Marta Struga,[a]* Jerzy Kossakowski,[a] Barbara. Miroslaw,[b] Anna E. Koziol,[b] and Andrzej Zimniak[c]

[a]Medical University, Department of Medical Chemistry, 02-007 Warsaw, Poland
[b]Faculty of Chemistry, Maria Curie-Sklodowska University, 20-031 Lublin, Poland
[c]Medical University, Department of Physical Chemistry, 02-097 Warsaw, Poland
*E-mail: marta.struga@wum.edu.pl

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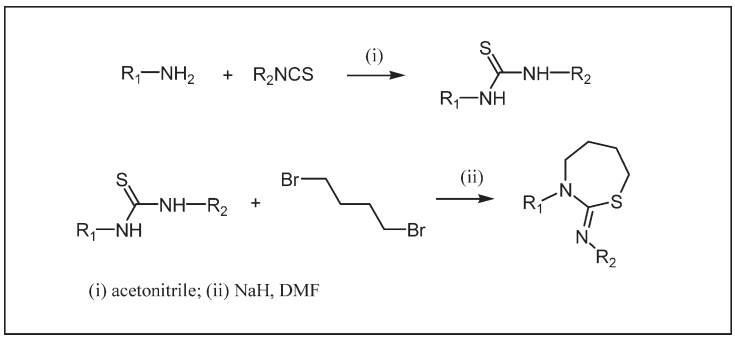

Condensation of thiourea derivatives with 1,4-dibromobutane gave 1,3-thiazepine derivatives (**1a**, **b**, **c** – **3a**, **b**, **c**). Elementary analysis, MS and ^{1}H NMR spectra confirmed the identity of the products. The molecular structure of **2b** was determined by an X-ray analysis.

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INTRODUCTION

Derivatives of 1,3-thiazepine rings are important because of their biological activity [1–4]. The 1,3-thiazepine rings is present in Omipatrilat, which is currently in the phase IV of clinical trials. By inhibiting the activity of the angiotensin converting enzyme (ACE), that causes blood vessels to constrict, Omapatrilat lowers blood pressure. Another advantage of this drug is inhibition of the enzyme known as neutral endopeptidase (NEP), which causes blood vessels to relax [5,6].

The noncondensed 1,3-thiazepine rings can be prepared by using various methods. They can be divided into two main groups.

The first synthetic route is based on the cyclocondensation of thiourea derivatives resulting in 1,3-thiazepine ring systems. Following this way, diethyl allylmalonate reacted with thiourea in an unique manner giving an excellent yield of ethyl 2-amino-7-methyl-4-oxo-4,5,6,7-tetrahydro-1,3-thiazepine-5-carboxylate [7,8]. By this method, 2-amino derivatives of 7-methyl-4-oxo-4,5,6,7-tetrahydro-1,3-thiazepine-5-carboxylic acid ester in reaction of 1-alkyl-3-pent-4-enoyl-thiourea with Br_2 were obtained [9,10]. Furthermore, 4-bromo-butyryl chloride was also used as a cyclizing agent of *N*,*N*'-diphenylthiourea [11]. Condensation reaction of 4-amino-butan-1-ol with isothiocyanate leads to thiourea derivatives. Cyclization reaction of these thiourea derivatives in acidic solution resulted in 4-substituted (methyl, benzyl and propyl) imino-4,5,6,7-tetrahydro-1,3-thiazepine [12–15].

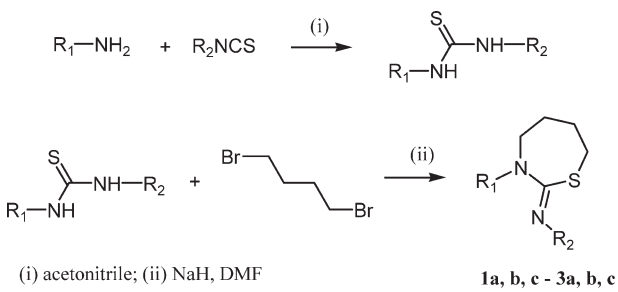
The second method for preparation of noncondensed 1,3-thiazepine ring systems is cyclization of compounds possessing N and S atoms in their chains. In this case, amines, aldehydes and halogen derivatives are utilized as highly effective cyclization reagents. Following this way, the reaction of 4-bromobutyl isothiocyanate with aromatic amines served as general preparative method for homologous 2-arylimino-1,3-thiazepines [16]. Further-more, hexahydro-1,3-thiazepin-4-ones were obtained *via* cyclocondensation of 4-mercapto-butyric acid alkyl ester with alkyl or aryl-aldehydes [17]. Moreover, 2*H*-hexa-hydro-1,3-thiazepine derivatives substituted by a nitro-methylene group in the second position were obtained in reaction of 1-methylo-thiolo-propylamine with 2,2,2-tri-halo-1-nitroethane [18]. 1,3-Thiazepine ring system was also synthesized by the alkilation of *N*-[1-mercapto-1-alkylamino-methylidene]-benzenesulfonamide sodium salt with dihaloalkanes [19].

