Chemotherapy of Leishmaniasis Part-VII: Synthesis and Bioevaluation of substituted Terpenyl Pyrimidines

ARTICLE *in* EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY · JANUARY 2007

Impact Factor: 3.45

1 AUTHOR:

Naveen Chandra Talniya

Lovely Professional University

15 PUBLICATIONS **68** CITATIONS

SEE PROFILE

Available online at www.sciencedirect.com
ScienceDirect
European Journal of Medicinal Chemistry 42 (2007) 1211–1217
EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY
http://www.elsevier.com/locate/ejmech

Original article

Chemotherapy of leishmaniasis. Part VII: Synthesis and bioevaluation of substituted terpenyl pyrimidines ☆

S.N. Suryawanshi [a,*], B.A. Bhat [a], Susmita Pandey [a], Naveen Chandra [a], Suman Gupta [b]

[a] *Division of Medicinal Chemistry, Central Drug Research Institute, Chatter Manzil, Lucknow 226001, Uttar Pradesh, India*
[b] *Division of Parasitology, Central Drug Research Institute, Chatter Manzil, Lucknow 226001, Uttar Pradesh, India*

Received 19 April 2006; received in revised form 30 September 2006; accepted 5 October 2006
Available online 11 May 2007

Abstract

Some novel 4-*N*-substituted terpenyl pyrimidines **5**(**a**–**d**) and **7**(**a**–**g**) have been synthesized using novel synthetic methods. The compounds were screened for in vivo antileishmanial screening. When compared to 4-thiomethoxy substituted pyrimidine **2** 4-*N*-substituted terpenyl pyrimidines **5**(**a**–**d**) and **7**(**a**–**g**) were found inactive.

Keywords: β-Ionone; Terpenyl pyrimidines; 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 as drugs for the treatment of both visceral (VL) and cutaneous leishmaniasis (CL) for more than 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. Natural products are being explored to generate new leads in the chemotherapy of leishmaniasis [5]. At the same time biochemical targets are also under investigation to generate novel small molecules as lead molecules [6]. Among the biochemical targets, dihydrofolate reductase (DHFR) [7] is being evaluated in the design of novel compounds. DHFR has been quite successful as a biochemical target in cancer [8] and malaria [9] and has resulted in the development of clinically active molecules i.e., pyrimethamine, trimethoprim, cycloguanil and methotrexate. However, these classical DHFR inhibitors showed very little selectivity towards leishmanial and trypanosomal enzymes [7].

Relatively very little has been reported on the development of specific inhibitors of leishmainal and trypanosome DHFR. Coombs group [8,9] investigated some 5-substituted 2,4-diaminopyrimidines that were good inhibitors of *Leishmania mexicana* DHFR in in vitro model. However, in a mouse study compounds were found toxic. Further studies by Sirawaraporn et al. [10] on substituted 5-benzyl-2,4-diaminopyrimidines were quite encouraging in the in vitro studies. In continuation of our studies on terpene-substituted pyrimidines [11], we synthesized some novel terpenyl pyrimidines and evaluated them for in vivo biological profile and the results are reported in this communication.

2. Chemistry

The ketene dithioacetal **1** was made available from commercially available β-ionone in quantitative yield [12]. The reaction of ketene dithioacetal **1** with guanidine in dry

☆ CDRI communication no. 6952.

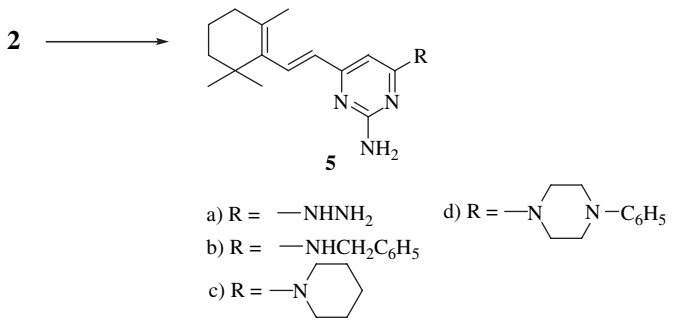
* Corresponding author. Tel.: +91 0522 2212411-18; fax: +91 0522 2223405/2223938/2229504.
E-mail address: shivajins@yahoo.co.in (S.N. Suryawanshi).

0223-5234/$ - see front matter © 2006 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2006.10.002

isopropanol (steel bomb, 120–130 °C, 24 h) furnished terpenyl pyrimidine **2** in 50% yield [11a] (Scheme 1). Direct replacement of 4-thiomethyl group in **2** with primary and secondary amines proved least useful and even at steel bomb condition starting material was recovered. We then thought of oxidizing 4-thiomethyl group in **2** to sulfonylmethoxy as in **3**, in view to make it more facile to SN^2 displacement reaction with various amines. After exploring various oxidation reactions, oxone in THF was found to be more successful [13]. The reaction of terpenyl pyrimidine **2** with oxone in THF (rt, 4 h) furnished **3** in 50% yield, contaminated with epoxy compound **4** as a side product in 25% yield.

