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Synthesis and Characterization of Some Novel Thiazole Derivatives

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Abstract: A series of substituted thiazole derivatives were synthesized by reaction of thiosemicarbazide with substituted vanillin under acidic condition and methanol as a solvent followed by cyclization using substituted phenacylbromides at room temperature. The characterizations of synthesized compounds were-done by ¹H and ¹³C NMR and Mass spectroscopy.

Keywords: Thiazoles, Vanillin, Phenacylbromide

Introduction

A major confront of modern synthetic chemistry is to design highly efficient chemical reaction sequences that provide maximum structural complexity and diversity with a minimum number of synthetic steps to assemble compounds having interesting properties. Great efforts have been focused on preparinglibraries of small heterocyclic molecules having high degree of structural diversity and extensive utility as therapeutic agents [1]. Thiazoles are very important class of heterocyclic chemistry as they possess potential pharmacological activities. Basically thiazole is a heterocyclic compound containing a nitrogen atom and a

sulfur atom as a part of five member aromatic ring.In addition, thiazole ring is highly reactive due to the presence of an acidic proton at C-2 and has emerged as an important synthon to generate variety of New Chemical Entities (NCE). Thiazole can bind to adenosine receptor namely A_1, A_2, A_3 , Dopamine receptor and HIVintegrase inhibitors [2]. This class of compounds is present in many natural and synthetic products with wide range of pharmacological activities, such as anti-viral [3], anti-convulsant [4], anti-fungal and anti-microbial [5-6], anti-inflammatory [7-8], anticancer [9-10], antidiabetic [11], antiHIVagents [12-15], antiproliferative [16-17]. Vanillin is most widely used flavoring agent in the world. It is chemically known as (4-hydroxy-3-methoxybenzaldehyde) and it is broadly used for biopreservative because of its antimicrobial and antioxidant properties [18]. It is an important raw material in pharmaceutical industries for production of drugs such as aldomet, dopamine, papaverine etc. [19-20]. In view of above mentioned findings and due to excellent activities and reactivity we tried to synthesize thiazole compounds using two substituted vanillin by easier methods that may be value in designing new, potent and selective pharmaceutically active compounds. The synthesis of different thiazole derivatives has been carried out via hydrazinecarbothioamide intermediate followed by cyclization using various substituted phenacylbromides.

Materials and Methods

All the reagents were purchased from Sigma Aldrich Corporation and Spectrochem Chemicals Ltd. HPLC grade methanol was purchased from Merck India Limited, Mumbai, India. Melting points were determined in electro thermal apparatus using open capillaries and are uncorrected. The reactions were monitored by thin layer chromatography (TLC). ¹H and ¹³C NMR spectra were recorded in DMSO-d6 solvent by Bruker 400 MHz spectrometer. Chemical shifts are expressed in δ ppm downfield from TMS as an internal standard. Mass spectra were recorded on Shimadzu GCMS-QP-2010 Ultra Model using Direct Injection Probe technique.

Experimental Procedure

General procedure for preparation of compound 2a-b

In an oven dried round bottom flask, substituted vanillin (**1a** and **1b**respectively) (0.01 mol) and thiosemicarbazide (0.01 mol) were mixed in around 4-5 ml of MeOH in the presence of catalytic amount of AcOH. The reaction mixture

was then heated with stirring at 80 °C for 2 hour. After completion of reaction as monitored by TLC using 30% ethyl acetate:hexane solvent system, the reaction mixture was cooled and the obtained solid product was filtered and washed with hexane.

General Procedure for preparation of compound 4a-n

In a clean and dryround bottom flask, the obtained product from first step (2a-b) (0.01 mol) and substituted Phenacylbromides (3a-g) were reacted at room temperature with stirring. The progress ofongoing reaction was gradually monitoring by TLC using10% chloroform:methanol solvent system. After completion of reaction, solid product was separated out by filtration and the isolated product was washed with water and dried well.

