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# Synthesis, antiinflammatory and analgesic activity of new hexahydropyrimidine derivatives

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A number of potentially active hexahydropyrimidine derivatives of pharmaceutical interest have been synthesized. Various diSchiff's bases prepared by reacting different aromatic aldehydes with 1,3-diaminopropane were suitably reduced to give their tetrahydro derivatives which were then condensed with appropriate aldehydes to give a series of hitherto unreported hexahydropyrimidines. The resulting products were evaluated by oral route for their antiinflammatory activity. The activity of compounds **11**, **23** and **4** was excellent and comparable to indomethacin. In addition to oral route of administration, the antiinflammatory activity of hexahydropyrimidine derivatives was also studied topically through transdermal gels. Compounds **11**, **23**, **4** and **22** produced significant inhibition in edema and showed good antiinflammatory activity comparable to diclofenac sodium gel (Relaxyl® gel). All these compounds were also tested for their analgesic activity and their $LD_{50}$ determined. Compounds **11**, **20** and **23** showed a comparable activity with aspirin. The MTD for all the compounds was found to be >1800 mg/kg.

## 1. Introduction

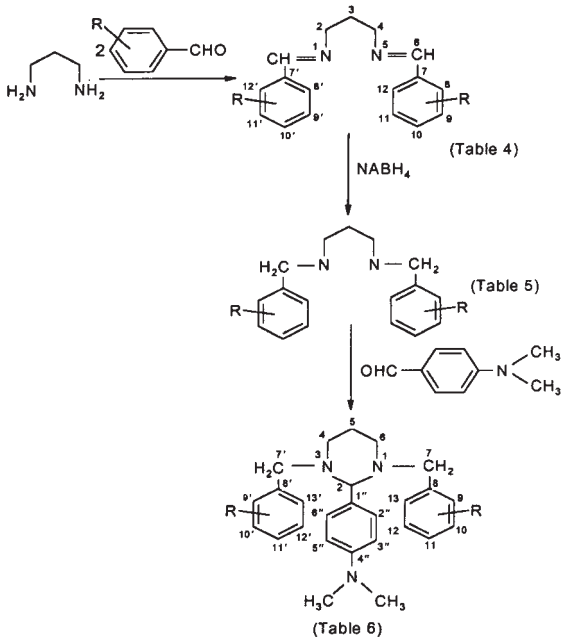
Pyrimidines and their reduced derivatives are known to posses antiinflammatory [1–3], antipyretic [4] and local anesthetic [5] properties. The physiological effects of pyrimidines on respiratory system [6], central nervous system [7], cardiovascular [8] and excretory system [9] have also been documented. Hexahydropyrimidine derivatives have been reported to possess antimycotic [10–12], sedative and hypnotic properties [13].

## 2. Investigations, results and discussion

### *2.1. Chemistry*

In view of the important medicinal properties associated with the pyrimidine skeleton, the hexahydropyrimidine nucleus was selected for further studies. We synthesized a number of 1,2,3-trisubstituted hexahydropyrimidines and evaluated their antiinflammatory and analgesic activity. These compounds were synthesized according to Scheme 1. diSchiff's bases were synthesised by reacting 1,3-diaminopropane with different aromatic aldehydes which were subsequently reduced to give the tetrahydrodiSchiff's bases. The reduced products were finally condensed with suitable aromatic aldehydes to give the title compounds. The structures of the intermediate diSchiff's bases were established on the basis of $^1$H NMR data and the structures of hexahydropyrimidine derivatives were established on the basis of 2D NMR (HH cosy and CH cosy) and MS data.

**Scheme 1**




### *2.2. Antiinflammatory activity*

The testing of antiinflammatory activity was carried out using Winter et al. [14] carrageenan-induced paw edema method in albino rats by oral route and by topical route through transdermal gels.

#### *2.2.1. Oral route of administration*

Indomethacin (20 mg/kg) was chosen as the reference standard antiinflammatory agent for studies on hexahydropyrimidine derivatives. All the test compounds (20 mg/kg) were given orally as carboxymethyl cellulose suspension 1 h before 0.05 ml of carrageenan injection (1% w/v suspension) into the subplantar region of the right hind paw of rats. The paw volume was determined plethysmographically before and 3 h after injection of carrageenan and the percent inhibition of edema of the standard and the test compounds was calculated at same dose level of 20 mg/kg.

Most of the test compounds had noticeable antiinflammatory activity. The activity of compounds **11**, **23** and **4** was found to be good and comparable to indomethacin. This was followed by compounds **20**, **26**, **29**, **8** and **32** which showed significant results. Further, compounds **14**, **47**, **41** and **44** also showed moderate antiinflammatory activity. Statistical analysis was done using Student's *t* test. The results are shown in Table 1.

#### *2.2.2. Transdermal route of administration*

Based on the results obtained with the antiinflammatory activity of hexahydropyrimidine derivatives when adminis-

**Table 1: Antiinflammatory activity in rats[a] determined by the carrageenan induced rat paw edema method (oral administration)**

| Compd. | Change in edema volume at 3 h (ml) | Inhibition (%) |
|---|---|---|
| Normal Saline[b] (control) | $0.64 \pm 0.05$ | – |
| Indomethacin | $0.20 \pm 0.04^{A}$ | 68.75 |
| **4** | $0.27 \pm 0.03^{A}$ | 57.81 |
| **8** | $0.35 \pm 0.02^{A}$ | 45.31 |
| **11** | $0.24 \pm 0.03^{A}$ | 62.50 |
| **14** | $0.39 \pm 0.04^{B}$ | 39.06 |
| **17** | $0.50 \pm 0.04$ | 21.85 |
| **20** | $0.29 \pm 0.04^{A}$ | 54.58 |
| **23** | $0.26 \pm 0.04^{A}$ | 59.37 |
| **26** | $0.31 \pm 0.03^{A}$ | 51.56 |
| **29** | $0.33 \pm 0.03^{A}$ | 48.47 |
| **32** | $0.37 \pm 0.02^{A}$ | 42.18 |
| **35** | $0.47 \pm 0.02^{B}$ | 26.56 |
| **38** | $0.52 \pm 0.04$ | 18.75 |
| **41** | $0.44 \pm 0.03^{B}$ | 31.25 |
| **44** | $0.45 \pm 0.04^{C}$ | 29.69 |
| **47** | $0.41 \pm 0.03^{B}$ | 35.93 |
| **50** | $0.56 \pm 0.03$ | 15.62 |

[a] Six rats in each group.
[b] Dose of control was 1 ml/kg.
[A–C] Student's *t* test: p values calculated against carrageenan administered normal saline control.
[A] $p < 0.001$; [B] $p < 0.01$; [C] $p < 0.02$

tered orally, it was decided to explore the activity of these compounds by topical application. The present studies were conducted on albino rats (Wistar strain) using 1% w/w diclofenac sodium gel (Relaxyl® gel, M/s Franco Indian Pharmaceuticals Ltd., India) as a standard topical antiinflammatory agent. The test compounds were studied by topical application in 1% w/w polyvinyl alcohol gel. The gel was prepared by dissolving 13 g polyvinyl alcohol in 100 ml of water. The usual method of administration of 0.05 ml of 1% w/v carrageenan suspension in the subplanar region of the right hind paw of rats was followed 1 h after gel application. Change in edema volume 3 h after carrageenan injection and percentage inhibition was calculated to assess the antiinflammatory activity. Statistical analysis of the data was done by Student's *t* test. The data is presented in Table 2.

