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Novel High Energy Intermediate Analogues with Triazasterol-related Structures as Inhibitors of the Ergosterol Biosynthesis V [1]. Synthesis of Hexahydro-5*H*-imidazo[1′,2′:1,2]pyrimido-[4,3-*a*]isoquinolines and 1-Alkyl Analogues Representing New 8,13,15-Triazasteroids

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Summary. The synthesis of 1,2,6,10b,11,12-hexahydro-5*H*-imidazo[1′,2′:1,2]pyrimido[4,3-*a*]isoquinolines representing new types of 8,13,15-triazasteroids is described. The tetracyclic title compounds were prepared from 4-(2-hydroxyalkylamino)tetrahydro-2*H*-pyrimidoisoquinolines, which furnish after conversion to the corresponding bromoalkylamino compounds and base-catalyzed intramolecular nucleophilic displacement cyclization of the latter the desired 1-substituted 8,13,15-triazasteroids with aromatic ring A. The structures of the compounds were proved and assigned on the basis of homo- and heteronuclear correlated 1D and 2D NMR experiments. The title compounds represent triaza-analogues of selected high energy intermediates (HEI) of steroidal substrates formed during the enzymatic transformation of squalene into ergosterol and are designed to act as inhibitory mimicries of HEIs and potential antimycotics.

Keywords. Hexahydro-5*H*-imidazo[1′,2′:1,2]pyrimido[4,3-*a*]isoquinolines; High energy intermediate analogues; Structure elucidation; Fungicides.

Introduction

Due to the increasing clinical importance of opportunistic fungal infections there is a continuing demand for improved antifungal agents [2–4]. Most of the antifungal drugs presently used belong to the ergosterol biosynthesis inhibitors, which have in

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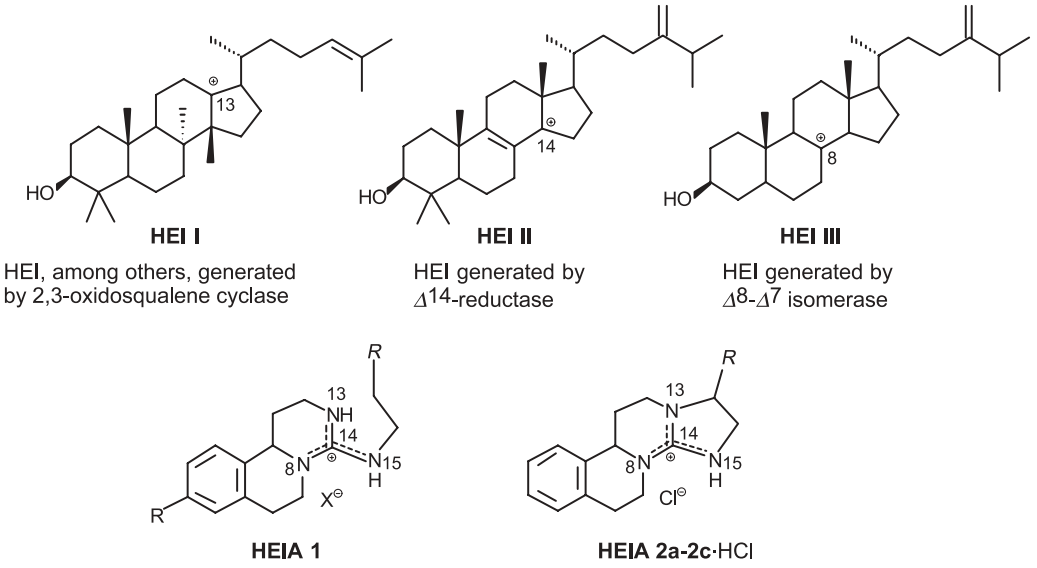


Fig. 1. Carbocationic HEIs and general formulae of corresponding HEIAs of type **1** and **2a**–**2c**·HCl

common the ability to block specific enzymes with the result of fatal malfunctions of the fungal cell membrane [5].

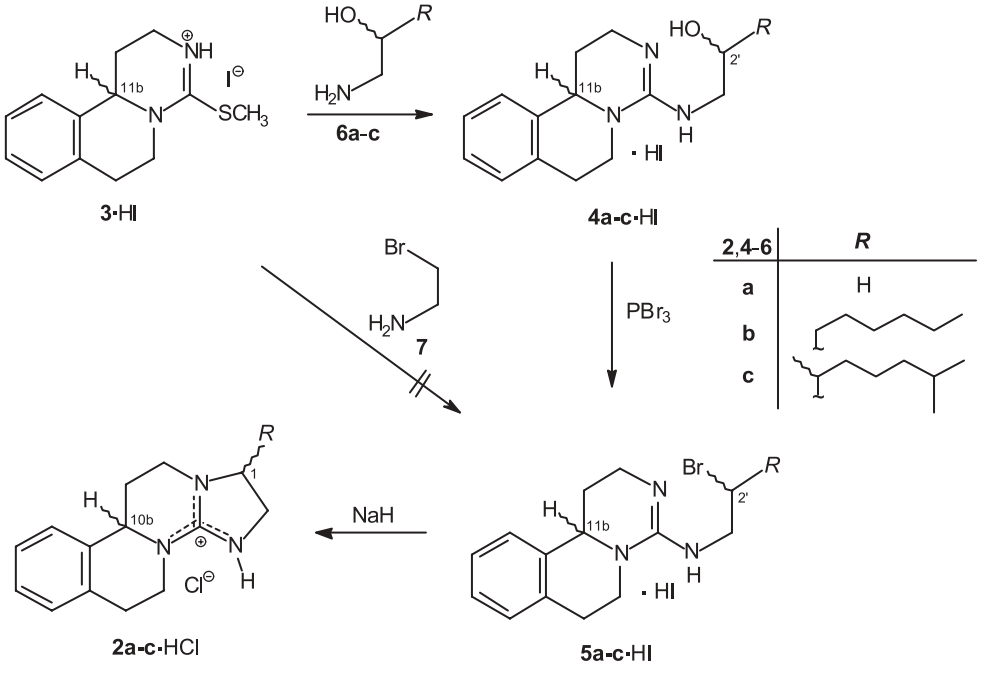
In the course of our efforts to develop new antimicrobial agents we have synthesized among others a series of N^4-alkyl- and N^4-alkenyltetrahydro-2*H*-pyrimido[4,3-*a*]isoquinolin-4-amine salts **1** [6] (Fig. 1). The design of this new type of triazasteroids was based on the knowledge, whereupon in the course of the enzymatic transformation of squalene into ergosterol the steroidal substrates are transformed into carbocationic transition state intermediates, so called high energy intermediates (HEI), and that HEI analogues (HEIAs) with positive charge are able to act as inhibitors of specific fungal enzymes [5, 7, 8]. The 8,13,15-triazasecosteroids **1** with integrated guanidinium moiety and hence very stable positive charge have been designed and prepared as HEIAs to mimic the HEI I–III (Fig. 1) [1, 6, 9]. Screening tests have shown recently, that HEIAs **1** indeed display significant antimycotic effects on fungal organisms, in some cases comparable with the activity observed for the potent azole derivative itraconazole [6].

