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Antileishmanial agents part-IV: synthesis and antileishmanial activity of novel terpenyl pyrimidines

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Abstract

Some novel N- and O-substituted terpenyl pyrimidines **4** (**a**–**j**) have been synthesized and screened for in vitro antileishmanial activity profile in promastigote model. Some of the compounds exhibited 100% inhibition at 10 μg ml^{-1} concentration.

Keywords: α-Ionone; Terpenyl pyrimidine; Antileishmanial agents

1. Introduction

The leishmaniasis is a complex of diseases caused by at least 17 species of the protozoan parasite *Leishmania*. The disease is distributed worldwide, but mainly in the tropics and subtropics, with a prevalence of 12 million cases and an approximated incidence of 0.5 million cases of visceral (VL) and 1.5 million cases of cutaneous leishmaniasis (CL). The main drug treatments, pentavalent antimonials [1], which were introduced some 50 years ago, are subject to development of resistance. Although new drugs i.e. amphoterecin B and its lipid complex [2] are quite effective but they are expensive and out of reach of poor people. Newly introduced first orally active drug miltefosine [3] is quite effective but shows teratogenic effects and cannot be used in the pregnant women. The search for new drugs continues, with bisphosphonates for example residronate and pamidronate. Natural products are not behind and derivatives of licochalcone A [4] and quinoline alkaloids [5] are reported to have activity against experimental animal infections.

Some biochemical targets trypanothione reductase [6], cysteine peptidases [7], sterol biosynthesis [8], dihydrofolate reductase (DHFR) [9], ornithine decarboxylase [10], and microtubule inhibitors [11] are under investigation at various stages of drug development.

Among the biochemical targets, DHFR is quite successful in malaria (pyrimethamine and cycloguanil), bacteria (trimethoprim) and cancer (methotrexate). However, these classical DHFR inhibitors show no selectivity for the leishmanial or trypanosomal enzymes. Computer aided modulation studies [12] between the leishmanial/trypanosomal and human enzyme yielded some new chemical entities with in vitro biological profile [13]. In our continuation of studies on natural product based pyrimidines [14], we synthesized some novel terpene substituted diaminopyrimidines and evaluated them for in vitro antileishmanial profile and the results are reported in this communication.

2. Chemistry

The reported methodology [14] gives an excellent access to oxygen substituted terpenyl pyrimidines. However, this methodology is least applicable to the synthesis of diaminopyrimidines. Moreover, in the synthesis of oxygen substituted pyrimidines, we used terpene based ketene acetals as key synthons which involves use of carbon disulfide which is an environmentally least friendly reaction. To do this, we visualized 1,3-ketoester **2** as a key synthon and can be extended to required diaminopyrimidines as shown in Scheme 1.

