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RESEARCH ARTICLE

Synthesis and Pharmacology of Some New N,N-Disubstituted Dithiocarbamate Derivatives

Fügen ÖZKANLI*, Ahu GÜNEY USANMAZ*, Keriman ÖZADALI*°, Engin YILDIRIM** and Kevser EROL**

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Summary

In this study, twenty two new N,N-disubstituted dithiocarbamate derivatives were synthesized. The structures of the compounds were confirmed by IR, 1H-NMR, mass spectroscopy and elemental analysis. Anticholinergic activities of the compounds were evaluated by the tests performed on isolated rat ileum and were compared with atropine sulfate. 1-(Diphenylamino)-1-oxopropan-2-yl 4-methylpiperazine dithiocarbamate 18 and 1-(α-naphthylamino)-1-oxopropan-2-yl 4-methylpiperidine dithiocarbamate 25 were found to show the best activity.

Key Words: *Dithiocarbamic acid esters, anticholinergic activity.*

Yeni Bazı N,N-Disübstitüe Ditiyokarbamat Türevlerinin Sentezi ve Farmakolojik Etkileri

Özet

Bu çalışmada, N,N-Disübstitüe ditiyokarbamat yapısında 22 yeni bileşiğin sentezi yapılmıştır. Bileşiklerin yapıları IR, 1H-NMR, kütle spektroskopisi ve elemental analiz ile kanıtlanmıştır. Bileşiklerin antikolinerjik aktiviteleri ise izole sıçan ileumunda atropine sülfat ile karşılaştırılarak değerlendirilmiştir. En yüksek aktiviteyi 1-(difenilamino)-1-oksopropan-2-il 4-metilpiperazin ditiyokarbamat 18 ve 1-(α-naftilamino)-1-oksopropan-2-il 4-metilpiperidin ditiyokarbamatın 25 gösterdiği bulunmuştur.

Anahtar Kelimeler: *Ditiyokarbamik asit esterleri, antikolinerjik aktivite.*

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INTRODUCTION

Anticholinergics represent a big group of drugs being used for the treatment of several diseases because of a large number of cholinergic receptors existing in different parts of the body (1, 2). Studies about anticholinergic drugs are still ongoing for some new areas such as gastroesophageal reflux disease (3).

Schizophrenia and Parkinson diseases are other special areas where anticholinergics are under investigation (4). Considering structural properties of anticholinergic agents, studies on anticholinergic and antiparkinson activities of disubstituted dithiocarbamates and structural similarity of N-aryl acetamide derivatives with Adifenine, Phencarbamide and other anticholinergics, we intended to make a synthesis of some new N,N-disubstituted dithiocarbamic acid 2-(arylamino)-2-oxoethyl ester derivatives, confirm their structure, and investigate their anticholinergic properties.

* Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Hacettepe University, Ankara, Turkey.
** Department of Pharmacology, Faculty of Medicine, Osman Gazi University, Eskişehir, Turkey.
° Corresponding Author E-mail: kozadali@hacettepe.edu.tr

According to the previous structure-activity relation studies, for a desirable anticholinergic activity, a quaterner amonium group or a reverse amine group which can form a cationic structure in biological media, linking to the originated carbon atom with an ester, ether or a hydrocarbon is required. Substituents of the originated carbon atom must be an aromatic group to make Van der Waals interaction with the receptor and a cycloaliphatic group for hydrophobic interaction (5). These previous studies prompted us to do some new N,N-disubstituted dithiocarbamic acid derivatives 6-27 (Scheme) having α-naphthyl and diphenyl as aryl group in 'N-aryl acetamide' and 'N-aryl propionamide' moiety, 4-substituted piperazines, 2/4-metilpiperidine and cyclohexylamine as amine group in 'Dithiocarbamic acid' moiety.

The structures of the compounds 6-27 were confirmed by IR, ^{1}H-NMR, mass spectroscopy and elemental analysis. Anticholinergic activities of the compounds were determined by the tests performed on isolated rat ileum. For this purpose, albino rats from both species with a weight of 200-250 g were used and each concentration was studied and evaluated separately. Each molecule was applicated to a different animal and the results were compared with atropine's. Student's test was used for comparison.

MATERIALS AND METHODS

Chemistry

All chemicals used in this study were supplied by Aldrich (Steinheim, Germany). Melting points were determined by Thomas Hoover capillary melting point apparatus (Philadelphia, PA, USA) and are uncorrected. IR spectra (KBr disc) were recorded on a Bruker Vector 22 IR (Beaconsfield, UK). ^{1}H-NMR spectra were recorded on a Bruker Avance 400 MHz FT NMR Spectrometer (Karlsruhe, Germany) using tetramethylsilane as an internal standard and DMSO-d_6, $CDCl_3$. All chemical shifts were reported as δ (ppm) values and coupling constants (J) in Hz. Mass spectra were determined using an Agilent 5973-Network Mass Selective Detector (Ringoes, NJ, USA) and Micromass ZQ-4000 single quadruple mass spectrometer. The purity of the compounds was controlled by a thin-layer chromatography (silicagel, HF254, type 60, 0.25 mm, E. Merck, Darmstadt, Germany). The elemental analyses (C, H, N, S) were performed using a Leco CHNS 932 (Leco Coop, St.Joseph, MI, USA) analyzer by the Instrumental Analysis Laboratories at the Scientific and Technical Research Council of Turkey (Ankara, Turkey). The elemental analysis results were within 0.4% of theoretical values.

