Bulgarian Chemical Communications, Volume 50, Issue 3, (pp. 445 – 451) 2018

Synthesis and spectral properties of new piperazine derivatives and a structural study

Z. Gokmen*, N. G. Deniz, M. E. Onan, C. Sayil

Istanbul University-Cerrahpasa, Engineering Faculty, Department of Chemistry, Division of Organic Chemistry, 34320 Avcilar, Istanbul, Turkey

Received May 15, 2017; Accepted April 18, 2018

In this study, new piperazine derivatives were synthesized by the reactions of *S*-substituted-3-nitro-1,3-butadienes with some piperazine derivatives: (1-(2-furoyl)-, 1-(4-fluorobenzyl)-, 1-(3-fluorophenyl)- and 1-(1-tetrahydro-2-furyl)piperazine) in $CHCl_3$ at room temperature. The structures of the new compounds were characterized by micro analysis, FT-IR, MS spectrometry, ^{1}H- and ^{13}C-NMR. The crystal structure analysis was performed on the synthesized compound **5d** by using the X-ray diffraction method. The compound **5d** crystallizes in the monoclinic space group $P2_1/c$ with a = 12.5503(2) Å, b = 11.2039(2) Å, c = 14.1007(4) Å, Z = 4. The structure was solved by direct methods (SIR92) and refined to the residual index $R_1 = 0.031$.

Keywords: Piperazine derivatives; X-ray study; Organic synthesis; Vinylic substitution

INTRODUCTION

Polyhalo-substituted-1,3-butadienes possess a broad spectrum of useful properties: they are employed as monomers for the preparation of valuable polymers and copolymers resistant to heat, light and chemical corrosion, and exhibit algicidal, bactericidal and fungicidal activities [1]. Moreover, the precursor perchloronitrobutadiene **1** proved to be active against cancer cells [2].

Piperazine analogues have drawn great interest for their biological activities in a number of different therapeutic areas [3]. These include anticancer, antifungal [4,5], antibacterial, antimalarial and antipsychotic agents [6], as well as HIV protease inhibitors and antidepressants. Also, the N-carbonyl piperazine moieties exhibit cardio-vascular properties [7].

EXPERIMENTAL

General

Melting points were measured on a Büchi B-540 melting point apparatus. FTIR spectra (cm^{-1}) were recorded as KBr pellets in nujol mulls on a Shimadzu IR Prestige 21 model Diamond spectrometer (ATR method). ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity Inova spectrometer at 499.83 MHz for ^{1}H and 125.48 MHz for ^{13}C using $CDCl_3$ as a solvent and TMS as an internal standard. Mass spectra were obtained on a hybrid triple quadrupole linear ion trap mass spectrometer (4000 QTRAP, ABSciex). The 4000 QTRAP was operated in the triple quadruple mass spectrometer mode by use of electrospray ionization (ESI) source. The crystal structure of compound **5d** was determined on Rikagu R-Axis Rapid-S X-Ray Single Crystal diffractometer. Micro analyses (C, H, N, S) were conducted using the Thermo Finnigan Flash EA 1112 elemental analyzer. Products were isolated by column chromatography on silica gel (Fluka Silica gel 60, particle size 63–200 μm). Kieselgel 60 F-254 plates (Merck) were used for thin layer chromatography (TLC). All chemicals were of reagent grade and were used without further purification. Moisture was excluded from the glass apparatus with $CaCl_2$ drying tubes.

General Method 1 for the synthesis of S-substituted-3-nitrobutadiene Compounds (3a-d)

4-(Hexadecylsulfanyl)-1,1,2,4-tetrachloro-3-nitro-1,3-butadiene **(3a)** [8], 4-(cyclo-pentylsulfanyl)-1,1,2,4-tetrachloro-3-nitro-1,3-butadiene **(3b)** [9], 4-(octadecyl-sulfanyl)-1,1,2,4-tetrachloro-3-nitro-1,3-butadiene **(3c)** [8] and 4-(ethylsulfanyl)-1,1,2,4-tetrachloro-3-nitro-1,3-butadiene **(3d)** [10] were synthesized by the reactions of **1** with **2a-d** according to the literature [8-10].

General method 2 for the synthesis of piperazine derivatives

The *S*-substituted-3-nitro-1,3-butadienes **3a-d** and equimolar amounts of the piperazine derivatives were stirred in chloroform (25 mL) for 8 h. Chloroform (30 mL) was added to the reaction mixture. The organic layer was washed with water (4×30 mL), and dried with Na_2SO_4. After the solvent was evaporated the residue was purified by column chromatography on silica gel.

[4-(1-(2-Furoyl)piperazin-1-yl]-4-(4-hexadecyl-sulfanyl)-1,1,2-trichloro-3-nitro-1,3-butadiene (5a): Compound **5a** was synthesized by the reaction

* To whom all correspondence should be sent:
E-mail: : gokm@istanbul.edu.tr

of **3a** (0.1 g, 0.2 mmol) with 1-(2-furoyl)piperazine **4** (0.036 g, 0.2 mmol) according to general method 2.

Yellow oil, yield: 0.062 g, 49% . R_f: 0.64 [PET:EtAc (2:1)]. FT-IR (KBr, cm^{-1}): ν= 2952, 2853 (C-H), 1649 (C=O_{Amide}), 1570 (C=C), 1529, 1487, 1274 (NO_2). ^{1}H NMR ($CDCl_3$, ppm): δ = 0.86-0.92 (t, 3H, C**H$_3$**), 1.24-1.32 (m, 24H, C**H$_2$**), 1.37-1.43 (m, 2H, C**H$_2$**), 1.65-1.72 (m, 2H, C**H$_2$**), 2.97-3.10 (s, 2H, S-C**H$_2$**), 3.40-3.85 (sbr, 4H, C**H$_{2piper.}$**), 4.05-4.32 (s, 4H, C**H$_{2piper.}$**), 6.53-6.57 (m, 1H, **H**$_{arom.}$), 7.15-7.17 (d, 1H, **H**$_{arom.}$), 7.52-7.55 (s, 1H, **H**$_{arom.}$). ^{13}C NMR ($CDCl_3$, ppm): δ= 14.14 (CH_3), 23.71, 28.73, 29.04, 29.37, 29.39, 29.53, 29.62, 29.67, 29,70, 29.75 (**C**H_2), 31.94 (S-**C**H_2), 35.66, 52.91 (**C**$_{piper.}$), 111.79, 118.00, 118.83 , 125.04, 126.53, 144.31 (**C**$_{butad.}$, **C**$_{arom.}$), 147.28 (**C**$_{furoyl}$), 169.30 (**C**=O). MS [+ESI]: m/z (%) 638 (100) $[M+H]^+$. Micro analysis: $C_{29}H_{44}Cl_3N_3O_4S$, (M_A = 637.1 g/mol). Calculated: C, 54.67; H, 6.96; N, 6.60; S, 5.03%; Found: C, 54.69; H, 7.00; N, 6.62; S, 5.02%.

