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Short communication

Chemotherapy of leishmaniasis Part VI: Synthesis and bioevaluation of some novel terpenyl *S*,*N*- and *N*,*N*-acetals ☆

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Abstract

Some novel terpene based oxoketene *S*,*N*-acetals **2**(**a**–**g**) and *N*,*N*-acetals **3**(**a**–**c**) have been synthesized from oxoketene dithioacetal **1**. The compounds were screened for their *in vivo* antileishmanial activity. Some of the compounds showed 50–70% inhibition in the hamster model.

Keywords: Ionones; Oxoketene *S*,*N*- and *N*,*N*-acetals; Antileishmanial activity

1. Introduction

Leishmaniasis is an infection caused by protozoa of the genus *Leishmania* presenting several forms of the disease such as cutaneous (CL), mucocutaneous (MCL) and visceral leishmaniasis (VL), which can be fatal when untreated. The chemotherapy currently available for leishmaniasis is far from satisfactory. Resistance to the pentavalent antimonials [1,2], which have been recommended drugs for the treatment of both visceral (VL) and cutaneous leishmaniasis (CL) for >50 years, is now widespread in India. Although new drugs have become available in recent years for the treatment of VL including amphotericin B lipid complex [3] and the oral drug miltefosine [4], treatment problems remain. Currently, efforts are being made to search for new molecules from natural sources and in this endeavour diaryl heptanoids [5,6,7], oxygenated abietanes [8], iridoids [9] and heterocyclic ionone-like molecules [10] are showing promise as new lead molecules. Randomly designed heterocyclic ionone-like molecules [10] and some novel terpenyl 2,4-diamino pyrimidines [11] are showing promising antimicrobial and dihydrofolate reductase inhibitory activities. Rationally designed 2,4-diamino pyrimidines [12] and some computer aided molecules [13] are also giving further inputs in the leishmanial dihydrofolate reductase activity. In continuation of our studies on terpenyl pyrimidines as novel antileishmanial agents [14], we synthesized some novel terpenyl *S*,*N*-acetals and *N*,*N*-acetals, and evaluated them for their *in vivo* antileishmanial activity and the results are reported in this communication.

2. Chemistry

The polarized ketene dithioacetals, the masked α-ketoacids are a novel class of compounds having considerable potential in synthetic organic chemistry [15]. However, their biological potential has not been fully explored. They are easily prepared by reacting the corresponding active methylene compounds with carbon disulfide in the presence of a suitable base followed by alkylation, often in a one pot reaction [16]. Many experimental variations have been developed within this broad procedural framework to suit the substrate characteristics such as the acidities of active methylene hydrogens, specific base