Terpenyl pyrimidine **2** reacted with hydrazine hydrate (Δ, 24 h) to furnish **5a** as a crystalline compound in 66% yield which melted at 250–251 °C. The structure of **5a** was confirmed by ^{1}H NMR and ^{13}C NMR data. The terpenyl pyrimidine **2** failed to react with benzyl amine at reflux conditions. Extended reaction time and reflux conditions were of less use. Even under steel bomb reaction conditions benzyl amine failed to react with terpenyl pyrimidine **2**. However, 4-sulfonylmethoxy pyrimidine **3** reacted with benzyl amine (isopropanol, Δ, 24 h) to furnish **5b** as a white crystalline solid in 25% yield. Under identical reaction conditions **5**(**c**–**d**) were synthesized as shown in Scheme 2.

In a synthetic sequence as shown in Scheme 1, the oxidation reaction with oxone was not a very clean reaction which always furnished epoxide **4** as a side product. To overcome this side product we visualized synthesis of 4-*N*-substituted pyrimidines as shown in Scheme 3. The reaction of **1** with aromatic amines furnished *S*, *N*-acetals **6**(**a**–**g**) in good yields (Table 1) [14]. Cyclohexyl amine also reacted with **1** under identical reaction conditions to furnish **6f** in good yield. Having been successfully synthesized *S*, *N*-acetals **6**(**a**–**g**) we subjected them towards pyrimidine formation reaction as shown in Scheme 3. To our expectations *S*,*N*-acetal **6a** reacted with guanidine in isopropanol (steel bomb, 130–140 °C, 15 h) to furnish pyrimidine **7a** in 46% yield (Table 2). The structure of **7a** was confirmed on the basis of ^{1}H and ^{13}C NMR spectra. Under identical reaction conditions **6**(**b**–**g**) were reacted with guanidine in isopropanol to furnish **7**(**b**–**g**) as shown in Scheme 3.



Scheme 2.

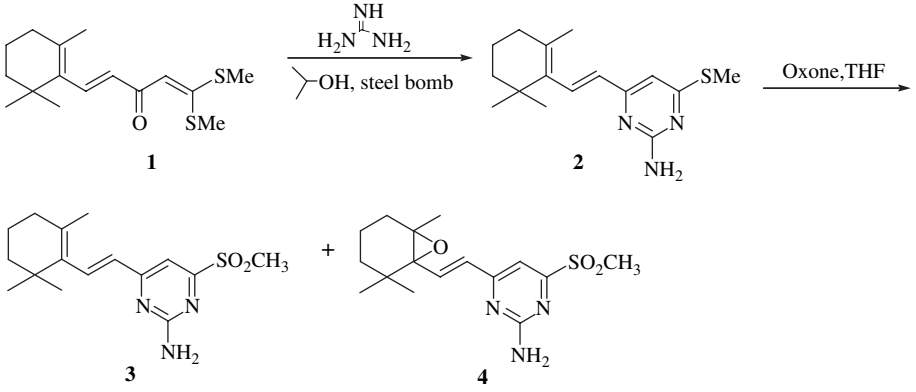
Having been successfully synthesized pyrimidines **7**(**a**–**g**) from *S*, *N*-acetals **6**(**a**–**g**), we planned to synthesize 4-*N*-substituted pyrimidines **9**(**a**–**b**) from *N*, *N*-acetals **8**(**a**–**b**) (Scheme 4). The reaction of morpholine with ketene dithioacetal **1** at ethanol reflux temperature did not provide *S*,*N*-acetal but furnished only *N*,*N*-acetal **8a** in 60% yield as a crystalline solid. Under identical reaction conditions ketene dithioacetal **1** reacted with piperazine to produce *N*, *N*-acetal **8b** in 81% yield.

The reaction of *N*, *N*-acetals **8**(**a**–**b**) with guanidine was not found very satisfactory. For instance, *N*,*N*-acetal **8a** on reaction with guanidine in isopropanol (130–140 °C, steel bomb, 15 h) furnished 4-*N*-substituted pyrimidine **9a** in 26% yield as a crystalline solid which melted at 139–140 °C. The structure was confirmed by ^{1}H and ^{13}C NMR. However, *N*,*N*-acetal **8b** on reaction with guanidine under identical reaction conditions furnished only *7*% of the required compound **9b**.