[4-(1-(2-Furoyl)piperazin-1-yl]-4-(4-octadecyl-sulfanyl)-1,1,2-trichloro-3-nitro-1,3-butadiene (5c): Compound **5c** was synthesized by the reaction of **3c** (0.1g, 0.2 mmol) with 1-(2-furoyl)piperazine **4** (0.035 g, 0.2 mmol) according to general method 2. Yellow oil, yield: 0.053 g, 42% . R_f: 0.30 [PET:EtAc (2:1)]. FT-IR (KBr, cm^{-1}): ν=2952, 2853 (C-H), 1649 (C=O_{Amide}), 1570(C=C), 1529, 1487, 1274 (NO_2). ^{1}H NMR ($CDCl_3$, ppm): δ = 0.87-0.90 (t, 3H, C**H$_3$**), 1.25-1.32 (m, 28H, C**H$_2$**), 1.39-1.42 (m, 2H, C**H$_2$**), 1.67-1.70 (m,2H,C**H$_2$**), 2.97-3.00 (d, 2H, S-C**H$_2$**), 3.99 (sbr, 8H, C**H$_{2piper.}$**), 6.53-6.54 (s, 1H, **H**$_{arom.}$), 7.13-7.14 (s, 1H, **H**$_{arom.}$), 7.51-7.52 (s, 1H, **H**$_{arom.}$).^{13}C NMR ($CDCl_3$, ppm): δ= 14.12 (**C**H_3), 22.69, 28.72, 29.02, 29.36, 29.38, 29.52, 29.61, 29.66 , 29.70, 29.74 (**C**H_2), 31.92 (S-**C**H_2), 35.63, 52.89 (**C**$_{piper.}$), 111.75, 117.94, 118.86 , 125.00, 126.54, 144.28, 158.99 (**C**$_{butad.}$,**C**$_{arom.}$), 147.27 (**C**$_{furoyl}$), 169.63 (**C**=O). MS [+ESI]: m/z (%) 688 (100) $[M+Na]^+$. Micro analysis: $C_{31}H_{48}Cl_3N_3O_4S$, (M_A = 665.15 g/mol). Calculated: C, 55.98; H, 7.27; N, 6.32; S, 4.82%; Found: C, 55.99; H, 7.29; N, 6.35; S, 4.86%.

*[4-(1-(2-Furoyl)piperazin-1-yl)]-4-(ethyl-sulfanyl)-1,1,2-trichloro-3-nitro-1,3-butadiene (5d) [11]***:** Compound **5d** was synthesized by the reaction of **3d** (0.1g, 0.34 mmol) with 1-(2-furoyl)piperazine **4** (0.057 g, 0.32 mmol) according to general method 2. Yellow solid, yield: 0.057 g, 46%. M.p.: 135.8-136.0°C.

[4-(1-(4-Fluorobenzyl)piperazin-1-yl]-4-(4-hexadecyl-sulfanyl)-1,1,2-trichloro-3-nitro-1,3-butadiene (7a): Compound **7a** was synthesized by the reaction of **3a** (0.1g, 0.2 mmol) with 1-(4-fluorobenzyl)piperazine **6** (0.039 g, 0.2 mmol) according to general method 2. Yellow solid, yield: 0.042 g, 32%. R_f: 0.63 [PET:EtAc (2:1)]. M.p.: 75°C. FT-IR (KBr, cm^{-1}): ν= 2924, 2853 (C-H), 1620, 1510 (C=C), 1530, 1279 (NO_2). ^{1}H NMR ($CDCl_3$, ppm): δ = 0.86-0.92 (t, 3H, C**H$_3$**), 1.24-1.32 (m, 24H, C**H$_2$**), 1.37-1.43 (m, 2H, C**H$_2$**), 1.65-1.72 (m, 2H, C**H$_2$**), 2.55-2.75 (sbr, 2H, Ph-C**H$_2$**), 2.97-3.10 (s, 2H, S-**C**H$_2$), 3.50-3.80 (s, 4H, C**H$_{2piper.}$**), 3.90-4.12 (sbr, 4H, C**H$_{2piper.}$**), 7.05-7.07 (t, 2H, **H**$_{arom.}$), 7.32-7.35 (s, 2H, **H**$_{arom.}$). ^{13}C NMR ($CDCl_3$, ppm): δ= 14.14 (**C**H_3), 23.71, 28.73, 29.04, 29.37, 29.39, 29.53, 29.62, 29.67, 29.70, 29.75, 31.94 (**C**H_2), 35.66 (S-**C**H_2), 52.40, 61.50 (**C**$_{piper.}$), 115.36, 115.53, 126.83 (**C**$_{butad.}$, **C**$_{arom.}$). MS [+ESI]: m/z (%) 652 (100) $[M+H]^+$. Micro analysis: $C_{31}H_{47}Cl_3FN_3O_2S$, (M_A = 651.15 g/mol). Calculated: C, 57.18; H, 7.28; N, 6.45; S, 4.92%; Found: C, 57.20; H, 7.26; N, 6.46; S, 4.90%.

