Reductive Cleavage of Potential Cholinomimetics Thiadiazolidinones: A New Family of Spiro Compounds

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Dedicated to Professor Dr. José Elguero on the ocassion of his 65th birthday

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The design, synthesis and evaluation of a series of 1,2,4-thiadiazolidinones with potential muscarinic receptor binding properties has been performed. During the synthesis of the target compounds, we observed an interesting reductive cleavage of the thiadiazolidinone system which leads to the formation of the novel piperidine spiro triazine heterocycle. The synthesis, structural elucidation (NMR spectroscopy and X-ray diffraction) and biological evaluation of the new compounds are described. With the structures unequivocally established, a mechanism for the formation of the spiro compound is proposed.

Introduction

The last decade has witnessed considerable research efforts focused on the development of muscarinic agonists. One of the principal reasons for this is the therapeutical potential of a centrally active muscarinic agonist in Alzheimer's disease.[1,2] Muscarinic M_1 receptors are distributed predominantly in the mammalian forebrain, located mainly on postsynaptic neurons, and are involved in memory and other cognitive functions. As their relative density appears to be unaltered in Alzheimer's disease, cholinergic agonists acting directly on muscarinic receptors in the central nervous system may be useful in the therapeutic management of this devastating neurodegenerative disease.

Based on the recently published pharmacophore model for the muscarinic M_1 agonist,[3] our chemical efforts continued[4] with the design, synthesis and evaluation of a series of 1,2,4-thiadiazolidinones (**I**) that initially fulfilled the proposed structural requirements: a tertiary amine surrounded by a lipophilic environment (*N*-methylpiperazine moiety), and an electronegative dipole, usually part of a planar mesomeric ester, amide or amidine function (the iminothiadiazolidinone framework) (Figure 1).

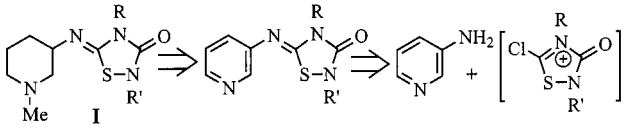

Figure 1. Designed iminothiadiazolidinones

During the synthesis of the target compounds, we observed an interesting reductive cleavage of the thiadiazolidinone system which leads to the formation of the novel triazine spiro piperidine heterocycle. The synthesis, structural elucidation (NMR spectroscopy and X-ray diffraction) and biological evaluation of these new compounds are described and a mechanism for formation of the spiro compound proposed.

Results and Discussion

The initial synthetic pathway designed for the target compounds started from pyridylimino-1,2,4-thiadiazolidinones which can be obtained by nucleophilic substitution on the oxathiadiazolium salts by 3-aminopyridine (Figure 1). The reactivity of these heterocyclic salts with aryl amines has previously been studied by our group.[5] Thus, chlorination of ethylisothiocyanate in an inert atmosphere, and subsequent reaction with *N*-alkylisocyanates, yields sparingly soluble 3-oxathiadiazolium salts via an iminochloroethylsulfenyl chloride intermediate. Only when the heterocyclic salts are not isolated and manipulated under a dry nitrogen atmosphere, can they easily be converted into the pyridyliminothiadiazolidinones **1** and **2** using diethyl ether as solvent and two equivalents of triethylamine for neutralising the hy-

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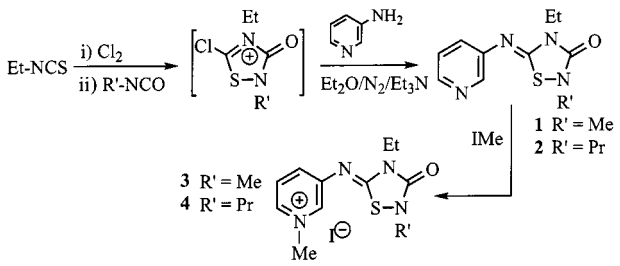
drogen chloride evolved in the reaction. The methylpyridinium salts **3** and **4** were obtained in quantitative yields by treating the previously obtained compounds with methyl iodide in acetone as solvent (Scheme 1).



Scheme 1. Synthesis of methylpyridinium salts

The analytical and spectroscopic data (^{1}H and ^{13}C NMR) of compounds **1–4** are collected in the Experimental Section. In principle, the synthesised imines could be a mixture of *Z*/*E* isomers but only one compound was detected in the reaction medium. The geometric isomer assignment was performed from the energy difference of the *Z* and *E* isomers calculated following the semiempirical AM1 method[6] using the Sybyl 6.0 molecular modeling program[7] as graphical interface. A full geometric optimisation was performed. Considering the $\Delta H_f°$ values depicted in Figure 2 , the *Z* imine configuration is the one proposed for compounds **1** and **2**. Furthermore, in the NOE difference spectra no correlation between the ethyl moiety attached to the thiadiazolidinone ring and the pyridine protons was observed, which corroborates the *Z* assignment.