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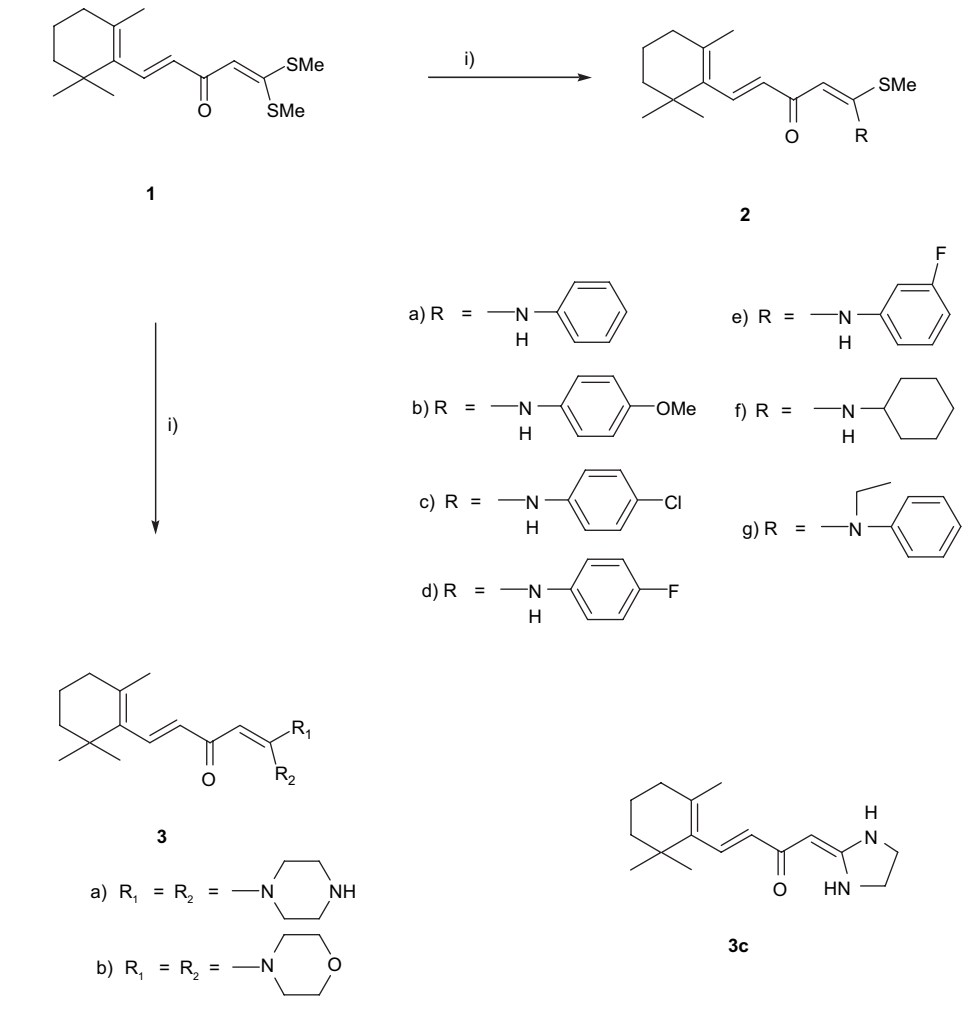
sensitive functional groups and the optimum yields of the corresponding dithioacetals.

The terpenyl ketene dithioacetal **1** was synthesized using our recently developed method [17]. The literature methods used in the synthesis of *S*,*N*- and *N*,*N*-acetals proved less useful for the synthesis of terpenyl *S*,*N*- and *N*,*N*-acetals.

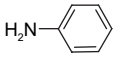
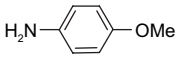
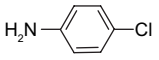
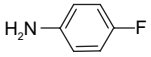
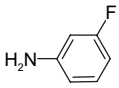
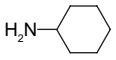
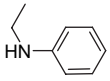
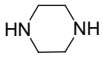
The reaction of β-ionone ketene dithioacetal **1** with aniline at ethanol reflux temperature was found to be very slow and it did not provide *S*,*N*- or *N*,*N*-acetal. However, the reaction of **1** with aniline in ethanol under steel bomb conditions (Table 1, entry-1) furnished **2a** in 59% yield. The reaction of *p*-methoxyaniline with **1** was more facile as expected (Table 1, entry-2) and it furnished *S*,*N*-acetal **2b** in quantitative yield. The method was found to be general and it worked on a series of amines (Table 1). Chloroaniline was found to be less reactive and did not react with **1** at ethanol reflux temperature. However, it reacted with **1** under steel bomb conditions (Table 1, entry-3) to furnish *S*,*N*-acetal **2c** as a crystalline compound which melted at 85–86 °C. The ^{1}H NMR spectrum of **2c** was in agreement with the assigned structure. Under identical reaction conditions *p*-fluoroaniline reacted with **1** to furnish **2d** in 42% yield. Similarly, *m*-fluoroaniline furnished **2e** in 30% yield. Cyclohexylamine, comparatively more reactive than arylamines, reacted with **1** in ethanol (reflux, 20 h) and furnished **2f** in 43% yield as a white crystalline solid, which melted at 75–76 °C.