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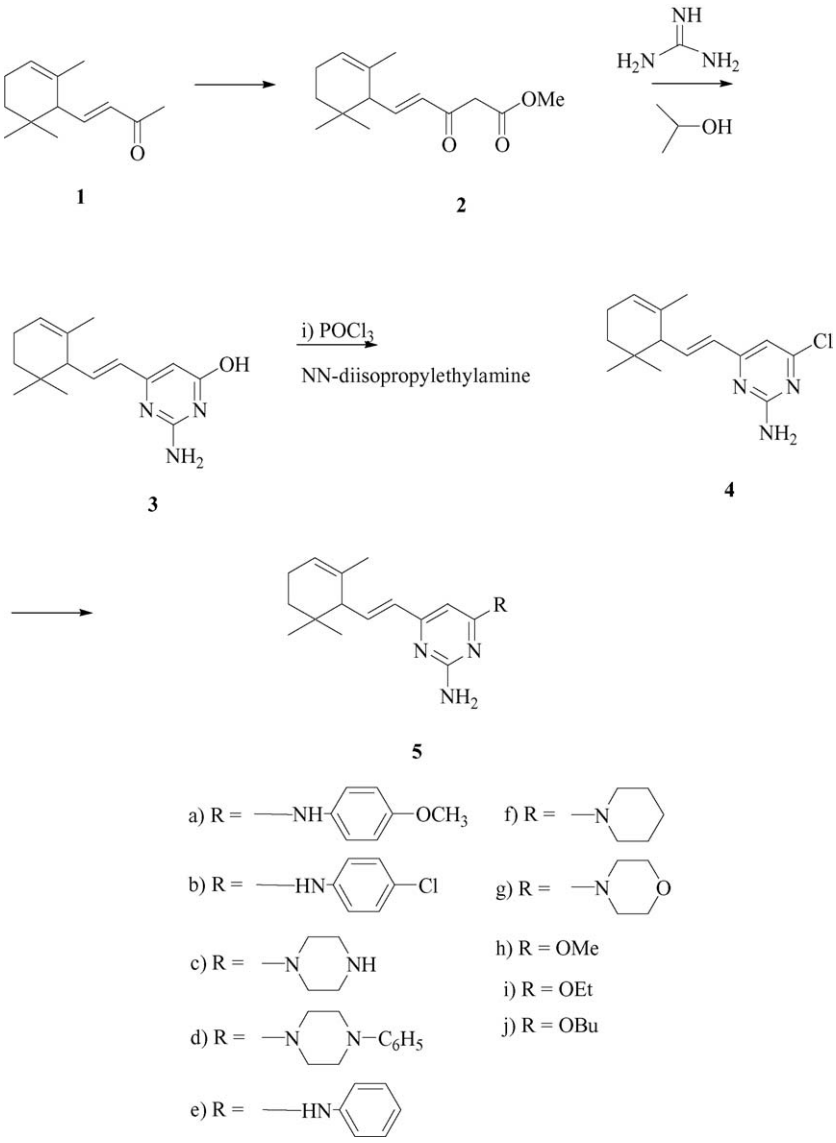

Scheme 1.

The commercially available α-ionone **1** on reaction with dimethyl carbonate and sodium hydride in refluxing toluene furnished 1,3-ketoester **2** in 72% yield [15]. The classical condensation of 1,3-ketoester **2** with pre-prepared guanidine in isopropanol (Δ, 16 h) furnished pyrimidone **3** in 54% yield. The poor yield of pyrimidone **3** forced us to undertake few exploratory studies. However, the results were not very encouraging. The modified method [16] using guanidine carbonate and azeotropic removal of water did not help us to improve the yield. The synthesis of chloride **4** was also problematic in the beginning. The classical methods used for the aryl substituted pyrimidines [16] were not very useful on labile terpenyl pyrimidone **3**. However, the reaction of **3** with $POCl_3$ in the presence of diisopropylethylamine [17] furnished chloro compound **4** in quantitative yield. Having achieved the synthesis of chloro compound on a comfortable scale it was used for the synthesis of a chemical library of diamino pyrimidines as shown in Scheme 1.

3. Biological activities

3.1. Material and methods

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 [18] 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. For extracellular (against promastigotes) leishmanicidal activity

The effect of 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 per well in 96-well flat bottom microtitre (MT) plates (CELLSTAR) and were incubated for 72 h in medium alone or in presence of serial dilutions of drugs (250 ng ml^{-1} to 10 μg ml^{-1}) in DMSO [18]. Parallel dilutions of DMSO were used as controls. After incubation, an aliquot (50 μl) of promastigote suspension was aspirated from each well of 96-well plate and mixed with equal volume of Steady Glo reagent (Promega) and luminescence was measured in luminometer. The values were expressed as relative luminescence unit (RLU).

4. Results and discussion

The diaminopyrimidines **5** (**a**–**g**) and oxygen substituted pyrimidines **5** (**h**–**j**) were subjected to in vitro antileishmanial screening in the promastigote model (Table 1). The compounds **5** (**a**–**j**) showed 100% inhibition at 10 μg ml^{-1} concentration. There is very little differentiation between anilino, morpholino and pyrrolidino substitution. *p*-anisidino substitution as in **5c** proved better which showed 98.8% inhibition at a 1 μg ml^{-1} concentration. The oxygen substituted pyrimidine **5i** and **5j** showed 99% inhibition at 5 μg ml^{-1} concentration. More compounds need to be prepared on a diaminopyrimidine and they will have to be subjected to in vitro screening followed by the in vivo testing.

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.

