Chemotherapy of Leishmaniasis Part III: Synthesis and Bioevaluation of Novel Aryl Substituted Terpenyl Pyrimidines as Antileishmanial Agents

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Short Communication

Chemotherapy of leishmaniasis part III: synthesis and bioevaluation of novel aryl substituted terpenyl pyrimidines as antileishmanial agents ☆

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Abstract

Some aryl substituted terpenyl pyrimidines **4** (**a**–**p**) have been synthesized using novel synthetic methods. The compounds were screened for in vitro antileishmanial activity against promastigotes. Compounds **4c**, **4i** and **4l** showed IC_{50} values as 35, 35 and 25 μg ml^{-1}.

Keywords: Ionones; Aryl substituted terpenyl pyrimidines; Antileishmanial activity; In vitro; MTT; *L. donovani*

1. Introduction

Leishmaniasis is an infection caused by protozoa of the genus *Leishmania* presenting several forms of the disease such as cutaneous, mucocutaneous and visceral leishmaniasis, 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 and cutaneous leishmaniasis for > 50 years, is now widespread in India. Although new drugs have become available in recent years for the treatment of visceral leishmaniasis 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 the natural sources and in this endeavor diaryl heptanoids [5–7], oxygenated abietanes [8], diterpene quinones [9] 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-diaminopyrimidines [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 designed some novel terpenyl pyrimidines, having added aryl substitution and evaluated for their in vitro antileishmanial activity and the results are reported in this communication.

2. Chemistry

The chalcones **3** (**a**–**h**) have been synthesized from α-ionone **1** and substituted benzaldehydes **2** as shown in Scheme 1.

Classical literature methods were of little help on a preparative scale as it resulted in excessive decomposition of α-ionone **1**. Powdered sodium hydroxide in aprotic solvents was also of little help [15]. However, phase transfer catalyzed conditions used for the phenolic ketones [16] proved useful. The reaction of α-ionone **1** with 3,4-dimethoxybenzaldehyde under phase transfer conditions was very facile and furnished chalcone **3a** in 75% yield. Similarly 3,4,5-trimethoxybenzaldehyde under identical reaction conditions furnished chalcone **3b** in quantitative yield. Under identical conditions *p*-chlorobenzaldehyde and *p*-fluoro benzaldehyde furnished **3c** and **3d** in quantitative

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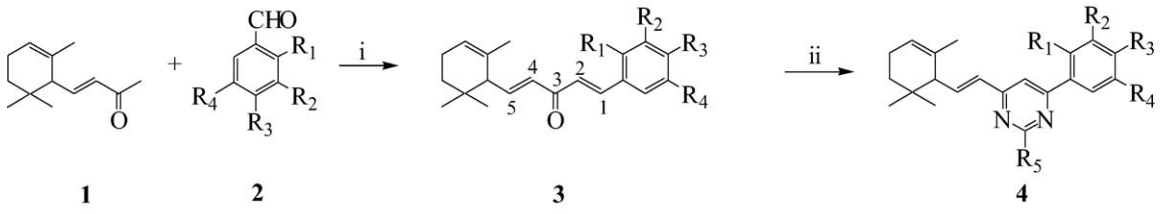


a). $R_1 = R_4 = H, R_2 = R_3 = OCH_3$
b). $R_1 = H, R_2 = R_3 = R_4 = OCH_3$
c). $R_1 = R_2 = R_4 = H, R_3 = Cl$
d). $R_1 = R_2 = R_4 = H, R_3 = F$
e). $R_1 = R_2 = R_4 = H, R_3 = OBn$
f). $R_1 = R_2 = R_4 = H, R_3 = NO_2$
g). $R_1 = NO_2, R_2 = R_3 = R_4 = H$
h). $R_1 = R_3 = R_4 = H, R_2 = NO_2$

a) $R_1 = R_4 = H, R_2 = R_3 = OCH_3, R_5 = NH_2$
b) $R_1 = H, R_2 = R_3 = R_4 = OCH_3, R_5 = NH_2$
c) $R_1 = R_2 = R_4 = H, R_3 = Cl, R_5 = NH_2$
d) $R_1 = R_2 = R_4 = H, R_3 = F, R_5 = NH_2$
e) $R_1 = R_2 = R_4 = H, R_3 = OBn, R_5 = NH_2$
f) $R_1 = R_2 = H, R_3 = R_4 = OCH_3, R_5 =$ –N O
g) $R_1 = H, R_2 = R_3 = R_4 = OCH_3, R_5 =$ –N O
h) $R_1 = R_2 = R_4 = H, R_3 = Cl, R_5 =$ –N O
i) $R_1 = R_2 = R_4 = H, R_3 =$OBn, $R_5 =$ –N O
j) $R_1 = R_2 = R_4 = H, R_3 = F, R_5 =$ –N O
k) $R_1 = R_2 = R_4 = H, R_3 = NO_2, R_5 = NH_2$
l) $R_1 = R_2 = R_4 = H, R_3 = NO_2, R_5 =$ –N O
m) $R_1 = NO_2, R_2 = R_3 = R_4 = H, R_5 = NH_2$
n) $R_1 = NO_2, R_2 = R_3 = R_4 = H, R_5 =$ –N O
o) $R_1 = R_3 = R_4 = H, R_2 = NO_2, R_5 =$ –N O
p) $R_1 = R_3 = R_4 = H, R_2 = NO_2, R_5 = NH_2$

Scheme 1.

yield. The reaction of *p*-benzyloxybenzaldehyde with α-ionone was equally facile and furnished chalcone **3e** in 89% yield as a pale yellow crystalline solid melting at 81–82 °C. Nitrobenzaldehydes were equally reactive and furnished chalcones **3** (**f**–**h**) in respectable yields.

