New non-symmetrical 2,5-disubstituted 1,3,4-oxadiazoles bearing a benzo[*b*]thiophene moiety

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Abstract

A series of new 2,5-disubstituted-1,3,4-oxadiazoles derived from benzo[*b*]thiophene was obtained by dehydrative cyclization of the corresponding *N*,*N*'-diacylhydrazines, in presence of an excess of phosphorous oxychloride. The structures of the new synthesized compounds were confirmed by spectral analysis.

Keywords: Benzo[*b*]thiophene, acylhydrazide, *N*,*N*'-diacylhydrazine, 2,5-disubstituted-1,3,4-oxadiazoles, cyclodehydration

Introduction

2,5-Disubstituted-1,3,4-oxadiazoles have been reported as remarkable antidepressive, anticonvulsive,[1,2] antiinflamatory,[3] antimitotic,[4] hypoglycemic,[5] antifungal,[6] antimicrobial[7] agents, as well as insecticides.[8,9] Moreover, they present interesting electrochemical[10] and fluorescent properties.[11] The benzothiophene nucleus has a great potential in medicinal chemistry due to its low toxicity and good lipophilicity. The biological activity of many structures containing this motif is increased by its presence. Several 1,3,4-oxadiazoles bearing the 3-chloro-benzo[*b*]thienyl moiety are known and were screened for antimicrobial activity.[12,13] The 2-amino-5-(3-chloro-benzothienyl) derivatives were synthesized by cyclodesulfurization of thiosemicarbazides,[12] while the corresponding 2-thioether-derivatives were obtained by alkylation of an 1,3,4-oxadiazole-2-thione.[13]

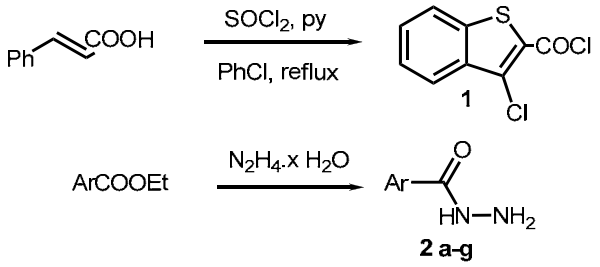
To our knowledge a study concerning the synthesis of unsymmetrical 2,5-diaryl-1,3,4-oxadiazoles substituted with a benzo[*b*]thiophene ring has not been reported. Herein, we describe

the synthesis and characterization of 2,5-disubstituted-1,3,4-oxadiazoles bearing a benzo[*b*]thiophene ring by dehydration of unsymmetrical *N,N'*- diacylhydrazines.

N,N'-diacylhydrazines are easily accessible starting from acids, acid chlorides or esters and respectively various hydrazides[10] and are valuable intermediates in the synthesis of cyclic compounds. The most common synthetic strategy for preparing 2,5-substituted-1,3,4-oxadiazoles involves the dehydrative cyclization of *N,N'*-diacylhydrazines using strong acids (dehydration agents) such as $POCl_3$,[14] $SOCl_2$,[15] P_2O_5[16] or H_2SO_4.[17] There have been also reported reactions of *N,N'*-diacylhydrazines grafted onto polymer support or under microwave irradiation,[18a,b] leading to 2,5-disubstituted-1,3,4-oxadiazoles in good yields. Recently, Katritzky et al.[18c] described an efficient one pot synthesis of 1,3,4-oxadiazoles from acylhydrazides and *N*-acylbenzotriazoles.

