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"Anti-Michael" and Michael Additions in the Reactions of 2-Arylmethyliden-1,3-Indandiones with 2-Aminothiophenol

Jessica J. Sánchez García[1], Alberto D. Hernández-Suzan[1], Elena Martínez-Klimova[1], Marcos Flores-Alamo[1], Teresa Ramírez Apan[2], Elena I. Klimova[1*]

[1]Departamento de Química Orgánica, Universidad Nacional Autónoma de México, Facultad de Química, Cd. Universitaria, Ciudad de México, México
[2]Instituto de Química, Universidad Nacional Autónoma de México, Facultad de Química, Cd. Universitaria, Ciudad de México, México
Email: *eiklimova@yahoo.com.mx

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Abstract

A novel 2-indano[2,3b]-2-ferrocenyl- and 2-indano[2,3b]-2-(*p*-methoxyphenyl)[1,5]benzo-2,5-dihydrothiazepine **5a,b** (addition Michael/cyclization) (~30.32%), indano[2,3b]-2-ferrocenyl- and 2-(*p*-methoxyphenyl)[1,4] benzothiazine **4a,b** (addition "anti-Michael"/cyclization) (~45.43%), respectively, were obtained by the condensation of 2-ferrocenyl-and 2-(*p*-methoxyphenyl)methyliden-1,3-indandiones **1a,b** with *o*-aminothiophenol **2** in the presence of AcOH and HCl. A new "anti-Michael" addition reaction of 1,4-*bis*-heteronucleophile **2** into 2-arylmethyliden-1,3-indandiones was reported. As a result of this reaction the product **1a,b** was obtained. The structures of the resultant compounds were elucidated by IR, ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, elemental and X-ray diffraction analysis. The *in vitro* antitumor activity of the obtained products was researched using the following human cancer cell lines: glioblastoma (CNS U-251), prostatic adenocarcinoma (PC-3), chronic myelogenous leukemia (K562), colorectal adenocarcinoma (HCT-15), mammary adenocarcinoma (MCF-7), and small cell lung cancer (SKLU) and the sulforhodamine B (SRB) method. Among these new compounds some thiazine and thiazepine derivatives showed compelling *in vitro* antitumor effects on cell lines K-562, HCT-15, SKLU-1 and MCF-7.

Keywords

Ferrocene, Addition "Anti-Michael", Reaction Cyclization, 1,5-Thiazepines, 1,4-Thiazines, Antitumor Cell Lines

1. Introduction

The common strategy for the construction of the 1,5-benzothiazepine moiety is

the reaction of 1,3-diarylprop-2-enones with *o*-aminothiophenol or 1,3-difunctional three-carbon building blocks. Among them, *α,β*-unsaturated carbonyl compounds such as 1,2-enones and 1,2-ynones are best suited for Michael addition and subsequent cyclocondensation [1]. The various reported methodologies involve the use of inorganic supports such as alumina, silica gel, AcOH, trifluoroacetic acid, HCl, piperidine, BF_3Et_2O, etc. to improve the reaction efficiency [2] [3] [4]. Likewise, the related 1,5-benzothiazepines display a comparable spectrum of biological activity. The 1,5-benzothiazepine framework has been identified as a pluripotent pharmacophore with derivatives encompassing CNS-acting agents [5], anti-HIV [6], anti-tuberculosis (TB) [7], anticancer drugs [8], antimicrobial [9], calmodulin antagonists [4], enzyme inhibitors [11], antifungal [4] [10], antibacterial [12], anti-inflammatory and analgesic agents [4]. Also, it is expected that new active benzo-1,5-thiazepines and other related derivatives could be used in the treatment of serious human diseases like Alzheimer's diabetes [4].

Ferrocene compounds are known to possess many chemotherapeutic properties [13]. The incorporation of a ferrocenyl-substituent into a benzo-1,5-thiazepine molecule will expand the spectrum of valuable characteristics. Ferrocenyl-substituted 1,5-benzothiazepines have not been extensively studied. The first synthesis of 2-ferrocenyl-4-(4-chlorophenyl)-1,5-benzothiazepine on the base of 1-(4-chlorophenyl)-3-ferrocenyl-2-propenone was reported in 2010 by Willy and Müller [14]. Recently, in 2015, Klimova *et al.* have published the synthesis of various 2- and 4-ferrocenyl-1,5-benzothiazepines as well as their spectroscopic and structural characteristics [15]. However, The use of 2-ferrocenyl-methyliden-1,3-diones in the synthesis of polycyclic systems with seven-membered heterocycles, such as dihydro-1,5-benzothiazepines and 1,5-benzothiaze-pines, has not been described until now. Therefore, the synthesis of polycyclic ferrocenyl-1,5-benzothiazepines has received considerable attention.

As a continuation of our previous investigations [15] in this field, the present work examines the possibility of synthesizing tetracyclic ferrocenyldihydro-1,5-benzothiazepines starting from 2-ferrocenyl- and 2-anisylmethyliden-1,3-indandiones **1a,b** and *o*-aminothiophenol **2** in the presence of acetic or hydrochloric acid.

2. Material and Methods

2.1. Chemistry

Solvents and reagents were purchased from Aldrich and used without further purification. Column chromatography was carried out on alumina (Brockmann activity III). The ^1H and ^{13}C NMR spectra were recorded on a Unity Inova Varian spectrometer (300 and 75 MHz) for solutions in $CDCl_3$ with Me_4Si as the internal standard. The IR spectra were measured with an FTIR spectrophotometer (Spectrum RXI Perkin-Elmer instruments) using KBr pellets. The mass spectra were obtained on a Varian MAT CH-6 instrument (EI MS, 70 eV). Elementar Analysensysteme LECO CHNS-900 was used for elemental analyses. The fol-

lowing reagents were purchased from Aldrich: ferrocenecarbaldehyde, 99%; p-anisaldehyde, 98%; 1,3-indandione, 97%; 2-aminothiophenol, 99%.

For general information, all experimental data, and copies of the NMR spectra and UV/Vis spectra, see the Supporting Information.

Condensation of 2-arylmethylidene-1,3-indandiones (1a,b) with 2-aminothiophenol (2). Tipical Procedure [16]. A mixture of the chalcones (2.5 mmol), 2-aminothiophenol (0.5 g, 4 mmol), AcOH (0.5 mL), HCl conc. (0.1 ml), Et_3N (0.1 mL) in methanol (50 mL) was heated to reflux (~60˚C - 65˚C) and stirred until complete dissolution of the enones **1a,b** occurred (~6 - 8 h). The organic layer was concentrated, and the residue was chromatographed on alumina (Brockmann activity III, hexane-ether, 3:1) to give 2-arylthiazoles **3a,b** (~9% - 11%) [17] [18] [19], ferrocenyl- and anisylthiazines **4a,b** (43% - 45%), ferrocenyl-and anisylthiazapines **5a,b** (30% - 32%), and indeno[2,1-b:2,3-b]bis [[1,4]benzothiazine **6** (~10%).

2-Ferrocenylbenzothiazole (3a): Orange crystals: Yield 0.14 g (9%); mp 111˚C - 112˚C (lit. [17] mp 112˚C). ^{1}H NMR (300 MHz, $CDCl_3$,TMS): δ = 4.14 (s, 5 H, C_5H_5), 4.48 (m, 2 H, C_5H_4), 4.99 (m, 2 H, C_5H_4), 7.33 (td, 1 H, J = 1.2, 8.1 Hz, *o*-C_6H_4), 7.43 (td, 1 H, J = 1.2, 8.1 Hz, *o*-C_6H_4), 7.80 (d, 1 H, J = 8.1 Hz, *o*-C_6H_4), 7.95 (d, 1 H, J = 8.1 Hz, *o*-C_6H_4) ppm. MS (EI, 70 eV) m/z 319 $[M]^+$. Anal calcd for $C_{17}H_{13}FeNS$: C, 64.00; H, 4.10; N, 4.40; S, 10.00; Found: C, 63.89; H, 4.26; N, 4.31; S, 9.84.

Indano[2,3b]-2-ferrocenylmethyl[1,4]benzothiazine (4a): Orange crystals: Yield 1.02 g (45%); mp 163˚C - 164˚C, IR (KBr): ν = 467, 481, 511, 729, 762, 812, 887, 999, 1042, 1104, 1163, 1216, 1250, 1344, 1441, 1450, 1552, 1599, 1629, 1718, 2944, 3052, 3081 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 2.81 (d, 1 H, J = 13.8 Hz, CH_2), 3.00 (d, 1 H, J = 13.8 Hz, CH_2), 3.92 (s, 5 H, C_5H_5), 3.68 (m, 1 H, C_5H_4), 3.71 (m, 1 H, C_5H_4), 3.75(m, 1 H, C_5H_4), 3.76 (m, 1 H, C_5H_4), 7.20 (td, 1 H, J = 1.2, 7.2 Hz, C_6H_4), 7.30 (dd, J = 1.2, 7.8 Hz, 1 H, C_6H_4), 7.42 (td, 1 H, J = 1.2, 7.8 Hz, C_6H_4), 7.53 (td, 1 H, J = 1.2, 7.2 Hz, C_6H_4), 7.64 (dd, 1 H, J = 1.2, 7.8 Hz, C_6H_4), 7.69 (dd, 1 H, J = 1.2, 7.2 Hz, C_6H_4), 7.76 (dd, 1H, J = 1.2, 7.2 Hz, C_6H_4), 8.02 (dd, 1 H, J = 1.2, 7.8 Hz, C_6H_4) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 49.25 (CH_2), 68.51 (C_5H_5), 67.75, 67.71, 69.26, 69.51 (C_5H_4), 80.21 (C_{ipsoFc}), 123.51, 123.30, 126.93, 127.08, 128.16, 128.93, 135.83, 138.30 (2 C_6H_4), 62.12, 122.52, 129.64, 132.58, 142.93, 145.31 (6 C), 160.19 (C=N), 195.50 (C=O) ppm. MS (EI, 70 eV): m/z 449 $[M]^+$. Anal calcd. for $C_{26}H_{19}FeNOS$; C, 69.51; H, 4.26; N, 3.12; S, 7.12; Found: C, 69.29; H, 4.34; N, 3.27; S, 7.03.

2-Indeno[2,3b]-2-ferrocenyl[1,5]benzo-2,5-dihydro-thiazepine (5a): Orange crystals: Yield 0.68 g (30%); mp 184˚C - 185˚C, IR (KBr): ν = 481, 497, 507, 733, 761, 817, 893, 1003, 1078, 1105, 1179, 1212, 1224, 1358, 1376, 1429, 1454, 1478,1540, 1578, 1594, 1619, 1681, 1701, 1735, 3008, 3187, 3361 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 4.16 (s, 5 H, C_5H_5), 3.41 (m, 1 H, C_5H_4), 3.74 (m, 1 H, C_5H_4), 4.00 (m, 1 H, C_5H_4), 4.26 (m, 1 H, C_5H_4), 5.41 (s, 1 H, CH), 6.94 (td, 1 H, J = 1.2, 7.5 Hz, C_6H_4), 7.09 (dd, J = 1.2, 7.8 Hz, 1 H, C_6H_4), 7.16 (dd, 1 H, J = 1.2, 7.8 Hz, C_6H_4), 7.27 (td, 1 H, J = 1.2, 7.8 Hz, C_6H_4), 7.33 (td, 1 H, J =

1.2, 7.5 Hz, C_6H_4), 7.38 (dd, 1 H, J = 1.2, 7.5 Hz, C_6H_4), 7.42 (td, 1 H, J = 1.2, 7.8 Hz, C_6H_4), 7.48 (bs, 1 H, NH), 7.56 (dd, 1 H, J = 1.2, 7.8 Hz, C_6H_4) ppm. ^{13}C NMR (75 MHz, $CDCl^3$, TMS): δ = 42.56 (CH), 68.93 (C_5H_5), 66.11, 67.04, 67.15, 68.05 (C_5H_4), 91.11 (C_{ipsoFc}), 115.46, 121.38, 121.76, 124.78, 128.65, 130.27, 131.34, 136.94 (2 C6H4), 147.66, 152.69, 154.55, 156.08, 172.44, 178.08 (6 C), 181.45 (C=O) ppm. MS (EI, 70 eV): m/z 449 $[M]^+$. Anal calcd. for $C_{26}H_{19}FeNOS$: C, 69.51; H, 4.26; N, 3.12; S, 7.12; Found: C, 69.04; H, 4.95; N, 3.54; S, 7.15.

2-(*p*-Methoxyphenyl)benzothiazole (3b): Yellow crystals: Yield 0.13 g (11%); mp 120˚C - 122˚C (lit. [18] mp 120˚C). ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 3.86 (s, 3 H, CH_3), 6.97 (d, 2 H, J = 9.0 Hz, *p*-C_6H_4), 7.34 (t, J = 7.5 Hz, 1 H, *o*-C_6H_4), 7.46 (t, 1 H, J = 8.1 Hz, *o*-C_6H_4), 7.85 (d, 1 H, J = 7.5 Hz, *o*-C_6H_4), 8.01 (d, 1 H, J = 8.1 Hz, *o*-C_6H_4), 8.03 (d, 2 H, J = 9.0 Hz, *p*-C_6H_4) ppm. MS (EI, 70 eV): m/z 241 $[M]^+$. Anal calcd for $C_{14}H_{11}NOS$: C, 69.70; H, 4.60; N, 5.80; S, 13.26; Found: C, 69.58; H, 4.81; N, 5.63; S 13.04.