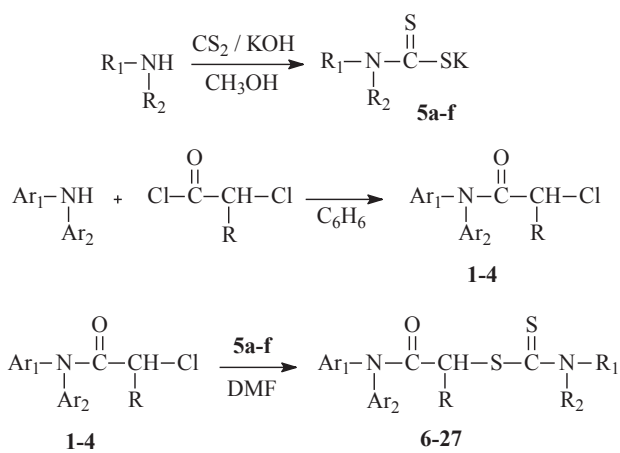


Figure. Synthetic pathway for compounds **6-27**.

General synthesis of α-chloro-N-arylacetamides (1-4)

α-Chloro-N-arylacetamides were synthesized from diphenylamine/α-naphthylamine and α-chloroacetyl chloride/α-chloropropionyl chloride according to literature methods (6, 7).

General synthesis of N,N-disubstituted dithiocarbamic acid salts (5a-f)

N,N-Disubstituted dithiocarbamic acid salts were prepared by the reaction of cyclohexylamine, piperazine and piperidine derivatives with carbon disulfide and potassium hydroxide according to literature methods (8, 9).

General synthesis of N,N-disubstituted dithiocarbamic acid-2-oxo-2-arylamino ethyl ester derivatives (6-17) (6)

A mixture of appropriate α-chloro-N-arylacetamide (0.001 mol) and appropriate N,N-disubstituted dithiocarbamic acid salt (0.001 mol) in 30 ml of methanol was refluxed for 8-12 hours. Then the reaction mixture was filtered off and poured into icedwater. The formed precipitate was washed with water and crystallized from an appropriate solvent.

2-(Diphenylamino)-2-oxoethyl 4-methylpiperazine dithiocarbamate (6)
IR (KBr) cm^{-1}; 3031 (ar. C-H), 2968, 2769, (al. C-H), 1656 (C=O), 1541 (C-N), 1271 (C=S), 1219-1030 (C-N), 1022 (C-S), 723 (C-H, monosubs. phenyl). ^{1}H-NMR (DMSO-d_6) δ 2.19 (s, 3H, -CH_3), 2.38 (t, 4H, piperazine $H^{3,5}$), 3.80 (t, 2H, piperazine H^2), 4.06 (t, 2H, piperazine H^6), 4.17 (s, 2H, -CH_2-), 7.1-7.6 (m, 10H, phenyl H). ESI-MS (m/e); 408 $[M+Na]^+$, 386 $[M+1]^+$ (100%), 217, 143, 118.

2-(Diphenylamino)-2-oxoethyl 4-ethylpiperazine dithiocarbamate (7)
IR (KBr) cm^{-1}; 3056 (ar. C-H), 2968, 2910 (al. C-H), 1660 (C=O), 1590 (C-N), 1470 (C-N), 1272 (C=S), 1240-1032 (C-N), 1016 (C-S), 694 (C-H, monosubs. phenyl). ^{1}H-NMR (DMSO-d_6) δ; 1.13 (t, 3H, -CH_3), 2.50 (q, 2H, -N-CH_2-), 2.58 (t, 4H, piperazine $H^{3,5}$), 4.05 (t, 4H, piperazine $H^{2,6}$), 4.35 (s, 2H, -CH_2-), 7.17-7.44 (m, 10H, phenyl H). ESI-MS (m/e); 399 $[M]^+$, 210, 188 (100%), 168, 113.

2-(Diphenylamino)-2-oxoethyl 4-phenylpiperazine dithiocarbamate (8)
IR (KBr) cm^{-1}; 3061, 3034 (ar. C-H), 2840 (al. C-H), 1678 (C=O), 1599, 1488 (C-N), 1277 (C=S), 1241-1153 (C-N), 1016 (C-S), 698, 755 (C-H, monosubs. phenyl). ^{1}H-NMR (DMSO-d_6) δ; 3.25 (t, 4H, piperazine $H^{3,5}$), 4.06 (t, 4H, piperazine $H^{2,6}$), 4.30 (s, 2H, -CH_2-), 6.77-7.49 (m, 15H, phenyl H). ESI-MS (m/e); 447 $[M]^+$, 279 (100%), 237, 205, 168.