Table 1
In vitro antileishmanial profile in promastigote model

Compound numbers	Concentration	Percent inhibition
4	5, 2, 1 μg ml^{-1}	71.0, 57.50, 19.0
5a	10, 5, 2.5 μg ml^{-1}	100, 94, 30
5b	10, 5, 2, 1 μg ml^{-1}	100, 99.22, 22.85, 10.4
5c	10, 5, 2, 1 μg ml^{-1}, 500, 250 ng ml^{-1}	100, 98.89, 99.86, 98.8, 78.72, 21.49
5d	10, 5, 2, 1 μg ml^{-1}	100, 99.94, 92.17, 61.47
5e	10, 5, 2, 1 μg ml^{-1}	100, 97.6, 58.7, 18.41
5f	10, 5, 2, 1 μg ml^{-1}, 500, 250 ng ml^{-1}	100, 99.8, 96.98, 88.06, 33.29, 30.31
5g	25, 10, 5, 1 μg ml^{-1}	100, 84.0, 92.38, 50.1
5h	ND	ND
5i	10, 5, 2, 1 μg ml^{-1}	100, 99.27, 58.0, 29.18
5j	10, 5, 2, 1 μg ml^{-1}	100, 99.1, 75.6, 39.6

*5.1. Methyl-5-(2,6,6-trimethyl-cyclohex-2-enyl)-3-keto-4-pentenoate (**2**)*

Sodium hydride (0.70 g, 29.00 mmol) was added to α-ionone **1** (1.49 g, 1.50 ml, 7.29 mmol) and dimethyl carbonate (1.70 g, 1.59 ml, 18.8 mmol) in dry toluene (15.00 ml). The magnetically stirred reaction mixture was held at 110 °C for 3 h. Upon cooling a mixture of ether (25.00 ml), conc. HCl (3.50 ml) and water (8.50 ml) was carefully added. After vigorous stirring, the organic layer and a subsequent ether extract of the aqueous phase were combined, dried (Na_2SO_4) and evaporated to yield **2** as a pale yellow oil (1.31 g, 72%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.80 (s, 3H), 0.90 (s, 3H), 1.25 (m, 1H), 1.45 (m, 1H), 1.55 (s, 3H), 2.00 (m, 2H), 2.20 (m, 1H), 3.60 (s, 2H), 3.70 (s, 3H), 5.45 (m, 1H), 5.72 (d, J = 16.00 Hz, 0.5H), 6.10 (d, J = 16.00 Hz, 0.5H), 6.50 (dd, J = 16.00, 10.00 Hz, 0.5H), 6.75 (dd, J = 16.00, 10.00 Hz, 0.5H).

*5.2. 2-Amino-6-[2-(2,6,6-trimethyl-cyclohex-2-enyl)-ethenyl]-3H-pyrimidine-4-one (**3**)*

To a solution **2** (2.50 g, 10 mmol) in dry isopropanol (20 ml) was added guanidine solution in isopropanol (20 ml, 10 mmol) and refluxed at 90 °C for 16 h. The reaction mixture was filtered through celite and the filtrate was extracted with ethylacetate (2 × 30 ml). The combined extract was washed with H_2O (2 × 30 ml), brine (2 × 30 ml) and dried (Na_2SO_4). The solvent was removed in vacuo. The crude product thus obtained was column chromatographed (SiO_2, 60–120 mesh). Elution with 2% MeOH in $CHCl_3$ furnished **3** (1.40 g, 54%) as a white crystalline compound. IR (cm^{-1}, KBr): 2918, 1631, 1465, 1366; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.80 (s, 3H), 0.90 (s, 3H), 1.20 (m, 1H), 1.40 (m, 3H), 1.50 (s, 3H), 2.00 (m, 2H), 2.25 (d, J = 10.00 Hz, 1H), 5.40 (m, 2H), 5.50 (s, 1H), 6.00 (d, J = 16.00 Hz, 1H), 6.50 (m, 1H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 2 × 22.958 (q), 26.925 (q), 27.959 (q), 31.303 (t), 32.349 (s), 54.056 (d), 100.367 (d), 121.439 (d), 130.283 (d), 133.378 (s), 138.584 (d), 155.575 (s), 161.439 (s), 163.755 (s); MS: m/z 260 (M^+ + 1).