Having successfully synthesized *S*,*N*-acetals of aryl/alkylamines we turned our attention towards secondary amines. The reaction of *N*-ethylaniline with **1** (Table 1, entry-7) furnished *S*,*N*-acetal **2g** in 60% isolated yield. The reaction of excess of morpholine with **1** was quite facile and it furnished *N*,*N*-acetal **3b** in 68% yield as a colourless crystalline solid which melted at 141–142 °C. The ^{1}H NMR spectrum of **3b** displayed a doublet at 7.20 ppm (J = 16.00 Hz) for H-5 proton, another doublet at 6.10 ppm (J = 16.00 Hz) for H-4 proton, a singlet at 4.60 ppm for the H-2 proton, and it confirmed the assigned structure. Similarly, the reaction of **1** with piperazine was equally facile (ethanol reflux, 5 h) to furnish *N*,*N*-acetal **3a** in quantitative yield. The reaction of **1** with 1,2-diaminoethane was quite facile and it furnished cyclic *N*,*N*-acetal **3c** in 60% yield (Table 1, entry-10).



Reaction conditions: 1) Amine, ethanol, steel bomb, heat.

Table 1

Serial no.	Substrate	Amine	Reaction conditions	Product	
				S,N-acetal, %	*N,N*-acetal, %
1	**1**		Steel bomb, EtOH, 100–110 °C, 9 h	**2a**, 59	–
2	**1**		EtOH, reflux, 15 h	**2b**, 87	–
3	**1**		Steel bomb, EtOH, 100–120 °C, 20 h	**2c**, 90	–
4	**1**		Steel bomb, EtOH, 100–120 °C, 22 h	**2d**, 42	–
5	**1**		EtOH, reflux, 40 h	**2e**, 30	–
6	**1**		EtOH, reflux, 20 h	**2f**, 43	–
7	**1**		EtOH, reflux, 20 h	**2g**, 68	–
8	**1**		EtOH, reflux, 5 h	–	**3a**, 81
9	**1**		EtOH, reflux, 5 h	–	**3b**, 60
10	**1**		EtOH, reflux, 5 h	–	**3c**, 60

3. Biological activities

The *in vivo* leishmanicidal activity was determined in golden hamsters (*Mesocricetus auretus*) infected with HOM/IN/80/DD8 strain of *Leishmania donovani* obtained through the courtesy of P.C.C. Garnham, Imperial College, London (U.K.).

For *in vivo* evaluation of compounds, the method of Beveridge [18] as modified by Bhatnagar et al. [19] and Gupta et al. [20] was employed. Male hamsters weighing 35–40 g were infected with 1×10^7 amastigotes and the intensity of infection after 20 days was assessed by spleen biopsy. Animals with 2^+ infections (5–15 amastigote/100 cell nuclei) were selected for screening the compounds. The infected animals were randomized into several groups on the basis of their parasitic burdens. Usually 4–6 animals were used for each compound and the same numbers were kept as untreated controls. The drug treatment was given intraperitoneally for five consecutive days at 50 mg/kg dose level (Table 2). To assess the effect of test compounds spleen biopsies were performed on each animal after 7 and 28 days of last drug administration and amastigote counts were assessed by Giemsa staining. The percentage inhibition in amastigote multiplication was calculated using the following formula:

$$\text{P.I.} = 100 - \frac{\text{ANAT} \times 100}{\text{INAT} \times \text{TIUC}}$$

P.I. = percent inhibition of amastigotes multiplication, ANAT = actual number of amastigotes in treated animals, INAT = initial number of amastigotes in treated animals, and TIUC = times increase of parasites in untreated control animals.