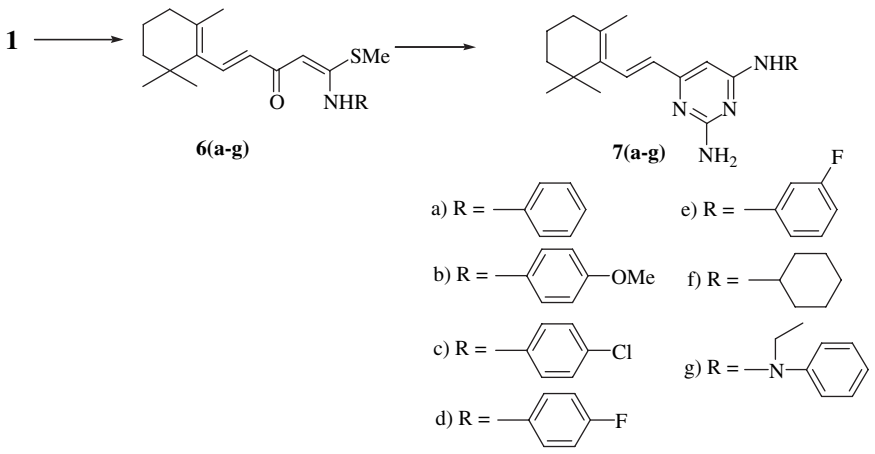
3. Biological activities

The in vivo leishmanicidal activity was determined in golden hamsters (*Mesocricetus auratus*) infected with HOM/IN/80/DD_8 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 [15] as modified by Bhatnagar et al. [16] and Gupta et al. [17] was employed. Male hamsters weighing 35–40 g were



Scheme 1.



Scheme 3.

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. 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.

Table 1
Synthesis of *S*, *N*- and *N*, *N*-acetals

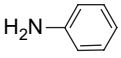
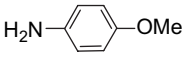
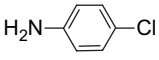
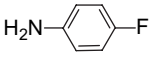
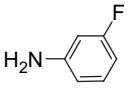
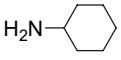
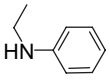
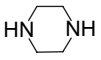
S. no.	Substrate	Amine	Reaction conditions	Product	
				S,*N*, %	*N*,*N*, %
1	**1**		Steel bomb, EtOH, 100–110 °C, 9 h	**6a**, 59	–
2	**1**		EtOH, reflux, 15 h	**6b**, 87	–
3	**1**		Steel bomb, EtOH, 100–120 °C, 20 h	**6c**, 90	–
4	**1**		Steel bomb, EtOH, 100–120 °C, 22 h	**6d**, 42	–
5	**1**		EtOH,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

Table 2
Synthesis of 4-*N*-substituted terpenyl pyrimidine

S. no.	Substrate	Reaction conditions	Product	Yield (%)
1	**6a**	Guanidine, isopropanol, steel bomb, 15 h	**7a**	46
2	**6b**	Guanidine, isopropanol, steel bomb, 15 h	**7b**	67
3	**6c**	Guanidine, isopropanol, Steel bomb, 20 h	**7c**	64
4	**6d**	Guanidine, isopropanol, steel bomb, 25 h	**7d**	71
5	**6e**	Guanidine, isopropanol, steel bomb, 25 h	**7e**	55
6	**6f**	Guanidine, isopropanol, steel bomb, 15 h	**7f**	88
7	**6g**	Guanidine, isopropanol, steel bomb, 15 h	**7g**	70[a]
8	**8a**	Guanidine, isopropanol, steel bomb, 15 h	**9a**	26[a]
9	**8b**	Guanidine, isopropanol, steel bomb, 15 h	**9b**	7

[a] Yield based on the basis of recovered starting.

4. Results and discussion

In earlier studies by us [11a,b,18] and others [19] have shown that pyrimidines attached to a suitable hydrophobic terpene handle form a unique pharmacophore and show antimicrobial and antileishmanial profile. We visualized that the terpene plays as good hydrophobic handle and activity profile is displayed by the pyrimidine ring. In view of this we undertook modification on the pyrimidine ring. 4-*O*-Substituted terpenyl pyrimidines displayed moderate antileishmanial activity profile [11a] and we visualized that they might be acting through immunostimulation. Therefore, we decided to introduce another nitrogen function at the 4-position which is required for the DHFR inhibition and we synthesized compounds via two different synthetic routes as shown in Schemes 2 and 3. The compound **2** displayed 66% inhibition on 50 mg/kg in a hamster model [11a]. The replacement of SMe by nitrogen substitution as in **5**(**a**–**d**) resulted in the loss of in vivo biological activity. To our surprise, even substitution of variously substituted anilines at 4-position as in **7**(**a**–**g**) did not show in vivo biological profile. Substitution of secondary amines as in **9**(**a**–**b**) also has no effect and compounds were found inactive (Table 3). In conclusion, replacement of thiomethoxy group in **2** by primary amines as well as secondary amines as in **5**(**a**–**d**) and **7**(**a**–**g**) resulted in loss of in vivo antileishmanial activity profile.

