

Synthesis of Ferrocenyl Oxindole Compounds with Potential Anticancer Activity

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Compostos oxindol-ferrocenos com potencial atividade anticâncer foram preparados a partir de reações de oxindóis substituídos e carboxaldeído-ferroceno na presença de KOH como catalisador. Os produtos foram caracterizados por dados espectroscópicos incluindo RMN de ¹H e ¹³C, infravermelho e espectrometria de massas. As configurações *E* e *Z* foram estabelecidas por experimentos de nOe ou NOESY.

A series of ferrocenyl oxindoles with potential anticancer activity were prepared from the reactions of substituted oxindoles and ferrocenylcarboxyaldehyde in the presence of KOH as catalyst. The products were characterized by spectral data including ¹H and ¹³C NMR, IR and mass spectrometry. The *E* and *Z* configurations were established by nOe or NOESY experiments.

Keywords: ferrocenyl oxindoles, oxindoles, ferrocenecarboxyaldehyde

Introduction

The ferrocenyl (Fc) group has been incorporated to the structure of a number of biologically active molecules resulting in increased anticancer^{1,2} and antimalarial³⁻⁵ activity, amongst others. Addition, alkylation, acylation, condensation-dehydration, coupling and nucleophilic substitution reactions have been employed to link this group to a variety of compounds.^{2-4,6,7} The mechanisms of the cytotoxicity of ferrocene derivatives have been investigated.⁸ Osella *et al.*⁹ proposed that the cytotoxic activity of ferrocenium salts is due to their ability to generate oxygen active species that induce oxidative DNA damage. Kondapi *et al.*^{10,11} have shown that ferrocene derivatives inhibit topoisomerase II, a major molecular target for a number of DNA-binding anticancer drugs.

Indolin-2-ones have been shown to exhibit antitumor activity by inhibiting receptor tyrosine kinases VEGF-R, PDGF-R δ or CDK.¹² The indolin-2-one **1** (*sunitinib*) has been approved by the U.S. Food and Drug Administration for the treatment of metastatic renal cell cancer

and gastrointestinal stromal tumors^{13,14} (Figure 1). Raghunathan *et al.*¹⁵ reported recently the synthesis of the ferrocenyl oxindole **2a** with (*E*)-configuration from the reaction of oxindole and ferrocenecarboxyaldehyde (FcC(O)H) in ethanol, in the presence of catalytic amounts of piperidine.

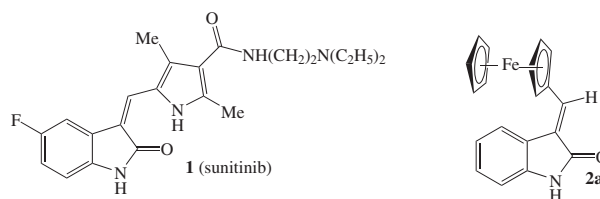
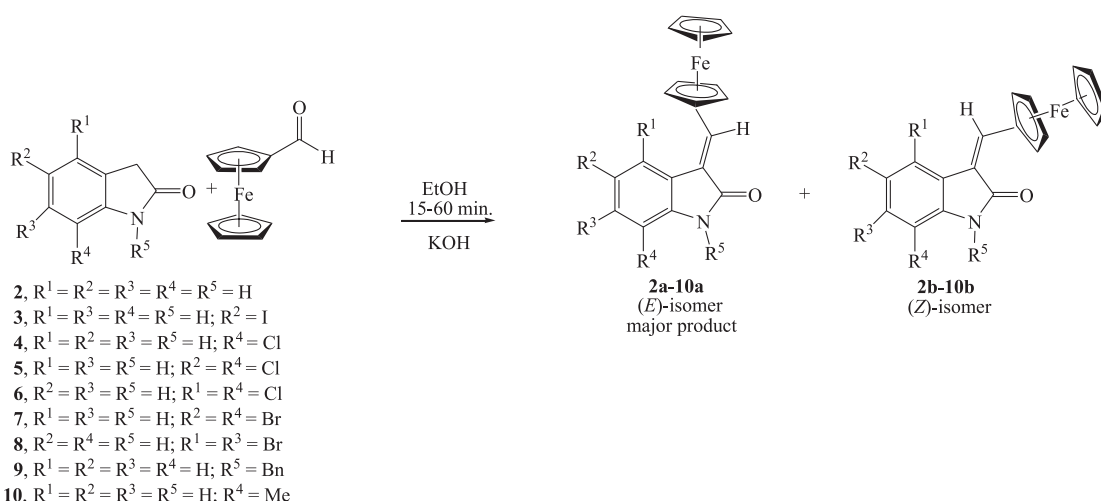


Figure 1. Structure of sunitinib (**1**) and ferrocenyl oxindole (**2a**) with (*E*)-configuration.

We describe herein the condensation reactions of several oxindole derivatives with FcC(O)H in the presence of KOH in EtOH from which good to excellent yields of the products with *E* and *Z* configurations were obtained (Scheme 1).¹⁶ The products were characterized by mass spectrometry and infrared, ¹H and ¹³C NMR spectroscopies, including nOe and NOESY experiments for the determination of the double-bond geometry.

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Scheme 1. Synthesis of ferrocenyl oxindoles.

Preliminary studies of the reaction of oxindole with FcC(O)H (Table 1) were carried out to assess the catalytic potential of various bases.

Table 1. Condensation of oxindole and FcC(O)H in ethanol, at room temperature, in the presence of various bases

Entry	Base	time	Yield (%)	
			2a (<i>E</i>)	2b (<i>Z</i>)
1	KOH (100 mg)	15 min	95	5
2	K ₂ CO ₃ (100 mg)	15 min	80	18
3	Piperidine (0.025 mL)	15 min	67	30
4	Morpholine (0.025 mL)	15 min	75	20
5	Et ₃ N (0.025 mL)	96 h	33	13

Except for Et₃N, all the bases employed led to good conversions. However, formation of products with both *E* and *Z* configurations depend on the base employed. The use of KOH in EtOH gave the best yield and selectivity for the *E*-isomer **2a** (entry 1). In the presence of piperidine (entry 3) we were able to isolate the *E*-isomer **2a** in 67% yield together with a 30% isolated yield for the corresponding *Z*-isomer **2b**. The geometries of isomers **2a** and **2b** were determined by nOe experiments and NOESY interactions. The NOESY experiment for **2a** shows a correlation between H4 and H2' of the cyclopentadienyl ring, thus revealing an (*E*)-configuration for this isomer. In the case of **2b**, we have observed a 2.15% intensity enhancement of the peak corresponding to H4 upon irradiation of H8, which confirms the (*Z*)-configuration (Figure 2).