Results and Discussion

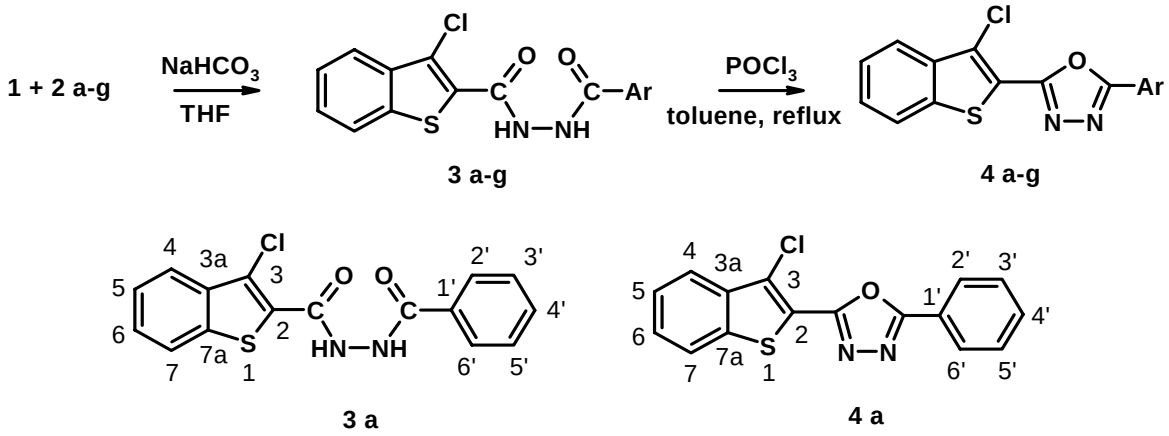
Synthesis of the 2,5-disubstituted-1,3,4-oxadiazoles required in a first step the preparation of the starting materials, namely the 3-chlorobenzo[*b*]thiophene-2-carboxyl chloride **1** and the acylhydrazides **2**. The synthesis of **1** was described by Higa and Krusbsak[19] and consists in treatment of cinnamic acid with thionyl chloride, in chlorobenzene at reflux, in presence of pyridine. The acylhydrazides **2** were obtained from ethyl esters in reaction with 100% hydrazine hydrate in very good yields, according to the literature.[20] (Scheme 1) All known compounds were characterized by NMR spectral analysis to confirm the structure.



Scheme 1. Synthesis of the 3-chlorobenzo[*b*]thiophene-2-carboxyl chloride 1 and of acylhydrazides **2a-g**.

The key intermediates for the synthesis of the 2,5-disubstituted-1,3,4-oxadiazoles **4** are the *N,N'*-diacylhydrazines **3**, which form as a result of the reaction between the acid chloride of 3-chlorobenzo[*b*]thiophene-2-carboxylic acid **1** and acylhydrazides **2**, in tetrahydrofuran, in presence of sodium bicarbonate (Scheme 2). All compounds are colorless crystals, except the compound **3f**, which is yellow. The melting points are high, over 180 ºC in all cases. The compounds bearing nitro groups have the highest melting points.

The synthesis of 2,5-disubstituted-1,3,4-oxadiazoles was performed by treatment of *N,N'*-diacylhydrazines **3** with an excess of $POCl_3$ in toluene at reflux.[21] By this method the new compounds **4** were obtained in good yield as colorless crystals, except from the compound **4f**, which is yellow, similar to the corresponding *N,N'*-diacylhydrazine.



Scheme 2. Synthesis of the 2,5-disubstituted-1,3,4-oxadiazoles and atom numbering for compounds **3a** and **4a** respectively.

The new compounds were characterized by elemental analysis, IR, NMR spectroscopy and mass spectrometry. NMR structural assignments were made on the basis of chemical shifts, coupling constants and by comparison with literature data for similar compounds. The ^{1}H-NMR and ^{13}C-NMR spectra of compounds **3a-g** and **4a-g** show all expected signals. In both cases, the appearance and chemical shifts of the protons from the benzo[*b*]thiophene ring are very similar to those from unsubstituted benzo[*b*]thiophene.

The carbonyl groups from compounds **3a-g** appear at ca. 160 ppm for the thiophene linked carbonyl and at ca. 165 ppm for the aryl linked one. However, in the case of **3b**, where the aryl substituent is replaced by a benzyl moiety, the signal for the corresponding carbonyl is shifted upfield by ca. 5 ppm. This proves the lack of conjugation between the benzyl moiety and the carbonyl group.