*5.3. 3-Chloro-5-[2-(2,6,6-trimethyl-cyclohex-2-enyl)-ethenyl]-phenyl amine (**4**)*

To a solution of **3** (500 mg, 1.92 mmol) in $POCl_3$ (1.16 ml, 9.40 mmol) was added *N*,*N*-diisopropylethylamine (0.40 ml, 1.92 mmol) dropwise and the resulting mixture stirred at room temperature for 8 h. Excess of $POCl_3$ was removed in vacuo and crude product was taken in dichloromethane (20 ml). It was neutralized with aq. sol. of NH_3. The combined extract was washed with H_2O (2 × 20 ml), brine (2 × 20 ml), dried (Na_2SO_4) and solvent was removed in vacuo to yield **4** as a brown oil (530 mg, 99%). IR (neat, cm^{-1}): 2924, 1628, 1554, 1461, 1307, 758; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.87 (s, 3H), 0.94 (s, 3H), 1.52 (m, 1H), 1.58 (m, 1H), 1.70 (s, 3H), 2.00 (m, 2H), 2.25 (d, J = 10.00 Hz, 1H), 5.10 (m, 2H), 5.49 (bs,

1H), 6.17 (d, J = 16.00 Hz, 1H), 6.60 (s, 1H), 6.90 (dd, J = 16.00, 10.00 Hz, 1H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 22.159 (q), 23.467 (t), 29.295 (q), 30.070 (q), 33.059 (s), 33.761 (t), 54.075 (d), 108.048 (d), 122.645 (d), 129.160 (d), 132.984 (s), 142.959 (d), 161.896 (s), 163.230 (s), 165.916 (s); MS: m/z 278 (M^+ + 1).

*5.3.1. N4-(4-methoxy-phenyl)-6-[2-(2,6,6-trimethyl-cyclohex-2-enyl)-ethenyl]-pyrimidine-2,4-diamine (**5a**)*

To a solution of **4** (530 mg, 1.91 mmol) in isopropanol (25.00 ml) was added *p*-methoxyaniline (472 mg, 3.84 mmol) and stirred for 12 h at room temperature. After completion of the reaction, it was concentrated in vacuo and the extract was taken in EtOAc (20 ml) followed by washing with H_2O (2 × 15 ml), brine (2 × 15 ml) dried (Na_2SO_4) and it was concentrated in vacuo. The crude product thus obtained was column chromatographed (SiO_2, 60–120 mesh). Elution with 30% ethyl acetate in hexane furnished **5a** as a crystalline compound (293 mg, 43%). M.p. 123–125 °C; IR (KBr, cm^{-1}): 3369, 3213, 2955, 1572, 1508, 1240; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.85 (s, 3H), 0.91 (s, 3H), 1.42 (m, 2H), 1.73 (s, 3H), 2.00 (m, 2H), 2.25 (d, J = 10.00 Hz, 1H), 5.85 (s, 1H), 6.10 (d, J = 16.00 Hz, 1H), 6.40 (m, 1H), 6.55 (dd, J = 16.00, 10.00 Hz, 1H), 6.90 (d, J = 8.00 Hz, 2H), 7.26 (d, J = 8.00 Hz, 2H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 23.409 (q), 23.504 (t), 27.285 (q), 28.336 (q), 31.674 (t), 32.674 (t), 32.969 (s), 54.967 (d), 55.903 (q), 92.950 (d), 2 × 114.983 (d), 122.124 (d), 2 × 125.948 (d), 130.510 (d), 133.560 (s), 134.797 (s), 139.322 (d), 157.523 (s), 163.248 (s), 163.345 (s), 163.873 (s); MS: m/z 365 (M^+ + 1). Analysis calculated for $C_{22}H_{28}N_4O$: C, 72.50, H, 7.74, N, 15.37. Found: C, 72.62; H, 7.85, N, 15.49.