The reaction of guanidine with chalcone **3** (**a**–**h**) was not only facile but it was also regiospecific in manner. The reaction of chalcone **3a** with guanidine in isopropanol in the presence of silver oxide furnished pyrimidine **4a** in 42% yield as a crystalline solid melting at 101–102 °C. The structure was assigned on the basis of ^{1}H and ^{13}C NMR spectra. The ^{1}H NMR spectrum of **4a** displayed a doublet at 6.30 ppm (j = 16.00 Hz) for the H-4 proton and doublet of doublets at 6.80 ppm (j = 16.00, 10.00 Hz, 1H) for the H-5 proton and it established the assigned structure **4a**. Under identical reaction conditions **4** (**b**–**e**) were synthesized in good yields. Morpholino substituted pyrimidines were also synthesized under identical reaction conditions. The reaction of chalcone **3a** with morpholino guanidine in the presence of silver oxide in isopropanol (Δ, 16 h) furnished morpholino pyrimidine **4f** in 38% yield as a crystalline solid melting at 123–125 °C. The structure was assigned on the basis of ^{1}H NMR which showed a doublet at 6.35 ppm (j = 16.00 Hz) for the H-4 proton and doublet of doublets at 6.8 ppm (j = 16.00, 10.00 Hz) for the H-5 proton. Under identical reaction conditions morpholino guanidine **4** (**g**–**j**) were synthesized. Nitro chalcones were equally more facile to react with guanidine and morpholino guanidine to furnish pyrimidines **4** (**k**–**p**) in quantitative yields (Scheme 2).

3. Biological activities

3.1. Material and methods

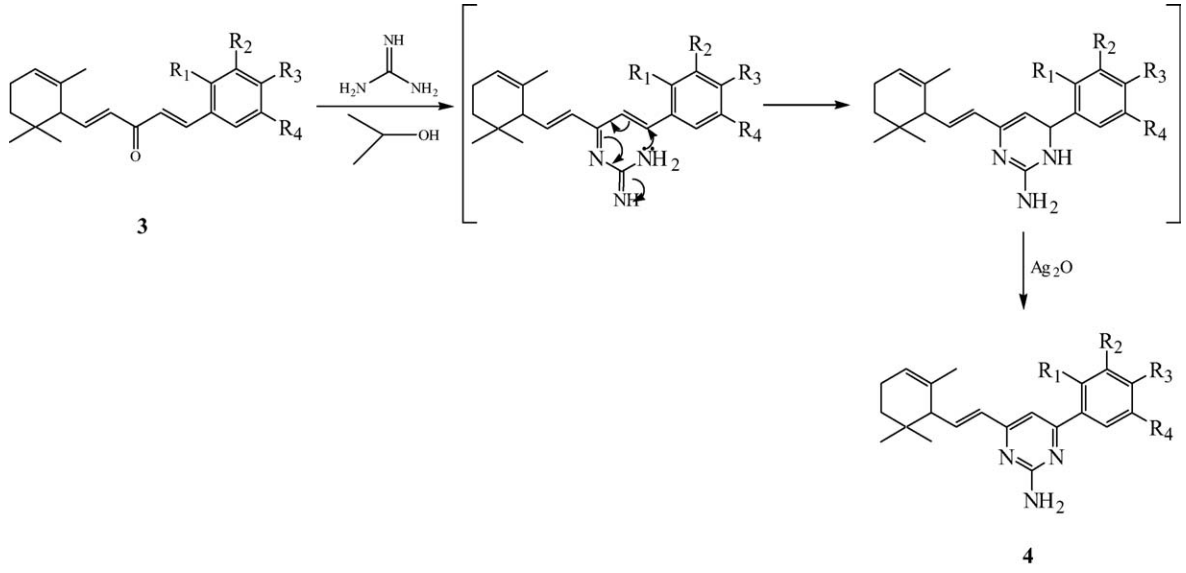
3.1.1. Parasite

The WHO reference strain of *Leishmania donovani* (MHOM/IN/80/Dd8) obtained from Imperial College, London (UK) in 1979 has been maintained since then in this laboratory in vitro as promastigotes in Medium 199 (Sigma Chemical Co., USA) supplemented with 10% fetal calf serum (GIBCO) and as amastigotes in golden hamsters.

3.2. In vitro assay

3.2.1. For extracellular (against promastigotes) leishmanicidal activity

The effect of compounds on the viability of *Leishmania* promastigotes was assessed by monitoring the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide] metabolism [17] (Sigma Chemical Co.) after a 96 h culture period in



Scheme 2.

the presence of the respective compounds. Parasites in stationary culture stage were seeded at 1×10^6/100 μl medium 199 per well in 96-well flat bottom microtitre plates (Cellstar). Further 100 μl of medium 199 per well with different concentrations of test compounds or drug standard, dissolved in DMSO were added in triplicate to achieve desired concentrations (12.5–200 μg ml^{-1}). Parallel dilutions of DMSO alone did not affect the parasite growth. The plates were incubated at 25 °C for 92 h prior to MTT (20 μl per well of a 5 mg ml^{-1} PBS stock) addition and then for further 4–5 hours. MTT processing was stopped and formazan crystals solubilized by adding 50 μl per well acidified 20% SDS (Qualigens, India) and incubating overnight at 37 °C. The relative amount of formazan per well produced by viable cells was measured photometrically at 570 nm. Two independent experiments were performed for the determination of sensitivity of each compound. As a control, the activity of each compound was determined, and no substantial interaction was found.

4. Results and discussion

The leishmanicidal activity of aryl substituted terpenyl pyrimidines **4** (**a**–**p**) was studied in vitro on *L. donovani* promastigotes. Substitution on the aryl ring has a profound effect on the leishmanicidal activity. Most of the compounds having methoxy substitution on the aromatic ring are either inactive or have very poor activity. However, compound **4i** (Table 1) having benzyloxy substitution on the aromatic ring showed IC_{50} and IC_{90} values as 35 ± 1.5 and 75 ± 2.0 μg ml^{-1}, respectively. Compounds having electron withdrawing halogen substitution at *p*-position on aromatic ring also showed respective figures of IC_{50} value as 35 ± 0.5 and IC_{90} value as 60 ± 2. 0 μg ml^{-1} in **4c**. Comparatively better profile was found in compound **4l** having *p*-nitro substitution which showed IC_{50} value as 25 ± 1.7 and IC_{90} value as 50 ± 3.5 μg ml^{-1}. However, none of the compound tested found better than pentamidine. Further synthesis of new aryl substituted terpenyl pyrimidines and in vitro screening against *L. donovani* promastigotes would be necessary to find improved drug candidates for 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 mass spectra were recorded on a Jeol JMS-D-300 spectrometer with