In the ^{13}C-NMR spectra of compounds **4a-g**, the two carbon atoms from the oxadiazole ring appear at ca. 160 ppm for the one linked to the benzo[*b*]thiophene moiety and at ca. 165 ppm for the one linked to the aryl group. The assignments were made by comparing with NMR data for 2,5-diphenyl-1,3,4-oxadiazole provided by Aldrich. The same chemical shifts are also observed in the case of intermediates **3a-g**, proving the negligible effect of the substituents in positions 2 and 5 on the oxadiazole ring. These very high chemical shift values are due to the fact that both carbon atoms are part of a C=N double bond and a single C-O bond. Furthermore, when changing the aryl group with a benzyl moiety (compound **4b**), no significant change was observed in the chemical shifts of the carbon atoms from the 1,3,4-oxadiazole ring. One may

explain this phenomenon by the lack of conjugation between the oxadiazole ring and the aryl moiety and may assume that the two rings are not planar.

Experimental Section

General Procedures. All chemicals were obtained from commercial sources and used without any further purification. The melting points were determined in open capillaries using a STUART SMP3 electrical melting point apparatus and are uncorrected. The IR spectra were recorded on a Brucker Vertex 70 spectrometer, in the range 4000-400 cm^{-1}. The elemental analysis was performed on a COSTECH Instruments EAS32 apparatus. The NMR spectra were recorded on a Varian Gemini 300 BB instrument, operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C, in DMSO-d_6 or $CDCl_3$, using TMS as internal standard. Mass spectra were obtained on a Finnigan MAT 90 spectrometer using CI technique (150eV, isobutane). Thin Layer Chromatography was performed on silicagel plates (Merck) and visualization was made using UV light (λ=254 nm).
The 3-chlorobenzo[*b*]thiophene-2-carboxyl chloride **1**[19] and the acylhydrazides **2a-g**[20] were prepared as described, and their purity was confirmed by means of melting points and NMR analysis.

General procedure for synthesis of *N,N'*-diacylhydrazines 3a-g.[10]
To an aqueous suspension of 10 mmoles of acylhydrazine **2a-g** in presence of stoechiometric amount of $NaHCO_3$, 10 mmoles of acid chloride **1,** dissolved in tetrahydrofuran, were added dropwise. The reaction mixture was stirred at reflux for 30 min, and then it was allowed to react overnight, at room temperature. The resulted precipitate was filtered, dried and recrystallized from the appropriate solvent to isolate the products **3a-g**.
***N*-(3-Chloro-benzothien-2-carbonyl)-*N'*-benzoyl hydrazine (3a).** The compound was obtained as colorless crystals by recrystallization from ethanol with mp 183-5 ºC; Yield 75 %. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.51-7.64 (5H, m, H-5, H-6, H-3', H-4', H-5'); 7.92-7.96 (m, 3H, H-4, H-2', H-6'); 8.14-8.18 (m, 1H, H-7); 10.50, 10.70 (2s, 2H, NHNH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 121.8, 129.3 (C-2, C-3); 122.6, 123.4, 126.1, 127.7 (C-4, C-5, C-6, C-7); 127.4 (C-3', C-5'); 128.5 (C-2', C-6'); 131.9 (C-4'); 132.3 (C-1'); 135.8, 136.8 (C-3a, C-7a); 160.0, 165.5 (2CONH); IR (ATR, cm^{-1}): 3172, 1596, 1568, 1517, 1497; Anal. Calcd. for $C_{16}H_{11}ClN_2O_2S$: C, 58.10; H, 3.35; N, 8.47; S, 9.69. Found: C, 58.33; H, 3.70; N, 8.72; S, 9.87.
***N*-(3-Chloro-benzothien-2-carbonyl)-*N'*-benzylcarbonyl hydrazine (3b).** The compound was obtained as colorless crystals by recrystallization from a mixture of acetone-petroleum ether with mp 197-8 ºC; Yield 90 %. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.37 (s, 2H, CH_2); 7.25-7.38 (m, 5H, Ph); 7.59-7.64 (m, 2H, H-5, H-6); 7.90-7.95 (m, 1H, H-4); 8.12-8.19 (m, 1H, H-7); 10.43 (bs, 2H, NHNH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 40.2 (CH_2); 120.6, 129.3 (C-2, C-3); 122.6, 123.5, 126.0, 127.7 (C-4, C-5, C-6, C-7); 126.5 (C-4'); 128.2, 129.1 (C-2', C-3', C-5', C-6'); 135.4

