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THE NEW S- AND N,S-SUBSTITUTED NITRODIENES FROM BROMOCHLORO-2-NITRODIENE

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Nitrodiene compound **1** gave S-substituted compound **3** with p-chlorothiophenol. Dibutadienyl piperazine compound **7** was obtained from the reaction of compound **3** with piperazine in CH_2Cl_2. Compounds **5a-g** and **11a-b** and **11h** were obtained from the reaction of compounds **3** and **10** with amines. Compound **3** gave dibutadienyl piperazine compounds (**9** and **12**) with compounds **8** and **9**.

INTRODUCTION

Mono- and polythiosubstituted compounds have been obtained from the reactions of 2H- and 1H-pentachlorbutadienes, 1,3-H- and 2,3-H-hexachlorobutenes, hexachlorobutene and perchlorobutene with some thiols.[1-5] It is known that mono-, di-, tris- and tetrakis thiosubstituted dienes were obtained from the reactions of nitrodienes with thiols and amines.[6-13]

The aim of this work was to synthesize the novel S-, N,S-substituted derivatives of bromochloro-2-nitrodiene and to characterize the structures of these compounds.

It is known that some thiosubstituted dienes exhibit high biological activity. The several substituted piperazine compounds are important for therapeutical use and also some piperazine compounds were used in gen transfer.[14-16]

The occurence of sulphur as a donor atom for transition metals is a well-known phenomenon. It acts as a very good ligating atom when in the form of the sulfide ion (S^{2-}) or as a mercaptide ion (RS^-), but complexes of sulphur as a thioether (RSR) are much less abundant.[17]

Mono(thio)substituted compound **3** was obtained when bromochloro-2-nitrodiene **1**[18] has been stirred with p-chlorothiophenol for a long time.

The ^{1}H-NMR spectra of compound **3** shows signals at δ= 7.0-7.7 ppm. Compound **3** probably was obtained from the addition intermediate product. Dibutadienyl piperazine compound **7** was produced from the reaction of compound **3** with piperazine (**6**). Compound **3** gave compound **9** with compound **8** in CH_2Cl_2. Compounds **7** and **9** are stable. The ^{1}H-NMR spectra of compound **7** and **9** shows signals for aryl and CH_2-groups of piperazine ring at known signals.

N,S-Substituted diene compounds **5a-g** and **11a, 11b, 11h** were obtained from the reactions of mono(thio)substituted diene compound **3** and **10** with amines (piperazine derivatives, piperidine and piperidine derivatives, morpholine and aniline, etc.) (Scheme 1).

The structures of these compounds were determined by microanalysis and spectroscopic data. Compound **5** and **11** probably were obtained from the addition intermediate product. Compound **12** was produced from the reaction of compound **10** with substituted piperazine derivatives. These compounds are stable too. It is known clearly that in the reactions of nitrodienes with diamines, piperazine derivatives react quickly with nitrodienes. We have seen in our previous study that diaminobenzene reacts slowly with nitrodienes. It is due to inductive effect and mesomeric effect.