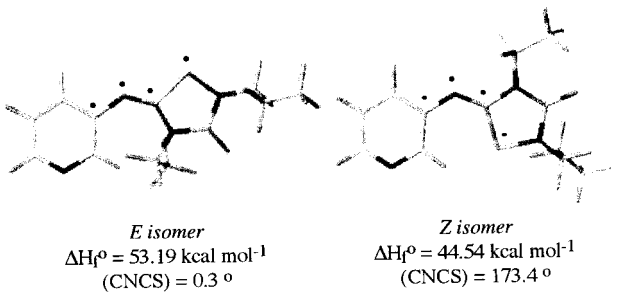
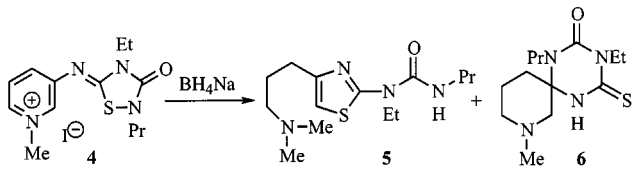


Figure 2. *Z* and *E* isomers of imine **2**

The last step in the synthetic pathway was the reduction of the methylpyridinium derivatives. Treatment of derivative **4** with $NaBH_4$ under standard conditions (MeOH, –10 °C) during 1 h afforded a complex mixture of compounds. By different chromatographic techniques (CC, CCTLC and TLC) derivatives **5** and **6** could be isolated in moderate yields (Scheme 2). With the aim of avoiding this mixture of compounds, several reaction conditions for the reduction step were tried ($NaBH_4$/anhydrous MeOH/N_2/–10 °C; $NaBH_4$/anhydrous EtOH/N_2/0 °C; H_2/Pd/MeOH; H_2/Pt/MeOH; H_2/PtO_2/MeOH). In all cases a similar mixture of compounds was obtained, with derivative **6** being the major product.



Scheme 2. Reduction of methylpyridinium salt **4**

The structural elucidation of the new compounds was established by the unequivocal assignment of their ^{1}H and ^{13}C NMR spectra through the concerted use of COSY, HMQC[8] and HMBC[9] two-dimensional experiments. The structure of the spiro derivative **6** was subsequently confirmed by an X-ray analysis.

The analytical data for compound **5** indicated a composition compatible with a $C_{14}H_{26}N_4OS$ molecular formula, which revealed the presence of one more carbon atom than in the thiadiazolidinone **4**. The ^{1}H NMR spectrum of **5** clearly showed the disappearance of the aromatic pyridine protons. Additionally, a broad triplet at $\delta = 9.71$, exchangeable with deuterium dioxide, and a quadruplet at $\delta = 3.91$, which collapsed to a triplet with the addition of D_2O, compatible with the NH–Pr moiety were observed. Taking all these data together, and using the HMQC and HMBC sequences for one bond and for long distance correlations, respectively, we could unequivocally assign this compound as the thiazole structure **5**.

Derivative **6** could be isolated as a white crystalline solid whose analytical data are compatible with a $C_{13}H_{24}N_4OS$ molecular formula. This indicated the complete hydrogenation of the pyridine heterocycle. The ^{1}H NMR spectrum showed the complex signals corresponding to the eight-spin system of the piperidine ring, which could be unequivocally assigned by means of COSY, HMQC and HMBC experiments. Worth mentioning is the nonequivalence observed for the methylenic signals of the propyl moiety. As a variable temperature experiment showed that the two sets of multiplets remained unchanged, without broadening or coalescence at temperatures as high as 313 K, the origin of the anisochrony of the methylene protons may be due to intrinsic structural factors such as the proximity to a chiral centre. A broad singlet belonging to an NH exchangeable with D_2O is also observed at $\delta = 7.83$. All these data, together with the correlations for one bond and long-range couplings observed in the bidimensional experiments performed, lead us to propose a spiro structure for derivative **6**, which was confirmed by X-ray analysis. The ORTEP perspective is depicted in Figure 3 , showing a chair conformation for the piperidine hexagonal ring. The racemic spiro compound **6** crystallises in the monoclinic system with a $P2_1/c$ symmetry; its fundamental crystal data are collected in Table 1.