[4-(1-(4-Fluorobenzyl)piperazin-1-yl]-4-(4-cyclopentyl-sulfanyl)-1,1,2-trichloro-3-nitro-1,3-butadiene (7b): Compound **7b** was synthesized by the reaction of **3b** (0.1g, 0.3 mmol) with 1-(4-fluorobenzyl)piperazine **6** (0.058 g, 0.3 mmol) according to general method 2. Orange solid, yield: 0.074 g, 51%. R_f : 0.41 [PET:EtAc (2:1)]. M.p.: 124°C. FT-IR (KBr, cm^{-1}): ν= 3052, 2961, 2871, 2805, 2768 (C-H), 1602 (C=C), 1529, 1278 (NO_2). ^{1}H NMR ($CDCl_3$, ppm): δ= 1.52-1.76 (m, 4H, C**H$_{2cyclo.}$**), 1.65-1.73 (s, 4H, C**H$_{2cyclo.}$**), 2.55 (sbr, 3H, S-C**H**$_{cyclo.}$ and Ph-C**H$_2$**), 3.45 (s, 4H, C**H$_{2piper.}$**), 3.50-3.91 (sbr, 4H, C**H$_{2piper.}$**), 6.90-7.00 (t, 2H, C**H**$_{arom.}$), 7.19-7.21 (m, 2H, C**H**$_{arom.}$). ^{13}C NMR ($CDCl_3$, ppm): δ= 24.61, 48.26 (**C**$_{cyclo.}$), 52.52, 53.35 (**C**$_{piper.}$), 115.26, 115.43, 118.12, 124.6, 126.88, 130.7, 130.53, 132.82, 161.26 (**C**$_{butad.}$, **C**$_{arom.}$), 163.21 (**C**$_{Farom.}$). MS [+ESI]: m/z (%) 494 (100) $[M]^+$. Micro analysis: $C_{20}H_{23}Cl_3FN_3O_2S$, (M_A = 494.84 g/mol). Calculated: C, 48.54; H, 4.68; N, 8.49; S, 6.48%; Found: C, 48.59; H, 4.69; N, 8.51; S, 6.47%.

[4-(1-(4-Fluorobenzyl)piperazin-1-yl]-4-(4-octadecyl-sulfanyl)-1,1,2-trichloro-3-nitro-1,3-butadiene (7c): Compound **7c** was synthesized by the reaction of **3c** (0.1g, 0.19 mmol) with 1-(4-fluorobenzyl)piperazine **6** (0.037 g, 0.19 mmol) according to general method 2. Oil, yield: 0.055 g, 43%. R_f: 0.59 [PET:EtAc (2:1)]. FT-IR (KBr ,cm^{-1}): ν= 2924, 2853 (C-H), 1610 (C=C), 1529, 1278 (NO_2). ^{1}H NMR ($CDCl_3$, ppm): δ= 0.78-0.82 (t, 3H, C**H$_3$**), 1.15-1.25 (m, 28H, C**H$_2$**), 1.28-1.35 (m, 2H, C**H$_2$**), 1.50-1.60 (m, 2H, C**H$_2$**), 2.55-2.75 (sbr, 2H, Ph-C**H$_2$**), 2.85-2.93 (t, 2H, S-C**H$_2$**), 3.45-3.58 (s, 4H, C**H$_{2piper.}$**), 3.62-3.83 (sbr, 4H, C**H$_{2piper.}$**), 6.96-6.99 (t, 2H, C**H**$_{arom.}$), 7.23-7.29 (sbr, 2H,

C**H**$_{arom.}$). ^{13}C NMR ($CDCl_3$, ppm): δ=14.15 (**C**H_3), 22.71, 28.69, 29.0, 29.38, 29.52, 29.62, 29.68, 29.71, 29.76, 31.94 (**C**H_2), 35.51 (S-**C**H_2), 61.48 (Ph-**C**H_2), 115.58, 128.02, 130.50, (**C**$_{butad.}$, C$_{arom.}$). MS [+ESI]: m/z (%) 680 (100) $[M+H]^+$. Micro analysis: $C_{33}H_{51}Cl_3FN_3O_2S$, (M_A = 679.2 g/mol). Calculated: C, 58.36; H, 7.57; N, 6.19; S, 4.72%; Found: C, 58.38; H, 7.58; N, 6.20; S, 4.75%.

[4-(1-(3-Fluorophenyl)piperazin-1-yl]-4-(4-hexadecyl-sulfanyl)-1,1,2-trichloro-3-nitro-1,3-butadiene (9a): Compound **9a** was synthesized by the reaction of **3a** (0.1g, 0.2 mmol) with 1-(3-fluorophenyl)piperazine **8** (0.037 g, 0.2 mmol) according to general method 2. Orange solid, yield: 0.036 g, 28%. R_f: 0.33 [PET:EtAc (9:1)]. M.p.: 82-83°C. FT-IR (KBr, cm^{-1}) : ν= 2919, 2850 (C-H), 1615, 1518 (C=C), 1533, 1277 (NO_2). ^{1}H NMR ($CDCl_3$, ppm): δ= 0.88-0.92 (t, 3H, C**H$_3$**), 1.23-1.33 (s, 24H, C**H$_2$**), 1.38-1.44 (m, 2H, C**H$_2$**), 1.67-1.73 (s, 2H, C**H$_2$**), 2.97-3.10 (s, 2H, S-C**H$_2$**), 3.35-3.45 (s, 4H, C**H**$_{2piper.}$), 3.65-4.05 (sbr, 4H, C**H$_2$**$_{piper.}$), 6.66-6.72 (m, 3H, **H**$_{arom.}$), 7.22-7.29 (t, 1H, **H**$_{arom.}$). ^{13}C NMR ($CDCl_3$, ppm): δ=14.15 (**C**H_3), 22.71, 28.55, 28.71, 29.04, 29.26, 29.38, 29.53, 29.62, 29.67, 29.71, 31.94, 35.63 (**C**H_2), 39.23, 48.79 (**C**$_{piper.}$), 107.3, 111.65 (**C**$_{butad.}$, **C**$_{arom.}$). MS [+ESI]: m/z (%) 638 (100) $[M+H]^+$. Micro analysis: $C_{30}H_{45}Cl_3FN_3O_2S$, (M_A = 637.12 g/mol). Calculated: C, 56.55; H, 7.12; N, 6.60; S, 5.03%; Found: C, 756.54; H, 7.13; N, 6.63; S, 5.07%.