All the test compounds showed some antiinflammatory activity. The compounds **11**, **23**, **4** and **20** produced significant inhibition in edema and showed good antiinflammatory activity comparable to the diclofenac sodium gel. This was followed by compounds **26**, **29** and **8** which also showed moderate antiinflammatory activity. The results are in close agreement with the results when the test compounds were given orally.

### *2.2. Analgesic activity*

The testing of analgesic activity was carried out using Witkin et al. [15] method of acetic acid induced writhing response in albino mice. The analgesic activity of hexahydropyrimidine derivatives was analyzed using aspirin (25 mg/kg, i.p.) as a standard analgesic agent.

All the test compounds (25 mg/kg, i.p.) were injected as CMC suspension. 20 min later, 3% v/v acetic acid solution (1 ml/100g body weight of albino mice) was administered to the animals. The severity of writhing response was recorded for 20 min after administration of acetic acid solution. The mean writhing scores in control groups treated with the compounds were calculated. The percentage protection for standard as well as test compounds was calculated at the same dose level of 25 mg/kg. Statistical analysis was done by Student's *t* test. The results are shown in Table 3.

**Table 2: Antiinflammatory activity after transdermal administration against carrageenan induced rat paw edema[a]**

| Compd. | Change in edema volume at 3 h (ml) | Inhibition (%) |
|---|---|---|
| Normal Saline[b] (control) | $0.60 \pm 0.04$ | – |
| Diclofenac sodium | $0.22 \pm 0.04$ | 63.33 |
| **4** | $0.26 \pm 0.03^{A}$ | 56.67 |
| **8** | $0.32 \pm 0.04^{A}$ | 46.67 |
| **11** | $0.22 \pm 0.05$ | 63.33 |
| **14** | $0.35 \pm 0.04^{A}$ | 41.67 |
| **20** | $0.27 \pm 0.07^{B}$ | 55.00 |
| **23** | $0.24 \pm 0.03^{A}$ | 60.00 |
| **26** | $0.29 \pm 0.02^{A}$ | 51.67 |
| **29** | $0.31 \pm 0.06^{B}$ | 48.33 |
| **32** | $0.36 \pm 0.04^{B}$ | 40.00 |
| **41** | $0.40 \pm 0.03^{B}$ | 33.33 |
| **47** | $0.38 \pm 0.04^{B}$ | 36.67 |

[a] Six rats in each group.
[A, B] Student's *t* test: p values calculated against carrageenan administered normal saline control.
[A] $p < 0.001$; [B] $p < 0.01$

Almost all the test compounds showed analgesic activity to some extent and significant results were obtained. Compounds **11**, **20** and **23** were found to be the most potent having an activity comparable to aspirin. These were closely followed by compounds **4**, **29**, **26** and **8**. Reasonably good analgesic activity was also seen in compounds **32**, **44**, **14**, **35**, **41**, **47** and **50**.

### *2.3. Acute toxicity studies*

The method of Miller and Tainter [16] for determination of $LD_{50}$ values of the test compounds was followed in the present studies. The synthesized hexahydropyrimidine de-

**Table 3: Analgesic effect of hexahydropyrimidine derivatives against acetic acid induced writhing response in mice[a]**

| Compd. | Number of writhing episodes in 20 min | Inhibition (%) |
|---|---|---|
| Normal Saline[b] (control) | $26.2 \pm 0.42$ | – |
| Aspirin | $9.7 \pm 0.36^{A}$ | 63.0 |
| **4** | $11.8 \pm 0.24^{A}$ | 55.0 |
| **8** | $12.7 \pm 0.32^{A}$ | 51.53 |
| **11** | $10.0 \pm 0.28^{A}$ | 61.8 |
| **14** | $14.0 \pm 0.24^{A}$ | 46.6 |
| **17** | $18.7 \pm 0.32^{A}$ | 28.63 |
| **20** | $10.3 \pm 0.32^{A}$ | 60.69 |
| **23** | $10.5 \pm 0.30^{A}$ | 59.90 |
| **26** | $12.3 \pm 0.36^{A}$ | 53.05 |
| **29** | $13.0 \pm 0.28^{A}$ | 53.08 |
| **32** | $13.4 \pm 0.24^{A}$ | 48.86 |
| **35** | $14.4 \pm 0.42^{A}$ | 45.04 |
| **38** | $20.8 \pm 0.32^{A}$ | 20.61 |
| **41** | $14.6 \pm 0.44^{A}$ | 44.28 |
| **44** | $13.8 \pm 0.24^{A}$ | 47.33 |
| **47** | $14.7 \pm 0.36^{A}$ | 43.08 |
| **50** | $15.6 \pm 0.44^{A}$ | 40.46 |

[a] Six mice in each group.
[A] Student's *t* test: p values calculated against acetic acid administered normal saline control.
[A] $p < 0.001$

