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Bioorganic & Medicinal Chemistry 13 (2005) 1893–1899
Bioorganic & Medicinal Chemistry

2,4,6-Trisubstituted pyrimidine derivatives as pregnancy interceptive agents

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Received 7 December 2004; revised 14 January 2005; accepted 14 January 2005
Available online 2 February 2005

Abstract—A series of 2,4,6-trisubstituted pyrimidine derivatives was synthesized and evaluated for their in vivo pregnancy interceptive activity in hamsters. Out of the 17 compounds synthesized three compounds showed 100% activity at a dose of 10 mg/kg.

1. Introduction

Interest in the development of non-steroidal post coital or morning after pills dates back to early sixties. In the late 50s the progesterone–estrogen combination pills with 21 days continuous use in a month were introduced for birth control. The pregnancy interceptive drugs appear to manifest its contraceptive action primarily by producing a synchrony between ovum transport and uterine preparation for its reception and do not affect the hypothalamo-pituitary ovarian axis or the embryo. The logical approach therefore is to develop need based agents that would not disturb pituitary or ovarian function but prevent pregnancy by interfering with the preimplantation effects. The knowledge that a critical balance between estrogen and progesterone is essential for the development of fertilized ovum and preparation of uterus for implantation is utilized to develop the envisaged contraceptive. Some others designed and synthesized non-steroidal estrogen antagonists with week estrogenic activity aimed to prevent pregnancy by disturbing the delicate ratio between estrogen and progesterone at the uterine level but without interfering with their synthesis or peripheral levels.[1,2]

Based on this concept a variety of heterocyclic molecules such as thiazoles, oxadiazoles, pyrazoles, isoxazoles, triazoles, isoquinolines and tetrahydro pyridines had been earlier evaluated as pregnancy interceptive agents.[3–10]

2. Chemistry

Dihydro-α-ionone **1** was reacted with different aldehydes (a–n, Fig. 1) in the presence of potassium hydroxide in methanol to afford the corresponding chalcones **2a**–**n**. In case of **2o** dihydro-α-ionone was refluxed with indole-3-carboxaldehyde in the presence of piperidine in methanol to afford the chalcone **2o**. The chalcones **2a**–**o** were further cyclized with guanidine hydrochloride in the presence of sodium isopropoxide (synthesized in situ by adding sodium metal in isopropanol) to afford the 2,4,6-trisubstituted pyrimidines **3a**–**o** as shown in (Scheme 1). Compound **3a** was further reacted with 1-(2-chloro-ethyl)-pyrrolidine and 1-(2-chloro-ethyl)-piperidine in the presence of potassium carbonate and tetra butyl ammonium iodide to afford **4a** and **4b** respectively (Scheme 2). The substitution took place only at the phenolic hydroxyl and not at the amino group (amino group is less basic due to the pyrimidine ring).

3. Biological activity

Syrian golden hamsters of the institute's animal colony weighing 85–120 g were used. Animals were maintained in air-conditioned quarters at 21 ± 2 °C and 60–70%

Keywords: Pregnancy interceptive; Pyrimidines; α-Ionone.
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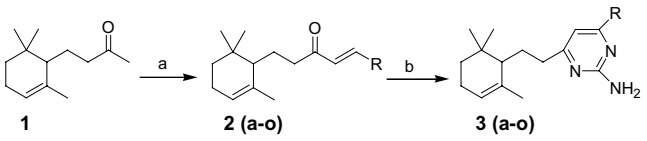
doi:10.1016/j.bmc.2005.01.020



Scheme 1. Reagents and conditions: (a) for **2a–n** different aldehydes, KOH, methanol, 0 °C–rt, 12 h. For **2o**: indole-3-carboxaldehyde, piperidine, methanol, reflux, 12 h. (b) Guanidine hydrochloride, sodium isopropoxide, isopropanol, reflux, 8 h.

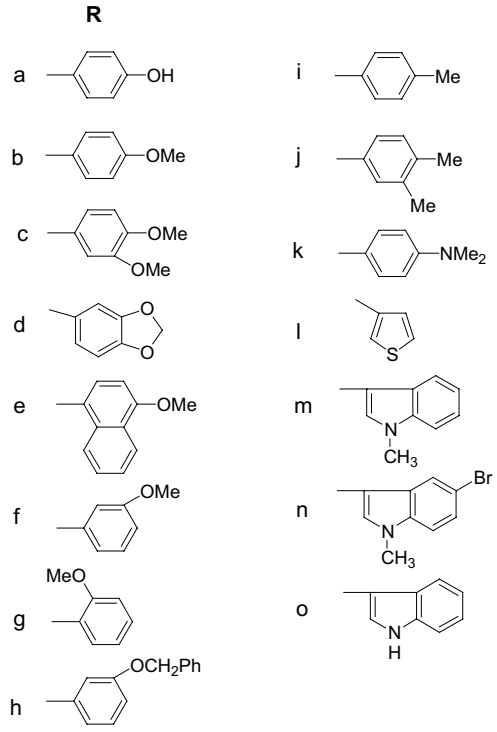
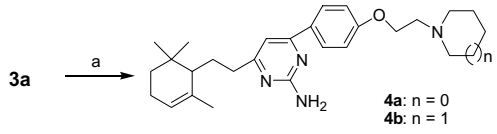


Figure 1.



Scheme 2. Reagents and conditions: (a) 1-(2-chloro-ethyl)-pyrrolidine or 1-(2-chloro-ethyl)-piperidine K_2CO_3, tetrabutylammonium iodide, acetone, reflux, 5 h.

humidity, with a regulated photoperiod (14 h light, 10 h dark) and uniform husbandry conditions were used. They were provided pelleted diet (Lipton India Ltd) and ad lib. tap water. The guidelines for care and use of animals approved by the institute were strictly followed. Regularly cyclic females in the proestrus stage were mated with coeval males (3:1 ratio) of respective species in sterile plastic cages overnight. The presence of spermatozoa in the vaginal smear on the following morning was considered as day 1 of gestration. For testing pregnancy interceptive efficacy the compounds were administered to mated hamsters on days 4–8 postcoitum. Compounds were administered subcutaneously (sc) by initially solubilizing them in 100% ethanol and adding olive oil to them and then the ethanol was evaporated on a water bath. Mated females were injected (sc) with compounds in respective dosage on days 4–8 postcoitum (pc) and autopsied on day 12pc. The numbers of implantations, resorbing foetuses and or endometrial scars were recorded. Potentiality percentage was calculated by dividing the number of animals showing resorbing foetuses, dead foetuses or endometrial scars against the animals showing normal/live embryos. Animals with no sign of implantation or having apparently normal looking uteri and the absence of corpora lutea were not included. Activity of all tested compounds is shown in Table 1.