[4-(1-(3-Fluorophenyl)piperazin-1-yl]-4-(4-cyclopentyl-sulfanyl)-1,1,2-trichloro-3-nitro-1,3-butadiene (9b): Compound **9b** was synthesized by the reaction of **3b** (0.1g, 0.3 mmol) with 1-(3-fluorophenyl)piperazine **8** (0.053 g, 0.3 mmol) according to general method 2. Orange solid, yield: 0.049 g, 35%. R_f: 0.53 [PET:EtAc (2:1)]. M.p.: 128.5°C. FT-IR (KBr, cm^{-1}): ν= 2962, 2868, 2826 (C-H), 1613 (C=C), 1529, 1273 (NO_2). ^{1}HNMR ($CDCl_3$, ppm): δ= 1.48-1.52 (s, 2H, C**H**$_{2cyclo.}$), 1.57-1.64 (s, 2H, C**H**$_{2cyclo.}$), 1.67-1.78 (s, 2H, C**H**$_{2cyclo.}$), 2.00-2.10 (m, 2H, C**H**$_{2cyclo.}$), 3.20-3.30 (s, 1H, S-C**H**$_{cyclo.}$), 3.50-4.00 (m, 8H, C**H**$_{2piper.}$), 6.49-6.52 (m, 2H, C**H**$_{arom.}$), 6.67-6.64 (d, 1H, C**H**$_{arom.}$), 7.13-7.20 (t,1H, C**H**$_{arom.}$). ^{13}C NMR ($CDCl_3$, ppm): δ= 24.64, 48.36 (**C**$_{cyclo.}$), 48.75, 52.72 (**C**$_{piper.}$), 103.26, 103.46, 107.27, 107.44, 111.64, 111,66, 124.94, 126.69, 130.50, 130.58 (**C**$_{butad.}$, **C**$_{arom.}$), 151.60 (N-**C**$_{phenyl}$) , 162.82, 164.76 (**C**-F$_{arom.}$). MS [+ESI]: m/z (%) 480 (100) $[M]^+$. Micro analysis: $C_{19}H_{21}Cl_3FN_3O_2S$, (M_A = 480.81 g/ mol). Calculated: C, 47.46; H, 4.40; N, 8.74; S, 6.67%; Found: C, 747.50; H, 4.43; N, 8.70; S, 6.69%.

[4-(1-(3-Fluorophenyl)piperazin-1-yl]-4-(4-octadecyl-sulfanyl)-1,1,2-trichloro-3-nitro-1,3-butadiene (9c): Compound **9c** was synthesized by the reaction of **3c** (0.1g, 0.3 mmol) with 1-(3-fluorophenyl)piperazine **8** (0.034 g, 0.3 mmol) according to general method 2. Orange solid, yield: 31%. R_f: 0.52 [PET:EtAc (4:1)]. M.p.: 96-97°C. FT-IR (KBr, cm^{-1}): ν= 2926, 2854 (C-H), 1615 (C=C), 1528, 1265 (NO_2). ^{1}H NMR ($CDCl_3$, ppm): δ= 0.77-0.84 (t, 3H, C**H$_3$**), 1.18-1.24 (d, 30H, C**H$_2$**), 1.50 (s, 2H, C**H$_2$**), 2.90 (s, 2H, S-C**H$_2$**), 3.30 (s, 4H, C**H**$_{2piper.}$), 3.65-4.10 (sbr, 4H, C**H**$_{2piper.}$), 6.50-6.64 (m, 2H, **H**$_{arom.}$), 7.14-7.20 (m, 2H, **H**$_{arom.}$). ^{13}C NMR ($CDCl_3$, ppm): δ= 14.15 (**C**H_3), 22.71, 28.71, 29.04, 29.36, 29.53, 29.63, 29.68, 29.71, 29.80, 31.94, 35.63 (**C**H_2), 48.79 (**C**$_{piper.}$), 103.29, 103.48, 107.47, 111.65, 130.53 (**C**$_{butad.}$, C$_{arom.}$). MS [+ESI]: m/z (%) 688 (100) $[M+Na]^+$. Micro analysis: $C_{32}H_{49}Cl_3FN_3O_2S$, (M_A = 665.17 g/mol). Calculated: C, 57.78; H, 7.42; N, 6.32; S, 4.82%; Found: C, 57.80; H, 7.44; N, 6.35; S, 4.83%.

[4-(1-(Tetrahydro-2-furyl)piperazin-1-yl]-4-(4-hexadecyl-sulfanyl)-1,1,2-trichloro-3-nitro-1,3-butadiene (11a): Compound **11a** was synthesized from the reaction of **3a** (0.1g, 0.19 mmol) with 1-(1-tetrahydro-2-furyl)piperazine **10** (0.037 g, 0.19 mmol) according to general method 2. Yellow oil, yield: 0.043 g, 34%. R_f: 0.67 [PET:EtAc (1:1)]. FT-IR (KBr, cm^{-1}): ν= 2952, 2853 (C-H), 1659 (C=O), 1529, 1273 (NO_2). H NMR ($CDCl_3$, ppm): δ=0.88-1.03 (t, 3H, C**H$_3$**), 1.22-1.26 (m, 28H, C**H$_2$**), 1.30-1.48 (m, 2H, C**H$_2$**), 1.58-1.65 (m, 2H, C**H**$_{2furyl}$), 2.95-2.98 (s, 2H, S-C**H$_2$**), 3.60-3.82 (m, 2H, C**H**$_{2furyl}$), 3.84-3.97 (m, 8H, C**H**$_{2piper.}$), 4.57-4.59 (t, 1H, C**H**$_{furyl}$). ^{13}C NMR ($CDCl_3$, ppm): δ= 14.12 (**C**H_3), 22.69, 25.58, 25.79, 27.90, 28.70 , 29.02, 29.35, 29.51, 29.60, 29.65, 29.67, 29.71, 29.70, 29.75, 31.92 (**C**H_2), 35.61 (S-**C**H_2), 41.75, 44.73 47.51 (**C**$_{furyl}$), 51.77, 53.49 (**C**$_{piper.}$), 69.18 (**C**$_{furyl}$), 118.77, 124.97, 126.56 (**C**$_{butad.}$), 169.88 (**C**=O). MS [+ESI]: m/z (%) 664 (100) $[M+Na]^+$. Micro analysis: $C_{29}H_{48}Cl_3N_3O_4S$, (M_A= 641.13 g/mol). Calculated: C, 54.33; H, 7.55; N, 6.55; S, 5.00%; Found: C, 54.37; H, 7.56; N, 6.58; S, 5.02%.