Table 3
Antileishmanial activity of compounds against *Leishmania donovani* in hamsters

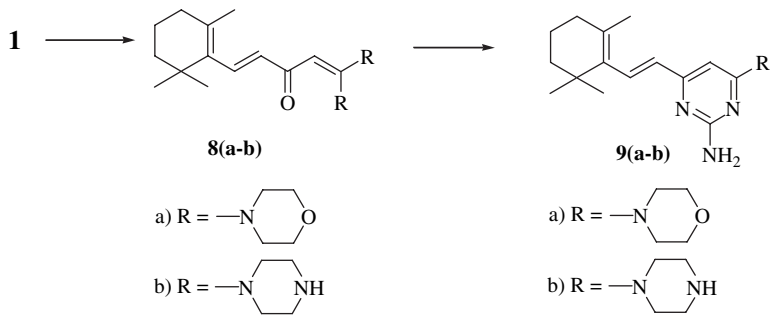
S. no.	Compound	Dose (mg/kg)	In vivo inhibition (%)	
			Day-7	Day-28
1	**2**	50	66	–
2	**3**	50	ND	–
3	**4**	50	ND	–
4	**5a**	50	NI	–
5	**5b**	50	NI	–
6	**5c**	50	NI	–
7	**5d**	50	NI	–
8	**7a**	50	31	–
9	**7b**	50	NI	–
10	**7c**	50	NI	–
11	**7d**	50	NI	–
12	**7e**	50	NI	–
13	**7f**	50	NI	–
14	**7g**	50	40	–
15	**9a**	50	NI	–
16	**9b**	50	NI	–

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 as internal standard, Aldrich) and are reported in parts per million downfield from Me_4Si. Proton and 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. 4-Methanesulfonyl-6-[2-(2,6,6-trimethyl-cyclohex-1-enyl)-ethenyl]-pyrimidin-2-ylamine (**3**)*

To a solution of **2** (0.578 g, 2 mmol) in THF (20 ml) was added oxone (3.690 g, 6 mmol) in water (20 ml) at 0 °C and stirred the reaction mixture for 4 h at room temperature. The reaction mixture was concentrated in vacuo and extracted



Scheme 4.

with ethylacetate (50 ml × 2). The ethylacetate extract was washed with brine (50 ml), dried (Na_2SO_4) and solvent was removed in vacuo. The crude product was column chromatographed (SiO_2, 60–120 mesh). Elution with 30% ethylacetate in hexane furnished **3** as a pale yellow foam (0.30 g, 50%). IR (neat, cm^{-1}) 3421, 2131, 1730, 1608, 1568; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.00 (s, 6H), 1.50 (m, 2H), 1.60 (m, 2H), 1.80 (s, 3H), 2.10 (m, 2H), 3.20 (s, 3H), 5.45 (m, 2H), 6.35 (d, $J = 16.00$ Hz, 1H), 7.50 (d, $J = 16.00$ Hz, 1H); MS: (*m/e*) 321 (M^+), 306 ($M^+ - CH_3$).

5.2. 4-Hydrazino-6-[2-(2,6,6-trimethyl-cyclohex-1-enyl)-ethenyl]-pyrimidin-2-ylamine (**5a**)

Compound **2**(0.578 g, 2 mmol) in neat hydrazine hydrate was refluxed for 24 h to furnish **5a** as crystalline solid in quantitative yield 66%. M.p. 250–251 °C; IR (KBr, cm^{-1}) 3322, 2924, 1590, 1410; ^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), 4.95 (m, 2H), 6.00 (s, 1H), 6.20 (d, $J = 16.00$ Hz, 1H), 6.30 (m, 3H), 7.30 (d, $J = 16.00$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 19.50 (t), 23.37 (q), 2 × 28.98 (q), 33.60 (s), 34.58 (t), 40.27 (t), 91.57 (d), 131.25 (s), 132.25 (d), 134.59 (s), 137.41 (d), 163.11 (s), 167.04 (s); MS: (*m/e*) 273 (M^+), 258 ($M^+ - CH_3$), 243 ($M^+ - NHCH_3$).

6. General procedure for the synthesis of 5(b–d)

To a solution of **3** (0.64 g, 2 mmol) in isopropanol (30 ml) were added various amines to furnish *N*-substituted terpenyl pyrimidines **5b–d** in quantitative yield.