Table 1. Pregnancy interceptive activity in hamsters by subcutaneous route

Compd no	Dose	Activity (%)
3a	10	100
3b	10	100
3c	10	100
3d	10	50
3e	10	0
3f	10	50
3g	10	0
3h	10	30
3i	10	50
3j	10	40
3k	10	0
3l	10	0
3m	10	0
3n	10	0
3o	10	50
4a	10	50
4b	10	50

4. Results and discussion

The present study has furnished a new lead as it is evident from the pregnancy interceptive activity of compounds. The structures of the active compounds indicate that the environment around the phenyl ring governs the ability of the compounds to evoke bioresponse. When the R group was 4-hydroxy phenyl the compound **3a** showed 100% activity in hamsters. On substituting the hydroxy group with methoxy group (**3b**) the activity was retained. On introduction of one more methoxy group at the 3-position (**3c**) it again showed 100% activity. When the R group was piperonal (**3d**) having two oxygen atoms similar to 3,4-dimethoxy phenyl **3c** the activity reduced to 50%. These results indicate the importance of oxygen atom with flexible groups in the molecule. When 2-ethyl pyrrolidine (**4a**) and 2-ethyl piperidine (**4b**) was attached to the oxygen atom at 4-position activity reduced to 50%. These results indicate the importance of oxygen atom with limited bulk at the 4-position of the phenyl ring. With R having 4-methoxy naphthalene (**3e**) the activity reduced to 0% due to the steric bulk. With R as 3-methoxy phenyl (**3f**) the activity reduced to 50% and when the phenyl ring had methoxy group at 2-position (**3g**) the activity diminished completely. These results emphasize the importance of methoxy group at 4-position. When the methoxy group

in **3f** was substituted with 3-benzyloxy (**3h**) group the activity reduced to 30%. These results indicate the importance of steric bulk. When R was 4-methyl phenyl (**3i**) the activity was 50% but when another methyl group was introduced at 3-position (**3j**) the activity reduced to 40%. When the R group was 3-thiophene (**3l**) it did not showed any activity. When the R group was indole (**3o**) it showed a activity of 50%, but when it was *N*-methyl indole (**3m**) and *N*-methyl-5-bromo-indole (**3n**) the activity diminished completely. These results emphasize the importance of free indolic NH in the molecule.

5. Conclusion

Out of the 17 synthesized, 2,4,6-trisubstituted pyrimidines, three compounds showed 100% activity at 10 mg/kg and six compounds showed 50% activity at 10 mg/kg. The compounds showed a good structure–activity relationship. These results suggest that structural modification in these compounds at the R position help the molecule to reach the uterus and show the activity. These findings are significant because the search for new chemical structures for the development of a once a month contraceptive is highly desirable.

6. Experimental details

IR spectra were recorded on Beckman Aculab-10, Perkin Elmer 881 and FTIR 8210 PC, Scimadzu spectrophotometers either on KBr discs or in neat. Nuclear magnetic resonance (NMR) spectra were recorded on either Bruker Avance DRX-300 MHz or Bruker DPX 200 FT spectrometers using TMS as an internal reference. FAB mass spectra were recorded on JEOL SX 102/DA 6000 mass spectrometer using Argon/Xenon (6 KV, 10 mA) as the FAB gas. Chemical analysis were carried out on Carlo-Erba-1108 instrument. The melting points were recorded on an electrically heated melting point apparatus and are uncorrected.

6.1. General procedure for the synthesis of compounds 2a–n

To a solution of dihydro-α-ionone **1** (1 equiv) in 50 mL of methanol or ethanol was added potassium hydroxide (1.5 equiv) in 5 mL of water over a period of 30 min at 0 °C–rt. Then the corresponding aldehyde (1.1 equiv) was added slowly to the reaction mixture. The reaction mixture was stirred at room temperature for 12 h. The solvent was removed from the reaction mixture under reduced pressure. Water was added and the aqueous phase was extracted with ethyl acetate. The organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography on silica gel (hexane/ethyl acetate 90:10) to afford the pure compound.

6.1.1. 1-(4-Hydroxy-phenyl)-5-(2,6,6-trimethyl-cyclohex-2-enyl)-pent-1-en-3-one. Viscous oil (**2a**), yield: 76%; MS 298 (M^{+1}); IR (KBr) 3426, 3214, 2938, 1708, 1476, 1274 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 7.86 (d, 2H, $J = 8.1$ Hz), 7.56 (d, 1H, $J = 15.8$ Hz), 6.94 (d, 2H, $J = 8.1$ Hz), 6.68 (d, 1H, $J = 15.8$ Hz), 5.31 (t, 1H, $J = 4.1$ Hz), 2.69 (t, 2H, $J = 5.2$ Hz), 1.99–2.01 (m, 2H), 1.82–1.86 (m, 1H), 1.76 (s, 3H), 1.67–1.71 (m, 2H), 1.55–1.59 (m, 2H), 0.99 (s, 3H), 0.87 (s, 3H). ^{13}C ($CDCl_3$, 50 MHz): 201.2, 154.1, 148.8, 143.2, 135.9, 130.2, 122.2, 122.1, 121.7, 113.5, 49.4, 41.1, 36.7, 31.8, 28.2, 26.3, 24.4, 24.1, 23.7.

6.1.2. 1-(4-Methoxy-phenyl)-5-(2,6,6-trimethyl-cyclohex-2-enyl)-pent-1-en-3-one. Viscous oil (**2b**), yield 92%; MS 313 (M^{+1}); IR (KBr) 3420, 3212, 2932, 1712, 1484, 1280 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 7.53 (d, 1H, $J = 16.2$ Hz), 7.47 (d, 2H, $J = 8.2$ Hz), 6.91 (d, 2H, $J = 8.2$ Hz), 6.65 (d, 1H, $J = 16.2$ Hz), 5.38 (t, 1H, $J = 4.6$ Hz), 3.84 (s, 3H, OCH_3), 2.67 (t, 2H), 1.99 (m, 2H), 1.85 (m, 1H), 1.75 (s, 3H), 1.71 (m, 2H), 1.56 (m, 2H), 0.99 (s, 3H), 0.86 (s, 3H). ^{13}C ($CDCl_3$, 50 MHz): 200.9, 156.3, 149.5, 143.4, 136.3, 130.4, 122.5, 122.1, 121.8, 113.4, 56.6, 49.2, 41.2, 36.7, 31.9, 28.1, 26.4, 24.37, 24.1, 23.8.

6.1.3. 1-(3,4-Dimethoxy-phenyl)-5-(2,6,6-trimethyl-cyclohex-2-enyl)-pent-1-en-3-one. Viscous oil (**2c**), yield: 79%; MS 343 (M^{+1}); IR (KBr) 3452, 3218, 2926, 1711, 1476, 1268 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 7.58 (d, 1H, $J = 15.8$ Hz), 7.48 (s, 1H), 7.36 (d, 1H, $J = 8.4$ Hz), 6.78 (d, 1H, $J = 8.4$ Hz), 6.56 (d, 1H, $J = 15.8$ Hz), 5.33 (t, 1H, $J = 4.1$ Hz), 3.97 (s, 3H, OMe), 3.92 (s, 3H, OMe), 2.71 (t, 2H, $J = 5.4$ Hz), 1.98–2.01 (m, 2H), 1.84–1.87 (m, 1H), 1.76 (s, 3H), 1.69–73 (m, 2H), 1.55–1.59 (m, 2H), 0.99 (s, 3H), 0.88 (s, 3H). ^{13}C ($CDCl_3$, 50 MHz): 200.5, 162.4, 161.5, 143.4, 143.1, 129.2, 123.8, 122.5, 121.1, 116.2, 112.1, 56.9, 56.6, 49.2, 40.8, 33.6, 31.9, 30.5, 28.2, 24.5, 24.1, 23.7.

