

Month 2015    Synthesis of Novel Quinoline-substituted 1,4-dihydropyridine Derivatives  
via Hantzsch Reaction in Aqueous Medium:  
Potential Bioactive Compounds

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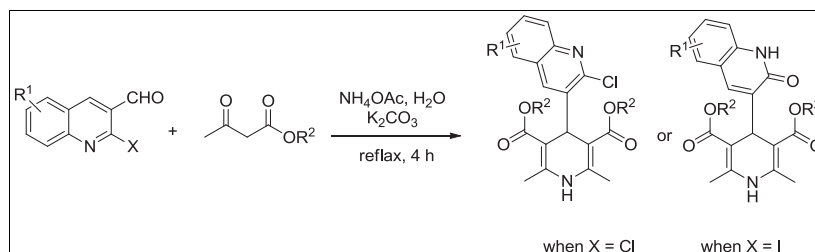
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The synthesis of a novel series of substituted 1,4-dihydropyridines was achieved in aqueous media by base-catalyzed three-component Hantzsch reaction of 2-chloroquinoline-3-carbaldehydes, ammonium acetate, and alkyl acetoacetate in good to high yields. Important advantages of this method are easy access to a library of novel quinoline and quinolone derivatives, green reaction conditions with water as solvent, and ease of purification.

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## INTRODUCTION

Remarkable pharmacological properties have been associated with quinoline derivatives. As a consequence, research on diverse aspects of quinolines has attracted much attention [1–7]. These compounds have displayed many applications in medicinal chemistry such as antimicrobial, antiviral, anti-inflammatory, antimalarial, antitumor, and antiparasitic activities [1–7]. On the other hand, 2-chloroquinoline-3-carbaldehydes have been used as highly diverse starting materials in the synthesis of a wide variety of quinoline derivatives [8,9].

Dihydropyridines (DHPs) are also a significant class of six-membered nitrogen-containing heterocycles [10,11]. Their molecular skeletons are plentiful in natural products [12]. DHPs are a common feature of various bioactive compounds such as antitumor, anti-inflammatory, vasodilator, bronchodilator, hepatoprotective, geroprotective, antiatherosclerotic, analgesic and antidiabetic agents [13–20]. These heterocycles can act as analogs of NADH coenzymes to mimic them [21]. Some clinically significant drugs such as nifedipine, nicardipine, amlodipine, diludine, felodipine, nimodipine, isradipine, lacidipine, and nitrendipine have been commercialized so far. It shows their therapeutic accomplishment, which is connected to their structural efficacy. Aromatization of 1,4-DHP has also attracted great attention recently for their interesting biological activities [22,23]. Also, they are used as hydride sources in a varied diversity of organocatalytic asymmetric

reductions [24]. These examples noticeably demonstrate the outstanding potential of novel DHP derivatives as a source of valued drug candidates.

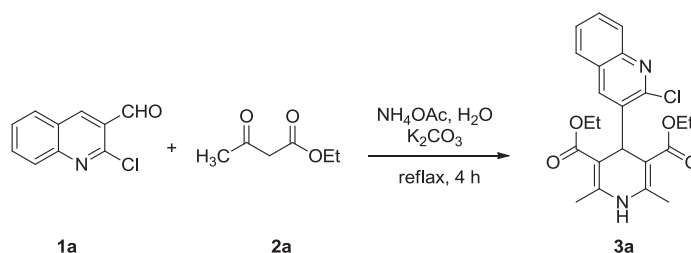
Among a number of methods established so far, the simplest synthetic route to symmetrical 1,4-DHPs is the classical Hantzsch reaction developed in 1882 [25]. Various methods based on microwave irradiation, solar thermal energy, and solid support and other green aspects have been examined [26–45]. Applying aqueous media and green catalyst without using hazardous reagents or solvents is of special importance.

Considering the significance of 1,4-DHPs and applying the green conditions, the diverse applications of 2-chloroquinoline-3-carbaldehydes and the limitation of the earlier synthetic methods, we herein wish to report a convenient approach for Hantzsch 1,4-DHPs reaction.

