

Synthesis of the new ring systems indeno[1,2-*d*]pyrimidinones, indeno[1,2-*e*]pyrrolo[1,2-*a*]pyrimidinones and indeno[1,2-*e*]pyrimido[1,2-*a*]izoindoles

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Dedicated to Professor Eusebio Juaristi on his 55th birthday
(received 17 Jun 05; accepted 20 Aug 05; published on the web 23 Aug 05)

Abstract

Indeno[1,2-*d*]pyrimidinones, indeno[1,2-*e*]pyrrolo[1,2-*a*]pyrimidinones and indeno[1,2-*e*]pyrimido[1,2-*a*]izoindoles were prepared as new ring systems by ring enlargement of azetidinone **2** and ring closure of amino ester **3** and 1,3-diamine **5**. These ring closures resulted in pure diastereomers, the stereochemistry of which was determined by NMR spectroscopy.

Keywords: Ring closure, ring enlargement, diastereoselective, NMR spectroscopy

Introduction

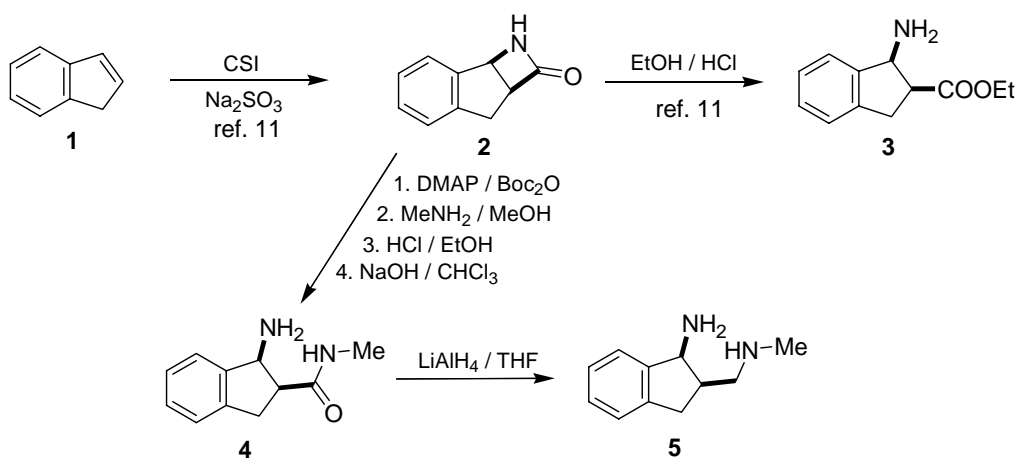
In the past two decades, a number of cyclic β -amino acid derivatives have been synthesized. Some of them have useful pharmacological effects,¹ and they are widely used for the preparation of saturated 1,3-heterocycles. The synthesis and stereochemical aspects have been thoroughly studied for the *cis*- or *trans*-cyclohexane-, -cyclohexene-, and *diexo*- and *diendo*-fused norbornane- and norbornene-1,3-heterocycles.² To date, only few indane-fused heterocycles have been prepared.³⁻¹⁰ Because of their therapeutic interest, the syntheses of cycloalkane-fused pyrimidinones have been studied,² but syntheses of their indane-condensed derivatives have not yet been reported.

Our present aim was to prepare new *cis*-1-aminoindane-2-carboxylic acid derivatives and to synthesize some indane-fused pyrimidines.

Results and Discussion

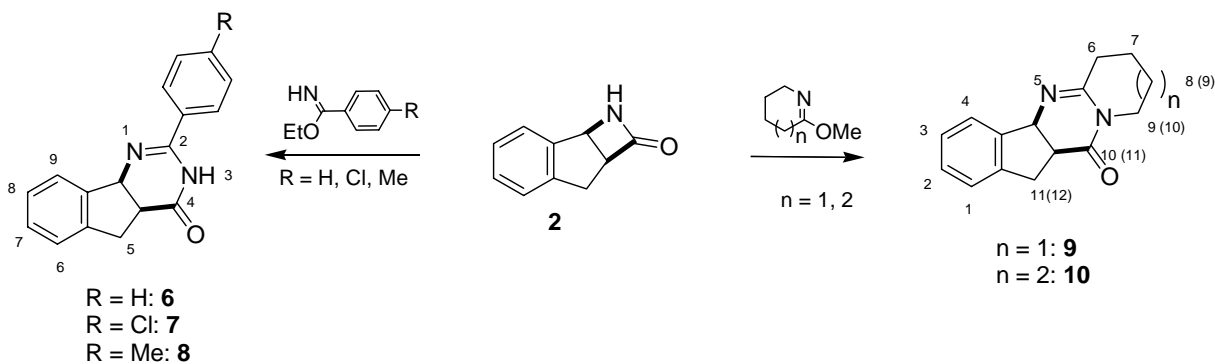
Syntheses

Racemic 3,4-benzo-6-azabicyclo[3.2.0]heptan-7-one (**2**) and ethyl *cis*-1-aminoindane-2-carboxylate (**3**) were prepared from indene by chlorosulfonyl isocyanate addition, followed by hydrolysis and ring opening.¹¹ Compounds **2** and **3** can be used as starting substances for the preparation of other bifunctional compounds, *e. g.* 1,3-aminoalcohols and 1,3-diamines. When amino ester **3** was reacted with MeNH₂, a mixture of *cis*- and *trans*-aminocarboxamides (*cis:trans* = 1:1) was formed. This is in accordance with our earlier results: isomerization was observed in the amidation of ethyl *cis*-2-aminocyclopentanecarboxylate.¹² For the preparation of *cis*-aminocarboxamide **4**, azetidinone **2** was activated with a Boc group. The reaction of the *N*-Boc derivative of **2** with MeNH₂ for 2 h at 4 °C, resulted in the protected *cis*-carboxamide. The Boc group was easily removed with HCl in dry EtOH at room temperature, which afforded the hydrochloride of **4**. *cis*-2-Methylaminomethylindan-1-ylamine (**5**) was prepared by LiAlH₄ reduction of **4** (Scheme 1).