**Table 4: Characterization data of diSchiff's bases synthesized**

| Compd. | R | Solvent of reaction* (Refluxing time in h) | m.p. (°C) (Solvent of crystallization)* | Appearance | Yield (%)** | Solvent of elution* ($R_f$ value) | $^1$H NMR | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Solvent used (instrument in MHz) | δ Values |
| **2** | 8(8′)-Cl, 12(12′)-Cl | b (24) | 44 (p) | Colouless shining needles | 72.07 | b : p; 6 : 4 (0.60) | $CDCl_3$ (60) | 2.3(p, H-3), 3.9 (t, H-2, H-4), 7.4 (m, H-9, H-9′, H-10, H-10′, H-11, H-11′), 8.6 (s, H-6, H-6′) |
| **6** | 8(8′(-Cl, 10(10′)-Cl | b (24) | 102 (p) | Cotton like fine long colourless needles | 76.58 | b : p; 1 : 9 (0.65) | $CDCl_3$ (60) | 2.0 (p, H-3), 3.7 (t, H-2, H-4), 7.2 (dd, H-11, H-11′), 7.3 (d, H-9, H-9′), 7.9 (d, H-12, H-12′), 8.65 (s, H-6, H-6′) |
| **9** | 9(9′)-Cl, 10(10′)-Cl | b (24) | 66 (p) | Colourless shining crystalline compound | 67.57 | b : p; 6 : 4 (0.64) | $CDCl_3$ (300) | 2.09 (p, H-3), 3.74 (t, H-2, H-4), 7.47 (m, H-8, H-8′, H-12, H-12′), 7.82 (d, H-11, H-11′), 8.2 (s, H-6, H-6′) |
| **12** | 8(8′)-$OCH_3$, 11(11′)-Br | b (12) | 98 (p) | Thick rhombic colourless crystals | 82.57 | b : p; 6 : 4 (0.64) | $CDCl_3$ (300) | 2.09 (p, H-3), 3.71 (t, H-2, H-4), 3.83 (s, $-OCH_3 \times 2$), 6.7 (dd, H-9, H-9′), 7.43 (dd, H-10, H-10′), 8.05 (dd, H-12, H-12′), 8.63 (s, H-6, H-6′) |
| **15** | 9(9′)-$OCH_3$, 10(10′)-$OCH_3$), 10(10′)-$OCH_3$ | b (8) | 85 (m) | Pale yellow rod like crystals | 74.55 | b:ea; 8:2 (0.64) | $CDCl_3$ (100) | 2.1 (p, H-3), 3.71 (t, H-2, H-4), 3.9 (s, $-OCH_3 \times 6$), 7.0 (s, H-8, H-8′, H-12, H-12′), 8.2 (s, H-6, H-6′) |
| **18** | 8(8′)-OH | b (6) | 44 (p) | Yellow shining needles | 85.82 | b:ea; 8:2 (0.63) | $CDCl_3$ (60) | 2.1 (p, H-3), 3.6 (t, J = 6 Hz, H-2, H-4), 6.9 and 7.2 (2m, H-9, H-9′, H-10, H-10′, H-11, H-11′, H-12. H-12′), 8.3 (s, H-6, H-6′) |
| **21** | 8(8′)-Cl | b (24) | 49–50 (p) | Colourless shining crystals | 78.01 | b:ea; 8:2 (0.64) | $CDCl_3$ (60) | 1.8 (p, H-3), 3.5 (t, H-2, H-4), 7.0 (unresolved broad singlet, H-9, H-9′, H-10, H-10′, H-11, H-11′), 7.7 (m, H-12, H-12′), 8.4 (s, H-6, H-6′) |
| **24** | 10(10′)-Cl | b (6) | 58 (p) | Colourless crystalline compound | 71.93 | b:ea; 8:2 (0.63) | $CDCl_3$ (100) | 2.09 (p, H-3), 3.70 (t, H-2, H-4), 7.44 (d, H-9, H-9′, H-11, H-11′), 7.72 (d, H-8, H-8′, H-12, H-12′), 8.25 (s, H-6, H-6′) |
| **27** | *** | b (48) | 58 (p) | Colourless shining thick needles | 69.93 | b:ea; 8:2 (0.64) | $CDCl_3$ (60) | 2.0 (p, H-3), 3.6 (t, J = 7 Hz, H-2, H-4), 6.9–7.5 (m, H-9, H-9′, H-10, H-10′, H-11, H-11′), 8.3 (s, H-6, H-6′) |
| **30** | 9(9′),10(10′)-Methylene dioxy | b (6) | 122–123 (m–d) | Colourless crystalline compound | 81.42 | b:ea; 8:2 (0.65) | $CDCl_3$ (60) | 1.7 (p, H-3), 3.4 (t, H-2, H-4), 3.7 (s, $OCH_2 \times 2$), 6.5 (d, J = 8 Hz, H-11, H-11′), 6.8 (dd, J = 8 Hz, 2 Hz, H-12, H-12′), 7.1 (d, J = 2 Hz, H-8, H-8′), 7.9 (s, H-6, H-6′) |
| **33** | 9(9′)-$OCH_3$, 10(10′)-$OCH_3$ | e (6) | 112–113 (e) | Colourless crystalline compound | 84.82 | b:ea; 8:2 (0.60) | $CDCl_3$ (60) | 2.0 (p, H-3), 3.6 (t, J = 7 Hz, H-2, H-4), 3.9 (s, $-OCH_3 \times 4$), 6.8 (d, J = 8 Hz, H-11, H-11′), 7.1 (dd, J = 8 Hz, 2 Hz, H-12, H-12′), 7.4 (d. J = 2 Hz, H-8, H-8′), 8.1 (s, H-6, H-6′) |
| **36** | H | e (48) | 32–33 (p) | Pale yellow shining needles | 63.56 | b:p; 4:6 0.62 | $CDCl_3$ (60) | 2.0 (p, H-3), 3.6 (t, J = 7 Hz, H-2, H-4), 7.2 and 7.6 (2m, H-8, H-8′, H-9, H-9′, H-10, H-10′, H-11, H-11′, H-12, H-12′), 8.2 (s, H-6, H-6′) |
| **39** | 10(10′)-$OCH_3$ | b (6) | 72 (p) | Colourless crystalline compound | 85.94 | b:ea; 8:2 (0.64) | $CDCl_3$ (60) | 2.0 (p, H-3), 3.6 (t, H-2, H-4), 3.7 (s, $-OCH_3 \times 2$), 6.8 (d, H-9, H-9′, H-11, H-11′), 7.6 (d, H-8, H-8′, H-12, H-12′), 8.1 (s, H-6, H-6′) |
| **42** | 8(8′)-$OCH_3$ | b (24) | 73 (p) | Colourless shining crystals | 64.19 | b:ea; 8:2 (0.62) | $CDCl_3$ (60) | 1.8 (p, H-3), 3.3 (t, H-2, H-4), 3.5 (s, $-OCH_3 \times 2$), 6.5 (m, H-9, H-9′, H-11, H-11′), 7.0 (m, H-10, H-10′), 7.5 (m, H-12, H-12′), 8.4 (s, H-6, H-6′) |
| **45** | 10(10′)-$N(CH_3)_2$ | b (7) | 135–136 (m–d) | Colourless crystalline compound | 84.07 | b:ea; 8:2 (0.64) | $CDCl_3$ (60) | 1.8 (p, J = 7 Hz, H-3), 2.9 (s, $-N(CH_3)_2 \times 2$), 3.4 (t, J = 7 Hz, H-2, H-4), 6.5 (d, J = 8 Hz, H-9, H-9′, H-11, H-11′), 7.4 (d, J = 8 Hz, H-8, H-8′, H-12, H-12′), 7.9 (s, H-6, H-6′) |
| **48** | 10(10′)-$CH_3$ | b (24) | 66 (p) | Colourless crystalline compound | 89.83 | b:ea; 2:8 (0.64) | $CDCl_3$ (60) | 1.9 (p, H-3), 2.2 (s, $C-CH_3 \times 2$), 3.4 (t, J = 7 Hz, H-2, H-4), 6.9 (d, H-9, H-9′, H-11, H-11′), 7.4 (d, H-8, H-8′, H-12, H-12′), 8.0 (s, H-6, H-6′) |