2-(Diphenylamino)-2-oxoethyl 4-methylpiperidine dithiocarbamate (9)
IR (KBr) cm^{-1}; 3060 (ar. C-H), 2966-2842, (al. C-H), 1670 (C=O), 1590 (C-N), 1265 (C=S), 1236-1000 (C-N), 1022 (C-S), 723 (C-H, monosubs. phenyl). ^{1}H-NMR (DMSO-d_6) δ; 0.89 (d, 3H, -CH_3), 0.90-1.20 (q, 2H, piperidine H^3), 1.60-1.80 (m, 3H, piperidine $H^{4,5}$), 3.15 (t, 2H, piperidine H^6), 4.03 (s, 2H, -CH_2-), 4.30-4.50 (br, 1H, piperidine H^{2a}), 5.0-5.3 (br, 1H, piperidine H^{2b}) 7.24-7.48 (m, 10H, phenyl H). ESI-MS (m/e); 407 $[M+Na]^+$ (100%), 385 $[M+1]^+$, 216, 210, 142.

2-(Diphenylamino)-2-oxoethyl 2-methylpiperidine dithiocarbamate (10)
IR (KBr) cm^{-1}; 3047 (ar. C-H), 2974-2860 (al. C-H), 1668 (C=O), 1591, 1490 (C-N), 1241 (C=S), 1253-1000 (C-N), 964 (C-S), 700, 757 (C-H, monosubs. phenyl). ^{1}H-NMR (DMSO-d_6) δ; 1.27 (d, 3H, -CH_3), 1.56-1.77 (m, 8H, piperidine $H^{3,4,5,6}$), 3.19 (br, 1H, piperidine H^2), 3.90-4.10 (s, 2H, -CH_2-), 7.17-7.43 (m, 10H, phenyl H). ESI-MS (m/e); 384 $[M]^+$, 216 (100%), 168, 142, 98.

2-(Diphenylamino)-2-oxoethyl cyclohexylamine dithiocarbamate (11)
IR (KBr) cm^{-1}; 3211 (N-H), 3009 (ar. C-H), 2935-2851 (al. C-H), 1668 (C=O), 1526, 1491 (C-N), 1237 (C=S), 1158-1075 (C-N), 985 (C-S), 694, 700 (C-H, monosubs. phenyl). ^{1}H-NMR (DMSO-d_6) δ; 1.19-1.28 (m, 6H, cyclohexane $H^{3,4,5}$), 1.55-1.87 (m, 5H, cyclohexane $H^{1,2,6}$), 4.00 (s, 2H, -CH_2-), 7.27-7.48 (m, 10H, phenyl H), 9.99 (d, 1H, -NH-). ESI-MS (m/e); 407 $[M+Na]^+$ (100%), 385 $[M+1]^+$, 286, 216, 142.

2-(α-Naphthylamino)-2-oxoethyl 4-methylpiperazine dithiocarbamate (12)
IR (KBr) cm^{-1}; 3254 (N-H), 3015 (ar. C-H), 2967-2768 (al. C-H), 1648 (C=O), 1536,1419 (C-N), 1247 (C=S), 1231-1007 (C-N), 994 (C-S), 794, 771 (C-H, α-subs.naphthalene). ^{1}H-NMR (DMSO-d_6) δ; 2.19 (s, 3H, -CH_3), 2.47 (t, 4H, piperazine $H^{3,5}$), 3.93 (br, 2H, piperazine H^2), 4.21 (br, 2H, piperazine H^6), 4.38 (s, 2H, -CH_2-), 7.44-8.11 (m, 7H, naphthalene H), 10.19 (s, 1H, -NH-). ESI-MS (m/e); 382 $[M+Na]^+$, 360 $[M+1]^+$ (100%), 217, 118, 99.

2-(α-Naphthylamino)-2-oxoethyl 4-ethylpiperazine dithiocarbamate (13)
IR (KBr) cm^{-1}; 3259 (N-H), 3031 (ar. C-H), 2968-2769, (al. C-H), 1656 (C=O), 1430 (C-N), 1271 (C=S), 1220-1033 (C-N), 1022 (C-S), 796, 774 (C-H, α-subs. naphthalene). ^{1}H-NMR (DMSO-d_6) δ; 1.20 (t, 3H, -CH_3), 2.63 (br, 6H, piperazine $H^{3,5}$, -N-CH_2-), 4.07 (s, 2H, -CH_2-), 4.43 (s, 4H, piperazine $H^{2,6}$), 7.44-8.05 (m, 7H, naphthalene H), 9.24 (s, 1H; -NH-). ESI-MS (m/e); 396 $[M+Na]^+$ (100%), 374 $[M+1]^+$, 231, 157.