Scheme 1

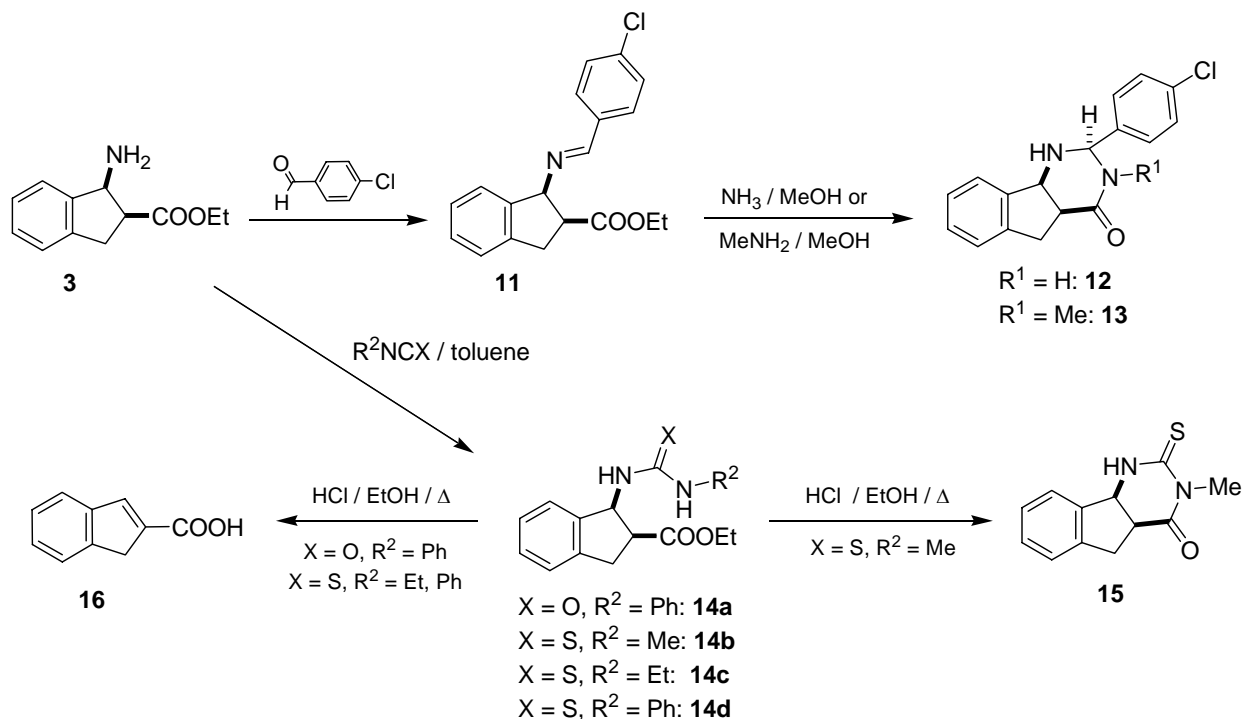
The indane-condensed pyrimidinones **6-10** were prepared by ring enlargement^{2,13} of azetidinone **2** with the corresponding imidates or lactim ethers. When **2** was melted with imidates or lactim ethers at 150 °C for 8 h, the desired pyrimidinones **6-10**, were formed. The first step in the reaction is the splitting-off of alcohol, resulting in an amidine intermediate which, after transamidation, yields the ring enlargement products (Scheme 2).



Scheme 2

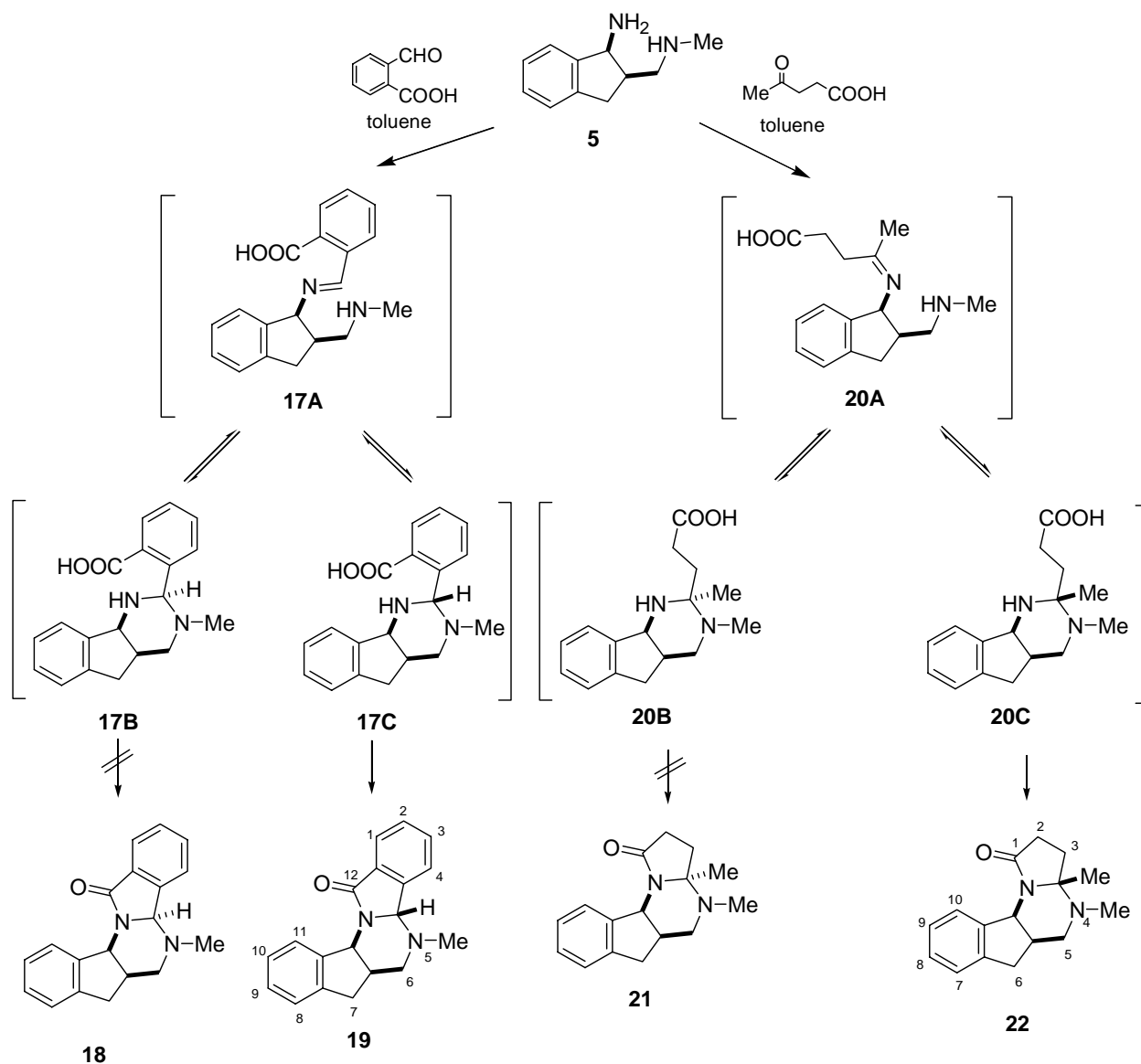
When amino ester **3** was reacted with one equivalent of *p*-chlorobenzaldehyde in toluene at room temperature Schiff base **11** was formed. This was treated with NH_3 or MeNH_2 in MeOH solution to afford a mixture of indeno[1,2-*a*]pyrimidin-4-one C-2 epimers (**12**, 2:1; **13**, 3:1); fractional crystallization furnished the *major* diastereomers.