6.1.4. 1-Benzo[1,3]dioxo-5-yl-5-(2,6,6-trimethyl-cyclohex-2-enyl)-pent-1-en-3-one. Viscous oil (**2d**), yield 81%; MS 327 (M^{+1}); IR (KBr) 3442, 3218, 2936, 1708, 1496, 1294 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 7.84 (d, 1H, $J = 17.4$ Hz), 7.16 (s, 1H), 7.04 (d, 1H, $J = 8.4$ Hz), 6.83 (d, 1H, $J = 8.4$ Hz), 6.58 (d, 1H, $J = 17.4$ Hz), 6.11 (s, 2H), 5.35 (t, 1H, $J = 4.2$ Hz), 2.67 (t, 2H, $J = 5.2$ Hz), 1.97–2.01 (m, 2H), 1.83–1.89 (m, 1H), 1.75 (s, 3H), 1.65–1.73 (m, 2H), 1.58–1.64 (m, 2H), 0.98 (s, 3H), 0.88 (s, 3H). ^{13}C ($CDCl_3$, 50 MHz): 202.1, 150.2, 148.6, 145.4, 139.8, 136.4, 122.6, 121.8, 121.4, 118.5, 114.2, 94.6, 49.4, 38.7, 33.1, 31.9, 30.5, 28.0, 24.5, 24.0, 23.5.

6.1.5. 1-(4-Methoxy-naphthalen-1-yl)-5-(2,6,6-trimethyl-cyclohex-2-enyl)-pent-1-en-3-one. Viscous oil (**2e**), yield 85%; MS 363 (M^{+1}); IR (KBr) 3452, 3218, 2936, 1711, 1486, 1268 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 8.12 (dd, 1H, $J = 7.6$, 2.5 Hz), 7.94 (dd, 1H, $J = 7.4$, 2.8 Hz), 7.56 (d, 1H, $J = 16.2$ Hz), 7.26–7.30 (m, 3H), 6.64 (d, 1H, $J = 8.2$ Hz), 6.54 (d, 1H, $J = 15.6$ Hz), 5.32 (t, 1H, $J = 4.2$ Hz), 4.02 (s, 3H, 3OMe), 2.71 (t, 2H, $J = 5.2$ Hz), 1.98–2.01 (m, 2H), 1.84–1.89 (m, 1H), 1.77 (s, 3H), 1.64–1.70 (m, 2H), 1.58–1.62 (m, 2H), 0.99 (s, 3H), 0.88 (s, 3H). ^{13}C ($CDCl_3$, 50 MHz): 200.8, 156.8, 143.8, 136.4, 132.1, 129.7, 128.2, 127.5, 126.3, 125.7, 125.6, 122.8, 121.7, 121.1, 111.5, 56.5, 49.3, 42.1, 38.6, 33.1, 31.9, 30.6, 28.1, 24.1, 23.5.

6.1.6. 1-(3-Methoxy-phenyl)-5-(2,6,6-trimethyl-cyclohex-2-enyl)-pent-1-en-3-one. Viscous oil (**2f**), yield 89%; MS 313 (M^{+1}); IR (KBr) 3442, 3218, 2936, 1708, 1496, 1294 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 7.58 (d, 1H, J = 16.1 Hz), 7.38 (s, 1H), 7.31 (d, 1H, J = 8.3 Hz), 7.15 (dd, 1H, J = 7.2, 2.6 Hz), 6.98 (d, 1H, J = 8.4 Hz), 6.76 (d, 1H, J = 16.1 Hz), 5.36 (t, 1H, J = 4.4 Hz), 2.69 (t, 2H, J = 4.6 Hz), 1.97–2.0 (m, 2H), 1.82–1.84 (m, 1H), 1.74 (s, 3H), 1.66–1.68 (m, 2H), 1.53–1.57 (m, 2H), 0.99 (s, 3H), 0.88 (s, 3H). ^{13}C ($CDCl_3$, 50 MHz): 201.1, 159.18, 143.4, 139.2, 137.26, 130.2, 122.1, 121.4, 119.1, 116.1, 115.1, 49.12, 41.1, 36.9, 31.6, 28.1, 26.9, 24.4, 24.1, 23.8.

6.1.7. 1-(2-Methoxy-phenyl)-5-(2,6,6-trimethyl-cyclohex-2-enyl)-pent-1-en-3-one. Viscous oil (**2g**), yield 88%; MS 313 (M^{+1}); IR (KBr) 3442, 3218, 2936, 1708, 1496, 1294 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 7.61 (d, 1H, J = 16.2 Hz), 7.56 (d, 1H, J = 8.2 Hz), 7.16 (dd, 1H, J = 7.4, 2.6 Hz), 6.96 (d, 1H, J = 8.4 Hz), 6.86 (dd, 1H, J = 7.6, 2.8 Hz), 6.75 (d, 1H, J = 16.2 Hz), 5.35 (t, 1H, J = 4.2 Hz), 3.84 (s, 3H, 3OMe), 2.70 (t, 2H, J = 5.1 Hz), 1.98–2.01 (m, 2H), 1.82–1.88 (m, 1H), 1.76 (s, 3H), 1.64–1.74 (m, 2H), 1.54–1.59 (m, 2H), 0.98 (s, 3H), 0.89 (s, 3H). ^{13}C ($CDCl_3$, 50 MHz): 201.4, 159.2, 143.6, 139.4, 137.3, 130.4, 122.4, 121.2, 119.2, 116.4, 115.2, 49.2, 41.1, 36.8, 31.5, 28.2, 26.9, 24.5, 24.1, 23.8.

6.1.8. 1-(3-Benzyloxy-phenyl)-5-(2,6,6-trimethyl-cyclohex-2-enyl)-pent-1-en-3-one. Viscous oil (**2h**), yield 78%; (**2h**) MS 389 (M^{+1}); IR (KBr) 3448, 3212, 2926, 1712, 1484, 1262 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 7.56 (d, 1H, J = 15.8 Hz), 7.48 (s, 1H), 7.42 (d, 1H, J = 8.6 Hz), 7.26–7.34 (m, 6H), 6.94 (d, 1H, J = 8.5 Hz), 6.58 (d, 1H, J = 15.8 Hz), 5.34 (t, 2H, J = 4.2 Hz), 5.16 (s, 2H, OCH_2), 2.70 (t, 2H, J = 5.6 Hz), 1.98–2.02 (m, 2H), 1.84–1.88 (m, 1H), 1.75 (s, 3H), 1.65–1.72 (m, 2H), 1.58–1.64 (m, 2H), 0.99 (s, 3H), 0.88 (s, 3H). ^{13}C ($CDCl_3$, 50 MHz): 200.4, 158.2, 144.2, 139.7, 136.6, 136.1, 128.8, 128.4, 128.2, 127.7, 121.2, 120.8, 120.1, 117.4, 113.7, 70.7, 49.4, 38.7, 33.1, 31.9, 30.5, 28.0, 24.5, 24.0, 23.5.

6.1.9. 1-*p*-Tolyl-5-(2,6,6-trimethyl-cyclohex-2-enyl)-pent-1-en-3-one. Viscous oil (**2i**), yield 95%; MS 297 (M^{+1}); IR (KBr) 3426, 3206, 2928, 1709, 1486, 1272 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 7.54 (d, 1H, J = 16.1 Hz), 7.42 (d, 2H, J = 8.2 Hz), 7.18 (d, 2H, J = 8.2 Hz), 6.64 (d, 1H, J = 16.1 Hz), 5.32 (t, 1H, J = 4.1 Hz), 2.46 (s, 3H, CH_3), 2.68 (t, 2H, J = 5.6 Hz), 1.99–2.01 (m, 2H), 1.82–1.86 (m, 1H), 1.75 (s, 3H), 1.69–1.73 (m, 2H), 1.54–1.58 (m, 2H), 0.99 (s, 3H), 0.87 (s, 3H) ^{13}C ($CDCl_3$, 50 MHz): 200.1, 144.54, 142.4, 136.38, 132.2, 128.5, 124.8, 118.4, 117.2, 49.1, 40.98, 36.4, 31.8, 28.2, 26.3, 24.46, 24.14, 23.81, 20.28.