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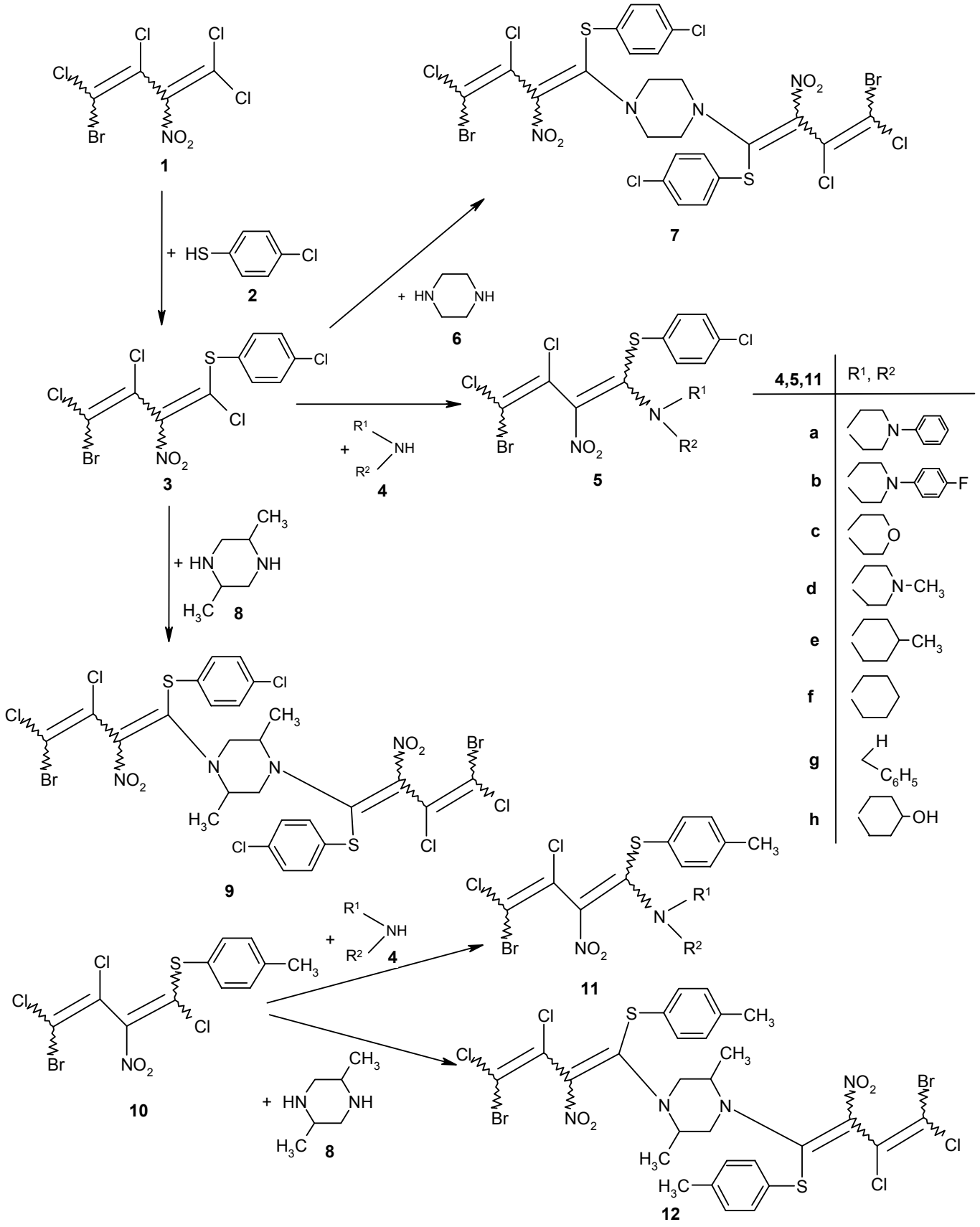

Scheme 1

EXPERIMENTAL PART

-H NMR: Bruker AC 200 L. –IR: Shimadzu FTIR-8101. – Microanalyses: Carlo-Erba 1106 Elemental Analyser. –UV: HP 8453. –Melting Points: Büchi SMP 20. Products were isolated by column chromatography on SiO_2 (Fluka Kieselgel 60, particle size 63-200μm). –TLC plates silica 60 F_{254} (Merck, Darmstadt), detection with ultraviolet light (254nm).

Preparation of S-Substituted polyhalonitrodienes.– General Procedure I: Equimolar amounts of 4-Bromo-1,1,3,4-tetrachloro-2-nitro-1,3-butadiene **(1)** and thiols were stirred for 36h at room temperature until completion of the reaction (TLC). Chloroform was added to the reaction mixture. The organic layer was separated and washed with water (4x30ml), and dried with $MgSO_4$. The solvent was evaporated and residue was purified by column chromatography on silica gel.