Indano[2,3b]-2-[(*p*-methoxyphenyl)methyl][1,4]benzothiazine (4b): Yellow crystals: Yield 0.40 g (43%); mp 109˚C - 110˚C, IR (KBr): ν = 467, 481, 511, 729, 762, 812, 887, 999, 1042, 1104, 1163, 1216, 1250, 1344, 1441, 1450, 1552, 1599, 1629, 1718, 2944, 3052, 3081 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$,TMS): δ = 2.96 (d, 1 H, J = 13.5 Hz, CH_2), 3.13 (d, 1 H, J = 13.5 Hz, CH_2), 3.62 (s, 3 H, CH_3), 6.53 (d, 2 H, J = 8.7 Hz, *p*-C_6H_4), 6.75 (d, 2 H, J = 8.7 Hz, *p*-C_6H_4), 7.21 (t, J = 7.5 Hz, 1 H, *o*-C_6H_4), 7.35 (t, 1 H, J = 8.1 Hz, *o*-C_6H_4), 7.44 (d, 1 H, J = 7.5 Hz, *o*-C_6H_4), 7.53 (d, 1 H, J = 8.1 Hz, *o*-C_6H_4), 7.66 (t, 1 H, J = 7.5 Hz, *o*-C_6H_4),7.69 (t, 1 H, J = 7.5 Hz, *o*-C_6H_4), 7.72 (d, 1 H, J = 7.8 Hz, *o*-C_6H_4), 8.01 (d, 1 H, J = 7.8 Hz, *o*-C_6H_4) ppm. ^{13}C NMR (75 MHz, $CDCl_3$,TMS): δ = 39.43 (CH_2), 55.11 (CH_3), 113.37, 130.66 (*p*-C_6H_4), 123.28, 123.49, 127.05, 127.26, 128.05, 129.14, 132.77, 136.08 (2 *o*-C_6H_4), 49.52, 122,75, 125.91, 138.21, 143.09, 145.20, 158.54, 159.87 (8 C), 199.38 (C=O) ppm. MS (EI, 70 eV): m/z 372 $[M]^+$. Anal calcd for $C_{23}H_{17}NO_2S$: C, 74.38; H, 4.62; N, 3.77; S, 8.62; Found: C, 74.21; H, 4.74; N, 3.56; S, 8.93.

2-Indeno[2,3b]-2-(*p*-methoxyphenyl)[1,5]benzo-2,5-dihydrothiazepine (5b): Orange crystals: Yield 0.30 g (32%); mp 126˚C - 127˚C, IR (KBr): ν = 481, 496, 622, 760, 892, 980, 1078, 1105, 1179, 1212, 1224, 1357, 1454, 1478, 1538, 1577, 1593, 1619, 1680, 1701, 3055, 3186, 3361 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 4.55 (s, 3H, CH_3), 6.05 (s, 1H, CH), 6.97 (d, 2 H, J = 9.0 Hz, *p*-C_6H_4), 8.02 (d, 2 H, J = 9.0 Hz, *p*-C_6H_4), 6.59 (td, 1 H, J = 1.5, 7.5 Hz, *o*-C_6H_4), 6.69 (dd, 1 H, J = 1.2, 7.5 Hz, *o*-C_6H_4), 7.13 (m, 3 H, *o*-C_6H_4), 7.36 (td, 1 H, J = 1.2, 7.8 Hz, *o*-C_6H_4), 7.46 (td, 1 H, J = 1.5, 7.5 Hz, C_6H_4), 7.82 (bs, 1 H, NH),7.84 (dd, 1 H, J = 1.2, 7.8 Hz, *o*-C_6H_4) ppm. ^{13}C NMR (75 MHz, $CDCl_3$,TMS): δ = 53,12 (CH), 58.24 (CH_3), 119.72, 136.44 (*p*-C_6H_4), 122.76, 123.82, 128.02, 128.76, 131.87, 133.04, 135.16, 137.52 (2 *o*-C_6H_4), 122,98, 124.06, 136.23, 138.91, 141.21, 144.63, 148.36, 155.17 (8 C), 197.34 (C=O) ppm. MS (EI, 70 eV): m/z 371 $[M]^+$. Anal calcd for $C_{23}H_{17}NO_2S$: C, 74.38; H, 4.62; N, 3.77; S, 8.62. Found: C, 74.56; H, 4.43; N, 3.89; S, 8.54.

Indano[2,1-b:2,3-b]*bis*[[1,4]benzothiazine (6): Yellow crystals: Yield 0.32 g

(10%); mp 200˚C - 201˚C (lit.[19]mp 201˚C - 203˚C). IR (KBr): ν = 635, 738, 755, 985, 1174, 1218, 1246, 1269, 1329, 1351, 1460, 1562, 1606, 1667, 1682, 3064, 3111 cm^{-1}. 1H NMR (300 MHz, $CDCl_3$, TMS): δ = 7.35 - 8.10 (m, 12 H,3 *o*-C_6H_4).^{13}C NMR (75 MHz, $CDCl_3$,TMS): δ =56.21 (C_{spiro}), 124.25, 124.49, 127.08, 127.26, 129.85, 130.16 (3 *o*-C_6H_4), 125,98, 128.84, 134.29 (6 C), 157.86 (2 C=N) ppm. MS (EI, 70 eV): m/z 356 $[M]^+$. Anal calcd for $C_{21}H_{12}N_2S_2$: C, 70.76; H, 3.39; N, 7.86; S, 17.99; Found: C, 69.40; H, 4.10; N, 8.20; S, 18.30.

Reaction of 1,3-indandione with 2-aminothiophenol 2. This was carried out analogously using of 1,3-indandione (5 mmol), 2-aminothiophenol (12 mmol), methanol (70 mL), AcOH (1.0 mL), HCl conc. (0.2 mL) and Et_3N (0.2 mL).The reaction mixture was performed as described above, the precipitate was filtered off and dried on a filter to give 0.85 g of a yellowish product, subsequent chromatography on Al_2O_3 (hexane-dichloromethane, 1:4) gave 2,2-*bis*-(2-aminophenylthio)indan-1,3-dione **8**. The filtrate was concentrated, and the residue was chromatographed on Al_2O_3 (hexane-dichloromethane, 2:1) to give indeno [2,1-b:2,3-b]*bis*[[1,4]benzothiazine **6**, yield 0.73 g (41%), m.p.201˚C; and 2,2-*bis*-(2-aminophenylthio)indan-1,3-dione **8**.

2,2-bis-(2-aminophenylthio)indan-1,3-dione (8): Yellow crystals: Yield 0.67 g (34%), mp 178˚C - 179˚C, IR (KBr): ν = 675, 742, 761, 898, 943, 1181, 1234, 1252, 1271, 1317, 1363, 1458, 1581, 1609, 1667, 1682, 3386, 3419 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 4.14 (s, 4 H, 2 NH_2), 7.71-8.02 (m, 10 H, 2*o*-C_6H_4 + *o*-C_6H_2), 9.66 (d, 2 H, J = 8.1 Hz, *o*-C_6H_2).MS (EI, 70 eV): m/z 392 $[M]^+$. Anal calcd. for $C_{21}H_{16}N_2O_2S_2$: C, 64.28; H, 4.11; N, 7.14; S, 16.31. Found: C, 64.45; H, 4.03; N, 7.29; S, 16.17.

2.2. X-Ray Analysis

Crystals of **4a** and **5a** were obtained by crystallization from dichloromethane; crystals of **6** were obtained by crystallization from chloroform. Data were obtained on an Oxford Diffraction Gemini Adiffractometer with a CCD area detector, and the CrystAlisPro and CrysAlis RED software packages were used for data collection and data integration [20]. The structures were solved using SHELXS-97 [21] and refined by full-matrix least-squares on F^2 with SHELXL-97. [22] Weighted R factors, Rw, and all goodness-of-fit indicators, S, were based F2. The observed criterion of ($F^2 > 2\sigma F^2$) was used only for calculating the R factors. All non-hydrogen atoms were refined with anisotropic thermal parameters in the final cycles of refinement. Hydrogen atoms were placed in ideal positions, with C-H distances of 0.93 and 0.98Å for aromatic and satured carbon atoms, respectively. The isotropic thermal parameters of the hydrogen atoms were assigned the values of Uiso = 1.2 times the thermal parameters of the parent non-hydrogen atom.

Crystal data for $C_{26}H_{19}FeNOS$ (4a): M = 449.33 gmol-1, monoclinic P21/n, a = 7.5018(2), b = 13.2011(5), c = 20.1153(7) Å, $\alpha = 90^\circ$, $\beta = 93.922(3)$, $\gamma = 90^\circ$, V = 1987.39(12) $Å^3$, T = 130(2) K, Z = 4, $\rho = 1.502$ Mg/m^3, wavelength 0.71073 Å, F(000) = 928, absorption coefficient 0.883 mm-1, index ranges $-8 \le h \le 10$, -13

≤ k ≤ 18, −25≤ l ≤ 25, scan range 3.414˚ ≤ θ ≤ 29.589˚, 4695 independent reflections, Rint = 0.0273, 10332 total reflections, 271 refinable parameters, final R indices [I > 2σ(I)] R_1 = 0.0331, wR_2 = 0.0710, R indices (all data) R_1 = 0.0468, wR_2 = 0.0766, goodness-of-fit on F_2 1.014, largest difference peak and hole 0.353/−0.300 eÅ^{-3}.

Crystal data for $C_{26}H_{19}FeNOS{\cdot}CH_2Cl_2$ (5a): M = 534.26 g·mol^{-1}, monoclinic P 21/n, a = 11.3274(9), b = 17. 8011(11), c = 11.9213(9) Å, α = 90, β = 109.584 (9), γ = 90˚, V = 2264.8(3) Å^3, T = 130(2) K, Z = 4, ρ = 1.567 Mg/m^3, wavelength 0.71073 Å, F(000) = 1096, absorption coefficient 1.016 mm-1, index ranges −15 ≤ h ≤ 9, −16 ≤ k ≤ 24, −16 ≤ l ≤ 16, scan range 3.628˚ ≤ θ ≤ 29.514˚, 5308 independent reflections, Rint = 0.0499, 10868 total reflections, 301 refinable parameters, final R indices [I>2σ(I)] R_1 = 0.0565, wR_2 = 0.1406, R indices (all data) R_1 = 0.0733, wR_2= 0.1597, goodness-of-fit on F_2 1.052, largest difference peak and hole 1.401/−1.182 eÅ^{-3}.

Crystal data for $C_{21}H_{12}N_2S_2$ (6): M = 356.45 g·mol^{-1}, monoclinic C2/c, a = 22.1186(19), b = 9.4445(6), c = 16.5628(12) Å, α = 92.750(9), β = 109.546(9), γ = 90˚, V = 3260.6(5) Å^3, T = 130(2) K, Z = 8, ρ = 1.452 Mg/m^3, wavelength 0.71073 Å, F(000) = 1472, absorption coefficient 0.332 mm^{-1}, index ranges −30 ≤ h ≤ 20, −12 ≤ k ≤ 12, −22 ≤ l ≤ 21, scan range 3.521 ≤ θ ≤ 29.469o, 3841 independent reflections, Rint = 0.0334, 7716 total reflections, 226 refinable parameters, final R indices [I > 2σ(I)] R1= 0.0407, wR_2 =0.0820, R indices (all data) R_1 = 0.0668, wR_2 = 0.0895, goodness-of-fit on F_2 1.012, largest difference peak and hole 0.298/−0.284 eÅ^{-3}.

2.3. Cytotoxicity Assay

The compounds were screened in vitro against human cancer cell lines HCT-15 (human colorectal adenocarcinoma), MCF-7 (human mammary adenocarcinoma), K562 (human chronic myelogenous leukemia), U251 (human glioblastoma), PC-3 (human prostatic adenocarcinoma), SKLU-1 (human lung adenocarcinoma). The cell lines were supplied by the National Cancer Institute (USA). The human tumor cytotoxicity was determined using the protein-binding dye sulforhodamine B (SRB) in the microculture assay to measure the cell growth, as is described in the protocols established by the NCI [23] [24]. The cell lines were cultured in the RPMI-1640 medium supplemented with 10% fetal bovine serum, 2 mM L-glutamine, 10,000 units/ml penicillin G sodium, 10 μg/ml streptomycin sulfate, 25 μg/ml amphotericin B (Gibco) and 1% non-essential amino acids (Gibco). The cultures were maintained at 37˚C in a humidified 5% CO_2 atmosphere. As determined using trypan blue, the viability of the cells used in the experiments exceeded 95%.

The cells were removed from the tissue culture flasks by treatment with trypsin and diluted with fresh media. 100-ml cell suspension aliquots, containing 5000 - 10,000 cells per well, were transferred into 96-well microtiter plates (Costar) and incubated at 37˚C for 24 h in a 5% CO_2 atmosphere.