On reaction with various isocyanates and isothiocyanates, **3** yielded the urea and thiourea derivatives **14a-d**. When attempts were made to cyclize **14a-d** to pyrimidinones, only *N*-methylthiourea **14b** was cyclized successfully to pyrimidinone **15** in EtOH containing 22% dry HCl. Under the same conditions, the other derivatives gave the elimination product indene-2-carboxylic acid (**16**) (Scheme 3).



Scheme 3

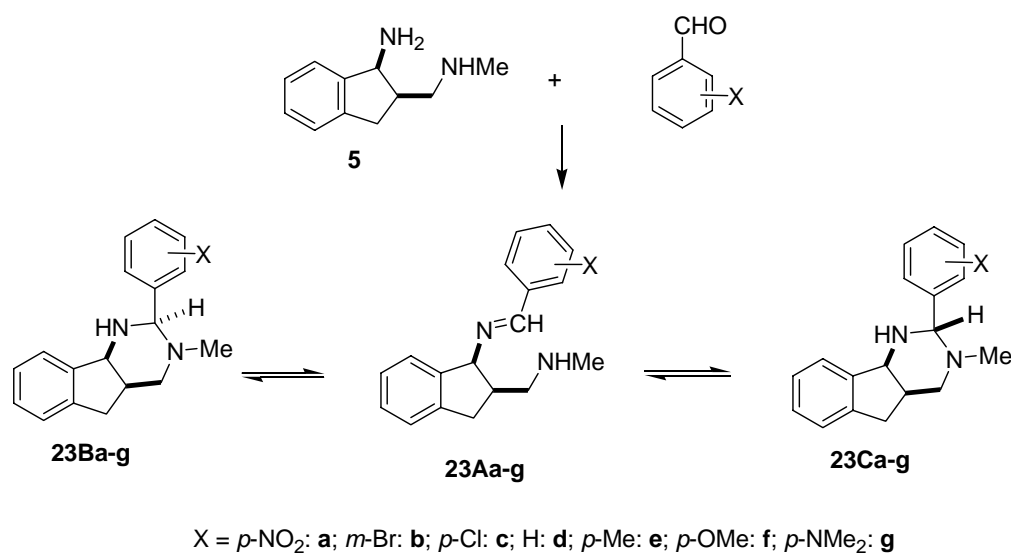
When *N*-methyldiamine **5** was reacted with levulinic acid or 2-formylbenzoic acid in boiling toluene, penta- and tetracycles **19** and **22** were formed in good yields. NMR measurements indicated that **19** and **22** were formed with excellent diastereoselectivity (*de* ~ 100%) with the relative configurations depicted in Scheme 4. The ring closures of **5** can be categorized as domino reactions.¹⁴ The intermediates **17** and **20** possess a ring-chain tautomeric character, the second ring closure step causing a shift in the tautomeric equilibrium. The high diastereoselectivity can be explained as a result of the kinetic control governing the second ring closure.¹⁵⁻¹⁷



Scheme 4

Diamine **5** was condensed in MeOH with seven aromatic aldehydes with different electronic characters. The reaction reached completion in a few hours, even at room temperature. After evaporation and purification, well-defined products **23a-g** were obtained. The ^1H NMR spectra clearly proved that these derivatives exist as ring-ring epimers. The ratios of the two ring forms were determined by integration of the well-separated N-CHAr-N (ring) singlets. The epimeric rates were practically constant (**23B:23C** = 6:4), independently of the electronic character of the aryl substituent.

These results are in accordance with those of our previous studies, because some of the *N*-substituted hexahydropyrimidinones and tetrahydroquinazolinones proved to be ring-chain tautomeric mixtures in CDCl_3 at 300 K, whereas the *N*-methylhexahydropyrimidine and *N*-methyltetrahydroquinazoline derivatives exist solely as ring forms.^{14,18}



Scheme 5

NMR spectroscopy

For **12** and **13**, the relative orientation of the 2-aryl substituent was determined by using characteristic NOE interactions. The clear NOESY cross-peak between H-2 and H-9b in **12** indicates a *trans* relationship for 2-aryl and H-9b. As regards **18** or **19**, the relative spatiality of H-4b was determined by modelling and consideration of the NOE interactions. The rigid structures show that in **18** significant NOE cross-talk should be observed between H-4b and H-11b, but this is not detected in the NOESY spectrum. All the other spectral parameters accord well with structure **19**. In **21** or **22**, an NOE signal can be detected from Me-3a to H-5ax. H-5ax exhibits a vicinal coupling ca. of 11 Hz and a weak NOESY cross-peak to H-5a. These strongly

support Me-3 and H-5a being situated on opposite sides of the heterocyclic ring, indicating structure **22**.

In the spectra of **23**, we found no sign of the azomethine proton of the open form. The proportions of the two ring forms were calculated from the integrals of the H-2 signals. The chemical shifts of H-2 of ring forms B and C were assigned via the NOESY NMR. The H-2 signal at around δ 4.2 ppm has an NOE cross-peak with H-9b, indicating the *cis* orientation (ring form B), while the H-2 signal at around δ 4.6 ppm has no NOE cross-peak with H-9b, indicating the *trans* orientation of these protons (ring form C).