Result and Discussion

Initially, we synthesize our target molecules with the help of vanillin as model substrate, MeOH as a solvent in presence of AcOH as catalyst at room temperature by reacting with thiosemicarbazide. Obtained product was then further treated with substituted phenecylbromides**3a-g** and cyclized to afford desired thiazole derivatives 4a-n. Under this observed condition the vield of the substituted thiazole derivative was varied from 46–94%. All the reactions were performed at room temperature and completed within 1-2 h. It is interesting to note that, the reaction was completed within 30 min in case of compound 4j, 4l and 4n. The structures of all title compounds4a-n have been elucidated on the basis of ¹H,¹³C NMR and Mass spectroscopy analysis.

Conclusion

The heterocyclic class of compounds known as thiazole is an important subunit with a wide range of applications in many fields. In this

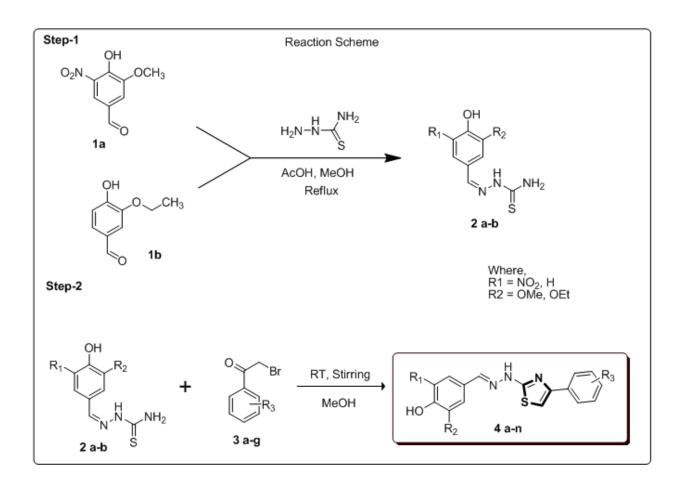
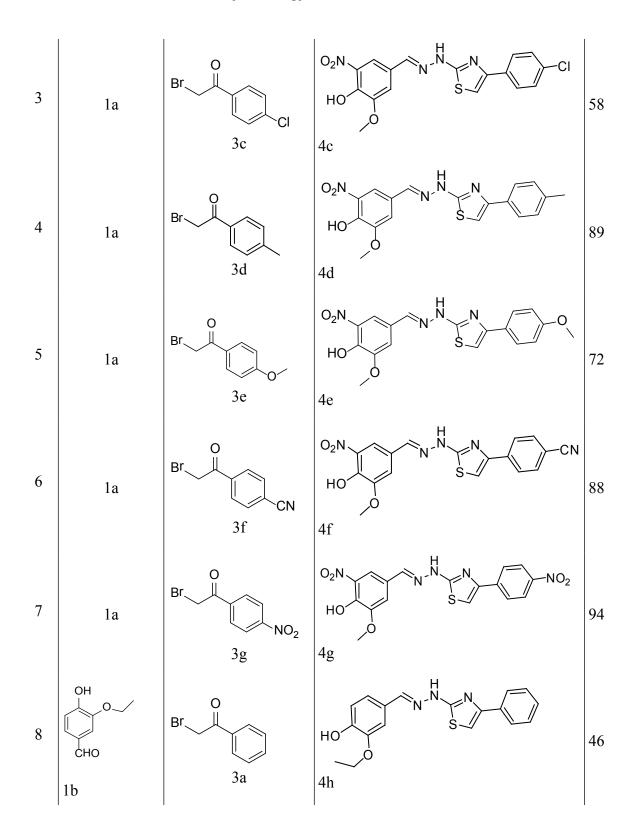
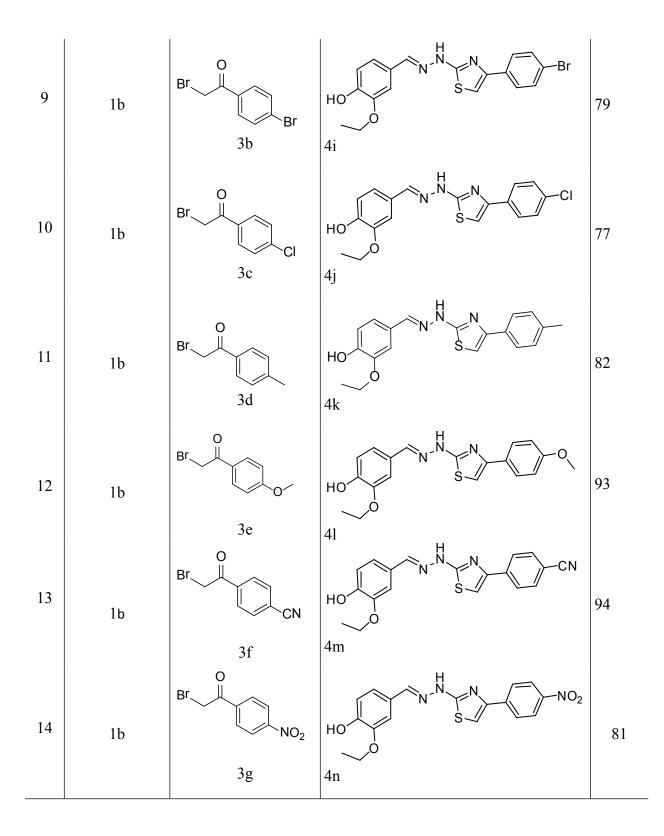