*4-Bromo-1,3,4-trichloro-1-(p-chlorophenylthio)-2-nitro-1,3-butadiene***(3)**: Compound **3** was synthesized from **1** (2.15 g, 6.8 mmol) and p-chlorophenylthiol **(2)** (0.98 g, 6.8 mmol) according to the *General procedure I*. Purification (CC, 400 g, 63-200μm, CCl_4) gave 0.8 g (28%) of **3**. R_f= 0.48 (CCl_4). – M.p. 110-112°C. -IR(KBr): ν = 1600, 1580 cm^{-1} (C=C), 1300, 1530 (C-NO_2), 3100 (Ar=CH). -UV (chloroform): λ_{max} = 245, 390 nm. -^{1}HNMR ($CDCl_3$) : δ = 7.0-7.7 ppm (m, 4H, Ar-H). -$C_{10}H_4Cl_4BrNO_2S$ (423.93): calcd. C, 28.33; H, 0.95; N, 3.30; found C, 28.47; H, 0.89; N, 3.40.

Preparation of N,S-Substituted polyhalonitrodienes.– General Procedure II: Equimolar amounts of S-substituted polyhalonitrodienes and amine derivatives were stirred in ether until completion of the reaction (TLC). Chloroform was added to the reaction mixture. The organic layer was separated and washed with water (4x30ml), and dried with $MgSO_4$. The solvent was evaporated and residue was either crystallized or purified by column chromatography on silica gel.

4-Bromo-3,4-dichloro-1-(p-chlorophenylthio)-2-nitro-1-(4-phenylpiperazine)-1,3-butadiene **(5a)**: Compound **5a** was synthesized from **3** (0.1 g, 0.23 mmol) and N-phenylpiperazine **(4a)** (0.038 g, 0.23 mmol) according to the *General procedure II*. Crystallization from methanol gave 0.06 g (%47) of **5a**. R_f= 0.24 (CCl_4/$CHCl_3$ 1:1). –M.p. 162-163°C. -IR(KBr): ν = 2840, 2900 cm^{-1} (C-H), 1600 (C=C), 1290, 1510 (C-NO_2), 3050 (Ar=CH). -UV (Chloroform): λ_{max} = 245 ve 350 nm. -^{1}HNMR ($CDCl_3$) : δ = 3.4-4.1 ppm (m, 4H, $2CH_2$-N-Ph), 2.6-3.2 (m, 4H, $2CH_2$-N), 6.6-7.6 (m, 9H, Ar-H). - $C_{20}H_{17}Cl_3BrN_3O_2S$ (549.704): calcd. C, 43.70; H, 3.11; N, 7.64; found C,43.84; H, 3.02; N, 7.76.

4-Bromo-3,4-dichloro-1-(p-chlorophenylthio)-1-(1-(4-fluorophenyl)piperazine)-2-nitro-1,3-butadiene **(5b)**: Compound **5b** was synthesized from **3** (0.1 g, 0.23 mmol) and 1-(4-fluorphenyl)piperazine **(4b)** (0.042 g, 0.23 mmol) according to the *General procedure II*. Crystallization from methanol gave 0.103 g (79%) of **5b**. R_f= 0.675 ($CHCl_3$). –M.p. 156-158°C. -IR(KBr): ν= 2800, 2900 cm^{-1} (C-H), 1580 (C=C), 1295, 1505 (C-NO_2), 3100 (Ar=CH). -^{1}H NMR ($CDCl_3$): δ= 2.6-4.0 ppm (m, 8H, $4CH_2$), 6.6-7.6 (m, 8H, 2Ar-H). -$C_{20}H_{16}Cl_3BrFN_3O_2S$ (567.695): calcd. C, 42.31; H, 2.84; N, 7.40; S, 5.64; found C, 42.45; H, 2.63; N, 7.62; S, 5.41.

4-Bromo-3,4-dichloro-1-(p-chlorophenylthio)-1-(4-morpholino)-2-nitro-1,3-butadiene **(5c)**: Compound **5c** was synthesized from **3** (0.1 g, 0.23 mmol) and morpholine **(4c)** (0.02 g, 0.23 mmol) according to the *General procedure II*. Crystallization from methanol gave 0.07 g (63%) of **5c**. R_f= 0.5454 (CCl_4/$CHCl_3$ 1:1). –M.p. 177-179°C. -IR(KBr): ν = 2800, 2900 cm^{-1} (C-H), 1585 (C=C), 1290, 1510 (C-NO_2), 3010 (Ar=CH). -UV (chloroform): λ_{max} = 245, 350 nm. -^{1}H NMR ($CDCl_3$): δ = 7.35-7.5 ppm (m, 4H, Ar-H), 3.3-3.8 (m, 8H, $4CH_2$). -$C_{14}H_{12}Cl_3BrN_2O_3S$(474.59): calcd. C, 35.43; H, 2.54; N, 5.90; found C, 35.51; H, 2.57; N, 6.15.

