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Original article

Chemotherapy of leishmaniasis part-VIII: Synthesis and bioevaluation of novel chalcones☆

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Abstract

Some novel dihydro-α-ionone based chalcones have been synthesized and evaluated for their in vitro antileishmanial activity in promastigote and amastigote model. Some of the compounds showed 100% inhibition at 5 and 2 μm/ml concentration.

Keywords: Dihydro-α-ionone; Chalcones; In vitro 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.

In view of the high toxicity associated with the existing antileishmanial drugs, efforts are being made to search for new molecules from natural sources, which can act as a new lead in the chemotherapy of *Leishmania*. In this endeavour, diaryl heptanoids [5], oxygenated abietanes [6], diterpene quinones [7,8], and chalcones [9] are showing promise in the in vitro antileishmanial studies. Curcumin **1** isolated from *Curcuma longa* Linn. (Fig. 1) is not only showing promise as anticancer agent [5a] but it is showing antileishmanial activity profile in the in vitro studies [5b,10]. Exhaustive analoging of curcumin has generated some interesting results [11]. Licochalcone **2** isolated from *Glycerrhiza* spp. was first reported for its antibacterial activity [12] is also showing promising antileishmanial activity [13]. Chemical library generated on the basis of Licochalcone as a lead molecule is showing promise in the in vitro antileishmanial studies [9a]. Phenolic diketone **3** isolated from *Zingiber officinale* [14] is a structural mimic of **1** and **2** and shows radical scavenging activities quite comparable to Curcumin **1**. In continuation of our efforts to generate natural product based novel antileishmanial agents [15] coupled with encouraging results on **1**–**3**, we synthesized some novel dihydro-α-ionone based chalcones and evaluated them for in vitro antileishmanial activity and the results are reported in this paper.

2. Chemistry

The dihydro-α-ionone **4** was made available using our published method [16]. The reaction of dihydro-α-ionone **4** with *p*-benzyloxy benzaldehyde **5a** in the presence of KF/Al_2O_3 under microwave irradiation (4–5 min) furnished chalcone **6a** in

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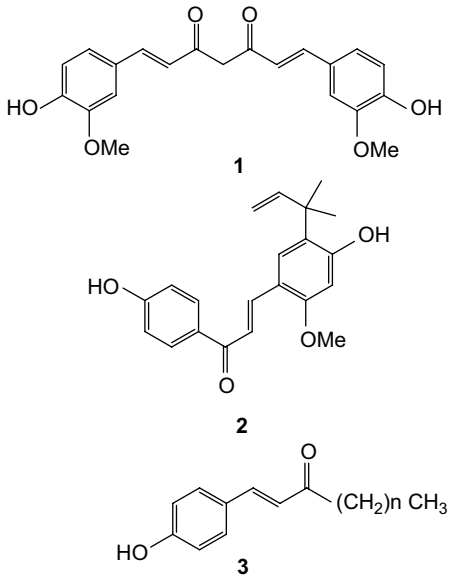


Fig. 1.

72% yield as a pale yellow crystalline solid, m.p. 99–101 °C. The ^{1}H NMR spectrum of **6a** displayed a three proton singlet at 1.60 for a C-2 methyl, a singlet at 5.08 for a benzylic CH_2, a broad singlet at 5.35 for a C-3 proton, and it confirmed the assigned structure of **6a**. Under identical reaction conditions, alkoxy aldehydes **5**(**b**–**d**) reacted smoothly with dihydro-α-ionone **4** to furnish chalcones **6**(**b**–**d**) in respectable yields (Scheme 1). Aldehydes with electron withdrawing group **5**(**e**–**h**) also reacted with dihydro-α-ionone **4** under identical reaction conditions to furnish **6**(**e**–**h**) in respectable yields.