(C-1'); 135.8, 136.8 (C-3a, C-7a); 159.6, 169.0 (2CONH). IR (ATR, cm^{-1}): 3171, 1590, 1562, 1514, 1454. Anal. Calcd. for $C_{17}H_{13}ClN_2O_2S$: C, 59.22; H, 3.80; N, 8.12; S, 9.30. Found: C, 59.61; H, 4.02; N, 8.37; S, 9.64.

***N*-(3-Chloro-benzothien-2-carbonyl)-*N'*-(4-methylbenzoyl) hydrazine (3c).** The compound was obtained as colorless crystals by recrystallization from ethanol with mp 185-7 ºC; Yield 76 %. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.40 (s, 3H, 4'-Me); 7.33 (d, 2H, *J* 8.2, H-3', H-5'); 7.58-7.65 (m, 2H, H-5, H-6); 7.86 (d, 2H, *J* 8.2, H-2', H-6'); 7.90-7.96 (m, 1H, H-4); 8.15-8.18 (m, 1H, H-7); 10.51, 10.64 (2s, 2H, NHNH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 120.7, 129.3 (C-2, C-3); 122.7, 123.5, 126.2, 127.7 (C-4, C-5, C-6, C-7); 127.5 (C-3', C-5'); 129.1 (C-2', C-6'); 129.4 (C-1'); 142.0 (C-4'); 135.8, 136.8 (C-3a, C-7a); 160.1, 165.4 (2CONH). IR (ATR, cm^{-1}): 3180, 1591, 1565, 1516, 1460. Anal. Calcd. for $C_{17}H_{13}ClN_2O_2S$: C, 59.22; H, 3.80; N, 8.12; S, 9.30. Found: C, 59.61; H, 4.02; N, 8.37; S, 9.64.

***N*-(3-Chloro-benzothien-2-carbonyl)-*N'*-(3-chlorobenzoyl) hydrazine (3d).** The compound was obtained as colorless crystals by recrystallization from ethanol with mp 220-2 ºC; Yield 65 %. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.56-7.71 (m, 4H, H-5, H-6, H-5', H-6'); 7.89-7.97 (m, 3H, H-4, H-2', H-4'); 8.15-8.18 (m, 1H, H-7); 10.62, 10.64, 10.82 (2s, 2H, NHNH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 120.7; 129.3 (C-2, C-3); 122.7, 123.5, 126.2, 127.7 (C-4, C-5, C-6, C-7); 126.2, 127.4 (C-5', C-6'); 130.7, 131.9 (C-2', C-4'); 132.4, 133.4 (C-1', C-3'); 135.8; 136.8 (C-3a, C-7a); 160.0, 164.1 (2CONH). IR (ATR, cm^{-1}): 3215, 1697, 1633, 1584, 1525, 1464. Anal. Calcd. for $C_{16}H_{10}Cl_2N_2O_2S$: C, 52.62; H, 2.76; N, 7.67; S, 8.78. Found: C, 52.89; H, 2.98; N, 7.88; S, 9.13.