6.1.10. 1-(3,4-Dimethyl-phenyl)-5-(2,6,6-trimethyl-cyclohex-2-enyl)-pent-1-en-3-one. Viscous oil (**2j**), yield 85%; MS 311 (M^{+1}); IR (KBr) 3412, 3228, 2928, 1709, 1496, 1284 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 7.58 (d, 1H, J = 15.8 Hz), 7.58 (s, 1H), 7.51 (d, 1H, J = 8.2 Hz), 7.04 (d, 1H, J = 8.2 Hz), 6.76 (d, 1H, J = 15.8 Hz), 5.32 (t, 1H, J = 4.1 Hz), 2.71 (t, 2H, J = 5.2 Hz), 1.98–2.01 (m, 2H), 1.85–1.89 (m, 1H), 1.76 (s, 3H), 1.66–1.74 (m, 2H), 1.58–1.64 (m, 2H), 0.99 (s, 3H), 0.87 (s, 3H). ^{13}C ($CDCl_3$, 50 MHz): 200.1, 144.6, 140.2, 138.5, 136.4, 135.2, 130.4, 128.6, 124.9, 121.4, 121.1, 49.5, 38.7, 33.2, 31.9, 30.6, 28.1, 25.2, 24.1, 23.4, 20.3, 20.1.

6.1.11. 1-(4-Dimethylamino-phenyl)-5-(2,6,6-trimethyl-cyclohex-2-enyl)-pent-1-en-3-one. Viscous oil (**2k**), yield 75%; MS 326 (M^{+1}); IR (KBr) 3445, 3215, 2924, 1709, 1484, 1264 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 7.53 (d, 1H, J = 15.6 Hz), 7.45 (d, 2H, J = 8.3 Hz), 6.69 (d, 2H, J = 8.3 Hz), 6.54 (d, 1H, J = 15.6 Hz), 5.39 (t, 1H, J = 4.6 Hz), 3.02 (s, 6H, NMe_2), 2.65 (t, 2H, J = 4.5 Hz), 1.98–2.01 (m, 2H), 1.84 (m, 1H), 1.76 (s, 3H), 1.74 (m, 2H), 1.54 (m, 2H), 0.98 (s, 3H), 0.86 (s, 3H). ^{13}C ($CDCl_3$, 50 MHz): 200.9, 152.28, 143.6, 136.26, 130.42, 122.54, 121.8, 121.22, 112.25, 48.88, 40.43, 40.99, 36.77, 31.5, 28.02, 26.82, 24.39, 24.06, 23.87.

6.1.12. 1-Thiophen-2-yl-5-(2,6,6-trimethyl-cyclohex-2-enyl)-pent-1-en-3-one. Viscous oil (**2l**), yield 74% (**2l**) MS 289 (M^{+1}); IR (KBr) 3441, 3208, 2928, 1714, 1486, 1252 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 7.78 (s, 1H), 7.52 (d, 1H, J = 15.6 Hz), 7.46 (s, 1H, J = 4.2 Hz), 7.26 (d, 1H, J = 4.2 Hz), 6.54 (d, 1H, J = 15.6 Hz), 5.32 (t, 1H, J = 4.1 Hz), 2.70 (t, 2H, J = 5.4 Hz), 1.98–2.03 (m, 2H), 1.85–1.9 (m, 1H), 1.77 (s, 3H), 1.66–1.72 (m, 2H), 1.58–1.62 (m, 2H), 0.98 (s, 3H), 0.88 (s, 3H). ^{13}C ($CDCl_3$, 50 MHz): 200.2, 143.2, 140.6, 135.8, 126.5, 126.1, 125.6, 121.3, 120.8, 49.3, 38.6, 33.1, 31.9, 30.5, 28.0, 24.4, 24.0, 23.4.

6.1.13. 1-(1-Methyl-1*H*-indol-2-yl)-5-(2,6,6-trimethyl-cyclohex-2-enyl)-pent-1-en-3-one. Viscous solid (**2m**), yield 87%; MS 336 (M^{+1}); IR (KBr) 3452, 3218, 2936, 1711, 1486, 1268 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 7.93 (d, 1H, J = 8.6 Hz), 7.78 (d, 1H, J = 16.1 Hz), 7.36 (s, 1H), 7.33 (d, 1H, J = 8.5 Hz), 7.28–7.32 (m, 2H), 6.79 (d, 1H, J = 16.1 Hz), 5.35 (t, 2H, J = 4.2 Hz), 3.79 (s, 3H, NCH_3), 2.72 (t, 2H, J = 5.2 Hz), 1.98–2.01 (m, 2H), 1.84–1.89 (m, 1H), 1.77 (s, 3H), 1.65–1.75 (m, 2H), 1.56–1.61 (m, 2H), 0.99 (s, 3H), 0.88 (s, 3H). ^{13}C ($CDCl_3$, 50 MHz): 201.2, 136.8, 136.2, 135.8, 129.9, 125.5, 123.2, 121.8, 121.3, 120.8, 120.1, 112.6, 111.8, 49.3, 41.4, 36.2, 33.1, 32.1, 28.1, 26.2, 24.4, 24.1, 23.4.

6.1.14. 1-(5-Bromo-1-methyl-1*H*-indol-2-yl)-5-(2,6,6-trimethyl-cyclohex-2-enyl)-pent-1-en-3-one. Viscous solid (**2n**), yield 89%; MS 415 (M^{+1}); IR (KBr) 3452, 3218, 2936, 1711, 1486, 1268 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 8.38 (s, 1H), 7.78 (d, 1H, J = 16.1 Hz), 7.65 (s, 1H), 7.32 (d, 1H, J = 8.6 Hz), 7.18 (d, 1H, J = 8.6 Hz), 6.79 (d, 1H, J = 16.1 Hz), 5.32 (t, 2H, J = 4.2 Hz), 3.80 (s, 3H, NCH_3), 2.71 (t, 2H, J = 5.4 Hz), 1.97–2.01 (m, 2H), 1.84–1.89 (m, 1H), 1.78 (s, 3H), 1.65–1.74 (m, 2H), 1.56–1.61 (m, 2H), 0.99 (s, 3H), 0.88 (s, 3H). ^{13}C ($CDCl_3$, 50 MHz): 201.1, 136.6, 136.3, 135.8, 129.8, 125.5, 123.2, 122.8, 122.1, 121.4, 118.2, 112.5, 111.7, 49.4, 41.4, 36.3, 33.1, 32.2, 28.1, 26.2, 24.4, 24.1, 23.4.

6.2. 1-(1*H*-Indol-2-yl)-5-(2,6,6-trimethyl-cyclohex-2-enyl)-pent-1-en-3-one (2o):

A solution of dihydro-α-ionone 1 (1.0 equiv), indole-3-carboxaldehyde (1.1 equiv) and piperidine (1.5 equiv) was refluxed in 50 mL of methanol or ethanol for 12 h. The solvent was removed from the reaction mixture under reduced pressure. Water was added and the aqueous phase was extracted with ethyl acetate. The organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography on silica gel (hexane/ethyl acetate, 60:40) to afford the pure compound.