Experimental Section

General Procedures. Melting points were determined with a Koffler apparatus and are not corrected. Elemental analyses were performed with a Perkin-Elmer 2400 CHNS instrument. Merck Kieselgel 60F254 plates were used for TLC: the eluent was toluene-MeOH 4:1. MS data were obtained with a Finnigan Mat 95S spectrometer in EI mode. Column chromatography was performed on silica gel (Merck 60, 70-230 mesh). ^1H NMR and ^{13}C NMR spectra were recorded in CDCl_3 solution in 5 mm tubes, at room temperature, on a Bruker DRX 400 spectrometer at 400.13 (^1H) and 100.61 (^{13}C) MHz, with the deuterium signal of the solvent as the lock and TMS as internal standard. For the equilibria to be established in the tautomeric compounds, samples were dissolved in CDCl_3 and the solutions were allowed to stand at ambient temperature for 1 day before the ^1H NMR spectra were run. The number of scans was usually 64. 3,4-Benzo-6-azabicyclo[3.2.0]heptan-7-one (**2**) and ethyl *cis*-1-aminoindane-2-carboxylate (**3**) were prepared according to reported methods.¹¹

***cis*-1-Aminoindane-2-carboxylic acid methylamide (4).** 3,4-Benzo-6-azabicyclo[3.2.0]heptan-7-one (**2**; 4.7 g, 0.03 mol) was dissolved in 20 ml dry CH_2Cl_2 . The solution was stirred, and 0.37 g 4-dimethylaminopyridine (DMAP) was added, followed by di-*tert*-butyldicarbonate (7.2 g, 0.033 mol). After stirring at room temperature for 5 h, the reaction mixture was left to stand overnight. The brownish reaction mixture was then extracted with brine and dried (Na_2SO_4). After evaporation, 7.1 g 3,4-benzo-6-*tert*-butoxycarbonyl-6-azabicyclo[3.2.0]heptan-7-one was obtained, as a white crystalline product. The crude protected β -lactam was dissolved in 60 ml of a 40% solution of MeNH_2 in dry MeOH. The reaction mixture was allowed to stand at 4 °C for 2 h and was next evaporated, first at room temperature and then on a 60 °C water bath. A white crystalline powder was obtained. The protected *cis*-aminocarboxamide hydrochloride was dissolved in 20 ml 3 M HCl solution in EtOH. For removal of the protecting group, the reaction mixture was left to stand at room temperature for 2 h and then evaporated at room temperature. After evaporation, 4.2 g **4** hydrochloride was obtained, which was purified by recrystallization from EtOH. Amide base **4** was obtained from the hydrochloride by alkaline treatment (10% NaOH), extraction (CH_2Cl_2), and evaporation under reduced pressure.

4. HCl: yield 3.7 g, 63%, mp 252-254 °C. Anal. Calcd. for C₁₁H₁₅ClN₂O (226.75): C, 58.21; H, 6.61; Cl, 15.66; N, 12.35. Found: C, 58.43; H, 6.87; N, 15.37. NMR data: ¹H NMR δ: 2.874 (3H, s, CH₃), 3.34-3.46 (2H, m, H-3), 3.65 (1H, dd, *J* = 15.1, 7.1 Hz, H-2), 5.05 (1H, d, *J* = 7.1 Hz, H-1), 7.44-7.55 (3H, m, H-5, H-6, H-7), 7.6 (1H, d, *J* = 7.3 Hz, H-4). ¹³C NMR δ: 26.39, 34.39, 46.46, 56.59, 125.42, 125.83, 128.18, 130.83, 137.19, 142.89, 173.94.

cis-2-Methylaminomethylindane-1-ylamine (5). To a stirred suspension of LiAlH₄ (1 g, 26 mmol) in 60 ml dry THF was added a solution of **4** amide (2 g, in 10 mmol dry THF). The resulting suspension was refluxed for 4 h and then decomposed by the addition of a mixture of 2 ml water and 10 ml THF. The inorganic material was filtered off and washed with THF (3 x 20 ml). After filtration, the solvent was evaporated off to give an oil, which was dissolved in EtOH (20 ml) and converted to the crystalline hydrochloride of **5** with 20% HCl in EtOH (2 ml) and Et₂O (50 ml). The crystals were filtered off and recrystallized from MeOH-Et₂O. Pure diamine base **5** was obtained from the hydrochloride by alkaline treatment (10% NaOH), extraction (CH₂Cl₂), and evaporation under reduced pressure. **5.** HCl: yield 1.49 g, 70%, mp 250-255 °C. Anal. Calcd. for C₁₁H₁₇ClN₂ (212.73): C, 62.05; H, 7.99; Cl, 16.69; N, 13.16. Found: C, 61.93; H, 7.82; Cl, 16.39; N, 13.32. NMR data: ¹H NMR δ: 2.93 (3H, s, CH₃), 3.19-3.29 (2H, m, CH₂N), 3.33-3.43 (2H, m, H-3), 3.58 (1H, dd, *J* = 12.5, 4.7 Hz, H-2), 5.03 (1H, d, *J* = 6.3 Hz, H-1), 7.45-7.58 (3H, m, H-4, H-5, H-6), 7.62 (1H, d, *J* = 7.5 Hz, H-7). ¹³C NMR δ: 34.4, 40.29, 48.1, 50.06, 57.87, 125.32, 125.72, 127.12, 130.14, 137.95, 143.81.

General procedure for the preparation of tetrahydroindeno[1,2-*d*]pyrimidin-4-ones **6-8**

A mixture of azetidinone **8** (0.5 g, 3.14 mmol) and the corresponding ethyl benzimidate (3.14 mmol) was kept at 150-160 °C for 8 h. The end of the reaction was detected by means of TLC. After cooling, the products were recrystallized from EtOH.

(4a*S,9b*S**)-2-Phenyl-3,4a,5,9b-tetrahydroindeno[1,2-*d*]pyrimidin-4-one (6).** yield 0.68 g, 83%, mp 231-232 °C. Anal. Calcd. for C₁₇H₁₄N₂O (262.31): C, 77.84; H, 5.38; N, 10.68. Found: C, 77.67; H, 5.42; N, 10.93. NMR data: ¹H NMR δ: 3.28-3.35 (2H, m, H-5), 3.55 (1H, dt, *J* = 12.0 Hz, 7.1 Hz, H-4a), 5.52 (1H, d, *J* = 7.1 Hz, H-9b), 7.23-7.25 (3H, m, H-7, H-8, H-9), 7.42-7.49 (3H, m, *m*-Ph, *p*-Ph), 7.52 (1H, d, *J* = 5.8 Hz, H-6), 7.78 (2H, d, *J* = 7.1 Hz, *o*-Ph) 8.47 (1H, bs, NH). ¹³C NMR δ: 35.10, 42.60, 64.80, 124.90, 124.97, 126.78, 127.74, 128.45, 129.23, 131.6, 134.12, 140.37, 143.65, 172.55, 176.57.