4-Bromo-3,4-dichloro-1-(p-chlorophenylthio)-1-(4-methylpiperazine)-2-nitro-1,3-butadiene **(5d)**: Compound **5d** was synthesized from **3** (0.1 g, 0.23 mmol) and 4-methylpiperazine **(4d)** (0.023 g, 0.23 mmol) according to the *General procedure II*. Crystallization from methanol gave 0.04 g (36%) of **5d**. R_f= 0.30 ($CHCl_3$). –M.p. 183-184°C. -IR(KBr): ν = 2800, 2950 cm^{-1} (C-H), 1600 (C=C), 1290, 1540 (C-NO_2). -^{1}H NMR ($CDCl_3$): δ = 2-2.5 ppm (m, 7H, $2CH_2$, CH_3), 3.3-4.0 (m, 4H, $2CH_2$-NH), 7.1-7.4 (m, 4H, Ar-H). -$C_{15}H_{15}Cl_3BrN_3O_2S$(488.543): calcd. C, 36.87; H, 3.09; N, 6.74; found C, 37.09; H, 3.11; N, 8.70.

4-Bromo-3,4-dichloro-1-(p-chlorophenylthio)-1-(4-methylpiperidino)-2-nitro-1,3-butadiene **(5e)**: Compound **5e** was synthesized from **3** (0.1 g, 0.23 mmol) and 4-methylpiperidin **(4e)** (0.023 g, 0.23 mmol) according to the *General procedure II*. Crystallization from methanol gave 0.095 g (83%) of **5e**. R_f= 0.40 (CCl_4/$CHCl_3$ 1:1). –M.p. 164-165°C. -IR(KBr): ν = 2800, 2900, 2920 cm^{-1} (C-H), 1285, 1520 (C-NO_2). -^{1}H NMR ($CDCl_3$): δ = 7.35-7.45 ppm (m, 4H, Ar-H), 3.4-4.2 (m, H, CH), 3.1-3.4 (m, 4H, $2CH_2$), 1.5-1.8 (m, 4H, $2CH_2$), 0.6-1.0 (m, 3H, CH_3). -$C_{16}H_{16}Cl_3BrN_2O_2S$(486.685): calcd. C, 39.48; H, 3.31; N, 5.75; found C, 39.29; H, 3.26; N, 5.48.

4-Bromo-3,4-dichloro-1-(p-chlorophenylthio)-2-nitro-1-piperidino-1,3-butadiene **(5f)**: Compound **5f** was synthesized from **3** (0.1 g, 0.23 mmol) and piperidine **(4f)** (0.02 g, 0.23 mmol) according to the *General procedure II*. Crystallization from methanol gave 0.08 g (73%) of **5f**. R_f= 0.725 ($CHCl_3$). –M.p. 160-161°C. -IR(KBr): ν = 2850, 2950 cm^{-1} (C-H), 1620 (C=C), 1290, 1530 (C-NO_2), 3100 (Ar=CH). -^{1}H NMR ($CDCl_3$): δ = 2.8-4.0 ppm (m, 4H, $2CH_2$-N), 0.8-2.0 (m, 6H, $3CH_2$), 7.1-7.6 (m, 4H, Ar-H). -$C_{15}H_{14}Cl_3BrN_2O_2S$(472.618): calcd. C, 38.12; H, 2.98; N, 5.92; found C, 38; H, 3.08; N, 5.48.