Table 1.Physical Data of final compounds. (4 a-n)

Sr. No.	Aldehyde	Phenacylbromide	Final Structure	%Yield
1	OH O ₂ N O	Br O	N ^{-N} N HO	78
	сно 1a	3a	O 4a	
2	la	Br Br	O ₂ N N N N Br	92
		3b	4b	

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context, vanillin containing this thiazole nucleus represents an outstanding source of compounds with a wide range of biological activities, which can play an important role in the development of new drugs in the treatment of human diseases. From the NMR data, it was concluded that the remarkable result shown that proton of thiazole ring system were varied in between 7.40-7.80 due to the various substitution in phenyl ring present at adjacent position.

Spectral & Physical Data:-

2-Methoxy-6-nitro-4-((2-(4-phenylthiazol-2 yl)hydrazono)methyl)phenol (4a)

Orange solid, Melting point: 192-194 °C, ¹H NMR (DMSO- d_6) δ 3.93 (s, 3H), 7.27 (s, 1H), 7.40 (d, J = 7.3 Hz, 2H), 7.42 – 7.44 (m, 2H), 7.47 (s, 1H), 7.80 – 7.86 (m, 2H), 8.04 (s, 1H). ¹³C NMR (DMSO- d_6) δ 56.50, 105.05, 112.17, 124.00, 126.26, 127.70, 128.51, 129.48, 135.50, 135.93, 148.47, 148.71, 150.68, 154.45, 169.62. MS: m/z 370

4-((2-(4-(4-Bromophenyl)thiazol-2yl)hydrazono)methyl)-2-methoxy-6nitrophenol (4b)

Orange solid, Melting point: 200-202 °C, ¹H NMR (DMSO- d_6) δ 3.95 (s, 3H), 7.28 (s, 1H), 7.29 – 7.31 (m, 1H), 7.43 – 7.47 (m, 1H), 7.55 (d, J = 7.5 Hz, 2H), 7.76 (d, J = 7.5 Hz, 2H), 8.04 (s, 1H). ¹³C NMR (DMSO- d_6) δ 56.48, 105.95, 112.17, 123.03, 124.00, 127.46, 128.51, 132.26, 132.52, 135.93, 148.47, 148.54, 148.71, 150.68, 169.62. MS: m/z 449