2-(α-Naphthylamino)-2-oxoethyl 4-phenylpiperazine dithiocarbamate (14)
IR (KBr) cm^{-1}; 3267 (N-H), 3053, 3034 (ar. C-H), 2995-2740 (al. C-H), 1662 (C=O), 1535, 1425 (C-N), 1272 (C=S), 1220-1150 (C-N), 1035 (C-S), 794, 758 (C-H, α-subs.naphthalene), 732, 692 (C-H, monosubs. phenyl). ^{1}H-NMR (DMSO-d_6) δ; 3.29 (t, 4H, piperazine

$H^{3,5}$), 4.11 (s, 2H, -CH_2-) 4.40 (t, 4H, piperazine $H^{2,6}$), 6.77-8.13 (m, 12H, naphthalene and phenyl H), 10.22 (s, 1H, -NH-). ESI-MS (m/e); 421 $[M]^+$, 279 (100%), 237, 205, 161.

2-(α-Naphthylamino)-2-oxoethyl 4-methylpiperidine dithiocarbamate (15)

IR (KBr) cm^{-1}; 3264 (N-H), 3051 (ar. C-H), 2995-2841 (al. C-H), 1660 (C=O), 1533, 1470 (C-N), 1267 (C=S), 1220-1020 (C-N), 965 (C-S), 791, 766 (C-H, α-subs. naphthalene). ^{1}H-NMR (DMSO-d_6) δ; 0.95 (d, 3H, -CH_3), 1.0-1.2 (q, 2H, piperidine H^3), 1.66-1.86 (m, 3H, piperidine $H^{4,5}$), 3.20 (t, 2H, piperidine H^6), 4.38 (s, 2H, -CH_2-), 4.40-4.60 (br, 1H, piperidine H^{2a}), 5.20-5.40 (br, 1H, piperidine H^{2b}), 7.46-8.12 (m, 7H, naphthalene H), 10.19 (s, 1H, -NH-). ESI-MS (m/e); 381 $[M+Na]^+$ (100%), 359 $[M+1]^+$, 184, 142, 98.

2-(α-Naphthylamino)-2-oxoethyl 2-methylpiperidine dithiocarbamate (16)

IR (KBr) cm^{-1}; 3267 (N-H), 3047 (ar. C-H), 2970-2846, (al. C-H), 1672 (C=O), 1503 (C-N), 1267 (C=S), 1233-1000 (C-N), 963 (C-S), 795, 772 (C-H, α-subs. naphthalene). ^{1}H-NMR (DMSO-d_6) δ; 1.32 (d, 3H, -CH_3), 1.50-1.90 (m, 8H, piperidine $H^{3,4,5,6}$), 3.10-3.40 (br, 1H, piperidine H^2), 4.4-4.6 (s, 2H, -CH_2-), 7.4-8.1 (m, 7H, naphthalene H), 9.42 (s, 1H, -NH-). ESI-MS (m/e); 358 $[M]^+$, 216 (100%), 184, 174, 142, 98.

2-(α-Naphthylamino)-2-oxoethyl cyclohexylamine dithiocarbamate (17)

IR (KBr) cm^{-1}; 3236 (N-H), 3040 (ar. C-H), 2936-2835 (al. C-H), 1647 (C=O), 1560, 1505 (C-N), 1299 (C=S), 1275-1000 (C-N), 967 (C-S), 791, 784, 765 (C-H, α-subs.naphthalene). ^{1}H-NMR (DMSO-d_6) δ; 1.09-1.96 (m, 10H, cyclohexane $H^{2,3,4,5,6}$), 4.18-4.26 (m, 1H, cyclohexane H^1), 4.28 (s, 2H, -CH_2-), 7.4-8.10 (m, 7H, naphthalene H), 10.10 (d, 1H, CS-N*H*-), 10.19 (s, 1H, -N*H*-CO). ESI-MS (m/e); 358 $[M]^+$, 217, 184, 143 (100%), 142.

General synthesis of N,N-disubstituted dithiocarbamic acid-1-methyl-2-oxo-2-arylamino ethyl ester derivatives (18-27) (10)

A mixture of appropriate α-chloro-N-arylpropionamide (0.001 mol) and appropriate N,N-disubstituted dithiocarbamic acid salt (0.001 mol) in 10 ml of DMF was stirred for nearly 2 hours at room temperature. The mixture was poured into iced water, and the precipitated compound was filtered, dried and crystallized from an appropriate solvent.

1-(Diphenylamino)-1-oxopropan-2-yl 4-methylpiperazine dithiocarbamate (18)

IR (KBr) cm^{-1}; 3055 (ar. C-H), 2976-2736 (al. C-H), 1657 (C=O), 1595, 1470 (C-N), 1287 (C=S), 1245-1000 (C-N), 979 (C-S), 758, 703, 692 (C-H, monosubs. phenyl). ^{1}H-NMR (DMSO-d_6) δ; 1.45 (d, 3H, -CH_3), 2.17 (s, 3H, -N-CH_3), 2.28-2.44 (m, 4H, piperazine $H^{3,5}$), 3.70-3.90 (br, 2H, piperazine H^2), 4.00-4.20 (br, 2H, piperazine H^6), 4.60-4.75 (q, 1H, -CH-), 7.10-7.60 (m, 10H, phenyl H). ESI-MS (m/e); 399 $[M]^+$, 231 (100%), 224, 196, 168, 143.