With the definite assignment of the structure, a mechanism for the formation of **5** and **6** can now be proposed (Scheme 3). We suppose that the reaction begins with the partial reduction of the methylpyridinium ring to a unique

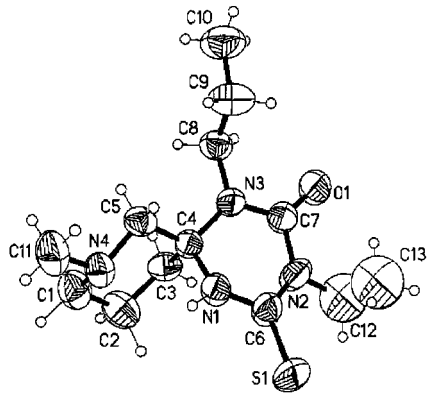
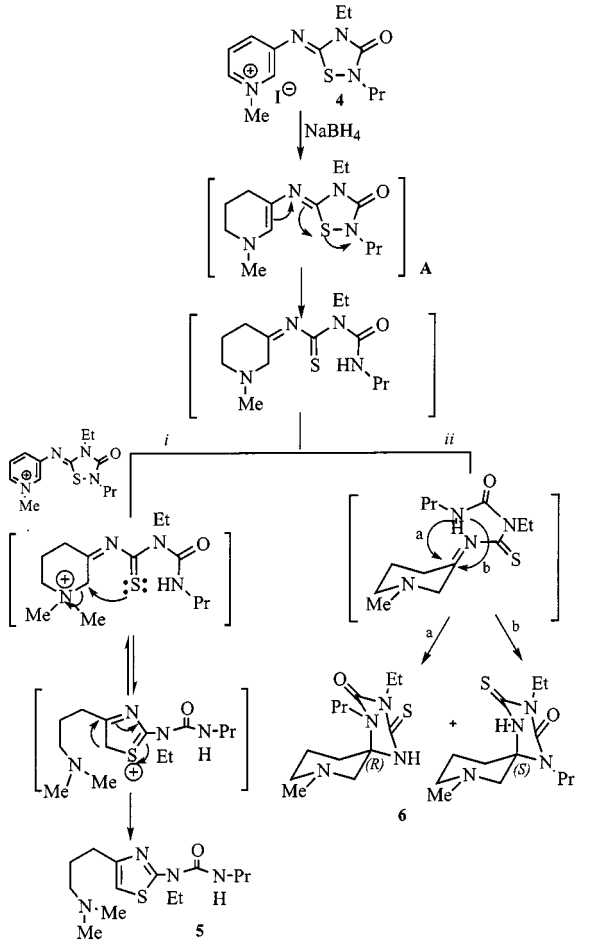


Figure 3. ORTEP crystal structure of compound **6**

Table 1. Crystal data and structure refinement for spiro compound **6**

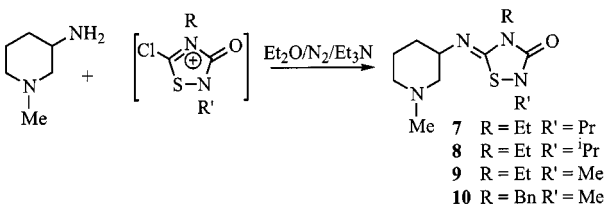
Empirical formula	$C_{13}H_{24}N_4OS$
Formula weight	284.42
Temperature	296 (2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 8.4387 (13) Å α = 90° b = 17.241 (3) Å β = 90.521 (3)° c = 10.989 (2) Å γ = 90°
Volume, Z	1598.8 (4) Å^3, 4
Density (calculated)	1.182 mg.m^{-3}
Absorption coefficient	0.202 mm^{-1}
F(000)	616
Crystal size	0.45 × 0.18 × 0.04 mm
θ range for data collection	2.41 to 20.81°
Limiting indices	–2 h 8, –15 k 15, –10 l 10
Reflections collected	3133
Independent reflections	1382 (R_{int} = 0.0343)
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	1382/0/ 215
Goodness-of-fit on F^2	1.073
Final R indices [$I > 2\sigma(I)$]	$R1$ = 0.0919, $wR2$ = 0.2554
R indices (all data)	$R1$ = 0.1137, $wR2$ = 0.2767
Extinction coefficient	0.006 (5)
Largest diff. peak and hole	0.895 and –0.417 eÅ^{-3}

tetrahydro derivative **A**. This intermediate is highly unstable. Then, the reductive cleavage of the thiadiazolidinone ring would be the first step yielding a thiourea derivative which evolves by different pathways. In one case (route *i* in Scheme 3), methylation of the piperidine nitrogen to a quaternary ammoniun derivative by the pyridinium salt **4** present in the reaction medium, followed by nucleophilic ring opening by sulfur, yields the previously described dimethylamino thiazole **5**. It is worth mentioning that it was possible to confirm by TLC the presence of the nonmethylated pyridine **2**. Another possible pathway for the evolution of the thiourea derivative is the one depicted in route *ii* in Scheme 3. In this case, an intramolecular cyclization yields the spiro compound **6**. As the nucleophilic nitrogen attack to the imine carbon could be performed from both sides of the imine bond, a racemic mixture of the novel spiro derivative is obtained. This last proposed pathway yields the main compound obtained in the reduction of methylpyridinium thiadiazolidinone **4**.



Scheme 3. Reaction pathway proposed for the formation of **5** and **6**

Finally, and with the aim of obtaining the target compounds proposed at the beginning of this work, nucleophilic substitution on the oxathiadiazolium salts by primary cycloalkylic amines was attempted (Scheme 4). Reaction of 3-amino-1-methyl-piperidine with oxathiadiazolium salts in an inert atmosphere and diethyl ether as solvent affords the thiadiazolidinone racemate derivatives **7–10** in moderate yields.