## RESULTS AND DISCUSSION

In the initial model experiment, 2-chloroquinoline-3-carbaldehydes **1a** [46], ethyl acetoacetate **2a**, and ammonium acetate in molar ratio of 1:2:1.2 were mixed in water and 1 equivalent of  $K_2CO_3$  (Scheme 1). The reaction was completed after 4 h to generate **3a** in 78% yield. The reaction in ethanol showed less efficiency compared with water. In the case of ethanol as solvent, more side products were observed and the reaction took longer. An improved yield in aqueous medium can be rationalized because of

Scheme 1



solubility and better catalytic activity of  $\text{K}_2\text{CO}_3$  in water. In addition to that, the products are much less soluble in water (than in ethanol), which serves as a driving force through the principle of Le Chatelier. These factors seem to contribute to an efficient aqueous method in terms of the yield and reaction time.

The efficacy of potassium carbonate compared with other basic catalysts was examined under the same reaction conditions as shown in Table 1. The results verified the superiority of  $\text{K}_2\text{CO}_3$  with respect to the rest in view of the reaction yields. Efficiency of ammonium source was checked so it was found that the yield of **3a** by using ammonium acetate is better than ammonium sulfate, ammonium chloride, and ammonium carbonate. Although catalyst-free and water-mediated Hantzsch reaction [31] has been reported, we found without base that the rate of this reaction is slow and even after 24 h could not be completed.

In order to study the scope and generality of the reaction in water, a series of DHPs were synthesized using 2-chloroquinoline-3-carbaldehyde and its derivatives including 6-methyl, 8-methyl, 6-methoxy, and 8-methoxy, and also methyl acetoacetate and ethylacetoacetate (Table 2, entries 2–8). In all cases as depicted in Table 2, the desired products were isolated in good yields, except for electron withdrawing substitutes such as 6-bromo-2-chloroquinoline-3-carbaldehyde and 2,6-dichloroquinoline-3-carbaldehyde, which afforded none of the products.

Table 1

Evaluation of different basic catalysts<sup>a</sup>.

Entry	Catalyst	Isolated yield (%)
1	$\text{K}_2\text{CO}_3$	78
2	$\text{Et}_3\text{N}$	40
3	KOH	A mixture of unidentified products
4	NaOH	
5	$\text{KHCO}_3$	
6	$\text{Na}_2\text{CO}_3$	
7	Pyridine	
8	DABCO	35

<sup>a</sup>2-Chloroquinoline-3-carbaldehyde (1 mmol), ethyl acetoacetate (2 mmol), ammonium acetate (1.2 mmol), base (1 mmol), and water (5 mL) reflux for 4 h.

To our surprise, when using 2-iodoquinoline-3-carbaldehyde as an aldehyde source, a different product was observed (Table 2, entries 9 and 10). Spectral data showed that under aqueous conditions, the iodide group on quinoline was replaced by hydroxyl group before formation of the corresponding DHP (Scheme 2). To verify this, 1,2-dihydro-2-oxoquinoline-3-carbaldehyde [47] was prepared and subjected to the same reaction for comparison. The latter in reaction with methyl acetoacetate and ammonium acetate generated DHP **3j** in 87% yield (Table 2, entry 11).