In the present paper the 1,3-thiazepine system was obtained by the condensation reaction of thiourea derivatives with 1,4-dibromobutane.

RESULTS AND DISCUSSION

The preparation of nine new 1,3-thiazepine derivatives of 10-isopropyl-8-methyl-4-azatricyclo [5.2.2.0^{2,6}] undec-8-ene-3,5-dione, 1-isopropyl-7-methyl-4-azatricyclo-[5.2.2.0^{2,6}]undec-8-ene-3,5-dione and 1,7,8,9,10-

Scheme 1



(i) acetonitrile; (ii) NaH, DMF

1a, b, c - 3a, b, c

penta-methyl-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5-dione (Scheme 1) is described.

Anhydrides and imides obtained in Diels-Alder reaction were used as starting materials. Anhydride or imide **1** was obtained in the reaction of enantiomeric (*R*)-(-)-α-phellandrene with furan-2,5-dione or pyrrole-2,5-dione [20,21]. The reaction of α-terpinene with furan-2,5-dione or pyrrole-2,5-dione gave compound **2** [21–23] while compound **3** was obtained in reaction of 1,2,3,4,5-penta-methylcyclopentadiene with furan-2,5-dione or pyrrole-2,5-dione [24,25].

Obtained tricyclic anhydrides or imides were subjected to the reaction of hydrazine (80 % aqueous solution) as described previously [26,27].

In order to obtain the corresponding thiourea derivatives of above compounds they were subjected to the reaction with phenyl-, 4-methoxyphenyl-, cyclohexyl-isothiocyanate [27].

Products were transformed into 1,3-thiazepine derivatives by condensation with 1,4-dibromobutane. This method of synthesis of 1,3-thiazepine noncondensed rings has not been described in literature so far. The general synthetic pathway is given in Scheme 1. Formula of the investigated compounds is given in Table 1.

Obtained compounds were purified by flash chromatography. Elementary analysis, MS and ^{1}H NMR spectra confirmed the identity of the products. The molecular structure of **2b** was determined by an X-ray analysis.

Compounds investigated using EI MS show distinct signals of molecular ions at the expected m/z values, *i.e.* for **1a**, **2a**, and **3a** the value 437 was noted, and for **2b** the corresponding value was 467.

In the spectrum of **3a** an intense (100%) signal due to the ion [M-135]$^{+\bullet}$ has been observed, apparently due to the elimination of phenylisothiocyanate (PhNCS). Analogous splitting was noted for **2a** and **1a**, whereas in case of **2b**, consequently, 4-methoxyphenylisothiocyanate (CH_3O-PhNCS) was severed. However, the intensities of these signals for **2a**, **1a,** and **2b** were only 6, 20 and 2 %, respectively.

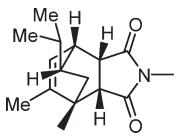
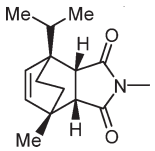
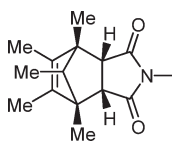
Furthermore, in the fragmentation patterns of **1a**, **2a,** and **2b** the most intense (100%) signal appeared at m/z 70. This value matches with the composition C_5H_{10} for which the isopentene cation-radical structure $[(CH_3)_2CHCH = CH_2]^{+\bullet}$ could be proposed, resulting from the sequential cleavage of the parent molecule. It might be assumed that above fragmentation path corresponds to the presence of the isopropyl substituent in the parent compounds **1a**, **2a,** and **2b**, which is absent in **3a**. Formation of the isopentene moiety from **2a** and **2b** requires a rearrangement of isopropyl substituent, whereas in **1a** the isopentane moiety already occurs as a part of condensed rings, serving as precursor for isopentene. The weak signal in the spectrum of **3a** at m/z 70 (13) occurs in close sequence of other signals showing similar intensity and was not referred to above fragmentation. Proposed fragmentation paths are shown in the Figure 1.