[4-(1-(Tetrahydro-2-furyl)piperazin-1-yl]-4-(4-octadecyl-sulfanyl)-1,1,2-trichloro-3-nitro-1,3-butadiene (11c): Compound **11c** was synthesized by the reaction of **3c** (0.1g, 0.19 mmol) with 1-(1-tetrahydro-2-furyl)piperazine **10** (0.353 g, 0.19 mmol) according to general method 2. Yellow solid, yield: 0.065 g, 51%. R_f: 0.42 [PET:EtAc (1:1)]. M.p.: 120°C. FT-IR (KBr, cm^{-1}): ν= 2952, 2853 (C-H), 1659 (C=O), 1613 (C=C), 1529, 1273 (NO_2). ^{1}H NMR ($CDCl_3$, ppm): δ= 0.79-0.83 (t, 3H,

C**H**$_3$), 1.15-1.25 (m, 28H, C**H**$_2$), 1.28-1.35 (m, 2H, C**H**$_2$), 1.57-1.63 (m, 2H, C**H**$_2$), 1.84-2.00 (m, 4H, C**H**$_{2furyl}$), 2.85-2.97 (s, 2H, S-C**H**$_2$), 3.40-3.70 (sbr, 4H, C**H**$_{2piper.}$), 3.75-3.81 (m, 2H, C**H**$_{2furyl}$), 3.83-3.98 (m, 4H, C**H**$_{2piper.}$), 4.47-4.57 (t, 1H, C**H**$_{furyl}$). ^{13}C NMR ($CDCl_3$, ppm): δ=14.14 (**C**H$_3$), 22.71, 25.79, 27.88, 28.70, 29.04, 29.37, 29.39, 29.53, 29.62, 29.67, 29.71, 29.76, 31.94 (**C**H$_2$), 35.61 (S-**C**H$_2$), 41.75, 44.74 (**C**$_{furyl}$), 52.63, 53.51 (**C**$_{piper.}$), 69.21 (**C**$_{furyl}$), 118.73, 124.98, 126.57 (**C**$_{butad.}$), 169.84 (**C**=O). MS [+ESI]: m/z (%) 692 (100) $[M+Na]^+$. Micro analysis: $C_{31}H_{52}Cl_3N_3O_4S$, (M_A= 669.19 g/mol). Calculated: C, 55.64; H, 7.83; N, 6.28; S, 4.79%; Found: C, 55.69; H, 7.86; N, 6.32; S, 4.84%.

[4-(1-(3,4-Dichlorophenyl)piperazin-1-yl]-4-(4-cyclopentyl-sulfanyl)-1,1,2-trichloro-3-nitro-1,3-butadiene (13b): Compound **13b** was synthesized by the reaction of **3b** (0.1g, 0.3 mmol) with 1-(3,4-dichlorophenyl)piperazine **12** (0.069 g, 0.3 mmol) according to general method 2. Orange solid, yield: 0.064 g, 41%. R_f: 0.53 [PET:EtAc (2:1)]. M.p.: 172-173°C. FT-IR (KBr, cm^{-1}): ν= 3054, 2986, 1610 (C=C), 1526, 1265 (NO_2). ^{1}HNMR ($CDCl_3$, ppm): δ=1.50-1.53 (s, 2H, C**H**$_{2cyclo.}$), 1.55-1.64 (s, 2H, C**H**$_{2cyclo.}$), 1.67-1.77 (s, 2H, C**H**$_{2cyclo.}$), 2.00-2.10 (m, 2H, C**H**$_{2cyclo.}$), 3.20 (s, 1H, S-C**H**$_{cyclo.}$), 3.45-4.20 (m, 8H, C**H**$_{2piper.}$), 6.67-6.71 (d, 1H, C**H**$_{arom.}$), 6.89 (d, 1H, C**H**$_{arom.}$), 7.24-7.28 (d, 1H, C**H**$_{arom.}$). ^{13}C NMR ($CDCl_3$, ppm): δ= 24.63, 48.36 (**C**$_{cyclo.}$), 48.82, 52.57 (**C**$_{piper.}$), 115.96, 117.90, 123.91, 126.61, 130.80, 131.17, 143.37 (**C**$_{butad.}$, **C**$_{arom.}$). MS [+ESI]: m/z (%) 532 (100) $[M]^+$. Micro analysis: $C_{19}H_{20}Cl_5N_3O_2S$, (M_A = 531.71 g/mol). Calculated: C, 42.92; H, 3.79; N, 7.90; S, 6.03%; Found: C, 42.93; H, 3.81; N, 7.92; S, 6.04%.

[4-(1-(3,4-Dichlorophenyl)piperazin-1-yl]-4-(4-octadecyl-sulfanyl)-1,1,2-trichloro-3-nitro-1,3-butadiene (13c): Compound **13c** was synthesized frbyom the reaction of **3c** (0.1g, 0.3 mmol) with 1-(3,4-dichlorophenyl)piperazine **12** (0.044 g, 0.3 mmol) according to general method 2. Orange solid, yield: 0.035 g, 26%. R_f: 0.48 [PET:EtAc (5:1)]. M.p.: 75-76°C. FT-IR (KBr,cm^{-1}): ν= 2921, 2852 (C-H), 1593 (C=C), 1528, 1272 (NO_2). ^{1}HNMR ($CDCl_3$, ppm): δ= 0.77-0.84 (t, 3H, C**H**$_3$), 1.15-1.25 (m, 26H, C**H**$_2$), 1.28-1.35 (m, 2H, C**H**$_2$), 1.47-1.53 (s, 2H, C**H**$_2$), 1.55-1.67 (m, 2H, C**H**$_2$), 2.87-2.97 (s, 2H, S-C**H**$_2$), 3.20-3.30 (s, 4H, C**H**$_{2piper.}$), 3.50-4.00 (sbr, 4H, C**H**$_{2piper.}$), 6.65-6.70 (d, 1H, **H**$_{arom.}$), 6.90 (d, 1H, **H**$_{arom.}$), 7.25-7.30 (d, 1H, **H**$_{arom.}$). ^{13}C NMR ($CDCl_3$, ppm): δ= 14.15 (**C**H$_3$), 22.71, 28.71, 29.04, 29.36, 29.53, 29.63, 29.68, 29.71, 29.80, 31.94, 35.63 (**C**H$_2$), 48.79 (**C**$_{piper.}$), 103.29, 103.48, 107.47, 111.65, 130.53 (**C**$_{butad.}$, **C**$_{arom.}$**)**. MS [+ESI]: m/z (%) 738 (100) $[M+Na]^+$. Micro analysis: $C_{32}H_{48}Cl_5N_3O_2S$, (M_A = 716.07 g/mol). Calculated: C, 53.67; H, 6.76; N, 5.87; S, 4.48%; Found: C, 53.72; H, 6.79; N, 5.88; S, 5.89%.