The condensation reactions of a series of substituted oxindoles with FcC(O)H were then investigated in the

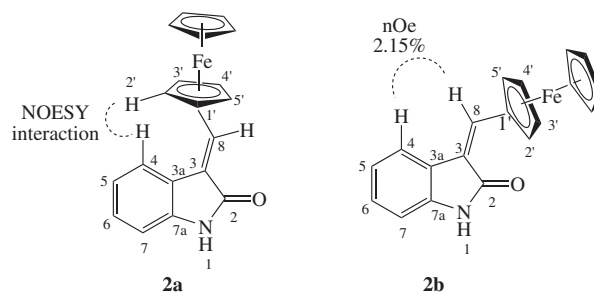


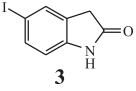
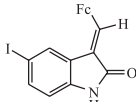
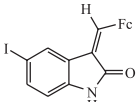
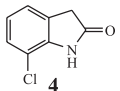
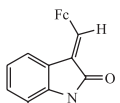
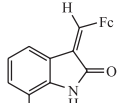
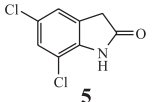
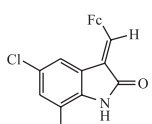
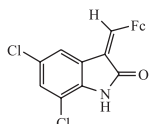
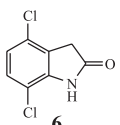
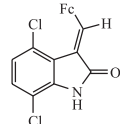
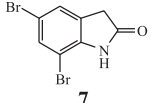
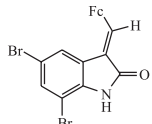
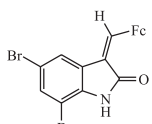
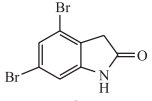
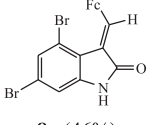
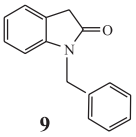
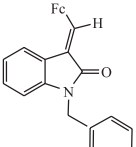
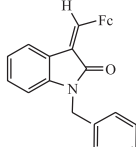
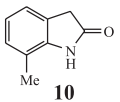
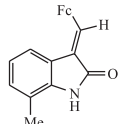
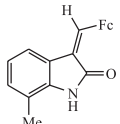
Figure 2. Hydrogen correlations that confirm the structures of compounds **2a** and **2b**.

presence of KOH in EtOH. Products and yields are summarized in Table 2.

The reactions of monosubstituted oxindoles **3**, **4** and **10** (entries 1, 2 and 8, respectively) gave good conversions and the same product distribution as that of oxindole, with *E*-products being formed as the major isomers in yields above 90%. Product yields decreased with further ring substitution, and were also sensitive to the relative position of the substituents: whereas the reactions of 5,7-dichloro and 5,7-dibromo oxindoles (**5** and **7**, entries 3 and 5, respectively) gave both isomers albeit in lower yields than oxindole, those of the 4,7-dichloro and 4,6-dibromo oxindoles (**6** and **8**, entries 4 and 6, respectively) resulted only in the formation of the *E*-isomer in around 45% yields.

As shown in Table 3, in all cases, the olefinic hydrogen H8 of *E*-isomer (**2a-10a**) appear at higher frequency than for the *Z*-isomer (**2b-10b**), due to the diamagnetic anisotropy effect of the carbonyl oxygen (C2) on H8 of *E*-isomers **2a-10a**. The same effect was observed for H3' and H5' of the *Z*-isomers **2b-10b**. H8 chemical shifts for compounds **6a** and **8a** at ζ 8.40 and 8.34 ppm, respectively, confirm the (*E*)-configuration.

Table 2. Condensation reactions of oxindole derivatives with FeC(O)H in the presence of KOH as catalyst

Entry	Substrate	Product yields (%) ^{a,b}	
1		 3a (93%)	 3b (6%)
2		 4a (93%)	 4b (6%)
3		 5a (60%)	 5b (3%)
4		 6a (44%)	
5		 7a (70%)	 7b (2%)
6		 8a (46%)	
7		 9a (60%)	 9b (2.5%)
8		 10a (90%)	 10b (8%)

^a yields are for isolated products after flash column chromatography on silica-gel; ^b Fc = ferrocenyl.

Table 3. Chemical shifts of H8, and H2' and H5' for compounds **2a,b** to **10a,b**

Compound	H8		H2' and H5'	
	a	b	a	b
2	7.54 (s)	7.41 (s)	4.68 (t, <i>J</i> 1.7Hz)	5.34 (t, <i>J</i> 1.9Hz)
3	7.71 (s)	7.39 (s)	4.75 (br, s)	5.33 (t, <i>J</i> 1.9Hz)
4	7.71 (s)	7.43 (s)	4.74 (br, s)	5.34 (t, <i>J</i> 1.9Hz)
5	7.79 (s)	7.44 (s)	4.75 (t, <i>J</i> 1.7Hz)	4.81 (t, <i>J</i> 1.6Hz)
6	8.40 (s)	-	5.39 (m)	-
7	7.76 (s)	7.43 (s)	4.66 (m)	5.34 (t, <i>J</i> 1.6Hz)
8	8.34 (s)	-	5.11 (t, <i>J</i> 1.9Hz)	-
9	7.76 (s)	7.30 (s)	4.77 (t, <i>J</i> 1.7Hz)	5.36 (t, <i>J</i> 1.9Hz)
10	7.67 (br, s)	7.39 (s)	4.80 (br, s)	5.34 (t, <i>J</i> 1.8Hz)

Conclusion

In conclusion we have described a simple, fast and efficient synthetic route to ferrocenyl oxindoles, potential model compounds for chemical and pharmacological studies.

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16. *General experimental procedure*: A mixture of oxindole (0.2 mmol), ferrocenecarboxyaldehyde (0.22 mmol), ethanol (5 mL) and 100 mg of KOH was allowed to stir at rt for 15 min (**2**) or under reflux for 1 h (**3-10**). The progress of the reactions was monitored by TLC. After total consumption of the substrate, the crude reaction mixture was extracted with ethyl acetate and washed with water. The organic layer was separated, dried (Na₂SO₄) and concentrated *in vacuo*. The *E* and *Z* products were separated by silica gel column chromatography (using hexane/ethyl acetate as eluent).

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Table S1. ¹H NMR data for compounds **2a-2b** to **10a-10b**