Table 1
Evaluation of in vitro antileishmanial activity of compounds against promastigotes by MTT assay

Compounds	Mean IC values (μg ml^{-1}) ± S.E. (*N*)	
	IC_{50}	IC_{90}
4a	100 ± 2.0	250 ± 1.5
4b	Inactive	Inactive
4c	35 ± 0.5	60 ± 2.0
4d	60 ± 3.0	200 ± 3.5
4e	50 ± 1.2	250 ± 2.5
4f	Inactive	Inactive
4g	Inactive	Inactive
4h	Inactive	Inactive
4i	35 ± 1.5	75 ± 2.0
4j	Inactive	Inactive
4k	Inactive	Inactive
4l	25 ± 1.7	50 ± 3.5
4m	75 ± 2.3	250 ± 2.8
4n	Inactive	Inactive
4o	Inactive	Inactive
4p	Inactive	Inactive
Pentamidine	2.5 ± 0.12	5.0 ± 0.35

N: pooled data of two independent experiments.

the ionization potential of 70 eV. Elemental analyses were carried out on a Carlo-Erba EA 1108 instrument.

5.1. General procedure for the synthesis of 1-(3,4-dimethoxyphenyl)-5-(2′,6′,6′-trimethyl-cyclohex-2′-en-1′-yl)-pent-1,4-diene-3-one (**3a**)

A mixture of α-ionone (1.92 g, 2.04 ml, 10 mmol), 3,4-dimethoxybenzaldehyde (1.83 g, 11 mmol), cetyltrimethyl ammonium bromide (0.14 g, 1 mmol), sodium hydroxide (1.0 g, 30 mmol) and water (50 ml) was stirred at room temperature for 24 h. After completion of the reaction (TLC monitoring), it was extracted with ethylacetate (2 × 50 ml). The combined organic extract was washed with water (2 × 50 ml), brine solution (50 ml), dried (Na_2SO_4), and the solvent was removed in vacuo. The crude product was purified by column chromatography (SiO_2, 60–120 mesh). Elution with 3% ethylacetate in hexane furnished dark yellow solid which on crystallization (ether/hexane) gave **3a**, as a pale yellow crystalline solid (2.55 g, 75%). M.p. 110–111 °C. IR (KBr, cm^{-1}) 2956, 1655, 1588, 1509. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.88 (s, 3H), 0.94 (s, 3H), 1.20 (m, 2H), 1.60 (s, 3H), 2.00 (m, 2H), 2.30 (d, j = 10.00 Hz, 1H), 3.90 (s, 3H), 5.50 (m, 1H), 6.40 (d, j = 16.00 Hz, 1H), 6.80 (m, 3H), 7.10 (m, 2H), 7.60 (d, j = 16.00 Hz, 1H). ^{13}C NMR ($CDCl_3$, 200 MHz) δ 23.283 (q), 23.460 (t), 27.279 (q), 28.238 (q), 31.641 (t), 33.051 (s), 54.960 (d), 2 × 53.352 (q), 110.436 (d), 111.550 (d), 122.966 (d), 123.368 (d), 123.616 (d), 128.250 (s), 130.721 (d), 132.495 (s), 143.509 (d), 148.694 (d), 149.671 (s), 151.716 (s) 189.151 (s). MS: (*m*/*e*) 341 (M^+ + 1). Analysis calculated for $C_{22}H_{28}O_3$: C, 74.56, H, 8.16. Found: C, 74.86; H, 8.29.

5.1.1. 1-(3,4,5-Trimethoxyphenyl)-5-(2′,6′,6′-trimethyl-cyclohex-2′-en-1′-yl)-pent-1,4-dien-3-one (**3b**)

Yield: 72%. M.p. 85–86 °C; IR (KBr, cm^{-1}) 3017, 2962, 1654, 1623, 1586. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.88 (s, 3H), 0.95 (s, 3H), 1.20 (m, 2H), 1.55 (s, 3H), 2.05 (m, 2H), 2.30 (d, j = 10.00 Hz, 1H), 3.85 (s, 9H), 5.50 (m, 1H), 6.40 (d, j = 16.00 Hz, 1H), 6.80 (m, 4H), 7.60 (d, j = 16.00 Hz, 1H). ^{13}C NMR ($CDCl_3$, 200 MHz) δ 23.295 (t), 23. 464 (q), 27.277 (q), 28.268 (q), 31.619 (t), 33.080 (s), 54.986 (d), 2 × 56.618 (q), 61.361 (q), 2 × 106.006 (d), 109.977 (s), 123.060 (d), 124.971 (d), 130.533 (d), 130.737 (s), 132.421 (s), 140.754 (s), 143.526 (d), 149.157 (d), 153.863 (s), 189.034 (s). MS: (*m*/*e*) 371 (M^+ + 1).

5.1.2. 1-(4-Chlorophenyl)-5-(2′,6′,6′-trimethyl-cyclohex-2′-en-1′-yl)-pent-1,4-dien-3-one (**3c**)

Yield: 80%. M.p. 86–87 °C. IR (KBr, cm^{-1}) 2960, 2924, 2869, 1658, 1598. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.90 (s, 3H), 0.95 (s, 3H), 1.20 (m, 2H), 1.55 (s, 3H), 2.05 (m, 2H), 2.30 (d, j = 10.00 Hz, 1H), 5.50 (m, 1H), 6.35 (d, j = 16.00 Hz, 1H), 6.80 (dd, j = 16.00, 10.00 Hz, 1H), 7.00 (d, j = 16.00 Hz, 1H), 7.50 (dd, 4H), 7.65 (d, j = 16.00 Hz, 1H). ^{13}C NMR ($CDCl_3$, 200 MHz) δ 23.277 (q), 23.464 (t), 27.259 (q) 28.301 (q), 31.614 (t), 33.093 (s), 55.016 (d), 123.145 (d), 125.549 (d), 2 × 129.590 (d), 2 × 129.854 (d), 130.943 (d), 132.344 (s), 133.765 (s), 136.629 (s), 141.929 (d), 149.573 (d), 189.040 (s). MS: (*m*/*e*) 315 (M^+ + 1). Analysis calculated for $C_{20}H_{23}OCl$: C, 76.29; H, 7.36. Found: C, 76.17; H, 7.57.