In this contribution we report on the synthesis of hexahydro-5*H*-imidazo[1′,2′:1,2]pyrimido[4,3-*a*]isoquinolines representing new 8,13,15-triazasteroids of HEIA-type **2** with complete tetracyclic skeleton and close structural resemblance to the native HEIs I–III generated by oxidosqualene lanosterol cyclase, Δ^{14}-reductase, and Δ^8-Δ^7-isomerase, respectively (Fig. 1). Further structural elements considered as important for antifungal activity of the 8,13,15-triazasteroid analogues **2a**–**2c**·HCl are the stable positive charge and appropriate 1-alkyl substituents, *i.e.* hexyl and 1,5-dimethylhexyl residues, at C-17 (steroid numbering). The positive charge in the guanidinium moiety of HEIAs **2** is delocalized and spread over N-8, N-13, N-15, and C-14, that means the charge can appear at the same ring positions as in native HEIs I–III.

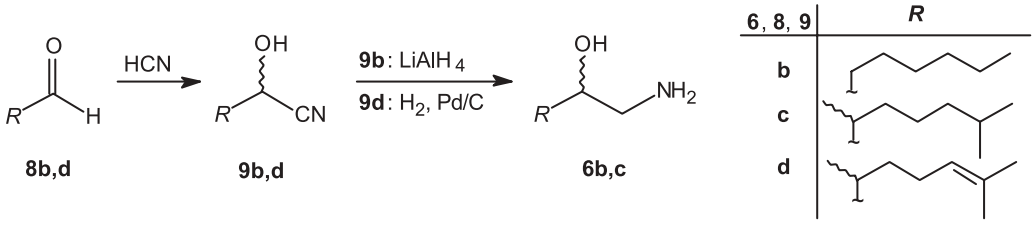
Results and Discussion

For the preparation of hexahydro-5*H*-imidazo[1′,2′:1,2]pyrimido[4,3-*a*]isoquinolines **2a**–**2c**·HCl we used the route illustrated in Scheme 1. In this approach the two types of requisite precursors, the tricyclic methylthio compound **3**·HI and aminoalkanols **6a**–**6c** (Scheme 2) are built up first separately, and then coupled to yield the 4-(2-hydroxyalkylamino)pyrimidoisoquinolines **4a**–**4c**·HI. The conversion of these salts into the corresponding bromoalkylamino compounds **5a**–**5c**·HI and intramolecular cyclization of the latter furnishes the desired tetracyclic compounds **2a**–**2c**·HCl with appropriate side chains at position 1.

The synthesis of the racemic 4-methylthio-1,6,7,11b-tetrahydro-2*H*-pyrimido-[4,3-*a*]isoquinoline hydroiodide (**3**·HI) has been described previously [9]. Accordingly, β-phenylethylamine was transformed in two steps into *N*-phenethyl-3-phthalimidopropionamide, which is subsequently cyclized, saponified, and reduced to yield 1-(aminoethyl)tetrahydroisoquinoline. Condensation of the latter with



Scheme 1



Scheme 2

carbon disulfide and *S*-methylation of the generated pyrimidoisoquinolinethione gives the angularly fused isothiuronium salt **3**·HI containing the rings A–C of the steroid nucleus.

The l-amino-2-octanols **6b** and **6c** as second building block for the target compounds **2b** and **2c** were synthesized in two steps as outlined in Scheme 2. First, the cyanohydrins **9b** and **9d** were prepared from the corresponding commercially available heptanal (**8b**) and (±)-2,6-dimethyl-5-heptenal (**8d**) through addition of hydrogen cyanide. The reaction proceeded readily in methanolic solution with potassium cyanide in the presence of glacial acetic acid [10] and was complete within 30 min affording yields of 94% or higher. Cyanohydrin **9b** was subsequently reduced with lithium aluminum hydride in diethyl ether to the (±)-1-amino-2-octanol (**6b**). In order to reduce the cyano group and the double bond simultaneously, the hydrogenation of dimethyloctenenitrile **9d** was carried out with palladium on charcoal as catalyst. After distillation a mixture of diastereomeric saturated 3,7-dimethylaminooctanols **6c** was isolated in 62% yield.

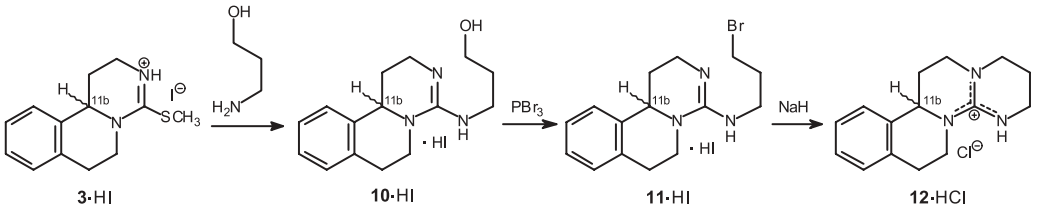
In initial efforts we tried to prepare bromoethylaminopyrimidoisoquinoline **5a**·HI in one step by direct reaction of methylthio compound **3**·HI with commercially available 2-bromoethylamine (**7**) under various conditions (Scheme 1), but the respective experiments were not successful.

Thus, we used the pathway *via* 4-(2-hydroxyalkylamino)pyrimidoisoquinolines **4a**–**4c**·HI, which were synthesized from **3**·HI and 2-aminoethanol (**6a**), as well as β-aminooctanols **6b** and **6c** (Scheme 1). Among various solvents examined for this reaction (methanol, butanol, *tert*-butanol, *THF*, acetonitrile) the highest efficiency was attained with acetonitrile. In the other solvents no (*THF*), or only little transformation (methanol), or the production of great amounts of unidentified side products (butanol, *tert*-butanol) were observed.

Next, the conversion of the alkanols **4a**–**4c**·HI into corresponding bromoalkyl compounds **5a**–**5c**·HI was performed through a mild and very efficient general method of bromination [11] by treatment of **4a**–**4c**·HI with a slight excess of phosphorus tribromide in dichloromethane at $-10°C$. The yields of isolated products **5a**–**5c**·HI were excellent. In contrast, treatment of hydroxy compounds **4a**–**4c**·HI with 48% hydrogen bromide in a two phase system (CH_2Cl_2/H_2O) under reflux resulted in only poor yields of the desired bromo compounds **5a**–**5c**·HI mixed with unseparable impurities.

Finally, the imidazole ring D of the triazasteroids **2a**–**2c** was closed by a base-catalyzed nucleophilic displacement of bromine in the N^4-alkyl side chain by the ring nitrogen N-3 of the pyrimidoisoquinolines **5a**–**5c**. The reaction was performed by treating a tetrahydrofuran solution of the salts **5a**–**5c**·HI with pure NaH at low temperatures under anhydrous conditions (Scheme 1). Thus, racemic hexahydroimidazo[1′,2′:1,2]pyrimido[4,3-*a*]isoquinoline hydochloride (**2a**·HCl) and the diastereomeric 1-hexyl analogue **2b**·HCl could be synthesized in yields of 70% and 60%, respectively. Purification, in particular of the diastereomeric 1-(1,5-dimethylhexyl) compound **2c**·HCl proved to be tedious, hence it was obtained in only 30% yield after chromatography.

In analogy to the above reaction sequence, the synthesis of the racemic *D-homo* derivative **12**·HCl was accomplished, *via* the 4-hydroxypropylamino and 4-bromopropylamino intermediates **10**·HI and **11**·HI, in 54% yield (Scheme 3).