*5.3.2. N4-(4-chloro-phenyl)-6-[2-(2,6,6-trimethyl-cyclohex-2-enyl)-ethenyl]-pyrimidine-2,4-diamine (**5b**)*

Yield: 47%. IR (neat, cm^{-1}): 3376, 2925, 1620, 1517, 1493, 1283, 761; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.86 (s, 3H), 0.92 (s, 3H), 1.25 (m, 2H), 1.45 (m, 2H), 1.60 (s, 3H), 2.00 (m, 2H), 5.00 (bs, 2H), 5.29 (s, 1H), 5.45 (bs, 1H), 6.00 (s, 1H), 6.15 (d, J = 16.00 Hz, 1H), 6.60 (d, J = 10.00 Hz, 1H), 6.70 (q, J = 16.00, 10.00 Hz, 1H), 7.08 (d, 2H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 23.407 (t), 23.520 (q), 27.269 (q), 28.374 (q), 31.660 (t), 33.003 (s), 32.969 (s), 55.016 (d), 93.530 (d), 2 × 116.650 (d), 122.309 (d), 123.622 (d), 129.648 (d), 133.386 (s), 137.825 (s), 140.176 (d), 145.403 (s), 162.546 (s), 162.546 (s), 162.989 (s), 163.376 (s).

*5.3.3. 4-Piprazine-1-yl-6-[2-(2,6,6-trimethyl-cyclohex-2-enyl)-ethenyl]-pyrimidine-2-ylamine (**5c**)*

Yield: 38%. IR (neat, cm^{-1}): 3344, 2925, 1581, 1417, 1356; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.80 (s, 3H), 0.85 (s, 3H), 1.35 (m, 2H), 1.50 (s, 3H), 1.90 (m, 2H), 2.20 (d, J = 10.00 Hz, 1H), 2.60 (m, 4H), 3.35 (m, 4H), 5.40 (m, 1H), 6.00 (m, 5H), 6.50 (dd, J = 16.00, 10.00 Hz, 1H); MS: m/z 328 (M^+ + 1).

*5.3.4. 4-(4-Phenyl-piprazine-1-yl)-6-[2-(2,6,6-trimethyl-cyclohex-2-enyl)-ethenyl]-pyrimidine-2-ylamine (**5d**)*

Yield: 41%. IR (neat, cm^{-1}): 3409, 2925, 1574, 1536, 1499, 1447, 1228, 992, 759; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.88 (s, 3H), 0.95 (s, 3H), 1.30 (m, 2H), 1.60 (s, 3H), 2.00 (m, 2H), 2.30 (d, J = 10.00 Hz, 1H), 3.25 (m, 4H), 3.80 (m, 4H), 4.80 (bs, 2H), 5.50 (m, 1H), 5.95 (s, 1H), 6.15 (d, J = 16.00 Hz, 1H), 6.60 (dd, J = 16.00, 10.00 Hz, 1H), 6.95 (m, 3H), 7.30 (m, 2H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 23.424 (q), 23.552 (t), 27.311 (q), 28.380 (q), 29.735 (t), 30.073 (d), 2 × 44.284 (t), 2 × 49.559 (t), 55.056 (d), 91.938 (d), 2 × 116.822 (d), 120.628 (d), 122.077 (d), 2 × 130.955 (d), 133.731 (s), 138.786 (d), 151.547 (s), 2 × 163.131 (s), 164.186 (s) MS: m/z 404 (M^+ + 1).

*5.3.5. N4-phenyl-6-[2-(2,6,6-trimethyl-cyclohex-2-enyl)-ethenyl]-pyrimidine-2,4-diamine (**5e**)*

Yield: 44%. IR (neat, cm^{-1}): 3488, 3309, 3185, 2923, 1571, 1449, 1404, 756; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.86 (s, 3H), 0.91 (s, 3H), 1.25 (m, 2H), 1.60 (s, 2H), 1.70 (s, 3H), 2.00 (m, 2H), 5.00 (m, 2H), 6.00 (s, 1H), 6.15 (d, 1H), 7.36 (m, 6H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 23.358 (q), 23.495 (t), 27.259 (q), 28.288 (q), 32.992 (t), 33.684 (s), 55.058 (d), 93.049 (d), 122.273 (d), 2 × 122.885 (d), 124.886 (d), 3 × 129.695 (d), 133.389 (s), 138.951 (s), 140.386 (d), 162.617 (s), 2 × 162.810 (s); MS: m/z 336 (M^+ + 2).