4-((2-(4-(4-Chlorophenyl)thiazol-2yl)hydrazono)methyl)-2-methoxy-6nitrophenol (4c)

Orange solid, Melting point: 212-214 °C, ¹H NMR (DMSO- d_6) δ 3.94 (s, 3H), 7.28 (s, 1H), 7.39 – 7.45 (m, 1H), 7.54 (d, J = 7.5 Hz, 2H), 7.81 – 7.86 (m, 1H), 8.00 – 8.10 (m, 3H). ¹³C NMR (DMSO- d_6) δ 56.50, 105.95, 112.17, 124.00, 127.10, 128.30, 128.51, 131.99, 135.12, 135.93, 148.47, 148.54, 148.71, 150.68, 169.62. MS: m/z 404

2-Methoxy-6-nitro-4-((2-(4-(p-tolyl)thiazol-2-yl)hydrazono)methyl)phenol (4d)

Orange solid, Melting point: 218-220 °C, ¹H NMR (DMSO- d_6) δ 2.33 (s, 3H), 3.97 (s, 3H), 7.25 (s, 1H), 7.27 (s, 2H), 7.29 – 7.32 (m, 1H), 7.44 – 7.47 (m, 1H), 7.84 (d, J = 7.5 Hz, 2H), 8.04 (s, 1H). ¹³C NMR (DMSO- d_6) δ 21.42, 56.50, 105.95, 112.17, 124.00, 127.32, 128.51, 129.38, 132.72, 135.93, 137.26, 148.47, 148.54, 148.71, 150.68, 169.62. MS: m/z 384

2-Methoxy-4-((2-(4-(4-methoxyphenyl) thiazol-2-yl)hydrazono)methyl)-6nitrophenol (4e)

Orange solid, Melting point: 196-198 °C, ¹H NMR (DMSO- d_6) δ 3.79 (s, 3H), 3.94 (s, 3H), 7.05 (d, J = 7.5 Hz, 2H), 7.27 (s, 1H), 7.41 – 7.44 (m, 1H), 7.68 (d, J = 7.5 Hz, 2H), 7.81 – 7.85 (m, 1H), 8.04 (s, 1H). ¹³C NMR (DMSO- d_6) δ 55.35, 56.50, 105.95, 112.17, 113.80, 124.00, 128.51, 128.67, 129.83, 135.93, 148.47, 148.54, 148.71, 150.68, 158.97, 169.62. MS: m/z 400

4-(2-(2-(4-Hydroxy-3-methoxy-5nitrobenzylidene)hydrazinyl)thiazol-4 yl) benzonitrile (4f)

Orange solid, Melting point: 230-232 °C,¹H NMR (DMSO- d_6) δ 3.96 (s, 3H), 7.54 (d, J = 1.5 Hz, 1H), 7.67 (s, 1H), 7.73 (d, J = 1.5 Hz, 1H), 7.88 (d, J = 8.4 Hz, 2H), 8.00 – 8.09 (m, 3H). ¹³C NMR (DMSO- d_6) δ 56.50, 107.61, 109.53, 112.16, 114.39, 118.95, 125.06, 126.05, 132.65, 137.16, 138.58, 139.93, 143.41, 148.64, 149.68, 168.36. MS: m/z 395

2-Methoxy-6-nitro-4-((2-(4-(4-nitrophenyl) thiazol-2-yl)hydrazono)methyl)phenol (4g)

Orange solid, Melting point: 240-242 °C, ¹H NMR (DMSO- d_6) δ 3.95 (s, 3H), 7.27 (s, 1H), 7.38 – 7.44 (d,J = 2.4 Hz, 1H), 7.80 – 7.87 (d, J= 2.4 Hz, 1H), 8.04 (s, 1H), 8.16 (d, J = 7.5 Hz, 2H), 8.28 (d, J = 7.5 Hz, 2H). ¹³C NMR (DMSO- d_6) δ 56.50, 105.95, 112.17, 124.00, 124.86, 127.15, 128.51, 134.96, 135.93, 145.99, 148.47, 148.54, 148.71, 150.68, 169.62. MS: m/z 415.