Scheme 3

The structures and complete signal assignments of the 4-substituted pyrimidoisoquinolines of type **4**·HI and **5**·HI, of the imidazopyrimidoisoquinolines **2a**–**2c**·HCl, and of the pyrimido-fused tetracyclus **12**·HCl were established by means of NMR spectroscopic studies based on ^{1}H and ^{13}C NMR, HH-COSY, N*O*ESY, *gs*-HSQC, *gs*-HMBC, and 1D N*O*E difference experiments as well as by increment calculations [12, 13].

Compounds **4a**·HI, **5a**·HI, **10**–**12**·HCl, and **2a**·HCl with only one chiral center at C-11b and C-10b are each racemates. Compounds **4b**·HI, **5b**·HI, and **2b**·HCl possess a second chiral center at C-2′ in the 4-(2-substituted octylamino) side chains and in the 1-position. The ^{13}C resonances of the chiral carbons C-11b and C-2′ of **4b**·HI and **5b**·HI, as well as of C-10b and C-1′ of **2b**·HCl are duplicated. Hence, these products are mixtures of two diastereomeric racemates each. The ^{1}H NMR spectra of the three salts in different solvents (*DMSO*-d_6 and $CDCl_3$) and at various temperatures (293, 298, 305 K) exhibit for nearly all hydrogen atoms only one signal each. Solely the ^{1}H NMR of tetracyclus **2b**·HCl shows two separated doublets of triplets for H-10b and two singlets for NH-3.

The salts **4c**·HI, **5c**·HI, and **2c**·HCl possess three chiral centers and could thus be mixtures of up to four diastereomeric racemates each. However, the ^{13}C NMR spectra of the three compounds exhibit again only for some of the chiral carbons (C-2′ of **4c**·HI, C-11b of **4c**·HI and **5c**·HI, C-1 and C-10b of **2c**·HI) duplicated resonances. This finding points towards the existence of only two diastereomers in each product, but does not prove it. Also the ^{1}H NMR spectra are not sufficiently different, duplicated signals were only observed for H-2′ and OH in case of **4c**·HI and H-11b of **5c**·HI.

The chemical shifts and signal patterns of the proton resonances for the tetrahydropyrimidoisoquinoline moieties of all angularly fused compounds of type **2**, **4**, and **5** as well as the N*O*E experiments reveal the existence of a half-chair conformation of the tetrahydropyridine ring with axially oriented methine protons H-10b (**2a**–**2c**·HCl) and H-11b (**4a**–**4c**·HI, **5a**–**5c**·HI). Due to the planar guanidinium moiety the fused tetrahydropyrimidine ring exhibited a sofa conformation as recently described [9]. As a consequence, the diastereomers of the tetracycles **2b**·HCl and **2c**·HCl differ mainly with respect to the relative configuration at C-1 and (in case of **2c**·HCl) C-1′ of the side chain. Efforts to determine the relative configuration at the chiral centers C-10b and C-1 of the two diastereomers to **2b**·HCl, as well as at C-10b, C-1, and C-1′ in the diastereomers of **2c**·HCl by means of N*O*E experiments were not successful so far. A detailed NMR study on the problem is in progress.

However, in case of the 1-(1,5-dimethyl)hexyl compound **2c**·HCl the signal for the methine proton H-1 appears as a triplet-doublet with $J = 10.4$ and 3.2 Hz, which is indicative for its axial location and a consequent equatorial orientation of the side chain, and an approximate *trans* position of H-1 at the nucleus and H-1′ of the side chain. Figure 2 shows exemplarily the stereoformulae of the tetracyclic ring systems of the (1*R*,10b*S*)- and (1*S*,10b*S*)-enantiomers of **2b**·HCl and **2c**·HCl.

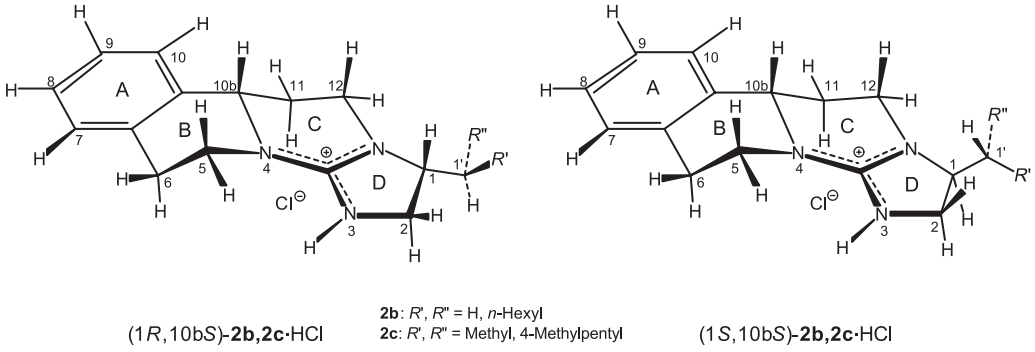


Fig. 2. The diastereomers of **2b**·HCl and **2c**·HCl

For practical purposes, the tricyclic alkanols **4b**·HI and **4c**·HI as well as the bromoalkyl compounds **5b**·HI and **5c**·HI were carried through the reaction sequences as mixtures of diastereomers. The separation of the components of the target compounds **2a**–**2c**·HCl by proper methods such as fractional crystallization, chromatography, and resolution is currently under investigation. The antimicrobial screening of the HEIA-type imidazopyrimidoisoquinolines **2a**–**c**·HCl is carried out presently with the racemates and racemic diasteroisomers.

Experimental

All reactions were carried out under Ar atmosphere. Melting points were determined on a *Kofler* melting point apparatus and are uncorrected. Thin-layer chromatograms (TLC) were run on TLC plastic sheets silica gel 60 F254 (E. Merck, Darmstadt). The spots were detected by visual examination under UV light (254 and 366 nm), and visualized with chlorine vapour or by spraying with an ethanolic solution of 0.5% vanillin and 80% H_2SO_4 and successive heating. Column chromatography (CC) was performed using silica gel 60 (0.063–0.200 mm, Merck). Infrared spectra were recorded with a 2000 FTIR spectrophotometer (s = strong, m = medium, w = weak). NMR spectra were aquired on a Varian 400 MHz Unity Inova NMR spectrometer equipped with a Sun Sparc 5 computer system and operating at an observation frequency of 399.98 MHz for ^{1}H and 100.59 MHz for ^{13}C. 1D and 2D NMR experiments were performed using a pulsed magnetic field gradient unit and a 5 mm inverse broadband probehead. The HH-COSY, *gs*-HSQC, *gs*-HMBC, N*O*ESY, and 1D N*O*E difference experiments were performed using the pulse programs supplied by the manufacturer. The *gs*-HMBC experiments were optimized for 4, 8 and 10 Hz $^nJ_{CH}$ giving delays of 125.0, 62.5, and 50.0 ms. All N*O*Es were measured in degassed samples. Amounts of 15–25 mg of the substances were dissolved in 0.5 cm^3 of deuterated solvents and measured at 298 K. All chemical shifts are reported with *TMS* as internal standard. For a convenient reading correlating spin systems are reported coherently, assignments marked with an asterisk are interchangeable. Elemental analyses (C, H, N, halogen) were performed by *J. Theiner*, Microanalytical Laboratory at the University of Vienna, Institute of Physical Chemistry; they were found to agree favourably with the calculated values.