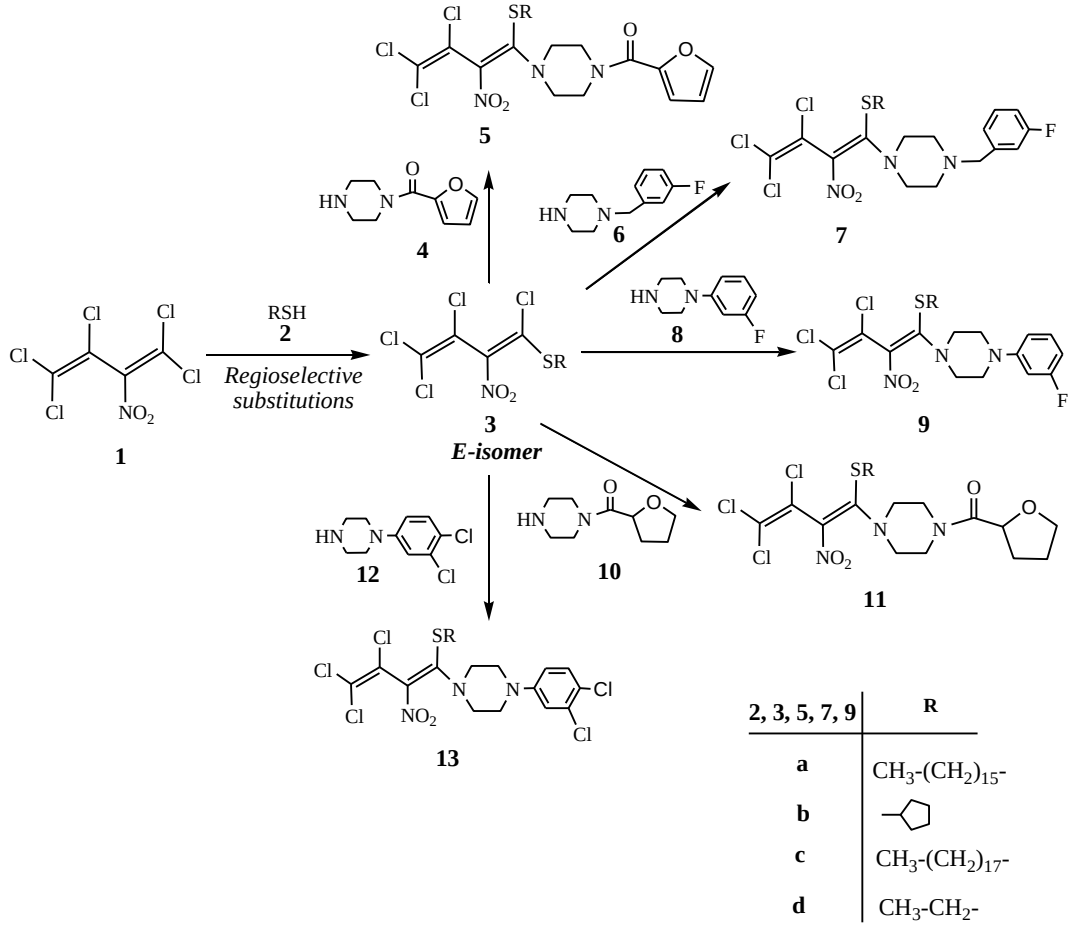
X-Ray Crystallography

Yellow crystals of compound **5d** suitable for X-ray diffraction analysis were obtained by slow evaporation of an ethanol/chloroform (10:1) solution at room temperature. The compound **5d**, $C_{15}H_{16}Cl_3N_3O_4S_1$, having approximate dimensions of 0.60 × 0.30 × 0.20 mm, was mounted on a glass fiber. All measurements were made on a Rigaku R-Axis Rapid-S imaging plate area detector with graphite monochromated Mo-Kα radiation (λ = 0.71073 Å). The crystal structures were solved by SIR 92 [12] and refined with CRYSTALS [13]. The non-hydrogen atoms were refined anisotropically. H atoms were located in geometrically idealized positions C-H = 0.95(6) Å and treated as riding and U_{iso}(H) = 1.2U_{eq}(C). Drawing was performed with the program ORTEP-III [14] with 50% probability displacement ellipsoid. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers. CCDC-1544558 for compound **5d** [15].

RESULTS AND DISCUSSION

The aim of this study was to synthesize new piperazine derivatives **5a**, **5c-d**, **7a-c**, **9a-c**, **11a**, **11c** and **13b-c** and to determine the exact structures of the new compounds by using spectroscopic techniques (^{1}H NMR, ^{13}C NMR, FTIR, MS) and X-ray diffraction method. In this work, the *S*-substituted-3-nitro-1,3-butadienes were obtained by direct reactions of pentachloro-3-nitrobutadiene with some *S*-nucleophiles [hexadecylthiol-, cyclopentylthiol, octadecylthiol and ethylthiol] [8-10].