4-Bromo-3,4-dichloro-1-(p-chlorophenylthio)-2-nitro-1-(phenylamino)-1,3-butadiene **(5g)**: Compound **5g** was synthesized from **3** (0.1 g, 0.23 mmol) and aniline **(4g)** (0.022 g, 0.23 mmol) according to the *General procedure II*. Crystallization from methanol gave 0.085 g (75%) of **5g**. R_f= 0.7926 (CCl_4/$CHCl_3$ 1:1). –M.p. 181-183°C. -IR(KBr): ν =1595 cm^{-1} (C=C), 1350, 1540 (C-NO_2), 3050 (Ar=CH), 3100 (NH). -^{1}H NMR ($CDCl_3$): δ = 11.6 ppm (s, H, NH), 6.8-7.2 (m, 9H, 2Ar-H). -$C_{16}H_{10}Cl_3BrN_2O_2S$(480.597): calcd. C, 39.98; H, 2.09; N, 5.82; found C, 40.18; H, 2.09; N, 5.73.

N,N′-Bis(4-Bromo-3,4-dichloro-1-(p-chlorophenylthio)-2-nitro-1,3-butadienyl)-piperazine **(7)**: Compound **7** was synthesized from **3** (0.1 g, 0.23 mmol) and piperazine **(6)** (0.02 g, 0.23 mmol) according to the *General procedure II*. Crystallization from methanol gave 0.06 g (30%) of **7**. R_f= 0.303 (CCl_4/$CHCl_3$ 1:1). –M.p. 221-222°C. -IR(KBr): ν = 2850, 2900 cm^{-1} (C-H), 1595 (C=C), 1295, 1520 (C-NO_2), 3050 (Ar=CH). -UV (chloroform): λ_{max}= 245 ve 340 nm. -^{1}H NMR ($CDCl_3$): δ = 2.5-3.3 ppm (m, 8H, $4CH_2$), 7.1-7.5 (m, 8H, 2Ar-H). $C_{24}H_{16}Cl_6Br_2N_4O_4S_2$(861.075).

N,N′-Bis(4-Bromo-3,4-dichloro-1-(p-chlorophenylthio)-2-nitro-1,3-butadienyl)-2,5-dimethylpiperazine **(9)**: Compound **9** was synthesized from **3** (0.1 g, 0.23 mmol) and 2,5-dimethylpiperazine **(8)** (0.02 g, 0.23 mmol) according to the *General procedure II*. Crystallization from methanol gave

0.02 g (10%) of **9**. R_f= 0.7353 ($CHCl_3$). –M.p. 180-183°C(decomposed). -IR(KBr): ν = 2810, 2990 cm^{-1} (C-H), 1560 (C=C), 1290, 1505 (C-NO_2). -^{1}H NMR ($CDCl_3$): δ = 1.4-1.6 ppm (s, 6H, $2CH_3$), 2.2-2.5 (m, 4H, $2CH_2$), 2.8-4.6 (m, 2H, 2CH), 7.1-7.6 (m, 8H, Ar-H). -$C_{26}H_{20}Cl_6Br_2N_4O_4S_2$ (889.128): calcd. C, 35.12; H, 2.27; N, 6.30; S, 7.21; found C, 34.95; H, 2.15; N, 6.02; S, 7.27.

4-Bromo-1,3,4-trichloro-1-(p-methylphenylthio)-2-nitro-1,3-butadiene **(10)**: Compound **10** was synthesized from **1** (0.5 g, 1.58 mmol) and p-methylphenylthio (0.197 g, 1.58 mmol) according to the *General procedure I* as recently described [10]. Yield and purity correspond with the data reported there.

4-Bromo-3,4-dichloro-1-(p-methylphenylthio)-2-nitro-1-(4-phenylpiperazine)-1,3-butadiene **(11a)**: Compound **11a** was synthesized from **10** (0.1 g, 0.245 mmol) and 4-phenylpiperazine **(4a)** (0.04 g, 0.245 mmol) according to the *General procedure II*. Crystallization from methanol gave 0.098 g (75%) of **11a**. R_f= 0.6585 ($CHCl_3$). –M.p. 179-180°C. -IR(KBr): ν = 2800, 2900 cm^{-1} (C-H), 1595 (C=C), 1290, 1510 (C-NO_2), 3050 (Ar=CH). -^{1}H NMR ($CDCl_3$): δ = 2.4 ppm (s, 3H, CH_3), 2.6-3.1 (m, 4H, $2CH_2$), 3.3-3.9 (m, 4H, $2CH_2$), 6.7-7.6 (m, 9H, Ar-H). -UV (chloroform): λ_{max} = 250, 390 nm. -$C_{21}H_{20}Cl_2BrN_3O_2S$ (529.032): calcd. C, 47.67; H, 3.81; N, 7.94; found C, 47.68; H, 3.78; N, 7.64.