Scheme 4. Synthesis of iminothiadiazolidinones **7**–**10**

The affinity of the synthesised compounds **1–4** and **7–10** for muscarinic receptors was determined by assessing the inhibition of specific ^{3}H-(R)-QNB binding to rat brain membranes. In general, the kind of thiadiazolidinones prepared here were inactive (IC_{50} > 100 μM) in binding assays and only the methylpyridinium derivative **4** showed low af-

finity (IC_{50} = 0.57 ± 0.12 μm) for muscarinic receptors in rat central nervous system.

Experimental Section

General: Melting points were determined with a Reichert-Jung Thermovar apparatus and are uncorrected. Flash column chromatography was carried out at medium pressure using silica gel (E. Merck, Grade 60, particle size 0.040–0.063 mm, 230–240 mesh ASTM) and preparative centrifugal circular thin layer chromatography (CCTLC) on a circular plate coated with a 1 mm layer of Kieselgel 60 PF_{254}, Merck, by using a Chromatotron® and the indicated solvent as eluent. Compounds were detected with UV light (254 nm). ^{1}H NMR spectra were obtained on Varian XL-300 and Gemini-200 spectrometers working at 300 and 200 MHz respectively. Typical spectral parameters: spectral width 10 ppm, pulse width 9 μs (57 °), data size 32 K. ^{13}C NMR experiments were carried out on the Varian Gemini-200 spectrometer operating at 50 MHz with acquisition parameters: spectral width 16 kHz, acquisition time 0.99 s, pulse width 9 μs (57 °), data size 32 K. Chemical shifts are reported in δ values (ppm) relative to internal Me_4Si and *J* values are reported in Hertz. Elemental analyses were performed by the analytical department at C.N.Q.O. (CSIC) and the results obtained were within ± 0.4% of the theoretical values.

2,4-Dialkyl-5-[imino-(3-pyridyl)]-1,2,4-thiadiazolidin-3-one (1–2, 7–10). – General Procedure: Chlorine was added slowly to a solution of alkylisothiocanate in dry hexane (25 mL) at –15 °C to –10 °C. Chlorine was generated by the addition of HCl 35% to $KMnO_4$. The temperature of the reaction mixture was carefully controlled during the addition step. At this point, *N*-alkyl-*S*-chloroisothiocarbamoyl chloride was formed. Afterwards, alkyl isocyanate was added. The mixture was stirred at room temperature for 12 h and the white solid, which fumes heavily in moist air, was separated under a dry nitrogen atmosphere by suction filtration to provide the corresponding thiadiazolium salts. These compounds were used in the next synthetic step without further purification. Subsequently, to an ethereal solution of this thiadiazolium salt were added the corresponding primary amine and triethylamine. The resulting mixture was stirred at room temperature for 12 h, and then filtered. The filtrate was evaporated to dryness in vacuo and the residue purified by silica gel column chromatography using the solvent indicated below.

4-Ethyl-5-[imino-(3-pyridyl)]-2-methyl-1,2,4-thiadiazolidin-3-one (1): Reagents: 5-chloro-4-ethyl-2-methyl-3-oxo-1,2,4-thiadiazolium chloride (0.67 g, 3.1 mmol), 3-aminopyridine (0.28 g, 3.1 mmol), triethylamine (0.62 g, 6.2 mmol). Purification: AcOEt/hexane (3:1). Yield: 0.23 g (31%) of yellow oil. – ^{1}H NMR ($CDCl_3$): δ = 8.35 (m, 1 H, H-6 pyridine), 8.28 (m, 1 H, H-2 pyridine), 7.24 (m, 2 H, H-4 pyridine and H-5 pyridine), 3.91 [q, *J* = 6.87 Hz, 2 H, C*H*$_2$CH$_3$], 3.08 (s, 3 H, CH_3), 1.32 [t, *J* = 6.87 Hz, 3 H, CH_2CH_3]. – ^{13}C NMR ($CDCl_3$): δ = 154.6 (C-5 thiadiazolidine), 152.0 (C-3 thiadiazolidine), 144.8, 142.9, 128.2, 123.8 (C aromatic), 39.2 (*C*H$_2$CH$_3$), 31.7 (CH_3), 12.5 (CH_2CH_3). – $C_{10}H_{12}N_4OS$ (378.43): calcd. C 45.97, H 4.59, N 21.45, S 12.26; found C 45.81, H 4.62, N 21.33, S 12.34