Viscous solid, yield 82%; MS 322 (M^{+1}); IR (KBr) 3452, 3218, 2936, 1711, 1486, 1268 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 8.76 (s, 1H, NH), 7.92 (d, 1H, $J = 8.7$ Hz), 7.82 (d, 1H, $J = 16.1$ Hz), 7.53 (s, 1H), 7.43 (d, 1H, $J = 8.2$ Hz), 7.32–7.26 (m, 2H), 6.85 (d, 1H, $J = 16.1$ Hz), 5.36 (t, 2H, $J = 4.1$ Hz), 2.71 (t, 2H, $J = 5.2$ Hz), 1.97–2.01 (m, 2H), 1.85–1.89 (m, 1H), 1.78 (s, 3H), 1.65–1.75 (m, 2H), 1.57–1.63 (m, 2H), 0.98 (s, 3H), 0.86 (s, 3H). ^{13}C ($CDCl_3$, 50 MHz): 202.1, 137.9, 137.4, 136.2, 130.6, 125.8, 123.8, 122.1, 121.9, 121.4, 120.8, 113.8, 112.6, 49.2, 41.4, 33.1, 32.0, 28.1, 26.1, 24.4, 24.1, 23.5.

6.3. General procedure for the synthesis of comounds 3a–o

To a solution of 1.1 equiv of guanidine hydrochloride in 50 mL of isopropanol, 1.1 equiv of sodium metal was added. The reaction mixture was refluxed for 2 h and then different chalcones (**2a**–**n**, 1.0 equiv) were added to it and refluxed for 8 h. The solvent was removed from the reaction mixture under reduced pressure. Water was added and the aqueous phase was extracted with ethyl acetate. The organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography on silica gel (hexane/ethyl acetate 80:20) to afford the pure compound.

6.3.1. 4-{2-Amino-6-[2-(2,6,6-trimethyl-cyclohex-2-enyl)-ethyl]-pyrimidin-4-yl}phenol (3a). White solid, yield: 68%, mp 144–146 °C; MS 338 (M^{+1}); IR (KBr) 3454, 3162, 2928, 1646, 1578, 1325, 1227 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 8.06 (d, 2H, $J = 8.7$ Hz), 7.12 (d, 2H, $J = 8.7$ Hz), 6.87 (s, 1H), 5.32 (t, 1H, $J = 4.2$ Hz), 5.09 (s, 2H, NH_2), 2.71 (t, 2H, $J = 4.6$ Hz), 1.98–2.01 (m, 2H), 1.83–1.86 (m, 1H), 1.77 (s, 3H), 1.71–1.75 (m, 2H), 1.52–1.58 (m, 2H), 0.98 (s, 3H), 0.86 (s, 3H); ^{13}C ($CDCl_3$, 50 MHz): 170.4, 169.3, 167.2, 157.8, 143.1, 130.6, 129.9, 123.2, 115.6, 108.2, 49.2, 42.1, 33.6, 31.8, 30.6, 28.1, 24.4, 24.1, 23.8. Anal. Calcd for $C_{21}H_{27}N_3O$: C, 74.74; H, 8.06; N, 12.45. Found: C, 74.62; H, 8.18; N, 12.62.

6.3.2. 4-(4-Methoxy-phenyl)-6-[2-(2,6,6-trimethyl-cyclohex-2-enyl)-ethyl]-pyrimidin-2ylamine (3b). White solid, yield: 72%, mp 106–108 °C; MS 352 (M^{+1}); IR (KBr) 3460, 3175, 2931, 1642, 1576, 1336, 1233 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 7.99 (d, 2H, $J = 8.9$ Hz), 7.01 (d, 2H, $J = 8.9$ Hz), 6.86 (s, 1H), 5.34 (t, 1H, $J = 4.8$ Hz), 5.04 (s, 2H, NH_2), 3.89 (s, 3H), 2.66 (t, 2H, $J = 4.6$ Hz), 1.98 (m, 2H), 1.84 (m, 1H), 1.75 (s, 3H), 1.71 (m, 2H), 1.55 (m, 2H), 0.99 (s, 3H), 0.87 (s, 3H); ^{13}C ($CDCl_3$, 50 MHz): 170.1, 169.6, 167.1, 162.6, 143.4, 130.2, 129.2, 122.9, 115.1, 110.4, 56.5, 49.3, 42.1, 33.6, 31.8, 30.6, 28.1, 24.4, 24.1, 23.8. Anal. Calcd for $C_{22}H_{29}N_3O$: C, 75.18; H, 8.32; N, 11.96. Found: C, 75.12; H, 8.54; N, 11.87.

6.3.3. 4-(3,4-Dimethoxy-phenyl)-6-[2-(2,6,6-trimethyl-cyclohex-2-enyl)-ethyl]-pyrimidin-2ylamine (3c). White solid, yield: 62%, mp 109–111 °C; MS 382 (M^{+1}); IR (KBr) 3445, 3169, 2936, 1647, 1579, 1342, 1245 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 7.64 (s, 1H), 7.54 (d, 1H, $J = 8.6$ Hz), 6.93 (d, 1H, $J = 8.6$ Hz), 6.85 (s, 1H), 5.34 (t, 1H, $J = 4.1$ Hz), 5.07 (s, 2H, NH_2), 3.98 (s, 3H, OMe), 3.94 (s, 3H, OMe), 2.70 (t, 2H, $J = 5.2$ Hz), 1.98–2.01 (m, 2H), 1.84–1.88 (m, 1H), 1.75 (s, 3H), 1.69–72 (m, 2H), 1.54–1.58 (m, 2H), 0.99 (s, 3H), 0.87 (s, 3H). ^{13}C ($CDCl_3$, 50 MHz): 170.1, 169.6, 167.1, 162.6, 161.7, 143.4, 130.2, 124.2, 122.9, 116.4, 115.1, 110.4, 56.9, 56.5, 49.3, 42.1, 33.6, 31.8, 30.6, 28.1, 24.5, 24.1, 23.8. Anal. Calcd for $C_{23}H_{31}N_3O_2$: C, 72.41; H, 8.19; N, 11.01. Found: C, 72.68; H, 8.04; N, 11.22.

6.3.4. 4-Benzo[1,3]dioxo-5-yl-6-[2-(2,6,6-trimethyl-cyclohex-2-enyl)-ethyl]-pyrimidin-2-ylamine (3d). White solid, yield: 60%, mp 126-128 °C; MS 366 (M^{+1}); IR (KBr) 3436, 3168, 2927, 1654, 1552, 1338, 1248 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 7.39 (s, 1H), 7.26 (d, 1H, $J = 8.2$ Hz), 7.06 (d, 1H, $J = 8.2$ Hz), 6.92 (s, 1H), 6.14 (s, 2H), 5.33 (t, 1H, $J = 4.1$ Hz), 2.69 (t, 2H, $J = 5.2$ Hz), 1.98–2.01 (m, 2H), 1.83–1.88 (m, 1H), 1.76 (s, 3H), 1.66–1.74 (m, 2H), 1.58–1.64 (m, 2H), 0.99 (s, 3H), 0.87 (s, 3H). ^{13}C ($CDCl_3$, 50 MHz): 173.4, 169.6, 167.2, 151.6, 149.4, 140.7, 136.8, 123.2, 121.8, 120.2, 115.6, 107.4, 94.8, 49.3, 38.7, 33.2, 31.9, 30.5, 28.0, 24.4, 24.0, 23.5. Anal. Calcd for $C_{22}H_{27}N_3O_2$: C, 72.30; H, 7.45; N, 11.50. Found: C, 72.52; H, 7.28; N, 11.67.