4. Results and discussion

In our earlier studies [21] we have shown α-oxoketene dithioacetals as good pharmacophores in the chemotherapy of

Table 2
Antileishmanial activity of compounds against *L. donovani* in hamsters

Serial no.	Compound no.	Dose, mg/kg	Day-7, % inhibition	Day-28, % inhibition
1	**2a**	50	NI (i.p.)	ND
2	**2b**	50	52 (i.p.)	ND
3	**2c**	50	18 (i.p.)	ND
4	**2d**	50	31 (i.p.)	ND
5	**2e**	50	53 (i.p.)	ND
6	**2f**	50	46 (i.p.)	ND
7	**2g**	50	NI (i.p.)	ND
8	**3a**	50	All died	ND
9	**3b**	50	NI	ND
10	**3c**	50	30 (i.p.)	65 (IP)
	3c	50	40 (oral)	71 (oral)
11	Stibanate	40	93 (i.p.)	75 (i.p.)
12	Miltefosine	12.5	94 (oral)	69 (oral)

leishmaniasis. We visualized that the activity profile of these compounds was probably due to their alkylating nature i.e. DNA alkylation properties. In the present study we visualized that *S*,*N*-acetals and *N*,*N*-acetals probably may not be good alkylating agents but they can be good metal chelates and the property is very much useful in the chemotherapy of cancer and leishmania [22a,b]. As we expected *S*,*N*-acetals **2b** and **2e** showed 50–53% *in vivo* antileishmanial profile on day-7. However, *S*,*N*-acetals having *p*-chloro and *p*-fluoro substitutions resulted in the diminition of biological activity. However, *N*,*N*-acetal **3c** was found more interesting. It did not show inhibition on day-7 but on day-28 it showed 65% activity by intraperitoneal route. By oral route it was found better on day-28 and it showed 71% activity. In view to access their full biological potential further optimization studies are in progress.

5. Experimental

The reported melting points (°C) are the uncorrected ones. The infrared spectra were recorded in KBr on a Perkin Elmer model 881. NMR spectra were obtained in $CDCl_3$ (with Me_4Si internal standard, Aldrich) and are reported in ppm downfield from Me_4Si. Proton, carbon NMR spectra were recorded on Bruker Advance DRX 2000 instrument. Electron impact (EI) mass spectra were recorded on a Jeol JMS-D-300 spectrometer with the ionization potential of 70 eV. Elemental analyses were carried out on a Carlo–Erba EA 1108 instrument.

*5.1. 1-Thiomethyl-1-N-phenyl amino-5-(2′,6′,6′-trimethyl)-cyclohex-2′-en-1′-yl-pent 1,4-dien-3-one (**2a**)*

To a solution of ketene dithioacetal **1** (0.296 g, 1 mmol) in absolute ethanol (20 ml) was added aniline (0.932 g, 10 mmol) and the resulting reaction mixture was heated in a steel bomb at 100–105 °C for 9 h. It was concentrated *in vacuo* and the residue was column chromatographed (SiO_2, 60–120 mesh). Elution with 2% ethylacetate in hexane furnished **2a** (0.20 g, 59%) as a pale brown oil. IR (neat, cm^{-1}) 2927, 1552; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.10 (s, 6H), 1.50 (m, 2H), 1.60 (m, 2H), 1.80 (s, 3H), 2.00 (m, 2H), 2.40 (s, 3H), 5.10 (s, 1H), 6.10 (d, $J = 16.00$ Hz, 1H), 7.30 (m, 6H), 13.60 (s, 1H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 15.042 (q), 19.506 (t), 22.180 (q), 2 × 29.311 (q), 33.358 (t), 34.621 (s), 40.232 (t), 93.550 (d), 2 × 125.271 (d), 126.489 (d), 2 × 129.387 (d), 132.428 (d), 133.893 (s), 137.196 (s), 138.703 (s), 138.895 (d), 167.233 (s), 184.436 (s); MS: *m/e* 342 (m^+), 295 ($m^+ - SCH_3$). Anal. calcd. for $C_{21}H_{27}NOS$: C, 73.86; H, 7.97; N, 4.10. Found: C, 74.0; H, 7.88; N, 4.20.