5.1.3. 1-(4-Fluorophenyl)-5-(2′,6′,6′-trimethyl-cyclohex-2′-en-1′-yl)-pent-1,4-dien-3-one (**3d**)

Yield: 77%. M.p. 185–187 °C. IR (KBr, cm^{-1}) 3016, 2959, 2921, 2867, 1658, 1598, 1509. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.89 (s, 3H), 0.94 (s, 3H), 1.28 (m, 2H), 1.45 (m, 1H), 1.59 (s, 3H), 2.05 (m, 2H), 2.40 (d, j = 10.00 Hz, 1H), 5.50 (m, 1H), 6.38 (d, j = 16.00 Hz, 1H), 6.80 (dd, j = 16.00, 10.00 Hz, 1H), 7.00 (d, j = 16.00 Hz, 1H), 7.15 (m, 2H), 7.65 (m, 2H), 7.70 (d, j = 16.00 Hz, 1H). ^{13}C NMR ($CDCl_3$, 200 MHz) δ 23.242 (q), 23.448 (t), 27.237 (q) 28.246 (q), 31.616 (t), 33.055 (s), 54.986 (d), 116.215 (d), 116.505 (d), 123.081 (d), 124.880 (d), 130.480 (d), 130.649 (d), 130.964 (d), 132.499 (s), 142.011 (d), 149.302 (d), 161.835 (s), 166.832 (s), 189.060 (s). MS: (*m*/*e*) 299 (M^+ + 1).

5.1.4. 1-(4-Benzyloxyphenyl)-5-(2′,6′,6′-trimethyl-cyclohex-2-en-1′-yl)-pent-1,4-dien-3-one (**3e**)

Yield: 89%. M.p. 81–82 °C. IR (KBr, cm^{-1}) 2913, 1664, 1625, 1583, 1564. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.90 (s, 3H), 0.95 (s, 3H), 1.25 (m, 1H), 1.55 (m, 1H), 1.60 (s, 3H), 2.10 (m, 2H), 2.35 (d, j = 10.00 Hz, 1H), 5.10 (s, 2H), 5.55 (m, 1H), 6.40 (d, j = 15.00 Hz, 1H), 6.80 (dd, j = 15.00, 10.00 Hz, 1H), 7.00 (m, 2H), 7.45 (m, 6H). ^{13}C NMR ($CDCl_3$, 200 MHz) δ 23.286 (q), 23.480 (t), 27.298 (q), 28.258 (q), 31.681 (t), 33.068 (s), 54.995 (d), 70.530 (t), 2 × 115.696 (d), 122.974 (d), 123.234 (d), 2 × 127.858 (d), 126.255 (s), 128.556 (d), 2 × 129.064 (d), 2 × 130.441 (d), 131.100 (d), 132.543 (s), 136.874 (s), 143.166 (d), 148.658 (d), 161.105 (s), 189.335 (s). MS: (*m*/*e*) 387 (M^+ + 1). Analysis calculated for $C_{27}H_{30}O_2$: C, 83.89, H, 7.82. Found: C, 83.29; H, 7.85.

5.1.5. 1-(4-Nitro-phenyl)-5-(2′, 6′, 6′-trimethyl-cyclohex-2-en-1′-yl)-pent-1,4-dien-3-one (**3f**)

Yield: 67%. M.p. 125–127 °C. IR (KBr, cm^{-1}) 2959, 2921, 1658, 1598, 1509. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.86 (s, 3H), 0.96 (s, 3H), 1.30 (m, 2H), 1.60 (s, 3H), 2.08 (m, 2H), 2.37 (d, j = 10.00 Hz, 1H), 5.54 (m, 1H), 6.40 (d, j = 16.00 Hz, 1H), 6.80 (dd, j = 16.00, 10.00 Hz, 1H), 7.10 (d, j = 16.00 Hz, 1H), 7.62 (m, 2H), 7.72 (d, j = 16.00 Hz, 1H), 8.26 (d, j = 8.00 Hz, 2H). ^{13}C NMR ($CDCl_3$, 200 MHz) δ 23.264 (q), 23.454 (t), 27.223 (q), 28.339 (q), 31.564 (t), 33.137 (s), 55.069 (d), 123.346 (d), 124.550 (d), 2 × 128.581 (d), 2 × 129.220 (d), 130.864 (d), 132.131 (s), 140.229 (d), 141.508 (s), 148.867 (s), 150.606 (d), 188.471 (s). MS: (*m*/*e*) 325 (M^+ + 1).

5.1.6. 1-(2-Nitro-phenyl)-5-(2′,6′,6′-trimethyl-cyclohex-2-en-1′-yl)-pent-1,4-dien-3-one (**3g**)

Yield: 73%. M.p. 115–117 °C. IR (KBr, cm^{-1}) 2968, 2911, 1638, 1558, 1509. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.88 (s, 3H), 0.98 (s, 3H), 1.20 (m, 2H), 1.60 (s, 3H), 2.00 (m, 2H), 2.35 (d, j = 10.00 Hz, 1H), 5.52 (m, 1H), 6.40 (d, j = 16.00 Hz, 1H), 6.86 (dd, j = 16.00, 10.00 Hz, 1H), 7.54 (d, j = 16.00 Hz, 1H), 7.67 (m, 2H), 7.72 (d, j = 16.00 Hz, 1H), 8.00 (d, j = 8.00 Hz,

2H). ^{13}C NMR ($CDCl_3$, 200 MHz) δ 23.205 (q), 23.426 (t), 27.181 (q) 28.260 (q), 31.540 (t), 33.044 (s), 55.020 (d), 123.190 (d), 125.301 (d), 129.506 (d), 130.641 (d), 132.190 (s), 133.904 (d), 134.107 (d), 134.450 (d), 138.447 (d), 141.508 (s), 148.893 (s), 150.606 (d), 188.918 (s). MS: (*m*/*e*) 325 ($M^+ + 1$).