Carbon	¹ H chemical shifts (δ/ppm, 250 MHz, CDCl ₃)							
	2a	2b	3a*	3b*	4a*	4b*	5a	5b
1	9.28 (s)	7.97 (s)	8.32 (s)	7.89 (s)	8.54 (s)	7.84 (s)	8.21 (s)	8.41 (s)
2	-	-	-	-	-	-	-	-
3	-	-	-	-	-	-	-	-
4	7.54 (d, <i>J</i> 7.5Hz)	7.49 (d, <i>J</i> 7.5Hz)	8.31 (br, s)	7.77 (d, <i>J</i> 1.6Hz)	7.17 (d, <i>J</i> 8.0Hz)	7.19 (d, <i>J</i> 8.0Hz)	7.21 (d, <i>J</i> 1.6Hz)	7.52 (d, <i>J</i> 1.4Hz)
5	7.10 (td, <i>J</i> 7.5, 1.0Hz)	7.21 (td, <i>J</i> 7.5, 1.1Hz)	-	-	6.89 (t, <i>J</i> 8.0Hz)	6.96 (t, <i>J</i> 8.0Hz)	-	-
6	6.86 (dd, <i>J</i> 7.5, 1.0Hz)	7.02 (td, <i>J</i> 7.5, 1.1Hz)	6.69 (d, <i>J</i> 8.2Hz)	7.50 (dd, <i>J</i> 8.0, 1.6Hz)	7.83 (d, <i>J</i> 8.0Hz)	7.37 (d, <i>J</i> 8.0Hz)	7.88 (d, <i>J</i> 1.6 Hz)	7.48 (d, <i>J</i> 1.4Hz)
7	6.81 (d, <i>J</i> 7.5Hz)	6.84 (d, <i>J</i> 7.5Hz)	7.53 (d, <i>J</i> 8.2Hz)	6.63 (d, <i>J</i> 8.0Hz)	-	-	-	-
8	7.54 (s)	7.41 (s)	7.71 (s)	7.39 (s)	7.71 (s)	7.43 (s)	7.79 (s)	7.44 (s)
9	-	-	-	-	-	-	-	-
10	-	-	-	-	-	-	-	-
1'	-	-	-	-	-	-	-	-
2'-5'	4.68 (t, <i>J</i> 1.7Hz)	5.34 (t, <i>J</i> 1.9Hz)	4.75 (br, s)	5.33 (t, <i>J</i> 1.9Hz)	4.74 (br, s)	5.34 (t, <i>J</i> 1.9Hz)	4.75 (t, <i>J</i> 1.7Hz)	4.81 (t, <i>J</i> 1.6Hz)
3'-4'	4.49 (t, <i>J</i> 1.7Hz)	4.60 (t, <i>J</i> 1.9Hz)	4.66 (br, s)	4.64 (t, <i>J</i> 1.9Hz)	4.60 (br, s)	4.64 (t, <i>J</i> 1.9Hz)	4.69 (t, <i>J</i> 1.7Hz)	4.62 (t, <i>J</i> 1.6Hz)
Cp	4.14 (s)	4.20 (s)	4.26 (s)	4.21 (s)	4.21 (s)	4.20 (s)	4.26 (s)	4.28 (s)
	6a	7a*	7b*	8a*	9a	9b	10a	10b
1	8.44 (s)	8.06 (br, s)	7.71 (s)	9.91 (s)	-	-	8.87 (s)	8.21 (s)
2	-	-	-	-	-	-	-	-
3	-	-	-	-	-	-	-	-
4	-	8.06 (br, s)	7.20 (d, <i>J</i> 1.4Hz)	-	7.99 (d, <i>J</i> 7.6Hz)	7.50 (d, <i>J</i> 7.0Hz)	7.82 (d, <i>J</i> 2.0Hz)	7.34 (d, <i>J</i> 7.4Hz)
5	7.08 (d, <i>J</i> 7.9Hz)	-	-	7.15 (d, <i>J</i> 1.4Hz)	7.15 (t, <i>J</i> 7.6Hz)	7.15 (td, <i>J</i> 7.0, 1.0Hz)	6.91-7.06 (br, m)	6.95 (t, <i>J</i> 7.4Hz)
6	6.95 (d, <i>J</i> 7.9Hz)	7.49 (s)	7.36 (d, <i>J</i> 1.4Hz)	-	6.95 (t, <i>J</i> 7.6Hz)	7.00 (td, <i>J</i> 7.0, 1.0Hz)	6.91-7.06 (br, m)	7.04 (d, <i>J</i> 7.4Hz)
7	-	-	-	6.85 (d, <i>J</i> 1.4Hz)	6.72 (d, <i>J</i> 7.6Hz)	6.72 (d, <i>J</i> 7.0Hz)	-	-
8	8.40 (s)	7.76 (s)	7.43 (s)	8.34 (s)	7.76 (s)	7.30 (s)	7.67 (br, s)	7.39 (s)
9	-	-	-	-	5.00 (s)	5.00	2.35 (s)	2.30 (s)
10	-	-	-	-	7.32 (m)	7.32 (m)	-	-
1'	-	-	-	-	-	-	-	-
2'-3'	5.39 (m)	4.66 (m)	5.34 (t, <i>J</i> 1.6Hz)	5.11 (t, <i>J</i> 1.9Hz)	4.77 (t, <i>J</i> 1.7Hz)	5.36 (t, <i>J</i> 1.9Hz)	4.80 (br, s)	5.34 (t, <i>J</i> 1.8Hz)
4'-5'	4.69 (m)	4.66 (m)	4.68 (t, <i>J</i> 1.6Hz)	4.49 (t, <i>J</i> 1.9Hz)	4.58 (t, <i>J</i> 1.7Hz)	4.58 (t, <i>J</i> 1.9Hz)	4.59 (br, s)	4.49 (t, <i>J</i> 1.8Hz)
Cp	4.22 (s)	4.25 (s)	4.21 (s)	4.07 (s)	4.25 (s)	4.21 (s)	4.24 (s)	4.19 (s)

* CDCl₃ + DMSO.