(2RS)-2-Hydroxyoctanenitrile (**9b**)

The reported procedure was modified according to Ref. [10]. Heptanal (**8b**) (7.00 g, 50 mmol) in 10 cm^3 of *Me*OH was added slowly to an ice-cooled solution of 4.90 g of KCN (75 mmol) in 100 cm^3 of *Me*OH. After stirring the mixture for 15 min, 6.00 g of glacial acetic acid (100 mmol) was added dropwise and stirred at 0°C for additional 15 min. Then the mixture was poured into

300 cm^3 of H_2O and extracted with 3×60 cm^3 of CH_2Cl_2. The combined organic layers were washed with H_2O, dried over Na_2SO_4, and concentrated under reduced pressure to give 6.61 g (94%) of 2-hydroxyoctanenitrile (**9b**) as yellowish liquid. TLC (light petroleum:Et_2O = 1:1): $R_f = 0.42$, visualization with vanillin-H_2SO_4; IR (neat): $\bar{\nu}$ = 3445(s), 2956(s), 2930(s), 2860(s), 2247(w), 1761(w), 1466(m), 1125(w), 1070(m) cm^{-1}; ^{1}H NMR ($CDCl_3$): see Ref. [14]. ^{13}C NMR ($CDCl_3$): 13.9 (C-8), 22.4 (C-7), 24.4 (C-4), 28.5 (C-6), 31.4 (C-5), 35.0 (C-3), 61.1 (C-2), 120.2 (C-1) ppm.

(2RS)-1-Amino-2-octanol (**6b**)

Cyanohydrin **9b** (6.40 g, 45.3 mmol) in 25 cm^3 of dry Et_2O was added dropwise to the solution of 3.44 g of $LiAlH_4$ (90.6 mmol) in 100 cm^3 of anhydrous Et_2O at 0°C. After warming to room temperature the mixture was stirred for 16 h. The reaction was cautiously quenched by successive addition of 3.5 cm^3 of H_2O, 3.5 cm^3 of 3 *N* NaOH, and 10 cm^3 of H_2O, and the formed white slurry was filtered through a pad of silica gel, which was washed twice with Et_2O. The combined organic phases were dried over Na_2SO_4 and the solvent was evaporated to give after distillation *in vacuo* 4.05 g (62%) of **6b** as a colourless liquid. Bp 82°C/5 mbar (Ref. [15] 130–132°C/26 torr), TLC (basic Al_2O_3, ethyl acetate:*Me*OH = 1:1): $R_f = 0.24$, visualization with vanillin-H_2SO_4; IR (neat): $\bar{\nu}$ = 3357(m), 2927(s), 1595(w), 1466(m), 1378(w), 1062(w), 964(w) cm^{-1}; ^{1}H NMR ($CDCl_3$): see Ref. [16]. ^{13}C NMR ($CDCl_3$): δ = 13.9 (C-8), 22.5 (C-7), 25.6 (C-4), 29.3 (C-5), 31.7 (C-6), 34.8 (C-3), 47.5 (C-1), 72.0 (C-2) ppm.

(2RS,3RS)-2-Hydroxy-3,7-dimethyl-6-octenenitrile (**9d**, $C_{10}H_{17}NO$)

Following the procedure described for **9b**, the reaction of 7.00 g of dimethylheptenal **8d** (50 mmol), 4.90 g of KCN (75 mmol), and 6.01 g of glacial acetic acid (100 mmol) in 100 cm^3 of *Me*OH afforded 8.35 g of pure yellowish liquid **9d** in quantitative yield. TLC (light petroleum:Et_2O = 1:1): $R_f = 0.47$, visualization with vanillin-H_2SO_4; IR (neat): $\bar{\nu}$ = 3445(s), 2968(s), 2920(s), 2859(s), 2246(w), 1673(m), 1647(w), 1453(s), 1379(s), 1060(s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 1.04 (d, J = 6.8 Hz, CH_3-3), 1.27 and 1.67 (m, H_a-4, and m, partly overlapped, H_b-4), 1.58 (s, H_3-8), 1.66 (s, H_3-7), 1.85 and 2.01 (m, H_a-5, and m, 1H, H_b-5), 1.97 (m, H-3), 3.43 (bs, OH), 4.33 (t, J = 5.6 Hz, H-2), 5.06 (t, J = 6.8 Hz, H-6) ppm; ^{13}C NMR ($CDCl_3$): δ = 14.7 (CH_3 at C-3), 17.6 (C-8), 25.0 (C-5), 25.6 (CH_3 at C-7), 31.5 (C-3), 37.2 (C-4), 65.7/66.0 (C-2), 119.2/119.6 (C-1), 123.4 (C-6), 132.3 (C-7) ppm.

(2RS,3RS)-1-Amino-3,7-dimethyl-2-octanol (**6c**, $C_{10}H_{23}NO$)

Octenol **9d** (7.25 g, 42.3 mmol) dissolved in 75 cm^3 of ethyl acetate was hydrogenated at 2.75 bar and room temperature in the presence of 0.60 g of 10% Pd/C. After the uptake of H_2 was complete (3 h), the catalyst was filtered off and the solvent was evaporated to yield after distillation *in vacuo* 4.57 g (62%) of **6c** as colourless oil. Bp 125°C/20 mbar, TLC (basic Al_2O_3, ethyl acetate:*Me*OH = 1:1): $R_f = 0.31$, visualization with vanillin-H_2SO_4; IR (neat): $\bar{\nu}$ = 3361(m), 2955(s), 2928(s), 1593(m), 1467(m), 1383(m), 1366(m) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 0.82 (d, J = 6.4 Hz, H_3-8), 0.84 (d, J = 6.4 Hz, H_3-7), 0.86 (d, J = 6.8 Hz, H_3-3), 1.08–1.12 (overlapping multiplets, H_2-6, H_2-5), 1.34 (m, H_2-4), 1.42 (m, partly overlapped, 1H, H-7), 1.48 (m, partly overlapped, H-3), 1.90 (b, OH, NH_2), 2.57 and 2.78 (m, H_a-1, and m, H_b-1), 3.25/3.33 (m, H-2) ppm; ^{13}C NMR ($CDCl_3$): δ = 14.5 (CH_3 at C-3), 22.5 (C-8*), 22.7 (CH_3 at C-7*), 24.8 (C-5), 27.9 (C-6), 32.7 (C-4), 36.7 (C-7), 39.2 (C-3), 44.4/45.1 (C-1), 75.6/75.9 (C-2) ppm.

*General Procedure for the Synthesis of 4-(2- and 3-Hydroxyalkylamino)tetrahydro-2H-pyrimido[4,3-a]isoquinoline hydroiodides **4a–4c**·HI and **10**·HI*

2-Methylthiopyrimidoisoquinoline salt **3**·HI (10 mmol) and 12 mmol of the respective aminoalcohols **6a–6c** were dissolved in 50 cm^3 of anhydrous acetonitrile and refluxed under TLC monitoring for

14–16 h. The CH_3SH liberated during this time was discharged successively into 20% aqueous $KMnO_4$ and 6 *N* NaOH solutions. After cooling, dry N_2 was passed through to remove remaining CH_3SH. Then the solvent was evaporated under reduced pressure. The obtained solid was triturated three times with 2 *N* aqueous HI and twice with H_2O, and filtered. After drying, the crude product was triturated successively twice with Et_2O and once with *n*-hexane, filtered, and dried *in vacuo* to yield the yellowish crystalline, slightly hygroscopic compounds.