6.1. 4-N-Benzyl-6-[2-(2,6,6-trimethyl-cyclohex-1-enyl)-ethenyl]-pyrimidine-2,4-diamine (**5b**)

Yield 25%. M.p. 81–83 °C; IR (KBr, cm^{-1}) 3193, 2925, 1575; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.20 (s, 6H), 1.50 (m, 2H), 1.75 (m, 4H), 1.80 (s, 3H), 2.10 (m, 2H), 4.60 (d, 2H), 4.80 (m, 2H), 5.00 (m, 2H), 5.80 (s, 1H), 6.20 (d, $J = 18.00$ Hz, 1H), 7.40 (m, 4H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 164.629 (s), 163.317 (s), 139.059 (s), 137.505 (s), 134.407 (d), 132.011 (s), 131.399 (d), 129.104 (d), 4 × 127.79 (d), 92.783 (d), 45.745 (t), 40.164 (t), 34.634 (s), 33.629 (t), 2 × 29.362 (q), 22.163 (q), 19.583 (t); MS: (*m/e*) 348 (M^+), 333 ($M^+ - CH_3$).

6.2. 4-Piperidin-1-yl-6-[2-(2,6,6-trimethyl-cyclohex-1-enyl)-ethenyl]-pyrimidin-2-ylamine (**5c**)

Yield 28%. M.p. 112–113 °C; IR (KBr, cm^{-1}) 3479, 3286, 3165, 3000, 1573, 1521, 1411, 980; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.20 (s, 6H), 1.70 (m, 10H), 1.90 (s, 1H), 2.10 (m, 2H), 3.60 (m, 4H), 4.70 (d, 2H), 6.00 (s, 1H), 6.20 (d, $J = 20.00$ Hz, 1H), 7.30 (d, $J = 20.00$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 19.585 (t), 22.161 (q), 25.173 (t), 2 × 26.015 (t), 2 × 29.363 (q), 33.577 (s), 34.607 (t), 40.153 (t), 2 × 45.445 (t), 92.439 (d), 131.555 (s), 131.949 (d), 133.709 (d), 137.630 (s), 162.873 (s), 163.251 (s), 163.965 (s); MS: (*m/e*) 326 (M^+), 311 ($M^+ - CH_3$).

6.3. 4-(4-Phenyl-piperazin-1-yl)-6-[2-(2,6,6-trimethyl-cyclohex-1-enyl)-ethenyl]-pyrimidin-2-ylamine (**5d**)

Yield 50%. M.p. 120–123 °C; IR (KBr, cm^{-1}) 3327, 3205, 2916; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.05 (s, 6H), 1.50 (m, 2H), 1.65 (m, 2H), 5.90 (s, 1H), 6.20 (d, $J = 16.00$ Hz, 1H), 6.90 (m, 3H), 7.30 (m, 3H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 19.63 (t), 22.24 (q), 2 × 29.44 (q), 33.65 (t), 34.67 (s), 40.12 (t), 2 × 44.30 (t), 2 × 49.56 (t), 92.46 (d), 2 × 116.83 (t), 120.62 (d), 2 × 129.63 (d), 131.90 (d), 134.24 (s), 137.62 (s), 151.57 (s), 163.31 (s), 164.23 (s); MS: (*m/e*) 403 (M^+).

7. General procedure for the synthesis of 6(a–g) and 8(a–b)

To a solution of ketene dithioacetal **1** in absolute alcohol (60 ml) were added various amines (20 mmol) and refluxed/or in steel bomb for 5–40 h to furnish *S*,*N*-acetals **6(a–g)** and *N*,*N*-acetals **8(a–b)** in good yields as shown in Table 1.

8. General procedure for the synthesis of 4-*N*-phenyl-6-[2-(2,6,6-trimethyl-cyclohex-1-enyl)-ethenyl]-pyrimidine-2,4-diamine (7a)

To a solution of sodium isopropoxide (prepared by dissolving sodium metal 0.23 g in 20 ml of dry isopropanol) was added guanidine hydrochloride (0.95 g, 10 mmol) and stirred the reaction mixture for 3 h at room temperature. The white solid was filtered off. To the filtrate was added **6a** (3.86 g, 10 mmol) and the reaction mixture was heated in steel bomb at 120–130 °C for 15 h. It was concentrated in vacuo and extracted with ethylacetate (50 ml × 4). Combined extract was washed with water (25 ml × 2), brine solution (50 ml), dried (Na_2SO_4) and the solvent was removed in vacuo. The crude product was column chromatographed (SiO_2, 60–120 mesh). Elution with 15% ethylacetate in hexane furnished **7a** as a thick liquid (3.07 g, 46%). IR (neat, cm^{-1}) 3408, 2927, 1600, 1550, 1500, 1400; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.10 (s, 6H), 1.50 (m, 2H), 1.65 (m, 2H), 1.80 (s, 3H), 2.05 (m, 2H), 5.00 (bs, 2H), 6.10 (s, 1H), 6.15 (d, $J = 16.00$ Hz, 1H), 7.30 (m, 6H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 19.541 (t), 22.152 (q), 2 × 29.319 (q), 33.653 (s), 34.221 (t), 40.152 (t), 93.410 (d), 2 × 122.880 (d), 124.670 (d), 2 × 129.663 (d), 130.993 (d), 132.437 (s), 135.084 (d), 137.429 (s), 139.252 (s), 163.007 (s), 163.259 (s), 163.772 (s); MS: (*m/e*) 335 ($M^+ + 1$), 320 ($M^+ - CH_3$).