s – singlet, d– doublet, dd – double douplet, t – triplet, p – pentet, m – multiplet; * b = benzene, p = petroleum ether, m = methanol, ea = ethylacetate, d = dichloromethane, e = ethanol. ** Yields of compounds were calculated on the basis on the amount of aromatic aldehyde used during the reaction. *** 2-thienyl in place of substituted phenyl

rivatives were evaluated in albino mice with ten animals in each group.
The test compounds were injected as suspension in 1% CMC by intraperitoneal route and the animals were observed for 2 h for death due to acute toxicity, followed by observation for mortality up to a period of 48 h.
All the compounds tested (**4**, **8**, **11**, **14**, **17**, **20**, **23**, **26**, **29**, **32**, **35**, **38**, **41**, **44**, **47** and **50**) were found to have a Maximum Tolerated Dose (MTD) >1800 mg/kg by i.p. route and showed no mortality for an observed time period of 48 hours.

### *2.4. Structure activity relationship*

The following structure activity relationship features were noted.

1. Introduction of chlorine atoms in the benzyl substituents of the hexahydropyrimidine skeleton showed optimal antiinflammatory and analgesic activity (compounds **11**, **23**, **4**, **26** and **8** showed maximum potency).
2. In addition to the chlorine atom, introduction of a hydroxyl group in the 1,3-aryl substituent also improved activity (compounds **20**, **26** and **8** showed appreciable antiinflammatory and analgesic activity).
3. Introduction of a thiophene ring instead of the phenyl ring at the 7 and 7′ positions (compound **29**) also resulted in good antiinflammatory and analgesic activity.
4. A 3,4-methylenedioxybenzyl group at 1 and 3 positions (compound **32**) led to moderate activity.
5. Introduction of other substituents like bromo, p-dimethylamino, methoxy or methyl group in the 1,3-aryl substituent did not show any marked effect on antiinflammatory and analgesic activity.

## 3. Experimental

The m.p.'s of all the compounds were recorded in open glass capillaries using paraffin bath. Purity of the compounds was checked by TLC on silica gel G plates and the spots were either located under uv light or through exposure to iodine vapours.
The solvents used were of LR grade and purified before use. Ethanol used throughout the studies was purified by distilling over NaOH. Benzene used was distilled over sodium wire. Azeotropic distillitation of the reactants was carried out in a Dean-Stark apparatus wherever mentioned to remove water generated during the course of the reaction.
The structures of all the newly synthesized compounds were established on the basis of $^1$H NMR and MS data. The $^1$H NMR spectra of all the compounds were recorded on Varian EM-360 60 MHz or Jeol JNM FX 100 FT NMR or Bruker Spectrospin DPX 300 MHz instrument. MS of the compounds were recorded on Jeol JMS-D300 instrument.
Since the correct assignment of peaks to different protons of the hexahydropyrimidine derivatives both in the aliphatic and aromatic regions was found to be difficult on the basis of $^1$H NMR spectra alone hence a recourse was taken to 2D NMR (HH cosy and CH cosy) spectrometric studies which could provide exact assignments.

#### *3.1. Synthesis of diSchiff's bases*

1,3-Diaminopropane (1 mol) was condensed with different aromatic aldehydes (2 mol), namely 2,6-dichlorobenzaldehyde, 2,4-dichlorobenzaldehyde, 3,4-dichlorobenzaldehyde, 5-bromo-*o*-anisaldehyde, 3,4,5-trimethoxybenzaldehyde, salicylaldehyde, *o*-chlorobenzaldehyde, *p*-chlorobenzaldehyde, thiophene-2-aldehyde, piperonal, veratraldehyde, benzaldehyde, *p*-anisaldehyde, *o*-anisaldehyde, *p*-dimethylaminobenzaldehyde and *p*-tolualdehyde to give the diSchiff's bases **2**, **6**, **9**, **12**, **15**, **18**, **21**, **24**, **27**, **30**, **33**, **36**, **39**, **42**, **45** and **48**.
Formation of diSchiff's base **2** from **1**: 1,3-Diaminopropane (1) (0.22 g ≡ 0.25 ml; 2.97 mmol) was dissolved in dry benzene (20.0 ml) and 2,6-dichlorobenzaldehyde (1.20 g; 5.71 mmol) was added. The contents were refluxed on a heating mantle in a Dean-Stark assembly for 24 h while removing the water formed azeotropically during the course of the reaction. After completion of the reaction, benzene was distilled off to give a pale yellow oily mass. It was crystallised from petroleum ether under cold conditions to give colourless shining needles (2), m.p. 44 °C, yield – 0.80 g (72.07%). A TLC examination in benzene : petroleum ether (6 : 4) solvent system showed a single spot ($R_f$: 0.60).
Similarly, other diSchiff's bases were synthesized (Table 4). The solvents used for carrying out the reactions and for the purpose of crystallisation along with m.p. (°C), appearance, % yield, TLC solvent system, $R_f$ values and spectral data are indicated in the Table. The structures of all these compounds were established on the basis of $^1$H NMR spectral data (Table 4).

#### *3.2. Synthesis of tetrahydrodiSchiff's bases*

The above diSchiff's bases were reduced by sodium borohydride to give the corresponding tetzrahydro derivatives. Sixteen new tetrahydrodiSchiff's bases were synthesized.
Formation of tetrahydrodiSchiff's base **3** from **2**: The diSchiff's base **2** (1.00 g, 2.58 mmol) was dissolved in methanol (15.0 ml) in a 100 ml conical flask and the solution stirred magnetically under cold conditions maintaining the temperature below 18 °C. A solution of sodium borohydride (0.60 g) was prepared in 2N NaOH (1.2 ml), diluted with $H_2O$ (6.0 ml) and then added dorpwise to the above cooled solution. The reaction mixture was further stirred for 7 h at room temperature. After completion of the reaction, methanol was removed by evaporation and the resulting colourless residue diluted with water (25.0 ml). An oily viscous liquid mass separated out which was extracted with ethyl ether, washed with water and dried over anhydrous sodium sulphate. The solvent was distilled off to give a colourless oily mass (**3**), yield – 0.80 g (79.21%). It gave a single spot on TLC examination in benzene : petroleum ether (8 : 2) solvent system ($R_f$: 0.61).