4-Ethyl-5-[imino-(3-pyridyl)]-2-propyl-1,2,4-thiadiazolidin-3-one (2): Reagents: 5-chloro-4-ethyl-3-oxo-2-propyl-1,2,4-thiadiazolium chloride (0.76 g, 3.1 mmol), 3-aminopyridine (0.28 g, 3.1 mmol), triethylamine (0.62 g, 6.2 mmol). Purification: AcOEt/hexane (3:1). Yield: 0.13 g (15%) of orange oil. – ^{1}H NMR ($CDCl_3$): δ = 8.50 (m, 1 H, H-6 pyridine), 8.36 (m, 1 H, H-2 pyridine), 7.88 (m, 2 H, H-4 pyridine and H-5 pyridine), 3.90 [q, *J* = 6.96 Hz, 2 H, C*H*$_2$CH$_3$], 3.52 [t, *J* = 6.96 Hz, 2 H, C*H*$_2$CH$_2$CH$_3$], 1.57 (m, 2 H, CH$_2$C*H*$_2$CH$_3$), 1.28 [t, *J* = 6.96 Hz, 3 H, CH$_2$C*H*$_3$], 0.89 [t, *J* = 7.32 Hz, 3 H, CH$_2$CH$_2$C*H*$_3$]. – ^{13}C NMR ($CDCl_3$): δ = 155.8 (C-5 thiadiazolidine), 154.1 (C-3 thiadiazolidine), 138.20, 136.80, 135.30, 128.30, 112.90 (C aromatic.), 47.2 (*C*H$_2$CH$_3$), 40.30 (*C*H$_2$CH$_2$CH$_2$), 27.20 (CH$_2$*C*H$_2$CH$_3$), 12.50 (CH$_2$*C*H$_3$), 11.50 (CH$_2$CH$_2$*C*H$_3$). – $C_{12}H_{16}N_4OS$ (406.48): calcd. C 54.52, H 6.10, N 21.19, S 12.12; found C 54.82, H 6.29, N 21.41, S 11.89

(±) 4-Ethyl-5-[imino-(1-methyl-piperidin-3-yl)]-2-propyl-1,2,4-thiadiazolidin-3-one (7): Reagents: 5-chloro-4-ethyl-3-oxo-2-propyl-1,2,4-thiadiazolium chloride (0.76 g, 3.1 mmol), 3-amino-*N*-methylpiperidine (0.35 g, 3.1 mmol), triethylamine (0.62 g, 6.2 mmol). Solvent: Tetrahydrofuran. Purification: CH_2Cl_2/MeOH (20:1). Yield: 0.22 g (23%) of yellow oil. – ^{1}H NMR ($CDCl_3$) δ = 3.71 [q, *J* = 7.0 Hz, 2 H, C*H*$_2$CH$_3$], 3.46 [t, *J* = 7.0 Hz, 2 H, C*H*$_2$CH$_2$CH$_3$], 2.91–1.62 (m, 9 H, H-piperidine), 2.27 (s, 3 H, CH_3), 1.53 (m, 2 H, CH$_2$C*H*$_2$CH$_3$), 1.16 [t, *J* = 7.0 Hz, 3 H, CH$_2$C*H*$_3$], 0.89 [t, *J* = 7.0 Hz, 3 H, CH$_2$CH$_2$C*H*$_3$]. – ^{13}C NMR ($CDCl_3$): δ = 152.2 (C-5 thiadiazolidine), 147.5 (C-3 thiadiazolidine), 61.2 (C-2 piperidine), 61.1 (C-3 piperidine), 46.8 (*C*H$_2$CH$_2$CH$_3$), 55.2 (C-6 piperidine), 46.0 (CH_3), 38.0 (*C*H$_2$CH$_3$), 30.8 (C-4 piperidine), 24.1 (C-5 piperidine), 21.7 (CH$_2$*C*H$_2$CH$_3$), 12.4 (CH$_2$*C*H$_3$), 11.0 (CH$_2$CH$_2$*C*H$_3$). – $C_{13}H_{24}N_4OS$ (426.56): calcd. C 52.00, H 8.00, N 18.66, S 10.66; found C 51.97, H 8.10, N 18.54, S 10.71

(±) 4-Ethyl-5-[imino-(1-methyl-piperidin-3-yl)]-2-isopropyl-1,2,4-thiadiazolidin-3-one (8): Reagents: 5-chloro-4-ethyl-2-isopropyl-3-oxo-1,2,4-thiadiazolium chloride (0.76 g, 3.1 mmol), 3-amino-*N*-methylpiperidine (0.35 g, 3.1 mmol), triethylamine (0.62 g, 6.2 mmol). Solvent: Tetrahydrofuran. Purification: CH_2Cl_2/MeOH (30:1). Yield: 0.07 g (7%) of a yellowish solid, m.p. 74–75 °C. – ^{1}H NMR ($CDCl_3$) δ = 4.45 (m, 1 H, C*H*(CH$_3$)$_2$), 3.70 [q, *J* = 6.8 Hz, 2 H, C*H*$_2$CH$_3$), 2.77–1.66 (m, 9 H, H-piperidine), 2.24 (s, 3 H, CH_3), 1.16 [d, *J* = 7.4 Hz, 6 H, CH(C*H*$_3$)$_2$], 1.15 [t, *J* = 6.8 Hz, 3 H, CH$_2$C*H*$_3$]. – ^{13}C NMR ($CDCl_3$): δ = 154.4 (C-5 thiadiazolidine), 147.6 (C-3 thiadiazolidine), 61.3 (C-2 piperidine), 61.2 (C-3 piperidine), 46.7 [*C*H(CH$_3$)$_2$], 55.1 (C-6 piperidine), 46.1 (CH_3), 38.1 (*C*H$_2$CH$_3$), 30.7 (C-4 piperidine), 24.0 (C-5 piperidine), 20.8 [CH$_2$(*C*H$_3$)$_2$], 12.3 (CH$_2$*C*H$_3$). – $C_{13}H_{24}N_4OS$ (426.56): calcd. C 52.00, H 8.00, N 18.66, S 10.66; found C 51.87, H 8.09, N 18.50, S 10.73