*5.3.6. 4-Piperidin-1-yl-6-[2-(2,6,6-trimethyl-cyclohex-2-enyl)-ethenyl]-pyrimidine-2-ylamine (**5f**)*

Yield: 55%. IR (neat, cm^{-1}): 3321, 2927, 2856, 1574, 1532, 1418; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.85 (s, 3H), 0.95 (s, 3H), 1.20 (m, 2H), 1.55 (s, 9H), 2.00 (m, 2H), 2.25 (d, J = 10.00 Hz, 1H), 3.55 (m, 4H), 4.35 (m, 2H), 5.45 (m, 1H), 5.90 (s, 1H), 6.10 (d, J = 16.00, 1H), 6.60 (q, J = 16.00, 10.00 Hz, 1H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 23.413 (q), 23.537 (t), 25.136 (t), 26.014 (t), 27.296 (q), 28.356 (q), 29.348 (s), 30.066 (t), 31.721 (t), 2 × 45.472 (t), 55.054 (d), 91.887 (d), 121.991 (d), 130.784 (d), 133.777 (s), 138.425 (d), 162.197 (s), 162.929 (s), 163.860 (s), ; MS: m/z 327 (M^+ + 1).

*5.3.7. 4-Morpholin-4-yl-6-[2-(2,6,6-trimethyl-cyclohex-2-enyl)-ethenyl]-pyrimidine-2-ylamine (**5g**)*

Yield: 40%. IR (neat, cm^{-1}): 2922, 1643, 1484, 1446, 1392, 1228, 1115, 984, 757; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.90 (s, 3H), 0.95 (s, 3H), 1.30 (m, 2H), 1.60 (s, 3H), 2.00 (m, 2H), 2.30 (d, 1H), 3.60 (m, 4H), 3.75 (m, 4H), 4.90 (m, 2H), 5.45 (bs, 1H), 5.90 (s, 1H), 6.10 (d, J = 16.00, 1H), 6.60 (q, J = 16.00, 10.00 Hz, 1H); MS: m/z 329 (M^+ + 1).

*5.3.8. 4-Methoxy-6-[2-(2,6,6-trimethyl-cyclohex-2-enyl)-ethenyl]-pyrimidine-2-ylamine (**5h**)*

To a solution of 25% CH_3ONa in methanol (2 ml) was added **4** (320 mg, 1.23 mmol) in methanol (15.00 ml) and the resulting mixture stirred at room temperature for 12 h. After completion, it was concentrated in vacuo and the residue was

taken in EtOAc (15 ml) followed by washing with H_2O (2 × 20 ml), brine (2 × 10 ml) dried (Na_2SO_4) and it was concentrated in vacuo. The crude product thus obtained was column chromatographed (SiO_2, 60–120 mesh). Elution with 10% ethyl acetate in hexane furnished **5h** (150 mg, 57%). IR (KBr, cm^{-1}): 3332, 2925, 1575, 1450, 1369, 1199; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.90 (s, 3H), 0.95 (s, 3H), 1.30 (m, 2H), 1.60 (s, 3H), 2.00 (m, 2H), 2.30 (d, J = 10.00 Hz, 1H), 3.90 (s, 3H), 4.90 (m, 2H), 5.50 (m, 1H), 6.00 (s, 1H), 6.20 (d, J = 16.00 Hz, 1H), 6.65 (dd, J = 16.00, 10.00 Hz, 1H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 23.363 (q), 23.503 (t), 27.285 (q), 28.277 (q), 31.731 (t), 32.977 (s), 53.757 (q), 54.969 (d), 95.101 (d), 122.213 (d), 129.993 (d), 133.468 (s), 140.050 (d), 163.116 (s), 164.579 (s), 171.834 (s); MS: m/z 275 ($M^+ + 1$). Analysis calculated for $C_{16}H_{23}N_3O$: C, 70.23; H, 8.48; N, 15.37. Found: C, 70.42; H, 8.65; N, 15.50.

*5.3.9. 4-Ethoxy-6-[2-(2,6,6-trimethyl-cyclohex-2-enyl)-ethenyl]-pyrimidine-2-ylamine (**5i**)*

Yield: 58%. M.p. 102–104 °C; IR (KBr, cm^{-1}): 3343, 3168, 2924, 1659, 1576, 1340; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.88 (s, 3H), 0.90 (s, 3H), 1.25 (m, 2H), 1.40 (t, 3H), 1.70 (s, 3H), 2.05 (m, 2H), 2.30 (d, J = 10.00 Hz, 1H), 4.30 (dd, 2H), 4.40 (m, 2H), 5.50 (m, 1H), 6.00 (s, 1H), 6.20 (d, J = 16.00 Hz, 1H), 6.60 (dd, J = 16.00, 10.00 Hz, 1H); MS: m/z 288 ($M^+ + 1$). Analysis calculated for $C_{17}H_{25}N_3O$: C, 71.04; H, 8.77; N, 14.62. Found: C, 71.22; H, 8.67; N, 14.77.

