b>	yellow	80	225-226	C <sub>27</sub> H <sub>24</sub> N <sub>2</sub> O <sub>4</sub> S	68.64	5.08	5.93	6.78
			DMF	472.23	(68.72)	(5.02)	(5.83)	(6.66)
<b>6b</b>	dark	82	264-266	C <sub>27</sub> H <sub>23</sub> N <sub>2</sub> O <sub>4</sub> SCl	63.96	4.54	5.53	6.32
	yellow		DMF	506.72	(64.23)	(4.44)	(5.52)	(6.38)
<b>6c</b>	orange	78	276-277	C <sub>27</sub> H <sub>23</sub> N <sub>3</sub> O <sub>6</sub> S	62.67	4.45	8.12	6.19
			DMF	517.23	(62.52)	(4.24)	(8.03)	(6.08)
<b>9a</b>	dark	84	258-259	C <sub>28</sub> H <sub>23</sub> N <sub>3</sub> O <sub>4</sub> S	67.61	4.63	8.45	6.44
	yellow		DMF	497.23	(67.43)	(4.52)	(8.62)	(6.27)
<b>9b</b>	bright	77	320-322	C <sub>28</sub> H <sub>22</sub> N <sub>3</sub> O <sub>4</sub> SCl	63.22	4.14	7.90	6.02
	brown		DMF	531.72	(63.04)	(4.03)	(7.84)	(6.14)
<b>7a</b>	yellow	81	329-331	C <sub>21</sub> H <sub>20</sub> N <sub>2</sub> O <sub>2</sub>	75.90	6.02	8.43	-
			DMF	332.19	(75.63)	(6.14)	(8.63)	-
<b>7b</b>	yellow	85	206-207	C <sub>21</sub> H <sub>19</sub> N <sub>2</sub> O <sub>2</sub> Cl	68.76	5.18	7.64	-
			DMF	366.68	(68.64)	(5.02)	(7.83)	-
<b>7c</b>	yellow	88	214-215	C <sub>21</sub> H <sub>19</sub> N <sub>3</sub> O <sub>4</sub>	66.84	5.04	11.14	-
			DMF	377.19	(66.90)	(5.13)	(11.24)	-
<b>10a</b>	dark	86	214-216	C <sub>22</sub> H <sub>19</sub> N <sub>3</sub> O <sub>2</sub>	73.95	5.32	11.76	-
	yellow		DMF	357.19	(73.63)	(5.21)	(11.54)	-
<b>10b</b>	bright	79	223-224	C <sub>22</sub> H <sub>18</sub> N <sub>3</sub> O <sub>2</sub> Cl	67.43	4.60	10.73	-
	brown		DMF	391.68	(67.13)	(4.73)	(10.94)	-

<b>10c</b>	dark	89	275-277	$C_{22}H_{18}N_4O_4$	65.67	4.48	13.93	-
	yellow		DMF	402.19	(65.51)	(4.32)	(13.83)	-
<b>12b</b>	dark	84	153-155	$C_{24}H_{20}N_3O_3Cl$	66.44	4.61	9.69	-
	yellow		EtOH	433..70	(66.12)	(4.51)	(9.82)	-
<b>12c</b>	dark	78	150-151	$C_{24}H_{20}N_4O_5$	64.86	4.50	12.61	-
	yellow		EtOH	444.21	(64.84)	(4.32)	(12.41)	-
<b>13b</b>	dark	77	241-242	$C_{29}H_{22}N_3O_3Cl$	70.23	4.44	8.48	-
	yellow		DMF	495.72	(70.13)	(4.24)	(8.21)	-
<b>13c</b>	brown	79	260-262	$C_{29}H_{22}N_4O_5$	68.77	4.35	11.07	-
			DMF	506.23	(68.63)	(4.11)	(10.90)	-
<b>14c</b>	red	81	250-251	$C_{22}H_{17}N_5O_5$	61.25	3.94	16.24	-
			DMF	431.19	(61.21)	(3.67)	(16.42)	-
<b>15b</b>	yellow	78	294-295	$C_{22}H_{17}N_2O_3Cl$	67.26	4.33	7.13	-
			DMF	392.67	(67.13)	(4.12)	(7.34)	-
<b>15c</b>	yellow	83	244-246	$C_{22}H_{17}N_3O_5$	65.51	4.22	10.42	-
			DMF	403.17	(65.23)	(4.12)	(10.35)	-