(±) 4-Ethyl-5-[imino-(1-methyl-piperidin-3-yl)]-2-methyl-1,2,4-thiadiazolidin-3-one (9): Reagents: 5-chloro-4-ethyl-2-methyl-3-oxo-1,2,4-thiadiazolium chloride (0.67 g, 3.1 mmol), 3-amino-*N*-methylpiperidine (0.35 g, 3.1 mmol), triethylamine (0.62 g, 6.2 mmol). Solvent: Tetrahydrofuran. Purification: CH_2Cl_2/MeOH (20:1). Yield: 0.30 g (43%) of yellow oil. – ^{1}H NMR ($CDCl_3$) δ = 3.73 [q, *J* = 7.0 Hz, 2 H, C*H*$_2$CH$_3$], 3.07 (s, 3 H, CH_3), 2.97–1.27 (m, 9 H, H-piperidine), 2.34 (s, 3 H, CH_3), 1.28 [t, *J* = 7.0 Hz, 3 H, CH$_2$C*H*$_3$]. – ^{13}C NMR ($CDCl_3$): δ = 154.4 (C-5 thiadiazolidine), 147.6 (C-3 thiadiazolidine), 60.6 (C-2 piperidine), 60.1 (C-3 piperidine), 55.0 (C-6 piperidine), 45.7 (CH_3), 38.7 (*C*H$_2$CH$_3$), 31.7 (CH_3), 30.4 (C-4 piperidine), 24.4 (C-5 piperidine), 12.4 (CH$_2$*C*H$_3$). – $C_{11}H_{20}N_4OS$ (398.50): calcd. C 48.52, H 8.82, N 20.58, S 11.76; found C 48.83, H 8.63, N 20.35, S 12.02

(±) 4-Benzyl-5-[imino-(1-methyl-piperidin-3-yl)]-2-methyl-1,2,4-thiadiazolidin-3-one (10): Reagents: 4-benzyl-5-chloro-2-methyl-3-oxo-1,2,4-thiadiazolium chloride (0.66 g, 3.1 mmol), 3-amino-*N*-methylpiperidine (0.35 g, 3.1 mmol), triethylamine (0.62 g, 6.2 mmol). Solvent: Tetrahydrofuran. Purification: CH_2Cl_2/MeOH (30:1). Yield: 0.065 g (10%) of orange oil. – ^{1}H NMR ($CDCl_3$) δ = 7.45–7.28 (m, 5 H, H aromatic), 4.85 (s, 2 H, C*H*$_2$Ph), 3.06 (s, 3 H, CH_3), 2.90–1.20 (m, 9 H, H-piperidine), 2.27 (s, 3 H, CH_3-

piperidine). – ^{13}C NMR ($CDCl_3$): δ = 154.5 (C-5 thiadiazolidine), 148.3 (C-3 thiadiazolidine), 136.5, 128.0, 126.9, 125.5 (C aromatic), 60.7 (C-2 piperidine), 59.9 (C-3 piperidine), 31.6 (CH_3), 55.1 (C-6 piperidine), 45.9 (CH_3), 46.5 (CH_2Ph), 30.5 (C-4 piperidine), 23.5 (C-5 piperidine). – $C_{15}H_{22}N_4OS$ (448.56): calcd. C 58.52, H 7.84, N 18.30, S 10.45; found C 58.80, H 7.90, N 18.52, S 10.21