2-Ethoxy-4-((2-(4-phenylthiazol-2-yl) hydrazono)methyl)phenol (4h)

White solid, Melting point: 216-218 °C,¹H NMR (DMSO- d_6) δ 1.37 (t, J = 6.95 Hz, 3H), 4.07 (q, J = 6.95 Hz, 2H), 6.87 (d, J = 8.14 Hz, 1H), 7.10 (dd, J = 8.21, 1.68 Hz, 1H), 7.25 (d, J= 1.67 Hz, 1H), 7.35 (t, J = 9.30 Hz, 2H), 7.44 (t, J = 7.58 Hz, 2H), 7.84 (d, J = 7.21 Hz, 2H), 8.02 (s, 1H). ¹³C NMR (DMSO- d_6) δ 14.71, 63.76, 103.54, 110.60, 115.67, 120.69, 125.65, 127.87, 128.63, 133.53, 143.46, 147.04, 148.76, 168.36.MS: m/z 339.

4-((2-(4-(4-Bromophenyl)thiazol-2-yl) hydrazono)methyl)-2-ethoxyphenol (4i)

White solid, Melting point: 202-204 °C, ¹H NMR (DMSO- d_6) δ 1.37 (t, J = 6.9 Hz, 3H), 4.08 (q, J = 6.9 Hz, 2H), 6.88 (d, J = 8.1 Hz, 1H), 7.10 (dd, 1H), 7.25 (d, J = 1.5 Hz, 1H), 7.40 (s, 1H), 7.63 (d, J = 8.5 Hz, 2H), 7.81 (d, J = 8.5 Hz, 2H), 8.02 (s, 1H).¹³C NMR (DMSO- d_6) δ 14.70, 63.75, 104.37, 110.55, 115.66, 120.78, 125.46, 127.62, 131.52, 132.93, 143.23, 143.32, 147.03, 147.66, 148.73, 168.45.MS: m/z 418

4-((2-(4-(4-Chlorophenyl)thiazol-2-yl) hydrazono)methyl)-2-ethoxyphenol (4j)

White solid, Melting point: 208-210 °C,¹H NMR (DMSO- d_6) δ 1.39 (t, J = 8.0 Hz, 3H), 4.13 (q, J = 8.0 Hz, 2H), 6.88 (d, J = 7.3 Hz, 1H), 7.00 (d, J = 8.1 Hz, 2H), 7.27 (s, 1H), 7.54 (d, J = 7.5 Hz, 2H), 8.01 – 8.08 (m, 3H). ¹³C NMR (DMSO- d_6) δ 14.65, 64.77, 105.95, 112.21, 115.80, 121.45, 127.10, 128.09, 128.30, 131.99, 135.12, 145.11, 147.39, 148.54, 152.07, 169.62. MS: m/z 373

2-Ethoxy-4-((2-(4-(p-tolyl)thiazol-2-yl) hydrazono)methyl)phenol(4k)

White solid, Melting point: 240-242 °C, ¹H NMR (DMSO- d_6) δ 1.37 (t, J = 6.9 Hz, 3H), 2.32 (s, 3H), 4.07 (q, J = 6.9 Hz, 2H), 6.85 (d, J = 8.1

Hz, 1H), 7.07 (dd, J = 8.2, 1.7 Hz, 1H), 7.21 (d, J = 8.3 Hz, 4H), 7.74 (d, J = 8.1 Hz, 2H), 7.92 (s, 1H). ¹³C NMR (DMSO- d_6) δ 14.71, 20.78, 63.75, 102.25, 110.43, 115.66, 120.28, 125.39, 125.84, 129.12, 132.05, 136.67, 141.76, 147.02, 148.41, 150.43, 168.24.MS: m/z 353