*5.2. 1-Thiomethyl-1-N-(p-methoxyphenyl amino)-5-(2′,6′,6′-trimethyl)-cyclohex-2′-en-1′-yl-pent-1,4-dien-3-one (**2b**)*

IR (neat, cm^{-1}) 3433, 1639, 1217; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.10 (s, 6H), 1.50 (m, 2H), 1.65 (m, 2H), 1.80 (s, 3H), 2.10 (m, 2H), 2.35 (s, 3H), 2.50 (m, 2H), 3.80 (s, 3H), 5.25 (s, 1H), 6.00 (d, $J = 16.00$ Hz, 1H), 6.80 (d, $J = 10.00$ Hz, 2H), 7.15 (d, $J = 10.00$ Hz, 1H), 7.35 (d, $J = 16.00$ Hz, 1H); ^{13}C NMR (200 MHz) δ 14.827 (q), 19.467 (t), 22.137 (q), 2 × 29.257 (q), 33.778 (s), 34.528 (t), 40.154 (t), 55.682 (q), 92.742 (d), 2 × 114.495 (d), 2 × 127.166 (d), 131.443 (s), 132.505 (d), 133.608 (s), 136.884 (s), 138.170 (d), 158.469 (s), 168.269 (s), 184.050 (s); MS: *m/e* 372 ($m^+ + 1$). Anal. calcd. for $C_{22}H_{29}NO_2S$: C, 71.17; H, 7.87; N, 3.77. Found C, 70.98; H, 7.67; N, 3.79.

*5.3. 1-Thiomethyl-1-N-(p-chlorophenyl amino)-5-(2′,6′,6′-trimethyl)-cyclohex-2′-en-1′-yl-pent-1,4-dien-3-one (**2c**)*

M.p. 85–86 °C; IR (KBr, cm^{-1}) 3390, 2925, 1598; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.00 (s, 6H), 1.40 (m, 2H), 1.60 (m, 2H), 1.75 (s, 3H), 2.00 (m, 2H), 2.30 (s, 3H), 5.20 (s, 1H), 6.05 (d, $J = 16.00$ Hz, 1H), 7.25 (m, 5H); ^{13}C NMR (200 MHz) δ 15.043 (q), 19.474 (t), 22.180 (q), 2 × 29.295 (q), 33.886 (t), 34.613 (t), 40.226 (t), 93.975 (d), 126.416 (d), 2 × 129.518, (d) 2 × 131.872 (d), 132.663 (s), 133.784 (s), 134.251 (s), 137.136 (s), 137.585 (s), 139.066 (d), 166.848 (s), 184.578 (s); MS: *m/e* 376 ($m^+ + 1$). Anal. calcd. for $C_{21}H_{26}OSClN$: C, 67.10; H, 6.97; N, 3.73. Found: C, 66.68; H, 7.36; N, 4.06.

*5.4. 1-Thiomethyl-1-N-(p-fluorophenyl amino)-5-(2′,6′,6′-trimethyl)-cyclohex-2′-en-1′-yl-pent-1,4-dien-3-one (**2d**)*

IR (neat, cm^{-1}) 3020, 2933, 1548, 1200, 750; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.10 (s, 6H), 1.45 (m, 2H), 1.60 (m, 2H), 1.75 (s, 3H), 2.00 (m, 2H), 2.25 (s, 3H), 5.25 (s, 1H), 6.10 (d, $J = 16.00$ Hz, 1H), 6.95 (d, $J = 16.00$ Hz, 1H), 7.25 (m, 4H); ^{13}C NMR (200 MHz) δ 14.830 (q), 19.455 (t), 22.120 (q), 2 × 29.250 (q), 33.815 (t), 34.554 (s), 40.177 (t), 93.376 (d), 115.934 (d), 116.385 (d), 127.279 (d), 127.446 (d), 132.241 (d), 133.962 (s), 134.878 (s), 135.711 (s), 137.094 (s), 138.718 (s), 167.574 (s), 184.394 (s); MS: *m/e* 360 ($m^+ + 1$), 312 ($m^+ - SCH_3$). Anal. calcd. for $C_{21}H_{26}NSOF$: C, 70.16; H, 7.28; N, 3.90. Found C, 70.25; H, 7.30; N, 3.82.