1-(Diphenylamino)-1-oxopropan-2-yl 4-phenylpiperazine dithiocarbamate (19)

IR (KBr) cm^{-1}; 3057, 3035 (ar. C-H), 2953, 2818, (al. C-H), 1666 (C=O), 1490 (C-N), 1272 (C=S), 1223-1000 (C-N), 989 (C-S), 755, 692 (C-H, monosubs. phenyl). ^{1}H-NMR (DMSO-d_6) δ; 1.40-1.54 (d, 3H, -CH_3), 3.20-3.40 (m, 8H, piperazine $H^{2,3,5,6}$), 4.60-4.80 (q, 1H, -CH-), 6.70-7.60 (m, 15H, phenyl H). ESI-MS (m/e); 461 $[M]^+$, 293 (100%), 237, 205, 168, 77.

1-(Diphenylamino)-1-oxopropan-2-yl 4-methylpiperidine dithiocarbamate (20)

IR (KBr) cm^{-1}; 3063 (ar. C-H), 2930-2860 (al. C-H), 1669 (C=O), 1594, 1490 (C-N), 1265 (C=S), 1225-1000 (C-N), 965 (C-S), 755, 700 (C-H, monosubs. phenyl). ^{1}H-NMR (DMSO-d_6) δ; 1.03 (d, 3H, -CH-CH_3), 1.10-1.40 (q, 2H, piperidine H^3), 1.67 (d, 3H, -S-CH-CH_3), 1.64-1.84 (m, 3H, piperidine $H^{4,5}$), 2.90-3.10 (t, 2H, piperidine H^6), 4.40-4.50 (q, 1H, -CH-), 4.50-4.70 (br, 1H, piperidine H^{2a}), 4.70-5.00 (br, 1H, piperidine H^{2b}) 7.00-7.60 (m, 10H, phenyl H). ESI-MS (m/e); 421 $[M+Na]^+$ (100%), 230, 224, 142.

1-(Diphenylamino)-1-oxopropan-2-yl 2-methylpiperidine dithiocarbamate (21)

IR (KBr) cm^{-1}; 3061, 3037 (ar. C-H), 2940, 2860, (al. C-H), 1668 (C=O), 1490 (C-N), 1264 (C=S), 1235-1000 (C-N), 962 (C-S), 756, 701 (C-H, monosubs. phenyl). ^{1}H-NMR (DMSO-d_6) δ; 1.18 (d, 3H, -CH-CH_3), 1.47

(d, 3H, -S-CH-CH_3), 1.50-1.80 (m, 6H, piperidine $H^{3,4,5}$), 2.46-2.56 (m, 3H, piperidine $H^{2,6}$), 4.60-4.80 (q, 1H, -C*H*-CH_3), 7.18-7.62 (m, 10H, phenyl H). ESI-MS (m/e); 398 $[M]^+$, 230 (100%), 168, 142, 98, 77.

1-(α-Naphthylamino)-1-oxopropan-2-yl 4-methylpiperazine dithiocarbamate (22)

IR (KBr) cm^{-1}; 3248 (N-H), 3053 (ar. C-H), 2971-2740 (al. C-H), 1653 (C=O), 1532, 1468 (C-N), 1292 (C=S), 1255-1020 (C-N), 999 (C-S), 784, 767 (C-H, α-subs. naphthalene). ^{1}H-NMR (DMSO-d_6) δ; 1.7 (d, 3H, -CH_3), 2.39 (s, 3H, -N-CH_3), 2.50-2.80 (br, 4H, piperazine $H^{3,5}$), 3.90-4.20 (br, 2H, piperazine H^2), 4.20-4.70 (br, 2H, piperazine H^6), 5.10-5.30 (q, 1H, -CH-), 7.20-8.20 (m, 7H, naphthalene H), 9.37 (s, 1H, -NH-). ESI-MS (m/e); 396 $[M+Na]^+$ (100%), 374 $[M+1]^+$, 198, 143, 99.

1-(α-Naphthylamino)-1-oxopropan-2-yl 4-ethylpiperazine dithiocarbamate (23)

IR (KBr) cm^{-1}; 3235 (N-H), 3053, 3034 (ar. C-H), 2982-2765 (al. C-H), 1658 (C=O), 1505, 1459 (C-N), 1267 (C=S), 1240-1000 (C-N), 987 (C-S), 794, 778, 762 (C-H, α–subs.naphthalene). ^{1}H-NMR (DMSO-d_6) δ; 1.00-1.30 (t, 3H, -CH_2-CH_3), 1.70 (d, 3H, -CH-CH_3), 2.40-2.80 (br, 6H, piperazine $H^{3,5}$, -N-CH_2-), 4.00-4.50 (br, 4H, piperazine $H^{2,6}$), 5.10-5.30 (q, 1H, -C*H*-CH_3), 7.20-8.20 (m, 7H, naphthalene H), 9.39 (s, 1H, -NH-). ESI-MS (m/e); 387 $[M]^+$, 245 (100%), 189, 157.