2-Ethoxy-4-((2-(4-(4-methoxyphenyl)thiazol-2-yl)hydrazono)methyl)phenol(4l)

White solid, Melting point: 204-206 °C,¹H NMR (DMSO- d_6) δ 1.38 (t, J = 6.9 Hz, 3H), 3.18 (s, 3H), 3.80 (s, 3H), 4.08 (q, J = 6.9 Hz, 2H), 6.89 (d, J = 8.1 Hz, 1H), 7.02 (d, J = 8.9Hz, 2H), 7.14 (dd, 1H), 7.20 (s, 1H), 7.28 (s, 1H), 7.77 (d, J = 8.8 Hz, 2H), 8.12 (s, 1H).¹³C NMR (DMSO- d_6) δ 14.70, 48.54, 55.19, 63.79, 101.77, 110.77, 114.05, 115.68, 121.11, 125.12, 127.27, 145.15, 147.06, 149.10, 159.27, 168.27. MS: m/z 369

4-(2-(2-(3-Ethoxy-4-hydroxybenzylidene) hydrazinyl)thiazol-4-yl)benzonitrile (4m)

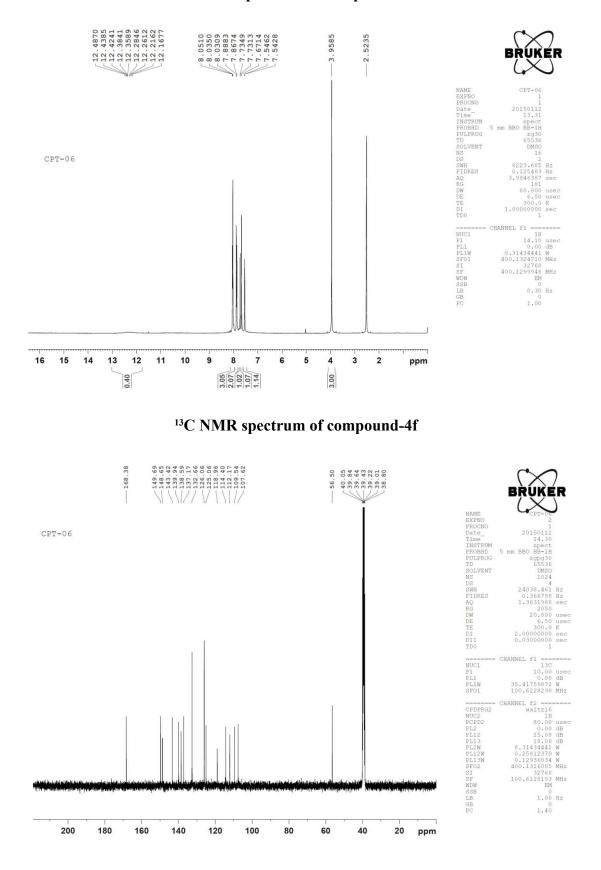
White solid, Melting point: 244-246 °C,¹H NMR (DMSO- d_6) δ 1.38 (t, J = 8.0 Hz, 3H), 4.13 (q, J = 8.0 Hz, 2H), 6.88 (d, J = 7.4 Hz, 1H), 6.98 – 7.05 (m, 2H), 7.27 (s, 1H), 7.74 (d, J= 7.5 Hz, 2H), 8.02 – 8.10 (m, 2H), 8.76 (s, 1H). ¹³C NMR (DMSO- d_6) δ 14.65, 64.77, 105.95, 111.51, 112.21, 115.80, 117.54, 121.45, 127.25, 128.09, 132.13, 134.01, 145.11, 147.39, 148.54, 152.07, 169.62. MS: m/z 364