***N*-(3-Chloro-benzothien-2-carbonyl)-*N'*-(2,4-dichlorobenzoyl) hydrazine (3e).** The compound was obtained as colorless crystals by recrystallization from ethanol with mp 233-4 ºC; Yield 78 %. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.58-7.65 (m, 4H, H-5, H-6, H-5', H-6'); 7.78 (t, 1H, *J* 1.3 Hz, H-3'); 7.91-7.97 (m, 1H, H-4); 8.15-8.18 (m, 1H, H-7); 10.71 (bs, 2H, NHNH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 121.0, 129.0 (C-2, C-3); 122.7, 123.5, 126.1, 127.8 (C-4, C-5, C-6, C-7); 127.5, 129.6 (C-3', C-5'); 131.8, 133.2, 135.5 (C-1', C-2', C-4'); 130.8 (C-6'); 135.8, 136.9 (C-3a, C-7a); 159.7, 164.5 (2CONH). IR (ATR, cm^{-1}): 3213, 1696, 1634, 1592,1433, 1387, 1527. Anal. Calcd. for $C_{16}H_9Cl_3N_2O_2S$: C, 48.08; H, 2.27; N, 7.01; S, 8.02. Found: C, 48.44; H, 2.54; N, 7.26; S, 8.39.

***N*-(3-Chloro-benzothien-2-carbonyl)-*N'*-(2-chloro-4-nitrobenzoyl) hydrazine (3f).** The compound was obtained as yellow crystals by recrystallization from ethanol with mp 261-3 ºC; Yield 78 %. ^{1}H NMR (300 MHz, DMSO-d6) δ: 7.60-7.64 (m, 2H, H-5, H-6); 7.78 (d, 1H, *J* 8.4 Hz, H-6'); 7.91-7.97 (m, 1H, H-4); 8.12-8.18 (m, 1H, H-7); 8.33 (dd, 1H, *J* 8.4, 2.2 Hz, H-5'); 8.18 (dd, 1H, *J* 2.2 Hz, H-3'); 10.71 (bs, 2H, NHNH). ^{13}C NMR (75 MHz, DMSO-d6) δ: 121.1, 128.9 (C-2, C-3); 122.5 (C-5'); 124.5 (C-3'); 122.7, 123.5, 126.2, 127.8 (C-4, C-5, C-6, C-7); 130.6 (C-6'); 131.6 (C-2'); 135.8, 136.9 (C-3a, C-7a); 140.1 (C-1'); 148.7 (C-4'); 159.7, 164.0 (2CONH). IR (ATR, cm^{-1}): 3180, 1658, 1623, 1526, 1509. Anal. Calcd. for $C_{16}H_9Cl_2N_3O_4S$: C, 46.85; H, 2.21; N, 10.24; S, 7.82. Found: C, 47.23; H, 2.44; N, 10.50; S, 8.19.

***N*-(3-Chloro-benzothien-2-carbonyl)-*N'*-(thien-2-carbonyl) hydrazine (3g).** The compound was obtained as colorless crystals by recrystallization from ethanol with mp 221-4 ºC; Yield 66 %. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.23 (1H, dd, *J* 5.0, 3.7 Hz, H-4'); 7.60-7.65 (2H, m, H-5, H-6); 7.87-7.96 (m, 3H, H-4, H-3', H-5'); 8.14-8.19 (1H, m, H-7); 10.27 (2H, bs, NHNH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 121.0, 129.0 (C-2, C-3); 122.6, 123.3, 126.0, 127.9 (C-4, C-5, C-6, C-7); 127.6, 129.2, 131.6 (C-3', C-4', C-5'); 137.0 (C-1'); 135.8, 136.7 (C-3a, C-7a); 160.0, 169.0 (2CONH). IR (ATR, cm^{-1}): 3201, 1664, 1588, 1513, 1458. Anal. Calcd. for $C_{14}H_9ClN_2O_2S_2$: C, 49.92; H, 2.69; N, 8.32; S, 19.04. Found: C, 50.28; H, 2.88; N, 8.58; S, 19.31.

General procedure for synthesis of 1,3,4-oxadiazoles 4a-g.[21]

To a suspension of 1 mmole of *N,N'*-diacylhydrazine in toluene, 5 mmoles phosphorous oxychloride were added dropwise and the mixture was stirred under reflux overnight. The reaction mixture was allowed to cool to room temperature and the toluene and the remained phosphorous oxychloride were removed under vacuum. The remained residue was taken in dichloromethane and washed with water, 5% aqueous sodium hydroxide solution and again water. The organic phase was dried on magnesium sulfate and evaporated. The crude product was dried under vacuum and recrystallized from the appropriate solvent.