**Table 5: Physical data of tetrahydrodiSchiff's bases synthesized**

| Compd.* | R | Solvent of reaction** (Stirring time in h) | Yield*** (%) | Solvent of elution** ($R_f$ value) |
|---|---|---|---|---|
| **3** | 8(8′)-Cl, 12(12′)-Cl | m (7) | 79.21 | b:p; 8:2 (0.61) |
| **7** | 8(8′)-Cl, 10(10′)-Cl | m (7) | 78.43 | b:p; 9:1 (0.60) |
| **10** | 9(9′)-Cl, 10(10′)-Cl | m (7) | 81.19 | b:p; 8:2 (0.60) |
| **13** | 8(8′)-$OCH_3$, 11(11′)-Br | m (7) | 83.33 | b:p; 8:2 (0.64) |
| **16** | 9(9′)-$OCH_3$, 10(10′)-$OCH_3$, 11(11′)-$OCH_3$ | m–d (8) | 89.11 | b:e; 8:2 (0.65) |
| **19** | 8(8′)-OH | m (8) | 84.16 | b:ea; 9:1 (0.63) |
| **22** | 8(8′)-Cl | m (8) | 84.98 | b:e; 8:2 (0.64) |
| **25** | 10(10′)-Cl | m (8) | 98.81 | b:e; 8:2 (0.64) |
| **28** | **** | m (8) | 73.89 | b:e; 8:2 (0.65) |
| **31** | 9(9′), 10(10′) methylenedioxy | m–d (7) | 98.68 | b:e; 8:2 (0.64) |
| **34** | 9(9′)-$OCH_3$, 10(10′)-$OCH_3$ | m–d (7) | 84.31 | b:e; 8:2 (0.63) |
| **37** | H | m (8) | 78.74 | b:e; 8:2 (0.68) |
| **40** | 10(10′)-$OCH_3$ | m (7) | 98.81 | b:e; 8:2 (0.65) |
| **43** | 8(8′)-$OCH_3$ | m (8) | 88.76 | b:e; 8:2 (0.64) |
| **46** | 10(10′)-$N(CH_3)_2$ | m–d (7) | 88.24 | b:e; 8:2 (0.68) |
| **49** | 10(10′)-$CH_3$ | m (7) | 84.31 | b:e; 8:2 (0.67) |

* All the compounds were obtained as colourless oily mass.
** m = methanol, d = dichloromethane, b = benzene, p = petroleum ether, e = ethanol, ea = ethylacetate.
*** Yields of the compounds were calculated on the basis of the amount of diSchiff's base used during the reaction.
**** 2-thienyl in place of substituted phenyl