*5.1.7. 1-(3-Nitro-phenyl)-5-(2′,6′,6′-trimethyl-cyclohex-2-en-1′-yl)-pent-1,4-dien-3-one (**3h**)*

Yield: 70%. M.p. 122–124 °C. IR (KBr, cm^{-1}) 2977, 2908, 1638, 1567, 1509. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.89 (s, 3H), 0.96 (s, 3H), 1.30 (m, 2H), 1.60 (s, 3H), 2.00 (m, 2H), 2.37 (d, j = 10.00 Hz, 1H), 5.54 (m, 1H), 6.39 (d, j = 16.00 Hz, 1H), 6.88 (dd, j = 16.00, 10.00 Hz, 1H), 7.28 (d, j = 16.00 Hz, 1H), 7.68 (d, j = 16.00 Hz, 1H), 7.87 (d, j = 16.00 Hz, 2H), 8.23 (d, j = 8.00 Hz, 2H). ^{13}C NMR ($CDCl_3$, 200 MHz) δ 23.257 (q), 23.449 (t), 27.230 (q) 28.333 (q), 31.574 (t), 33.127 (s), 55.073 (d), 122.719 (d), 123.312 (d), 124.847 (d), 127.535 (d), 130.352 (d), 130.943 (d), 132.164 (s), 134.483 (d), 137.113 (s), 140.314 (d), 149.128 (s), 150.395 (d), 188.484 (s). MS: (*m*/*e*) 325 ($M^+ + 1$).

*5.2. General procedure for the synthesis of 4-(3,4-dimethoxy-phenyl)-6-[2-(2,6,6-trimethyl-cyclohex-2-enyl)-ethenyl]-pyrimidin-2-ylamine (**4a**)*

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. To the filtrate was added **3a** (3.86 g, 10 mmol) and silver oxide (4.64 g, 20 mmol) and the reaction mixture was refluxed at 100–110 °C for 16 h. It was filtered through celite and the filtrate was extracted with ethylacetate (25 ml × 2). Combined extract was washed with water (25 ml × 2), brine solution (25 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 20% ethylacetate in hexane furnished **4a** as a white crystalline solid (1.59 g, 42%). M.p 101–102 °C. IR (KBr, cm^{-1}) 3177, 2957, 1569, 1522, 1354. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.90 (s, 3H), 0.95 (s, 3H), 1.24 (m, 2H), 1.62 (s, 3H), 2.05 (m, 2H), 2.34 (d, j = 8.00 Hz, 1H), 3.93 (s, 3H), 3.97 (s, 3H), 5.02 (m, 2H), 5.94 (m, 1H), 6.30 (d, j = 16.00 Hz, 1H), 6.80 (dd, j = 16.00, 10.00 Hz, 1H), 6.90 (s, 2H), 7.60 (m, 2H). ^{13}C NMR ($CDCl_3$, 200 MHz) δ 23.214 (q), 23.349 (t), 27.118 (q), 28.167 (q), 31.559 (t), 32.884 (s), 54.937 (d), 56.187 (q), 56.240 (q), 104.727 (d), 110.217 (d), 111.133 (d), 120.259 (d), 122.153 (d), 130.435 (d), 130.670 (s), 133.276 (s), 140.449 (d), 149.408 (s), 151.342 (s), 163.507 (s), 154.323 (s), 165.462 (s). MS: (*m*/*e*) 380 ($M^+ + 1$).

*5.2.1. 4-(3,4,5-Trimethoxy-phenyl)-6-[2-(2,6,6-trimethyl-cyclohex-2-enyl)-ethenyl]-pyrimidin-2-ylamine (**4b**)*

Yield: 45%. M.p. 124–125 °C. IR (KBr, cm^{-1}) 3399, 2957, 1565, 1364, 1092. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.90 (s, 3H), 0.95 (s, 3H), 1.25(m, 2H), 1.60 (s, 3H), 2.05 (m, 2H), 2.30 (d, j = 10.00 Hz, 1H), 5.00 (m, 2H), 5.45 (m, 1H), 6.30 (d, j = 16.00 Hz, 1H), 6.80 (dd, j = 16.00, 10.00 Hz, 1H), 6.90 (s, 1H), 7.45 (d, 2H), 7.95 (d, 2H). ^{13}C NMR ($CDCl_3$, 200 MHz) δ 23.393 (q), 23.537 (t), 27.301 (q), 28.379 (q), 31.741 (t), 33.088 (s), 55.139 (d), 105.115 (d), 122.447 (d), 2 × 128.738 (d), 2 × 129.276 (d), 130.453 (d), 133.345 (s), 136.542 (s), 136.829 (s), 141.279 (s), 163.785 (s) 164.855 (s), 165.052 (s). MS: (*m*/*e*) 354 ($M^+ + 1$).

*5.2.2. 4-(4-Chloro-phenyl)-6-[2-(2,6,6-trimethyl-cyclohex-2-enyl)-ethenyl]-pyrimidin-2-ylamine (**4c**)*

Yield: 48%. M.p. 151–152 °C. IR (KBr, cm^{-1}) 3324, 3174, 1565, 1364, 1092. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.90 (s, 3H), 0.95 (s, 3H), 1.25 (m, 2H), 1.60 (s, 3H), 2.05 (m, 2H), 2.30 (d, j = 10.00 Hz, 1H), 5.10 (m, 2H), 5.45 (m, 1H), 6.30 (d, j = 16.00 Hz, 1H), 6.80 (dd, j = 16.00, 10.00 Hz, 1H), 6.90 (s, 1H), 7.45 (d, 2H), 7.95 (d, 2H). ^{13}C NMR ($CDCl_3$, 200 MHz) δ 23.393 (q), 23.537 (t), 27.301 (q), 28.379 (q), 31.741 (t), 33.088 (s), 55.139 (d), 105.115 (d), 122.447 (d), 2 × 128.738 (d), 2 × 129.276 (d), 130.453 (d), 133.345 (s), 136.542 (s), 136.829 (s), 141.279 (d), 163.785 (s) 164.855 (s), 165.052 (s). MS: (*m*/*e*) 354 ($M^+ + 1$). Analysis calculated for $C_{21}H_{24}N_3Cl$: C, 71.37, H, 6.84, N, 11.89, Cl, 10.03. Found: C, 71.60, H, 6.99, N, 12.17, Cl, 10.22.