1-(α-Naphthylamino)-1-oxopropan-2-yl 4-phenylpiperazine dithiocarbamate (24)

IR (KBr) cm^{-1}; 3228 (N-H), 3050 (ar. C-H), 2977-2819, (al. C-H), 1658 (C=O), 1504 (C-N), 1273 (C=S), 1225-1025 (C-N), 1006 (C-S), 795, 777 (C-H, α-subs. naphthalene), 758, 693 (C-H, monosubs. phenyl). ^{1}H-NMR (DMSO-d_6) δ; 1.67 (d, 3H, -CH_3), 3.20-3.40 (t, 4H, piperazine $H^{3,5}$), 4.00-4.40 (br, 4H, piperazine $H^{2,6}$), 4.90-5.10 (q, 1H, -C*H*-CH_3), 6.70-8.10 (m, 12H, naphthalene and phenyl H), 10.27 (s, 1H, -NH-). ESI-MS (m/e); 435 $[M]^+$, 237, 236, 161, 132 (100%), 77.

1-(α-Naphthylamino)-1-oxopropan-2-yl 4-methylpiperidine dithiocarbamate (25)

IR (KBr) cm^{-1}; 3254 (N-H), 3052 (ar.C-H), 2985-2843 (al. C-H), 1655 (C=O), 1534 (C-N), 1249 (C=S), 1225-1010 (C-N), 968 (C-S), 785, 768 (C-H, α-subs.naphthalene). ^{1}H-NMR (DMSO-d_6) δ; 0.90 (d, 3H, -CH-CH_3), 1.10 (d, 3H, -S-CH-CH_3), 1.50-1.90 (m, 5H, piperidine $H^{3,4,5}$), 3.20 (t, 2H, piperidine H^6), 4.30-4.60 (q, 1H, -CH-), 4.80-5.00 (br, 1H, piperidine H^{2a}), 5.20-5.40 (br, 1H, piperidine H^{2b}), 7.40-8.20 (m, 7H, naphthalene H), 10.24 (s, 1H, -NH-). ESI-MS (m/e); 395 $[M+Na]^+$ (100%), 230, 198, 142.

1-(α-Naphthylamino)-1-oxopropan-2-yl 2-methylpiperidine dithiocarbamate (26)

IR (KBr) cm^{-1}; 3257 (N-H), 3049 (ar.C-H), 2971-2863 (al. C-H), 1695 (C=O), 1535, 1499 (C-N), 1252 (C=S), 1230-1000 (C-N), 957 (C-S), 794, 771 (C-H, α-subs. naphthalene). ^{1}H-NMR (DMSO-d_6) δ; 1.10-1.80 (m, 12H, piperidine $H^{3,4,5}$, -S-CH-CH_3, -CH-CH_3), 3.10-3.40 (m, 3H, piperidine $H^{2,6}$), 4.80-5.00 (q, 1H, -C*H*-CH_3), 7.40-8.10 (m, 7H, naphthalene H), 10.22 (s, 1H, -NH-). ESI-MS (m/e); 372 $[M]^+$, 230 (100%), 198, 174, 142, 98.

1-(α-Naphthylamino)-1-oxopropan-2-yl cyclohexylamine dithiocarbamate (27)

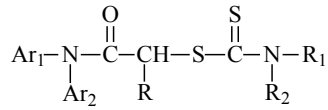
IR (KBr) cm^{-1}; 3188 (N-H), 3013 (ar. C-H), 2955-2853, (al. C-H), 1678 (C=O), 1502 (C-N), 1249 (C=S), 1205-1010 (C-N), 983 (C-S), 797, 774 (C-H, α-subs. naphthalene). ^{1}H-NMR (DMSO-d_6) δ; 1.09-1.96 (m, 13H, cyclohexane $H^{2,3,4,5,6}$, -CH_3), 4.30-4.50 (m, 1H, cyclohexane H^1), 4.94-5.02 (q, 1H, -C*H*-CH_3), 7.40-8.20 (m, 7H, naphthalene H), 9.17 (s, 1H, CS-N*H*-), 9.46 (s, 1H, -N*H*-CO). ESI-MS (m/e); 395 $[M+Na]^+$ (100%), 230, 174, 142.