## CONCLUSION

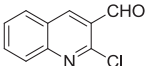
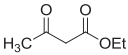
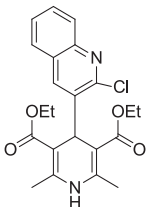
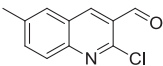
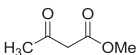
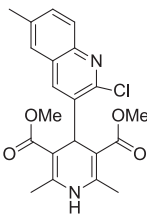
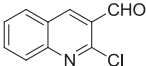
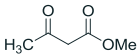
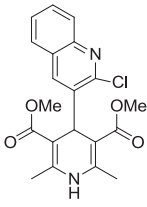
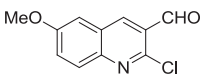
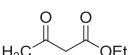
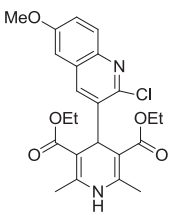
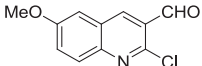
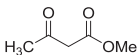
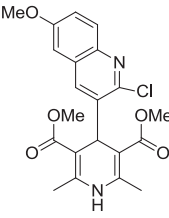
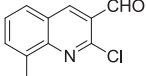
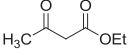
In conclusion, a library of new 1,4-DHPs containing 2-chloroquinoline-3-carbaldehyde derivatives was prepared via Hantzsch reactions applying both green solvent and catalyst. The products were obtained in good to high yields. The products were purified simply without the need for column chromatography. These 1,4-DHPs comprising quinolone carbaldehyde, which have both shown biological properties, may be of more pharmacological interest to be studied in the near future.

## EXPERIMENTAL

**General.** Chemicals were purchased from Fluka, Merck, and Aldrich chemical companies. Melting points are uncorrected. IR spectra were recorded on a Shimadzu Infra Red Spectroscopy IR-435 (Shimadzu, Japan). Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 400 MHz Spectrometer (Billerica, MA) in  $\text{CDCl}_3$  as solvent. A Leco CHNS, model 932, was used for elemental analysis. 2-Chloroquinoline-3-carbaldehydes [46], 2-iodoquinoline-3-carbaldehyde [47], and 1,2-dihydro-2-oxoquinoline-3-carbaldehyde [48] have been prepared as per previous reports.

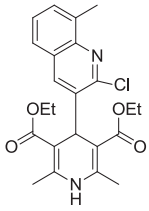
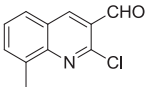
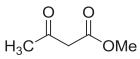
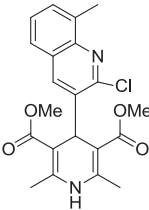
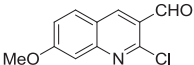
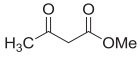
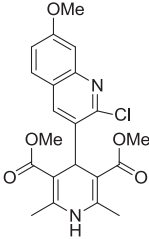
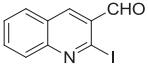
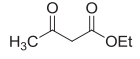
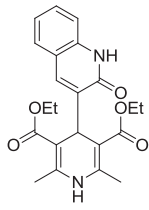
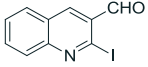
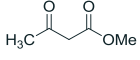
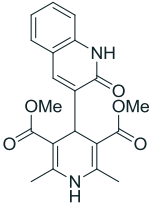
**Synthesis of 1,4-dihydropyridines.** A mixture of aldehyde (1 mmol),  $\beta$ -ketoester (2 mmol), and  $\text{NH}_4\text{OAc}$  (1.2 mmol) was taken;  $\text{K}_2\text{CO}_3$  (1 mmol) in 5 mL water was added to the mixture and stirred at reflux for 4 h. The reaction was monitored by TLC. The crude solid thus

**Table 2**  
Synthesis of quinolinyl-1,4-DHPs via Hantzsch reaction<sup>a</sup>.

Entry	Aldehyde	Ketoester	DHPs	Yield (%)
1			 <b>3a</b>	78
2			 <b>3b</b>	79
3			 <b>3c</b>	82
4			 <b>3d</b>	85
5			 <b>3e</b>	88
6				75

(Continued)

**Table 2**  
(Continued)

Entry	Aldehyde	Ketoester	DHPs	Yield (%)
			 <p><b>3f</b></p>	
7			 <p><b>3g</b></p>	78
8			 <p><b>3h</b></p>	84
9			 <p><b>3i</b></p>	85
10			 <p><b>3j</b></p>	83

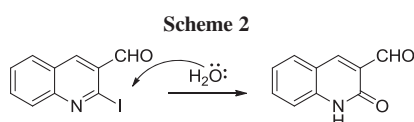
(Continued)

**Table 2**  
(Continued)

Entry	Aldehyde	Ketoester	DHPs	Yield (%)
11				87

DHP, dihydropyridine.