4-Bromo-3,4-dichloro-1-(1-(4-fluorophenyl)piperazine)-1-(p-methylphenylthio)-2-nitro-1,3-butadiene **(11b)**: Compound **11b** was synthesized from **10** (0.2 g, 0.49 mmol) and 1-(4-fluorphenyl)piperazine **(4b)** (0.089 g, 0.49 mmol) according to the *General procedure II*. Crystallization from methanol gave 0.08 g (30%) of **11b**. R_f= 0.4827 ($CHCl_3$). –M.p. 144-145°C. -IR(KBr): ν = 2800, 2900 cm^{-1} (C-H), 1590 (C=C), 1280, 1505 (C-NO_2), 3050 (Ar=CH). -^{1}H NMR ($CDCl_3$): δ = 2.4 ppm (s, 3H, CH_3), 2.5-3.0 (m, 4H, $2CH_2$), 3.4-3.8 (m, 4H, $2CH_2$), 6.6-7.4 (m, 8H, 2Ar-H). -$C_{21}H_{19}Cl_2BrFN_3O_2S$ (547.276): calcd. C, 46.08; H, 3.49; N, 7.67; found C, 45.89; H, 3.45; N, 7.47.

4-Bromo-3,4-dichloro-1-(p-methylphenylthio)-2-nitro-1-(4-piperidinol)-1,3-butadiene **(11h)**: Compound **11h** was synthesized from **10** (0.1 g, 0.24 mmol) and 4-piperidinol **(4h)** (0.025 g, 0.24 mmol) according to the *General procedure II*. Crystallization from methanol gave 0.08 g (73%) of **11h**. R_f= 0.125 ($CHCl_3$). –M.p. 139-141°C. -IR(KBr): ν = 2800, 2890 cm^{-1} (C-H), 1595 (C=C), 1290, 1520 (C-NO_2), 3500 (OH). -^{1}H NMR ($CDCl_3$): δ = 1.1-1.9 ppm (m, 6H, $2CH_2$, CH, OH), 2.2-2.5 (m, 3H, CH_3), 3.1-4.0 (m, 4H, $2CH_2$-N), 7.05-7.6 (m, 4H, Ar-H). -$C_{16}H_{17}Cl_2BrN_2O_3S$ (468.198): calcd. C, 41.04; H, 3.65; N, 5.98; found C, 41.25; H, 3.74; N, 5.69.

N,N'-Bis(4-Bromo-3,4-dichloro-1-(p-methylphenylthio)-2-nitro-1,3-butadienyl)-2,5-dimethylpiperazine **(12)**: Compound **12** was synthesized from **10** (0.2 g, 0.49 mmol) and 2,5-dimethylpiperazine **(8)** (0.057 g, 0.49 mmol) according to the *General procedure II*. Crystallization from methanol gave 0.09 g (23%) of **12**. R_f= 0.7222 ($CHCl_3$). –M.p. 169-170°C. -IR(KBr): ν = 2800, 2990 cm^{-1} (C-H), 1600 (C=C), 1280, 1520 (C-NO_2). -^{1}H NMR ($CDCl_3$): δ = 2.1-2.5 ppm (m, 12H, $4CH_3$), 3.3-3.7 (m, 4H, $2CH_2$), 4.4-4.6 (m, 2H, 2CH), 7.2-7.6 (m, 8H, Ar-H). -$C_{28}H_{26}Cl_4Br_2N_4O_4S_2$ (848.292): calcd. C, 39.64; H, 3.08; N, 6.60; S, 7.55; found C, 39.41; H, 2.84; N, 6.42; S, 7.80.

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