Pharmacology (11)

The pharmacological assays were performed on the ileum of albino rats of either sex weighing 200–250 g. They were supplied from Osmangazi University, Experimental Animals Breeding Department, Eskisehir (Turkey). In the assays Krebs-Henseleit solution was used [(mmol/L) NaCl: 116; KCl: 5.9; $CaCl_2$: 2.5; $MgSO_4$: 1.2; $NaHPO_4$: 1.2; NaH_2PO_4: 1.2; $NaHCO_3$: 325.5; glucose: 11]. The isometric contractions were recorded by an isometric transducer (T-FDT10-A), May TDA 95 Transducer Data Acquisition System (May, Commat, Ankara, Turkey).

Twenty three animals were used in all the pharmacological studies. Animals entered the test after having fasted overnight. After animals had been

Table 1. Some characteristics of the compounds.



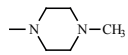
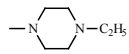
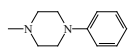
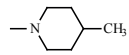
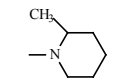
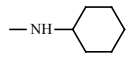
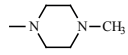
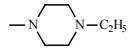
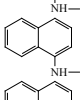
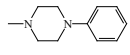
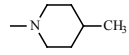
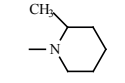
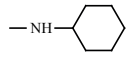
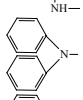
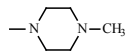
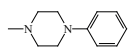
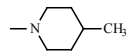
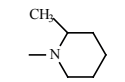
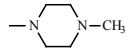
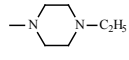
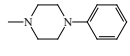
Comp.	–NAr$_1$Ar$_2$	R	–NR$_1$R$_2$	Yield (%)	M.p. (°C)	Crys. Solv.
6		H		73.4	164-6	Ethanol-water
7		H		76.1	145-7	Ethanol-water
8		H		59.7	154-6	Ethanol
9		H		70.9	188-90	Ethanol-water
10		H		55.6	131-3	Ethanol-water
11		H		52.7	140-2	Ethanol-water
12		H		63.2	165-7	Ethanol-water
13		H		67.3	148-50	Ethanol-water
14		H		60.8	178-80	Ethanol
15		H		75.1	138-40	Ethanol-water
16		H		74.8	121-3	Ethanol-water
17		H		40.4	oil	Ethanol-water
18		CH3		54.5	oil	Ethanol-water
19		CH3		53.7	oil	Ethanol
20		CH3		59.2	oil	Ethanol
21		CH3		58.6	oil	Ethanol
22		CH3		63.4	153-5	Ethanol-water
23		CH3		61	150-2	Ethanol-water
24		CH3		62.4	155-7	Ethanol
25		CH3		63	144-6	Ethanol
26		CH3		59.1	oil	Ethanol-water
27		CH3		57.8	133-5	Ethanol-water

Table 2. Anticholinergic activity results and the effective dose (EC_{50}) of the compounds (n=6) and atropine sulfate (% Inhibition ± SD).

Compound	Inhibition (%)			EC_{50} (n)*
	10^{-6} M	10^{-5} M	10^{-4} M	
6	16.33±8.52 (n=6)	29.50±6.02(n=6)	61.33±7.34(n=6)	$6.03\pm2.16\times10^{-5}$
7	22.67±8.50 (n=4)	30.83 ±18.73(n=6)	46.50±20.40(n=6)	$>10^{-4}$
8	6.10±4.31 (n=4)	23.00±9.97(n=6)	34.83±14.09(n=6)	$>10^{-4}$
9	0 (n=6)	45.20±21.32 (n=5)	59.33±9.71(n=6)	$6.47\pm3.07\times10^{-5}$ (n=4)
10	19.33±6.92 (n=6)	30.58±14.68(n=6)	58.17±8.18(n=6)	$7.20\pm3.35\times10^{-5}$
11	15.00±8.72 (n=4)	32.33±12.93(n=6)	55.50±12.32(n=6)	6.19±1.72x10-5 (n=4)
12	5.13±2.95 (n=4)	16.80±7.55 (n=5)	59.00±16.82 (n=6)	$6.43\pm2.13\times10^{-5}$
13	11.00±4.04 (n=5)	32.25±13.10 (n=5)	33.00±17.06 (n=6)	$>10^{-4}$
14	24.93±11.57(n=6)	44.50±9.73(n=6)	51.33±9.75(n=6)	$4.25\pm1.78\ x10^{-5}$(n=4)
15	28.50±8.89 (n=6)	47.67±14.28 (n=6)	59.50±6.35 (n=6)	$4.15\pm1.41\times10^{-5}$ (n=4)
16	0 (n=6)	0 (n=6)	0 (n=6)	-
17	10.22±5.84 (n=6)	26.83±9.60(n=6)	50.00±15.57(n=6)	$>10^{-4}$
18	13.80±7.46 (n=6)	40.17±9.99(n=6)	70.67±9.14(n=6)	$3.67\pm1.64\times10^{-5}$
19	7.00±5.52 (n=4)	29.00±14.58 (n=5)	37.75±18.08 (n=5)	$>10^{-4}$
20	9.80±4.65 (n=4)	40.40±13.26(n=5)	61.17±12.40(n=5)	$4.20\pm1.48\times10^{-5}$ (n=4)
21	26.00±7.01 (n=6)	44.17±11.51(n=6)	53.83±16.31(n=6)	$6.48\pm2.57\times10^{-5}$ (n=4)
22	16.07±9.08 (n=4)	31.00±12.77(n=6)	71.33±10.86(n=6)	$5.08\pm2.07\times10^{-5}$
23	13.33±7.76 (n=6)	34.67±11.40(n=6)	70.33±11.86(n=6)	$5.40\pm1.08\times10^{-5}$ (n=4)
24	19.80±5.02 (n=5)	36.80±13.17(n=5)	60.20±9.88(n=5)	$4.10\pm1.25\times10^{-5}$ (n=4)
25	24.93±15.52(n=5)	46.40±12.68(n=5)	67.20±11.30(n=5)	$3.53\pm1.21\times10^{-5}$ (n=4)
26	9.08±4.81 (n=4)	29.40±7.13(n=5)	49.00±11.53(n=5)	$>10^{-4}$
27	22.00±16.82(n=6)	48.17±15.14(n=6)	65.00±14.07(n=6)	$4.90\pm1.86\times10^{-5}$ (n=4)
Atropine sulfate	91.83±7.28*(n=6)	100 (n=6)	–	$<10^{-6}$