6.3.5. 4-(4-Methoxy-naphthalen-1-yl)-6-[2-(2,6,6-trimethyl-cyclohex-2-enyl)-ethyl]-pyrimidin-2ylamine (3e). White solid, yield: 65%, mp 119–120 °C; MS (M^{+1}); IR (KBr) 3464, 3179, 2936, 1658, 1574, 1342, 1252 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 8.35 (dd, 1H, $J = 4.4$ Hz), 8.20 (dd, 1H, $J = 4.5$ Hz), 7.56–7.40 (m, 3H), 6.86 (d, 1H, $J = 8.2$ Hz), 6.73 (s, 1H), 5.33 (t, 1H, $J = 4.2$ Hz), 5.26 (s, 2H, NH_2), 4.03 (s, 3H, 3OMe), 2.73 (t, 2H, $J = 5.1$ Hz), 1.97–2.00 (m, 2H), 1.84–1.88 (m, 1H), 1.79 (s, 3H), 1.63–1.70 (m, 2H), 1.57–1.64 (m, 2H), 0.99 (s, 3H), 0.87 (s, 3H). ^{13}C ($CDCl_3$, 50 MHz): 172.8, 168.0, 163.6, 156.9, 136.4, 132.0, 129.7, 128.0, 127.5, 126.2, 125.8, 125.6, 122.7, 121.2, 111.5, 103.6, 56.0, 49.4, 42.1, 38.6, 33.1, 31.9, 30.6, 28.0, 24.0, 23.5. Anal. Calcd for $C_{26}H_{31}N_3O$: C, 77.77; H, 7.78; N, 10.46. Found: C, 77.86; H, 7.69; N, 10.42.

6.3.6. 4-(3-Methoxy-phenyl)-6-[2-(2,6,6-trimethyl-cyclohex-2-enyl)-ethyl]-pyrimidin-2ylamine (3f). Creamish coloured solid, yield: 61%, mp 68–70 °C; MS 352 (M^{+1}); IR (KBr) 3456, 3174, 2926, 1648, 1571, 1348, 1248 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 7.58 (s, 1H), 7.50 (d, 1H, $J = 8.5$ Hz), 7.35 (dd, 1H, $J = 7.6$, 3.0 Hz), 7.01 (d, 1H, $J = 8.5$ Hz), 6.87 (s, 1H), 5.34 (t, 1H,

J = 4.7 Hz), 5.21 (s, 2H, NH_2), 3.87 (s, 3H, 3OMe), 2.71 (t, 2H, J = 4.9 Hz), 1.98–2.00 (m, 2H), 1.84–1.86 (m, 1H), 1.78 (s, 3H), 1.70–1.74 (m, 2H), 1.55–1.57 (m, 2H), 0.98 (s, 3H), 0.86 (s, 3H). ^{13}C ($CDCl_3$, 50 MHz): 173.3, 165.6, 163.7, 160.4, 139.6, 136.4, 130.1, 121.1, 119.9, 116.6, 112.7, 107.1, 57.2, 50.1, 38.6, 33.1, 31.9, 29.4, 27.8, 24.8, 23.9, 23.6. Anal. Calcd for $C_{22}H_{29}N_3O$: C, 75.18; H, 8.32; N, 11.96. Found: C, 75.34; H, 8.46; N, 11.77.

6.3.7. 4-(2-Methoxy-phenyl)-6-[2-(2,6,6-trimethyl-cyclohex-2-enyl)-ethyl]-pyrimidin-2ylamine (3g). light yellow solid, yield: 54%, mp 60–62 °C; MS 352 (M^{+1}); IR (KBr) 3472, 3179, 2938, 1649, 1584, 1346, 1239 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 7.78 (d, 1H, J = 8.4 Hz), 7.35 (dd, 1H, J = 7.8, 2.6 Hz), 7.1 (d, 1H, J = 8.4 Hz), 7.01 (dd, 1H, J = 7.4, 2.8 Hz), 6.96 (s, 1H), 5.33 (t, 1H, J = 4.2 Hz), 5.04 (s, 2H, NH_2), 3.86 (s, 3H, 3OMe), 2.70 (t, 2H, J = 5.3 Hz), 1.97–2.00 (m, 2H), 1.86-1.88 (m, 1H), 1.77 (s, 3H), 1.67–1.70 (m, 2H), 1.57–1.59 (m, 2H), 0.99 (s, 3H), 0.88 (s, 3H). ^{13}C ($CDCl_3$, 50 MHz): 173.5, 165.3, 163.7, 160.5, 139.4, 136.4, 130.4, 121.3, 119.8, 116.6, 112.8, 107.4, 56.2, 49.9, 38.7, 33.4, 31.9, 29.8, 27.8, 24.8, 23.8, 23.7. Anal. Calcd for $C_{22}H_{29}N_3O$: C, 75.18; H, 8.32; N, 11.96. Found: C, 75.26; H, 8.44; N, 11.82.

6.3.8. 4-(3-Benzyloxy-phenyl)-6-[2-(2,6,6-trimethyl-cyclohex-2-enyl)-ethyl]-pyrimidin-2-ylamine (3h). White solid, yield: 59%, mp 96–98 °C; MS 428 (M^{+1}); IR (KBr) 3442, 3164, 2939, 1648, 1554, 1345, 1236 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 7.65 (s, 1H), 7.57 (d, 1H, J = 8.4 Hz), 7.31–7.46 (m, 6H), 7.09 (d, 1H, J = 8.2 Hz), 6.87 (s, 1H), 5.34 (t, 2H, J = 4.1 Hz), 5.14 (s, 2H, OCH_2), 5.03 (s, 2H, NH_2), 2.71 (t, 2H, J = 5.4 Hz), 1.99–2.02 (m, 2H), 1.84–1.89 (m, 1H), 1.77 (s, 3H), 1.66–1.74 (m, 2H), 1.57–1.64 (m, 2H), 0.99 (s, 3H), 0.87 (s, 3H). ^{13}C ($CDCl_3$, 50 MHz): 173.4, 165.5, 163.7, 159.6, 139.7, 137.3, 136.4, 130.1, 129.0, 128.4, 127.9, 121.2, 120.2, 117.5, 113.9, 107.1, 70.6, 49.4, 38.7, 33.1, 31.9, 30.5, 28.0, 24.5, 24.0, 23.5. Anal. Calcd for $C_{28}H_{33}N_3O$: C, 78.65; H, 7.78; N, 9.83. Found: C, 78.78; H, 7.43; N, 9.57.

6.3.9. 4-*p*-Tolyl-6-[2-(2,6,6-trimethyl-cyclohex-2-enyl)-ethyl]-pyrimidin-2ylamine (3i). White solid, yield: 74%, mp 112–114 °C; MS 336 (M^{+1}); IR (KBr) 3460, 3175, 2931, 1642, 1576, 1336, 1233 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 7.56 (d, 2H, J = 8.4 Hz), 7.32 (d, 2H, J = 8.4 Hz), 6.84 (s, 1H), 5.33 (t, 1H, J = 4.2 Hz), 2.48 (s, 3H, CH_3), 2.71 (t, 2H, J = 5.4 Hz), 1.98–2.01 (m, 2H), 1.82–1.86 (m, 1H), 1.76 (s, 3H), 1.69–1.72 (m, 2H), 1.54–1.58 (m, 2H), 0.99 (s, 3H), 0.88 (s, 3H). ^{13}C ($CDCl_3$, 50 MHz): 172.84, 165.86, 163.42, 144.2, 137.67, 133.4, 128.7, 118.5, 117.4, 107.62, 49.2, 40.96, 36.46, 31.82, 28.24, 26.35, 24.46, 24.18, 23.78, 20.24. Anal. Calcd for $C_{22}H_{29}N_3$: C, 78.76; H, 8.71; N, 12.53. Found: C, 78.82; H, 8.98; N, 12.64.