8.1. 4-N-(4-Methoxyphenyl)-6-[2-(2,6,6-trimethyl-cyclohex-1-enyl)-ethenyl]-pyrimidine-2,4-diamine (**7b**)

Yield 67%. M.p. 74–76 °C; IR (KBr, cm^{-1}) 3400, 3000, 1600, 1568, 1506, 1240; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.10 (s, 6H), 1.40 (m, 2H), 1.50 (m, 2H), 1.75 (s, 3H), 2.00 (m, 2H),

3.80 (s, 3H), 5.30 (m, 2H), 5.95 (s, 1H), 6.10 (d, $J = 16.00$ Hz, 1H), 6.80 (d, $J = 8.00$ Hz, 2H), 7.20 (d, $J = 8.00$ Hz, 2H), 7.20 (d, 1H), 7.95 (m, 1H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 19.539 (t), 22.137 (q), 2×29.299 (q), 33.607 (t), 35.078 (s), 40.119 (t), 55.821 (q), 92.761 (d), 2×114.908 (d), 126.022 (d), 131.370 (s), 131.933 (d), 132.126 (s), 134.554 (d), 137.434 (s), 157.409 (s), 163.435 (s), 163.641 (s), 163.995 (s); MS: (*m/e*) 365 ($M^+ + 1$).

*8.2. 4-N-(4-Chlorophenyl)-6-[2-(2,6,6-trimethyl-cyclohex-1-enyl)-ethenyl]-pyrimidine-2,4-diamine (**7c**)*

Yield 64%. M.p. 55–56 °C; IR (KBr, cm^{-1}) 3310, 2928, 1570, 1491, 1398; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.10 (s, 6H), 1.50 (m, 2H), 1.65 (m, 2H), 1.70 (s, 3H), 2.10 (m, 2H), 5.95 (s, 2H), 6.15 (s, 1H), 6.20 (d, $J = 16.00$ Hz, 1H), 7.30 (d, 2H), 7.40 (d, $J = 16.00$ Hz, 1H), 7.85 (d, 2H), 8.75 (s, 1H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 20.321 (t), 22.459 (q), 2×29.783 (q), 34.169 (t), 35.292 (s), 40.840 (t), 96.180 (d), 2×122.635 (d), 127.376 (s), 2×129.711 (d), 132.275 (s), 132.709 (d), 134.390 (d), 138.321 (s), 141.040 (s), 163.501 (s), 163.710 (s), 164.628 (s); MS: (*m/e*) 369 ($M^+ + 1$).

*8.3. 4-N-(4-Fluorophenyl)-6-[2-(2,6,6-trimethyl-cyclohex-1-enyl)-ethenyl]-pyrimidine-2,4-diamine (**7d**)*

Yield 71%. M.p. 105–106 °C; IR (KBr, cm^{-1}) 3412, 2928, 1574, 1507, 1405, 1217; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.89 (s, 6H), 1.40 (m, 2H), 1.50 (m, 2H), 1.65 (s, 3H), 1.90 (m, 2H), 5.70 (m, 2H), 5.95 (s, 1H), 6.00 (d, $J = 16.00$ Hz, 1H), 6.90 (m, 2H), 7.25 (d, $J = 16.00$ Hz, 1H), 7.60 (m, 2H), 8.50 (s, 1H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 20.292 (t), 22.376 (q), 2×29.738 (q), 34.122 (t), 35.283 (s), 40.839 (t), 95.794 (d), 115.992 (d), 116.435 (d), 122.119 (d), 123.270 (d), 132.093 (s), 132.788 (d), 134.147 (d), 138.365 (s), 157.032 (s), 161.787 (s), 163.445 (s), 163.724 (s), 164.615 (s); MS: (*m/e*) 353 ($M^+ + 1$).