Stock solutions of the test compounds initially dissolved in DMSO (20 mM)

were prepared and further diluted in the medium to produce the desired concentrations. 100-ml aliquots of the diluted solutions of the test compounds were added to each well. The cultures were exposed to the compound at concentrations 50 μM for 48 h. After the incubation period, the cells were fixed to a plastic substratum by the addition of 50 μl of cold 50% aqueous trichloroacetic acid. The plates were incubated at 4˚C for 1 h, washed with tap H_2O, and air-dried. The cells fixed with trichloroacetic acid were stained by the addition of 0.4% SRB. Free SRB solution was removed by washing with 1% aqueous acetic acid. The plates were air-dried, and the bound dye was solubilized by the addition of 100 μL of 10 Mm un buffered Tris base. The plates were placed on a shaker for 5 min prior to analysis. The optical densities were determined using a Ultra Microplated Reader (Elx 808: Bio-Tek Instruments, Inc., Winooski, VT, USA) at a test wavelength of 515 nm.

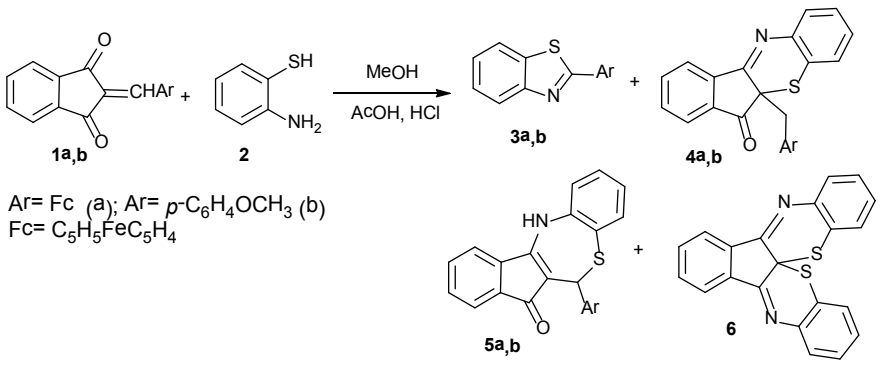
3. Results and Discussion

3.1. Chemistry

The starting compounds **1a,b** were prepared by condensation of the respective ferrocenyl- and anisylcarbaldehydes with 1,3-indandione under standard conditions [25] [26] [27]. It was found that *o*-aminothiophenol **2** reacted with chalcones **1a,b** on refluxing condition in methanol in the presence of acetic and hydrochloric acids to give indeno[2,3b]-2-ferrocenylmethyl- and indano[2,3b]-2-anisylmethyl[1,4]benzo-2,3-dihydrothiazines **4a,b** (~43% - 45%), and 2-inde-no [2,3b]-2-ferroceny-and 2-*p*-anisyl[1,5]benzo-2,5-dihydrothiazepines **5a,b** (~30% - 32%), respectively. (Scheme 1)

In all cases, the reactions were accompanied by fragmentation [28] of the starting compounds **1a,b** to form 2-ferrocenyl- and 2-anisylbenzothiazoles **3a,b** (~8% - 11%) [20] [21] respectively, and indano[2,1-b:2,3-b] *bis*[[1,4]-benzothiazine**6** (~10%) [19].

The structures of compounds **3a, b**, **4a, b**, **5a,b** and **6** were isolated by column chromatography on alumina and established based on the data from IR and NMR spectroscopy, mass spectrometry and elemental analysis (see Experimental part). The ^{1}H NMR spectrum of ferrocenyl-1,4-thiazine **4a** contains two characteristic doublets for two protons of the methylene group (δ 2.81, 3.00, *J* =



Scheme 1. Reactions of 2-arylmethylidenindan-1,3-dione with o-aminothiophenol.

13.8 Hz), one singlet for the protons of unsubstituted C_5H_5 ring of ferrocene, and multiplets for protons of two *o*-C_6H_4 groups. The presence in the ^{13}C NMR spectrum of compound **4a** of one signal for one methylene group (δ 42.25), one ferrocenyl fragment [δ 68.51 (C_5H_5)], one C_{ipsoFc} carbon atom (δ 80.21), one C=O group (δ 195.50), one C=N fragment (δ 160.19), and six quaternary carbon atoms (δ 62.12, 122.52, 129.64, 132.58, 142.93, 145.31) corroborates completely the suggested structure. The spectroscopic data (^1H and ^{13}C NMR) suggest that compound **4b** represent also structure of anisyl-1,4-benzothiazine.

The spatial structure of **4a** was elucidated by X-ray diffraction analysis of a single crystal obtained by crystallization from dichloromethane. The general view of the molecule **4a** is shown in Figure 1 and the main geometrical parameters are given in Table 1. Data from X-ray analysis proved the structure of **4a** as indano[2,3b]-2-ferrocenylmethyl[1,4]benzothiazines.

Table 1. Selected bond lengths and bond angles for compounds **4a**, **5a** and **6**.

Selected bond lengths (Å)		Selected bond angles (˚)	
	4a		
O(1)-C(13)	1.214(2)	N(1)-C(20)-C(12)	126.73(16)
S(1)-C(26)	1.768(18)	C(20)-N(1)-C(21)	118.65(15)
N(2)-C(21)	1.413(2)	C(26)-S(1)-C(12)	97.12(8)
N(1)-C(20)	1.278(2)	C(11)-C(12)-S(1)	112.64(12)
S(1)-C(12)	1.810(18)	C(13)-C(2)-S(1)	109.82(12)
C(12)-C(13)	1.537(2)	C(20)-C(12)-S(1)	106.92(12)
C(11)-C(12)	1.5402)	C(13)-C(12)-C(11)	110.44(14)
	5a		
N(1)-C(20)	1.349(4)	C(12)-C(11)-S(1)	109.1(2)
C(21)-N(1)	1.414(4)	O(1)-C(13)-C(12)	127.4(3)
S(1)-C(11)	1.856(3)	N(1)-C(20)-C(12)	131.4(3)
C(12)-C(20)	1.377(4)	C261)-S(1)-C(11)	101.13(13)
C(11)-C(12)	1.441(4)	C(20)-N1)-C(21)	133.5(2)
O(1)-C(13)	1.235 (4)	C(20)-C(12)-C(11)	127.2(3)
C(26)-S(1)	1.768(3)	N(1)-C(20)-C(19)	119.0(3)
	6		
S(1)-C(1)	1.819(19)	C(11)-N(1)-C(10)	118.39(15)
C(1)-S(2)	1.819(18)	C(2)-N(2)-C(22)	118.05(16)
N(2)-C(2)	1.279(2)	C(16)-S(1)-C(1)	95.13(9)
C(2)-C(3)	1.474(2)	C(17)-S(2)-C(1)	95.57(8)
N(1)-C(10)	1.277(2)	C(2)-C(1)-C(10)	103.92(14)
N(1)-C(11)	1.400(2)	S(2)-C(1)-C(2)	105.3(12)
C(1)-C(2)	1.523(3)	S(1)-C(1)-C(2)	116.01(13)
C(1)-C(10)	1.527(2)	N(2)-C(2)-C(1)	126.97(15)
C(10)-C(9)	1.459(3)	S(2)-C(1)-S(1)	113.32 (9)
C(22)-N(2)	1.408(2)	N(2)-C(2)-C(3)	124.69(18)

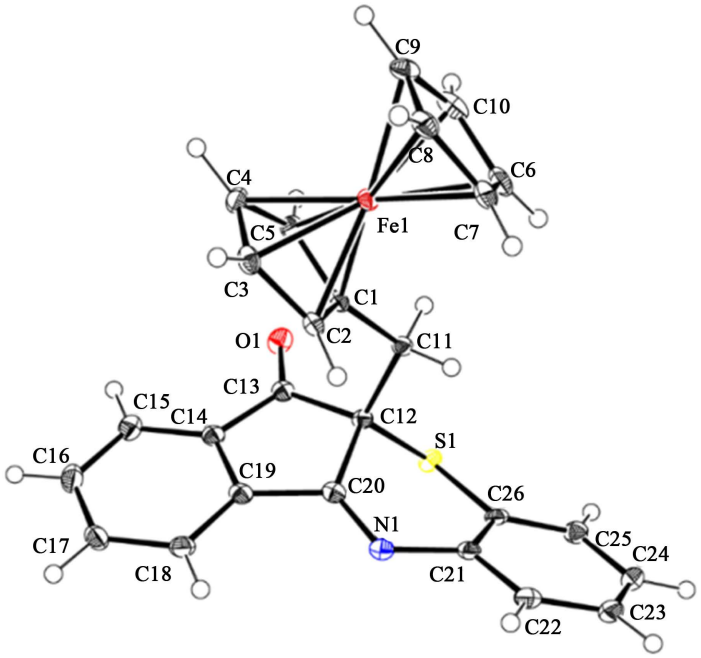


Figure 1. X-ray crystal structure of **4a**.

The ^{1}H NMR spectrum of **5a** contains characteristic signals for one proton of the CH group in δ 5.41ppm, one proton of the NH group in δ 4.26 ppm, one singlet for the protons of the unsubstituted C_5H_5 ring of one ferrocene δ 4.16 ppm and multiplets for the eight protons of two *o*-C_6H_4 groups. The data from ^{13}C NMR spectroscopy of this compound are in full accord with the proposed structure. And X-ray diffraction analysis was performed on a single crystal grown by crystallization from dichloromethane. The general view of the molecule **5a** is shown in Figure 2 and the main geometrical parameters are given in Table 1. Data from the X-ray analysis demonstrated that **5a** is 2-indeno [2,3b]-2-ferrocenyl[1,5]benzo-2,5-dihydrothiazepine.

The structures of 2-ferrocenyl- and 2-p-anisylbenzothiazoles **3a,b** and indano[2,1-b:2,3-b]*bis*[[1,4] benzothiazine**6** were also confirmed by ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, and data from literature [17] [18] [19]. These facts confirm the assumed structures.

The spatial structure of single crystals of indano[2,1-b:2,3-b]*bis*[1,4] benzothiazine **6** prepared by crystallization from chloroform was determined by X-ray diffraction analysis (Figure 3). The principal geometric parameters of this molecule with a "three-petal" system of fused two six- and one five-membered rings and a quaternary carbon atom C(1) are listed in Table 1. The bond lengths C(1)-S(1) (1.8196Å), and C(1)-S(2) (1.8191 Å) are somewhat larger, and the N(1)-C(1)(1.277Å) and N(2)-C(1) (1.279 Å) bond lengths are somewhat shorter than the standard values [24].

The results of this study indicate cyclocondensation reactions of 2-arylmethylidenindan-1,3-dione **1a,b** with *o*-aminothiophenol**2** and breakage of the Cα=Cβ multiple bond [28] in the initial **1a,b** compounds subjected to the action of 1,4-bis-nucleophile **2**. In this regard, these interactions can be viewed as a step

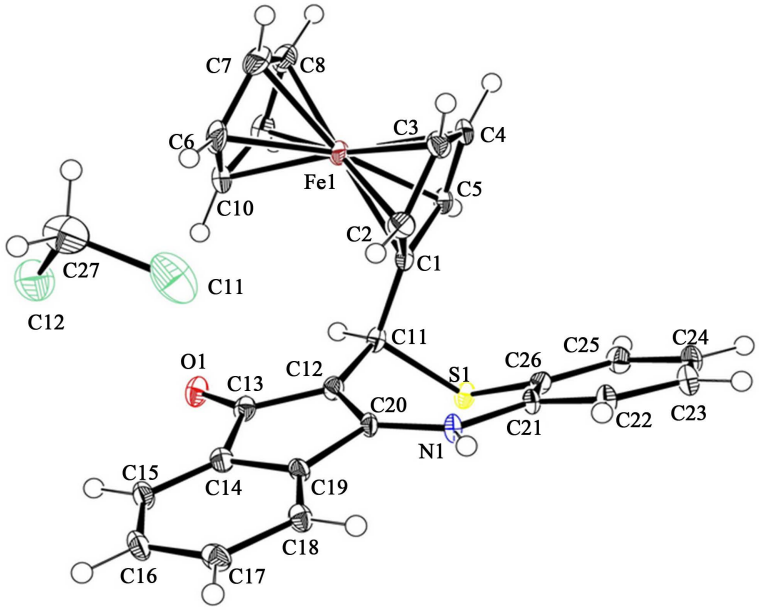


Figure 2. X-ray crystal structure of **5a**.