(11bRS)-4-(2-Hydroxyethylamino)-1,6,7,11b-tetrahydro-2H-pyrimido[4,3-a]isoquinoline hydroiodide (**4a**·HI, $C_{14}H_{20}IN_3O$)

Yield: 2.65 g (71%), mp 45°C, TLC (CH_2Cl_2:*Me*OH = 4:1): $R_f = 0.60$, visualization with Cl_2; IR (KBr): $\bar{\nu} = 3260$(s), 2928(m), 2876(m), 1612(s), 1492(m), 1451(m), 1392(m), 1346(m), 1152(m), 1041(m) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 1.84$ (m, H_a-1), 2.64 (dm, $J = 13.6$ Hz, H_b-1), 2.86 (m, H_a-7), 3.00 (m, H_b-7), 3.24 (m, H_2-1′), 3.36 (m, H_2-2, H_a-6), 3.53 (t, $J = 5.6$ Hz, H_2-2′), 3.92 (dt, $J = 12.8$, 4.8 Hz, H_b-6), 4.77 (dd, $J = 10.0$, 4.0 Hz, H-11b), 5.09 (bs, OH), 7.25 (m, H-8, H-9, H-10), 7.33 (d, $J = 6.8$ Hz, H-11), 7.51 (bs, H-4), 8.00 (bs, H-3); ^{13}C NMR (*DMSO*-d_6): $\delta = 27.7$ (C-1), 28.0 (C-7), 37.1 (C-2), 43.4 (C-6), 44.0 (C-1′), 53.7 (C-11b), 59.4 (C-2′), 125.4 (C-11), 126.4 (C-10*), 127.0 (C-9*), 128.5 (C-8), 134.2 (C-7a), 135.5 (C-11a), 152.6 (C-4) ppm.

(11bRS)-4-[(2RS)-2-Hydroxyoctylamino]-1,6,7,11b-tetrahydro-2H-pyrimido[4,3-a]isoquinoline hydroiodide (**4b**·HI, $C_{20}H_{32}IN_3O$)

Yield: 3.97 g (87%), mp 60°C, TLC (CH_2Cl_2:*Me*OH = 6:1): $R_f = 0.88$, visualization with Cl_2; IR (KBr): $\bar{\nu} = 3258$(s), 2927(s), 2855(s), 1613(s), 1454(m), 1306(m), 1244(m), 1068(m) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 0.85$ (t, $J = 6.8$ Hz, H_3-8′), 1.25 (m, H_2-4′, H_2-5′, H_2-6′, H_2-7′), 1.38 (m, H_2-3′), 1.83 and 2.61 (m, H-1_{ax}, and dm, $J = 12.8$ Hz, H-1_{eq}), 2.84 and 2.98 (dm, $J = 15.6$ Hz, H-7_{eq} and m, H-7_{ax}), 3.21 (m, H_2-1′), 3.36 and 3.98 (m, partly overlapped, H-6_{ax}, and dt, $J = 12.8$, 5.6 Hz, H-6_{eq}), 3.34 (m, partly overlapped, H_2-2) 3.60 (m, H-2′), 4.76 (dd, $J = 10.4$, 4.8 Hz, H-11b), 5.13 (d, $J = 3.6$ Hz, OH), 7.25 (m, H-8, H-9, H-10), 7.33 (d, $J = 6.8$ Hz, H-11), 7.57 (t, $J = 5.2$ Hz, H-4), 8.14 (bs, H-3) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 13.9$ (C-8′), 22.0 (C-7′), 24.9 (C-5′), 27.8 (C-1), 28.7 (C-7), 31.2 (C-6′), 31.3 (C-4′), 34.1 (C-3′), 37.1 (C-2), 43.4 (C-6), 47.9 (C-1′), 54.0/54.1 (C-11b), 68.5/68.7 (C-2′), 125.1 (C-11), 126.6 (C-10*), 127.1 (C-9*), 128.4 (C-8), 134.4 (C-7a), 135.7 (C-11a), 152.8 (C-4) ppm.

(11bRS)-4-[(2RS, 3RS)-2-Hydroxy-3,7-dimethyloctylamino]-1,6,7,11b-tetrahydro-2H-pyrimido[4,3-a]isoquinoline hydroiodide (**4c**·HI, $C_{22}H_{36}IN_3O$)

Yield: 4.22 g (87%), mp 48°C, TLC (CH_2Cl_2:*Me*OH = 6:1): $R_f = 0.76$, visualization with Cl_2; IR (KBr): $\bar{\nu} = 3274$(s), 2927(s), 1614(s), 1458(m), 1364(m), 1244(m), 1041(m) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 0.80$ (d, $J = 7.2$ Hz, CH_3-3), 0.85 (d, $J = 6.8$ Hz, H_3-8′, CH_3-7), 1.11 (m, H_2-6′, H_2-5′), 1.37 (m, H_2-4′), 1.50 (m, H-3′, H-7′), 1.83 and 2.63 (m, H_a-1, and m, H_b-1), 2.85 and 2.96 (dm, $J = 14.8$ Hz, H-7_{eq}, and m, H-7_{ax}), 3.20 (m, H_2-1′), 3.28 and 3.92 (m, partly overlapped, H-6_{ax}, and dt, $J = 14.8$, 6.0 Hz, H-6_{eq}), 3.37 (m, partly overlapped, H_2-2), 3.47/3.55 (m/m, H-2′), 4.77 (dd, $J = 10.8$ Hz, 4.4 Hz, H-11b), 5.02/5.10 (d/d, $J = 5.2$ Hz, OH), 7.16 (m, H-8, H-9, H-10), 7.32 (d, $J = 7.4$ Hz, H-11), 7.40 (t, $J = 5.6$ Hz, H-4), 8.04 (bs, H-3) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 19.3$ (CH_3 at C-3′), 22.5 (C-8′*), 22.7 (CH_3 at C-7′*), 24.4 (C-5′), 26.7 (C-1), 27.4 (C-4′), 27.9 (C-7), 29.8 (C-7′), 35.3 (C-3′), 37.2 (C-2), 38.7 (C-6′), 39.6 (C-1′), 43.5 (C-6), 54.0/54.2 (C-11b), 72.3/72.9 (C-2′), 125.2 (C-11), 126.7 (C-10*), 127.2 (C-9*), 128.4 (C-8), 134.5 (C-7a), 135.8 (C-11a), 152.1 (C-4) ppm.