Base labile aldehyde, *p*-hydroxy benzaldehyde **5i** under classical conditions (aq. KOH, methanol) was not a very clean reaction. However, under solvent free microwave conditions it furnished chalcone **6i** in good yield. Under identical reaction conditions pyridine-3-aldehyde **7** reacted smoothly with dihydro-α-ionone **4** to furnish *E*/*Z* unseparable mixture of chalcone **8** in good yield. The furano aldehyde **9** under identical reaction conditions reacted with dihydro-α-ionone **4** to furnish chalcone **10** in quantitative yield.

3. Biological activities

3.1. Material and method

Parasite: luciferase transfected *Leishmania donovani* promastigotes (MHOM/IN/80/Dd-8, obtained from Imperial College, London) which are more stable under the influence of G 418 [17] were maintained at 25 ± 1 °C in medium 199 (Sigma Chemical Co., USA) supplemented with 10% foetal calf serum (GIBCO).

3.2. In vitro assay

3.2.1. Antipromastigote activity

The *L. donovani* promastigotes (MHOM/IN/Dd-8; originally obtained from Imperial college, London) were transfected with firefly luciferase gene, and the transfectants were maintained in medium 199 (Sigma Chemical Co., USA) supplemented with 10% foetal calf serum (GIBCO) and 1% penicillin (50 μg/ml), streptomycin (50 μg/ml) solution (Sigma) under pressure of G418 (Sigma) [18]. The in vitro effect of the compounds on the growth of promastigotes was assessed by monitoring the luciferase activity of viable cells after treatment. The transgenic promastigotes of late log phase were seeded at 5×10^5/100 μl medium 199 in 96-well flat bottomed microtitre (MT) plates (CELLSTAR) and incubated for 72 h in medium alone or in the presence of serial dilutions of drugs (0.25–10 μg/ml) in DMSO. Parallel dilutions of DMSO were used as controls. After incubation, an aliquot (50 μl) of promastigote suspension was aspirated from each well of a 96-well plate and mixed with an equal volume of stready Glo® reagent (Promega) and luminescence was measured by a luminometer. The values were expressed as relative luminescence unit (RLU). The inhibition of parasitic growth was determined by comparing the luciferase activity of drug treated parasites with that of untreated controls by the general formula:

$$\%\ \text{Inhibition} = \frac{N - n}{N} \times 100$$

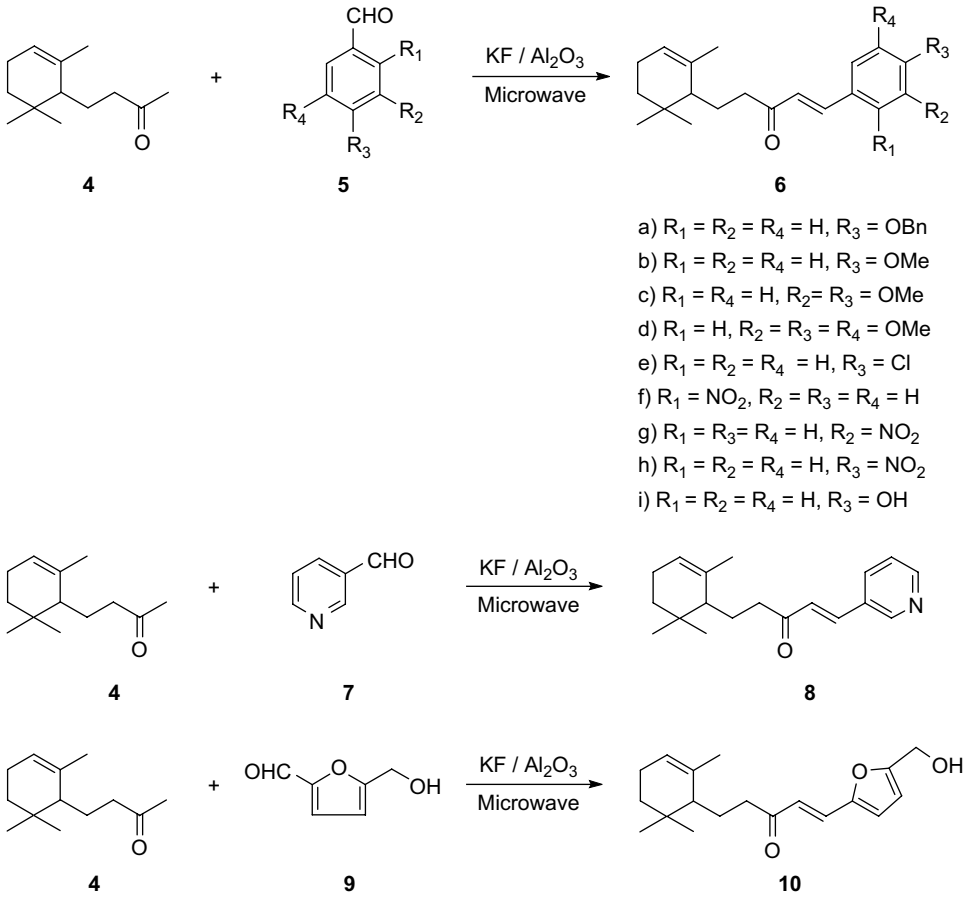
where N is average relative luminescence unit (RLU) of control wells; n is average RLU of treated wells.