2-Ethoxy-4-((2-(4-(4-nitrophenyl)thiazol-2yl)hydrazono)methyl)phenol(4n)

White solid, Melting point: 236-238 °C,¹H NMR (DMSO- d_6) δ 1.37 (t, J = 6.9 Hz, 3H), 4.08 (q, J = 6.9 Hz, 2H), 6.86 (d, J = 8.1 Hz, 1H), 7.08 (dd, J = 8.2, 1.7 Hz, 1H), 7.23 (d, J= 1.7 Hz, 1H), 7.71 (s, 1H), 7.97 (s, 1H), 8.11 (d, J = 8.9 Hz, 2H), 8.28 (d, J = 8.9 Hz, 2H).¹³C NMR (DMSO- d_6) δ 14.70, 63.73, 108.20, 110.44, 115.65, 120.47, 124.07, 125.60, 126.28, 140.56, 142.53, 146.10, 147.03, 148.20, 148.59, 168.72. MS: m/z 384

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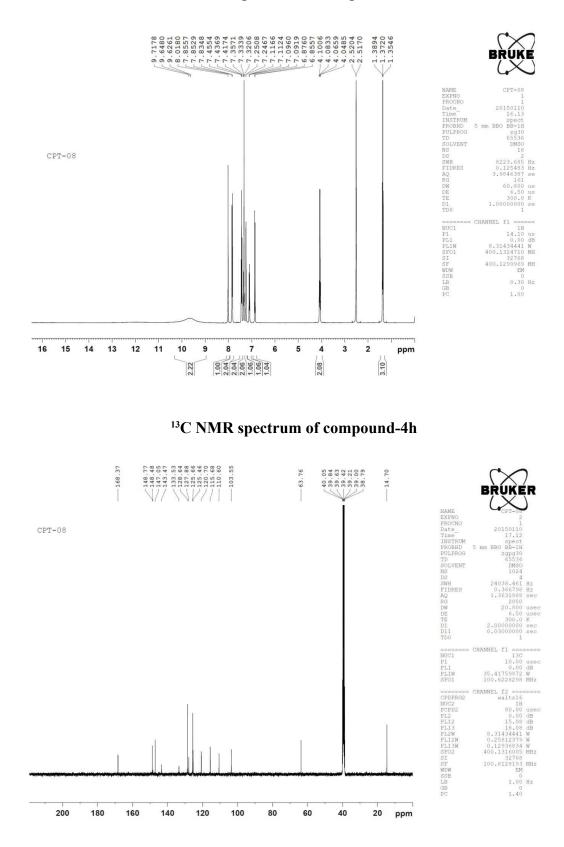
¹H NMR spectrum of compound-4f