* $p<0.05$:different from all the others

sacrificed by ether anesthesia, the ileum (10-15 cm of the terminal portion) was immediately removed. After discarding the 5-8 cm segment proximal to the ileocaecal junction, 1.2-2.0 cm long segments were mounted vertically in a 20-ml organ bath containing Krebs-Henseleit solution. The bath contents were maintained at 37°C and aerated by 95% O_2 and 5% CO_2**.** A tension of 2 g was applied. All compounds were diluted in DMSO and added to the organ bath in volumes of 0.2 ml. and the control responses were taken after the addition of 0.2 ml DMSO.

The preparations were allowed to equilibrate for at least 60 min, with regular washes every 15 min**.** Contractions were induced by 10^{-5} mol/L acetylcholine. The contraction in the ileum was accepted as 100% and tested again after incubating each compound for 2 minutes. Their deconstructive effects were determined as % inhibition and were compared with atropine sulfate (CAS 5908-99-6). The data were expressed as means ±S.D. Students' t test was used for statistical analysis. P values <0.05 were considered to be statistically significant.

Procedures involving animals and their care were conducted in conformity with international laws and policies and the studies on animals were accepted by the Osmangazi University Ethics Committee (Number: 2004-09-16).

RESULTS AND DISCUSSION

N,N-disubstituted dithiocarbamic acid derivatives (6-27) were synthesized by the reaction of α-chloro-N-arylacetamide derivatives (1-4) which were prepared by the reaction of appropriate arylamine with chloroacetylchloride (or 2-chloropropionylchloride) with potassium salts of related N,N-disubstituted dithiocarbamic acid (5a-f) according to synthetic pathway in Scheme. Some characteristics of the compounds are given in Table 1The structures of the synthesized compounds were assigned on the bases of their spectral data (IR, ^{1}H-NMR, mass spectra) and elemental analyses. In the IR spectra of the compounds, characteristic N-H and C=O stretching bands were seen. In the ^{1}H-NMR spectra, -CH_3, -CH_2-S-, and -CH-S- protons appeared at 1.1-1.7 (d), 3.9-4.6 (s) and 4.3-5.3 (q) ppm, respectively. N-H protons in aromatic and cyclic amine moiety of the compounds were seen at expected chemical shift values.

The mass spectra of the compounds were recorded using the electron impact (7, 8, 10, 14, 16-19, 21, 23, 24, 26) and electrospray ionization (6, 9, 11-13, 15, 20, 22, 25, 27) technique. Molecular ion peaks were seen in the mass spectra of all compounds. The base peak frequently was resulted from C-N cleavage next to the aromatic rings. Further fragments peculiar to the dithiocarbamate and aromatic/cyclic amine moieties were also observed in the mass spectra of these compounds. Finally elemental analysis results were also consistent with the postulated structures.

Anticholinergic activities of the compounds were determined by tests performed on isolated rat ileum and compared with atropine sulfate. The results of the pharmacological assays are reported as both % inhibition of the contractions induced by acetylcholine and the effective dose (EC_{50}) of the compounds (Table 2)**.** The results of EC_{50} values showed that compounds with piperazine and piperidine rings were more active than the compounds with cyclohexylamine moiety. Thus, 1-(diphenylamino)-1-oxopropan-2-yl 4-methylpiperazine dithiocarbamate **18** and 1-(α-naphthylamino)-1-oxopropan-2-yl 4-methylpiperidine dithiocarbamate **25** were found as the most active compounds in the series. Examination of the anticholinergic activity test results show that the compounds having a branched side chain in their structures are more active than the unbranched ones.

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