**Table 6: Characterization data of hexahydropyrimidine derivatives**

| Compd. | R | Reaction time in h; m.p.; (solvent used for crystallization)**; appearance of crystals | Yield (%)*** | Solvent system** ($R_f$ value) | $^1$H NMR assignments based on 2D (HH cosy) (δ values) and Mass spectral data (m/z) | $^{13}$C NMR assignments based on CH cosy (δ values) |
|---|---|---|---|---|---|---|
| **4** | 9(9′)-Cl, 13(13′)-Cl | 12; 168; (m–d); Colourless shining needles | 53.92 | b:ea; 9:1 (0.60) | $CDCl_3$; 1.4 and 1.9 (2s, H-5), 2.5 and 2.85 (t and m, H-4, H-6), 2.9 (s, $-N(CH_3)_2$), 3.8 and 4.0 (2d, H-7, H-7′), 3.9 (s, H-2), 6.8 (d, H-3″, H-5″), 7.0 (m, H-11, H-11′), 7.2 (m, H-10, H-10′, H-12, H-12′), 7.6 (d, H-2″, H-6″) $M^+$: 523, 403, 362, 333, 161 | 20 (C-5), 40 ($-N(CH_3)_2$), 47 (C-4, C-6), 54 (C-7, C-7′), 87.8 (C-2, 112 (C-3″, C-5″), 128 (C-10, C-10′, C-12, C-12′), 130 (C-11, C-11′), 130.5 (C-2″, C-6″) |
| **8** | 9(9′)-Cl, 11(11′)-Cl | 8; 155; (m–d); Colourless shining thick needles | 66.04 | b:p; 1:9 (0.64) | $CDCl_3$; 1.4 and 1.8 (d and m, H-5), 2.1 and 3.1 (t and m, H-4, H-6), 2.9 (s, $-N(CH_3)_2$), 3.2 and 3.4 (2d, H-7, H-7′), 3.7 (s, H-2), 6.6 (d, H-3″, H-5″), 7.2 (dd, H-12, H-12′), 7.3 (d, H-10, H-10′), 7.4 (d, H-13, H-13′), 7.5 (d, H-2″, H-6″) $M^+$: 523, 404, 363, 334, 161 | 25 (C-5), 40 ($-N(CH_3)_2$), 51 (C-4, C-6), 54 (C-7, C-7′), 88 (C-2), 112 (C-3″, C-5″), 126 (C-13, C-13′), 129 (C-10, C-10′), 130 (C-12, C-12′), 131 (C-2″, C-6″) |
| **11** | 10(10′)-Cl, 11(11′)-Cl | 24; 122; (m–d); Colourless shining needles | 50.46 | b:p; 9:1 (0.62) | $CDCl_3$; 1.3 and 1.8 (d and m, H-5), 2.0 and 2.85 (t and m, H-4, H-6), 2.9 (s, $-N(CH_3)_2$), 2.75 and 3.58 (2d, H-7, H-7′), 3.4 (s, H-2), 6.65 (d, H-3″, H-5″), 7.0 (d, H-13, H-13′), 7.2 (s, H-9, H-9′), 7.28 (d, H-12, H-12′), 7.4 (d, H-2″, H-6″) $M^+$: 523, 403, 362, 333, 161 | 25 (C-5), 40 ($-N(CH_3)_2$), 52 (C-4, C-6), 55 ($-OCH_3 \times 4$), 57 (C-7, C-7′), 88 (C-2), 112 (C-3″, C-5″), 128 (C-13, C-13′), 129 (C-9, C-9′), 130 (C-2″, C-6″), 130.5 (C-12, C-12′) |
| **14** | 9(9′)-$OCH_3$, 12(12′)-Br | 8; 186; (m–d); Colourless shining needles | 54.69 | b:p; 9.5:0.5 (0.63) | $CDCl_3$; 1.4 and 1.9 (d and m, H-5), 2.1 and 3.0 (t and d, H-4, H-6), 2.9 (s, $-N(CH_3)_2$), 3.15 and 3.4 (2d, H-7, H-7′), 3.7 (s, H-2), 3.75 (s, $-OCH_3 \times 2$), 6.6 (d, H-10, H-10′), 6.65 (d, H-3″, H-5″), 7.2 (dd, H-11, H-11′), 7.4 (d, H-2″, H-6″), 7.5 (d, H-13, H-13′) $M^+$: 601, 605, 481, 485, 402, 404, 199, 201, 120 | 24 (C-5), 40 ($-N(CH_3)_2$), 51 (C-7, C-7′), 52 (C-4, C-5), 89 (C-2), 111 (C-10, C-10′), 112 (C-3″, C-5″), 129 (C-11, C-11′), 130 (C-2″, C-6″), 132 (C-13, C-13′) |
| **17** | 10(10′)-$OCH_3$, 11(11′)-$OCH_3$, 12(12′)-$OCH_3$ | 12; 148; (m–d); Colourless shining fine needles | 53.85 | b:ea; 9:1 (0.60) | $CDCl_3$; 1.5 and 1.9 (d and m, H-5), 2.1 and 3.1 (t and d, H-4, H-6), 2.9 (s, $-N(CH_3)_2$), 2.75 and 3.7 (2d, H-7, H-7′), 3.5 (s, H-2), 3.8 (2s, $-OCH_3 \times 6$), 6.45 (s, H-9, H-9′, H-13, H-13′), 6.7 (d, H-3″, H-5″), 7.5 (d, H-2″, H-6″) $M^+$: 565, 446, 385, 328, 181 | 24 (C-5), 40 ($-N(CH_3)_2$), 52 (C-4, C-6), 56 and 61 ($-OCH_3 \times 6$), 59 (C-7, C-7′), 88 (C-2), 105 (C-9, C-9′; C-13, C-13′), 112 (C-3″, C-5″), 130 (C-2″, C-6″) |
| **20**** | 9(9′)-OH | 8; 156–158; (m–d); Colourless shining needles | 65.07 | b:ea; 8:2 (0.64) | $CDCl_3$; 1.5 and 1.9 (2m, H-5), 2.1 and 3.0 (t and d, H-4, H-6), 2.8 (s, $-N(CH_3)_2$), 3.2 and 3.7 (2d, H-7, H-7′), 3.5 and 3.6 (2s, H-2), 6.6 (d, H-3″, H-5″), 6.65 (m, H-10, H-10′), 6.85 (m, H-12, H-12′), 7.0 (m, H-11, H-11′), 7.3 (m, H-13, H-13′), 7.5 (d, H-2″, H-6″) | 25 (C-5), 39 ($-N(CH_3)_2$), 51 (C-7, C-7′), 52 (C-4, C-6), 90 (C-2), 110 (C-10, C-10′), 112 (C-3″, C-5″), 120 (C-12, C-12′), 127 (C-11, C-11′), 129 (C-2″, C-6″), 130 (C-13, C-13′) |
| **23** | 9(9′)-Cl | 8, 140–142; (m–d); Colourless shining thick needles | 74.50 | b:ea; 9:1 (0.62) | $CDCl_3$; 1.4 and 1.9 (d and m H-5), 2.1 and 3.0 (t and d, H-4, H-6), 2.8 (s, $-N(CH_3)_2$), 3.4 and 3.6 (2d, H-7, H-7′), 3.8 (s, H-2), 6.6 (d, H-3″, H-5″), 7.0 (m. H-12, H-12′), 7.1 (m, H-11, H-11′), 7.25 (d, H-13, H-13′), 7.5 (d, H-2″, H-6″), 7.6 (d, H-10, H-10′) $M^+$: 453, 333, 328, 125 | 25 (C-5), 40 ($-N(CH_3)_2$), 51 (C-4, C-6), 55 (C-7, C-7′), 88 (C-2), 112 (C-3″, C-5″), 126 (C-11, C-11′), 127 (C-12, C-12′), 129 (C-13, C-13′), 130 (C-2″, C-6″), 130.5 (C-10, C-10′) |
| **26** | 11(11′)-Cl | 8; 152–154; (m–d); Colourless shining thick needles | 71.12 | b:e; 9.5:0.5 (0.62) | $CDCl_3$; 1.4 and 1.8 (d and m, H-5), 2.1 and 3.0 (t and m, H-4, H-6), 2.8 and 3.6 (2d, H-7, H-7′), 2.9 (s, $-N(CH_3)_2$), 3.5 (s, H-2), 6.65 (d, H-3″, H-5″), 7.2 (d, H-9, H-9′), H-10, H-10′, H-12, H-12′, H-13, H-13′), 7.4 (d, H-2″, H-6″) $M^+$: 453, 333, 314, 125 | 25 (C-5), 40 ($-N(CH_3)_2$), 52 (C-4, C-6), 57 (C-7, C-7′), 89 (C-2), 112 (C-3″, C-5″), 128 (C-10, C-10′, C-12, C-12′), 130 (C-9, C-9′, C-13, C-13′, C-2″, C-6″) |