*5.2.3. 4-(4-Fluro-phenyl)-6-[2-(2,6,6-trimethyl-cyclohex-2-enyl)-ethenyl]-pyrimidin-2-ylamine (**4d**)*

Yield: 46%. M.p. 149–150 °C. IR (KBr, cm^{-1}) 3338, 3175, 1572, 1364, 1160. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.90 (s, 3H), 0.95 (s, 3H), 1.25 (m, 1H), 1.50 (m, 1H), 1.59 (s, 3H), 2.05 (m, 2H), 2.33 (d, 1H), 5.29 (m, 2H), 5.30 (m, 1H), 6.29 (d, j = 16.00 Hz, 1H), 6.79 (dd, j = 16.00, 10.00 Hz, 1H), 6.90 (s, 1H), 7.12 (m, 2H), 7.99 (m, 2H). ^{13}C NMR ($CDCl_3$, 200 MHz) δ 23.395 (q), 23.536 (t), 27.295 (q), 28.381 (q), 31.737 (t), 33.069 (s), 55.137 (d), 104.978 (d), 115.812 (d), 116.244 (d), 122.426 (d), 2 × 129.345 (d), 130.504 (d), 2 × 133.372 (s), 134.226 (s), 141.109 (d), 163.846 (s) 164.921 (s), 165.029 (s). MS: (*m*/*e*) 338 ($M^+ + 1$).

*5.2.4. 4-(4-Benzyloxy-phenyl)-6-[2-(2,6,6-trimethyl-cyclohex-2-enyl)-ethenyl]-pyrimidin-2-ylamine (**4e**)*

Yield: 40%. M.p. 110–111 °C. IR (KBr, cm^{-1}) 3019, 2923, 1574, 1530, 1371. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.90 (s, 3H), 0.95 (s, 3H), 1.30 (m, 2H), 1.70 (s, 3H), 2.40 (d, j = 10.00 Hz, 1H), 5.10 (m, 2H), 5.15 (s, 2H) 5.50 (m, 1H), 6.30 (d, j = 16.00 Hz, 1H), 6.75 (dd, j = 16.00, 10.00 Hz, 1H), 6.90 (s, 1H), 7.05 (d, j = 9.00 Hz, 2H), 7.40 (m, 5H), 8.00 (d, j = 9.00 Hz, 2H). ^{13}C NMR ($CDCl_3$, 200 MHz) δ 23.451 (q), 23.574 (t), 27.347 (q), 28.410 (q), 31.782 (t), 33.086 (s), 55.154 (d), 104.647 (d), 2 × 115.374 (d), 122.371 (d), 2 × 127.905 (d), 128.489 (d), 129.038 (d), 4 × 130.701 (d), 133.492 (s), 137.078 (s), 140.687 (d), 161.131 (s), 163.837 (s), 164.562 (s), 165.641 (s). MS: (*m*/*e*) 426 ($M^+ + 1$).

*5.2.5. 4-{4-(3,4-Dimethoxy-phenyl)-6-[2-(2,6,6-trimethyl-cyclohex-2-enyl)-ethenyl]-pyrimidin-2-yl}morpholine (**4f**)*

Yield: 38%. M.p. 123–125 °C. IR (KBr, cm^{-1}) 2954, 2849, 1572, 1541, 1357. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.95 (s, 3H),

1.00 (s, 3H), 1.30 (m, 2H), 1.60 (s, 3H), 2.10 (m, 2H), 2.40 (d, j = 10.00 Hz, 1H), 3.90 (m, 4H), 3.95 (s, 3H), 4.00 (s, 4H), 5.55 (m, 1H), 6.35 (d, j = 16.00 Hz, 1H), 6.85 (dd, j = 16.00, 10.00 Hz, 1H), 6.90 (s, 1H), 7.00 (d, j = 8.00 Hz, 1H), 7.70 (d, j = 8.00 Hz, 1H), 7.70 (s, 1H). ^{13}C NMR ($CDCl_3$, 200 MHz) δ 24.258 (q), 24.546 (t), 28.573 (q), 29.475 (q), 33.194 (t), 34.345 (s), 2 × 46.091 (t), 56.293 (d), 57.313 (q), 57.467 (q), 2 × 68.697 (t), 104.864 (d), 111.708 (d), 112.892 (d), 121.778 (d), 123.3907 (d), 132.425 (d), 132.592 (s), 134.968 (s), 141.295 (d), 150.776 (s), 152.777 (s), 163.760 (s), 165.099 (s), 165.974 (s). MS: (m/e) 450 (M^+ + 1).

*5.2.6. 4-{4-(3,4,5-Trimethoxy-phenyl)-6-[2-(2,6,6-trimethyl-cyclohex-2-enyl)-ethenyl]-pyrimidin-2-yl}morpholine (**4g**)*

Yield: 40%. M.p. 123–125 °C. IR (KBr, cm^{-1}) 2960, 2856, 1542, 1502, 1357. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.95 (s, 3H), 1.00 (s, 3H), 1.30 (m, 2H), 1.60 (s, 3H), 2.10 (m, 2H), 2.40 (d, j = 10.00 Hz, 1H), 3.90 (m, 4H), 3.95 (s, 3H), 4.00 (s, 4H), 5.55 (m, 1H), 6.35 (d, j = 16.00 Hz, 1H), 6.85 (dd, j = 16.00, 10.00 Hz, 1H), 6.90 (s, 1H), 7.00 (d, j = 8.00 Hz, 1H), 7.70 (d, j = 8.00 Hz, 1H), 7.70 (s, 1H). ^{13}C NMR ($CDCl_3$, 200 MHz) δ 23.244 (q), 23.427 (t), 27.248 (q), 28.168 (q), 31.885 (t), 33.040 (s), 2 × 44.790 (t), 53.849 (d), 54.981 (q), 56.561 (q), 56.678 (q), 2 × 67.334 (t), 104.065 (d), 104.962 (d), 122.235 (d), 131.022 (d), 133.569 (s), 133.978 (s), 140.202 (d), 140.717 (s), 153.745 (s), 153.841 (s), 162.406 (s), 163.911 (s), 164.835 (s). MS: (m/e) 480 (M^+ + 1).