3.2.2. Antiamastigote activity

For assessing the activity of compounds against the amastigote stage of the parasite, mouse macrophage cell line (J-774A.1) infected with promastigotes expressing luciferase firefly reporter gene was used [18]. Cells were seeded in a 96-well plate (5×10^4 cell/100 μl/well) in RPMI-1640 containing 10% foetal calf serum and the plates were incubated at 37 °C in a CO_2 incubator. After 24 h, the medium was replaced with fresh medium containing stationary-phase promastigotes (2.5×10^5/100 μl/well). Promastigotes invade the macrophage and are transformed into amastigote. The taste material in appropriate concentrations (0.25–10 μg/ml) in complete medium was added after replacing the previous medium and the plates were incubated at 37 °C in a CO_2 incubator for 24 h or more. After incubation, the drug containing medium was decanted and 50 μl PBS was added in each well and mixed with an equal volume of steady Glo® reagent. After gentle shaking for 1–2 min, the reading was taken in a luminometer. The inhibition of parasitic growth was determined as described above.

4. Results and discussion

In our earlier studies we have shown that ketene acetals of aromatic substrates [19] and ketene acetals and their *S*, *N*, and *N*,*N*-acetals of terpene substrates [20] showed pronounced in vitro and in vivo antileishmanial profile. In view to further optimise the activity profile, we synthesized series of dihydro-α-ionone based simple chalcones **6**(**a**–**i**), **8** and **10** as shown in Scheme 1. The compounds were subjected to in vitro antileishmanial activity



Scheme 1.

profile as shown in Table 1. From the results we found that the substitution on aromatic ring has profound role to play in the biological activity of these compounds. The chalcones having *p*-methoxy and 3,4-dimethoxy substitution as in **6b** and **6c** showed very good activity in promastigote as well as amastigote model. However, 3,4,5,-trimethoxy substitution as in **6d** showed activity in promastigote model but was found inactive in the amastigote model. Electron withdrawing substituents on the aromatic ring have role to play in the activity profile as **6e** and **6h** which showed very good activity in the promastigote as well as amastigote model. Next, we synthesized pyridine and furan based chalcones **8** and **10** as shown in Scheme 1. Among them pyridine based chalcone **8** (Table 1) showed very good profile in the promastigote as well as amastigote model. However, chalcones **6b**, **6c**, **6e** and **8** showed marginal in vivo activity in the hamster model.