(11bRS)-4-(3-Hydroxypropylamino)-1,6,7,11b-tetrahydro-2H-pyrimido[4,3-a]isoquinoline hydroiodide (**10**·HI, $C_{15}H_{22}IN_3O$)

Yield: 2.54 g (66%), mp 72°C, TLC (CH_2Cl_2:*Me*OH = 6:1): $R_f = 0.53$, visualization with Cl_2; IR (KBr): $\bar{\nu} = 3256$(s), 2929(m), 2876(m), 1610(s), 1492(m), 1345(m), 1243(m), 1060(m) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 1.69$ (quin, $J = 6.4$ Hz, H_2-2′), 1.84 (m, H_a-1), 2.63 (dd, $J = 13.2$, 4.0 Hz, H_b-1), 2.84 (dt, $J = 16.4$, 4.4 Hz, H_a-7), 2.98 (m, H_b-7), 3.20 (m, H_2-1′), 3.36 (m, H_2-2, H_a-6), 3.47 (q, $J = 4.8$ Hz, H_2-3′), 3.88 (dt, $J = 13.2$, 4.8 Hz, H_b-6), 4.63 (t, $J = 4.4$ Hz, OH), 4.76 (dd, $J = 10.4$, 4.8 Hz, H-11b), 7.25 (m, H-8, H-9, H-10), 7.33 (d, $J = 6.4$ Hz, H-11), 7.44 (t, $J = 5.2$ Hz, H-4), 8.04 (s, H-3) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 27.5$ (C-1), 28.0 (C-7), 31.3 (C-2′), 37.1 (C-2), 38.5 (C-1′), 43.3 (C-6), 53.5 (C-11b), 57.9 (C-3′), 125.2 (C-11), 126.1 (C-10*), 126.9 (C-9*), 128.7 (C-8), 134.2 (C-7a), 135.1 (C-11a), 152.3 (C-4) ppm.

*General Procedure for the Synthesis of 4-(2- and 3-Bromoalkylamino)tetrahydro-2H-pyrimido[4,3-a]isoquinoline hydroiodides **5a–5c**·HI and **11**·HI*

Phosphorus tribromide (9.60 mmol) was added dropwise to a cold solution of the respective hydroxyalkylaminopyrimidoisoquinoline (8 mmol) **4a–4c**·HI and **10**·HI in 50 cm^3 of dry CH_2Cl_2 maintaining the reaction temperature at − 10°C and stirring for 1 h. After warming to room temperature the reaction mixture was stirred for 15 h and then quenched cautiously with 2 cm^3 of H_2O. After that, the reaction mixture was dried (Na_2SO_4) and the solvent evaporated under reduced pressure. The obtained solid was treated successively twice with 2 *N* aqueous HI and Et_2O, filtered, and dried at room temperature (1 mbar). Trituration of the crystalline product with hexane gave the yellow compounds.

(11bRS)-4-(2-Bromoethylamino)-1,6,7,11b-tetrahydro-2H-pyrimido[4,3-a]isoquinoline hydroiodide (**5a**·HI, $C_{14}H_{19}BrIN_3$)

Yield: 2.23 g (64%), mp 147°C, TLC (CH_2Cl_2:*Me*OH = 6:1): $R_f = 0.55$, visualization with Cl_2; IR (KBr): $\bar{\nu} = 3423$(m), 3169(m), 2928(m), 1603(s), 1493(m), 1301(m), 1244(m), 1189(m) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 1.84$ and 2.61 (m, H-1_{ax}, and dm, $J = 13.6$ Hz, H-1_{eq}), 2.84 and 3.01 (dt, $J = 16.0$, 4.0 Hz, H-7_{eq}, and m, H-7_{ax}), 3.23 (t, $J = 6.8$ Hz, H_2-1′), 3.30 (m, H_2-2), 3.51 (t, $J = 6.8$ Hz, H_2-2′), 3.66 and 3.92 (m, H-6_{ax}, and dt, $J = 13.2$, 5.6 Hz, H-6_{eq}), 4.75 (dd, $J = 10.0$, 4.8 Hz, H-11b), 7.25 (m, H-8, H-9, H-10), 7.33 (d, $J = 6.0$ Hz, H-11), 7.79 (q, $J = 5.6$ Hz, H-4), 8.27 (bs, H-3) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 27.7$ (C-1), 27.8 (C-7), 37.2 (C-2), 44.1 (C-1′), 43.4 (C-6), 54.1 (C-11b), 59.4 (C-2′), 125.2 (C-11), 126.7 (C-10*), 127.2 (C-9*), 128.4 (C-8), 134.5 (C-7a), 135.7 (C-11a), 152.8 (C-4) ppm.

(11bRS)-4-[(2RS)-2-Bromooctylamino]-1,6,7,11b-tetrahydro-2H-pyrimido[4,3-a]isoquinoline hydroiodide (**5b**·HI, $C_{20}H_{31}BrIN_3$)

Yield: 4.16 g (100%), mp 68°C, TLC (CH_2Cl_2:*Me*OH = 6:1): $R_f = 0.67$, visualization with Cl_2; IR (KBr): $\bar{\nu} = 3175$(m), 2927(s), 2856(s), 1613(s), 1454(m), 1307(w), 1242(m), 1003(m) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 0.85$ (t, $J = 6.8$ Hz, H_3-8′), 1.26 (m, H_2-4′, H_2-5′, H_2-6′, H_2-7′), 1.53 and 1.71 (m, H_a-3′, and m, H_b-3′), 1.86 and 2.64 (m, H_a-1, and m, H_b-1), 2.87 and 3.01 (dm, $J = 16.8$ Hz, H-7_{eq}, and m, H-7_{ax}), 3.35 (m, H_2-2), 3.49 and 3.98 (m, partly overlapped, H-6_{ax}, and dt, $J = 13.2$, 5.2 Hz, H-6_{eq}), 3.54 (m, H_2-1′), 4.31 (m, H-2′), 4.80 (dd, $J = 10.0$, 4.4 Hz, H-11b), 7.25 (m, H-8, H-9, H-10), 7.33 (d, $J = 5.6$ Hz, H-11), 7.81 (m, H-4), 8.29 (bs, H-3) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 13.9$ (C-8′), 22.0 (C-7′*), 22.2 (C-5′*), 27.8 (C-1), 28.4 (C-7), 31.0 (C-6′), 31.3 (C-4′), 35.1 (C-3′), 37.1 (C-2), 43.8 (C-6), 47.9 (C-1′), 54.1/54.3 (C-11b), 68.6/68.8 (C-2′), 125.1 (C-11), 126.7 (C-10*), 127.2 (C-9*), 128.4 (C-8), 134.4 (C-7a), 135.6 (C-11a), 152.3 (C-4) ppm.

(11bRS)-4-[(2RS, 3RS)-2-Bromo-3,7-dimethyloctylamino]-1,6,7,11b-tetrahydro-2H-pyrimido[4,3-a]isoquinoline hydroiodide (**5c**·HI, $C_{22}H_{35}BrIN_3$)