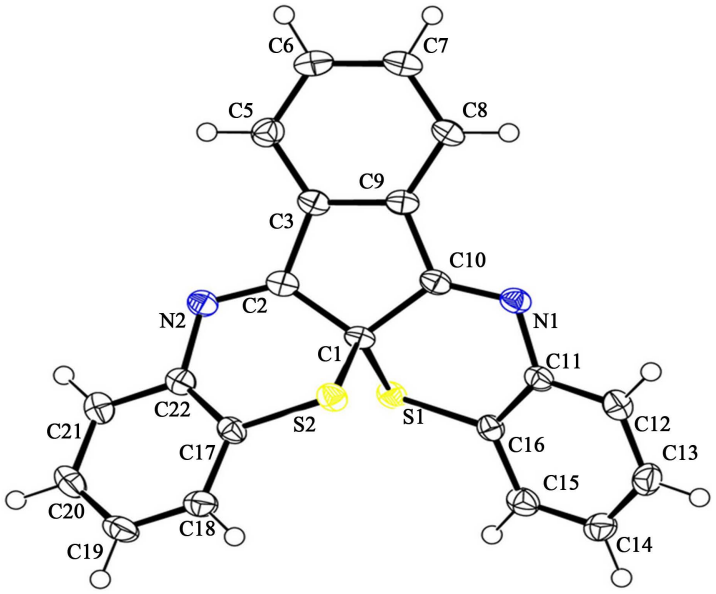
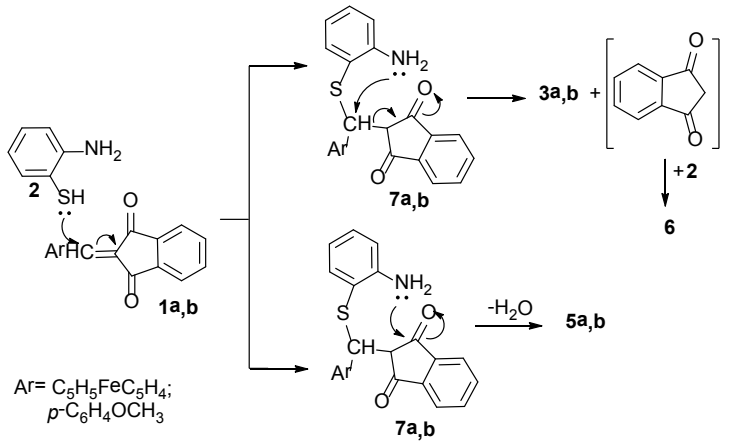


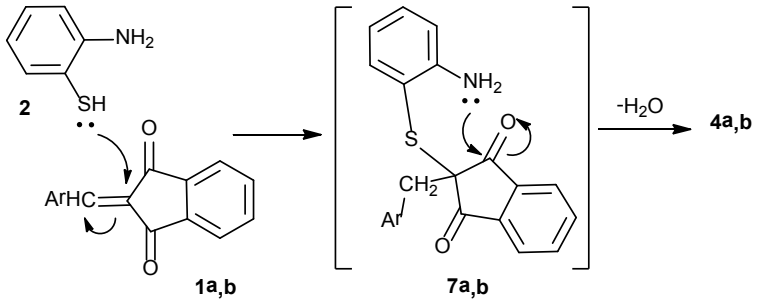
Figure 3. X-ray crystal structure of **6**.

wise process consisting of several stages: 1) Michael addition of the molecule of a *o*-aminophenol **2** to substrates **1a,b** gave intermediates **7a,b**; 2) Intramolecular cyclization of **7a,b** into tetracyclic thiazepines **5a,b**; 3) Breaking of the σ-Cα- Cβ bond in the addition intermediates **7a,b** (Scheme 2); 4) "Anti- Michael" addition of *o*-aminophenol **2** to substrates **1a,b** gave intermediates **7a,b**; 5) Intramolecular cyclization of **7a,b** into tetracyclic thiazines **4a,b** (Scheme 3).

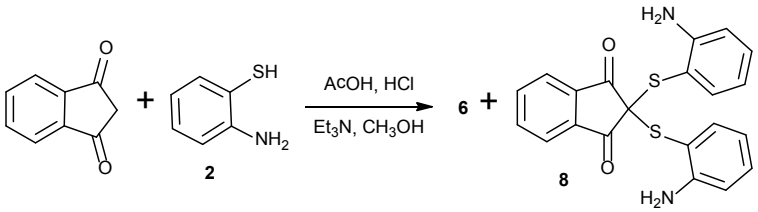
To confirm the latter statement, we performed a specially aimed synthesis of compound **6**, using indan-1,3-dione and *o*-aminothiophenol **2** as the initial substrates (Scheme 4). The products **6** and **8** were obtained in yields ~41% and 34%, respectively.



Scheme 2. The mechanism proposed for the process leading to indano[2,3b]-2-ferrocenylmethyl[1,4]benzothiazines and 2-indeno[2,3*b*]-2-ferrocenyl[1,5]benzo-2,5-dihydrothiazepines.



Scheme 3. Formation of the compounds **4a,b**.



Scheme 4. Reaction of 1,3-indandione with 2-aminothiophenol **2**.

3.2. Cytotoxicity of the Benzothiazepines

In this study, cytotoxicity assays of the four benzothiazepine compounds **4a,b** and **5a,b** (Figure 4) were performed as described in the Experimental Section by using different cancer cell lines, including human glioblastoma (CNS U251), human prostatic adenocarcinoma (PC-3), human chronic myelogenous leukemia (K562), human colorectal adenocarcinoma (HCT-15), human mammary adenocarcinoma (MCF-7), and small cell lung cancer (SKLU) and the protein-binding dye sulforhodamine B (SRB) assay in microculture to determine cell growth [24]. The initial cytotoxic screening data listen in Table 2, show excellent activities specifically toward K-562, HCT-15, and SKLU-1 tumor cell lines. From those data, we observe good values of cell growth inhibition, **4b** being the most active compound (Table 2).

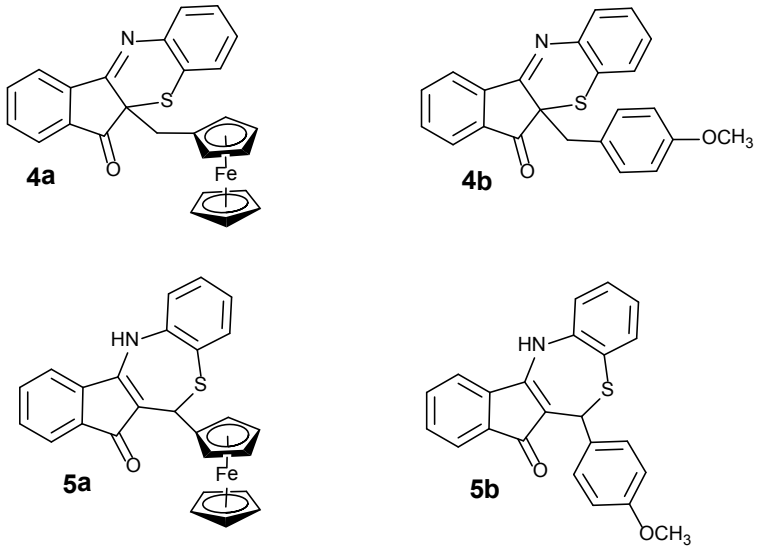


Figure 4. Variations in the structure of benzothiazepines.

Table 2. Inhibition of the Growth (%) of Human Tumor Cell Lines for **4a, b** and **5a, b** at 25 μM in DMSO[a].

Compd	% of growth inhibition in Cell lines					
	U-251	PC-3	K562	HCT-15	MCF-7	SKLU-1
4a	37.8 ± 2.4	36.0 ± 7.7	10.8 ± 0.1	30.9 ± 3.9	25.5 ± 3.2	37.2 ± 2.2
4b	77.8 ± 5.8	63.9 ± 7.0	>100	90.2 ± 4.9	68.9 ± 8.1	>100
5a	62.2 ± 6.7	78.3 ± 9.4	68.7 ± 2.5	61.4 ± 9.5	90.8 ± 6.7	71.3 ± 4.8
5b	48.6 ± 5.1	52.7 ± 5.4	8**co**2.0 ± 9.9	66.6 ± 6.9	68.4 ± 7.4	62.9 ± 3.1
Cisplatin	89.9 ± 8.1	86.7 ± 4.1	74.4 ± 2.1	81.8 ± 7.1	77.9 ± 2.5	95.8 ± 2.1

[a]Results express mean ± standard error (SEM) obtainedfrom 3 independentexperimentsperformedat 48 h.

The results of the cytotoxic screening demonstrate that the presence of the substituent ferrocene for compounds **4a,5a** and anisole compounds **4b**,**5b**, have the influence in the cytotoxic activity disappears, obtaining good activity for (K-562, HCT-15 and SKLU-1) tumor cell lines.

4. Conclusion

Reactions of 2-ferrocenyl- and 2-(*p*-methoxyphenyl) methylidenindandiones with 2-aminothiophenol in a MeOH medium in the presence of AcOH/HCl gave novel indano[2,3b]-2-ferrocenyl-and 2-[(p-methoxyphenyl)methyl][1,4] benzo-thiazines **4a,b** (products of "Anti-Michael"-addition/cyclization) and 2-indeno [2,3b]-2-ferrocenyl-and 2-(*p*-methoxyphenyl)[1,5]benzo-2,5-dihydrothiaze-pines **5a,b** respectively (products of Michael-addition/cyclization). These new compounds were obtained in ~30% - 45% yields. The reactions take place only via breakage of the ArCα = Cβ double bond with the formation of derivatives of arylcarbaldehydes(2-ferrocenyl- and 2-p-methoxyphenylbenzothiazoles **3a,b**), as well as indandione (indano [2,1-b:2,3-b]*bis*[1,4]benzothiazine **6**). The obtained

compounds were structurally characterized by elemental analysis, IR, ^{1}H and ^{13}C NMR spectroscopy, mass-spectrometry, and single crystal X-ray diffraction analysis. The synthesized compounds **4a,b** and **5a,b** were evaluated for their *in vitro* anticancer activities against six human tumor cell lines: U-251, PC-3, K-562, HCT-15, MCF-7, SKLU-1. The compound **4b** showed high activity against three tumoral cell lines (K-562, HCT-15 and SKLU-1).

Acknowledgements

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Supplementary Material

The crystallographic data for **4a**, **5a** and **6** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication under the CCDC numbers 1423550, 1423551 and 1423552. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge DB2 1EZ, UK; Fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

For general information, all experimental data and copies of the NMR spectra and UV/V are Spectra.

The 1H and 13C NMR spectra were recorded on a Unity Inova Varian spectrometer (300 and 75 MHz) for solutions in CDCl3 with Me4Si as the internal standard. The IR spectra were measured with an FTIR spectrophotometer (Spectrum RXI Perkin-Elmer instruments) using KBr pellets. The mass spectra were obtained on a Varian MAT CH-6 instrument (EI MS, 70 eV). Elementar Analysensysteme LECO CHNS-900 was used for elemental analyses.

Compound 3a "2-Ferrocenylbenzothiazole"

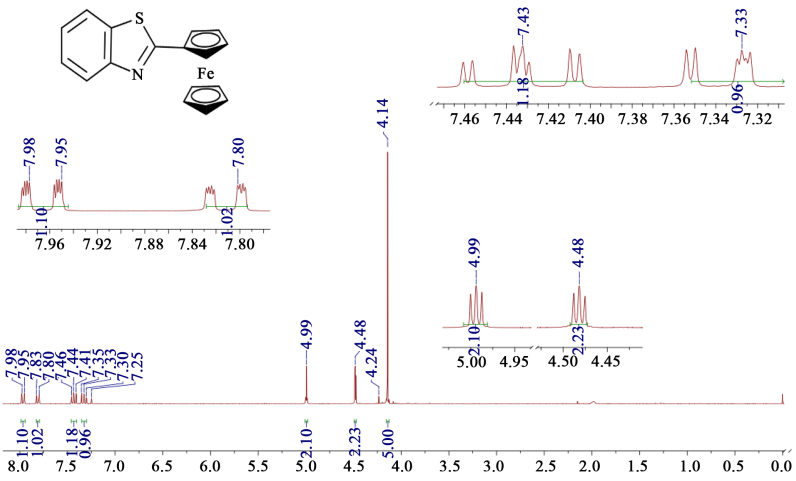


Figure S1. 1H NMR (300 MHz, CDCl3, TMS) spectrum of compound **3a**.

Compound 3b "2-(p-Methoxyphenyl)benzothiazole "

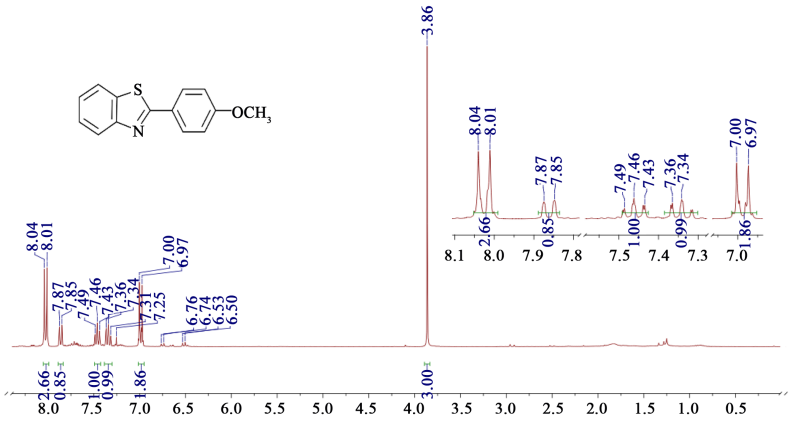


Figure S2. 1H NMR (300 MHz, CDCl3, TMS) spectrum of compound **3b**.