Table 1
Antileishmanial activity of compounds against *L. donovani*

Serial number	Compound number	Antipromastigote activity		Antiamastigote activity	
		Concentration (μg/ml)	% Inhibition	Concentration (μg/ml)	% Inhibition
1	**6a**	5	100	5	Nl
		2	61	2	
2	**6b**	5	98	5	81
		2	98	2	40
3	**6c**	5	100	5	95
		2	100	2	79
4	**6d**	5	90	5	Nl
		2	50	2	Nl
5	**6e**	5	100	5	93
		2	100	2	88
6	**6f**	5	53	5	Nl
		2	34	2	Nl
7	**6g**	5	99	5	65
		2	98	–	–
8	**6h**	5	99	5	80
		2	95	2	74
9	**6i**	5	100	5	Nl
		2	76	2	Nl
10	**8**	5	100	5	92
		2	100	2	33
11	**10**	5	93	5	Nl
		2	65	2	Nl

5. Experimental

The reported melting points are the uncorrected ones. The infrared spectra were recorded in KBr on a Perkin–Elmer model 881. ^{1}H NMR spectra and ^{13}C NMR (in $CDCl_3$) spectra (chemical shift in δ, ppm downfield from TMS) were recorded on Bruker Advance DRX-2000 instrument. Electron impact (EI) mass spectra were recorded on a Joel JMS-D-300

spectrometer with the ionization potential 70 eV. The reaction was carried out in unmodified microwave oven (LG made, 850 W, 2450 MHz) at medium power 450 W for 4–5 min.

5.1. 1-(4-Benzyloxy-phenyl)-5-(2,6,6-trimethylcyclohex-2-enyl)-pent-1-en-3-one (**6a**)

A mixture of dihydro-α-ionone **4** (1.00 g, 5.15 mmol), 4-benzyloxy benzaldehyde **5a** (1.28 g, 6 mmol) and KF/Al_2O_3 (1.00 g) was subjected to microwave irradiation for 5 min. On cooling, the crude product was taken up in ethylacetate (15 ml) and filtered. The filterate was concentrated *in vacuo*. The pale yellow crude liquid thus obtained was chromatographed (SiO_2; 60–120 mesh). Elution with 4% ethylacetate in hexane furnished yellow solid which on crystallization (ether:hexane) gave **6a** as a pale yellow crystalline solid (1.43 g, 72%). M.p. 99–101 °C; IR (KBr, cm^{-1}): 2940, 1639, 1599, 1510; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.89 (s, 3H), 1.00 (s, 3H), 1.45 (m, 5H), 1.60 (s, 3H), 2.00 (m, 2H), 2.70 (m, 2H), 5.08 (s, 2H), 5.35 (m, 1H), 6.60 (d, $J = 16.00$ Hz, 1H), 7.00 (d, $J = 8.00$ Hz, 2H), 7.45 (m, 8H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 23.427 (q), 24.005 (t), 25.608 (t), 2 × 28.095 (q), 31.995 (s), 33.045 (t), 41.483 (t), 49.108 (d), 70.518 (t), 2 × 115.720 (d), 121.397 (d), 124.611 (d), 124.924 (s), 127.858 (d), 127.927 (d), 128.567 (d), 2 × 129.075 (d), 2 × 130.357 (d), 136.176 (s), 136.869 (s), 142.369 (d), 161.097 (s), 200.905 (s); MS (*m*/*z*): 389 ($M^+ + 1$).

5.2. 1-(4-Methoxy-phenyl)-5-(2,6,6-trimethylcyclohex-2-enyl)-pent-1-en-3-one (**6b**)