The novel piperazine derivatives **5a**, **5c**, **5d** [11], **7a-c**, **9a-c**, **11a**, **11c** and **13b-c** were synthesized by the reaction of the *S*-substituted-3-nitro-1,3-butadienes (**3a** [8], **3b** [9], **3c** [8] and **3d** [10]) with (1-(2-furoyl)piperazine **4**, 1-(4-fluorobenzyl) piperazine **6**, 1-(3-fluorophenyl) piperazine **8**, 1-(1-tetrahydro-2-furyl) piperazine **10**, and 1-(3,4-dichlorophenyl) piperazine **12** in $CHCl_3$, respectively, as shown in Scheme 1.



Scheme 1. Synthesis of piperazine derivatives.

The FT-IR spectra of compounds **5a** and **5c**, **11a** and **11c** showed the absorption bonds of the amide carbonyl group at 1649 and 1659 cm^{-1}, respectively. The proton NMR data of compounds **5a**, **5c**, **7a-c**, **9a-c** and **13b-c** showed the aromatic protons within the range 6.42-7.55 ppm. In the ^{13}C NMR spectra of all compounds signals were observed at 49-62 ppm for the methylene carbon atom of the piperazine ring. Due to the aromatic ring of furoyl, in the carbon NMR spectra of compounds **5a** and **5c** signals were observed at δ = 147 ppm for the furoyl (C-O) carbons. The (C-O) signals of the tetrahydrofuroyl units were observed at 69 ppm in the carbon NMR spectra of **11a** and **11c**. The carbon NMR shift of the carbonyl groups of compounds **5a**, **5c**, **11a** and **11c** appeared around δ =169-170 ppm. The (+ESI) mode mass spectra of **5c** revealed at *m/z* (%) 688 (100) $[M+23]^+$ which corresponds to the addition of one sodium ion. The (+ESI) mass spectrum of **5c** is shown in Fig. 1.

X-ray study

The crystals used in the X-ray diffraction study were obtained by recrystallization of compound **5d** from a solution of ethanol-chloroform (10:1). The crystal structure of compound **5d** is shown in Fig. 2.

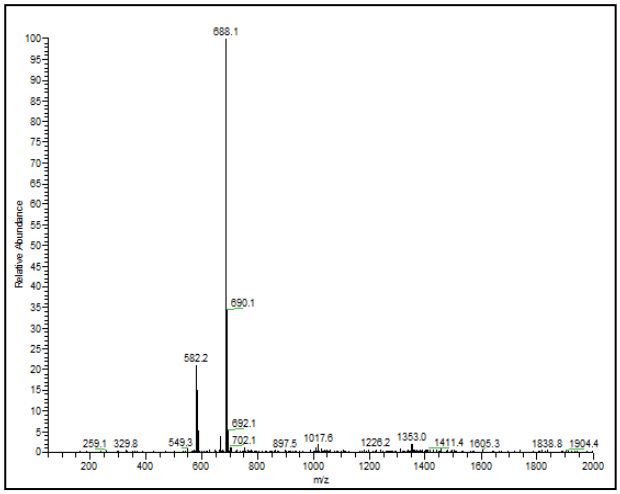


Fig. 1. MS[+ESI] spectrum of compound **5c**

The butadiene unit is not planar as would be if the two double bonds were fully conjugated. Non-coplanar structures of the butadiene fragments of these molecules and the clear C2-C3 single bonds indicate the lack of delocalization of π-electron density in the butadiene chains, which is apparently one of the major reasons for the inertness of polychlorobutadienes and their functional derivatives with non-planar molecular structure relative to 1,4-addition. Crystal data and refinement parameters are summarized in Table 1 and the selected bond distances, bond and torsion angles are listed in Table 2 for compound **5d**.

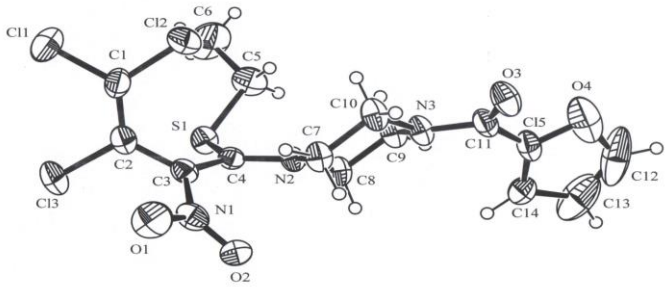


Fig. 2. Molecular structure of compound **5d**. Displacement ellipsoids are plotted at the 40% probability level (symmetry transformations used to generate equivalent atoms: (i)−x, −y, −z).

Table 1. Main crystallographic parameters of compound **5d**

Empirical formula	$C_{15}H_{16}Cl_3N_3O_4S_1$
Crystal colour, habit	Yellow, chunk
Crystal size (mm)	0.60 × 0.30 × 0.20
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	P21/c
Cell dimensions	*a* = 12.5503(2)Å *b* = 11.2039(2)Å *c* = 14.1007(4)Å
Cell volume (Å^3)	1924.60(7)
Cell formula units (Z)	4
Density (g.cm^{-3})	1.521
μ [cm^{-1}]	0.610
F_{000}	904.00
h,k,l . ranges	-17≤h≤17, -15≤k≤15, -20≤l≤17
Reflections collected	112600
Independent reflections	5845 [R_{int} = 0.086]
Data/restraints/parameters	4293/0/251
Goodness of fit indicator	1.115
Final R indices [I>2σ(I)]	R_1 = 0.081 wR_2 = 0.031
Largest diff. peak and hole	0.035 and −0.035 e.Å^{-3}
CCDC deposition number	1544558

Table 2. Selected bond distances (Å), bond and torsion angles (°) for compound **5d**

Bond distances		Bond angles		Torsion angles	
C1-C2	1.330(4)	C1-C2-C3	124.4(3)	C1-C2-C3-C4	-60.2(5)
C2-C3	1.459(4)	C2-C3-C4	124.0(3)	N2-C8-C9-N3	52.4(3)
C3-C4	1.398(4)	O1-N1-O2	122.3(3)	N2-C7-C10-N3	-56.4(3)
C4-S1	1.734(3)	C7-N2-C8	112.1(2)	C2-C3-C4-S1	-38.2(3)
C4-N2	1.338(4)	C9-N3-C10	112.5(3)	C2-C3-C4-N2	140.2(3)
C11-O3	1.204(4)	Cl1-C1-Cl2	113.5(2)	C1-C2-C3-N1	118.1(4)