(4a*S,9b*S**)-2-(*p*-Chlorophenyl)-3,4a,5,9b-tetrahydroindeno[1,2-*d*]pyrimidin-4-one (7).** yield 0.75 g, 81%, mp 205-210 °C. Anal. Calcd. for C₁₇H₁₃ClN₂O (296.76): C, 68.81; H, 4.42; Cl, 11.95; N, 9.44. Found: C, 69.11; H, 4.32; Cl, 11.83; N, 9.23. NMR data: ¹H NMR δ: 3.28-3.35 (2H, m, H-5), 3.54 (1H, dt, *J* = 12 Hz, 7.5 Hz, H-4a), 5.52 (1H, d, *J* = 7.5 Hz, H-9b), 7.24-7.28 (3H, m, H-7, H-8, H-9), 7.41-7.43 (2H, m, *m*-Ar), 7.50 (1H, d, *J* = 6.4 Hz, H-6), 7.74 (2H, d, *J* = 8.6 Hz, *o*-Ar), 8.47 (1H, bs, NH). ¹³C NMR δ: 34.94, 42.33, 64.67, 124.69, 124.80, 127.60, 127.97, 128.34, 129.28, 132.31, 137.66, 141.25, 143.25, 162.67, 172.34.

(4a*S,9b*S**)-2-(*p*-Tolyl)-3,4a,5,9b-tetrahydroindeno[1,2-*d*]pyrimidin-4-one (8).** yield 0.62 g, 77%, mp 215-218 °C. Anal. Calcd. for C₁₈H₁₆N₂O (276.13): C, 78.24; H, 5.84; N, 10.14. Found:

C, 78.37; H, 5.98; N, 10.42. NMR data: ^1H NMR δ : 2.39 (3H, s, CH_3), 3.26-3.34 (2H, m, H-5), 3.55 (1H, dt, $J = 11.9$ Hz, 7.5 Hz, H-4a), 5.50 (1H, d, $J = 7.5$ Hz, H-9b), 7.23-7.26 (5H, m, *m*-Ar, H-7, H-8, H-9), 7.52 (1H, d, $J = 6.6$ Hz, H-6), 7.66, (2H, d, $J = 8.1$ Hz, *o*-Ar), 8.40 (1H, bs, NH). ^{13}C NMR δ : 21.62, 34.87, 42.45, 64.53, 124.71, 124.74, 126.46, 127.9, 128.18, 129.69, 131.07, 140.19, 141.79, 143.53, 167.34, 172.35.

General procedure for the synthesis of **9** and **10**

A mixture of azetidinone **2** (0.5 g, 3.14 mmol) and the corresponding lactim ether (6.28 mmol) was kept at 150-160 °C for 8 h. The excess of lactim ether was then evaporated off and the residue was dissolved in Et_2O (20 ml), treated with charcoal, filtered and left to stand at 4 °C. The product **9** or **10** was filtered off and recrystallized from *n*-hexane.

(4bS*,10aS*)-6,7,8,9,10a,11-Hexahydro-4bH-indeno[1,2-*e*]pyrido[1,2-*a*]pyrimidine (9**).** yield 0.44 g, 58%, mp 47-49 °C. Anal. Calcd. for $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}$ (240.31): C, 74.97; H, 6.71; N, 11.66. Found: C, 75.21; H, 6.83; N, 11.72. NMR data: ^1H NMR δ : 1.71-1.83 (4H, m, H-6, H-7), 2.49-2.64 (2H, m, H-8), 3.21-3.30 (2H, m, H-9), 3.39-3.47 (1H, m, H-11), 3.58-3.65 (1H, m, H-11), 3.70-3.78 (1H, m, H-10a), 5.14 (1H, d, $J = 7.5$ Hz, H-4b) 7.20-7.26 (3H, m, H-1, H-2, H-3), 7.52 (1H, m, H-4). ^{13}C NMR δ : 19.77, 22.32, 31.96, 35.50, 40.83, 42.70, 62.36, 124.39, 124.50, 127.25, 127.84, 140.34, 143.66, 151.63, 170.80.

(4bS*,11aS*)-4b,6,7,8,9,10,11a,12-Octahydroindeno[1,2-*e*]azepino[1,2-*a*]pyrimidine (10**).** yield 0.42 g, 53%, mp 70-72 °C. Anal. Calcd. for $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}$ (254.34): C, 75.56; H, 7.13; N, 11.01. Found: C, 75.63; H, 7.37; N, 11.29. NMR data: ^1H NMR δ : 1.54-1.71 (4H, m, H-6, H-7), 1.71-1.84 (2H, m, H-8), 2.61-2.68 (2H, m, H-9), 3.19 (1H, dt, $J = 5.1, 7.8$ Hz, H-11a), 3.26 (1H, dd, $J = 15.2, 7.6$ Hz, H-10), 3.37 (1H, dd, $J = 15.2, 5.1$ Hz, H-10), 3.80 (1H, dd, $J = 13.6, 5.1$ Hz, H-12), 3.90 (1H, dd, $J = 15.2, 5.2$ Hz, H-12), 5.14 (1H, d, $J = 7.9$ Hz, H-4b), 7.20-7.26 (3H, m, H-1, H-2, H-3), 7.52 (1H, m, H-4). ^{13}C NMR δ : 26.23, 28.98, 29.21, 35.62, 37.21, 41.77, 42.22, 62.38, 124.28, 124.46, 127.25, 127.80, 140.39, 143.64, 156.41, 170.76.