*5.2.7. 4-{4-(4-Chloro-phenyl)-6-[2-(2,6,6-trimethyl-cyclohex-2-enyl)-ethenyl]-pyrimidin-2-yl}morpholine (**4h**)*

Yield: 45%. IR (KBr, cm^{-1}) 3013, 2959, 1542, 1362, 1113. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.90 (s, 3H), 0.96 (s, 3H), 1.25 (m, 2H), 1.60 (s, 3H), 2.10 (m, 2H), 2.35 (d, j = 10.00 Hz, 1H), 3.80 (m, 4H), 3.90 (m, 4H), 5.50 (m, 1H), 6.30 (d, j = 16.00 Hz, 1H), 6.80 (dd, j = 16.00, 10.00 Hz, 1H), 6.90 (s, 1H), 7.40 (d, j = 8.00 Hz, 2H), 8.00 (d, j = 8.00 Hz, 2H). ^{13}C NMR ($CDCl_3$, 200 MHz) δ 23.444 (q), 23.544 (t), 27.390 (q), 28.236 (q), 31.922 (t), 33.092 (s), 2 × 44.782 (t), 55.049 (d), 67.162 (t), 67.400 (t), 103.664 (d), 122.302 (d), 2 × 128.690 (d), 2 × 129.163 (d), 130.036 (d), 133.583 (s), 136.663 (s), 136.942 (s), 140.556 (d), 162.571 (s), 163.861 (s), 164.365 (s). MS: (m/e) 424 (M^+ + 1).

*5.2.8. 4-{4-(4-Benzyloxy-phenyl)-6-[2-(2,6,6-trimethyl-cyclohex-2-enyl)-ethenyl]-pyrimidin-2-yl}morpholine (**4i**)*

Yield: 42%. IR (KBr, cm^{-1}) 3014, 2958, 1596, 1538, 1361. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.88 (s, 3H), 0.95 (s, 3H), 1.25 (m, 2H), 1.63 (s, 3H), 2.40 (d, j = 10.00 Hz, 1H), 3.80 (m, 4H), 3.90 (m, 4H), 5.10 (m, 2H), 5.12 (s, 2H) 5.50 (m, 1H), 6.37 (d, j = 16.00 Hz, 1H), 6.75 (dd, j = 16.00, 10.00 Hz, 1H), 6.90 (s, 1H), 7.00 (d, j = 9.00 Hz, 2H), 7.35 (m, 5H), 8.00 (d, 2H). ^{13}C NMR ($CDCl_3$, 200 MHz) δ 22.050 (q), 22.140 (t), 25.878 (q), 26.825 (q), 30.261 (t), 31.639 (s), 43.394 (t), 53.563 (d), 66.019 (t), 69.088 (t), 101.897 (d), 113.841 (d), 114.267 (d), 121.822 (d), 2 × 126.424 (d), 127.026 (d), 127.117 (d), 127.628 (d), 129.011 (d), 129.679 (d), 129.843 (d), 131.115 (s), 132.294 (s), 135.696 (s), 138.532 (d), 141.728 (d), 147.194 (d), 159.675(s), 161.098 (s), 162.472 (s), 163.154 (s). MS: (m/e) 496 (M^+ + 1).

*5.2.9. 4-{4-(4-Fluro-phenyl)-6-[2-(2,6,6-trimethyl-cyclohex-2-enyl)-ethenyl]-pyrimidin-2-yl}morpholine (**4j**)*

Yield: 49%. IR (KBr, cm^{-1}) 2920, 2959, 1544, 1363. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.90 (s, 3H), 0.95 (s, 3H), 1.27 (m, 1H), 1.60 (s, 3H), 2.06 (m, 2H), 2.34 (d, j = 10.00 Hz, 1H), 3.79 (m, 4H), 3.88 (m, 4H), 5.50 (m, 1H), 6.31 (d, j = 16.00 Hz, 1H), 6.80 (dd, j = 16.00, 10.00 Hz, 1H), 6.90 (s, 1H), 7.12 (m, 2H), 8.04 (m, 2H). ^{13}C NMR ($CDCl_3$, 200 MHz) δ 23.438 (q), 23.549 (t), 27.387 (q), 28.223 (q), 31.932 (t), 33.085 (s), 2 × 44.793 (t), 55.047 (d), 2 × 67.409 (t), 103.591 (d), 116.116 (d), 116.668 (d), 122.276 (d), 129.260 (d), 129.429 (d), 130.642 (d), 131.086 (s), 133.616 (s), 134.636 (s), 140.422 (d), 162.512 (s) 164.012 (s), 164.250 (s). MS: (m/e) 408 (M^+ + 1).

*5.2.10. 4-(4-Nitro-phenyl)-6-[2-(2,6,6-trimethyl-cyclohex-2-enyl)-ethenyl]-pyrimidin-2-ylamine (**4k**)*

Yield: 48%. M.p. 176–178 °C. IR (KBr, cm^{-1}) 3166, 2955, 1570, 1546, 1345. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.91 (s, 3H), 0.96 (s, 3H), 1.30 (m, 2H), 1.62 (s, 3H), 2.10 (m, 2H), 2.40 (d, 1H), 5.08 (m, 2H), 5.51 (s, 1H), 6.33 (d, j = 16.00 Hz, 1H), 6.90 (dd, j = 16.00, 10.00 Hz, 1H), 7.10 (s, 1H), 8.25 (dd, 4H). ^{13}C NMR ($CDCl_3$, 200 MHz) δ 23.382 (q), 23.531 (t), 27.277 (q), 28.401 (q), 31.705 (t), 33.114 (s), 55.158 (d), 105.896 (d), 122.596 (d), 2 × 124.241 (d), 2 × 128.342 (d), 130.168 (d), 133.189 (s), 142.074 (s), 144.108 (s), 149.323 (s), 163.504 (s) 163.848 (s), 165.586 (s). MS: (m/e) 365 (M^+ + 1). Analysis calculated for $C_{21}H_{24}N_4O_2$: C, 69.20, H, 6.63, N, 15.37. Found: C, 69.89, H, 6.76, N, 15.48.