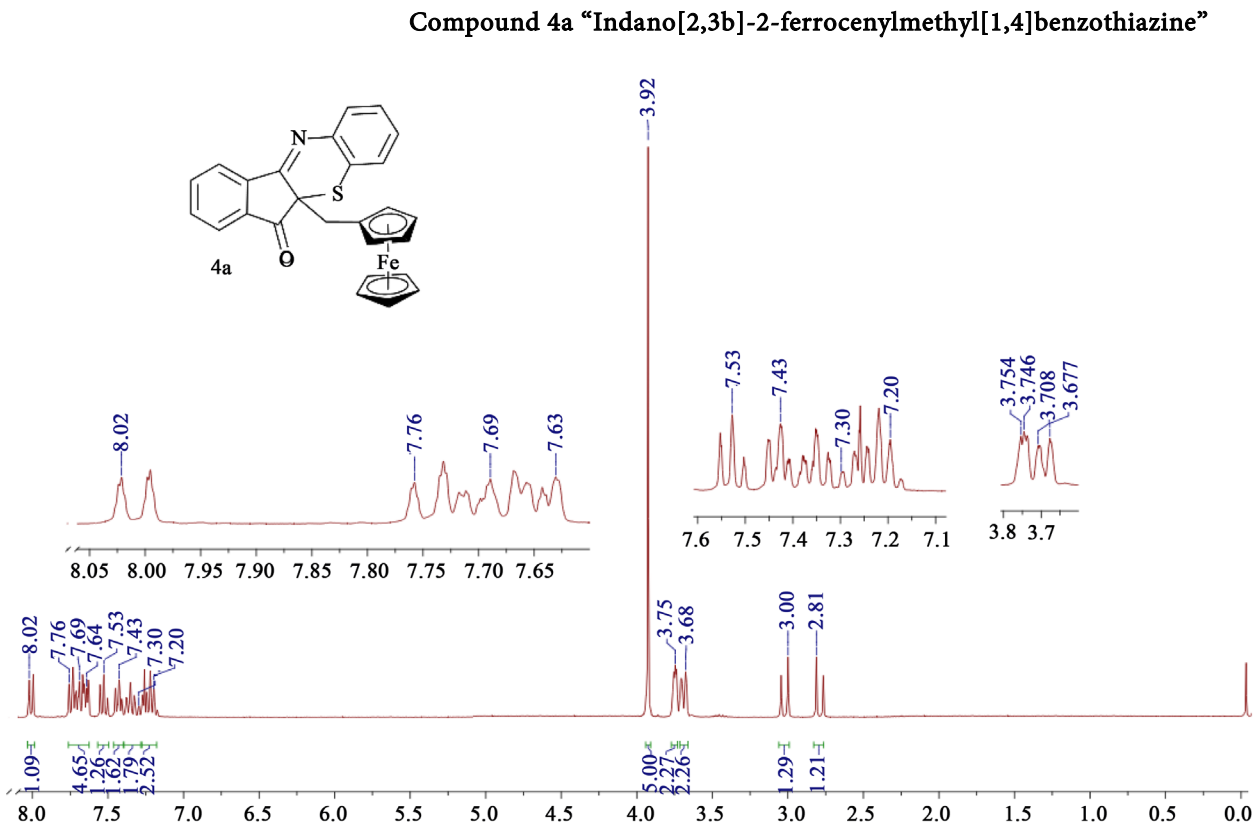


Figure S3. 1H NMR (300 MHz, CDCl3, TMS) spectrum of compound **4a**.

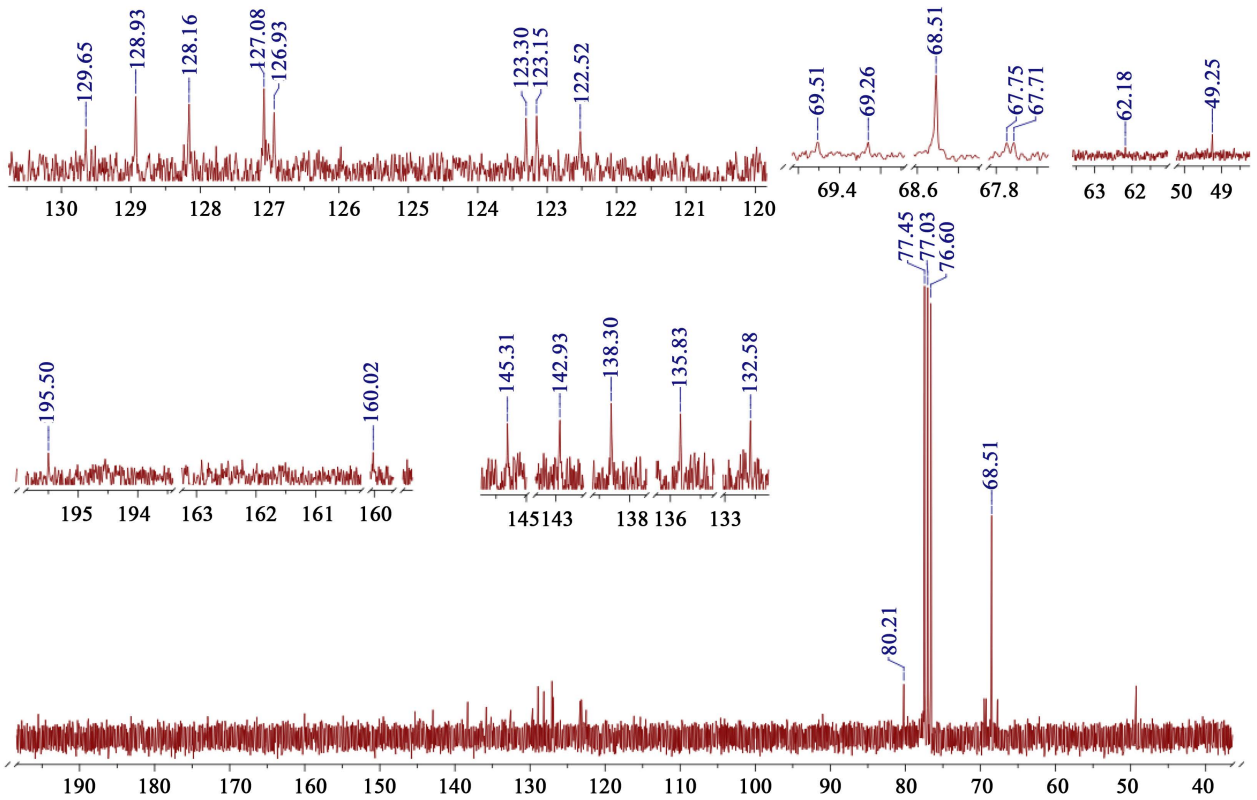


Figure S4. 13C NMR (75 MHz, CDCl3, TMS) spectrum of compound **4a**.

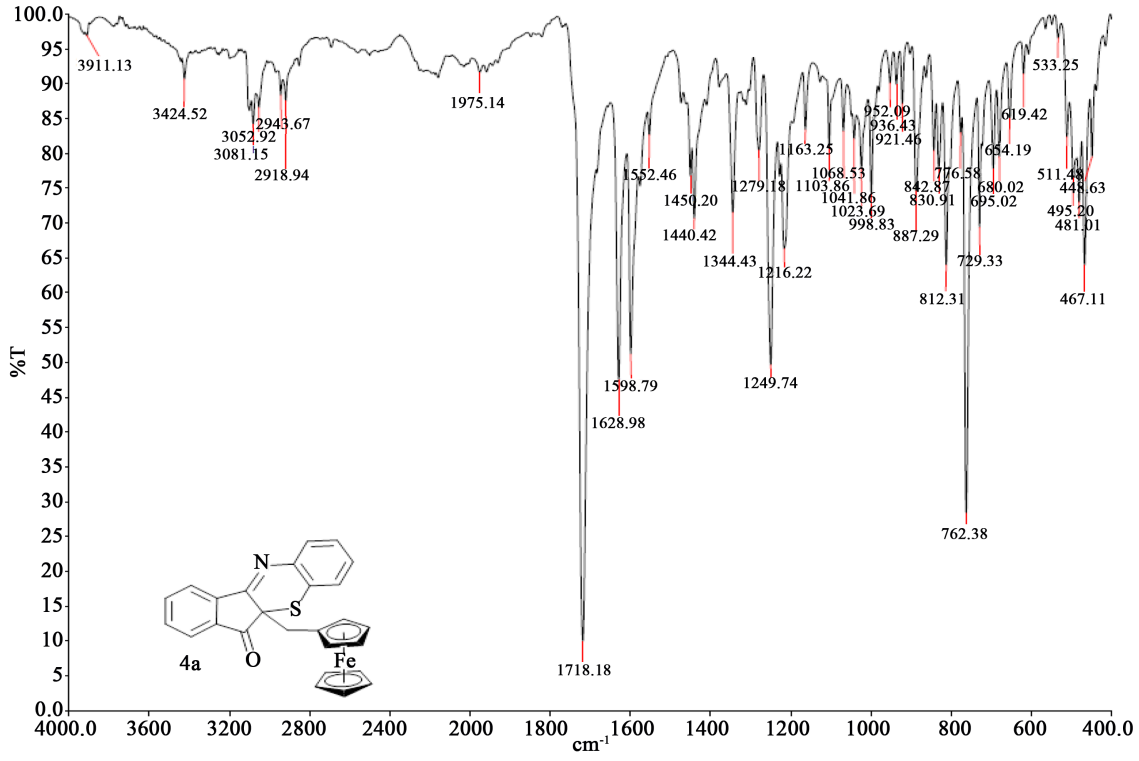


Figure S5. IR (KBr) spectrum of compound **4a**.

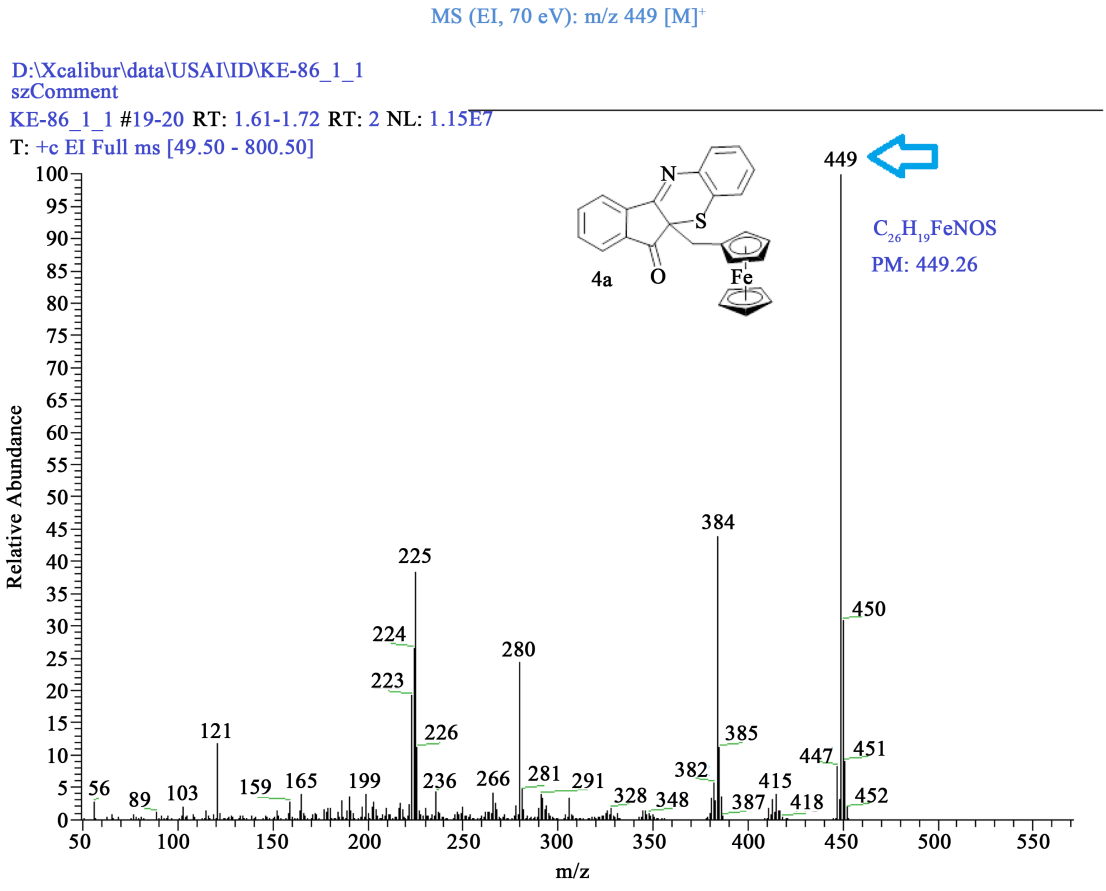


Figure S6. Mass Spectrometry spectrum of compound **4a**.