Ethyl *cis*-1-(4-chlorobenzylideneamino)indane-2-carboxylate (11**).** To a solution of amino ester **3** (1.54 g, 7.51 mmol) in 20 ml absolute MeOH, an equivalent amount of *p*-chlorobenzaldehyde was added, and the mixture was left to stand at ambient temperature for 4 h. Crystalline product **11** was then filtered off: yield 2.4 g, 98%, mp 110-111 °C. Anal. Calcd. for $\text{C}_{19}\text{H}_{18}\text{ClNO}_2$ (327.10): C, 69.62; H, 5.53; Cl, 10.82; N, 4.27. Found: C, 69.85; H, 5.69; Cl, 11.13; N, 4.52. NMR data: ^1H NMR δ : 1.10 (3H, t, $J = 7.1$ Hz, CH_2CH_3), 3.11 (1H, dd, $J = 15.6$ Hz, 7.9 Hz, H-3), 3.62 (1H, dt, $J = 8.7, 7.8$ Hz, H-2), 3.73 (1H, dd, $J = 15.6$ Hz, 9.3 Hz, H-3), 4.00-4.14 (2H, m, CH_2CH_3), 5.09 (1H, d, $J = 7.0$ Hz, H-1), 7.12-7.21 (2H, m, H-4, H-5), 7.26 (1H, td, $J = 7.4$ Hz, 1.2 Hz, H-6), 7.32 (3H, d, $J = 8.4$ Hz, *m*-Ar, H-7), 7.63 (2H, d, $J = 8.4$ Hz, *o*-Ar), 8.34 (1H, s, $\text{CH}=\text{N}$). ^{13}C NMR δ : 14.79, 33.51, 51.02, 60.79, 76.18, 125.18, 125.45, 127.23, 128.93, 129.18, 130.03, 134.89, 137.16, 142.21, 143.15, 159.46, 172.34.

(2S*,4aS*,9bS*)-2-(4-Chlorophenyl)-1,2,3,4a,5,5a,9a,9b-octahydroindeno[1,2-*a*]pyrimidin-4-one (12**).** Compound **2** (0.7 g, 2.1 mmol) was left to stand in room temperature for 5 days with a MeOH solution of NH_3 (50 ml, 25%), after which the solvent was evaporated off. The crude

product was a mixture of the diastereomers (2:1), which was recrystallized from EtOAc-EtOH to give the *major* diastereomer: yield 0.35 g, 55%, mp 175-178 °C. Anal. Calcd. for C₁₇H₁₅ClN₂O (298.77): C, 68.34; H, 5.06; Cl, 11.87; N, 9.38. Found: C, 68.51; H, 5.33; Cl, 11.92; N, 9.51. NMR data: ¹H NMR δ: 1.50 (1H, s, NH-1), 3.18 (1H, dt, *J* = 6.9 Hz, 9.5 Hz, H-4a), 3.30 (1H, dd, *J* = 16.4 Hz, 9.1 Hz, H-5), 3.48 (1H, dd, *J* = 16.4 Hz, 9.8 Hz, H-5), 4.68 (1H, t, *J* = 7.6 Hz, H-9b), 5.46 (1H, d, *J* = 9.0 Hz, H-2), 6.28 (1H, s, NH-3), 7.19-7.30 (3H, m, H-7, H-8, H-9), 7.35-7.42 (5H, m, H-6, Ar). ¹³C NMR δ: 35.46, 43.66, 61.87, 70.36, 70.45, 125.47, 125.83, 127.63, 128.27, 129.43, 129.69, 135.69, 138.12, 142.03, 173.69.

(2*S,4*aS**,9*bS**)-3-Methyl-2-(4-chlorophenyl)-1,2,3,4*a*,5,5*a*,9*a*,9*b*-octahydroindeno[1,2-*a*]pyrimidin-4-one (13).** Compound **2** (0.7 g, 2.1 mmol) was left to stand in room temperature for 5 days with a MeOH solution of MeNH₂ (50 ml, 40%) and the solvent was evaporated off. The crude product was a mixture of the diastereomers (3:1), which was recrystallized from EtOAc-EtOH to give the *major* diastereomer: yield 0.37 g, 56%, mp 168-172 °C. Anal. Calcd. for C₁₈H₁₇ClN₂O (312.80): C, 69.12; H, 5.48; Cl, 11.33; N, 8.96. Found: C, 69.31; H, 5.53; Cl, 11.47; N, 8.69. NMR data: ¹H NMR δ: 2.16 (1H, bs, NH-1), 2.90 (3H, s, CH₃), 3.11 (1H, dt, *J* = 9.7 Hz, 7.3 Hz, H-4a), 3.33 (1H, dd, *J* = 16.7, 7.3 Hz, H-5), 3.42 (1H, dd, *J* = 16.7, 9.8 Hz, H-5), 4.35 (1H, d, *J* = 7.1 Hz, H-9b), 5.26 (1H, s, H-2), 7.18-7.26 (4H, m, H-6, H-7, H-8, H-9), 7.32 (2H, d, *J* = 8.4 Hz, *m*-Ar), 7.41 (2H, dt, *J* = 8.4 Hz, 1.8 Hz, *o*-Ar). ¹³C NMR δ: 32.81, 35.59, 43.78, 57.52, 74.94, 125.12, 125.19, 127.22, 128.70, 129.25, 129.67, 134.61, 137.12, 140.98, 142.19, 171.81.

General procedure for the preparation of urea and thiourea compounds 14a-f

To a magnetically stirred toluene solution of amino ester base **3** (0.5 g, 2.43 mmol in 20 ml), one equivalent of the appropriate isocyanate or isothiocyanate in toluene (20 ml) was added dropwise. The mixture was left to stand overnight at ambient temperature. The crystalline products were separated by filtration and recrystallized from EtOAc-MeOH.

***cis*-*N*-Phenyl-*N'*-(2-ethoxycarbonylindanyl)urea (14a).** yield 0.63 g, 81%, mp 193-194 °C. Anal. Calcd. for C₁₉H₂₀N₂O₃ (324.38): C, 70.35; H, 6.21; N, 8.64. Found: C, 70.48; H, 6.48; N, 8.54. NMR data: ¹H NMR (400 MHz, CDCl₃) δ: 1.19 (3H, t, *J* = 7.1 Hz, CH₂CH₃), 3.12 (1H, dd, *J* = 16.3 Hz, 8.5 Hz, H-3), 3.29 (1H, dd, *J* = 16.3 Hz, 5.5 Hz, H-3), 3.62 (1H, dt, *J* = 5.5, 8.2 Hz, H-2), 4.06 (2H, q, *J* = 7.14 Hz, CH₂CH₃), 5.56 (1H, d, *J* = 7.9 Hz, NH), 5.78 (1H, dd, *J* = 8.2, 7.9 Hz, H-1), 6.66 (1H, bs, NHPh), 7.02-7.08 (1H, m, *p*-Ph), 7.15-7.34 (8H, m, *o*-Ph, *m*-Ph, H-4, H-5, H-6, H-7). ¹³C NMR (100 MHz, CDCl₃) δ: 14.54, 34.12, 48.13, 56.26, 61.01, 120.59, 123.64, 124.33, 124.67, 127.30, 128.37, 129.19, 140.65, 143.39, 145.31, 161.96, 167.37.