Yield: 4.34 g (99%), mp 70°C, TLC (CH_2Cl_2:*Me*OH = 6:1): $R_f = 0.68$, visualization with Cl_2; IR (KBr): $\bar{\nu} = 3234$(m), 2952(s), 2867(m), 1613(s), 1457(m), 1365(w), 1242(w), 1126(w), 1010(m) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 0.84$ (d, $J = 6.8$ Hz, H_3-3′), 0.86 (t, $J = 6.4$ Hz, H_3-8′, H_3-7′), 1.09–1.25 (overlapping multiplets, H_2-5′, H_2-6′), 1.45 (m, H_2-4′), 1.50 (m, partly overlapped, H-7′), 1.68 (m, partly overlapped, H-3′) 1.76 and 2.19 (m, partly overlapped, H_a-1′, and m, H_b-1′), 1.83 and 2.64 (m, partly overlapped, H_a-1, and m, H_b-1), 2.85 and 2.99 (dm, $J = 15.2$ Hz, H-7_{eq}, and m, H-7_{ax}), 3.34 and 3.95 (m, partly overlapped, H-6_{ax}, and dt, $J = 13.2$, 4.0 Hz, H-6_{eq}), 3.36 (m, H_2-2), 3.55 (m, H-2′), 4.75/4.78 (dd/dd, $J = 10.0$, 4.4 Hz, H-11b), 7.25 (m, H-8, H-9, H-10), 7.33 (d, $J = 6.0$ Hz, H-11), 8.14 (m, H-3, H-4) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 18.5$ (CH_3 at C-3′), 22.4 (C-8*), 22.6 (CH_3 at C-7′*), 24.3 (C-5′), 27.0 (C-4′), 27.3 (C-1), 27.7 (C-7), 28.0 (C-7′), 33.0 (C-3′), 36.7 (C-6′), 38.6 (C-1′), 39.8 (C-2), 43.3 (C-6), 53.7/54.0 (C-11b), 67.0/67.4 (C-2′), 125.3 (C-11), 126.4 (C-10*), 127.1 (C-9*), 128.3 (C-8), 134.4 (C-7a), 135.4 (C-11a), 152.8 (C-4) ppm.

(11bRS)-4-(3-Bromopropylamino)-1,6,7,11b-tetrahydro-2H-pyrimido[4,3-a]isoquinoline hydroiodide (**11**·HI, $C_{15}H_{21}BrIN_3$)

Yield: 2.70 g (75%), mp 106°C, TLC (CH_2Cl_2:*Me*OH = 6:1): $R_f = 0.57$, visualization with Cl_2; IR (KBr): $\bar{\nu} = 3169$(m), 2929(m), 1604(s), 1493(m), 1395(m), 1242(m), 1125(w), 1041(w) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 1.85$ and 2.64 (m, H-1_{ax}, and dq, $J = 13.6$, 4.4 Hz, H-1_{eq}), 2.08 (quin, $J = 6.8$ Hz, H_2-2′), 2.84 and 2.99 (dt, $J = 16.4$, 4.0 Hz, H-7_{eq}, and m, H-7_{ax}), 3.28 (t, $J = 6.8$ Hz, H_2-1′), 3.34 (m, partly overlapped, H_2-2), 3.37 and 3.89 (m, H-6_{ax}, and dt, $J = 12.8$, 4.8 Hz, H-6_{eq}), 3.58 (t, $J = 6.8$ Hz, H_2-3′), 4.76 (dd, $J = 10.0$, 4.4 Hz, H-11b), 7.25 (m, H-8, H-9, H-10), 7.33 (d, $J = 6.0$ Hz, H-11), 7.52 (t, $J = 5.6$ Hz, H-4), 8.11 (bs, H-3) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 27.5$ (C-1), 27.8 (C-7), 31.4 (C-2′), 31.8 (C-3′), 37.2 (C-2), 39.7 (C-1′), 43.4 (C-6), 54.0 (C-11b), 125.1 (C-11), 126.7 (C-10*), 127.1 (C-9*), 128.3 (C-8), 134.4 (C-7a), 135.6 (C-11a), 152.3 (C-4) ppm.

General Procedure for the Synthesis of Hexahydro-5H-imidazo[1′,2′:1,2]pyrimido[4,3-a]-isoquinoline hydrochlorides ***2a–2c***·*HCl and of the Pyrimido-fused Derivative* ***12***·*HCl*

Sodium hydride 60% oil suspension (1.20 g) was washed three times with *n*-hexane and filtered under Ar. The pure NaH (0.72 g, 30 mmol) was immediately dissolved in dry 80 cm^3 of *THF*, cooled to − 10°C, and the respective 4-bromoalkylaminopyrimidoisoquinoline **5a**–**5c**·HI, **11**·HI (5 mmol) was added in portions over 10 min. Stirring was continued for 1 h at − 10°C and then, after warming to room temperature, for additional 20 h. Then, 2 cm^3 of *Et*OH were added dropwise to destroy excessive NaH. The reaction mixture was diluted with ethyl acetate (50 cm^3) and filtered over a bed of Celite 545, which was washed twice with ethyl acetate. To the filtrate 10 cm^3 of *Et*OH and 5 cm^3 of 6 *N* ethanolic HCl were added and it was evaporated to dryness. The residue was triturated with hexane (**2a**·HCl, **2c**·HCl) or light petroleum (**2b**·HCl), filtered, and dried under reduced pressure. Next, the solid was dissolved in 10 cm^3 of acetone, and Et_2O (100 cm^3) was added slowly to precipitate the crude product, which was purified by column chromatography (CC).

(10bRS)-1,2,6,10b,11,12-Hexahydro-5H-imidazo[1′,2′:1,2]pyrimido[4,3-a]isoquinoline hydrochloride (**2a**·HCl, $C_{14}H_{18}ClN_3$)

CC (CH_2Cl_2:*Me*OH = 6:1), yield 1.24 g (70%), beige powder, mp 74°C; TLC (CH_2Cl_2:*Me*OH = 6:1): $R_f = 0.46$, visualization with Cl_2; IR (KBr): $\bar{\nu} = 3151$(m), 2930(m), 1650(s), 1572(s), 1452(m), 1368(m), 1299(s), 1145(w), 1084(w), 1040(w) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 1.88$ and 2.67 (m, H-11_{ax}, and dq, $J = 13.6$, 4.0 Hz, H-11_{eq}), 2.83 and 2.96 (dt, $J = 16.4$, 3.2 Hz, H-6_{eq}, and m, H-6_{ax}),

3.34 and 3.44 (m, partly overlapped, H-12$_{ax}$, and td, $J = 13.6$, 4.0 Hz, H-12$_{eq}$), 3.38 and 3.85 (m, partly overlapped, H-5$_{ax}$, and dt, $J = 12.8$, 3.2 Hz, H-5$_{eq}$), 3.60 and 3.64 (t, $J = 9.2$ Hz, H$_a$-2, and m, partly overlapped, H$_b$-2), 3.66 and 3.70 (m, partly overlapped, H$_a$-1, and t, $J = 9.2$ Hz, H$_b$-1), 4.77 (dd, $J = 10.8$, 3.2 Hz, H-10b), 7.23 (m, H-7, H-8, H-9), 7.37 (d, $J = 7.6$ Hz, H-10), 8.45 (s, NH) ppm; ^{13}C NMR (*DMSO*-d$_6$): $\delta = 27.8$ (C-11), 28.1 (C-6), 40.7 (C-12), 43.3 (C-5), 43.0 (C-2), 48.7 (C-1), 54.0 (C-10b), 125.6 (C-10), 126.4 (C-9*), 127.0 (C-8*), 128.6 (C-7), 133.8 (C-6a), 134.5 (C-10a), 155.3 (C-3a) ppm.