Above results concerning the m/z values of molecular ions and also the fragmentation patterns confirm the expected composition of investigated compounds.

The structure of 1,3-thiazepine and the exocyclic imino form of thiourea fragment were confirmed by the X-ray crystallography of **2b**. In its crystal structure two conformations of thiazepine ring are stabilized. The disorder of S1 and C4 atoms results in twist chair (TC) and deformed boat (B) conformers which are energetically nearly equivalent [28]. The major component (TC)

Table 1

Structure of the investigated compounds **1a**,**b**,**c**–**3a**,**b**,**c**.

	R_1		
R_2	C_6H_5—	(4−OCH_3)C_6H_5—	C_6H_{11}
	**1a**	**1b**	**1c**
	**2a**	**2b**	**2c**
	**3a**	**3b**	**3c**

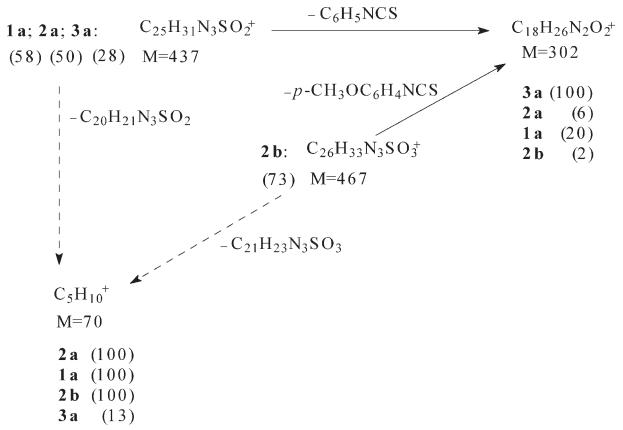


Figure 1. Selected proposed fragmentation patterns for investigated compounds. The relative intensities of the signals are given for each fragment in parentheses. The dashed arrows indicate multistep fragmentation.

with the population of about 88 % is presented on Figure 2.

EXPERIMENTAL

Melting points were determined in a Kofler's apparatus and are uncorrected. The ^{1}H NMR spectra were recorded on a Bruker AVANCE DMX400 spectrometer, operating at 400 MHz. The chemical shift values are expressed in ppm relative to TMS as an internal standard. Elemental analyses were recorded with a CHN 2400 Perkin-Elmer model. Mass spectra of **1a**, **2a**, **3a,** and **2b** were recorded on an AMD-604 double focusing spectrometer with BE geometry (AMD Intectra, Germany). EI low resolution spectra were obtained with electron energy 70 eV, acceleration voltage 8 kV and ion source temperature 220°C. Samples were introduced using a direct insertion probe heated, when required, in the range 30–120°C. Mass spectral ESI measurements for **1b**, **3b**, **1c**, **2c**, **3c** were carried out on Waters ZQ Micromass instruments with quadrupol mass analyzer. The spectra were performed in the positive ion mode at a declustering potential of 40–60 V. The sample was previously separated on a UPLC column (C18) using UPLC ACQUITY^{TM} system by Waters connected with DPA detector.

Diffraction data for **2b** were measured at 292 K on a KM4 diffractometer using variable scan speed in the ω/2θ scan mode and graphite monochromated Cu K_α radiation (λ = 1.54178 Å). A single crystal of dimensions 0.46 × 0.43 × 0.43 mm^3 was used for the data collection.

Flash chromatography was performed on Merck silica gel 60 (200-400 mesh) using chloroform as eluant. Analytical TLC was carried out on silica gel F_{254} (Merck) plates (0.25 mm thickness).

1,3-THIAZEPINE DERIVATIVES (1a,b,c–3a,b,c)

General procedure. Sodium hydride dispersion (60%) in mineral oil (0.44 g, ∼10 mmol) was added in a single portion to a stirred solution of thiourea derivative (10 mmol) in anhydrous *N*,*N*-dimethylformamide at room temperature. After hydrogen evolution ceased, 1,4-dibromobutane (15 mmol) was added to the reaction mixture, after 5 and 15 min. respectively. The mixture was stirred for 6 h. Evaporation in vacuum gave a residue which was then purified by column chromatography (chloroform was used as eluant). The compound was crystallized from ethanol.