*5.3.10. 4-Butoxy-6-[2-(2,6,6-trimethyl-cyclohex-2-enyl)-ethenyl]-pyrimidine-2-ylamine (**5j**)*

Yield: 55%. IR (Neat, cm^{-1}): 3341, 3172, 2923, 1669, 1646, 1325; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.88 (s, 6H), 0.90 (s, 3H), 1.25 (m, 4H), 1.40 (t, 3H), 1.70 (s, 5H), 2.05 (m, 2H), 2.30 (d, J = 10.00 Hz, 1H), 4.30 (dd, 4H), 4.40 (m, 2H), 5.52 (m, 1H), 6.10 (s, 1H), 6.20 (d, J = 16.00 Hz, 1H), 6.65 (dd, J = 16.00, 10.00 Hz, 1H); MS: m/z 315 ($M^+ + 1$).

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References

[1] E. Moore, D. O'Flaherty, H. Heuvelmans, J. Seaman, H. Veeken, S. De Wit, R.N. Davidson, Bull. World Health Organ. 79 (2001) 388–393.
[2] D.R. Goldsmith, C.M. Perry, Drugs 64 (2004) 1905–1911.
[3] S.L. Croft, K. Seifert, M. Duchene, Mol. Biochem. Parasitol. 126 (2003) 165–172.
[4] M. Chen, L. Zhai, S.B. Christensen, T.G. Theander, A. Kharazmi, Antimicrob. Agents Chemother. 45 (2001) 2023–2029.
[5] C. Yates, Curr. Opin. Invest. Drugs 3 (2002) 1446–1452.
[6] D.S. Fries, A.H. Fairlamb, in: D.J. Abraham (Ed.), Burger's Medicinal Chemistry and Drug Discovery, vol. 5, sixth ed., Wiley, pp. 1033–1087.
[7] M. Sajid, J.R. Mckerro, Mol. Biochem. Parasitol. 120 (2002) 1–21.
[8] C.W. Roberts, R. Mc Leod, D.W. Rice, M. Ginger, M.L. Chance, L.J. Goad, Mol. Biochem. Parasitol. 126 (2003) 129–142.
[9] I.H. Gilbert, Biochem. Biophys. Acta 1587 (2002) 249–257.
[10] S. Muller, G.H. Coombs, R.D. Walter, Trends Parasitol. 17 (2001) 242–249.
[11] K.G. Jayanarayan, C.S. Dey, J. Clin. Pharm. Ther. 27 (2002) 313–320.
[12] F. Shafinaz Chowdhury, R. Di Lucrezia, R. Hurtado Guerrero, R. Brun, J. Goodman, L.M. Ruiz-Perez, et al., Bioorg. Med. Chem. Lett. 11 (2001) 977–980.
[13] D. Pez, I. Leal, F. Zuccotto, C. Boussard, R. Brun, S.L. Croft, et al., Bioorg. Med. Chem. 11 (2003) 4693–4711.
[14] S. Pandey, S.N. Suryawanshi, S. Gupta, V.M.L. Srivastava, Eur. J. Med. Chem. 39 (2004) 969–973.
[15] D. Herlem, J. Kervagoret, D. Yu, F. Khuong Huu, A.S. Kende, Tetrahedron 49 (1993) 607–618.
[16] D.R. Hannah, E.C. Sherer, R.V. Davies, R.B. Titman, C.A. Laughton, M.F.G. Stevens, Bioorg. Med. Chem. 8 (2000) 739–750.
[17] E.O. Osmo Hormi, A.M. Paakkanen, J. Org. Chem. 52 (1987) 5275–5276.
[18] Ashutosh et al., Poster presented in Chemistry Biology Interface: Synergistic New Frontiers Nov. 21–26, 2004, New Delhi, India.