The nitro group is nearly coplanar with the butadiene unit to which it is attached, with torsion angles of (O1–N1–C3–C2) and (O1–N1–C3–C4) -11.3(4)° and 167.0(3)°, respectively. The four carbon atoms of the piperazine ring (C7-C8-C9-C10) are planar with a maximum deviation of 0.0102(1)Å and they adopt a chair conformation; the perpendicular distances of the two chair atoms

in the para positions (N2 and N3) from the plane of the other four atoms of the six-membered piperazine ring are 0.6066(1) and -0.6332(1) Å, respectively. The two ethyl groups, at N2 and N3, adopt an *anti* conformation. The furan ring (C12-C13-C14-C15-O4) is planar with a maximum deviation of 0.0296(1)Å. The dihedral angle between the piperazine ring and the furan ring is 142.4(1)°.

CONCLUSIONS

In this study, new piperazine derivatives were obtained by the reaction of *S*-substituted-3-nitro-1,3-butadienes with some piperazine derivatives in $CHCl_3$ at room temperature. The substitution reaction proceeds by an addition-elimination mechanism (nucleophilic vinylic substitution (**S_NV**in). First, an addition of the attacking reagent to the C,C double bond occurs and in a second step the intermediate product is stabilized by elimination of hydrogen chloride. The novel piperazine derivatives were obtained in good yields, and are yellow solids or oils. They are soluble in organic solvents such as chloroform, petroleum ether. The crystal structure of compound **5d** was solved by X-ray diffraction method. The crystal structure showed that piperazinyl-substituted-3-nitrobutadienes were *E*-isomers.

Acknowledgement: *The authors would like to express their gratitude to the Scientific Research Projects Coordination Unit of Istanbul University for financial support (Project Number: 49993).*

REFERENCES

1. L. M. Kalatskaya, A. A. Malama, *Mikrobiologiya*, **55**, 618 (1986).
2. P.E. Blower, J. H. Chung, J. S. Verducci, S. Lin, J. K. Park, Z. Dai, C. G. Liu, T. D. Schmittgen, W. C. Reinhold, C. M. Croce, J. N. Weinstein, W. Sadee, *Mol. Cancer Ther*., **7**, 1 (2008).
3. M. Berkheij, L. van der Sluis, C. Sewing, D. J. den Boer, J. W. Terpstra, H. Hiemstra, W. I. I. Bakker, A. van den Hoogenband, J. H. van Maarseveena, *Tetrahedron Lett.*, **46**, 2369 (2005).
4. R. S. Upadhayaya, N. Sinha, S. Jain., N. Kishore, R. Chandra, S.K. Arora, *Bioorg. Med. Chem.*, **12**, 2225 (2004).
5. Z. Gokmen, N. G. Deniz, M. E. Onan, M. Stasevych, V. Zvarych, O. Komarovska-Porokhnyavets, V. Novikov, *Wulfenia*, **22**(12), 371 (2015).
6. P. Chaudhary, R. Kumar, A. K. Verma, D. Singh, V. Yadav, A. K. Chhillar, G. L. Sharma, R. Chandra, *Bioorg. Med. Chem.*, **14**, 1819 (2006).
7. D. Dauzonne, J. M. Gillardin, F. Lepage, R. Pointet, S. Risse, G. Lamotte, P. Demerseman, *Eur. J. Med. Chem.*, **30**, 53 (1995).
8. C. Ibis, C. Sayil, *Rev. Roum Chim.*, **46** (3), 211 (2001).
9. N. G. Deniz, C. Ibis, *Heteroatom Chem*., **26**, 51 (2015).
10. C. Ibis, C. Sayil, *Phosphorus, Sulfur, and Silicon*, **92**, 39 (1994).
11. Z. Gokmen, N. Hanay, N. G. Deniz, *J. Chem. Soc. Pak.*, **38**, 1159 (2016).
12. A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. Burla, G. Polidori, M. Camalli, *J. Appl. Cryst*., **27**, 435 (1994).
13. D. J. Watkin, C. K. Prout, J. R. Carruthers, J. R. Betteridge, *Crystals*, **10**, P. W. Chemical Crystallography Laboratory: Oxford, UK, (1996).
14. L. J. Farrugia, *J. Appl. Crystallogr*, **30**, 565 (1997).
15. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited in the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-1544558 for **5d**. Copies of the data can be obtained free of charge, via www.ccdc.cam.ac.uk /conts/retrieving. html or from the Cambridge Crystallographic Data Centre, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033. E-mail: deposit@ccdc.cam.ac.uk.

СИНТЕЗ И СПЕКТРАЛНИ СВОЙСТВА НА НОВИ ПИПЕРАЗИНОВИ ПРОИЗВОДНИ И СТРУКТУРЕН АНАЛИЗ

З. Гокмен*, Н. Г. Дениз, М. Е. Онан, Ц. Саил

Истанбулски университет Церахпаша, Инженерен факултет, Департамент по химия, Отдел по органична химия, 34320 Авчилар, Истанбул, Турция

Постъпила на 15 май, 2017 г. ; приета на 18 април, 2018 г.

(Резюме)

Синтезирани са нови производни на пиперазина чрез реакции на *S*-заместени-3-нитро-1,3-бутадиени с някои производни на пиперазина: (1-(2-фуроил)-, 1-(4-флуоробензил)-, 1-(3-флуорофенил)- и 1-(1-тетрахидро-2-фурил) пиперазин) в $CHCl_3$ при стайна температура. Структурите на новите съединения са охарактеризирани чрез микроанализ, FT-IR, масспектрометрия, ^{1}H- и ^{13}C-NMR. Кристалната структура на синтезираното съединение **5d** е определена по метода на рентгеновата дифракция. Съединението **5d** кристализира в моноклинната пространствена група $P2_1/c$ с a = 12.5503(2) Å, b = 11.2039(2) Å, c = 14.1007(4) Å, Z = 4. Структурата е определена чрез директен метод (SIR92) и е прецизирана спрямо остатъчния индекс R_1 = 0.031.