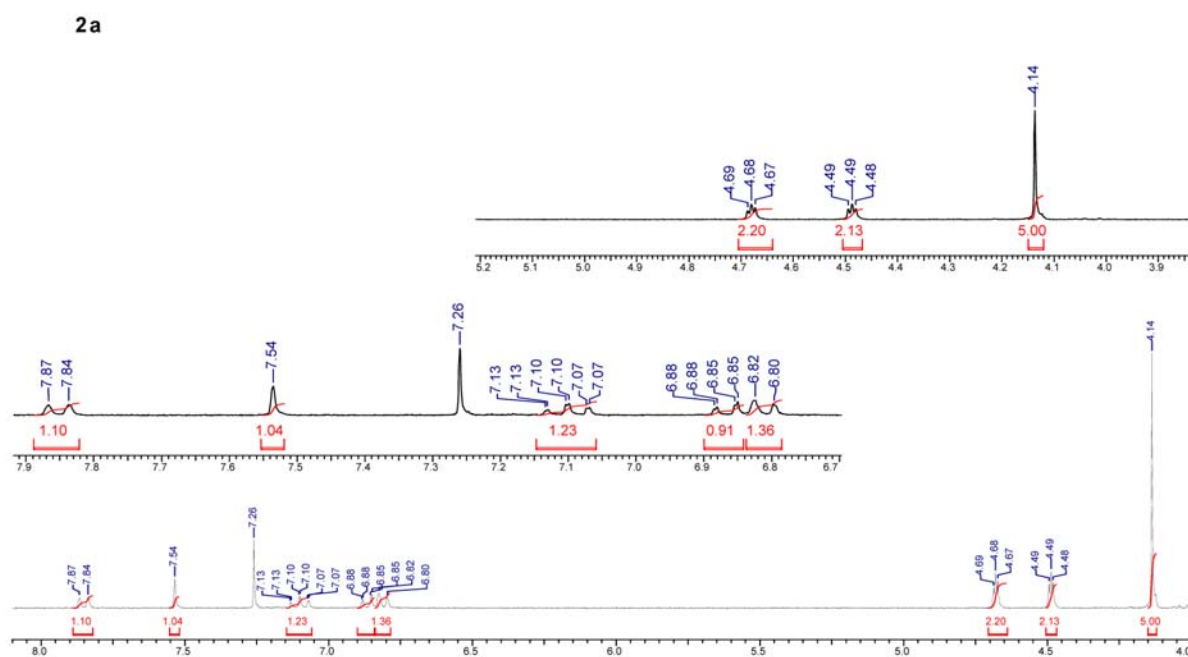
*e-mail: barbara.iq@gmail.com

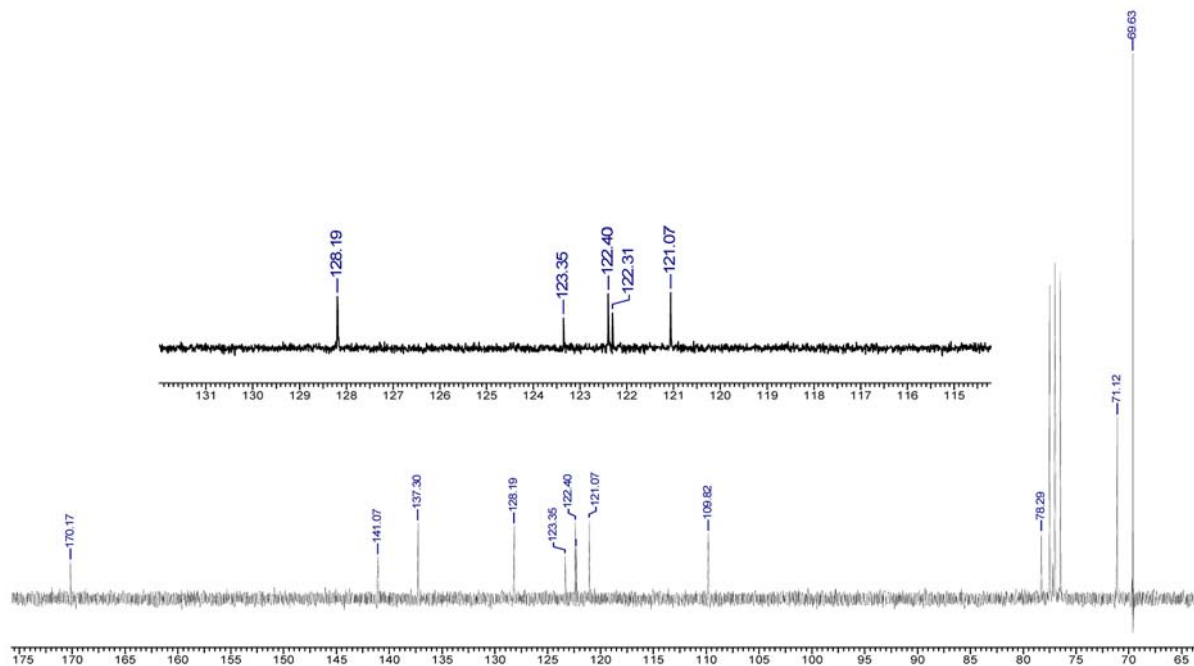
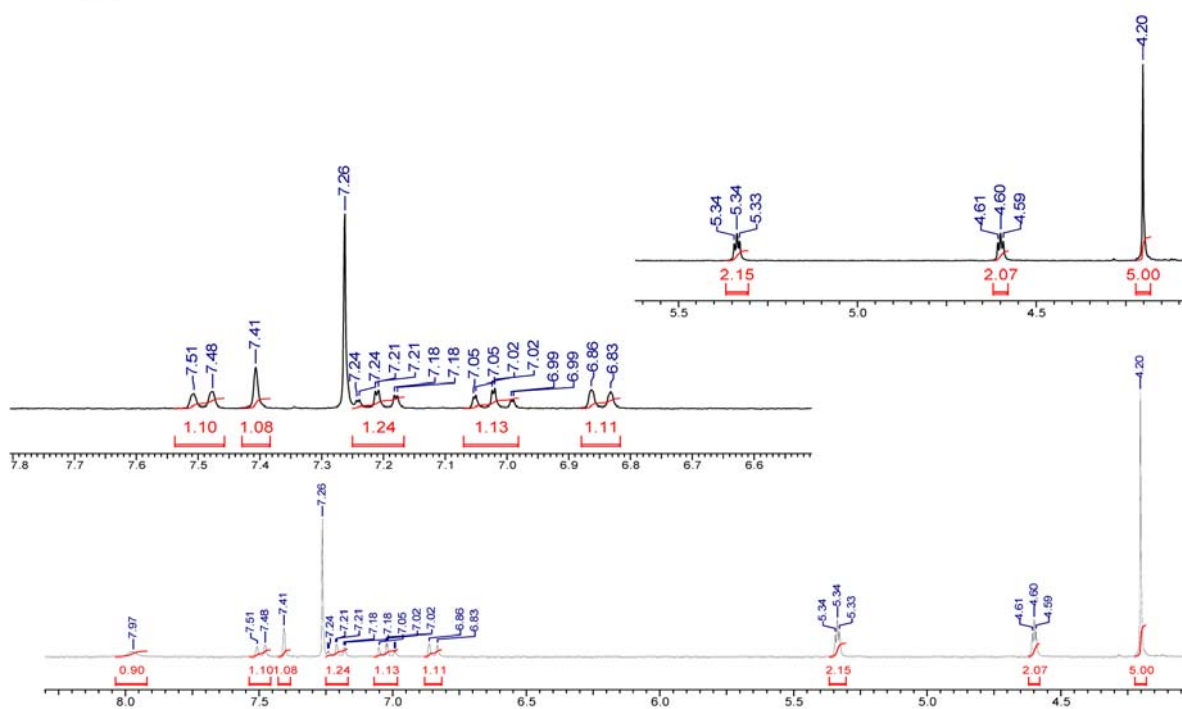
Table S2. ^{13}C NMR data for compounds **2a-2b** to **10a-10b**

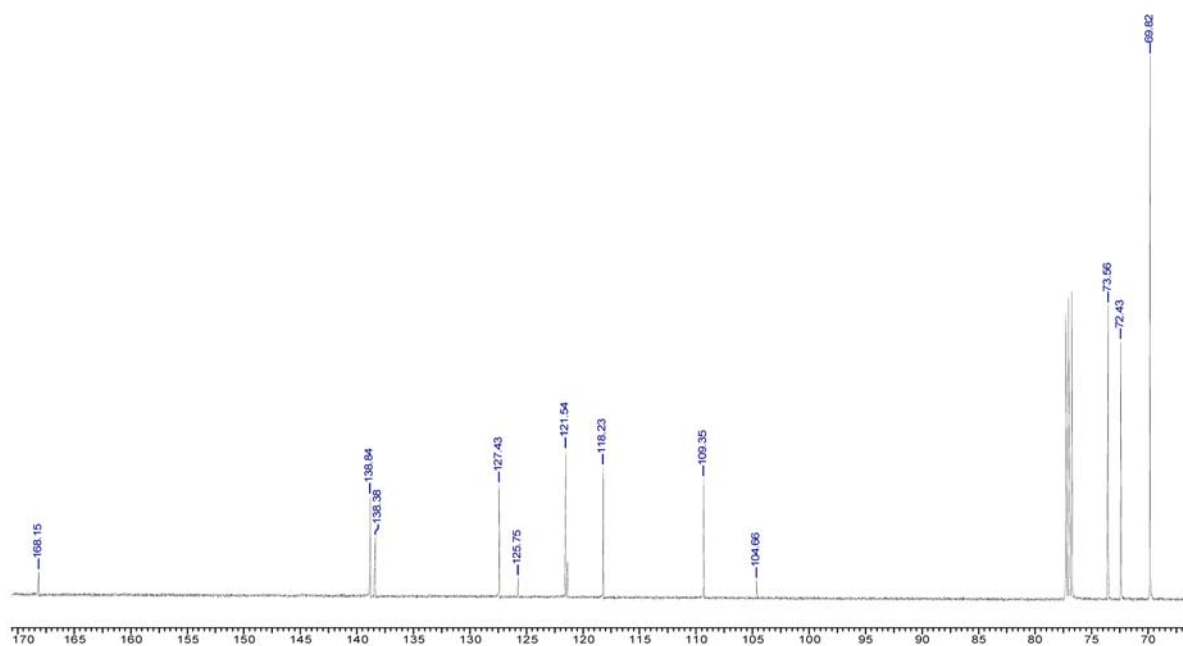
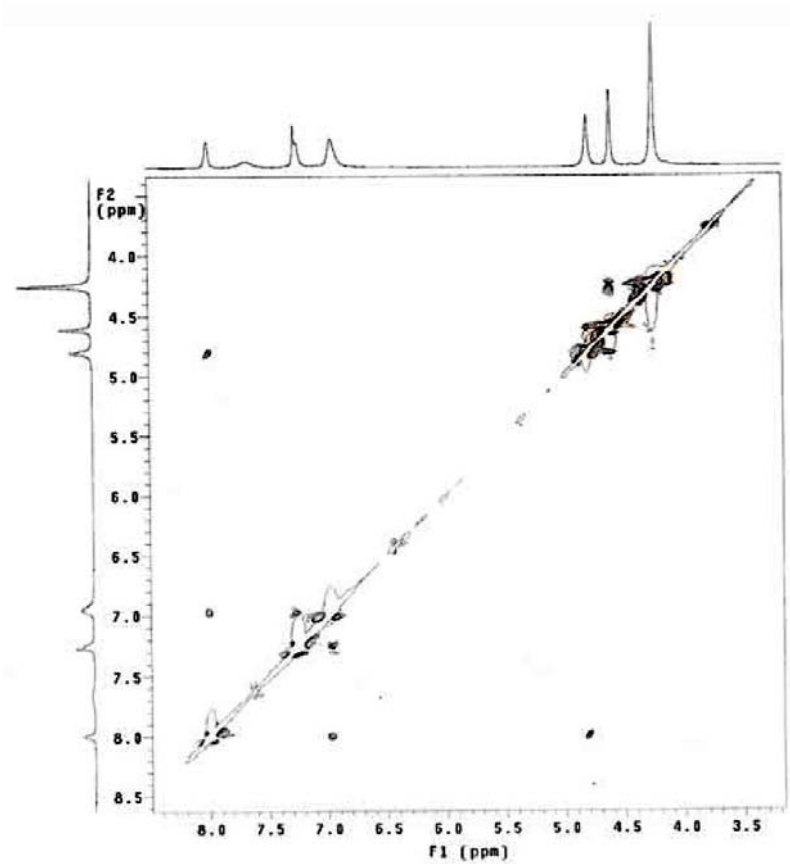
	^{13}C chemical shifts (δ/ppm , 62.5 MHz, CDCl_3)
2a	170.2, 141.1, 137.3, 128.2, 123.3, 122.4, 122.3, 121.1, 109.8, 78.3, 71.1, 69.6
2b**	168.2, 138.8, 138.4, 127.4, 125.7, 121.5, 118.2, 109.3, 104.7, 73.6, 72.4, 68.9
3a*	
3b	
4a*	169.4, 140.2, 138.1, 127.9, 124.1, 122.6, 122.3, 120.8, 115.2, 71.9, 71.5, 70.0
4b	
5a	168.9, 142.3, 136.4, 127.2, 127.2, 125.0, 121.4, 120.9, 115.4, 72.6, 71.8, 70.2
5b	
6a	
7a	
7b	
8a*	167.6, 143.2, 142.1, 128.0, 121.4, 120.5, 119.7, 115.4, 111.7, 74.0, 72.8, 70.1
9a	168.4, 142.3, 138.3, 136.3, 128.7, 128.3, 127.4, 127.3, 122.7, 122.5, 122.1, 121.6, 108.9, 108.9, 73.1, 71.3, 69.9
9b	
10a	
10b	