Compound 4b Indano[2,3b]-2-[(p-methoxyphenyl) methyl][1,4]benzo-thiazine

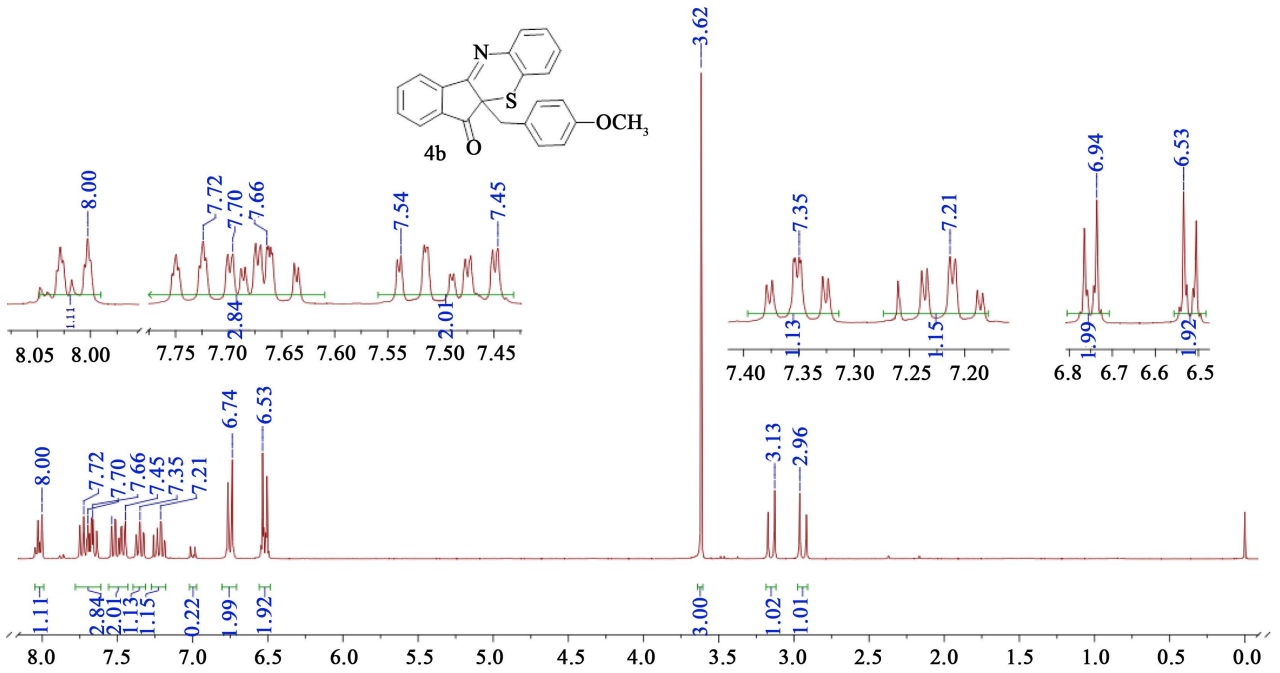


Figure S7. 1H NMR (300 MHz, CDCl3, TMS) spectrum of compound **4b**.

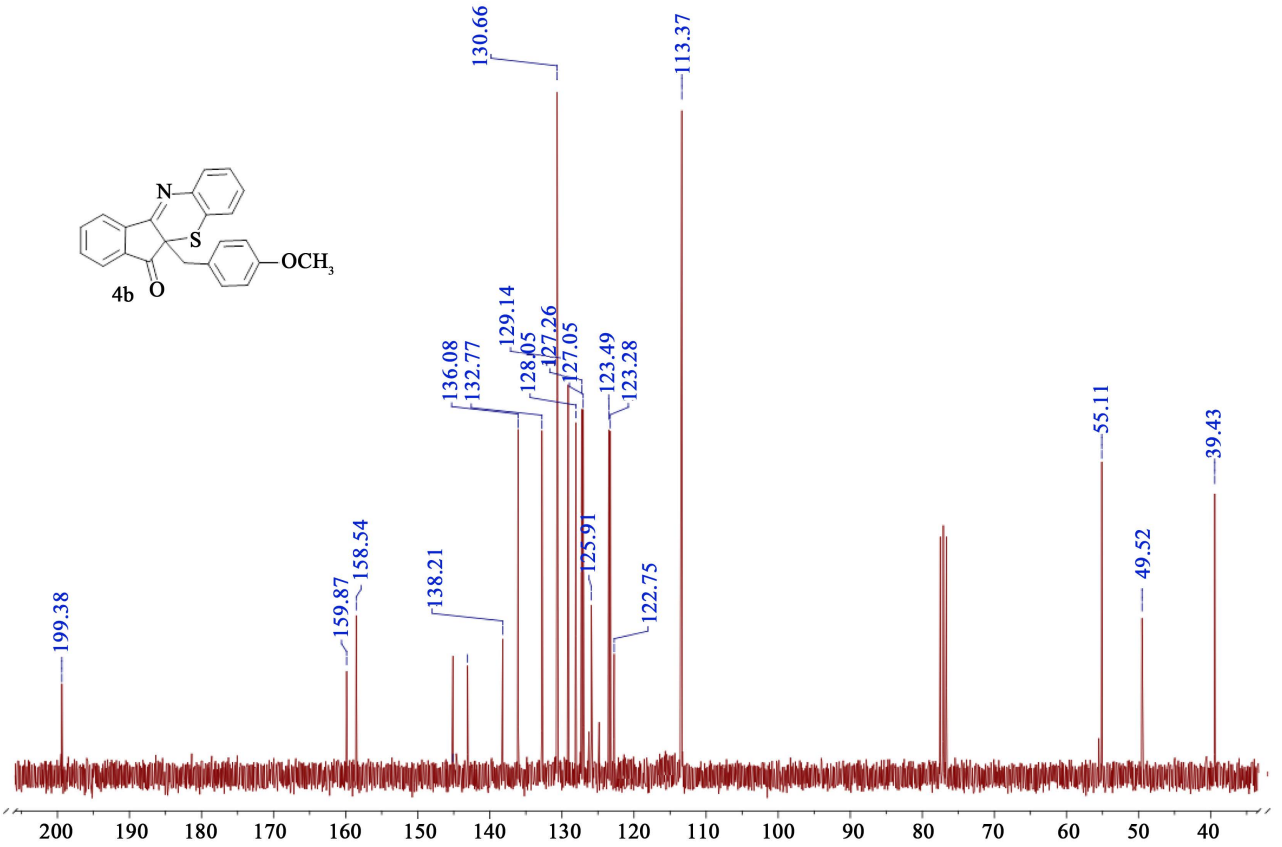


Figure S8. 13C NMR (75 MHz, CDCl3, TMS) spectrum of compound **4b**.

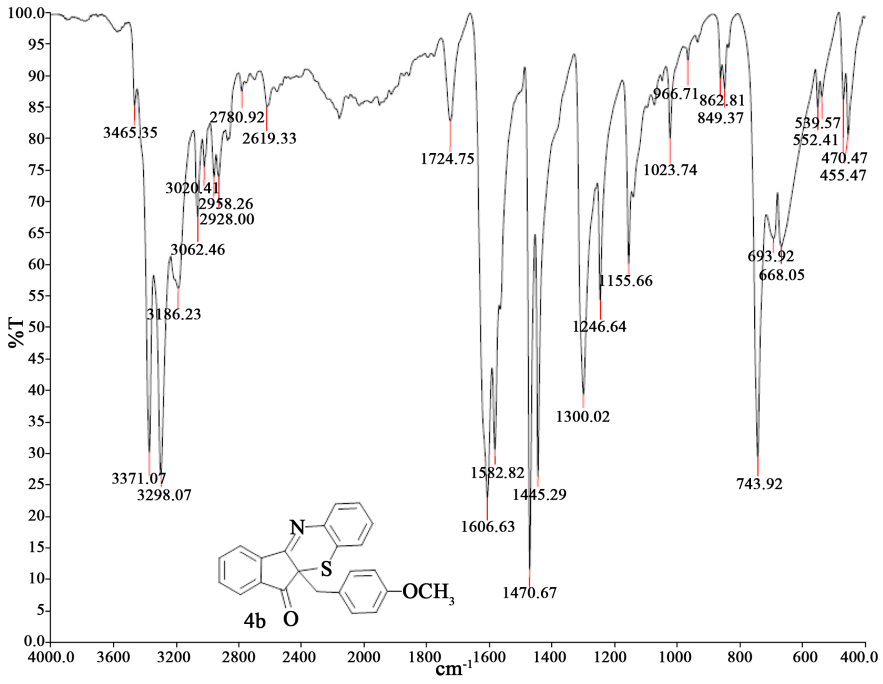


Figure S9. IR (KBr) spectrum of compound **4b**.

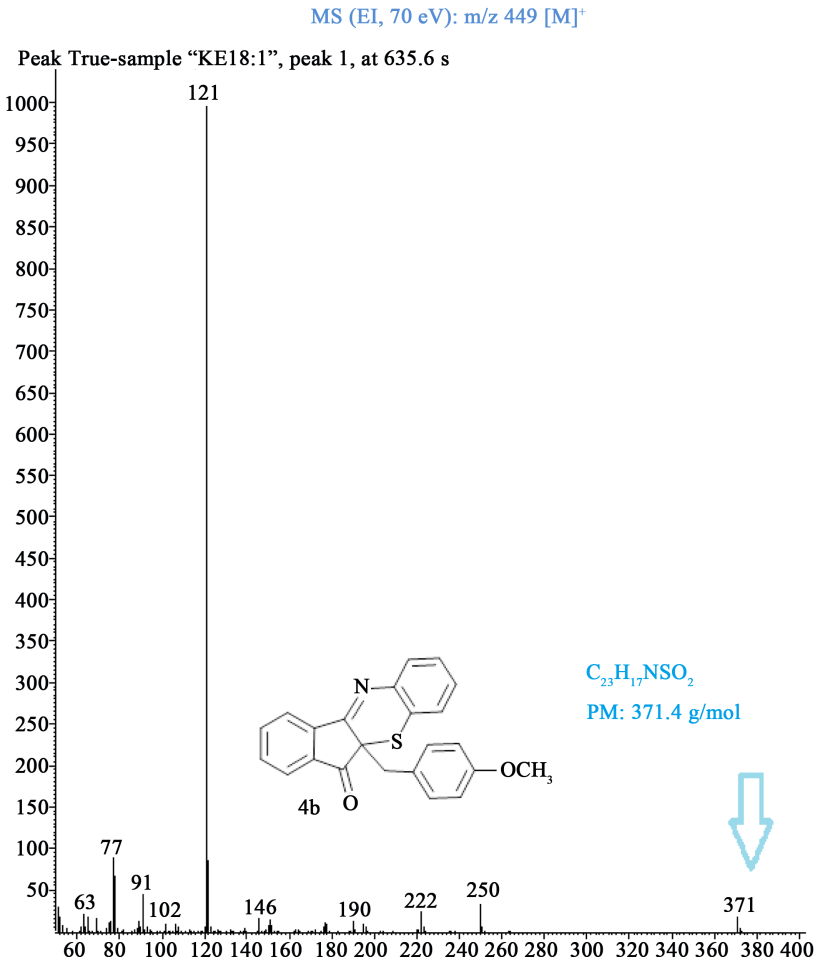


Figure S10. Mass Spectrometry spectrum of compound **4b**.

Compound 5a 2-Indeno[2,3b]-2-ferrocenyl[1,5]benzo- 2,5-dihydrothia-zepine

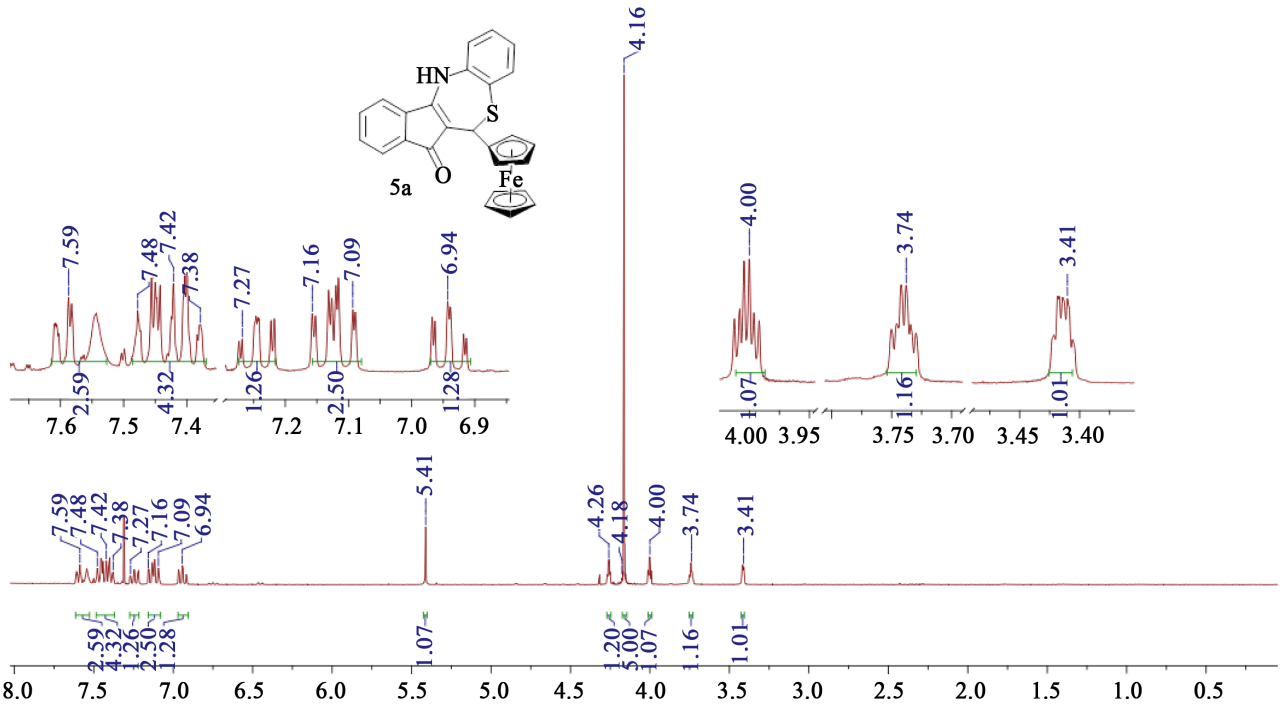


Figure S11. 1H NMR (300 MHz, CDCl3, TMS) spectrum of compound **5a**.