***cis*-*N*-Methyl-*N'*-(2-ethoxycarbonylindanyl)thiourea (14b).** yield 0.52 g, 77%, mp 124-125 °C. Anal. Calcd. for C₁₄H₁₈N₂O₂S (278.38): C, 60.41; H, 6.52; N, 10.06. Found: C, 60.63; H, 6.58; N, 10.21. NMR data: ¹H NMR δ: 1.25 (3H, t, *J* = 7.1 Hz, CH₂CH₃), 2.93 (3H, s, CH₃(Me)), 3.21 (1H, dd, *J* = 8.2 Hz, 16.4 Hz, H-3), 3.27 (1H, dd, *J* = 4.8 Hz, 16.4 Hz, H-3), 3.68 (1H, dt, *J* = 4.8, 7.8 Hz, H-2), 4.08 (2H, q, *J* = 7.1 Hz, CH₂CH₃), 6.26 (1H, bs, NHMe), 6.36 (1H, dd, *J* = 8.0, 7.8 Hz, H-1), 6.73 (1H, d, *J* = 8.0 Hz, NH), 7.19-7.27 (3H, m, H-4, H-5, H-6), 7.38 (1H,

d, $J = 7.2$ Hz, H-7). ^{13}C NMR δ : 14.04, 34.44, 34.66, 47.71, 60.59, 61.11, 124.13, 124.62, 127.31, 128.40, 140.18, 141.40, 162.88, 167.64.

cis-N-Ethyl-N'-(2-ethoxycarbonylindanyl)thiourea (14c). yield 0.56 g, 79%, mp 122-123 °C. Anal. Calcd. for: $\text{C}_{15}\text{H}_{20}\text{N}_2\text{O}_2\text{S}$ (292.40) C, 61.62; H, 6.89; N, 9.58. Found: C, 61.69; H, 7.18; N, 9.31. NMR data: ^1H NMR δ : 1.21 (3H, t, $J = 7.2$ Hz, CH_2CH_3), 1.26 (3H, t, $J = 7.2$ Hz, $\text{CH}_3\text{CH}_2\text{NH}$), 3.17-3.30 (2H, m, H-3), 3.34 (2H, bs, $\text{CH}_3\text{CH}_2\text{NH}$) 3.68 (1H, dt, $J = 4.9$ Hz, 7.7Hz, H-2), 4.08 (2H, q, $J = 7.1$ Hz, CH_2CH_3), 6.14 (1H, bs, $\text{CH}_3\text{CH}_2\text{NH}$), 6.38 (1H, t, $J = 7.8$ Hz, H-1), 6.73 (1H, d, $J = 8.2$ Hz, NH), 7.19-7.26 (3H, m, H-4, H-5, H-6) 7.37 (1H, d, $J = 7.2$ Hz, H-7). ^{13}C NMR δ : 13.97, 14.54, 34.69, 47.66, 48.29, 60.52, 61.09, 124.07, 124.61, 127.28, 128.34, 140.11, 141.44, 174.36, 181.72.

cis-N-Phenyl-N'-(2-ethoxycarbonylindanyl)thiourea (14d). yield 0.62 g, 75%, mp 169-170 °C. Anal. Calcd. for $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_2\text{S}$ (340.45): C, 67.03; H, 5.92; N, 8.23. Found: C, 67.31; H, 5.78; N, 8.55. NMR data: ^1H NMR δ : 1.18 (3H, t, $J = 7.2$ Hz, CH_2CH_3), 3.20 (2H, d, $J = 6.3$ Hz, H-3), 3.69 (1H, dt, $J = 7.3, 6.3$ Hz, H-2), 3.99-4.07 (2H, m, CH_2CH_3), 6.49 (1H, t, $J = 9.1, 7.3$ Hz, H-1), 7.04 (1H, d, $J = 9.1$ Hz, NH), 7.16-7.27 (6H, m, *p*-Ph, *m*-Ph, H-4, H-5, H-6), 7.31-7.34 (1H, m, H-7), 7.35-7.41 (2H, m, *o*-Ph), 8.09 (1H, bs, *NHPh*). ^{13}C NMR δ : 13.99, 34.76, 47.70, 60.94, 61.15, 123.82, 124.45, 124.91, 127.16, 127.27, 128.35, 130.04, 135.84, 140.20, 140.94, 173.57, 180.58.

(4aS*,9bS*)-3-Methyl-2-thioxo-1,2,3,4a,5,5a,9a,9b-octahydroindeno[1,2-a]pyrimidin-4-one (15). Thiourea derivative **14b** (0.70 g, 2.51 mmol) was dissolved in EtOH containing 22% dry HCl (20 ml) and the solution was refluxed for 12 h. After standing overnight, the crystalline product obtained was separated by filtration and recrystallized from EtOH. Yield 0.29 g, 50%, mp 169-170 °C. Anal. Calcd. for $\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_2\text{S}$ (232.31): C, 62.04; H, 5.21; N, 12.06. Found: C, 62.32; H, 5.48; N, 12.23. NMR data: ^1H NMR δ : 3.28-3.37 (1H, m, H-4a), 3.45-3.53 (2H, m, H-5), 3.54 (3H, s, CH_3), 4.95 (1H, dd, $J = 7.2, 3.2$ Hz, H-9b), 7.27-7.40 (4H, m, H-6, H-7, H-8, H-9). ^{13}C NMR δ : 33.59, 35.13, 43.59, 57.12, 123.71, 125.28, 127.77, 129.36, 139.53, 140.65, 168.84, 181.18.