* * CDCl_3 + DMSO; ** 125 MHz.**Table S3.** Infrared data for compounds **2a-2b** to **10a-10b**

	IR (KBr) $\nu_{\text{max}}/\text{cm}^{-1}$
2a	3362, 3122, 3066, 3020, 2902, 2838, 1693, 1621, 1608, 1465, 1338, 1220
2b	3434, 3133, 3064, 3021, 2923, 2850, 1695, 1619, 1600, 1473, 1211
3a	3435, 3145, 3101, 8248, 1697, 1618, 1600, 1442, 1223
3b	3447, 3141, 3097, 2918, 1688, 1615, 1596, 1473, 1201
4a	3367, 3170, 3135, 3079, 3002, 2879, 2802, 1695, 1623, 1602, 1481, 1438, 1330, 1205, 1187
4b	3446, 3161, 3003, 2880, 1685, 1260, 1586, 1481, 1439, 1369, 1189
5a	3445, 3132, 3073, 2971, 1688, 1594, 1577, 1468, 1208, 1162
5b	3419, 3112, 2921, 2850, 1697, 1600, 1573, 1448, 1301, 1151
6a	3481, 3135, 2921, 2850, 1692, 1614, 1578, 1466, 1323, 1146
7a	3441, 3135, 3066, 2956, 2848, 1697, 1621, 1599, 1584, 1447, 1227, 1132
7b	3357, 3127, 3005, 2924, 2854, 1709, 1689, 1591, 1463, 1443, 1207, 1155
8a	3428, 3114, 3081, 2958, 2921, 2852, 1689, 1604, 1581, 1178
9a	3442, 3130, 3137, 3079, 1695, 1623, 1604, 1604, 1483, 1330, 1187, 1130
9b	3442, 3128, 3052, 2956, 2917, 1695, 1616, 1604, 1484, 1168
10a	3461, 3357, 3144, 2918, 2833, 1690, 1608, 1594, 1336, 1218, 1189
10b	3466, 3419, 3138, 2917, 2849, 1686, 1626, 1596, 1369, 1206, 1044

**Figure S1.** ^1H NMR of **2a**.

2aFigure S2. ¹³C NMR of 2a.**2b**Figure S3. ¹H NMR of 2b.

2bFigure S4. ^{13}C NMR of **2b**.Figure S5. NOESY of **2a**.