6.3.10. 4-(3,4-Dimethyl-phenyl)-6-[2-(2,6,6-trimethyl-cyclohex-2-enyl)-ethyl]-pyrimidin-2ylamine (3j). White solid, yield: 70%, mp 124–125 °C; MS 349 (M^{+1}); IR (KBr) 3456, 3174, 2932, 1652, 1590, 1352, 1242 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 7.77 (s, 1H), 7.69 (d, 1H, J = 8.4 Hz), 7.21 (d, 1H, J = 8.4 Hz), 6.87 (s, 1H), 5.34 (t, 1H, J = 4.6 Hz), 5.02 (s, 2H, NH_2), 2.70 (t, 2H, J = 5.3 Hz), 1.97–2.01 (m, 2H), 1.85–1.89 (m, 1H), 1.78 (s, 3H), 1.65–1.75 (m, 2H), 1.57–1.63 (m, 2H), 0.98 (s, 3H), 0.86 (s, 3H). ^{13}C ($CDCl_3$, 50 MHz): 173.2, 165.9, 163.8, 139.6, 137.3, 136.5, 135.7, 130.4, 128.6, 124.9, 121.12, 106.7, 49.5, 38.7, 33.1, 31.9, 30.6, 28.0, 25.3, 24.1, 23.5, 20.3, 20.2. Anal. Calcd for $C_{23}H_{31}N_3$: C, 79.04; H, 8.94; N, 12.02. Found: C, 79.24; H, 8.79; N, 11.92.

6.3.11. 4-(Dimethylamino-phenyl)-6-[2-(2,6,6-trimethyl-cyclohex-2-enyl)-ethyl]-pyrimidin-2ylamine (3k). White solid, yield: 67%, mp 118–120 °C; MS 365 (M^{+1}); IR (KBr) 3445, 3169, 2936, 1647, 1579, 1342, 1245 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 7.64 (d, 2H, J = 8.4 Hz), 6.75 (d, 2H, J = 8.4 Hz), 6.88 (s, 1H), 5.34 (t, 1H, J = 4.2 Hz), 3.03 (s, 6H, NMe_2), 2.71 (t, 2H, J = 5.2Hz), 1.98–2.01 (m, 2H), 1.84–1.88 (m, 1H), 1.75 (s, 3H), 1.69–72 (m, 2H), 1.54–1.58 (m, 2H), 0.99 (s, 3H), 0.87 (s, 3H). ^{13}C ($CDCl_3$, 50 MHz): 173.2, 165.9, 163.4, 152.5, 136.5, 130.5, 122.6, 121.8, 112.4, 107.4, 49.2, 40.4, 40.9, 36.7, 31.4, 28.1, 26.7, 24.4, 24.1, 23.8. Anal. Calcd for $C_{23}H_{32}N_4$: C, 75.78; H, 8.85; N, 15.37. Found: C, 75.82; H, 8.54; N, 15.48.

6.3.12. 4-Thiophen-2-yl-6-[2-(2,6,6-trimethyl-cyclohex-2-enyl)-ethyl]-pyrimidin-2-ylamine (3l). Creamish coloured solid, yield: 65%, mp 101–102 °C; MS (M^{+1}); IR (KBr) 3442, 3164, 2939, 1648, 1554, 1345, 1236 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 8.00 (s, 1H), 7.61 (s, 1H, J = 4.2 Hz), 7.38 (d, 1H, J = 4.2Hz), 6.76 (s, 1H), 5.34 (t, 1H, J = 4.2 Hz), 5.21 (s, 2H, NH_2), 2.68 (t, 2H, J = 5.5 Hz), 1.98–2.02 (m, 2H), 1.84–1.89 (m, 1H), 1.76 (s, 3H), 1.66–1.73 (m, 2H), 1.58–1.63 (m, 2H), 0.99 (s, 3H), 0.87 (s, 3H). ^{13}C ($CDCl_3$, 50 MHz): 173.4, 163.7, 161.2, 141.2, 136.4, 126.7, 126.6, 126.3, 121.2, 106.8, 49.3, 38.6, 33.1, 31.9, 30.5, 28.0, 24.4, 24.0, 23.4. Anal. Calcd for $C_{19}H_{25}N_3S$: C, 69.68; H, 7.69; N, 12.83; S, 9.79. Found: C, 69.84 H, 7.94; N, 12.65; S, 9.86.

6.3.13. 4-(1-Methyl-1*H*-indol-3-yl)-6-[2-(2,6,6-trimethyl-cyclohex-2-enyl)-ethyl]-pyrimidin-2-ylamine (3m). White solid, yield: 68%, mp 130–132 °C; MS 375 (M^{+1}); IR (KBr) 3442, 3164, 2939, 1648, 1554, 1345, 1236 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 8.35 (d, 1H, J = 8.6 Hz), 7.77 (s, 1H), 7.37 (d, 1H, J = 8.5Hz), 7.23–7.27 (m, 2H), 6.86 (s, 1H), 5.34 (t, 2H, J = 4.2 Hz), 4.96 (s, 2H, NH_2), 3.84 (s, 3H, N–CH_3), 2.69 (t, 2H, J = 5.3 Hz), 1.98–2.01 (m, 2H), 1.84–1.90 (m, 1H), 1.78 (s, 3H), 1.65–1.73 (m, 2H), 1.56–1.64 (m, 2H), 0.98 (s, 3H), 0.88 (s, 3H). ^{13}C ($CDCl_3$, 50 MHz): 172.0, 163.6, 162.9, 138.3, 136.6, 131.3, 126.5, 122.8, 122.0, 121.4, 121.1, 114.5, 110.1, 106.5, 49.4, 38.7, 33.6, 33.1, 31.9, 30.6, 28.1, 24.5, 24.1, 23.5. Anal. Calcd for $C_{24}H_{30}N_4$: C, 76.97; H, 8.09; N, 14.96. Found: C, 76.68; H, 8.34; N, 14.63.

6.3.14. 4-(5-Bromo-1-methyl-1*H*-indol-3-yl)-6-[2-(2,6,6-trimethyl-cyclohex-2-enyl)-ethyl]-pyrimidin-2-ylamine (3n). White solid, yield: 71%, mp 200–202 °C; MS 454 (M^{+1}); IR (KBr) 3436, 3148, 2928, 1651, 1552, 1354,

1228 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) 8.56 (s, 1H), 7.71 (s, 1H), 7.38 (d, 1H, $J = 8.6$ Hz), 7.21 (d, 1H, $J = 8.6$ Hz), 6.77 (s, 1H), 5.35 (t, 2H, $J = 4.3$ Hz), 4.97 (s, 2H, NH_2), 3.83 (s, 3H, N–CH_3), 2.69 (t, 2H, $J = 5.3$ Hz), 1.98–2.01 (m, 2H), 1.84–1.90 (m, 1H), 1.78 (s, 3H), 1.64–1.72 (m, 2H), 1.57–1.64 (m, 2H), 0.99 (s, 3H), 0.89 (s, 3H). ^{13}C ($CDCl_3$, 50 MHz): 172.4, 163.5, 162.8, 138.4, 136.5, 131.4, 126.5, 122.8, 122.4, 122.1, 117.4, 114.4, 110.1, 106.5, 49.4, 38.6, 33.6, 33.1, 31.9, 30.6, 28.1, 24.5, 24.1, 23.5. Anal. Calcd for $C_{24}H_{29}BrN_4$: C, 63.57; H, 6.45; N, 12.36. Found: C, 63.68; H, 6.58; N, 12.52.