(1RS, 10bRS)-1-Hexyl-1,2,6,10b,11,12-hexahydro-5H-imidazo[1′,2′:1,2]pyrimido-[4,3-a]isoquinoline hydrochloride (**2b**·HCl, $C_{20}H_{30}ClN_3$)

Yield 1.05 g (60%), yellowish, hygroscopic crystals, mp 42°C; TLC (CH_2Cl_2:*Me*OH = 6:1): $R_f = 0.76$, visualization with Cl_2; IR (KBr): $\bar{\nu} = 3424$(m), 3147(m), 2927(s), 2855(m), 1649(s), 1569(s), 1456(m), 1306(m), 1039(m) cm^{-1}; ^{1}H NMR (*DMSO*-d$_6$): $\delta = 0.85$ (t, $J = 6.8$ Hz, H$_3$-6′), 1.28 (m, H$_2$-2′, H$_2$-3′, H$_2$-4′, H$_2$-5′), 1.53 and 1.90 (m, H$_a$-1′, and m, H$_b$-1′), 1.74 and 2.62 (m, H-11$_{ax}$, and dm, $J = 13.6$ Hz, H-11$_{eq}$), 2.84 and 2.94 (dm, $J = 16.0$ Hz, H-6$_{eq}$, and m, H-6$_{ax}$), 3.25 and 3.76 (t, $J = 14.0$ Hz, H$_a$-2, and dd, $J = 14.0$, 9.2 Hz, H$_b$-2), 3.30 (m, partly overlapped, H$_2$-12), 3.46 and 3.85 (m, partly overlapped, H-5$_{ax}$, and dm, $J = 12.4$ Hz, H-5$_{eq}$), 3.94 (m, H-1), 4.76/4.79 (dd/dd, $J = 10.4$, 3.2 Hz, H-10b), 7.23 (m, H-7, H-8, H-9), 7.37 (d, $J = 8.0$ Hz, H-10), 8.41/8.53 (s/s, H-3) ppm; ^{13}C NMR (*DMSO*-d$_6$): $\delta = 13.9$ (C-6′), 21.9 (C-5′), 23.5 (C-3′), 27.6 (C-6), 28.0 (C-11), 28.6 (C-2′), 30.1 (C-1′), 31.0 (C-4′), 38.4 (C-12), 43.2 (C-5), 45.8 (C-2), 52.6/52.9 (C-10b), 59.6/60.3 (C-1), 125.4 (C-10), 126.7 (C-9*), 127.0 (C-8*), 128.6 (C-7), 133.6 (C-6a), 134.5 (C-10a), 155.4 (C-3a) ppm.

(1RS, 10bRS)-1-[(1RS)-1,5-Dimethylhexyl]-1,2,6,10b,11,12-hexahydro-5H-imidazo[1′,2′:1,2]-pyrimido [4,3-a]isoquinoline hydrochloride (**2c**·HCl, $C_{22}H_{34}ClN_3$)

CC (CH_2Cl_2:*Me*OH = 15:1), yield 0.56 g (30%), yellow crystals, mp 65°C; TLC (CH_2Cl_2: *Me*OH = 15:1): $R_f = 0.46$, visualization with Cl_2; IR (KBr): $\bar{\nu} = 3421$(m), 3178(m), 2953(s), 2928(s), 2868(m), 1651(s), 1606(s), 1456(m), 1364(w), 1124(w), 1040(w) cm^{-1}; ^{1}H NMR (*DMSO*-d$_6$): $\delta = 0.85$ (m, H$_3$-6′, H$_3$-5′), 0.87 (d, $J = 6.8$ Hz, CH$_3$ at C-1′), 1.07–1.27 (overlapping multiplets, H$_2$-4′, H$_2$-3′, H$_2$-2′), 1.37 (m, H-5′), 1.51 (m, H-1′), 1.96 and 2.62 (m, H$_a$-11, and m, H$_b$-11), 2.84 and 2.96 (dm, $J = 16.0$ Hz, H-6$_{eq}$, and m, H-6$_{ax}$), 3.32 and 3.60 (m, partly overlapped, H$_a$-2, and t, $J = 10.4$ Hz, H$_b$-2), 3.38 (m, H$_2$-12), 3.45 and 3.84 (m, H-5$_{ax}$, and td, $J = 13.2$, 4.0 Hz, H-5$_{eq}$), 4.03 (td, $J = 10.4$, 3.2 Hz, H-1), 4.79 (m, H-10b), 7.23 (m, H-7, H-8, H-9), 7.36 (d, $J = 6.8$ Hz, H-10), 8.40/8.51 (s/s, H-3) ppm; ^{13}C NMR (*DMSO*-d$_6$): $\delta = 22.4$ (C-6′), 22.5 (CH$_3$ at C-5′), 22.6 (CH$_3$ at C-1′), 27.3 (C-11), 27.6 (C-6), 27.9 (C-5′), 30.8 (C-1′), 32.0 (C-3′), 37.2 (C-12), 38.5 (C-4′), 40.9 (C-2), 47.2 (C-5), 52.6/53.0 (C-10b), 62.9/63.9 (C-1), 125.8 (C-10), 126.7 (C-9*), 127.1 (C-8*), 128.6 (C-7), 133.7 (C-6a), 134.5 (C-10a), 154.7 (C-3a) ppm.

(11bRS)-2,3,7,11b,12,13-Hexahydro-1H,6H-pyrimido[1′,2′:1,2]pyrimido[4,3-a]isoquinoline hydrochloride (**12**·HCl, $C_{15}H_{20}ClN_3$)

Workup: Under cooling the reaction mixture was made alkaline with 2 *N* NaOH solution (40 cm^3) and then extracted with 2×20 cm^3 of *Et*$_2$O and 1×20 cm^3 of ethyl acetate. The combined extracts were washed with H_2O, dried over Na_2SO_4, filtered, and the solvent was evaporated to dryness *in vacuo*. The residue was mixed with 6 *N* ethanolic HCl (2 cm^3) and it was evaporated to an oily residue, which was next triturated successively twice with ethyl acetate and *Et*$_2$O to yield 0.75 g (54%) of **12**·HCl as beige, very hygroscopic powder (no melting point determination possible). TLC (CH_2Cl_2:*Me*OH = 9:1): $R_f = 0.23$, visualization with Cl_2; IR (KBr): $\bar{\nu} = 3406$(s), 3210(s), 2935(s), 1605(s), 1595(s), 1442(m), 1323(s), 1210(m), 1042(m) cm^{-1}; ^{1}H NMR (*DMSO*-d$_6$): $\delta = 1.89$ (m, H$_2$-2), 1.94 and 2.59

(m, partly overlapped, H-12$_{ax}$, dm, $J = 10.4$ Hz, H-12$_{eq}$), 2.81 and 2.97 (dm, $J = 16.4$ Hz, H-7$_{eq}$, and m, H-7$_{ax}$), 3.22 (m, partly overlapped, H_2-13), 3.29 and 3.98 (m, H-6$_{ax}$, and dm, $J = 13.6$ Hz, H-6$_{eq}$), 3.32 and 3.51 (m, partly overlapped, H-3$_{eq}$, and tm, $J = 11.2$ Hz, H-3$_{ax}$), 3.38 (m, partly overlapped, H_2-1), 4.70 (dm, $J = 7.6$ Hz, H-11b), 7.22 (m, H-8, H-9, H-10), 7.32 (d, $J = 6.4$ Hz, H-11), 8.39 (s, H-4) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 20.1$ (C-2), 27.7 (C-12), 27.9 (C-7), 38.1 (C-13), 43.1 (C-6), 45.9 (C-3), 47.3 (C-1), 53.5 (C-11b), 125.1 (C-11), 126.6 (C-10*), 127.0 (C-9*), 128.3 (C-8), 134.3 (C-7a), 135.6 (C-11a), 150.5 (C-4a) ppm.

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