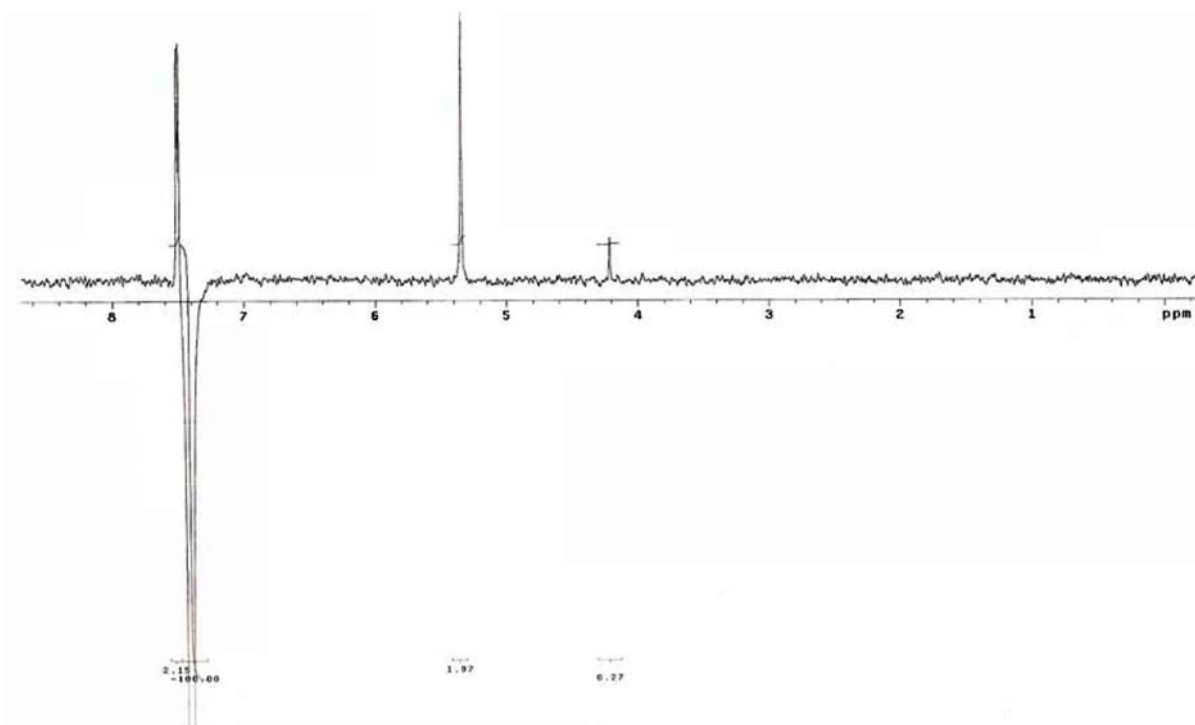
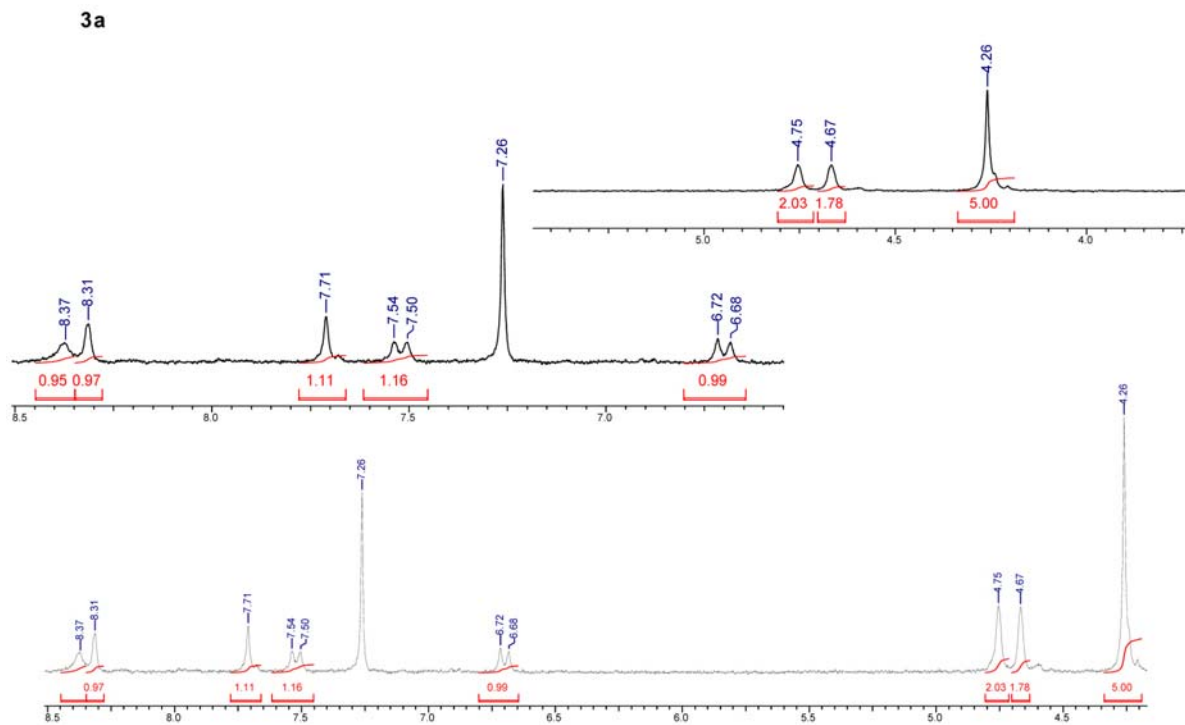
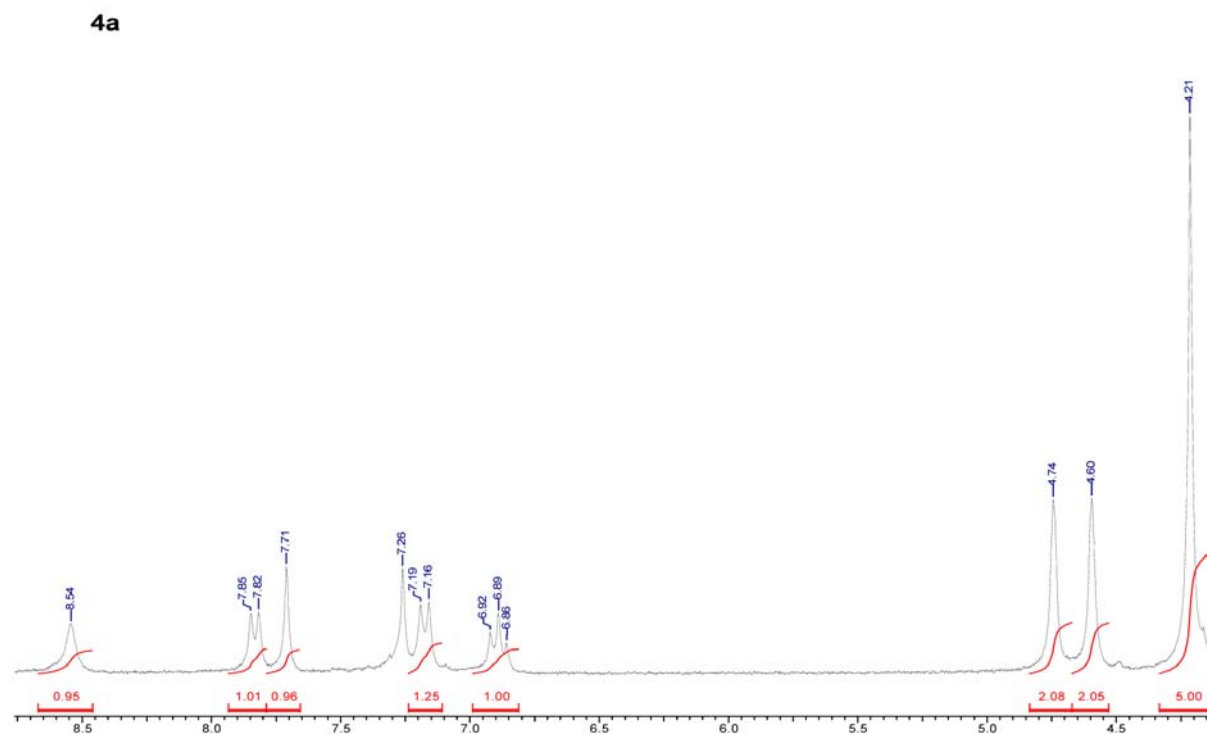
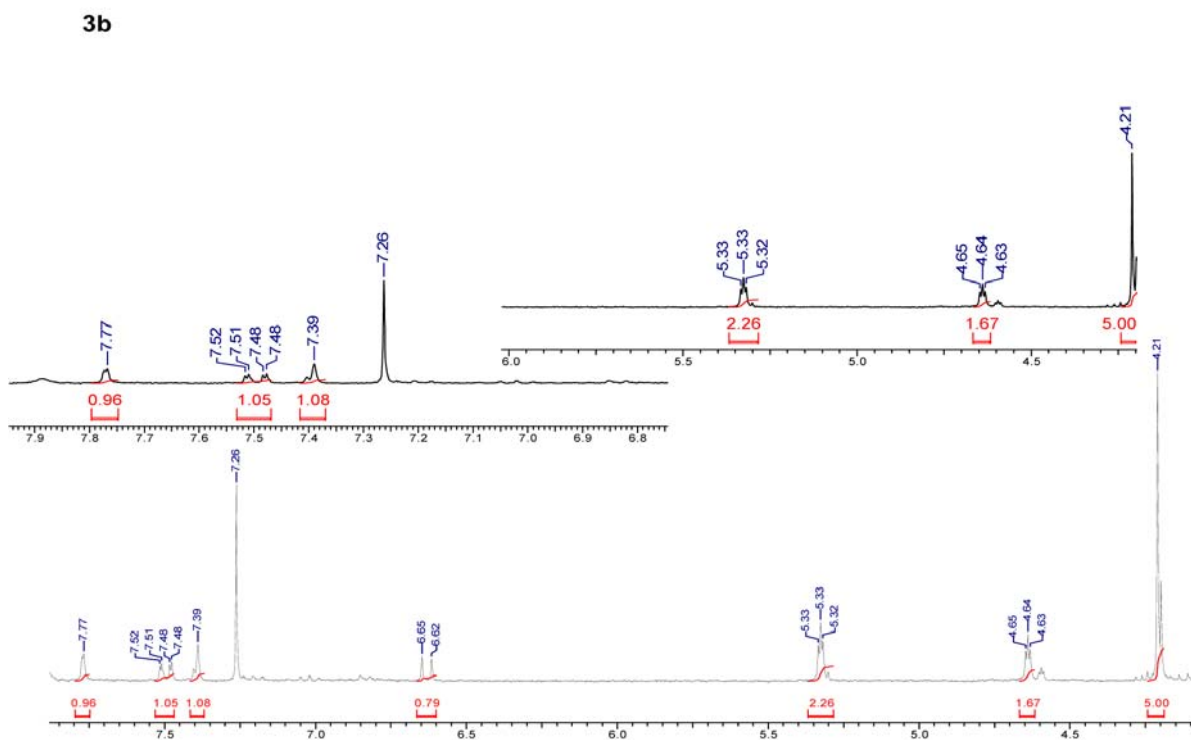