*8.4. 4-N-(3-Fluorophenyl)-6-[2-(2,6,6-trimethyl-cyclohex-1-enyl)-ethenyl]-pyrimidine-2,4-diamine (**7e**)*

Yield 55%. M.p. 51–52 °C; IR (KBr, cm^{-1}) 3414, 3306, 2932, 1572, 1444; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.02 (s, 6H), 1.50 (m, 2H), 1.60 (m, 2H), 1.70 (s, 3H), 2.00 (m, 2H), 5.60 (m, 2H), 6.10 (s, 1H), 6.15 (d, $J = 16.00$ Hz, 1H), 6.80 (m, 1H), 7.00–7.40 (m, 4H), 8.20 (m, 1H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 19.497 (t), 22.114 (q), 2×29.261 (q), 33.671 (s), 34.580 (t), 40.113 (t), 94.073 (d), 110.897 (d), 117.158 (d), 117.212 (d), 130.272 (d), 130.473 (d), 132.895 (s), 135.622 (d), 137.319 (s), 141.122 (s), 141.334 (s), 161.104 (s), 165.972 (s), 178.578 (s); MS: (*m/e*) 353 ($M^+ + 1$).

*8.5. 4-N-Cyclohexyl-6-[2-(2,6,6-trimethyl-cyclohex-1-enyl)-ethenyl]-pyrimidine-2,4-diamine (**7f**)*

Yield 88%. M.p. 75–76 °C; IR (KBr, cm^{-1}) 3415, 2931, 1579, 1215; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.10 (s, 6H), 1.30 (m, 10H), 1.50 (m, 2H), 1.60 (m, 2H), 1.80 (s, 3H), 2.00 (m, 2H), 3.60 (m, 1H), 4.80 (d, 1H), 4.90 (m, 2H), 5.75 (s, 1H), 6.15 (d, $J = 16.00$ Hz, 1H), 7.30 (d, $J = 16.00$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 19.566 (t), 22.134 (q), 2×25.173 (q), 25.670 (t), 2×29.333 (q), 29.727 (t), 2×33.642 (t), 34.607 (s), 40.145 (t), 50.00 (d), 95.749 (d), 131.431 (d), 131.815 (d), 134.226 (d), 137.558 (s), 162.865 (s), 163.256 (s), 163.713 (s); MS: (*m/e*) 340 (M^+), 320 ($M^+ - CH_3$).

*8.6. 4-N-Ethyl-N-4-phenyl-6-[2-(2,6,6-trimethyl-cyclohex-1-enyl)-ethenyl]-pyrimidine-2,4-diamine (**7g**)*

Yield 88%. IR (neat, cm^{-1}) 3415, 2927, 1581, 1215; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.15 (s, 6H), 1.30 (s, 3H), 1.50 (m, 2H), 1.70 (m, 2H), 1.80 (s, 3H), 2.10 (m, 2H), 2.95 (m, 2H), 3.60 (m, 2H), 5.00 (m, 2H), 5.80 (s, 1H), 6.15 (d, $J = 16.00$ Hz, 1H), 7.30 (m, 6H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 19.586 (t), 22.184 (q), 2×29.371 (q), 30.110 (q), 33.639 (s), 34.638 (t), 40.168 (t), 42.930 (t), 93.00 (d), 126.924 (d), 2×129.046 (d), 2×129.181 (d), 131.221 (d), 132.042 (s), 134.453 (d), 137.537 (s), 139.302 (s), 162.00 (s), 163.165 (s), 164.462 (s); MS: (*m/e*) 363 ($M^+ + 1$).

*8.7. 4-Morpholin-4-yl-6-[2-(2,6,6-trimethyl-cyclohex-1-enyl)-ethenyl]-pyrimidin-2-ylamine (**9a**)*

Yield 26%. IR (neat, cm^{-1}) 2922, 1643, 1484, 1446, 1392, 1228, 980; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.20 (s, 6H), 1.50 (m, 2H), 1.80 (s, 3H), 2.10 (m, 3H), 3.60 (m, 4H), 3.75 (m, 4H), 4.90 (d, 2H), 5.45 (m, 1H), 5.90 (s, 1H), 6.10 (d, $J = 16.00$ Hz, 1H), 6.60 (d, $J = 16.00$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 17.572 (q), 25.173 (t), 2×26.362 (q), 33.577 (s), 36.607 (t), 40.153 (t), 2×54.426 (t), 2×70.335 (t), 92.439 (d), 128.858 (d), 131.949 (d), 133.709 (d), 137.630 (d), 162.873 (d), 168.262 (d), 171.654 (d); MS: (*m/e*) 329 ($M^+ + 1$).