*5.5. 1-Thiomethyl-1-N-(3-fluorophenyl amino)-5-(2′,6′,6′-trimethyl)-cyclohex-2′-en-1′-yl-pent-1,4-dien-3-one (**2e**)*

IR (neat, cm^{-1}) 3400, 3020, 2931, 1550, 1215; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.00 (s, 6H), 1.45 (m, 2H), 1.60 (m, 2H), 1.80 (s, 3H), 2.00 (m, 2H), 2.40 (s, 3H), 5.20 (s, 1H), 6.10 (d, $J = 16.00$ Hz, 1H), 6.85 (d, $J = 16.00$ Hz, 1H), 7.25 (m, 4H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 15.08 (q), 19.458 (t), 22.167 (q), 2 × 29.282 (q), 33.879 (t), 34.598 (s), 40.212 (t), 94.310 (d), 120.357 (d), 120.418 (d), 130.449 (d), 130.634 (d), 2 × 132.081 (d,s), 134.328 (s), 137.107 (s), 2 × 139.163 (d,s), 167.477 (s), 184.570 (s); MS: *m/e* 360 ($m^+ + 1$), 344 ($m^+ - CH_3$), 312 ($m^+ - SCH_3$). Anal. calcd.

for. $C_{21}H_{26}NSOF$: C, 70.16; H, 7.28; N, 3.90. Found C, 70.01; H, 7.18; N, 3.82.

5.6. 1-Thiomethyl-1-cyclohexyl amino-5-(2′,6′,6′-trimethyl)-cyclohex-2′-en-1′-yl-pent-1,4-dien-3-one (**2f**)

M.p. 75–76 °C; IR (KBr, cm^{-1}) 3394, 2935, 1662, 1554, 1215; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.00 (m, 6H), 1.40 (m, 12H), 1.80 (s, 3H), 2.00 (m, 2H), 2.40 (s, 3H), 3.60 (m, 1H), 5.00 (s, 1H), 6.00 (d, $J = 16.00$ Hz, 1H), 7.20 (d, $J = 16.00$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 14.531 (q), 19.525 (t), 22.123 (q), 2×24.809 (t), 25.779 (t), 2×29.265 (q), 2×33.57 (t), 33.702 (t), 34.573 (s), 40.161 (t), 53.339 (d), 90.778 (d), 132.619 (s), 133.147 (d), 137.270 (d), 137.359 (s), 168.010 (s), 183.345 (s); MS: *m/e* 347 (m^+), 299 ($m^+ - SCH_3$). Anal. calcd. for $C_{21}H_{33}ONS$: C, 72.88; H, 9.91; N, 4.03. Found: C, 72.88; H, 10.15; N, 4.69.

5.7. 1-Thiomethyl-1-(N-ethyl-N-phenyl amino)-5-(2′,6′,6′-trimethyl)-cyclohex-2′-en-1′-yl-pent-1,4-dien-3-one (**2g**)

IR (KBr, cm^{-1}) 3020, 1558, 1473, 1215, 760; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.10 (s, 6H), 1.45 (m, 2H), 1.60 (m, 2H), 1.75 (s, 3H), 2.00 (m, 2H), 2.40 (s, 3H), 2.95 (m, 3H), 3.55 (m, 2H), 5.00 (s, 1H), 6.05 (d, $J = 16.00$ Hz, 1H), 7.30 (m, 6H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 14.578 (q), 19.544 (q), 22.167 (q), 2×29.310 (q), 33.782 (t), 34.605 (s), 36.702 (t), 40.218 (t), 46.135 (t), 91.218 (d), 127.033 (d), 4×129.115 (d), 132.928 (d), 133.063 (s), 137.272 (s), 137.584 (d), 138.737 (s); MS: *m/e* 370 ($m^+ + 1$). Anal. calcd. for $C_{23}H_{31}NOS$: C, 74.75; H, 8.45; N, 3.79. Found: C, 74.51; H, 8.37; N, 3.82.