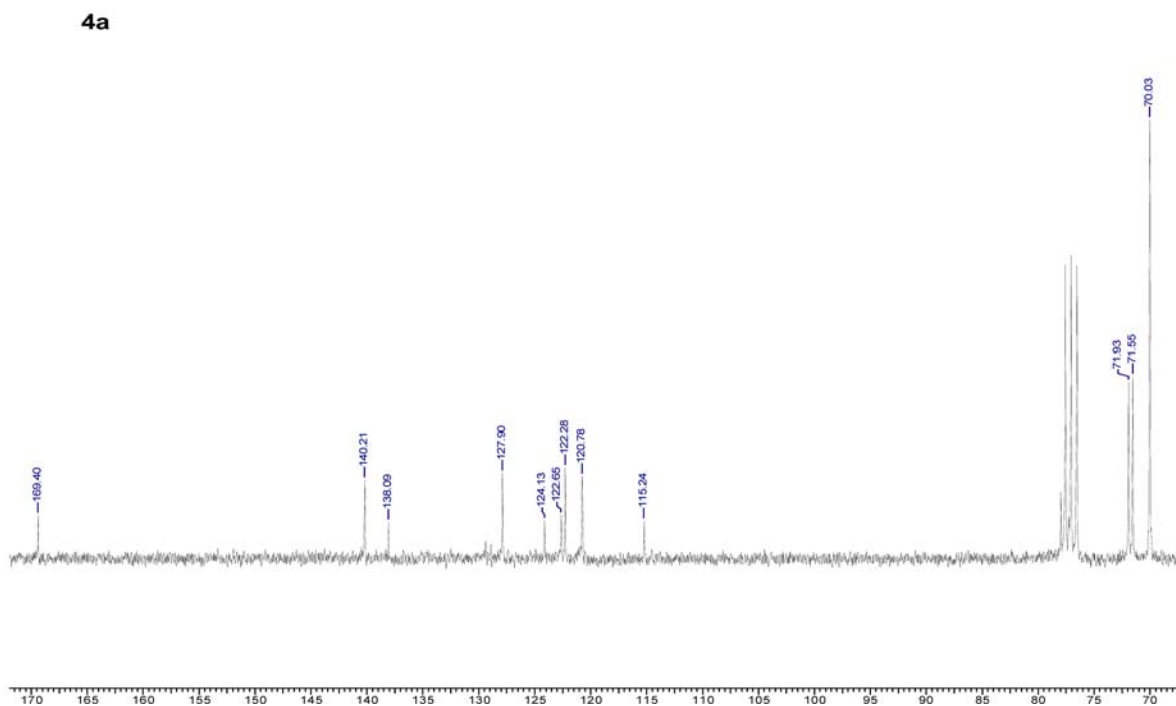
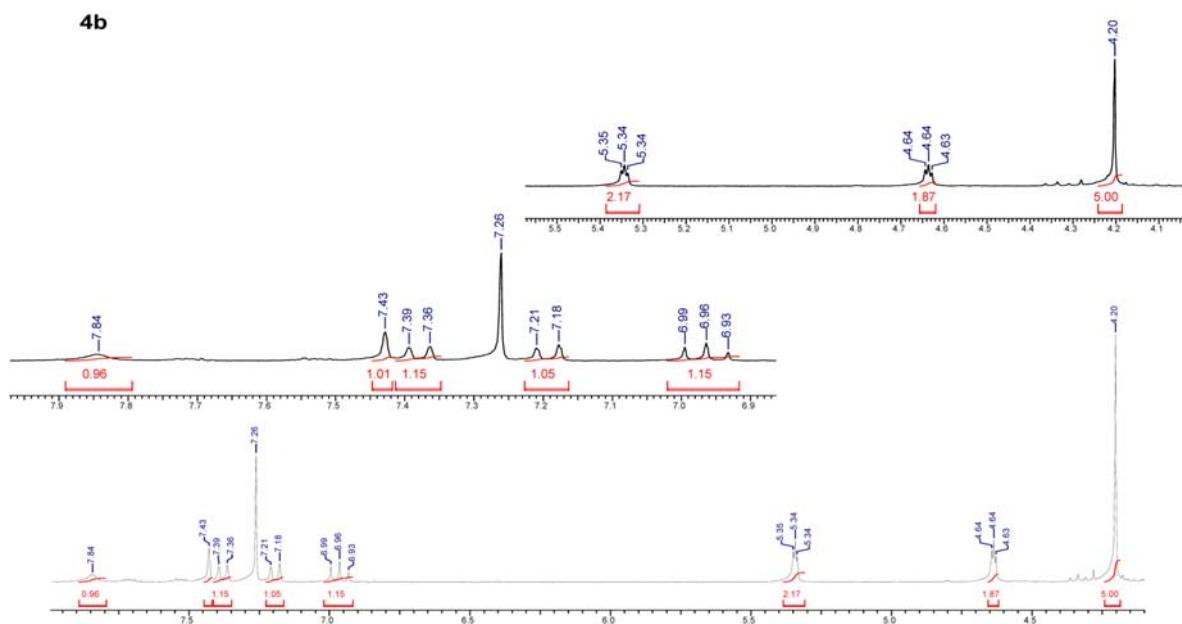
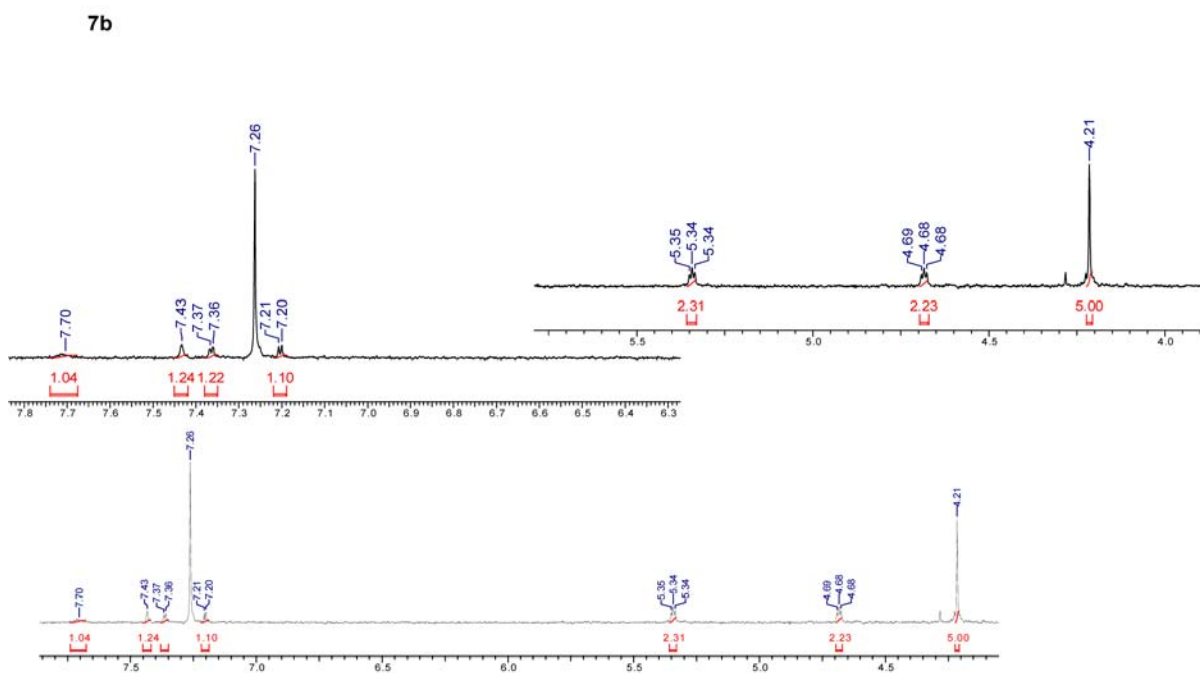
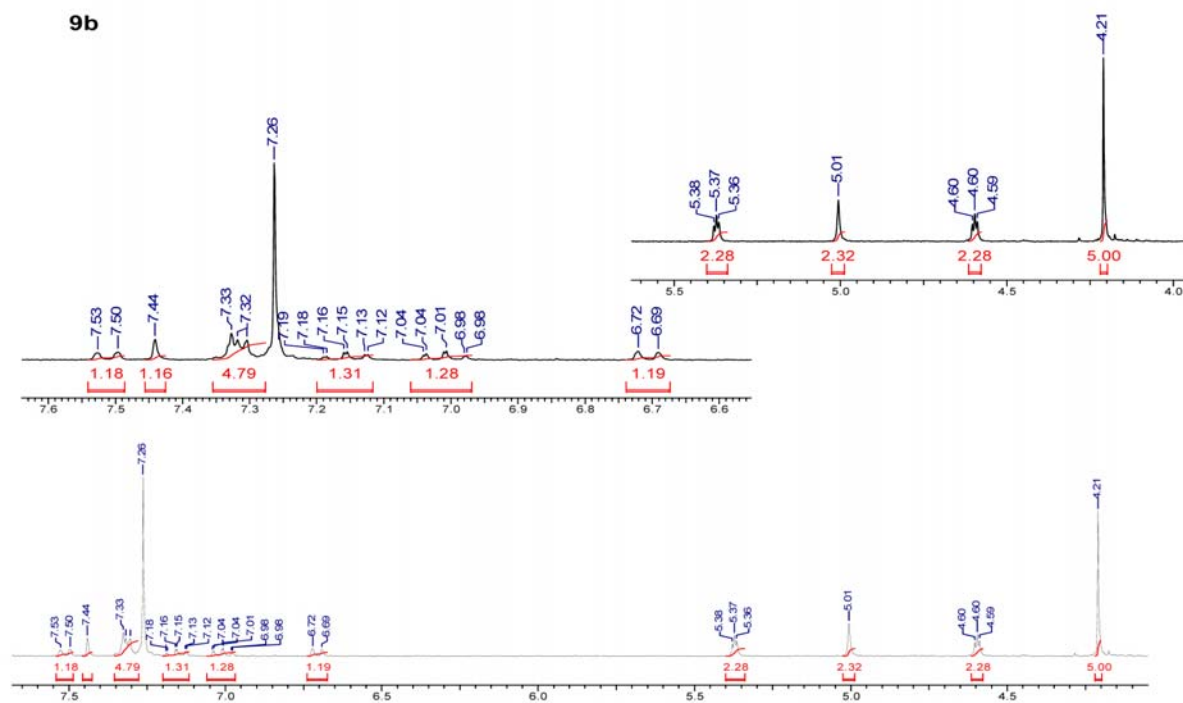