*8.8. 4-Piprazine-1-yl-6-[2-(2,6,6-trimethyl-cyclohex-1-enyl)-ethenyl]-pyrimidin-2-ylamine (**9b**)*

Yield 7%. IR (neat, cm^{-1}) 3344, 2925, 1581, 1417, 1356; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.20 (s, 6H), 1.55 (m, 2H), 1.70 (s, 3H), 2.10 (m, 3H), 3.50 (m, 4H), 3.85 (m, 4H), 4.95 (d, 2H), 5.45 (m, 1H), 5.90 (s, 1H), 6.20 (d, $J = 16.00$ Hz, 1H), 6.50 (d, $J = 16.00$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 17.560 (q), 25.173 (t), 2×26.362 (q), 34.658 (s), 38.656 (t), 42.852 (t), 52.450 (t), 54.426 (t), 70.335 (t), 74.457 (t), 92.439 (d), 129.866 (d), 132.957 (d), 134.799 (d), 139.434 (d), 161.762 (d), 168.262 (d), 170.275 (d); MS: (*m/e*) 328 ($M^+ + 1$).

Acknowledgements

Financial support to B.A. Bhat by NOVA-NORDIX, S.P. and N.C. by MOH (India) and technical support by Mrs. Manju are gratefully acknowledged.

References

[1] R.N. Davidson, Practical guide for the treatment of leishmaniasis, Drugs 56 (1998) 1009–1018.
[2] B.L. Herwaldt, Leishmaniasis, Lancet 354 (1999) 1191–1199.
[3] D.R. Goldsmith, C.M. Perry, Drugs 64 (2004) 1905–1911.
[4] S.L. Croft, K. Seifert, M. Duchene, Mol. Biochem. Parasitol. 126 (2003) 165–172.
[5] (a) Manuel Jesus Chan Bacab, Luis Manuel Pede-Rodriguez, Nat. Prod. Rep. 18 (2001) 674–688;
(b) Paulo B. de Carvalho, Elizabeth I. Ferreira, Fitotherapia 72 (2001) 599–618.
[6] (a) S.L. Croft, G.H. Coombs, Trends Parasitol. 19 (11) (2003) 502–508;
(b) S.L. Croft, M.P. Barrett, J.A. Urbina Trends Parasitol. 21(11) (2005) 508–512.
[7] I.H. Gilbert, Biochem. Biophys. Acta 1587 (2002) 249–257.
[8] D.A. Scott, G.H. Coombs, B.E. Sanderson, Biochem. Pharmacol. 36 (1987) 2043–2045.
[9] C.A. hunter, G.H. Coombs, Med. Sci. Res. 15 (1987) 1233–1234.
[10] W. Sirawaraporn, R. Sertsrivanich, R.G. Booth, C. Hansch, R.A. Neal, D.V. Santi, Mol. Biochem. Parasitol. 31 (1988) 79.
[11] (a) Susmita Pandey, S.N. Suryawanshi, Suman Gupta, V.M.L. Srivastava, Eur. J. Med. Chem. 39 (2004) 969–973;
(b) Naveen Chandra, Ramesh, Ashutosh, Neena Goyal, S.N. Suryawanshi, Suman Gupta, Eur. J. Med. Chem. 40 (2005) 552–556.
[12] S.N. Suryawanshi, A. Rani, B. Kumar, D.S. Bhakuni, J. Indian Inst. Sci. 74 (1994) 627–631.
[13] (a) B.M. Trost, D.P. Curran, Tetrahedron Lett. 1287 (1981);
(b) R.J. Kennedy, A.M. Stock, J. Org. Chem. 25 (1960) 1901.
[14] (a) M. Augustin, Ch. Groth, J. Prakt. Chem. 321 (1979) 215–225;
(b) M. Augustin, Ch. Groth, H. Kristen, K. Peseke, Ch. Wiechmann, J. Prakt. Chem. 321 (1979) 205–214.
[15] S. Beveridge, in: R.J. Shnitzer, F.I. Hanoking (Eds.), Experimental Chemotherapy, vol.1, 1963, pp. 257–280.
[16] S. Bhatnagar, P.Y. Guru, J.C. Katiyar, R. Srivastava, A. Mukherjee, M.S. Akhtar, M. Seth, A.P. Bhaduri, Indian J. Med. Res. 89 (1989) 439.
[17] S. Gupta, S. Tiwari, A.P. Bhaduri, G.K. Jain, Acta Tropica 84 (2002) 165–173.
[18] Naveen Chandra, Susmita Pandey, Ramesh, S.N. Suryawanshi, Suman Gupta, Eur. J. Med. Chem. 41 (2006) 779–785.
[19] (a) M. Anzaldi, E. Sottofottori, R. Rizzetto, Barbara Granello di Casaleto, Alesandro Balbi, Eur. J. Med. Chem. 34 (1999) 837–842;
(b) A. Rosowsky, A.T. Papoulis, S.F. Queener, J. Heterocycl. Chem. 36 (1999) 723–728.