5.8. 1,1-Dipiperazino-5-(2′,6′,6′-trimethyl)-cyclohex-2′-en-1′-yl-pent-1,4-dien-3-one (**3a**)

IR (neat, cm^{-1}) 3419, 2927, 1500; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.00 (s, 6H), 1.45 (m, 2H), 1.45 (m, 1H), 1.55 (m, 2H), 1.75 (s, 3H), 2.00 (m, 2H), 2.80 (m, 8H), 3.20 (m, 8H), 4.45 (s, 1H), 6.00 (d, $J = 16.00$ Hz, 1H), 7.08 (d, $J = 16.00$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 19.507 (t), 22.141 (q), 2×29.299 (q), 33.704 (s), 34.537 (t), 40.212 (t), 4×46.45 (t), 4×50.055 (t), 88.585 (d), 132.501 (s), 134.464 (d), 136.259 (d), 137.264 (s), 167.087 (s), 184.026 (s); MS: *m/e* 372 (m^+).

5.9. 1,1-Dimorpholino-5-(2′,6′,6′-trimethyl)-cyclohex-2′-en-1′-yl-pent-1,4-dien-3-one (**3b**)

M.p. 141–142 °C; IR (KBr, cm^{-1}) 2916, 1637, 1581, 1500, 1440, 1363; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.00 (s, 6H), 1.40 (m, 2H), 1.50 (m, 2H), 1.65 (s, 3H), 2.00 (m, 2H), 3.20 (m, 8H), 3.70 (m, 8H), 4.60 (s, 1H), 6.10 (d, $J = 16.00$ Hz, 1H), 7.20 (d, $J = 16.00$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 19.519 (t), 22.157 (q), 2×29.314 (q), 33.740 (t), 34.560 (s), 40.228 (t), 4×50.546 (t), 4×67.146 (t), 88.650 (d), 132.765 (s), 134.322 (d), 136.858 (d), 137.235 (s), 166.118 (s), 184.511 (s); MS: *m/e* 374 (m^+). Anal. calcd. for: $C_{22}H_{34}N_2O_3$: C, 70.55; H, 9.15; N, 7.48. Found: C, 70.62; H, 9.57; N, 7.50.

5.10. 1,1-Diaminoethyl-5-(2′,6′,6′-trimethyl)-cyclohex-2′-en-1′-yl-pent-1,4-dien-3-one (**3c**)

M.p. 195–196 °C; IR (KBr, cm^{-1}) 3400, 3018, 2916, 1710, 1595; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.04 (s, 6H), 1.45 (m, 2H), 1.55 (m, 2H), 1.75 (s, 3H), 2.00 (m, 2H), 3.65 (m, 2H), 4.80 (m, 2H), 5.95 (d, $J = 16.00$ Hz, 1H), 7.06 (s, 1H), 7.10 (d, $J = 16.00$ Hz, 1H); ^{13}C NMR (200 MHz) δ 19.568 (t), 22.034 (q), 2×29.246 (q), 33.622 (t), 34.561 (s), 40.164 (t), 2×43.565 (t), 78.888 (d), 131.838 (s), 133.583 (d), 135.506 (d), 137.390 (s), 165.895 (s), 184.005 (s); MS: *m/e* 262 ($m^+ + 2$). Anal. calcd. for: $C_{16}H_{24}N_2O$: C, 72.52; H, 7.69; N, 15.38. Found: C, 72.57; H, 8.01; N, 15.41.

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