<sup>a</sup>2-Chloroquinoline-3-carbaldehyde (1 mmol), ethyl acetoacetate (2 mmol), ammonium acetate (1.2 mmol), K<sub>2</sub>CO<sub>3</sub> (1 mmol), and water (5 mL) reflux for 4 h.



separated was filtered, washed with excess water and Et<sub>2</sub>O, and dried to obtain pure product.

Copies of <sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectra are provided in the Supporting Information.

Spectral and physical data for compounds are as follows.

**(3a).** White powder, mp >300°C. FT-IR (KBr):  $\nu_{\max}$  = 3376, 3246, 2924, 1638, 1155, 628 cm<sup>-1</sup>. H-NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 1.2 (t, *J* = 7.2, 6H), 2.4 (s, 6H), 4.1 (m, 4H), 5.5 (s, 1H), 5.9 (s, 1H), 7.5 (t, *J* = 7.4, 1H), 7.7 (t, *J* = 7.6, 1H), 7.8 (d, *J* = 8, 1H), 8 (d, *J* = 8.4, 1H), 8.2 (s, 1H) ppm. <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 14.3, 19.7, 38.2, 59.9, 103.5, 126.6, 127.2, 127.7, 128, 129.9, 140.1, 140.3, 144.4, 146.2, 150.3, 167 ppm. Elem. Anal. for C<sub>22</sub>H<sub>23</sub>ClN<sub>2</sub>O<sub>4</sub>: (Calc) C, 63.69; H, 5.59; N, 6.75. Found: C, 63.22; H, 5.17; N, 6.44.

**(3b).** White powder, mp 224–226°C. FT-IR (KBr):  $\nu_{\max}$  = 3301, 3087, 2949, 1654, 1215, 650 cm<sup>-1</sup>. H-NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 2.3 (s, 6H), 2.5 (s, 3H), 3.6 (s, 6H), 5.4 (s, 1H), 5.8 (s, 1H), 7.49 (d, *J* = 1.6, 1H), 7.5 (d, *J* = 1.2, 1H), 7.87 (d, *J* = 8.4, 1H), 8 (s, 1H) ppm. <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 19.5, 21.5, 37.6, 50.9, 103.9, 126, 127.7, 128, 132.1, 136.5, 138.9, 141.3, 144.4, 144.8, 149.4, 167.6 ppm. Elem. Anal. for C<sub>21</sub>H<sub>21</sub>ClN<sub>2</sub>O<sub>4</sub>: (Calc) C, 62.92; H, 5.28; N, 6.99. Found: C, 62.73; H, 5.42; N, 6.65.

**(3c).** White powder, mp 237–239°C. FT-IR (KBr):  $\nu_{\max}$  = 3195, 3087, 2945, 1702, 1211, 753 cm<sup>-1</sup>. H-NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 2.4 (s, 6H), 3.6 (s, 6H), 5.5 (s, 1H), 5.9 (s, 1H), 7.5 (t, *J* = 7.4, 1H), 7.67 (m, 1H), 7.76 (d, *J* = 8, 1H), 8 (d, *J* = 8.4, 1H), 8.1 (s, 1H) ppm. <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 19.5, 37.6, 50.9, 52.5, 103.8, 126, 126.6, 127.2, 127.7, 127.7, 127.8, 128, 128.4, 129.9, 131.2, 137.7, 139.6, 141.5, 144.5, 146.2, 147.2, 150.3, 167.6 ppm. Elem. Anal. for C<sub>20</sub>H<sub>19</sub>ClN<sub>2</sub>O<sub>4</sub>: (Calc) C, 62.10; H, 4.95; N, 7.24. Found: C, 62.19; H, 5.12; N, 7.43.