A mixture of dihydro-α-ionone **4** (1.00 g, 5.15 mmol), 4-methoxy benzaldehyde **5b** (0.82 g, 6 mmol) and KF/Al_2O_3 (1.00 g) was subjected to microwave irradiation for 5 min. On cooling, the crude product was taken up in ethylacetate (15 ml) and filtered. The filterate was concentrated *in vacuo*. The pale yellow crude liquid thus obtained was chromatographed (SiO_2; 60–120 mesh). Elution with 4% ethylacetate in hexane furnished thick yellow liquid **6b** (1.12 g, 70%). IR (neat, cm^{-1}): 2949, 1700, 1655, 1601; 1512, 1457; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.93 (s, 3H), 0.96 (s, 3H), 1.60 (m, 5H), 1.70 (s, 3H), 1.80 (m, 2H), 2.70 (m, 2H), 3.90 (s, 3H), 5.40 (m, 1H), 6.65 (d, $J = 16.00$ Hz, 1H), 6.95 (d, $J = 8.00$ Hz, 2H), 7.50 (m, 3H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 23.402 (t), 23.981 (q), 25.577 (t), 2 × 28.060 (q), 31.964 (t), 33.020 (t), 49.068 (d), 53.826 (d), 55.783 (s), 114.417 (d), 114.801 (d), 121.368 (d), 124.472 (d), 127.653 (s), 2 × 130.331 (d), 136.156 (s), 142.433 (d), 161.920 (s), 200.959 (s); MS (*m*/*z*): 313 ($M^+ + 1$).

5.3. 1-(3,4-Dimethoxy-phenyl)-5-(2,6,6-trimethylcyclohex-2-enyl)-pent-1-en-3-one (**6c**)

A mixture of dihydro-α-ionone **4** (1.00 g, 5.15 mmol), 3,4-dimethoxy benzaldehyde **5c** (0.99 g, 6 mmol) and KF/Al_2O_3 (1.00 g) was subjected to microwave irradiation for 5 min. On cooling, the crude product was taken up in ethylacetate (15 ml) and filtered. The filterate was concentrated *in vacuo*. The light yellow oil thus obtained was chromatographed (SiO_2; 60–120 mesh). Elution with 5% ethylacetate in hexane furnished thick yellow liquid which on crystallization (ether:-hexane) furnished white solid **6c** (1.28 g, 73%). M.p. 99–100 °C; IR (KBr, cm^{-1}): 3020, 2936, 1685, 1592, 1512, 1460; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.89 (s, 3H), 0.96 (s, 3H), 1.25 (m, 2H), 1.50 (m, 2H), 1.75 (s, 3H), 1.90 (m, 1H), 2.00 (m, 2H), 2.70 (m, 2H), 3.95 (s, 3H), 3.97 (s, 3H), 5.36 (m, 1H), 6.61 (d, $J = 16.00$ Hz, 1H), 6.87 (m, 2H), 7.01 (m, 2H), 7.41 (m, 3H) ; MS (*m*/*z*): 343 ($M^+ + 1$).

5.4. 1-(3,4,5-Trimethoxy-phenyl)-5-(2,6,6-trimethylcyclohex-2-enyl)-pent-1-en-3-one (**6d**)

A mixture of dihydro-α-ionone **4** (1.00 g, 5.15 mmol), 3,4,5-trimethoxy benzaldehyde **5d** (1.18 g, 6 mmol) and KF/Al_2O_3 (1.00 g) was subjected to microwave irradiation for 5 min. On cooling, the crude product was taken up in ethylacetate (15 ml) and filtered. The filterate was concentrated *in vacuo*. The pale yellow crude liquid thus obtained was chromatographed (SiO_2; 60–120 mesh). Elution with 4% ethylacetate in hexane furnished thick yellow liquid which on crystallization (ether:hexane) furnished white crystalline solid **6d** (1.43 g, 76%). M.p. 89–90 °C; IR (KBr, cm^{-1}): 2938, 1657, 1588, 1503, 1458; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.89 (s, 3H), 0.95 (s, 3H), 1.20 (m, 2H), 1.54 (m, 2H), 1.71 (s, 3H), 2.00 (m, 3H), 2.70 (m, 2H), 3.91 (s, 9H), 5.40 (m, 1H), 6.62 (d, $J = 16.00$ Hz, 1H), 6.75 (s, 2H), 7.50 (d, $J = 16.00$ Hz, 1H); MS (*m*/*z*): 371 ($M^+ - 1$).