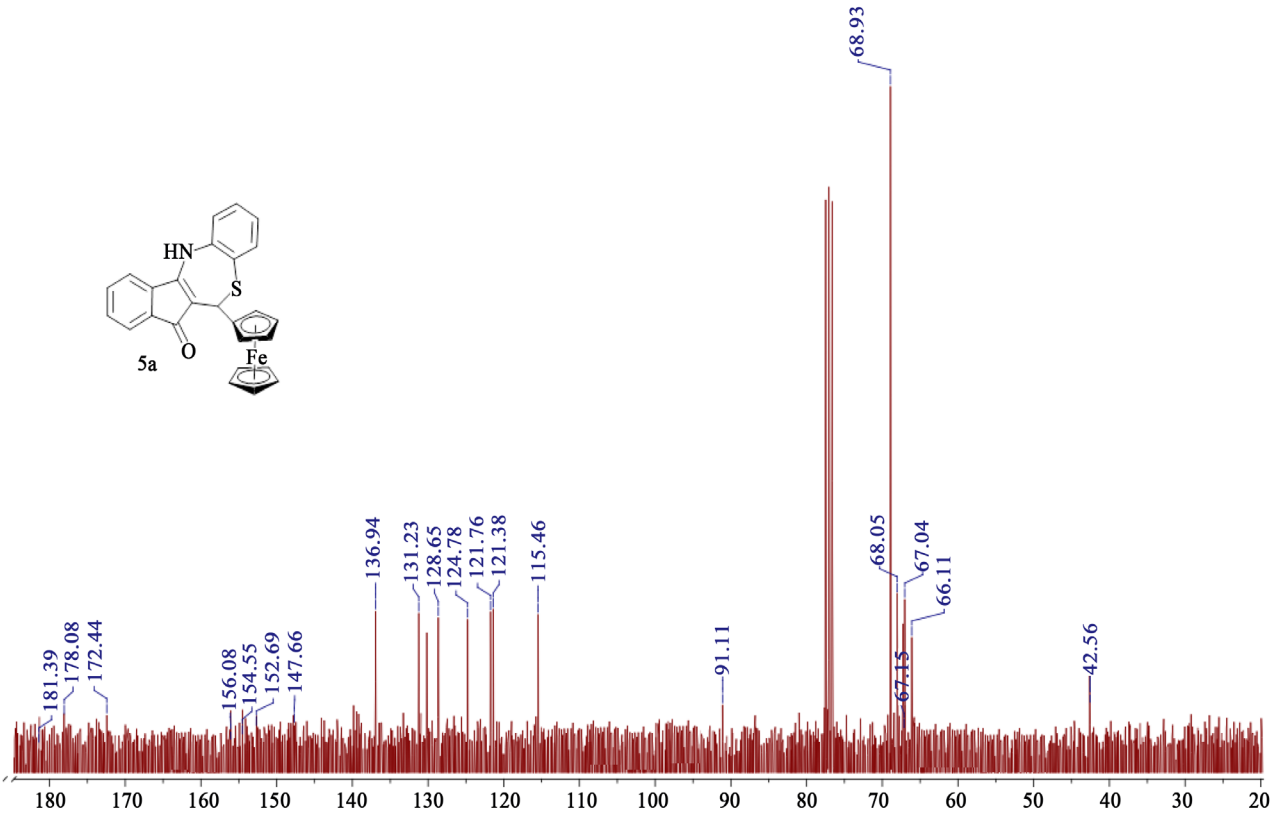


Figure S12. 13C NMR (75 MHz, CDCl3, TMS) spectrum of compound **5a**.

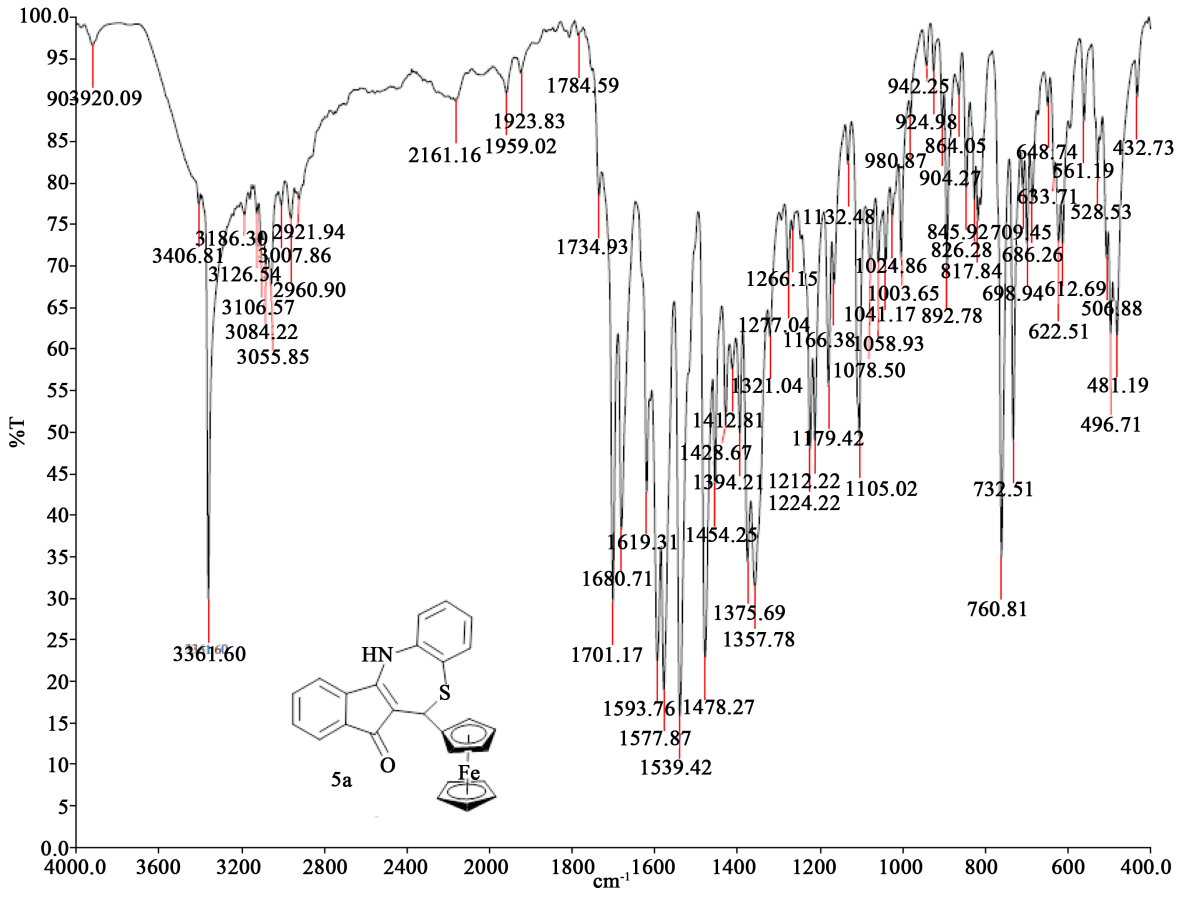


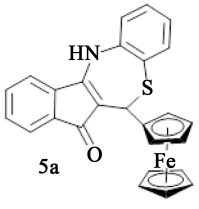
Figure S13. IR (KBr) spectrum of compound **5a**.

UNIDAD DE SERVICIOS DE APOYO A LA INVESTIGATION (USAI)
FACULTAD DE QUIMICA, UNAM
AV. UNIVERSIDAD 3000. COL. COPILCO
C.P. 04510, MEXICO, D.F.
Phone: 56232523
Fax: 56232522

User ID	M en C. Nayeli Lopez & M en I. Victor Lemus
Comments	MUESTRA: KE053 REALIZO: VICTOR LEMUS

Run	Weight	Carbon	Hydrogen	Nitrogen	Sulfur	Created on
7946770476B	2.19	69.02%	4.91%	3.54%	7.2%	4/24/2014 1:31:01 PM
7946770476A	2.305	69.07%	4.99%	3.5%	7.11%	4/24/2014 1:23:47 PM

	Weight	Carbon	Hydrogen	Nitrogen	Sulfur
Average	2.248	69.045	4.950	3.520	7.155
Variance	0.007	0.001	0.003	0.001	0.004
Standard Deviation	0.081	0.035	0.057	0.028	0.064



$C_{26}H_{19}FeNOS$
PM: 449.26

C... 69.51%
H... 4.26%
Fe... 12.43%
N... 3.12%
O... 3.56%
S... 7.12%

Figure S14. Elemental Analysis spectrum of compound **5a**.

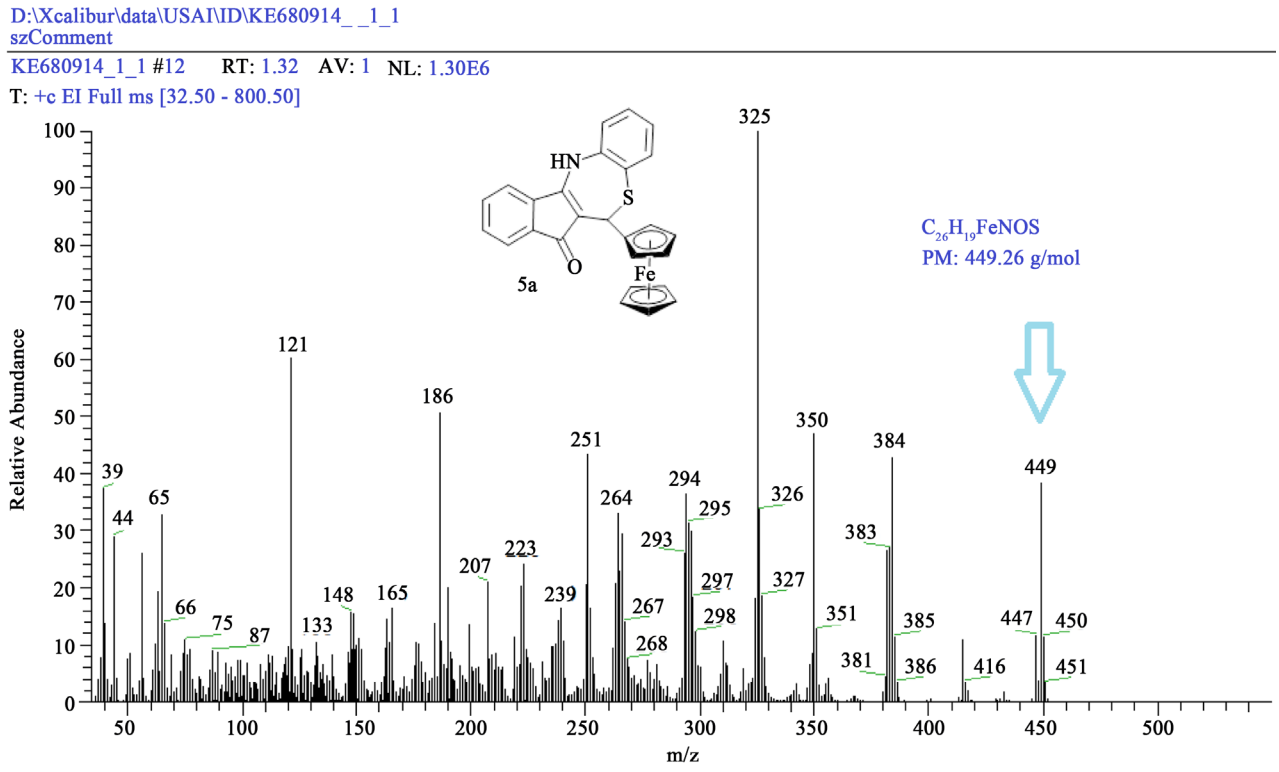


Figure S15. Mass Spectrometry spectrum of compound **5a**.