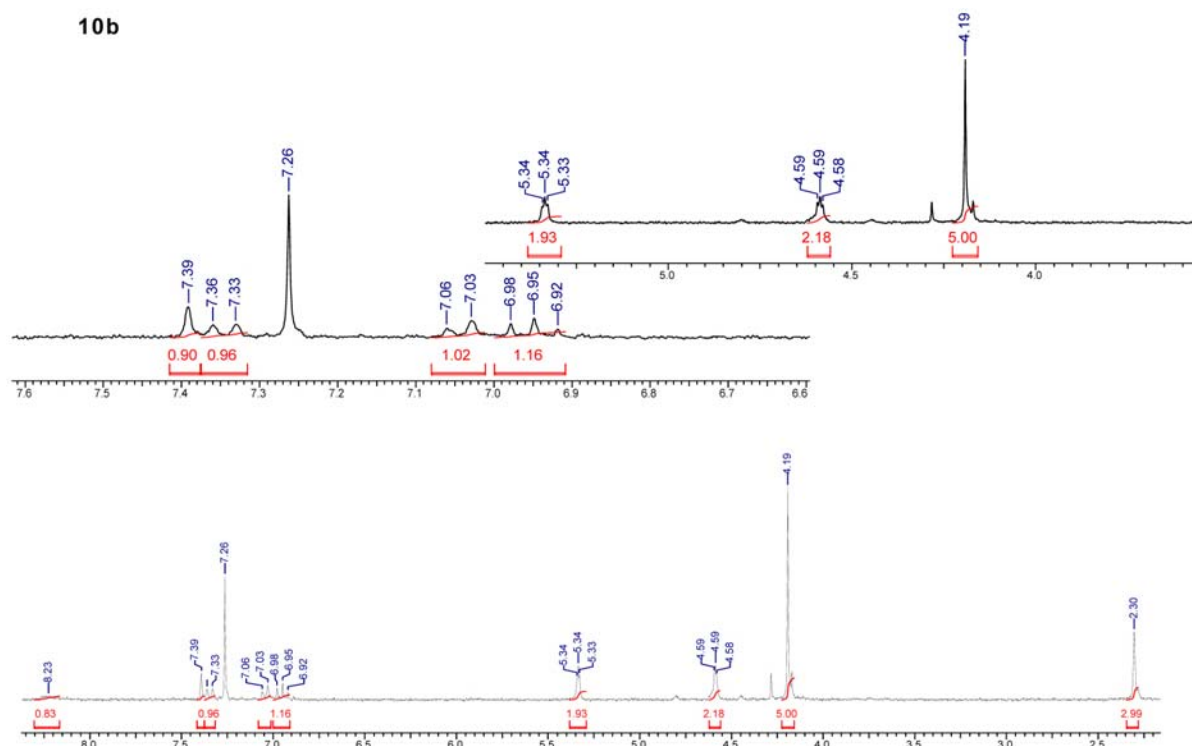
Figure S6. nOe of 2b.

Figure S7. ¹H NMR of 3a.



Figure S10. ^{13}C NMR of 4a.Figure S11. ^1H NMR of 4b.

Figure S12. ^1H NMR of **7b**.Figure S13. ^1H NMR of **9b**.

Figure S14. ^1H NMR of **10b**.