**Table 6: Continued**

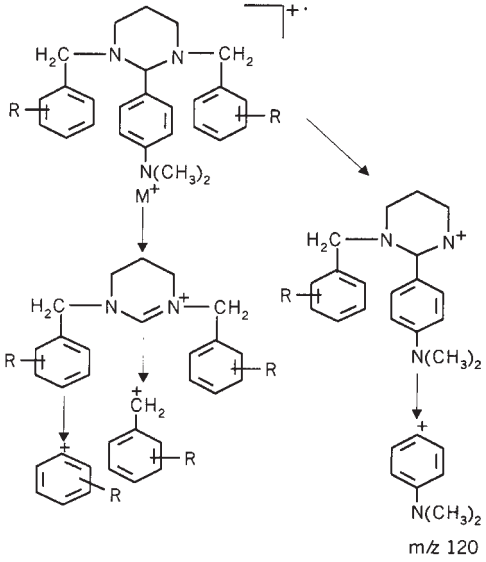
| Compd. | R | Reaction time in h; m.p.; (solvent used for crystallization)**; appearance of crystals | Yield (%)*** | Solvent system** ($R_f$ value) | $^1$H NMR assignments based on 2D (HH cosy) (δ values) and Mass spectral data (m/z) | $^{13}$C NMR assignments based on CH cosy (δ values) |
|---|---|---|---|---|---|---|
| **29** | ***** | 6; 110–112; (m–d); Colourless shining needles | 58.04 | b:e; 9.5:0.5 (0.63) | $CDCl_3$; 1.4 and 1.8 (d and m, H-5), 2.1 and 3.1 (t and d, H-4, H-6), 2.9 (s, $-N(CH_3)_2$), 3.3 and 3.7 (2d, H-7, H-7′), 3.6 (s, H-2), 6.6 (d, H-3″, H-5″), 6.7 (d, H-10, H-10′), 6.85 (dd, H-11, H-11′), 7.1 (d, H-12, H-12′), 7.5 (d, H-2″, H-6″) $M^+$: 397, 277, 97, 83 | 25 (C-5), 40 ($-N(CH_3)_2$), 51 (C-4, C-6), 53 (C-7, C-7'), 86 (C-2), 112 (C-3″, C-5″), 124.5 (C-12, C-12′), 125.5 (C-10, C-10′), 126.5 (C-11, C-11′), 130.5 (C-2″, C-6″) |
| **32** | 10(10′), 11(11′)-methyl-enedioxy | 6; 124–125; (m–d) Colourless shining needles | 69.57 | b:e ; 9.5:0.5 (0.63) | $CDCl_3$; 1.4 and 1.8 (d and m, H-5), 2.0 and 3.1 (t and d, H-4, H-6), 2.7 and 3.6 (2d, H-7, H-7′), 3.0 (s, $-N(CH_3)_2$), 3.5 (s, H-2), 5.9 (s, $-O-CH_2-O \times 4$), 6.6 (unresolved doublet, H-9, H-9′, H-12, H-12′), 6.7 (d, H-3″, H-5″), 6.8 (unresolved doublet, H-13, H-13′), 7.5 (d, H-2″, H-6″) $M^+$:473, 353, 161, 135 | 25 (C-5), 41 ($-N(CH_3)_2$), 52 (C-4, C-6), 59 (C-7, C-7′), 90 (C-2), 100 ($-O-CH_2-O- \times 2$), 107 (C-12, C-12′), 109 (C-13, C-13′), 112 (C-3″, C-5″), 121 (C-9, C-9′), 130 (C-2″, C-6″) |
| **35** | 10(10′)-$OCH_3$– 11(11′)-$OCH_3$ | 6; 140–142; (m–d); Colourless shining crystalline compound | 77.59 | b:e; 9.5:0.5 (0.66) | $CDCl_3$; 1.5 and 1.9 (d and m, H-5), 2.1 and 3.1 (t and d, H-7, H-7′), 3.0 (s, $-N(CH_3)_2$), 3.5 (s, H-2), 3.9 and 4.0 (2s, $-OCH_3 \times 4$), 6.65 (m, H-3″, H-5″), 6.7 (m, H-9, H-9′, H-12, H-12′, H-13, H-13′), 7.5 (d, H-2″, H-6″) $M^+$: 505, 385, 354, 151, 134 | 25 (C-5), 40 ($-N(CH_3)_2$), 52 (C-4, C-6), 56 ($-OCH_3 \times 4$), 58 (C-7, C-7′), 90 (C-2), 110 (C-3″, C-5″), 111.8 (C-9, C-9′), 112 (C-12, C-12′), 121 (C-13, C-13′), 130 (C-2″, C-6″) |
| **38** | H | 6; 120–121; (m–d); Long colourless shining needles | 75.91 | b:e; 9.5:0.5 (0.65) | $CDCl_3$; 1.4 and 1.8 (d and m, H-5), 2.0 and 3.0 (t and d, H-4, H-6), 2.8 and 3.7 (m and d, H-7, H-7′), 2.9 (s, $-N(CH_3)_2$), 3.5 (s, H-2), 6.7 (d, H-3″, H-5″), 7.2 (m, H-11, H-11′), 7.3 (m, H-9, H-9′, H-13, H-13′), 7.35 (m, H-10, H-10′, H-12, H-12′), 7.5 (d, H-2″, H-6″) $M^+$: 385, 265, 91, 77 | 25 (C-5), 40 ($-N(CH_3)_2$), 52 (C-4, C-6), 58.8 (C-7, C-7′), 88 (C-2), 112 (C-3″, C-5″), 126.5 (C-11, C-11′), 128 (C-9, C-9′, C-13, C-13′), 128.7 (C-10, C-10′, C-12, C-12′), 130 (C-2″, C-6″) |
| **41** | 11(11′)-$OCH_3$ | 6; 111–112; (m–d); Colourless shining needles | 77.47 | b:e; 9.5:0.5 (0.63) | $CDCl_3$; 1.4 and 1.8 (d and m, H-5), 2.0 and 3.1 (t and d, H-4, H-6), 2.7 and 3.7 (2d, H-7, H-7′), 3.0 (s, $-N(CH_3)_2$), 3.5 (s, H-2), 3.8 (s, $-OCH_3 \times 2$), 6.6 (H-3″, H-5″), 6.7 (d, H-10, H-10′, H-12, H-12′), 7.1 (d, H-9, H-9′, H-13, H-13′), 7.4 (d, H-2″, H-6″) $M^+$: 445, 325, 121 | 25 (C-5), 40 ($-N(CH_3)_2$), 52 (C-4, C-6), 55 ($-OCH_3 \times 2$), 59 (C-7, C-7′), 89 (C-2), 112.2 (C-3″, C-5″), 113.5 (C-10, C-10′, C-12, C-12′), 130 (C-9, C-9′, C-13, C-13′), 130.2 (C-2″, C-6″) |
| **44** | 9(9′)-$OCH_3$ | 8; 168–169; (m–d); Colourless shining thick small needles | 70.53 | b:e; 9.5:0.5 (0.62) | $CDCl_3$; 1.4 and 1.9 (d and m, H-5), 2.0 and 3.1 (t and d, H-4, H-6), 2.55 (s, $-N(CH_3)_2$), 3.2 and 3.5 (2d, H-7, H-7′), 3.6 (s, H-2, $-OCH_3 \times 2$), 6.7 (m, H-10, H-10′), 6.8 (d, H-3″, H-5″), 6.9 (m, H-12, H-12′), 7.1 (m, H-11, H-11′), 7.5 (m, H-13, H-13′), 7.55 (d, H-2″, H-6″) $M^+$: 445, 325, 121, 107 | 25 (C-5), 40 ($-N(CH_3)_2$), 51 (C-7, C-7′), 52 (C-4, C-6), 55 ($-OCH_3 \times 2$), 89 (C-2), 110 (C-10, C-10′), 112 (C-3″, C-5″), 120.5 (C-12, C-12′), 127 (C-11, C-11′), 130 (C-13, C-13′), 130.4 (C-2″, C-6″) |
| **47** | 11(11′)-$N(CH_3)_2$ | 6; 136–138; (m–d); Thick colourless shining needles | 72.22 | b:e; 9.5:0.5 (0.63) | $CDCl_3$; 1.4 and 1.8 (d and m, H-5), 2.0 and 3.0 (t and d, H-4, H-6), 2.7 and 3.7 (2d, H-3, H-7′), 2.9 (2s, $-N(CH_3)_2 \times 3$), 3.5 (s, H-2), 6.6 (d, H-10, H-10′, H-12, H-12′), 6.65 (d, H-3″, H-5″), 7.1 (d, H-9, H-9′, H-13, H-13′), 7.5 (d, H-2″, H-6″) $M^+$: 471, 162, 134 | 25 (C-5), 41 ($-N(CH_3)_2$), 52 (C-4, C-6), 58 (C-7, C-7′), 90 (C-2), 112 (C-3″, C-5″), 112.5 (C-10, C-10′, C-12, C-12′), 129.5 (C-9, C-9′, C-13, C-13′), 130 (C-2″, C-6″) |