2-Phenyl-5-(3-chloro-benzothien-2-yl)-1,3,4-oxadiazole (4a). The compound was obtained as colorless crystals by recrystallization from ethanol with mp 174-5 ºC; Yield 90 %. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.45-7.53 (5H, m, H-5, H-6, H-3', H-4', H-5'); 7.78-7.83 (1H, m, H-4); 7.89-7.94 (1H, m, H-7); 8.10-8.14 (2H, m, H-2', H-6'). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 119.0, 123.4, 123.8 (C-2, C-3, C-1'); 122.7, 123.2, 125.7, 127.8 (C-4, C-5, C-6, C-7); 127.1 (C-3', C-5'); 129.1 (C-2', C-6'); 132.0 (C-4'); 136.8, 138.1 (C-3a, C-7a); 159.6, 164.7 (2C, oxadiazole ring). IR (ATR, cm^{-1}): 1594, 1581, 1431, 1312. MS *m/z* (%): 353(10) [M(^{35}Cl)]+Na+NH_4^+; 315(40) [M(^{37}Cl)]+H^+; 313(100) [M(^{35}Cl)]+H^+; 221(9). Anal. Calcd. for $C_{16}H_9ClN_2OS$: C, 61.44; H, 2.90; N, 8.96; S, 10.25. Found: C, 61.66; H, 3.12; N, 9.20; S, 10.47.

2-Benzyl-5-(3-chloro-benzothien-2-yl)-1,3,4-oxadiazole (4b). The compound was obtained as colorless crystals by recrystallization from ethanol with mp 147-9 ºC; Yield 82 %. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 4.32 (2H, s, CH_2), 7.30-7.42 (5H, m, H-2', H-3', H-4', H-5', H-6'); 7.47-7.57 (2H, m, H-5, H-6); 7.79-7.83 (m, 1H, H-4), 7.89-7.94 (1H, m, H-7). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 31.8 (CH_2)**;** 118.8, 124.2 (C-2, C-3); 122.7, 123.3, 125.8, 127.7 (C-4, C-5, C-6, C-7); 127.8, 128.9, 129.0 (C-2', C-3', C-4', C-5', C-6'); 133.5 (C-1'); 136.7, 138.0 (C-3a, C-7a); 160.2, 165.5 (2C, oxadiazole ring). IR (ATR, cm^{-1}): 3053, 1590, 1562, 1429 1307. MS *m/z* (%): 329(35) [M(^{37}Cl)]+H^+; 327(100) [M(^{35}Cl)]+H^+; 235(6). Anal. Calcd. for $C_{17}H_{11}ClN_2OS$: C, 62.48; H, 3.39; N, 8.57; S, 9.81. Found: C, 62.84; H, 3.63; N, 8.90; S, 10.08.

2-(4-Methylphenyl)-5-(3-chloro-benzothien-2-yl)-1,3,4-oxadiazole (4c). The compound was obtained as colorless crystals by recrystallization from ethanol with mp 142-5 ºC; Yield 65 %. ^{1}H-NMR (300 MHz, $CDCl_3$ + TFA) δ: 2.43 (3H, s, CH_3); 7.37 (d, 2H, *J* 8.2 Hz, H-3', H-5'); 7.49-7.54 (m, 2H, H-5, H-6); 7.82-7.85 (m, 1H, H-4); 7.92-7.96 (m, 1H, H-7); 7.98 (d, 2H, *J* 8.2

Hz, H-2', H-6'). ^{13}C-NMR (75 MHz, $CDCl_3$ + TFA) δ: 21.5 (Me); 116.4, 118.1, 126.7 (C-2, C-3, C-1'); 123.1, 123.9, 126.5, 129.1 (C-4, C-5, C-6, C-7); 127.9 (C-2', C-6'); 130.7 (C-3', C-5'); 136.7, 138.8 (C-3a, C-7a); 145.7 (C-1'); 159.8, 165.6 (2C, oxadiazole ring). IR (ATR, cm^{-1}): 3062, 1579, 1553, 1433, 1311. MS *m/z* (%): 329(9) [M(^{37}Cl)]+H$^+$; 327(25) [M(^{35}Cl)]+H$^+$; 251(30); 241(100); 195(25). Anal. Calcd. for $C_{17}H_{11}ClN_2OS$: C, 62.48; H, 3.39; N, 8.57; S, 9.81. Found: C, 62.84; H, 3.63; N, 8.90; S, 10.08.