10-Isopropyl-8-methyl-4-{2-[(Z)-phenylimino]-1,3-thiazep-an-3-yl}-4-aza-tricyclo[5.2.2.0^{2,6}]undec-8-ene-3,5-dione (1a). Yield 30 %; mp 174-175°C; ^{1}H NMR ($CDCl_3$):d 0.83 (d, J = 6.6 Hz, 3H, CH_3); 0.91 (d, J = 6.6 Hz, 3H, CH_3); 1.01-1.17 (m, 2H, CH_2); 1.27-1.42 (m, 2H, CH_2); 1.52-1.63 (m, 1H, CH); 1.77 (s, 3H, CH_3), 1.81-1.85 (m, 3H, CH, CH_2); 2.0-2.09 (m, 2H, CH); 2.67-2.85 (m, 2H, CH_2-N); 3.2-3.24 (m, 2H, CH—C=O); 3.87-3.95 (m, 2H, CH_2—S); 5.74 (d, J = 6.3 Hz, 1H, CH=); 6.82-7.04 (m, 5H, phenyl). Anal. Calcd for $C_{25}H_{31}N_3O_2S$: C, 68.62; H, 7.14; N, 9.6. Found: C, 68.46; H, 6.98; N, 9.60. ei ms: m/z = 437 (58%).

10-Isopropyl-4-{2-[(Z)-4-methoxy-phenylimino]-1,3-thiaze-pan-3-yl}-8-methyl-4-aza-tricyclo[5.2.2.0^{2,6}]undec-8-ene-3,5-dione (1b). Yield 40%; mp 178-179°C; ^{1}H NMR ($CDCl_3$): d 0.82 (d, J = 6.6 Hz, 3H, CH_3); 0.91 (d, J = 6.6 Hz, 3H, CH_3); 1.01-1.18 (m, 2H, CH_2); 1.27-1.46 (m, 2H, CH_2); 1.52-1.63 (m, 1H, CH); 1.76 (s, 3H, CH_3), 1.81-1.85 (m, 3H, CH, CH_2); 2.0-2.09 (m, 2H, CH); 2.67-2.85 (m, 2H, CH_2—N); 3.2-3.24 (m, 2H, CH—C=O); 3.79 (s, 3H, OCH_3); 3.87-3.95 (m, 2H, CH_2—S); 5.74 (d, J = 6.3 Hz, 1H, CH=); 6.82-7.04 (m, 4H, CH phenyl). Anal. Calcd for $C_{26}H_{33}N_3O_3S$: C, 66.78; H, 7.11; N, 8.99. Found: C, 66.70; H, 7.09; N, 9.03. esi ms: m/z = 468.2 $[M + H]^+$ (100%).

4-{2-[(Z)-Cyclohexylimino]-1,3-thiazepan-3-yl}-10-isopropyl-8-methyl-4-aza-tricyclo[5.2.2.0^{2,6}]undec-8-ene-3,5-dione (1c). Yield 40%; mp 173-174°C; ^{1}H NMR ($CDCl_3$): d 0.82 (d, J = 8.4 Hz, 3H, CH_3); 0.91 (d, J = 8.4 Hz, 3H,

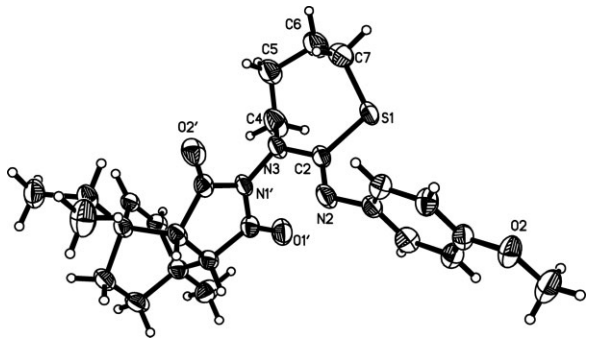


Figure 2. Perspective view of the molecule **2b**. Bond lengths (Å) within the 1,3-thiazepine ring are: C2–S1 1.769(3), S1–C7 1.785(4), C7–C6 1.497(6), C6–C5 1.511(5), C5–C4 1.476(6), C4–N3 1.501(5), N3–C2 1.390(4). The endocyclic torsion angle values (°) for TC conformer are: S1–C2–N3–C4 31.0(4), C2–N3–C4–C5 -91.7(4), N3–C4–C5–C6 79.9(5), C4–C5–C6–C7 -59.8(6), C5–C6–C7–S1 71.0(5) C6–C7–S1–C2 –79.0(4), C7–S1–C2–N3 38.4(4).