**Table 6: Continued**

| Compd. | R | Reaction time in h; m.p.; (solvent used for crystallization)**; appearance of crystals | Yield (%)*** | Solvent system** ($R_f$ value) | $^1$H NMR assignments based on 2D (HH cosy) (δ values) and Mass spectral data (m/z) | $^{13}$C NMR assignments based on CH cosy (δ values) |
|---|---|---|---|---|---|---|
| **50** | 11(11′)-$CH_3$ | 6; 126–127; (m–d); Colourless shining needles | 83.87 | b:e; 9.5:0.5 | $CDCl_3$; 1.4 and 1.8 (d and m, H-5), 2.1 and 3.1 (t and d, H-4, H-6), 2.3 (s, $-C-CH_3 \times 2$), 2.8 and 3.7 (2d, H-7, H-7′), 2.9 (s, $-N(CH_3)_2$), 3.5 (s, H-2), 6.6 (d, H-3″, H-5″), 7.0 (d, H-10, H-10′, H-12, H-12′), 7.2 (d, H-9, H-9′, H-13, H-13′), 7.5 (d, H-2″, H-6″) $M^+$: 413, 289, 105,91 | 21 ($C-CH_3 \times 2$), 25 (C-5), 41 ($-N(CH_3)_2$), 52 (C-4, C-6), 59 (C-7, C-7′), 90 (C-2), 113 (C-3″, C-5″), 130 (C-9, C-9′, C-10, C-10′, C-12, C-12′, C-13, C-13′), 132 (C-2″, C-6″) |

* Solvent for reaction used for all the compounds synthesized was ethanol (dried over NaOH).
** b = benzene, m = methanol, d = dichloromethane, ea = ethylacetate, p = petroleum ether, e = ethanol.
*** Yields of compounds were calculated on the basis of the amount of tetrahydrodiSchiff's base used during the reaction.
s – singlet, d – doublet, dd – double doublet, t – triplet, m – multiplet.
**** Spectrum indicates presence of minor streoisomers also.
***** 2-thienyl in place of substituted phenyl

## Scheme 2




Similarly, other tetrahydrodiSchiff's bases were prepared. The solvent used in reaction, stirring time, % yield, TLC solvent system and $R_f$ values are reported in Table 5).

### *3.3. Synthesis of hexahydropyrimidine derivatives*

The tetrahydrodiSchiff's bases were condensed with *p*-dimethylaminobenzaldehyde to give sixteen new hexahydropyrimidine derivatives
Characterization of all the newly synthesized hexahydropyrimidine derivatives was done on the basis of $^1$H NMR and MS data (Table 6) and Scheme 2. For correct assignments of the signals of hexahydropyrimidine derivatives, 2D NMR (HH cosy and CH cosy) spectra were recorded and carefully studied.
Formation of hexahydropyrimidine derivative **4** from **3** and *p*-dimethylamino-benzaldehyde: The tetrahydrodiSchiff's base **3** (0.80 g; 1.70 mmol) and *p*-dimethylaminobenzaldehyde **5** (0.25 g; 1.68 mmol) were dissolved in ethanol (4.0 ml). The reaction mixture was shaken for 12 h on a wrist action shaker by adding a few granules of molecular sieves Type 5A. A colourless solid mass separated out which was filtered and washed with ethanol to remove unreacted aldehyde. The insoluble residue was crystallized from a mixture of methanol and dichloromethane to give colourless shining needles (**4**), m.p. 168 °C, yield – 0.55 g (53.92%). It was found to be a single entity on TLC examination in benzene : ethylacetate (9 : 1) solvent system ($R_f$: 0.60).
Similarly, other hexahydropyrimidine derivatives were also synthesized. Their reaction time, m.p. (°C), solvent used for crystallization, appearence, % yield, TLC solvent system, $R_f$ values, $^1$H NMR spectral data based on 2D (HH cosy), MS data and $^{13}$C NMR assignments based on CH cosy are reported in Table 6.

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**References**

1 Bruno, O.; Schenone, S.; Ranaise, A.; Biondavalli, W.; Falcone, G.; Motola, G.; Mazzeo, F.: Farmaco **54**, 95 (1999)
2 Chouini-Lalanne, N.; Defais, M.; Paillous, N.: Biochem. Pharmacol. **55**, 441 (1998)
3 Al-Ashmawy, M. I.; el-Feky, Sa.; el-Samii, Z. K.; Osman, N. A.: Boll. Chim. Farm. **136**, 492 (1997)
4 Bruno, O.; Ranaise, A.; Bondavalli, F.; Schenone, P.; D'Amico, M.; Filippelli, A.; Filippelli, W.; Rossi, F.: Farmaco **48**, 949 (1993)
5 Ranaise, A.; Bruno, O.; Schenone, S.; Bondavalli, F.; Falcone, G.; Filippelli, W.; Sorrentino, S.: Farmaco **52**, 547 (1997)
6 Finney, M. J.; Karlson, J. A.; Persson, C. G.: Br. J. Pharmacol. **85**, 29 (1985)
7 DeLander, D. W.; Hopkins, C. J.: J. Pharmacol. Exp. Ther. **239**, 88 (1986)
8 DuCharme, D. W.; Freyburger, W. A.; Graham, B. E.; Carlson, R. G.: J. Pharmacol. Exp. Ther. **184**, 662 (1973)
9 Velazquez, H.: Renal Physiol. **10**, 184 (1987)
10 Billmann, J. H.; Meisenheimer, J. L.: J. Med. Chem. **7**, 682 (1963)
11 Billman, J. H.; Khan, M. S.: J. Pharm. Sci. **57**, 1817 (1968)
12 Billman, J. H.; Khan, M. S.: J. Med. Chem. **11**, 312 (1968)
13 Knabe, J.; Buch, H. P.; Biwersi, J.: Arch. Pharm. **326**, 79 (1993)
14 Winter, C. A.; Risley, E. A.; Nuss, G. W.: Proc. Soc. Exp. Biol. Med. **111**, 544 (1962)
15 Witkin, L. B.; Huebner, C. F.; Galdi, F.; O'Keefe, E.; Spitaletta, P.; Plummer, A. J.; J. Pharmacol. Exp. Ther. **133**, 400 (1961)
16 Miller, L. C.; Tainter, M. L.: Proc. Soc. Exp. Biol. Med. **57**, 261 (1944)

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