**(3d).** White powder, mp 226–228°C. FT-IR (KBr):  $\nu_{\max}$  = 3200, 3086, 2982, 1678, 1212, 766 cm<sup>-1</sup>. H-NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 1.2 (t, *J* = 7.2, 6H), 2.3 (s, 6H), 3.9 (s, 3H), 4.1 (m, 4H), 5.5 (s, 1H), 5.9 (d, *J* = 9.6, 1H), 7 (d, *J* = 2.8, 1H), 7.3 (m, 1H), 7.85 (d, *J* = 9.2, 1H), 8 (s, 1H) ppm. <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 14.38, 19.7, 38.1, 55.5, 59.9, 103.6, 104.7, 122.5, 128.7, 129.4, 138.8, 140.5, 142.4, 144.2, 147.7, 157.7, 167.3 ppm. Elem. Anal. for C<sub>23</sub>H<sub>25</sub>ClN<sub>2</sub>O<sub>5</sub>: (Calc) C, 62.09; H, 5.66; N, 6.30. Found: C, 62.16; H, 5.54; N, 6.46.

**(3e).** White powder, mp 235–237°C. FT-IR (KBr):  $\nu_{\max}$  = 3345, 3087, 2945, 1704, 1210, 744 cm<sup>-1</sup>. H-NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 2.4 (s, 6H), 3.6 (s, 6H), 3.9 (s, 3H), 5.45 (s, 1H), 5.7 (s, 1H), 7 (d, *J* = 2.4, 1H), 7.3 (q, 1H), 7.9 (d, *J* = 9.2, 1H), 8 (s, 1H) ppm. <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 19.5, 37.6, 50.9, 55.5, 103.9, 104.7, 122.6, 129, 129.4, 138.4, 141.4, 142.3, 144.3, 147.8, 157.8, 167.6 ppm. Elem. Anal. for C<sub>21</sub>H<sub>21</sub>ClN<sub>2</sub>O<sub>5</sub>: (Calc) C, 60.51; H, 5.08; N, 6.72. Found: C, 60.74; H, 5.17; N, 6.46.

**(5f).** White powder, mp 232–234°C. FT-IR (KBr):  $\nu_{\max}$  = 3290, 3094, 2979, 1696, 1136, 707 cm<sup>-1</sup>. H-NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 1.2 (t, *J* = 7, 6H), 2.4 (s, 6H), 2.7 (t, *J* = 6.4, 3H), 4 (m, 4H), 5.5 (s, 1H), 5.7 (s, 1H), 7.3 (s, 1H), 7.4 (d, 1H), 7.5 (m, 1H), 8.1 (s, 1H) ppm. <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 14.3, 17.9, 19.6, 19.7, 38.3, 59.9, 103.4, 125.1, 126.3, 127.7, 129.8, 136.2, 139.5, 140.2, 144.2, 145.6, 149.2, 167.3 ppm.

**(5g).** White powder, mp 254–256°C. FT-IR (KBr):  $\nu_{\max}$  = 3325, 3098, 2940, 1704, 1210, 649 cm<sup>-1</sup>. H-NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 2.4 (s, 6H), 2.7 (s, 3H), 3.6 (s, 6H), 5.5 (s, 1H), 5.7 (s, 1H), 7.4 (t, *J* = 7.6, 1H), 7.5 (d, *J* = 6.8, 1H), 7.6 (d, *J* = 8, 1H), 8.0 (s, 1H) ppm. <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 17.8, 19.6, 37.6, 50.9, 104.0, 125.0, 126.3, 128.0, 129.8, 136, 139.7, 140.7, 144.2, 145.6, 149.2, 167.6 ppm. Elem. Anal. for C<sub>23</sub>H<sub>25</sub>ClN<sub>2</sub>O<sub>4</sub>: (Calc) C, 65.21; H, 5.47; N, 7.60. Found: C, 65.04; H, 5.29; N, 7.74.