3-[5-(4-Ethyl-2-methyl-3-oxo)imino-1,2,4-thiadiazolidyl]-1-methylpyridinium iodide (3): To a solution of derivative **1** (0.20 g, 0.8 mmol) in acetone (10 mL) was slowly added methyl iodide (0.36 g, 2.54 mmol). The reaction mixture was stirred at room temperature for 18 h. After this time the solution was concentrated under reduced pressure. The product was precipitated by addition of diethyl ether to give **3** (0.24 g, 77%) as a yellow solid, m.p. 92–94 °C. – ^{1}H NMR ($CDCl_3$) δ = 9.06 [d, *J* = 6.0 Hz, 1 H, H-6 pyridine), 8.51 (s, 1 H, H-2 pyridine), 8.05 [t, *J* = 7.8 Hz, 1 H, H-5 pyridine], 7.99 [d, *J* = 7.8 Hz, 1 H, H-4 pyridine], 4.67 (s, 3 H, CH_3), 3.93 [q, *J* = 6.90 Hz, 2 H, C*H*$_2$CH$_3$], 3.20 (s, 3 H, CH_3), 1.32 [t, *J* = 6.90 Hz, 3 H, CH$_2$C*H*$_3$]. – ^{13}C NMR ($CDCl_3$): δ = 155.6 (C-5 thiadiazolidine), 153.6 (C-3 thiadiazolidine), 148.4, 140.3, 138.6, 136.5, 129.1 (C aromatic), 49.8 (CH_3), 39.70 (*C*H$_2$CH$_3$), 31.9 (CH_3), 12.05 (CH$_2$*C*H$_3$) . – $C_{11}H_{15}IN_4OS$ (520.37): calcd. C 34.92, H 6.34, N 14.81, S 8.46; found C 34.81, H 6.51, N 14.82, S 8.39

3-[5-(4-Ethyl-3-oxo-2-propyl)imino-1,2,4-thiadiazolidyl]-1-methylpyridinium iodide (4): Following the above procedure a solution of derivative **2** (0.22 g, 0.84 mmol) and methyl iodide (0.36, 2.54 mmol) in acetone (10 mL) was stirred for 18 h to yield 0.27 g of **4** (80%) as a yellow solid, m.p. 70–72 °C. – ^{1}H NMR ($CDCl_3$) δ = 9.03 [d, *J* = 6.0 Hz, 1 H, H-6 pyridine], 8.52 (s, 1 H, H-2 pyridine), 8.04 [t, *J* = 7.8 Hz, 1 H, H-5 pyridine], 7.93 [d, *J* = 7.8 Hz, 1 H, H-4 pyridine], 4.63 (s, 3 H, CH_3), 3.87 [q, *J* = 7.08 Hz, 2 H, C*H*$_2$CH$_3$], 3.53 [t, *J* = 6.96 Hz, 2 H, C*H*$_2$CH$_2$CH$_3$], 1.60 (m, 2 H, CH$_2$C*H*$_2$CH$_3$), 1.27 [t, *J* = 7.08, 3 H, C*H*$_2$CH$_3$], 0.88 [t, *J* = 7.32 Hz, 3 H, CH$_2$CH$_2$C*H3*]. – ^{13}C NMR ($CDCl_3$): δ = 155.8 (C-5 thiadiazolidine), 153.3 (C-3 thiadiazolidine), 148.5, 140.4, 138.6, 136.4, 129.1 (C aromatic), 49.8 (CH_3), 46.8 (*C*H$_2$CH$_3$), 39.5 (*C*H$_2$CH$_2$CH$_3$), 21.9 (CH$_2$*C*H$_2$CH$_3$), 15.5 (CH$_2$*C*H$_3$), 10.08 (CH$_2$CH$_2$*C*H$_3$). – $C_{13}H_{19}IN_4OS$ (548.42): calcd. C 38.42, H 4.68, N 13.70, S 7.80; found C 39.09, H 5.16, N 13.11, S 7.66

***N*'-Ethyl-*N*'-[2-(4-dimethylaminopropyl)-1,3-thiazolyl]-*N*-propylurea (5) and (±) 5-Ethyl-1'-methyl-4-oxo-perhydro-3-propyl-6-thioxo-1,3,5-triazine-2-spiro-3'-piperidine (6):** To a solution of derivative **4** (0.8 g, 1.97 mmol) in methanol (40 mL) at –10 °C was slowly added sodium borohydride (0.15 g, 3.95 mmol). The reaction mixture was stirred at –10 °C for 1 h. After that time the total conversion of starting product was observed by TLC. The solvent was then evaporated under reduced pressure. The residue was dissolved in water and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The organic phase was dried over sodium sulfate and the solvent evaporated under reduced pressure. The residue was purified on silica gel column using CH_2Cl_2/MeOH (100:1) as eluent isolating two fractions. The first fraction was purified by preparative thin layer chromatography using CH_2Cl_2/MeOH (50:1) as eluent to give 0.07 g of **5** (12%) as a yellow oil. – ^{1}H NMR ($CDCl_3$): δ = 9.71 (m, 1 H, NH), 6.39 (s, 1 H, H-4), 3.91 [q, *J* = 7.0 Hz, 2 H, C*H*$_2$CH$_3$], 3.31 (q, 2 H, C*H*$_2$CH$_2$CH$_3$), 2.62 (t, 2 H, H-6), 2.30 (t, 2 H, H-8), 2.22 [s, 6 H, N(CH$_3$)$_2$], 1.84 (m, 2 H, H-7), 1.59 (m, 2 H, CH$_2$C*H*$_2$CH$_3$), 1.28 [t, *J* = 7.0 Hz, 3 H, CH$_2$C*H*$_3$], 0.97 [t, *J* = 6.88 Hz, 3 H, CH$_2$CH$_2$C*H*$_3$]. – ^{13}C NMR ($CDCl_3$): δ = 165.3 (C-3), 153.8 (C-2), 152.7 (C-5), 104.1 (C-4), 59.1 (C-8), 45.4 (N(CH$_3$)$_2$), 43.7 (*C*H$_2$CH$_3$), 42.2 (*C*H$_2$CH$_2$CH$_3$), 29.4 (C-6), 26.7 (C-7), 22.9 (CH$_2$*C*H$_2$CH$_3$), 12.9 (CH$_2$*C*H$_3$), 11.6 (CH$_2$CH$_2$*C*H$_3$. – $C_{14}H_{26}N_4OS$ (440.58): calcd. C 53.50, H 8.28, N 17.83, S 10.19; found C 53.90, H 8.00, N 17.51, S 10.00