1H-Indene-2-carboxylic acid (16). Thiourea derivative **14a**, **14c** or **14d** (2.51 mmol) was dissolved in EtOH containing 22% dry HCl (20 ml) and the solution was refluxed for 12 h. After standing overnight, the crystalline product obtained was separated by filtration. Yield 48-53%, mp 230-232 (decomp)°C, lit¹⁹ mp 234-236 °C, ^1H NMR δ : 3.73 (2H, d, $J = 1.7$ Hz, H-1), 7.33-7.40 (2H, m, H-6, H-7), 7.52-7.58 (2H, m, H-4, H-5), 7.87 (1H, t, $J = 1.7$ Hz, H-3). ^{13}C NMR δ : 38.19, 123.72, 124.38, 124.79, 127.0, 128.07, 136.21, 136.61, 143.54, 169.42. MS m/z (r.i.) 160 (65), 142 (3), 132 (6), 115 (100), 103 (3), 89 (8), 77 (4), 63 (9), 57 (3), 51 (2), 39 (3). Exact mass calculated for $\text{C}_{10}\text{H}_8\text{O}_2$: 160.05243. Found: 160.05258.

(4aS*,6aS*,11bS*)-4b,5-Dimethyl-4b,6,6a,7,11b,12-hexahydro-5H-indeno[1,2-e]pyrimido-[1,2-a]isoindole (19). To a solution of diamine base **5** (0.6 g, 3.4 mmol) in 20 ml absolute toluene, an equivalent amount of 2-carboxybenzaldehyde (0.51 g, 3.4 mmol) was added, and the mixture was refluxed for 5 h. The solvent was evaporated off and the residue was crystallized from *i*Pr₂O and then recrystallized from *i*Pr₂O-EtOAc. Yield 0.64 g, 65%, mp 150-153 °C. Anal.

Calcd. for C₁₉H₁₈N₂O (290.37): C, 78.59; H, 6.25; N, 9.65. Found: C, 78.71; H, 6.32; N, 9.73. NMR data: ¹H NMR δ: 2.09 (3H, s, CH₃), 2.52 (1H, d, *J* = 15.9 Hz, H-7), 2.84 (1H, t, *J* = 12.4 Hz, H-6), 2.91-3.00 (1H, m, H-6a), 3.06 (1H, dd, *J* = 12.4 Hz, 5.3 Hz, H-6), 3.14 (1H, dd, *J* = 15.9 Hz, 6.5 Hz, H-7), 5.1 (1H, s, H-4b), 5.96 (1H, d, *J* = 6.6 Hz, H-11b), 7.15-7.29 (4H, m, H-8, H-9, H-10, H-11), 7.48-7.59 (3H, m, H-2, H-3, H-4), 7.94 (1H, d, *J* = 7.2 Hz, H-1). ¹³C NMR δ: 30.29, 34.06, 34.35, 55.72, 55.81, 73.05, 123.60, 123.87, 124.26, 125.45, 127.11, 127.93, 129.29, 129.47, 131.54, 133.02, 140.84, 141.71, 167.29.

(3aR*,5aS*,10bS*)-3a,4-Dimethyl-1,2,3a,4,5,5a,6,10b-octahydro-3H-indeno[1,2-*e*]pyrrolo-[1,2-*a*]pyrimidine (22). To a solution of diamine base **5** (0.4 g, 2.27 mmol) in 20 ml absolute toluene, an equivalent amount of levulinic acid (0.27 g, 2.27 mmol) was added, and the mixture was refluxed for 8 h. The solvent was evaporated off and the residue was chromatographed on silica. Elution with EtOAc afforded the pentacyclic **21**, as the only diastereomer. Yield 0.37 g, 63%, mp 93-94 °C. Anal. Calcd. for C₁₆H₂₀N₂O (256.35): C, 74.97; H, 7.86; N, 10.93. Found: C, 74.74; H, 7.98; N, 10.72. NMR data: ¹H NMR δ: 0.9 (3H, s, CH₃), 2.01 (2H, dd, *J* = 9.6 Hz, 4.6 Hz, H-3), 2.18 (3H, s, NCH₃), 2.37 (1H, t, *J* = 12.1 Hz, H-5), 2.47-2.64 (3H, m, H-2, H-6), 2.66 (1H, dd, *J* = 12.1, 6.4 Hz, H-5), 2.74-2.83 (1H, m, H-5a), 3.04 (1H, dd, 15.8 Hz, 6.7 Hz, H-6), 5.62 (1H, d, *J* = 7.1 Hz, H-10b), 7.12-7.15 (4H, m, H-7, H-8, H-9, H-10). ¹³C NMR δ: 15.37, 29.66, 34.35, 34.50, 36.09, 37.76, 51.39, 54.78, 77.35, 124.58, 125.09, 126.76, 127.42, 140.66, 141.31, 173.33.

General procedure to react diamine **5** with aromatic aldehydes **23a-g**

To a suspension of diamine **5** (0.2 g, 1.13 mmol) in 20 ml absolute MeOH, an equivalent amount of aromatic aldehyde was added (liquid aldehydes were freshly distilled), and the mixture was allowed to stand at ambient temperature for 1 day. The solvent was then evaporated off and the evaporation was repeated after the addition of 10 ml toluene. The crystalline products were filtered off and recrystallized from *i*Pr₂O-EtOAc. The oily product **23b** was dried in a vacuum desiccator for 24 h.

Table 1. Physical data on compounds **23a-g**

Compound	Mp (°C)	Yield (%)	Formula	M.W	δ _{pN-CHAr-N} ring (B) (<i>J</i> [Hz])	δ _{pN-CHAr-N} ring (C) (<i>J</i> [Hz])
23a	143-144	72	C ₁₈ H ₁₉ N ₃ O ₂	309.37	4.62 (6.3)	4.20 (5.2)
23b	oil	-	C ₁₈ H ₁₉ BrN ₂	343.28	4.62 (6.2)	4.19 (5.2)
23c	103-104	73	C ₁₈ H ₁₉ ClN ₂	298.92	4.60 (6.2)	4.19 (5.2)
23d	78-82	80	C ₁₈ H ₂₀ N ₂	264.38	4.62 (6.2)	4.21 (5.2)
23e	90-93	75	C ₁₉ H ₂₂ N ₂	278.40	4.60 (6.2)	4.20 (5.2)
23f	95-97	75	C ₁₉ H ₂₂ N ₂ O	294.40	4.61 (6.2)	4.20 (5.1)
23g	118-120	82	C ₂₀ H ₂₅ N ₃	307.44	4.61 (5.5)	4.20 (0.57)

Acknowledgements

We thank Ms. Erika Horváth for her kind assistance in the synthetic work. The authors acknowledge receipt of OTKA grant T 034901.

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