6.3.15. 4-(1*H*-Indol-2-yl)-6-[2-(2,6,6-trimethyl-cyclohex-2-enyl)-ethyl]-pyrimidin-2-ylamine (3o). White solid, yield 71%, mp decomposes at 126 °C; MS 361 (M^{+1}); IR (KBr) 3456, 3168, 2938, 1656, 1568, 1338, 1248 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 9.12 (s, 1H, NH), 8.35 (d, 1H, $J = 8.7$ Hz), 7.83 (s, 1H), 7.40 (d, 1H, $J = 8.4$ Hz), 7.26–7.21 (m, 2H), 6.87 (s, 1H), 5.33 (t, 2H, $J = 4.0$ Hz), 5.14 (s, 2H, NH_2), 2.71 (t, 2H, $J = 5.4$ Hz), 1.98–2.01 (m, 2H), 1.85–1.89 (m, 1H), 1.77 (s, 3H), 1.66–1.75 (m, 2H), 1.54–1.63 (m, 2H), 0.99 (s, 3H), 0.88 (s, 3H). ^{13}C ($CDCl_3$, 50 MHz): 172.1, 163.5, 163.2, 137.4, 136.5, 126.9, 125.8, 123.2, 121.8, 121.7, 121.1, 116.0, 112.1, 106.8, 49.4, 38.6, 33.1, 31.9, 30.6, 28.1, 24.56, 24.0, 23.5. Anal. Calcd for $C_{23}H_{28}N_4$: C, 76.63; H, 7.83; N, 15.54. Found: C, 76.46; H, 7.64; N, 15.42.

6.4. General procedure for the synthesis of comounds 4a and b

To a solution of 1.0 equiv of **3a** in acetone, 1.2 equiv of 1-(2-chloro-ethyl)-pyrrolidine (for **4a**), 2.0 equiv of K_2CO_3 and 1.1 equiv of tetrabutyl ammonium iodide was taken and the reaction mixture was refluxed for a period of 5h. The reaction mixture was filtered from sintered funnel to filter out K_2CO_3 and the solvent was removed under reduced pressure. Water was added and the aqueous phase was extracted with ethyl acetate. The organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography on silica gel (hexane/ethyl acetate 70:30) to afford the pure compound.

6.4.1. 4-[4-(2-Pyrrolidin-1-yl-ethoxy)-phenyl]-6-[2-(2,6,6-trimethyl-cyclohex-2-enyl)-ethyl]-pyrimidin-2-ylamine (4a). White solid, yield: 82%, mp 98–100 °C; MS (M^{+1}); IR (KBr) 3448, 3158, 2930, 1648, 1542, 1336, 1238 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 7.97 (d, 2H, $J = 8.6$ Hz), 7.00 (d, 2H, $J = 8.6$ Hz), 6.84 (s, 1H), 5.29 (t, 1H, $J = 4.2$ Hz), 5.0 (s, 2H, NH_2), 4.22 (t, 2H, $J = 5.1$ Hz), 3.12 (t, 2H, $J = 5.1$ Hz), 2.76 (t, 2H, $J = 5.4$ Hz), 2.68 (t, 4H, $J = 4.2$ Hz), 1.99–2.02 (m, 2H), 1.84–1.89 (m, 1H), 1.75 (s, 3H), 1.66–1.71 (m, 2H), 1.57–1.61 (m, 2H), 1.50 (t, 4H, $J = 4.1$ Hz), 0.98 (s, 3H), 0.87 (s, 3H). ^{13}C: 170.4, 169.3, 167.2, 157.8, 143.1, 130.6, 129.9, 123.2, 115.6, 108.2, 49.2, 42.1, 33.6, 31.8, 30.6, 28.1, 24.4, 24.1, 23.8. Anal. Calcd for $C_{28}H_{33}N_3O$: C, 74.61; H, 8.81; N, 12.89. Found: C, 74.79; H, 8.62; N, 12.61.

6.4.2. 4-[4-(2-Piperidin-1-yl-ethoxy)-phenyl]-6-[2-(2,6,6-trimethyl-cyclohex-2-enyl)-ethyl]-pyrimidin-2-ylamine (4b). White solid, yield: 85%, mp 104–106 °C; MS (M^{+1}); IR (KBr) 3445, 3156, 2928, 1636, 1548, 1342, 1234 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 7.96 (d, 2H, $J = 8.8$ Hz), 6.98 (d, 2H, $J = 8.8$ Hz), 6.84 (s, 1H), 5.33 (t, 1H, $J = 4.2$ Hz), 5.17 (s, 2H, NH_2), 4.20 (t, 2H, $J = 4.8$ Hz), 3.36 (t, 2H, $J = 4.8$ Hz), 2.82 (t, 2H, $J = 5.6$Hz), 2.72 (t, 4H, $J = 4.8$ Hz), 1.98–2.02 (m, 2H), 1.84–1.89 (m, 1H), 1.77 (s, 3H), 1.66–1.72 (m, 2H), 1.57–1.62 (m, 2H), 1.55 (m, 6H), 0.99 (s, 3H), 0.88 (s, 3H). ^{13}C ($CDCl_3$, 50 MHz): 170.6, 169.4, 167.5, 157.8, 143.2, 130.6, 129.9, 123.3, 115.6, 108.2, 82.6, 65.2, 49.4, 44.5, 42.1, 33.6, 31.8, 30.6, 28.1, 26.2, 25.7, 24.4, 24.1, 23.8. Anal. Calcd for $C_{28}H_{33}N_3O$: C, 74.96; H, 8.99; N, 12.49. Found: C, 74.78; H, 8.68; N, 12.57.

Acknowledgements

A.A. thanks the Council of Scientific and Industrial Research (India) for the award of fellowship. We are also thankful to S.A.I.F., CDRI, Lucknow for providing spectroscopic data. Thanks are also due to Mrs. Shakti Kitchlu for her help in evaluating the biological activity of compounds. CDRI communication No 6664.

References and notes

1. Kamboj, V. P.; Ray, S.; Dhawan, B. N. *Drugs Today* **1992**, *28*, 227.
2. Singh, M. M. *Med. Res. Rev.* **2001**, *21*, 302.
3. Mehrotra, P. K.; Neelima; Bhaduri, A. P.; Kamboj, V. P. *Ind. J. Med. Res.* **1986**, *83*, 614–617.
4. Neelima; Mehrotra, P. K.; Bhaduri, A. P.; Kamboj, V. P. *Ind. J. Med. Res.* **1987**, *86*, 256–259.
5. Singh, M. M.; Mehrotra, P. K.; Agnihotri, A. *Contraception* **1987**, *36*, 239–250.
6. Mukherjee, A.; Akhtar, M. S.; Sharma, V. L. J. *Med. Chem.* **1989**, *32*, 2297–2300.
7. Shukla, R.; Mehrotra, P. K.; Dwivedi, A.; Kamboj, V. P. *Contraception* **1992**, *45*, 605–612.
8. Winters, G.; Oddaso, G.; Conti, M.; Galliani, G. *Eur. J. Med. Chem.* **1984**, *19*, 215–218.
9. Mehrotra, P. K.; Shukla, R.; Dwivedi, A. *Contraception* **1991**, *43*, 507–519.
10. Mehrotra, P. K.; Kitchlu, S.; Batra, S. *Contraception* **2001**, *64*, 187–191.