5.5. 1-(4-Chloro-phenyl)-5-(2,6,6-trimethylcyclohex-2-enyl)-pent-1-en-3-one (**6e**)

A mixture of dihydro-α-ionone **4** (1.00 g, 5.15 mmol), 4-chloro benzaldehyde **5e** (0.84 g, 6 mmol) and KF/Al_2O_3 (1.00 g) was subjected to microwave irradiation for 4 min. On cooling, the crude product was taken up in ethylacetate (15 ml) and filtered. The filterate was concentrated *in vacuo*. The crude liquid thus obtained was chromatographed (SiO_2; 60–120 mesh). Elution with 3% ethylacetate in hexane furnished **6d** as a thick yellow liquid (1.28 g, 79%). IR (neat, cm^{-1}): 2927, 1693, 1609; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.85 (s, 3H), 0.90 (s, 3H), 1.50 (m, 4H), 1.60 (s, 3H), 1.90 (m, 3H), 2.60 (m, 2H), 5.28 (m, 1H), 6.60 (d, $J = 16.00$ Hz, 1H), 7.40 (m, 4H), 7.50 (d, $J = 16.00$ Hz, 1H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 21.985 (q), 22.480 (q), 23.890 (t), 26.605 (q), 30.565 (t), 31.534 (s), 40.253 (t), 47.510 (t), 52.433 (d), 120.067 (d), 125.893 (d), 2 × 128.156 (d), 2 × 128.349 (d), 132.153 (s), 134.590 (s), 135.180 (s), 139.373 (d), 199.239 (s); MS (*m*/*z*): 317 ($M^+ + 1$).

5.6. 1-(2-Nitro-phenyl)-5-(2,6,6-trimethylcyclohex-2-enyl)-pent-1-en-3-one (**6f**)

A mixture of dihydro-α-ionone **4** (1.00 g, 5.15 mmol), 2-nitro benzaldehyde **5f** (0.91 g, 6 mmol) and KF/Al_2O_3 (1.00 g)

was subjected to microwave irradiation for 4 min. On cooling, the crude product was taken up in ethylacetate (15 ml) and filtered. The filterate was concentrated *in vacuo*. The pale yellow crude liquid thus obtained was chromatographed (SiO_2; 60–120 mesh). Elution with 5% ethylacetate in hexane furnished **6f** thick yellow liquid (1.16 g, 69%). IR (neat, cm^{-1}): 2928, 1699, 1611, 1528, 1348, 1216; ^1H NMR (200 MHz, $CDCl_3$): δ 0.82 (s, 3H), 0.92 (s, 3H), 1.40 (m, 4H), 1.62 (s, 3H), 1.90 (m, 3H), 2.66 (m, 2H), 5.28 (m, 1H), 6.51 (d, $J = 16.00$ Hz, 1H), 7.71 (m, 3H), 8.00 (m, 2H); MS (*m/z*): 328 ($M^+ + 1$).

*5.7. 1-(3-Nitro-pheny)-5-(2,6,6-trimethylcyclohex-2-enyl)-pent-1-en-3-one (**6g**)*

A mixture of dihydro-α-ionone **4** (1.00 g, 5.15 mmol), 3-nitro benzaldehyde **5g** (0.91 g, 6 mmol) and KF/Al_2O_3 (1.00 g) was subjected to microwave irradiation for 3 min. On cooling, the crude product was taken up in ethylacetate (15 ml) and filtered. The filterate was concentrated *in vacuo*. The crude liquid thus obtained was chromatographed (SiO_2; 60–120 mesh). Elution with 5% ethylacetate in hexane furnished thick yellow liquid which on crystallization (ether:hexane) furnished **6g** as a yellow crystalline solid (0.88 g, 68%). M.p. 114–116 °C; IR (KBr, cm^{-1}): 2949, 1722, 1669, 1618; 1532, 1449, 1352; ^1H NMR (200 MHz, $CDCl_3$): δ 0.82 (s, 3H), 0.87 (s, 3H), 1.15 (m, 2H), 1.40 (m, 2H), 1.70 (s, 3H), 1.90 (m, 3H), 2.70 (m, 2H), 5.30 (m, 1H), 6.70 (d, $J = 16.00$ Hz, 1H), 7.40 (d, $J = 16.00$ Hz, 2H), 7.62 (d, $J = 8.00$ Hz, 2H), 8.18 (d, $J = 8.00$ Hz, 2H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 21.096 (q), 23.953 (t), 2 × 25.049 (q), 31.968 (t), 53.956 (d), 122.833 (d), 124.851 (d), 129.288 (d), 130.338 (d), 134.182 (d), 139.250 (d), 139.448 (d), 200.340 (s); MS (*m/z*): 328 ($M^+ + 1$).