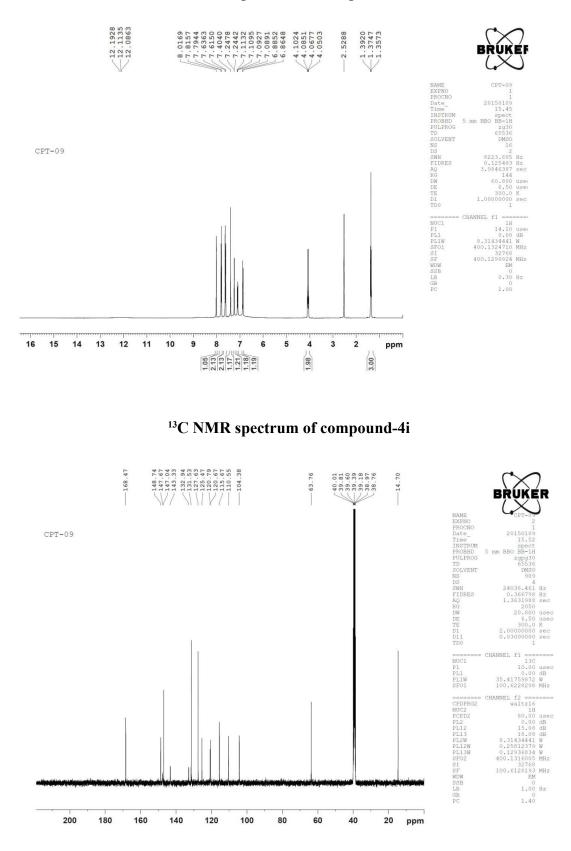
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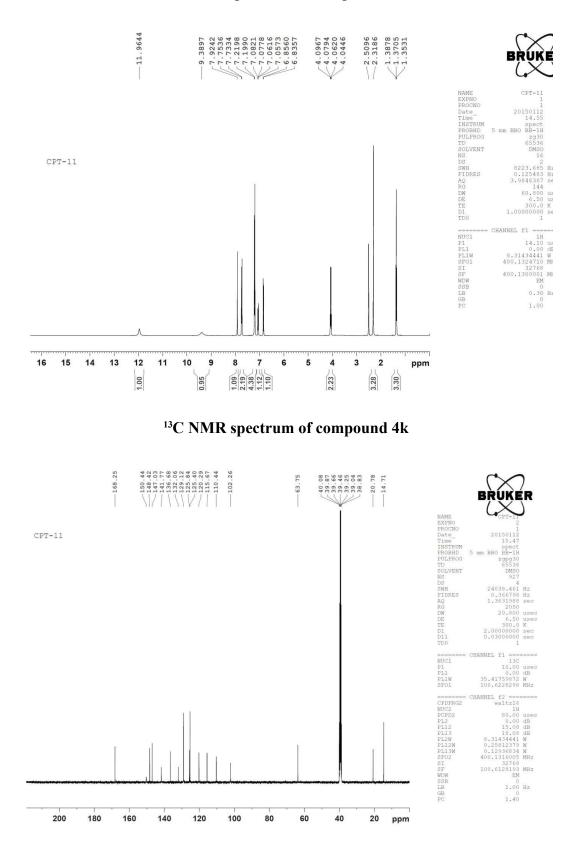
¹H NMR spectrum of compound-4h



¹H NMR Spectrum of compound 4i



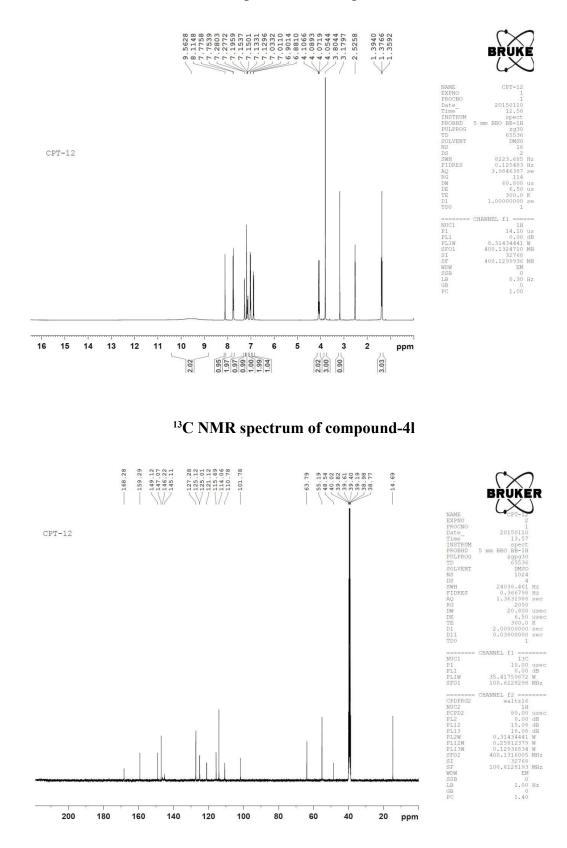
¹H NMR spectrum of compound 4k



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¹H NMR spectrum of compound-4l



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