2-(3-Chlorophenyl)-5-(3-chloro-benzothien-2-yl)-1,3,4-oxadiazole (4d). The compound was obtained as colorless crystals by recrystallization from ethanol with mp 186-8 ºC; Yield 86 %. ^{1}H-NMR (300 MHz, $CDCl_3$ + TFA) δ: 7.41 (t, 1H, *J* 8.0 Hz, H-5'); 7.42-7.48 (m, 3H, H-5, H-6, H-4'); 7.74-7.81 (m, 1H, H-4); 7.86-7.91 (m, 1H, H-7); 7.95-7.99 (m, 1H, H-5'); 8.06 (t, 1H, *J* 1.8 Hz, H-2'). ^{13}C-NMR (75 MHz, $CDCl_3$+ TFA) δ: 116.8, 122.2 (C-2, C-3); 123.4 (C-1'); 123.2, 124.1; 126.6; 127.7 (C-4, C-5, C-6, C-7); 125.9, 129.2, 131.3, 133.8 (C-2', C-4', C-5', C-6'); 136.2 (C-3'); 136.9, 139.1 (C-3a, C-7a); 160.5, 164.4 (2C, oxadiazole ring). IR (ATR, cm^{-1}): 3052, 1577, 1545, 1428, 1309. MS *m/z* (%): 389(12) [M(^{35}Cl^{35}Cl)]+Na+NH_4^+; 351(12) [M(^{37}Cl^{37}Cl)]+H$^+$; 349(65) [M(^{35}Cl^{37}Cl)]+H$^+$; 347(100) [M(^{35}Cl^{35}Cl)]+H$^+$; 255(5). Anal. Calcd. for $C_{16}H_8Cl_2N_2OS$: C, 55.35; H, 2.32; N, 8.07; S, 9.23. Found: C, 55.60; H, 2.57; N, 8.32; S, 9.49.

2-(2,4-Dichlorophenyl)-5-(3-chloro-benzothien-2-yl)-1,3,4-oxadiazole (4e). The compound was obtained as colorless crystals by recrystallization from ethanol with mp 227-9 ºC; Yield 68 %. ^{1}H-NMR (300 MHz, $CDCl_3$ + TFA) δ: 7.49 (dd, 1H, *J* 8.5, 1.9 Hz, H-5'); 7.57-7.62 (m, 2H, H-5, H-6); 7.65 (d, 1H, *J* 1.9 Hz, H-3'); 7.86-7.92 (m, 1H, H-4); 7.97- 8.02 (m, 1H, H-7); 8.04 (d, 1H, *J* 8.5 Hz, H-6'). ^{13}C-NMR (75 MHz, $CDCl_3$+ TFA) δ: 116.2, 120.0 (C-2, C-3); 122.8, 123.2, 124.1, 127.1 (C-4, C-5, C-6, C-7); 128.1, 131.6, 132.2 (C-3', C-5', C-6'); 126.8 (C-1'); 134.4, 140.0 (C-2', C-4'); 136.5, 138.6 (C-3a, C-7a); 160.3, 162.7 (2C, oxadiazole ring). IR (ATR, cm^{-1}): 3043, 1586, 1562, 1422, 1308. MS *m/z* (%): 423(15) [M(^{35}Cl^{37}Cl^{35}Cl)]+Na+NH_4^+; 387(5) [M(^{37}Cl^{37}Cl^{37}Cl)]+H$^+$; 385(35) [M(^{35}Cl^{37}Cl^{37}Cl)]+H$^+$; 383(100) [M(^{35}Cl^{35}Cl^{37}Cl)]+H$^+$; 381(98) [M(^{35}Cl^{35}Cl^{35}Cl)]+H$^+$; 363(9) [M(^{37}Cl^{37}Cl)]-Cl+NH_4^+; 361(19) [M(^{37}Cl^{35}Cl)]-Cl+NH_4^+; 359(15) [M(^{35}Cl^{35}Cl)]-Cl+NH_4^+; 327(11); 289(9). Anal. Calcd. for $C_{16}H_7Cl_3N_2OS$: C, 50.35; H, 1.85; N, 7.34; S, 8.40. Found: C, 50.56; H, 2.11; N, 7.60; S, 8.66.