*5.8. 1-(4-Nitro-phenyl)-5-(2,6,6-trimethylcyclohex-2-enyl)-pent-1-en-3-one (**6h**)*

A mixture of dihydro-α-ionone **4** (1.00 g, 5.15 mmol), 4-nitro benzaldehyde **5h** (0.91 g, 6 mmol) and KF/Al_2O_3 (1.00 g) was subjected to microwave irradiation for 5 min. On cooling, the crude product was taken up in ethylacetate (15 ml) and filtered. The filterate was concentrated *in vacuo*. The crude liquid thus obtained was chromatographed (SiO_2; 60–120 mesh). Elution with 5% ethylacetate in hexane furnished thick yellow liquid which on crystallization (ether:hexane) furnished **6h** as a yellow crystalline solid (1.14 g, 67 %). M.p. 107–08 °C; IR (KBr, cm^{-1}): 2929, 1664, 1609, 1522, 1345, 1217; ^1H NMR (200 MHz, $CDCl_3$): δ 0.85 (s, 3H), 0.95 (s, 3H), 1.20 (m, 2H), 1.50 (m, 2H), 1.65 (s, 3H), 1.90 (m, 3H), 2.70 (m, 2H), 5.35 (m, 1H), 6.80 (d, $J = 16.00$ Hz, 1H), 7.50 (d, $J = 16.00$ Hz, 1H), 7.65 (d, $J = 8.00$ Hz, 2H), 8.20 (d, $J = 8.00$ Hz, 2H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 21.057 (q), 21.206 (t), 23.962 (t), 2 × 25.030 (q), 31.953 (t), 40.558 (s), 42.027 (t), 48.943 (d), 121.665 (d), 124.363 (d), 124.558 (d), 2 × 129.971 (d), 130.275 (d), 135.842 (d), 139.385 (s), 141.275 (s), 148.924 (s), 200.057 (s); MS (*m/z*): 328 ($M^+ + 1$).

*5.9. 1-(4-Hydroxy-phenyl)-5-(2,6,6-trimethyl-cyclohex-2-enyl)-pent-1-en-3-one (**6i**)*

A mixture of dihydro-α-ionone **4** (1.00 g, 5.15 mmol), 4-hydroxy benzaldehyde **5i** (0.75 g, 6 mmol) and KF/Al_2O_3 (1.00 g) was subjected to microwave irradiation for 4 min. On cooling, the crude product was taken up in ethylacetate (15 m) and filtered. The filterate was concentrated *in vacuo*. The pale yellow crude liquid thus obtained was chromatographed (SiO_2; 60–120 mesh). Elution with 5% ethylacetate in hexane furnished **6i** as a thick yellow liquid (0.55 g, 36%). IR (neat, cm^{-1}): 3288, 2930, 1637, 1584; ^1H NMR (200 MHz, $CDCl_3$): δ 0.90 (s, 3H), 1.30 (m, 4H), 1.70 (s, 3H), 1.80 (s, 3H), 2.70 (m, 2H), 5.40 (m, 1H), 6.65 (d, $J = 16.00$ Hz, 1H), 6.90 (d, 2H), 7.50 (d, 2H), 7.60 (d, $J = 16.00$ Hz, 1H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 21.731 (q), 23.952 (q), 24.861 (t), 28.004 (q), 30.068 (t), 31.957 (s), 49.113 (d), 2 × 53.794 (d), 116.563 (s), 121.544 (d), 123.869 (d), 127.111 (s), 2 × 130.760 (d), 132.963 (s), 135.980 (s), 143.825 (d), 162.969 (s), 202.968 (s); MS (*m/z*): 299 ($M^+ + 1$).