CH_3); 0.98-1.23 (m, 2H, CH_2); 1.4-1.74 (m, 14H, CH_2, CH); 1.77 (s, 3H, CH_3), 1.83-1.91 (m, 2H, CH_2); 2.10-2.12 (m, 2H, CH); 2.95-2.99 (m, 1H, CH—C=O); 3.2-3.26 (m, 3H, CH—C=O, CH_2—N); 3.55-3.57 (m, 2H, CH_2—S); 4.03 (d, J = 8.8 Hz, 1H, CH—N=); 5.96 (d, 1H, CH—). *Anal*. Calcd for $C_{25}H_{37}N_3O_2S$: C, 67.68; H, 8.41; N, 9.47. Found: C, 68.04; H, 8.52; N, 9.51. esi ms: m/z = 444.1 $[M + H]^+$ (100%).

1-Isopropyl-7-methyl-4-{2-[(Z)-phenylimino]-1,3-thiazep-an-3-yl}-4-aza-tricyclo[5.2.2.0^{2,6}]undec-8-ene-3,5-dione (2a). Yield 45%; mp 147-148°C; ^{1}H NMR ($CDCl_3$): d 0.99 (d, J = 6.8 Hz, 3H, CH_3); 1.11 (d, J = 6.4 Hz, 3H, CH_3); 1.22-1.35 (m, 2H, CH_2); 1.4-1.47 (m, 3H, CH, CH_2); 1.51 (s, 3H. CH_3); 1.71-1.77 (m, 2H, CH_2); 1.9-1.97 (m, 2H, CH_2); 2.63 (dd, J = 8 Hz, 2H, CH—C=O), 2.98-3.06 (m, 2H, CH_2—N); 3.77-3.84 (m, 2H, CH_2—S); 6.04 (dd, J = 8.4 Hz, 2H, CH=); 6.68 (d, J = 7.6 Hz, 2H, CH phenyl); 6.98-7.03 (m, 1H, CH phenyl); 7.2-7.24 (m, 2H, CH phenyl). *Anal*. Calcd for $C_{25}H_{31}N_3O_2S$: C, 68.62; H, 7.14; N, 9.60. Found: C, 68.76; H, 7.10; N, 9.51. ei ms: m/z = 437 (50%).

1-Isopropyl-4-{2-[(Z)-4-methoxy-phenylimino]-1,3-thiaz-epan-3-yl}-7-methyl-4-aza-tricyclo[5.2.2.0^{2,6}]undec-8-ene-3,5-dione (2b). Yield 49%; mp 185-186°C; ^{1}H NMR ($CDCl_3$): d 0.99 (d, J = 6.8 Hz, 3H, CH_3); 1.12 (d, J = 6 Hz, 3H, CH_3); 1.26-1.37 (m, 2H, CH_2); 1.4-1.46 (m, 3H, CH, CH_2); 1.5 (s, 3H. CH_3); 1.71-1.73 (m, 2H, CH_2); 1.96-1.98 (m, 2H, CH_2); 2.62 (dd, J = 8 Hz, 2H, CH—C=O), 2.99-3.07 (m, 2H, CH_2—N); 3.75-3.78 (m, 2H, CH_2—S); 3.75 (s, 3H, O—CH_3); 6.04 (dd, J = 8.4 Hz, 2H, CH=); 6.6-6.66 (m, 2H, CH phenyl); 6.76-6.81 (m, 2H, CH phenyl). *Anal*. Calcd for $C_{26}H_{33}N_3O_3S$: C, 66.78; H, 7.11; N, 8.99. Found: C, 66.49; H, 7.11; N, 8.99. ei ms: m/z = 467 (73%).

Crystal data for **2b**: monoclinic, space group $P2_1/c$, a = 14.407(3), b = 11.586(2), c = 14.851(3) Å, β = 92.92(3)°, V = 2475.7(8) Å^3, Z = 4, d_{calc} = 1.255 g/cm^3, μ(Cu K_α) = 1.415 mm^{-1}. In the θ range 3.07–73.51°, 4971 reflections were collected of which 4793 were unique (R_{int} = 0.0264). The structure was solved by direct methods using SHELXS-97 program [29] and refined by full-matrix least-squares on F^2 using SHELXL-97 program [29]. The non-H atoms were refined with anisotropic displacement parameters, except of S1A and C4A atoms. The two atoms of thiazepine ring are disordered over two positions with sof's of 0.877(4) and 0.123(4) for S1, C4, and S1A, C4A, respectively. H-atom positions were calculated from the geometry. H-atoms were given isotropic factors of 1.2 or 1.5 Ueq of the bonded C-atoms; the C–H bond 'riding' model was used in the refinement.

Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as CCDC No. 684835. Copies of the data can be obtained on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

4-{2-[(Z)-Cyclohexylimino]-1,3-thiazepan-3-yl}-1-isoprop-yl-7-methyl-4-aza-tricyclo[5.2.2.0^{2,6}]undec-8-ene-3,5-dione (2c). Yield 21%, mp 151-152°C; ^{1}H NMR ($CDCl_3$): d 0.85-0.88 (m, 6H, CH_2); 0.99 (d, J = 7.2 Hz, 3H, CH_3); 1.12 (d, J = 6.8 Hz, 3H, CH_3); 1.25-1.32 (m, 7H, CH, CH_2); 1.5 (s, 3H, CH_3); 1.74-1.91 (m, 4H, CH_2); 2.33-2.37 (m, 2H, CH_2); 2.54-2.64 (m, 2H, CH—C=O); 3.37-3.43 (m, 2H, CH_2—N); 3.52-3.56 (m, 2H, CH_2—S); 4.36-4.42 (m, 1H, CH—N=); 5.87 (dd, J = 8.8 Hz, 2H, CH=). *Anal*. Calcd for $C_{25}H_{37}N_3O_2S$: C, 67.68; H, 8.41; N, 9.47. Found: C, 67.25; H, 8.82; N, 9.32. esi ms: m/z = 444.1 $[M + H]^+$ (100%).

1,7,8,9,10-Pentamethyl-4-{2-[(Z)-phenylimino]-1,3-thiazep-an-3-yl}-4-aza-tricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5-dione (3a). Yield 41%; mp 107-108°C; ^{1}H NMR ($CDCl_3$): d 0.61 (d, J = 6.4 Hz, 3H, CH_3); 1.22-1.32 (m, 2H, CH_2); 1.36 (s, 6H, CH_3); 1.62 (s, 6H, CH_3); 1.6-1.64 (m, 1H, CH); 1.96-1.99 (m, 2H, CH_2); 2.91-3.18 (m, 4H, CH—C=O, CH_2—N); 3.75-3.78 (m, 2H, CH_2—S); 6.77-7.07 (m, 5H, CH phenyl). *Anal*. Calcd for $C_{25}H_{31}N_3O_2S$: C, 68.62; H, 7.14; N, 9.59. Found: C, 68.28; H, 6.92; N, 9.16. ei ms: m/z = 437 (28%).

1,7,8,9,10-Pentamethyl-4-{2-[(Z)-4-methoxy-phenylimino]-1,3-thiazepan-3-yl}-4-aza-tricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5-di-one (3b). Yield 19%; mp 126-127°C; ^{1}H NMR ($CDCl_3$): d 0.61 (d, J = 6.4 Hz, 3H, CH_3); 1.22-1.32 (m, 2H, CH_2); 1.36 (s, 6H, CH_3); 1.62 (s, 6H, CH_3); 1.6-1.64 (m, 1H, CH); 1.96-1.99 (m, 2H, CH_2); 2.91-3.18 (m, 4H, CH—C=O, CH_2—N); 3.75-3.78 (m, 2H, CH_2—S); 3.77 (s, 3H, O—CH_3); 6.57-6.63 (m, 2H, CH phenyl); 6.78 (d, 2H, CH phenyl). *Anal*. Calcd for $C_{26}H_{33}N_3O_3S$: C, 66.78; H, 7.11; N, 8.99. Found: C, 66.56; H, 7.2; N, 8.99. esi ms: m/z = 468.2 $[M + H]^+$ (100%).

4-{2-[(Z)-Cyclohexylimino]-1,3-thiazepan-3-yl}-4-aza-tricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5-dione (3c). Yield 23%; mp 112-113°C; ^{1}H NMR ($CDCl_3$): d 0.61 (d, J = 5.6 Hz, 3H, CH_3); 1.05-1.26 (m, 6H, CH_2); 1.32 (s, 6H, CH_3); 1.38-1.95 (m, 9H, CH, CH_2); 1.53 (s, 6H, CH_3); 2.7-2.73 (m, 2H, CH_2—N); 2.8-2.84 (m, 2H, CH—C=O); 3.3-3.36 (m, 2H, CH_2—S); 3.94-4.0 (m, 1H, CH—N=). *Anal*. Calcd for $C_{25}H_{37}N_3O_2S$: C, 67.68; H, 8.41; N, 9.47. Found: C, 67.60; H, 8.52; N, 9.40. esi ms: m/z = 444.1 $[M + H]^+$ (100%).

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