2-(2-Chloro-4-nitrophenyl)-5-(3-chloro-benzothien-2-yl)-1,3,4-oxadiazole (4f). The compound was obtained as yellow crystals by recrystallization from ethanol with mp 272-3 ºC; Yield 89 %. ^{1}H-NMR (300 MHz, $CDCl_3$ + TFA) δ: 7.58-7.67 (m, 2H, H-5, H-6); 7.91-7.95 (m, 1H, H-4); 8.02-8.08 (m, 1H, H-7); 8.35 (s, 2H, H-5', H-6'); 8.52 (t, 1H, *J* 1.5 Hz, H-3'). ^{13}C-NMR (75 MHz, $CDCl_3$ + TFA) δ: 116.5, 118.8 (C-2, C-3); 122.8; 123.4; 126.4; 127.8 (C-4, C-5, C-6, C-7); 124.4, 129.7, 133.0 (C-3', C-5', C-6'); 128.1 (C-1'); 135.3 (C-2'); 136.7, 139.1 (C-3a, C-7a); 150.2 (C-4'); 161.5, 162.3 (2C, oxadiazole ring). IR (ATR, cm^{-1}): 3035, 1580, 1535, 1422, 1298. MS *m/z* (%): 432(15) [M(^{35}Cl^{35}Cl)]+Na+NH_4^+; 396(14) [M(^{37}Cl^{37}Cl)]+H$^+$; 394(35) [M(^{35}Cl^{37}Cl)]+H$^+$; 392(100) [M(^{35}Cl^{35}Cl)]+H$^+$; 349(28); 347(41). Anal. Calcd. for $C_{16}H_7Cl_2N_3O_3S$: C, 49.0; H, 1.80; N, 10.71; S, 8.17. Found: C, 49.24; H, 2.04; N, 10.92; S, 8.38.

2-(Thien-2-yl)-5-(3-chloro-benzothien-2-yl)-1,3,4-oxadiazole (4g). The compound was obtained as colorless crystals by recrystallization from ethanol with mp 178-9 ºC; Yield 80 %. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.20 (dd, 1H, *J* 5.0, 3.7 Hz, H-4'); 7.47-7.53 (m, 2H, H-5, H-6); 7.60 (dd, 1H; *J* 5.0, 1.2 Hz, H-5'); 7.80-7.86 (m, 1H, H-4); 7.87 (dd, 1H; *J* 3.7; 1.2 Hz, H-3'); 7.91-7.97 (m, 1H, H-7). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 118.6, 123.9 (C-2, C-3); 122.6, 123.2, 125.7, 127.8 (C-4, C-5, C-6, C-7); 124.6 (C-1'); 128.3 (C-4'); 130.4 (C-3'); 130.7 (C-5'); 136.7, 138,1 (C-3a, C-7a); 159.0, 160.9 (2C, oxadiazole ring). IR (ATR, cm^{-1}): 3076, 1572, 1501, 1428, 1308. MS *m/z* (%): 321(35) [M(^{37}Cl)]+H$^+$; 319(100) [M(^{35}Cl)]+H$^+$; 195(7). Anal. Calcd for $C_{14}H_7ClN_2OS_2$: C, 52.75; H, 2.21; N, 8.79; S, 20.12. Found: C, 53.0; H, 2.53; N, 9.05; S, 20.41.

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