**(5h).** White powder, mp 259–261°C. FT-IR (KBr):  $\nu_{\max}$  = 3272, 3080, 2948, 1698, 1276, 760 cm<sup>-1</sup>. H-NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 2.4 (s, 6H), 3.6 (s, 6H), 3.9 (s, 1H), 5.4 (s, 1H), 5.8 (s, 1H), 7.1 (m, 1H), 7.3 (t, *J* = 4.2,

1H), 7.4 (m, 1H), 7.6 (d,  $J=9.2$ , 1H), 8.0 (s, 1H) ppm.  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta=19.4$ , 19.5, 37.4, 50.9, 55.5, 103.9, 106.2, 119.8, 123.2, 128.1, 138.7, 139.2, 144.2, 148.0, 150.4, 161.1, 167.7 ppm. Elem. Anal. for  $\text{C}_{23}\text{H}_{25}\text{ClIN}_2\text{O}_4$ : (Calc) C, 65.21; H, 5.47; N, 7.60. Found: C, 65.42; H, 5.64; N, 7.45.

(3i): yellow powder, mp 176–178°C. FT-IR (KBr):  $\nu_{\text{max}}=3345$ , 3087, 2945, 1704, 1210, 744  $\text{cm}^{-1}$ . H-NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta=1.04$  (t,  $J=7$ , 6H), 2.2 (s, 6H), 4 (m, 4H), 5.1 (s, 1H), 7.57 (m, 1H), 7.7 (m, 1H), 7.8 (d,  $J=8.4$ , 1H), 7.9 (d,  $J=7.6$ , 1H), 8 (s, 1H), 9.1 (s, 1H) ppm.  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta=14.9$ , 18.7, 18.8, 39.3, 39.5, 39.7, 39.9, 40.1, 40.4, 40.6, 42.7, 59.3, 102.8, 126.4, 127.4, 127.9, 128.1, 128.2, 130.4, 136.9, 145.7, 145.8, 146.9, 147.5, 167.2, 168.2 ppm. Elem. Anal. for  $\text{C}_{22}\text{H}_{23}\text{IN}_2\text{O}_4$ : (Calc) C, 52.19; H, 4.58; N, 5.53. Found: C, 52.37; H, 4.64; N, 5.25.

(3j): yellow powder, mp 159–161°C. FT-IR (KBr):  $\nu_{\text{max}}=3345$ , 3087, 2945, 1704, 1210, 744  $\text{cm}^{-1}$ . H-NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta=2.2$  (s, 6H), 3.6 (s, 6H), 5.1 (s, 1H), 7.1 (t,  $J=7.2$ , 1H), 7.2 (d,  $J=9.6$ , 1H), 7.3 (s, 1H), 7.4 (m, 1H), 7.6 (d,  $J=7.6$ , 1H), 8.9 (s, 1H), 11.6 (s, 1H) ppm.  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta=18.2$ , 35.4, 39.3, 39.5, 39.7, 39.9, 40.1, 40.3, 40.6, 50.1, 99.7, 114.8, 119.7, 121.9, 128.1, 129.8, 135.0, 136.8, 138.2, 145.8, 161.5, 168.2 ppm. Elem. Anal. for  $\text{C}_{20}\text{H}_{19}\text{IN}_2\text{O}_4$ : (Calc) C, 50.22; H, 4.00; N, 5.86. Found: C, 50.41; H, 4.12; N, 5.71.

(Entry 11) (3j). Yellow powder, mp 159–161°C. FT-IR (KBr):  $\nu_{\text{max}}=3345$ , 3087, 2945, 1704, 1210, 744  $\text{cm}^{-1}$ . H-NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta=2.2$  (s, 6H), 3.6 (s, 6H), 5.1 (s, 1H), 7.1 (t,  $J=7.2$ , 1H), 7.2 (d,  $J=8$ , 1H), 7.3 (s, 1H), 7.4 (m, 1H), 7.6 (d,  $J=8$ , 1H), 8.9 (s, 1H), 11.5 (s, 1H) ppm.

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