*5.2.11. 4-{4-(4-Nitro-phenyl)-6-[2-(2,6,6-trimethyl-cyclohex-2-enyl)-ethenyl]-pyrimidin-2-yl}morpholine (**4l**)*

Yield: 43%. m.p. 194–196 °C. IR (KBr, cm^{-1}) 2961, 1545, 1486, 1356. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.91 (s, 3H), 0.96 (s, 3H), 1.30 (m, 2H), 1.65 (s, 3H), 2.10 (m, 2H), 2.40 (d, j = 10.00 Hz, 1H), 3.80 (m, 4H), 4.00 (m, 4H), 5.55 (bs, 1H), 6.35 (d, j = 16.00 Hz, 1H), 6.85 (dd, j = 16.00, 10.00 Hz, 1H), 7.00 (s, 1H), 8.30 (dd, 4H). ^{13}C NMR ($CDCl_3$, 200 MHz) δ 23.435 (q), 23.545 (t), 27.364 (q), 28.275 (q), 31.877 (t), 33.122 (s), 2 × 44.754 (t), 55.077 (d), 2 × 67.360 (t), 104.391 (d), 122.459 (d), 2 × 124.170 (d), 2 × 128.258 (d), 130.768 (d), 133.421 (s), 141.351 (d), 144.549 (s), 149.262 (s), 162.508 (s) 162.590 (s), 164.899 (s). MS: (m/e) 435 (M^+ + 1). Analysis calculated for $C_{25}H_{30}N_4O_3$: C, 69.10, H, 6.95, N, 12.89. Found: C, 69.31, H, 7.12, N, 13.14.

*5.2.12. 4-(2-Nitro-phenyl)-6-[2-(2,6,6-trimethyl-cyclohex-2-enyl)-ethenyl]-pyrimidin-2-ylamine (**4m**)*

Yield: 46%. M.p. 218–220 °C. IR (KBr, cm^{-1}) 3310, 3196, 1575, 1535, 1363. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.89 (s, 3H), 0.95 (s, 3H), 1.30 (m, 2H), 1.60 (s, 3H), 2.05 (m, 2H), 2.40 (d, j = 10.00 Hz, 1H), 5.00 (m, 2H), 5.50 (bs, 1H), 6.30 (d, j = 16.00 Hz, 1H), 6.75 (s, 1H), 6.85 (dd, j = 16.00, 10.00 Hz, 1H), 7.65 (m, 3H), 7.95 (d, j = 8.00 Hz, 1H). ^{13}C

NMR ($CDCl_3$, 200 MHz) δ 23.393 (q), 23.511 (t), 27.284 (q), 28.375 (q), 31.700 (t), 33.105 (s), 55.101 (d), 107.279 (d), 122.500 (d), 124.784 (d), 130.114 (d), 130.261 (d), 131.115 (s), 132.900 (d), 133.244 (s), 141.975 (d), 149.342 (s), 163.294 (s), 164.871 (s), 165.199 (s). MS: (*m*/*e*) 365 (M^+ + 1). Analysis calculated for $C_{21}H_{24}N_4O_2$: C, 69.20, H, 6.63, N, 15.37. Found: C, 69.41, H, 6.70, N, 15.55.

*5.2.13. 4-{4-(2-Nitro-phenyl)-6-[2-(2,6,6-trimethyl-cyclohex-2-enyl)-ethenyl]-pyrimidin-2-yl}morpholine (**4n**)*

Yield: 40%. IR (KBr, cm^{-1}) 3019, 2962, 1544, 1363. ^1H NMR ($CDCl_3$, 200 MHz) δ 0.89 (s, 3H), 0.95 (s, 3H), 1.30 (bs, 2H), 1.70 (s, 3H), 2.10 (bs, 2H), 2.40 (d, j = 10.00 Hz, 1H), 3.80 (bs, 8H), 5.50 (bs, 1H), 6.30 (d, j = 16.00 Hz, 1H), 6.70 (s, 1H), 6.80 (dd, j = 16.00, 10.00 Hz, 1H), 7.60 (m, 3H), 8.00 (d, 1H). ^{13}C NMR ($CDCl_3$, 200 MHz) δ 23.420 (q), 23.521 (t), 27.365 (q), 28.206 (q), 31.892 (t), 33.097 (s), 2 × 44.646 (t), 55.023 (d), 2 × 67.293 (t), 105.439 (d), 122.366 (d), 2 × 124.440 (d), 2 × 129.541 (d), 130.762 (d), 133.449 (s), 141.209 (d), 141.199 (s), 150.210 (s), 161.911 (s) 163.371 (s), 164.742 (s). MS: (*m*/*e*) 435 (M^+ + 1).

*5.2.14. 4-{4-(3-Nitro-phenyl)-6-[2-(2,6,6-trimethyl-cyclohex-2-enyl)-ethenyl]-pyrimidin-2-yl}morpholine (**4o**)*

Yield: 41%. IR (KBr, cm^{-1}) 2958, 2922, 1540, 1352. ^1H NMR ($CDCl_3$, 200 MHz) δ 0.90 (s, 3H), 0.99 (s, 3H), 1.27 (m, 2H), 1.65 (s, 3H), 2.10 (bs, 2H), 2.37 (d, j = 10.00 Hz, 1H), 3.80 (d, 4H), 3.95 (d, 4H), 5.52 (bs, 1H), 6.30 (d, j = 16.00 Hz, 1H), 6.70 (dd, 1H), 6.90 (s, 1H), 7.63 (m, 3H), 8.33 (dd, 1H). MS: (*m*/*e*) 435 (M^+ + 1).

*5.2.15. 4-(3-Nitro-phenyl)-6-[2-(2,6,6-trimethyl-cyclohex-2-enyl)-ethenyl]-pyrimidin-2-ylamine (**4p**)*

Yield: 44%. M.p. 202–204 °C. IR (KBr, cm^{-1}) 3305, 3187, 1580, 1535, 1365. ^1H NMR ($CDCl_3$, 200 MHz) δ 0.98 (s, 3H), 0.95 (s, 3H), 1.25 (m, 2H), 1.659 (s, 3H), 2.00 (bs, 2H), 2.42 (d, j = 10.00 Hz, 1H), 5.50 (bs, 1H), 6.35 (d, j = 16.00 Hz, 1H), 6.73 (dd, 1H), 6.88 (s, 1H), 7.61 (m, 3H), 8.21 (dd, 1H). MS: (*m*/*e*) 365 (M^+ + 1).

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