Compound 5b 2-Indeno[2,3b]-2-(p-methoxyphenyl)[1,5]benzo-2,5-dihydrothiazepine

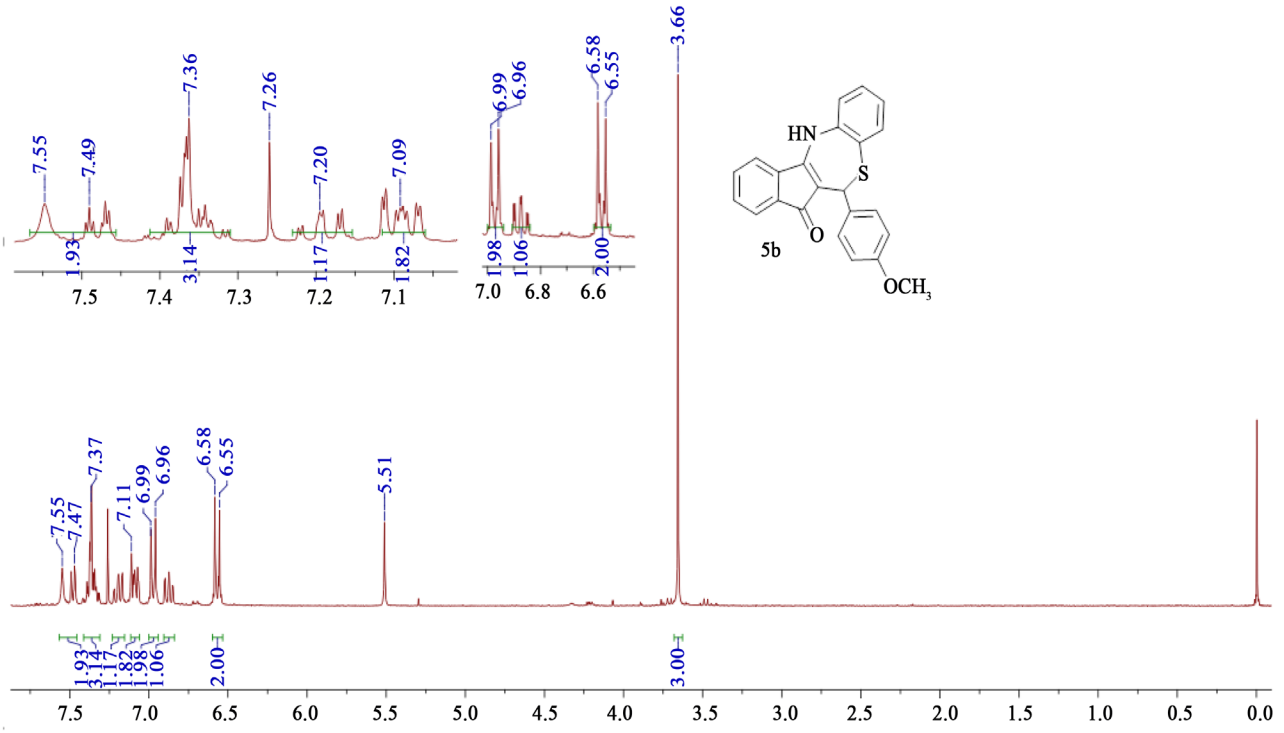


Figure S16. 1H NMR (300 MHz, CDCl3, TMS) spectrum of compound **5b**.

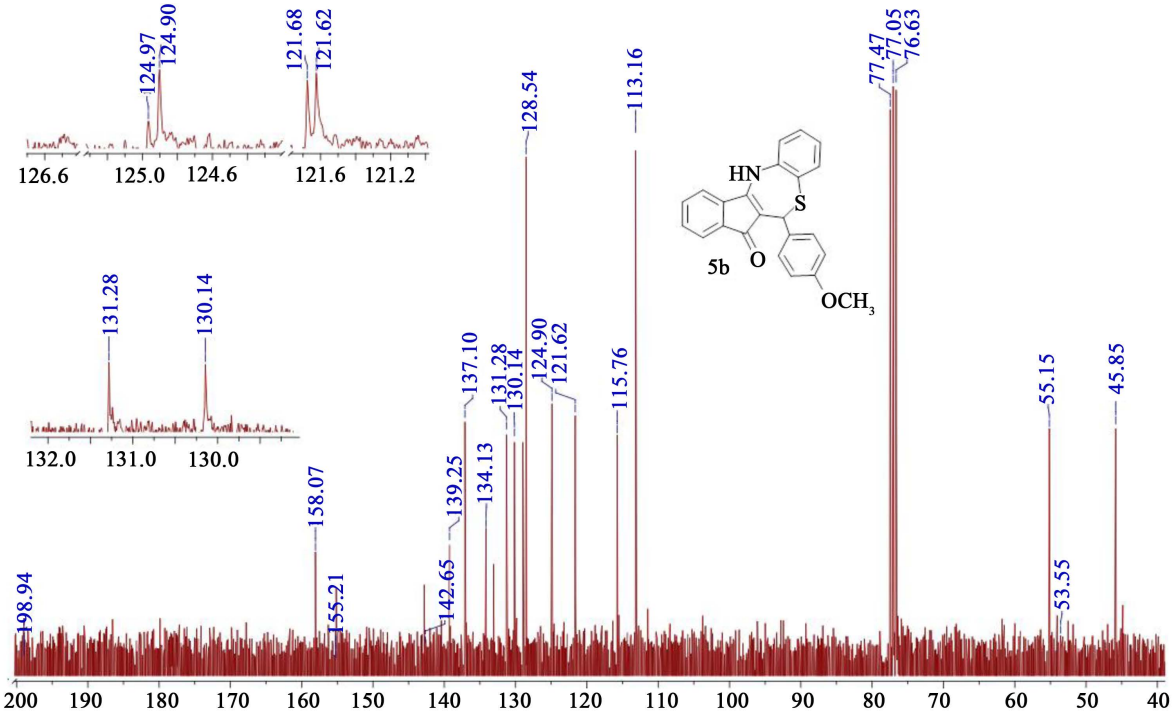


Figure S17. 13C NMR (75 MHz, CDCl3, TMS) spectrum of compound **5b**.

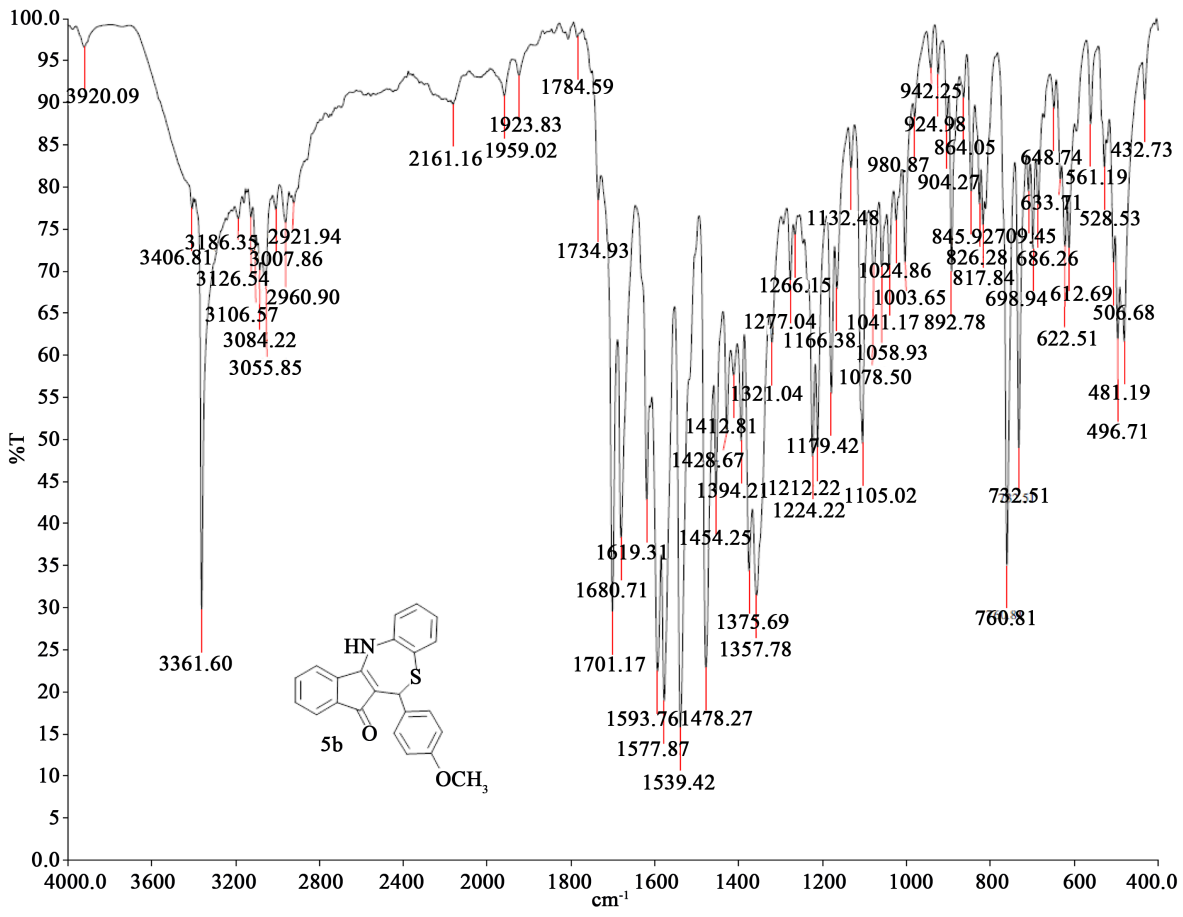


Figure S18. IR (KBr) spectrum of compound **5b**.

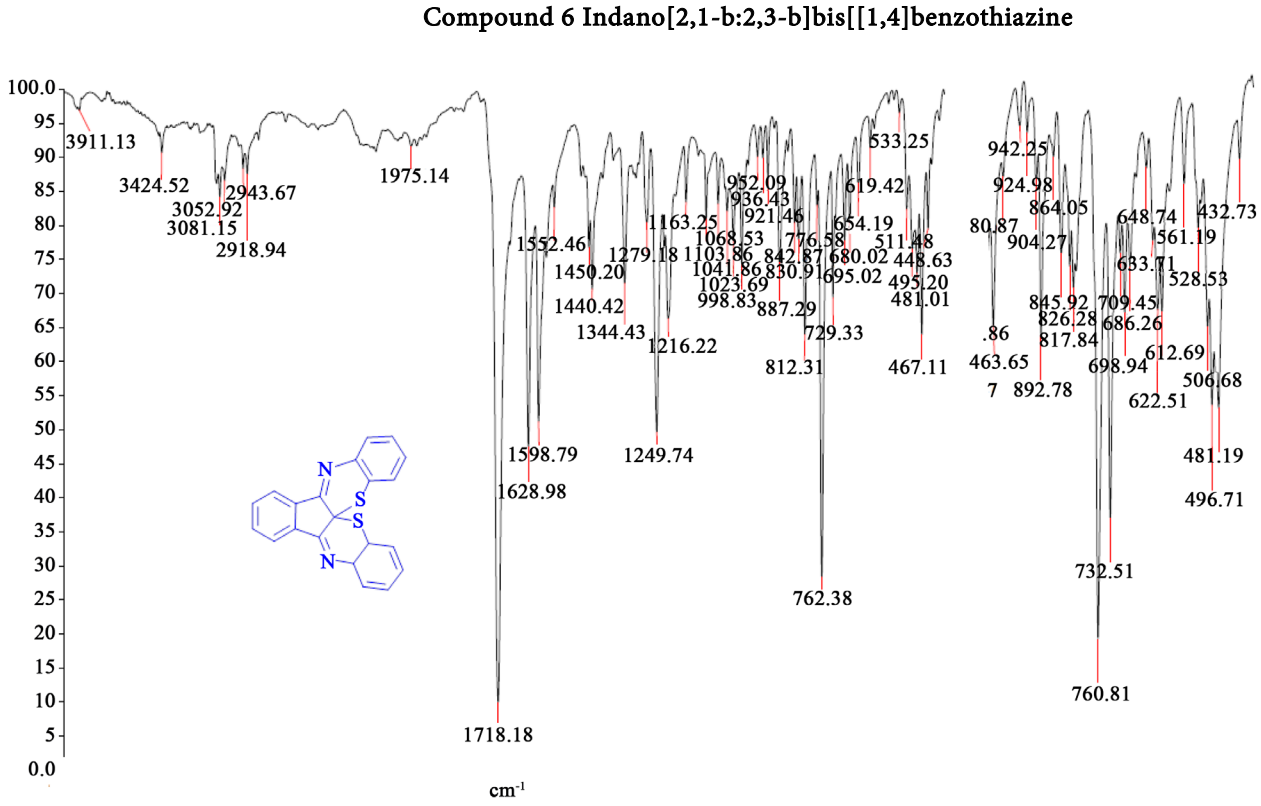


Figure S19. IR (KBr) spectrum of compound **6**.