The second fraction was purifed by CCTLC using AcOEt/Hexane (10:1) as eluent to yield 0.18 g of **6** (31%) as a white crystalline solid, m.p. 64–65 °C. – ^{1}H NMR ($CDCl_3$): δ = 7.83 (m, 1 H, NH), 4.21 [q, *J* = 7.0 Hz, 2 H, C*H*$_2$CH$_3$], 3.47 (m, 1 H, C*H*$_2$CH$_2$CH$_3$), 2.98 (m, 1 H, C*H*$_2$CH$_2$CH$_3$), 2.73 (m, 2 H, H-$_2$'ax piperidine and H-6'ax piperidine), 2.26 (s, 3 H, CH_3), 2.19 [d, *J* = –10.5 Hz, 1 H, H-$_2$'ec piperidine], 1.80 (m, 3 H, H-4'ax piperidine, H-5'axpiperidine and H-6'ec piperidine), 1.60 (m, 1 H, CH$_2$C*H*$_2$CH$_3$), 1.55 (m, 1 H, CH$_2$C*H*$_2$CH$_3$), 1.44 (m, 2 H, H-4'ec piperidine and H-5'ec piperidine), 1.23 [t, *J* = 7.0 Hz, 3 H, CH$_2$*CH*$_3$], 0.87 (t, *J* = 6.88 Hz, 3 H, CH$_2$CH$_2$*CH*$_3$). – ^{13}C NMR ($CDCl_3$): δ = 177.9 (C=S), 149.9 (C=O), 69.0 (C-3'), 62.4 (C-2'), 54.6 (C-6'), 46.0 (CH_3), 44.2 (*C*H$_2$CH$_2$CH$_3$), 42.1 (*C*H$_2$CH$_3$), 31.4 (C-4'), 23.5 (CH$_2$*C*H$_2$CH$_3$), 21.4 (C-5'),13.2 (CH$_2$*C*H$_3$,), 11.2 (CH$_2$CH$_2$*C*H$_3$). – $C_{13}H_{24}N_4OS$ (426.56): calcd. C 54.92, H 8.45, N 19.71, S 11.26; found C 54.30, H 8.62, N 19.25, S 11.09

X-ray Structure Determination: A summary of the fundamental crystal and refinement data are given in Table 1. A colourless crystal showing well-defined faces was mounted on a Bruker-Siemens Smart CCD diffractometer equipped with a normal focus, 2.4 kW sealed tube X-ray source (Molybdenum radiation, λ = 0.71073 Å) operating at 50 kV and 20 mA. Data were collected over a quadrant of the reciprocal space by a combination of two exposure sets. The cell parameters were determined and refined by a least-squares fit of all the reflections collected. Each exposure of 10 s covered 0.3° in *w*. The crystal to detector distance was 6.05 cm. Coverage of the unique set was over 92% complete to at least 23° in θ. The first 50 frames were recollected at the end of the data collection to monitor crystal decay. The spectrum was very poor and no-significative intensities were found above 20.4° in θ. The intensities were corrected for Lorentz and polarization effects. The structure was solved by Multan using SHELXS-97[10] and Fourier methods. Full-matrix least-square refinement was carried out using SHELXTL minimizing $w(F_o^2 - F_c^2)^2$. Weighted *R* factors (*Rw*) and all goodness-of-fit *S* are based on *F2*, conventional *R* factors (*R*) are based on *F*.

Muscarinic Receptor Binding: Receptor binding studies were carried out by evaluating the ability of ligands to compete with 50 pM ^{3}H-(*R*)-quinuclidinyl benzilate [^{3}H-(*R*)-QNB] in a suspension of brain membranes, as previously described.[11] The IC_{50} values were determined from displacement curves. The values here are reported as means ± SEM of three independent experiments.

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