**Table 2.** IR and  $^1H$ -NMR spectroscopic data

Compd. no.	IR (cm <sup>-1</sup> )	$^1H$ NMR ( $\delta$ ppm)	M <sup>+</sup>
<b>6a</b>	3350 (NH)	2.6 (m, 2H); 3.8 (s, 3H); 3.9 (s, 3H); 4.1 (m, 2H); 6.9 (s, 1H); 7.0-7.7 (m, 10H); 7.8 (s, 1H); 7.9 (s, 1H), 8.8 (s, 1H)	472
<b>6b</b>	3380 (NH)	3.0 (m, 2H); 3.8 (s, 6H); 4.1 (m, 2H); 7.0 (s, 1H); 7.2-7.6 (m, 10H); 7.9 (s, 2H).	507
<b>6c</b>	3446 (NH)	3.1 (m, 2H); 3.8 (s, 6H); 4.1 (m, 2H); 6.9 (s, 1H); 7.1-8.5 (m, 12H).	517
<b>9a</b>	2216 (CN), 3417 (NH)	3.0 (m, 2H); 3.8 (s, 6H); 4.1 (m, 2H); 6.9 (s, 1H); 7.0-7.6 (m, 11H); 7.7 (s, 1H)	497
<b>9b</b>	2219 (CN), 3415 (NH)	2.8 (m, 2H); 3.8 (s, 3H); 3.9 (s, 3H); 4.1 (m, 2H); 7.2 (s, 1H); 7.3-7.7 (m, 10H); 7.9 (s, 1H)	532
<b>7a</b>	3386 (NH)	2.9 (m, 2H); 3.3 (s, 3H); 3.4 (s, 3H); 3.8 (m, 2H); 6.7 (s, 1H); 6.8 (s, 1H); 6.9 (s, 1H), 7.1 (s, 1H) 7.2-7.6 (m, 6H)	332
<b>7b</b>	3252 (NH)	2.9 (m, 2H); 3.8 (s, 3H); 3.9 (s, 3H); 4.1 (m, 2H); 6.3 (s, 1H); 6.4 (s, 1H); 6.7 (s, 1H); 7.1 (s, 1H); 7.4-7.8 (m, 5H)	367
<b>7c</b>	3323 (NH)	2.9 (m, 2H); 3.8 (s, 3H); 3.9 (s, 3H); 4.2 (m, 2H); 6.4 (s, 1H); 6.5 (s, 1H); 6.7 (s, 1H), 6.9 (s, 1H) 7.1-7.6 (m, 5H)	377
<b>10a</b>	2221 (CN), 3316 (NH)	2.9 (m, 2H); 3.8 (s, 3H); 3.9 (s, 3H); 4.0 (m, 2H); 6.3 (s, 1H); 6.4 (s, 1H); 6.7 (s, 1H); 7.2-7.6 (m, 5H)	357

<b>10b</b>	2225 (CN), 3420(NH)	2.9 (m, 2H); 3.8 (s, 3H); 3.9 (s, 3H); 4.0 (m, 2H); 6.8 (s, 1H); 6.9 (s, 1H); 7.1 (s, 1H); 7.4-8.2 (m, 5H)	392
<b>10c</b>	2200 (CN), 3307(NH)	2.8 (m, 2H); 3.6 (s, 3H); 3.7 (s, 3H); 4.0 (m, 2H); 6.4 (s, 1H); 6.9 (s, 1H); 7.1 (s, 1H); 7.4-8.2 (m, 5H)	402
<b>12b</b>	1656(CO), 2217 (CN)	2.8 (m, 2H); 3.7 (s, 3H); 3.9 (s, 6H); 4.0 (m, 2H); 6.7 (s, 1H); 7.0 (s, 1H); 7.4-8.2 (m, 5H)	434
<b>12c</b>	1658(CO), 2210(CN)	2.0 (s, 3H); 2.9 (m, 2H); 3.9 (s, 6H); 4.0 (m, 2H); 6.5 (s, 1H); 6.8 (s, 1H); 7.4-7.6 (m, 4H); 7.9 (s, 1H)	444
<b>13b</b>	1654(CO), 2211(CN)	2.9 (m, 2H); 3.8 (s, 3H); 3.9 (s, 3H); 4.1 (m, 2H); 6.7 (s, 1H); 7.3-8.2 (m, 11H)	496
<b>13c</b>	1672 (CO), 2210(CN)	3.0 (m, 2H); 3.9 (s, 6H); 4.6 (m, 2H); 6.8 (s, 1H), 7.3 (s, 1H); 7.4-8.2 (m, 10H)	506
<b>14c</b>	2218(CN)	2.7 (m, 2H); 3.8 (s, 6H); 4.0 (m, 2H); 6.7 (s, 1H); 6.8 (s, 1H); 7.4-8.2 (m, 5H)	431
<b>15b</b>	1659 (CO), 2216 (CN)	2.8 (m, 2H); 3.7 (s, 3H); 3.9 (s, 3H); 4.0 (m, 2H); 6.7 (s, 1H); 6.8 (s, 1H); 7.4-8.2 (m, 5H)	393
<b>15c</b>	1666(CO), 2218 (CN)	2.7 (m, 2H); 3.8 (s, 3H); 4.0 (s, 3H); 4.1 (m, 2H); 6.7 (s, 1H); 6.9 (s, 1H); 7.4-8.2 (m, 5H)	403

Compound **10c**:  $^{13}\text{C}$ -NMR 27.54, 41.51, 56.78, 56.92, 100.73, 112.06, 113.92, 118.62, 119.82, 120.05, 123.40, 124.31, 130.70, 133.72, 135.31, 139.32, 142.12, 147.82, 148.65, 157.69.

Compound **9a**:  $^{13}\text{C}$ -NMR 28.95, 47.44, 58.31, 58.39, 95.67, 108.45, 112.09, 114.03, 115.60, 119.22, 119.72, 126.32, 130.29, 130.79, 130.96, 132.51, 133.62, 136.76, 150.08, 152.21, 155.38, 155.94, 157.48, 158.58.

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