*5.10. 1-Pyridin-3-yl-5- (2,6,6-trimethyl-cyclohex-2-enyl)-pent-1-en-3-one (**8**)*

A mixture of dihydro-α-ionone **4** (1.00 g, 5.15 mmol), pyridine-3-aldehyde **7** (0.64 ml, 6 mmol) and KF/Al_2O_3 (1.00 g) was subjected to microwave irradiation for 5 min. On cooling, the crude product was taken up in ethylacetate (15 ml) and filtered. The filterate was concentrated *in vacuo*. The crude product thus obtained was chromatographed (SiO_2; 60–120 mesh). Elution with 7% ethylacetate in hexane furnished **8** as a thick brown liquid (0.75 g, 52%). IR (neat, cm^{-1}): 2932, 1664, 1617, 1341; ^1H NMR (200 MHz, $CDCl_3$): δ 0.90 (s, 3H), 0.95 (s, 3H), 1.25 (m, 2H), 1.50 (m, 2 H), 1.60 (s, 3H), 2.00 (m, 3H), 2.75 (m, 2H), 5.40 (m, 1H), 6.35 (d, $J = 16.00$ Hz, 1H), 7.15 (d, $J = 16.00$ Hz, 1H), 7.60 (d, $J = 8.00$ Hz, 2H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 21.127 (q), 23.935 (t), 2 × 25.127 (q), 33.049 (t), 40.186 (s), 41.722 (t), 48.945 (d), 123.208 (d), 124.142 (d), 130.788 (d), 2 × 132.201 (d), 139.488 (d) 2 × 149.425 (d); MS (*m/z*): 283 ($M^+ + 1$).

*5.11. 1-(5-Hydroxymethyl-furan-2-yl)-5-(2,6,6-trimethyl-cyclohex-2-enyl)-pent-1-en-3-one (**10**)*

A mixture of dihydro-α-ionone **4** (1.00 g, 5.15 mmol), hydroxymethyl furfuraldehyde **9** (0.76 ml, 6 mmol) and KF/Al_2O_3 (1.00 g) was subjected to microwave irradiation for 5 min. On cooling, the crude product was taken up in ethylacetate (15 ml) and filtered. The filterate was concentrated *in vacuo*. The crude product thus obtained was chromatographed (SiO_2; 60–120 mesh). Elution with 6% ethylacetate in hexane furnished **10** as a thick yellow liquid (1.18 g, 76%). IR (neat, cm^{-1}): 3411, 2927, 1613, 1576; ^1H NMR (200 MHz, $CDCl_3$): δ 0.88 (s, 3H), 0.90 (s, 3H), 1.22 (m, 2H), 1.53 (m, 4H), 1.70 (s, 3H), 1.90 (m, 3H), 2.70 (m, 2H), 4.65 (s, 2H), 5.40 (m, 1H), 6.40 (m, 1H), 6.65 (s, 1H), 6.70 (d, $J = 14.00$ Hz, 1H); ^{13}C

NMR (200 MHz, $CDCl_3$): δ 23.367 (t), 23.949 (q), 25.377 (t), 28.019 (q), 28.045 (q), 30.065 (t), 32.987 (s), 41.994 (t), 49.003 (d), 57.929 (t) 110.738 (d), 116.996 (d), 121.446 (d), 123.585 (d), 128.674 (d), 136.024 (s), 151.335 (s), 157.296 (s), 200.768 (s); MS (*m/z*): 303 ($M^+ + 1$).

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